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Number 157

Diagnosis of Right Lower Quadrant Pain and Suspected Acute Appendicitis



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Diagnosis of Right Lower Quadrant Pain and Suspected Acute Appendicitis

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

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In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

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Structured Abstract

Background. The reliable identification of patients with abdominal pain who need surgical intervention for acute appendicitis can improve clinical outcomes and reduce resource use. The test performance and impact on outcomes of alternative diagnostic strategies are unclear.

Study eligibility criteria. We searched PubMed[®], Embase[®], the Cochrane Central Register of Controlled Trials, and the Cumulative Index to Nursing and Allied Health Literature[®] to identify primary research studies meeting our criteria for cohort studies that reported information on test accuracy for the diagnosis of acute appendicitis or harms, and for comparative studies (randomized or nonrandomized) that reported information on patient-relevant outcomes and resource use (last search, August 6, 2014, for PubMed; August 12, 2014, for all other databases).

Study appraisal and synthesis methods. A single investigator extracted data from each study and a second investigator verified extracted data from comparative studies; we also extracted data in duplicate for a sample of noncomparative studies. We performed Bayesian meta-analyses to estimate summary test performance using random-effects models; data on other outcomes were synthesized qualitatively. We also assessed the strength and applicability of the evidence.

Results. Information on the test performance of diagnostic tests was available from 903 studies: clinical symptoms and signs (137 studies), laboratory tests (217 studies), imaging tests (519 studies), multivariable diagnostic scores (127 studies), and diagnostic laparoscopy (55 studies). Trials directly comparing diagnostic tests were too heterogeneous to support definitive conclusions; therefore, most of our results pertain to the test performance of individual tests. Clinical symptoms and signs, and laboratory tests had relatively low sensitivity and specificity when used in isolation. Their combination in multivariable scores performed somewhat better; however, the most studied scores were developed before the widespread use of imaging, thus lessening the applicability of their results to current practice. Computed tomography (CT) had high sensitivity (summary estimates ranging from 0.96 to 1) and specificity (0.91 to 1) in all populations of interest to this report; magnetic resonance imaging (MRI) had high sensitivity (0.94 to 1) but appeared to have variable specificity (0.86 to 1), mainly because of the smaller number of studies, which focused on its use for pregnant women. In adult populations, ultrasound (US) had lower sensitivity (0.85) and specificity (0.90) than CT and MRI, and produced more nondiagnostic scans. In children, the specificity of US was similar to that of CT (0.91 vs. 0.92), but CT had greater sensitivity (0.89 vs. 0.96); these results were based on a large number of studies (85 for US and 34 for CT). In the same patient population, MRI had a specificity of 0.96 and sensitivity of 0.97, but data were derived from only seven studies. Among pregnant women CT, MRI, and US had similar specificity (0.91, 0.98, and 0.95, respectively), but CT and MRI had higher sensitivity than US (0.99, 0.98, and 0.72, respectively). Information on diagnostic test performance among the elderly was limited. Studies of test performance were deemed to be at moderate risk of bias, mostly because of concerns about differential and incomplete verification.

Information on patient-relevant outcomes and resource use was available from a small number of trials with moderate risk of bias that assessed heterogeneous comparisons between various tests and nonrandomized studies that did not appropriately adjust for potential confounding factors. Only a few studies reported information on harms, leading to concerns about selective outcome reporting. Therefore, no definitive conclusions could be drawn about patient-relevant outcomes or harms.

Limitations. Patient-level data were unavailable, and information about study- or population-level characteristics was too limited to allow the identification of modifiers of test performance, patient-centered outcomes, or harms. Studies reported adverse events incompletely and did not provide details of outcome ascertainment methods.

Conclusions. The literature on the diagnosis of acute appendicitis is large but consists almost exclusively of studies assessing the performance of individual tests. The evidence on individual tests indicates that imaging tests have adequate test performance, while clinical symptoms and signs and laboratory tests used in isolation have lower discriminatory capacity. The evidence is largely insufficient to support conclusions about comparative effectiveness for clinical outcomes because studies assessing more than two test strategies on the same population are few and have evaluated different test comparisons. More research is needed to evaluate the comparative performance and effectiveness of individual tests, test combinations, and integrated diagnostic algorithms; to identify potential modifiers; and to evaluate the impact of testing strategies on patient-relevant outcomes, resource use, and harms. Decision and simulation models using information from this review could inform the design of future studies and guide decisionmaking.

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Appendix C. Studies Assessing the Test Performance of Clinical Signs and Symptoms, Laboratory and Imaging Tests, and Multivariable Diagnostic Scores

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Appendix F. Risk of Bias Assessment for Studies of Test Performance

Executive Summary

Background

Abdominal pain is a common presenting symptom for patients seeking care at emergency departments, with approximately 3.4 million expected cases per year in the United States.¹ Appendicitis is a frequent cause of abdominal pain and occurs in approximately 8 to 10 percent of the population over a lifetime.^{2,3} Appendicitis has its highest incidence between the ages of 10 and 30 years. The ratio of incidence in men and women is 3:2 through the mid-20s and then equalizes after age 30. Appendicitis is the most common abdominal surgical emergency, with over 250,000 appendectomies performed annually in the United States. The risk of acute appendicitis in pregnant women is not much lower than that of the general population, making appendicitis the most common nonobstetric emergency during pregnancy.^{4,7} Untreated appendicitis can lead to perforation of the appendix, which typically occurs within 24 to 48 hours of the onset of symptoms.⁸ Perforation of the appendix can cause intra-abdominal infection, sepsis, intraperitoneal abscesses, and rarely death.⁴ In order to avoid the sequelae of perforated appendicitis, a low percentage of “negative” appendectomies (i.e., removing a normal noninflamed appendix in patients mistakenly diagnosed with appendicitis) is generally accepted from a surgical standpoint.

Clinical symptoms and signs suggestive of appendicitis include a history of central abdominal pain migrating to the right lower quadrant (RLQ), anorexia, fever, and nausea/vomiting. On examination, RLQ tenderness, along with “classical” signs of peritoneal irritation (e.g., rebound tenderness, guarding, rigidity, referred pain), may be present. Other signs (e.g., the psoas or obturator signs) may help the clinician localize the inflamed appendix.⁹⁻¹¹ However, many patients have a less typical presentation, necessitating the use of laboratory or imaging tests to establish a diagnosis. Laboratory evaluations potentially useful for the diagnosis of appendicitis include the white blood cell and granulocyte counts, the proportion of polymorphonuclear blood cells, and serum C-reactive protein.¹⁰⁻¹² Imaging tests, such as ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI), are used extensively for the diagnosis of appendicitis.¹³⁻¹⁹ Imaging tests can be used alone or in combination. For example, US is sometimes used as a triage test to separate patients in whom sonography alone is adequate to establish a diagnosis from those who require further imaging.²⁰ Different factors may affect the performance of alternative tests and their impact on clinical outcomes. For example, US examination is considered to be highly operator dependent²¹ and is technically challenging in obese patients or women in late pregnancy. CT scanning can be performed with or without the use of contrast agents, and contrast can be administered orally, rectally, intravenously, or via combinations of these routes.²⁰

Clinical symptoms and signs, along with the results of laboratory or imaging tests, can be combined into multivariable diagnostic scores (sometimes referred to as “clinical prediction rules”) that synthesize the findings of different investigations to determine the most likely diagnosis.²² In adults, the most commonly used diagnostic score for appendicitis is the Alvarado score,²³ which is based on eight items: pain migration, anorexia, nausea, RLQ tenderness, rebound pain, elevated temperature, leukocytosis, and shift of white blood cell count to the left.²⁴ Although the Alvarado score is also used in pediatric populations,^{25,26} the Pediatric Appendicitis Score has been specifically developed and validated for use in children.²⁷

Diagnostic laparoscopy is also used for the evaluation of patients with RLQ pain and suspected acute appendicitis, primarily when a diagnosis cannot be established via other means.

Although diagnostic laparoscopy is generally considered safe, studies have reported variable rates of morbidity and mortality from the procedure.²⁸

In general these diagnostic tests are widely available in the United States. Clinical symptoms and signs can be evaluated relatively easily and inexpensively. Evidence from the National Hospital Ambulatory Medical Care Survey suggested that CT and complete blood counts are obtained in the majority of patients presenting to the emergency department with abdominal pain. The survey also showed that over time (between 1992 and 2006) the use of CT for both adults and children has increased. Over the same period, the use of the complete blood count increased in adults but decreased in children.^{29,30} Various sources suggest that the use of US and MRI is increasing in populations in which exposure to ionizing radiation is of particular concern (e.g., children and pregnant women).³¹⁻³⁷

As with all diagnostic tests, the modalities used in the diagnostic investigation of patients with RLQ pain affect clinical outcomes indirectly through their impact on clinicians' diagnostic thinking and decisionmaking.³⁸ More accurate and timely diagnosis of appendicitis can minimize the time to the indicated intervention (e.g., surgery), thus reducing the time patients are in pain and improving clinical outcomes (e.g., reducing the rate of perforated appendicitis and its attendant complications).³⁹ Conversely, time-consuming or unnecessary diagnostic workup (an important outcome, but hard to operationalize) may delay the indicated treatment and increase the risk of complications or result in false-positive results and more negative appendectomies. Furthermore, diagnostic testing can impact resource use for the management of patients with acute abdominal pain. For example, examination with CT may reduce length of stay by avoiding prolonged observation in cases in which a diagnosis cannot be established clinically or by eliminating the need for additional diagnostic testing.¹⁸ In some cases, CT can also facilitate direct therapeutic intervention. For example, in patients with perforated appendicitis complicated by an abscess, the radiologist can not only detect but also treat the abscess by percutaneous drainage, thus avoiding the need for immediate operative intervention.

The diagnostic workup of acute appendicitis is complex because patients with acute abdominal pain of different etiologies can present with similar symptoms. Diagnosis is particularly challenging in children, women of reproductive age, pregnant women, and frail or elderly patients.^{20,40,41} In young children (especially toddlers and preschool-age children), acute appendicitis is often diagnosed after perforation has occurred.⁴²⁻⁴⁴ Children have a thinner appendiceal wall and less developed omentum, and thus may not readily wall off a perforation. In addition, many common childhood illnesses have symptoms similar to those of early acute appendicitis. Young children may also have difficulty communicating about their discomfort or describing their symptoms.¹¹ In addition, the use of modalities that involve ionizing radiation (e.g., CT) entails greater risks for children than for older patients.²⁰ A large proportion of women of reproductive age with appendicitis are misdiagnosed.^{41,45} Establishing a diagnosis in this patient group can be particularly challenging because symptoms of acute appendicitis can mimic those of common gynecologic diseases (e.g., pelvic inflammatory disease, ectopic pregnancy). In pregnant women the diagnosis of suspected acute appendicitis can also be challenging because some symptoms of appendicitis (nausea and vomiting) are common in normal pregnancies and because enlargement of the uterus can alter the location of the appendix, which often moves higher and to the back.⁴⁶ Anatomic changes induced by pregnancy make the clinical examination of pregnant patients with abdominal pain more challenging and result in technical difficulties when using US.^{37,47,48} Tests involving ionizing radiation (e.g., CT) are also generally avoided during pregnancy to prevent exposure of the fetus to radiation. Finally, obtaining a white blood

cell count may not be helpful in the diagnosis of acute appendicitis because leukocytosis is common during pregnancy. The elderly typically present with appendicitis in a more advanced stage because they may delay seeking care, and definitive diagnosis is sometimes delayed further because competing etiologies for abdominal pain (e.g., malignancy or diverticulitis) are considered more likely.⁴⁹ Therefore, the performance of diagnostic tests may be modified by patient age, and elderly and frail individuals with appendicitis have a higher complication rate and a higher risk of mortality than younger and less frail patients.

Rationale for Evidence Review

Accurate testing of patients presenting with symptoms consistent with acute appendicitis to identify those who need treatment can improve clinical outcomes and reduce resource use. There is a lack of specific guidance for selecting diagnostic modalities, particularly in patient subgroups in whom the diagnosis is known to be particularly challenging (e.g., children, women of reproductive age, pregnant women, and the elderly). Existing systematic reviews typically assess a single diagnostic modality, focus almost exclusively on test performance outcomes rather than patient-relevant outcomes, and do not address factors that may modify test performance. No review to date has comprehensively examined all tests of interest or focused on comparisons between alternative strategies.

Key Questions

With input from clinical experts, we developed the following Key Questions to clarify the focus of the proposed systematic review.

Key Question 1: What is the performance of alternative diagnostic tests, alone or in combination, for patients with RLQ pain and suspected acute appendicitis?

- a. What are the performance and comparative performance of alternative diagnostic tests in the following patient populations: children, adults, nonpregnant women of reproductive age, pregnant women, the elderly (age ≥ 65 years)?
- b. What factors modify the test performance and comparative test performance of available diagnostic tests in these populations?

Key Question 2: What is the comparative effectiveness of alternative diagnostic tests, alone or in combination, for patients with RLQ pain and suspected acute appendicitis?

- a. For the populations listed under Key Question 1a, what is the effect of alternative testing strategies on diagnostic thinking, therapeutic decisionmaking, clinical outcomes, and resource utilization?
- b. What factors modify the comparative effectiveness of testing for patients with RLQ pain and suspected acute appendicitis?

Key Question 3: What are the harms of diagnostic tests per se, and what are the treatment-related harms of test-directed treatment for tests used to diagnose RLQ pain and suspected acute appendicitis?

Methods

We performed a systematic review of the published literature using established methods as outlined in the Agency for Healthcare Research and Quality (AHRQ) “Methods Guide for Effectiveness and Comparative Effectiveness Reviews” (Methods Guide).⁵⁰ We followed the reporting requirements of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).⁵¹ All key methodological decisions were made a priori. The protocol was developed with input from external clinical and methodological experts in consultation with the AHRQ Task Order Officer (TOO) and was posted online to solicit additional comments. The review’s PROSPERO registration number is CRD42013006480.

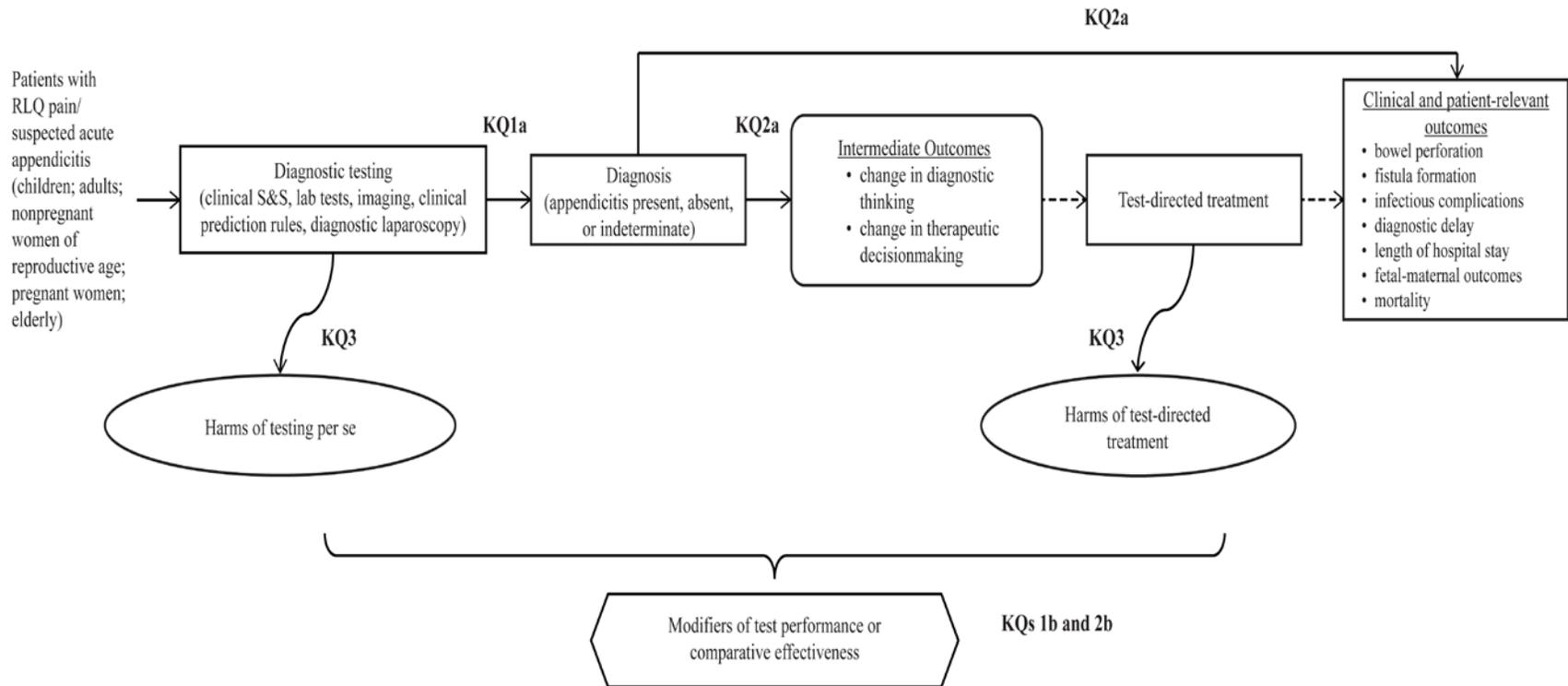
AHRQ TOO and External Stakeholder Input

A panel of Key Informants, including patients and other stakeholders, gave input on the Key Questions to be examined. These Key Questions were posted on AHRQ’s Effective Health Care Web site for public comment and revised in response to comments. A Technical Expert Panel, including representatives of professional societies and experts in the diagnosis and treatment of RLQ abdominal pain and appendicitis, provided input to help further refine the Key Questions and protocol, identify important issues, and define the parameters for the review of evidence. The AHRQ TOO was responsible for overseeing all aspects of this project. Discussions among the Evidence-based Practice Center, TOO, and Technical Expert Panel occurred during a series of teleconferences and via email.

Analytic Framework

We used an analytic framework (Figure A) that maps the Key Questions within the context of populations, interventions, comparators, and outcomes of interest.

Figure A. Analytic framework



KQ = Key Question; RLQ = right lower quadrant; S&S = symptoms and signs

Inclusion and Exclusion Criteria

Populations and Conditions of Interest

The population of interest for all Key Questions was patients with acute RLQ abdominal pain (≤ 7 days duration) for whom appendicitis was considered in the differential diagnosis. Separate analyses were performed for children (age < 18 years), adults (age ≥ 18 years), women of reproductive age, pregnant women, and the elderly. We initially planned to separately examine the subgroup of very young children (< 2 years and 2–5 years of age); however, information for these subgroups was poorly reported and we were unable to perform these subgroup analyses.

Interventions

For all Key Questions, the interventions of interest were diagnostic tests (alone or in combination) for diagnosing appendicitis, including clinical symptoms, clinical signs, laboratory tests, multivariable diagnostic scores, imaging tests, nuclear imaging studies, and diagnostic laparoscopy.

Comparators (Index and Reference Standard Tests)

For all Key Questions, the comparators were alternative tests or test combinations (listed previously) or clinical observation.

Outcomes

For Key Question 1, the outcome of interest was test performance, using pathology or clinical followup as the reference standard. For Key Question 2, we examined the impact of testing on diagnostic thinking, on therapeutic decisionmaking, and on patient-centered and resource use outcomes (negative appendectomy rate, bowel perforation, fistula formation, infectious complications, delay in diagnosis, length of hospital stay, fetal/maternal outcomes, and mortality). For Key Question 3, we considered adverse effects, including direct harms of testing and harms of test-directed treatment. When outcome definitions were not provided by the included studies, we adopted the terms used by the studies at face value.

Timing

Studies were considered regardless of duration of followup.

Setting

All health care settings were considered.

Study Design and Additional Criteria

For studies assessing test performance, we used previously completed systematic reviews to identify relevant studies and obtain specific data items. We updated these reviews to include more recent studies identified through literature searches. For index tests for which no relevant systematic review of test performance meeting our selection criteria could be identified, we performed a de novo systematic review. We accepted both randomized and nonrandomized comparative studies but analyzed them separately. We included only English-language studies because our preliminary searches indicated that non-English-language studies represented a small portion of the evidence base for any given test modality and were unlikely to change conclusions.

Literature Search and Abstract Screening

Appendix A in the full report describes our literature search strategies. Searches were conducted in PubMed[®], Embase[®], the Cochrane Central Register of Controlled Trials, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL[®]) databases to identify primary research studies meeting our criteria (last search on August 6, 2014, for PubMed; August 12, 2014, for all other databases). We also used the PubMed search results to identify systematic reviews of the tests of interest (last search, July 31, 2013; search for systematic reviews not updated). All reviewers screened a common set of 200 abstracts, and discrepancies were discussed in order to standardize screening practices and ensure understanding of screening criteria. The remaining citations were split into nonoverlapping sets, each screened by two reviewers independently. Discrepancies were resolved by consensus involving a third investigator. We asked the Technical Expert Panel to provide citations of potentially relevant articles and identified additional studies through the perusal of reference lists of eligible studies, clinical practice guidelines, relevant reviews, and conference proceedings. The Technical Expert Panel reviewed the final list of included studies to ensure that no key publications had been missed.

Study Selection and Data Abstraction

Potentially eligible citations were reviewed in full text for eligibility. A single reviewer examined each article; a second reviewer independently examined a subset of 350 articles. Disagreements were resolved by consensus involving a third reviewer. We included only English-language studies during full-text review because our preliminary searches indicated that non-English-language studies had small sample sizes and represented a small portion of the evidence base for any given test modality, so their exclusion is unlikely to have affected our conclusions. We excluded studies published exclusively in abstract form because they are typically not peer reviewed, they report only partial results, and their findings may change substantially when fully published. A detailed description of quality control measures is available in the protocol (www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=1827). The lists of included and excluded studies (organized by reason for exclusion) are in Appendix B of the full report.

Previously published reviews were used as sources of eligible studies of test performance and as sources of data for objective data elements from these studies (bibliographic information, characteristics of included populations, and counts of individuals stratified by diagnostic test result and disease status). We verified all data from studies included in previously published systematic reviews against the full text of the corresponding publications. Because of the large number of studies, a single reviewer extracted data from each eligible noncomparative study of test performance; for nonrandomized comparative studies (NRCs) and randomized controlled trials (RCTs), one reviewer extracted and a second reviewer verified the data. For RCTs, when possible, data were extracted according to the intention-to-treat principle. We verified the data extraction and risk-of-bias assessment in a random sample of 368 noncomparative test performance studies (1,487 separate estimates of test performance). Overall, agreement was excellent on items capturing information about the index and reference standard tests and numerical information on test performance. Agreement was less good for some risk-of-bias items; information on these items was reextracted for all included studies following a series of standardization exercises.

Assessment of the Risk of Bias of Individual Studies

We assessed the risk of bias for each study using the assessment methods detailed by the AHRQ Methods Guide.⁵⁰ We used items from the updated QUADAS (Quality Assessment of Diagnostic Accuracy Studies) 2 instrument to assess the risk of bias of the diagnostic test studies included in the review.⁵²⁻⁵⁵ For studies of other designs, we used appropriate items to assess risk of bias: for NRCSSs, we used items from the Newcastle-Ottawa scale;⁵⁶ for RCTs, we used items from the Cochrane Risk of Bias tool.⁵⁷ We rated each study as having low, intermediate, or high risk of bias on the basis of adherence to accepted methodological principles.

Evidence Synthesis

We summarized the included studies qualitatively and present important features of the study populations, designs, interventions, outcomes, and results in summary tables in the full report and its appendixes. All studies evaluating the test performance of the same single index test in a similar patient population were synthesized jointly, regardless of their source (our own literature searches or previously published reviews). Analyses were performed separately for the following patient populations: children, women of reproductive age, pregnant women, and the elderly. For each comparison of interest, we judged whether the eligible studies were sufficiently similar for meta-analysis on the basis of clinical heterogeneity of patient populations and testing strategies, as well as methodological heterogeneity of study designs and outcomes reported.

When five or more sufficiently similar studies evaluated the test performance of the same test in the same population, we used a bivariate-bivariate normal meta-analysis model to obtain summary sensitivity and specificity estimates.^{58,59} We used the model estimates to calculate summary positive and negative likelihood ratios (LRs)⁶⁰ and to construct summary receiver operating characteristic (ROC) curves.^{61,62} Meta-analyses were conducted using Bayesian methods with flat (minimally informative) priors.⁶³ We assessed heterogeneity by inspecting plots of study estimates in the ROC space and by examining the posterior distribution of the between-study heterogeneity parameters (for logit-sensitivity and logit-specificity). We explored heterogeneity using subgroup and meta-regression analyses. There were not enough studies comparing the same test strategies to allow meta-analysis for clinical outcomes and resource use.

In cases in which only a subset of the available studies could be quantitatively combined, we synthesized findings across all studies qualitatively by taking into account the magnitude and direction of effects and estimates of performance.

Grading the Strength of Evidence and Assessing Applicability

We followed the Methods Guide⁵⁰ to evaluate the strength of the body of evidence for each Key Question with respect to the following domains: risk of bias, consistency, directness, precision, and reporting bias.^{50,64} Briefly, we assessed risk of bias (low, medium, or high) on the basis of the study design and the methodological quality of the studies. We rated the consistency of the data on the basis of the direction, magnitude, and statistical significance of all studies and made a determination. We assessed directness of the evidence on the basis of the use of surrogate outcomes or the need for indirect comparisons. We assessed the precision of the evidence on the basis of the degree of certainty surrounding each effect estimate. The potential for reporting bias was evaluated with respect to publication bias, selective outcome reporting bias, and selective analysis reporting bias. For all types of reporting bias, we made qualitative dispositions rather than performing formal statistical tests to evaluate differences in the effect sizes between more

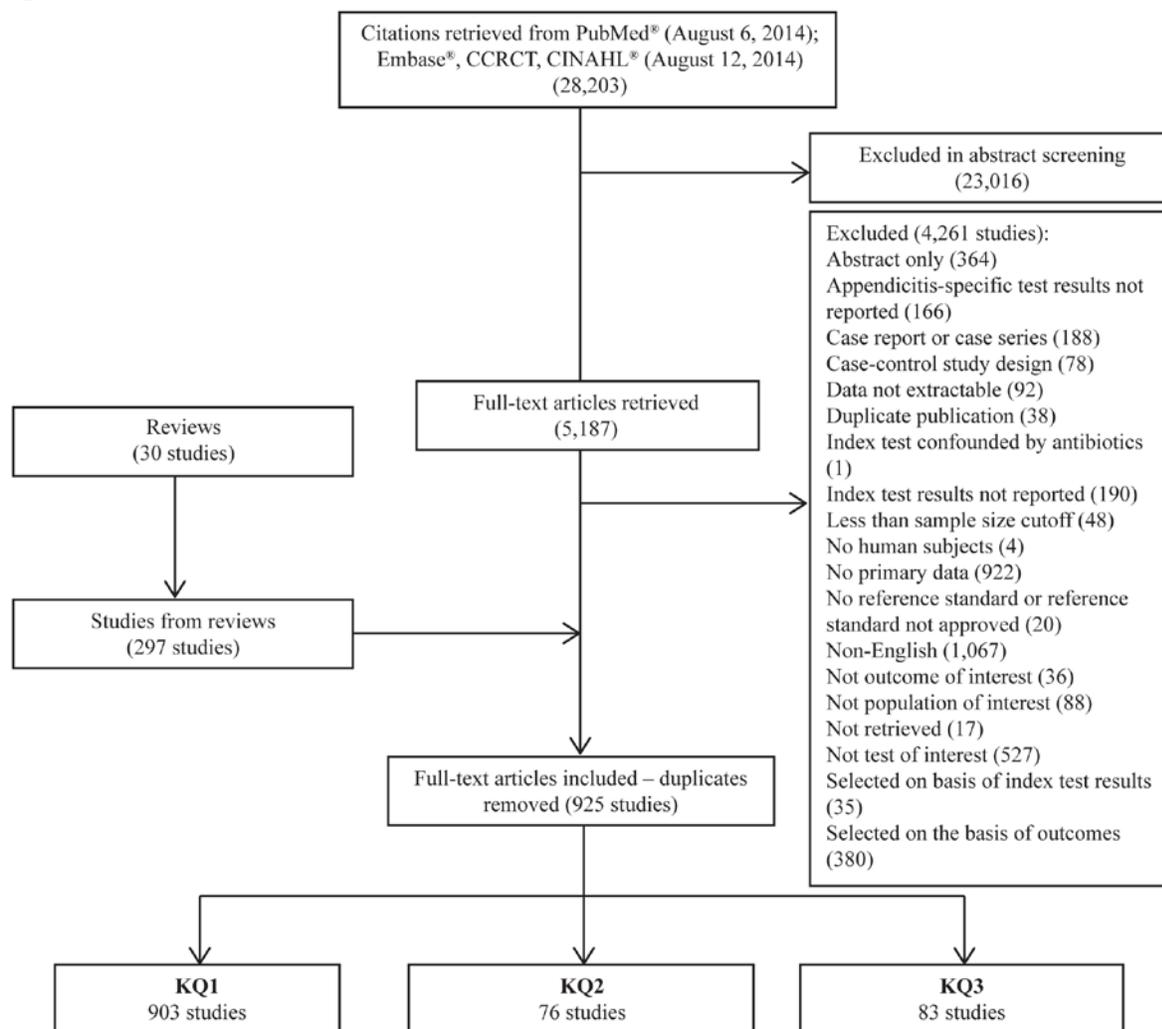
precise (larger) and less precise (smaller) studies. Instead of relying on statistical tests, we evaluated the reported results across studies qualitatively on the basis of completeness of reporting, number of enrolled patients, and numbers of observed events.^{63,64} Judgment on the potential for selective outcome reporting bias was based on reporting patterns for each outcome of interest across studies. Finally, we rated the overall strength of the body of evidence using four levels: high, moderate, low, and insufficient.⁴⁷

We followed the Methods Guide⁵⁰ to evaluate the applicability of included studies to patient populations of interest. We considered important population subgroups separately and evaluated the duration of symptoms before enrollment, outcomes reported, and setting of care.

Results

We reviewed the full text of 5,187 publications, of which 969 were considered eligible for inclusion in the review. Figure B presents the literature flow; our search strategies are presented in Appendix A; the lists of included and excluded studies (organized by reason for exclusion) are provided in Appendix B of the full report.

Figure B. Flow chart of included studies



CCRCT = Cochrane Central Register of Controlled Trials; KQ = Key Question

Key Question 1: What is the performance of alternative diagnostic tests, alone or in combination, for patients with RLQ pain and suspected acute appendicitis?

In total, 903 studies published between 1956 and 2014 met the inclusion criteria for Key Question 1. In this Executive Summary we present information on the tests that we thought were most clinically relevant on the basis of our reading of the literature, discussions with local clinical experts, and discussions with Key Informants and the Technical Expert Panel. The full report and appendixes present complete data on all tests we examined. Throughout, results for each test are presented separately for adults, children, women of reproductive age, pregnant women, and mixed populations (typically including male and female patients of all ages).

Studies of Test Performance

In general, studies of test performance were deemed to be at moderate to high risk of bias. Estimates of test performance often appeared to be affected by characteristics of study design

that may be related to risk of bias, particularly partial and incomplete verification. In most cases, factors indicative of high risk of bias were associated with higher values of estimated test performance. These findings suggest that study conduct may have affected estimates of test performance in our meta-analyses. However, the assessment of the impact of risk of bias had to rely on information that was often poorly reported in the primary studies. Because each risk-of-bias item was examined individually and because different items may be correlated with each other and with other study characteristics that may affect test performance, we do not believe that definitive conclusions about specific items can be reached at this time.

Test Performance of Clinical Symptoms and Signs (in Isolation)

Table A presents key test performance results for selected clinical symptoms and signs. Symptoms and signs had limited test performance when used in isolation. There was substantial heterogeneity in sensitivity and specificity for most clinical symptoms and signs.

Table A. Summary estimates of test performance of clinical symptoms and signs for the diagnosis of acute appendicitis

Symptom or Sign	Population	N Studies (N Affected/N Unaffected)	Sensitivity (95% CrI or Range*)	Specificity (95% CrI or Range*)
Fever	Adults	15 (2,082/1,796)	0.46 (0.29 to 0.64)	0.63 (0.47 to 0.77)
	Children	22 (3,952/3,845)	0.51 (0.41 to 0.61)	0.72 (0.66 to 0.77)
	Children <5 years	2 (196/77)	0.88 (0.83 to 0.93)	0.34 (0.29 to 0.39)
	Women of reproductive age	2 (37/36)	0.36 (0.20 to 0.53)	0.94 (0.89 to 1.00)
	Pregnant women	10 (309/166)	0.33 (0.14 to 0.59)	0.65 (0.37 to 0.86)
	Mixed	33 (8,766/5,386)	0.50 (0.39 to 0.61)	0.72 (0.62 to 0.80)
Guarding	Adults	5 (771/1,158)	0.67 (0.36 to 0.89)	0.69 (0.43 to 0.87)
	Children	8 (870/1,554)	0.64 (0.49 to 0.77)	0.69 (0.54 to 0.81)
	Women of reproductive age	1 (17/27)	0.76	0.85
	Pregnant women	4 (144/103)	0.63 (0.14 to 0.76)	0.55 (0.43 to 0.74)
	Mixed	18 (3,151/4,231)	0.63 (0.47 to 0.78)	0.69 (0.53 to 0.81)
Pain Migration	Adults	11 (1,831/864)	0.56 (0.45 to 0.67)	0.65 (0.50 to 0.78)
	Children	15 (2,049/3,535)	0.57 (0.39 to 0.73)	0.74 (0.66 to 0.81)
	Women of reproductive age	1 (17/27)	0.53	0.67
	Pregnant women	1 (42/14)	0.57	0.86
	Mixed	23 (4,475/6,156)	0.61 (0.49 to 0.71)	0.67 (0.56 to 0.76)
Tenderness	Children	2 (206/474)	0.63 (0.26 to 1.00)	0.57 (0.46 to 0.68)
	Children <5 years	1 (155/28)	0.98	0.25
	Women of reproductive age	1 (17/27)	1.00	0.04
	Mixed	10 (1,450/1,510)	0.99 (0.95 to 1.00)	0.30 (0.08 to 0.67)
Rebound Tenderness	Adults	11 (1,423/1,540)	0.67 (0.50 to 0.81)	0.70 (0.51 to 0.83)
	Children	11 (1,013/1,895)	0.60 (0.43 to 0.77)	0.73 (0.57 to 0.84)
	Children <5 years	1 (155/28)	0.85	0.86
	Women of reproductive age	1 (26/79)	0.42	0.65
	Pregnant women	5 (160/111)	0.71 (0.36 to 0.92)	0.58 (0.21 to 0.88)
	Mixed	30 (5,859/6,738)	0.74 (0.65 to 0.82)	0.60 (0.48 to 0.72)

*We report sensitivity and specificity values as medians and report central 95% credible intervals (95% CrI) when ≥ 5 studies were available. We report medians and minimum-to-maximum values when < 5 studies were available. When a single study was available, we report the estimate from that study.

Test Performance of Laboratory Tests (in Isolation)

Table B presents key test performance results for selected laboratory tests. The performance of individual laboratory tests was also rather limited, but it was better than that of clinical symptoms and signs. There was substantial heterogeneity in sensitivity and specificity for most laboratory tests. Nevertheless, in most cases, summary ROC lines appeared to fit the data relatively well.

Table B. Summary estimates of test performance of laboratory values for the diagnosis of acute appendicitis

Laboratory Value	Population	N studies (N Affected/N Unaffected)	Sensitivity (95% CrI or Range*)	Specificity (95% CrI or Range*)
CRP	Adults	15 (1,541/983)	0.84 (0.73 to 0.92)	0.67 (0.50 to 0.81)
	Children	22 (2,226/1,635)	0.73 (0.66 to 0.80)	0.72 (0.61 to 0.81)
	Elderly	2 (213/72)	0.91 (0.91 to 0.92)	0.21 (0.17 to 0.25)
	Women of reproductive age	3 (169/133)	0.79 (0.44 to 0.97)	0.70 (0.33 to 0.93)
	Pregnant women	1 (31/8)	0.68	0.50
	Mixed	52 (8,742/5,903)	0.79 (0.74 to 0.83)	0.65 (0.57 to 0.72)
WBC	Adults	26 (4,070/2,452)	0.81 (0.74 to 0.87)	0.54 (0.42 to 0.64)
	Children	41 (6,595/4,473)	0.80 (0.73 to 0.85)	0.65 (0.56 to 0.73)
	Elderly	3 (287/82)	0.71 (0.69 to 0.77)	0.50 (0.38 to 0.70)
	Women of reproductive age	2 (49/18)	0.64 (0.60 to 0.69)	0.67 (0.67 to 0.67)
	Pregnant women	6 (197/82)	0.63 (0.21 to 0.92)	0.75 (0.38 to 0.95)
	Mixed	84 (19,074/10,883)	0.78 (0.75 to 0.82)	0.62 (0.58 to 0.66)
WBC + CRP	Adults	2 (194/68)	0.93 (0.86 to 1.00)	0.62 (0.37 to 0.86)
	Children	5 (566/132)	0.81 (0.42 to 0.96)	0.73 (0.54 to 0.85)
	Elderly	1 (77/8)	0.96	0.13
	Women of reproductive age	1 (29/9)	0.93	0.44
	Mixed	15 (4,145/1,734)	0.72 (0.42 to 0.91)	0.73 (0.54 to 0.88)

CRP = C-reactive protein; WBC = white blood cell count

*We report sensitivity and specificity values as medians and report central 95% credible intervals (95% CrI) when ≥ 5 studies were available. We report medians and minimum-to-maximum values when < 5 studies were available. When a single study was available, we report the estimate from that study.

Test Performance of Multivariable Diagnostic Scores

Information on one or more multivariable diagnostic scores was reported in 127 studies. The authors usually proposed two types of cutpoints for these scores: a low value, below which patients might be safely discharged or observed (we refer to this cutpoint as the “low-risk cutoff”), and a high value, above which patients should be referred for treatment without additional investigation (we refer to this cutoff as the “high-risk cutoff”). The low- and high-risk cutoff values can be used to define three patient groups at different risk for appendicitis: low, intermediate, and high risk. If the diagnostic score has adequate classification performance and good calibration, the preferred test-and-treat strategy for each group will be different. When studies reported results at multiple cutpoints, we performed analyses at low-risk and high-risk cutpoints suggested by the original score developers or recommended in studies conducted after

the ones examined. For scores developed specifically for binary classification, we used a single cutpoint. Test performance results for commonly used scores are presented in Tables C and D.

The majority of multivariable diagnostic scores were developed prior to the widespread use of diagnostic imaging with CT and US. More recently developed scores were designed with the intention of identifying a low-risk group in which imaging can be omitted. Furthermore, multivariable models were often developed and evaluated in the same patient sample. It is likely that the lack of separation between the training and testing datasets led to optimistic estimates of test performance. Lack of external validation also limited our ability to assess the generalizability of many diagnostic scores.

Table C. Summary estimates of test performance of Alvarado diagnostic score test (low-risk cutoff) for the diagnosis of acute appendicitis

Test	Population	N Studies (N Affected/N Unaffected)	Sensitivity (95% CrI or Range*)	Specificity (95% CrI or Range*)
Alvarado	Adults	3 (407/264)	0.91 (0.89 to 0.93)	0.31 (0.24 to 0.78)
	Children	6 (674/898)	0.99 (0.92 to 1.00)	0.48 (0.24 to 0.74)
	Mixed	20 (3,986/4,073)	0.96 (0.92 to 0.98)	0.46 (0.34 to 0.58)
	Women of reproductive age	2 (89/50)	0.99 (0.98 to 1.00)	0.24 (0.22 to 0.25)
	Children <5 years	1 (17/10)	1.00	0.20

*We report sensitivity and specificity values as medians and report central 95% credible intervals (95% CrI) when ≥ 5 studies were available. We report medians and minimum-to-maximum values when < 5 studies were available. When a single study was available, we report the estimate from that study.

Table D. Summary estimates of test performance of diagnostic score tests (high-risk cutoff) for the diagnosis of acute appendicitis

Test	Population	N Studies (N Affected/N Unaffected)	Sensitivity (95% CrI or Range*)	Specificity (95% CrI or Range*)
Alvarado	Adults	16 (2,354/1,212)	0.75 (0.59 to 0.87)	0.75 (0.57 to 0.87)
	Children	9 (855/1,163)	0.85 (0.75 to 0.93)	0.84 (0.61 to 0.96)
	Mixed	30 (4,475/4,337)	0.77 (0.69 to 0.84)	0.79 (0.74 to 0.84)
	Women of reproductive age	5 (202/177)	0.70 (0.35 to 0.92)	0.91 (0.65 to 0.99)
	Children <5 years	1 (17/10)	0.76	0.60
Alvarado Modified	Adults	4 (254/126)	0.68 (0.54 to 0.89)	0.60 (0.14 to 0.89)
	Children	5 (109/110)	0.89 (0.71 to 0.98)	0.80 (0.37 to 0.97)
	Elderly	1 (7/10)	0.86	0.80
	Mixed	6 (412/139)	0.82 (0.63 to 0.93)	0.62 (0.24 to 0.89)
	Women of reproductive age	4 (186/69)	0.60 (0.17 to 0.91)	0.50 (0.17 to 1.00)
PAS	Children	1 [108/18]	0.95	0.11

PAS = Pediatric Appendicitis Score

*We report sensitivity and specificity values as medians and report central 95% credible intervals when ≥ 5 studies were available. We report medians and minimum-to-maximum values when < 5 studies were available. When a single study was available, we report the estimate from that study.

Test Performance of Imaging Tests

Table E presents key test performance results for selected imaging tests. Positive and negative LRs were generally higher for CT and MRI than for US, but all three tests had LRs that are clinically relevant (> 5 and < 0.2 for positive and negative LRs, respectively). US had substantially higher rates of nondiagnostic exams. The median percentage of nondiagnostic scans for CT was lower than 6% for all populations examined; the median proportion was substantially higher for US (ranging from 0% in women of reproductive age to 77.3% in pregnant women). However, the reporting of information on nondiagnostic scans was inconsistent across studies,

raising concerns about reporting bias. The full report presents the results of sensitivity analyses for the test performance of imaging tests under different assumptions about nondiagnostic scans. Heterogeneity in sensitivity and specificity was moderate or high for most tests with adequate data for assessment, yet in most cases summary ROC lines appeared to fit the data relatively well. CT had high sensitivity (summary estimates ranging from 0.95 to 1) and specificity (0.91 to 0.99) in all populations of interest for this report. MRI had high sensitivity (0.91 to 1) but appeared to have variable specificity (0.86 to 1), mainly because of the smaller number of available studies, and the findings are most applicable to pregnant women. In adult populations, US had lower sensitivity (0.83) and specificity (0.89) than CT and MRI, and produced more nondiagnostic scans. In children, the specificity of US was similar to that of CT (0.92 vs. 0.91), but CT had greater sensitivity (0.89 vs. 0.96); these results were based on a large number of studies (72 for US and 32 for CT). In the same patient population, MRI had a specificity of 0.99 and sensitivity of 1, but data were derived from only three studies and are therefore less reliable than those for other imaging tests. Among pregnant women, CT (5 studies), MRI (10 studies), and US (10 studies) had similar specificity (0.98, 0.98, and 0.95, respectively), but CT and MRI had higher sensitivity than US (0.95, 0.98, and 0.73, respectively).

Table E. Summary estimates of test performance of diagnostic imaging for acute appendicitis

Test	Population	N Studies (N Affected/N Unaffected)	Sensitivity (95% CrI or Range*)	Specificity (95% CrI or Range*)
CT	Adults	72 (7,833/14,469)	0.96 (0.95 to 0.97)	0.96 (0.93 to 0.97)
	Children	34 (3,581/3,122)	0.96 (0.94 to 0.98)	0.92 (0.85 to 0.96)
	Elderly	4 (144/582)	1.00 (0.94 to 1.00)	1.00 (0.43 to 1.00)
	Women of reproductive age	11 (596/652)	0.99 (0.96 to 1.00)	0.91 (0.75 to 0.97)
	Pregnant women	5 (26/84)	0.99 (0.96 to 1.00)	0.91 (0.75 to 0.97)
	Mixed	93 (9,341/10,357)	0.96 (0.95 to 0.97)	0.94 (0.91 to 0.95)
MRI	Adults	7 (512/467)	0.95 (0.88 to 0.98)	0.92 (0.87 to 0.95)
	Children	7 (359/665)	0.97 (0.87 to 1.00)	0.96 (0.84 to 0.99)
	Women of reproductive age	1 (50/88)	1.00	0.86
	Pregnant women	11 (76/570)	0.98 (0.92 to 1.00)	0.98 (0.96 to 1.00)
	Mixed	5 (243/141)	0.94 (0.83 to 0.99)	1.00 (0.97 to 1.00)
US	Adults	38 (3,560/3,656)	0.85 (0.79 to 0.90)	0.90 (0.83 to 0.95)
	Children	85 (8,539/15,167)	0.89 (0.86 to 0.92)	0.91 (0.89 to 0.94)
	Women of reproductive age	11 (516/539)	0.72 (0.51 to 0.88)	0.92 (0.75 to 0.98)
	Pregnant women	13 (188/198)	0.72 (0.45 to 0.92)	0.95 (0.84 to 0.99)
	Mixed	125 (11,902/14,314)	0.86 (0.83 to 0.89)	0.90 (0.87 to 0.92)

CT = computed tomography; MRI = magnetic resonance imaging; US = ultrasound

*We report sensitivity and specificity values as medians and report central 95% credible intervals when ≥ 5 studies were available. We report medians and minimum-to-maximum values when < 5 studies were available. When a single study was available, we report the estimate from that study.

Test Performance of Diagnostic Laparoscopy

Fifty-five studies published between 1974 and 2014 reported information on the test performance of diagnostic laparoscopy. The reporting of methods and outcomes in these studies was less complete than that of studies of other tests. When possible to discern such information

from the reported data, patients undergoing diagnostic laparoscopy often presented atypically and had already been examined with a number of other diagnostic modalities. In addition, studies of laparoscopy did not fully report information on the final diagnosis of patients for whom the procedure did not reveal an inflamed appendix. Studies often did not report operational definitions for the absence of any pathology and had heterogeneous management policies for such cases. These features of the studies can influence the estimates of test performance; for this reason, we did not perform any quantitative synthesis for the test performance of diagnostic laparoscopy. It is important to note that patients included in studies of diagnostic laparoscopy are likely to be different from patients included in studies of noninvasive tests, even if the selection criteria are not clearly presented. They may, for example, have more severe symptoms or have atypical findings on other tests. Thus, indirect comparisons of diagnostic laparoscopy with noninvasive tests are not meaningful.

Sensitivity and Specificity

For the 54 studies for which they could be calculated, the median sensitivity and specificity were 100 and 89 percent, respectively. However, there was a wide range, with sensitivity ranging from 37 to 100 percent (25th percentile, 95%; 75th percentile, 100%) and specificity ranging from 0 to 100 percent (25th percentile, 73%; 75th percentile, 100%). This variability likely reflects the heterogeneous populations evaluated in these studies. In the 16 studies that reported on women of reproductive age, the median sensitivity was 100 percent (25th percentile, 100%; 75th percentile, 100%), and the median specificity was 89 percent (25th percentile, 79%; 75th percentile, 100%).

Tests Positive for Other Pathology

Forty-one studies reported some information on other pathology diagnosed at laparoscopy. The median proportion of patients identified with nonappendiceal pathology was 22 percent (25th percentile, 11.5%; 75th percentile, 34%). Only six small studies reported that other pathology was found when appendicitis was also present. The median was 5 percent (25th percentile, 2%; 75th percentile, 13%). In studies of women of reproductive age, the median proportion of patients identified with nonappendiceal pathology was 23 percent (25th percentile, 18%; 75th percentile, 26%); no nonappendiceal pathologies were found in patients who had appendicitis.

Other

Information on other test performance outcomes of diagnostic laparoscopy—for example, the proportion of cases in which the appendix could not be visualized and the proportion of cases in which no cause of pain was identified (i.e., nonproductive abdominal explorations)—is presented in the full report.

Modifiers of Test Performance

The vast majority of studies did not report adequate data to assess factors that may affect test performance; for this reason we relied on comparisons across studies via meta-regression analyses to identify such factors. Overall, no distinct pattern emerged to establish a particular factor as a modifier of test performance. For all clinically relevant factors examined, credible intervals were wide, indicating substantial uncertainty regarding the relative performance of tests over levels of the modifiers. Details on the impact of patient- and test-related characteristics on the test performance of various tests in specific subpopulations are presented in the full report.

Comparative Assessments of Test Performance

Our assessment of comparative test performance relied on randomized and nonrandomized direct (i.e., within-study) comparisons of tests. Overall, on the basis of items from the Cochrane risk-of-bias tool, RCTs were deemed to be at moderate risk of bias. NRCSs were at high risk of bias because they either did not make any attempt to address differences among groups receiving different test strategies or failed to consider at least some important factors (e.g., age, sex, or duration and severity of symptoms).

Randomized Comparisons of Alternative Tests

Although 36 RCTs reported information on comparative test performance, each possible comparison was examined by only one or two small trials, and these trials did not report information on the same outcomes. Therefore, it was not possible to draw strong conclusions about the comparative performance of different tests.

Nonrandomized Comparisons of Alternative Tests

Nonrandomized Comparisons of Diagnostic Scores

Eight studies reported direct comparisons among alternative diagnostic scores for appendicitis. Three studies included only children, one included women of reproductive age, and four included mixed populations. Across all eight studies, differences in test performance between scores were small; this was particularly true for the comparison of the Alvarado score and Pediatric Appendicitis Scores applied to children with suspected acute appendicitis. The one exception was a study that compared a multivariable diagnostic score based on clinical symptoms and signs versus a score combining the same clinical variables with the addition of US: incorporation of imaging information improved test performance substantially with respect to both sensitivity and specificity.

Nonrandomized Comparisons of CT and US

Fifty-three studies reported results in cohorts using both CT and US as index tests, potentially permitting direct nonrandomized comparisons of these modalities. Ten studies investigated CT as a replacement for US, 13 investigated US as a triage test for CT, and 30 studies were unclear about the actual role of testing that was being evaluated (often using convenience samples of patients selected using criteria that were poorly reported). Nine of the studies had a paired design and 44 had a parallel-group design. In general, CT had better test performance than US when used as a replacement test or when the role of testing being evaluated was unclear. In the triage context, CT had high test performance (diagnostic odds ratios higher than 10 and often higher than 100) in patient populations selected on the basis of US results (typically, patients with nondiagnostic US findings or negative US findings in the presence of symptoms suggestive of appendicitis).

Nonrandomized Comparisons of MRI and US

Eight studies reported results in cohorts using both MRI and US as index tests. Four studies investigated MRI as a replacement for US, one investigated US as a triage test for MRI, and three studies were unclear about the actual role of testing that was being evaluated (tending to use convenience samples of patients selected for a specific test using criteria that were poorly reported). Four of the studies had a paired design and four had a parallel-group design. MRI,

when used as a replacement test for US, had greater test performance; however, the available studies are few and, when combined, produce rather imprecise results.

Key Question 2: What is the comparative effectiveness of alternative diagnostic tests, alone or in combination, for patients with RLQ pain and suspected acute appendicitis?

Of 925 included studies, 54 reported information on comparative effectiveness outcomes related to diagnostic tests (36 RCTs and 18 NRCSs). Many of the included RCTs were small and may have produced unstable estimates of event rates and treatment effects. Furthermore, selection criteria differed substantially among trials, rendering cross-study comparisons uninformative.

Key Question 3: What are the harms of diagnostic tests per se, and what are the treatment-related harms of test-directed treatment for tests used to diagnose RLQ pain and suspected acute appendicitis?

Of 925 included studies, only 83 mentioned harms related to diagnostic tests: 17 RCTs, 13 NRCSs, and 53 diagnostic cohort studies. Eight studies (3 RCTs and 5 diagnostic cohort studies) reported an absence of adverse events for all tests except diagnostic laparoscopy. The fact that so few studies reported harms raises concerns about selective outcome reporting.

Contrast-Related Adverse Events

Eight studies (3 RCTs and 5 diagnostic cohort studies) reported on adverse events related to contrast administration. Of these, three reported that the contrast was well tolerated. The others reported a combination of nonfatal adverse events.

Exposure to Ionizing Radiation

No studies reported direct evidence on the effect of ionizing radiation on patient-relevant outcomes. Twelve studies (3 RCTs, 4 NRCSs, and 5 diagnostic cohort studies) reported radiation doses for CT, and three of these discussed strategies to reduce CT-related radiation exposure in a population, but they did not link this information with clinical outcomes.

Maternal/Fetal Adverse Events

Six studies (3 studies of US, 3 of MRI, and 2 of multiple clinical and lab tests, some studies evaluating more than 1 test) reported information on maternal outcomes. One study of MRI reported that 17 patients without appendicitis progressed to uneventful labor and delivery. A second study of MRI reported that not using oral contrast sped up the imaging process. The remaining four studies reported that there was no maternal mortality.

Seven studies (5 studies of US, 2 of MRI, 1 of CT, and 1 of clinical symptoms and signs, some studies evaluating more than 1 test) reported information on fetal outcomes. One study of US reported that 18 of 22 patients had a normal-term delivery; there were two spontaneous abortions (in patients with no clinical or sonographic evidence of acute appendicitis) and two elective abortions. The second study examined US and clinical and laboratory tests, and found that all 20 women delivered healthy infants. The third study gave fetal outcomes for only 2 of the 45 participants who underwent US for the diagnosis of appendicitis. One was a spontaneous abortion in a woman with surgically confirmed acute appendicitis without perforation, and the

other was a premature delivery in a patient with no evidence of appendicitis at followup through delivery. The fourth study reported a total of nine adverse fetal outcomes (5/31 who had MRI and 4/44 in the US or clinical group); none were in the perioperative period. The fifth study reported outcomes for US, MRI, and CT. In the US group, one patient, who had an open appendectomy in the first trimester, developed severe preeclampsia and had a premature delivery at 33 weeks. (This patient also had a diagnostic CT.) There was one fetal death after a negative open appendectomy, but neither the fetal death nor the early delivery was related directly to the appendectomy, and one patient with perforated appendicitis had abruptio placentae and vaginal hemorrhage. Only one patient had MRI, and she delivered a healthy baby at term. Of 13 patients who had a diagnostic CT, 9 delivered healthy infants; 1, who had an open appendectomy in the first trimester, developed severe preeclampsia and had a premature delivery at 33 weeks (previously mentioned); and 3 were lost to followup. The sixth study reported fetal outcomes for 55 of 80 patients who had CT. Fifty-one had a live infant at or near term, one had a premature delivery of a live 30-week infant 3 days after CT-diagnosed gastric cancer, two had spontaneous vaginal delivery of a nonviable fetus (1 at 18 weeks with sepsis after normal CT and normal laparotomy, and 1 at 22 weeks with chorioamnionitis, 5 days after normal CT). There was one fetal death at 26 weeks (4 weeks after a CT examination with normal findings). The seventh study reported that in a group evaluated using symptoms and signs, there were seven therapeutic abortions and two perioperative spontaneous abortions (first trimester), and four women without appendicitis had severe perinatal morbidity or mortality.

Surgical Complications in Studies of Diagnostic Laparoscopy

Thirty-four studies of diagnostic laparoscopy mentioned surgery-related harms. Eight RCTs (469 patients) and 8 NRCSs (4,084 patients) described complications related to laparoscopy compared with open appendectomy; 25 diagnostic cohort studies (5,553 patients) reported on complications of diagnostic laparoscopy. In general, the rates of specific complications were low (generally less than 10% and in most cases less than 2%). Few studies attributed specific adverse events to diagnostic laparoscopy (as opposed to additional surgical intervention). Nine studies, including five RCTs, reported that there were no complications related to the diagnostic laparoscopic procedure.

Discussion

Key Findings and Strength-of-Evidence Assessment

The literature on the test performance of various clinical symptoms and signs, laboratory and imaging tests, and diagnostic scores is vast but consists almost exclusively of studies assessing the test performance of individual tests. Information on test performance of multiple tests applied jointly and conditional test performance (i.e., test performance among patients already examined with other tests) was limited. The few studies that provided information on more than one index test were typically not designed with the goal of providing comparative information, and cross-study comparisons cannot provide reliable evidence on relative performance. Studies meeting our selection criteria provided limited information on the test performance or comparative effectiveness of diagnostic pathways (i.e., well-defined sequences of diagnostic and treatment steps). We assessed the strength of evidence for key outcomes selected on the basis of our reading of the literature and discussions with Key Informants and Technical Experts. Our

assessment integrates subjective judgments on risk of bias, consistency of findings, directness of the available information, and precision of estimates.

Test Performance

Clinical symptoms and signs used in isolation, including classical signs of peritoneal irritation, fever, and various assessments of abdominal pain, appeared to have limited test performance for all the populations of interest to this report. Among laboratory tests, white blood cell count, C-reactive protein, and tests derived from combinations of measurements on the complete blood count and differential had test performance that was generally higher than that of clinical symptoms and signs (especially with respect to sensitivity using a low-risk threshold) but still rather limited (e.g., in terms of summary LRs). These observations were relatively stable across the patient populations examined. Because studies did not allow an examination of the performance of multiple tests applied jointly and because conditional test performance was not reported uniformly across studies, the clinical implications of the relatively limited test performance of many nonimaging tests is not clear. Furthermore, symptoms and signs are variable in a patient (over the course of disease) and among patients, and it is hard to assess their clinical usefulness based on test performance. Importantly, the clinical examination forms the basis of the investigation of acute abdominal pain and suspected acute appendicitis and, even if poorly reported, all studies of imaging tests use some form of clinical examination (e.g., for patient selection). Multivariable diagnostic scores appeared to have test performance that was superior to the individual clinical signs, symptoms, or laboratory tests they included but still rather limited (e.g., in terms of summary LRs). Of note, the majority of studies assessed scores that had been developed before the widespread availability of CT and US imaging, suggesting that their results may be less applicable to current clinical practice.

Among imaging tests, CT and MRI had high sensitivity and specificity, resulting in clinically relevant summary LRs. CT has been investigated in a large number of diagnostic cohort studies, leading to precise estimates of test performance in all populations of interest for this report. In contrast, MRI has been investigated in a relatively small number of studies, mainly focused on pregnant women; therefore, the results may not be applicable to other populations. US has been investigated in a large number of studies and results were somewhat heterogeneous, suggesting that the average estimate of test performance may not apply to all populations for which US is considered. Possible explanations for this heterogeneity are the operator dependence of the test performance of US and the fact that studies were conducted in different settings. Despite the heterogeneity, the data suggest that US had lower overall test performance than CT and MRI, and resulted in a substantially greater proportion of nondiagnostic examinations. Diagnostic laparoscopy appeared to have good test performance, but studies were poorly reported and differed in their policies regarding removal of the appendix when no pathology was macroscopically visible, which may bias test performance results. Furthermore, patients included in studies of diagnostic laparoscopy are likely to be very different from patients included in studies of noninvasive tests. Therefore, our results for the test performance of laparoscopy should not be compared with the other diagnostic tests reviewed in this report. Table F summarizes our findings regarding the strength of evidence for the diagnostic performance of selected tests. When interpreting these results, readers should remember that test performance is not directly related to clinical outcomes, and high sensitivity and specificity do not necessarily imply better patient-relevant outcomes.

Table F. Assessment of the strength of evidence for test performance of individual tests

Test or Score	Strength of Evidence	Test Sensitivity in Key Subgroups—Subgroup (N Studies): Sensitivity (95% CrI)	Test Specificity in Key Subgroups—Subgroup (N Studies): Specificity (95% CrI)
WBC count	Moderate	Adults (26): 0.81 (0.74 to 0.87) Children (41): 0.80 (0.73 to 0.85) Elderly (3): 0.71 (0.69 to 0.77) Women of reproductive age (2): 0.64 (0.60 to 0.69) Pregnant women (6): 0.63 (0.21 to 0.92)	Adults (26): 0.54 (0.42 to 0.64) Children (41): 0.65 (0.56 to 0.73) Elderly (3): 0.50 (0.38 to 0.70) Women of reproductive age (2): 0.67 (0.67 to 0.67) Pregnant women (6): 0.75 (0.38 to 0.95)
CRP	Low	Adults (15): 0.84 (0.73 to 0.92) Children (22): 0.73 (0.66 to 0.80) Elderly (2): 0.91 (0.91 to 0.92) Women of reproductive age (3): 0.79 (0.44 to 0.97) Pregnant women (1): 0.68	Adults (15): 0.67 (0.50 to 0.81) Children (22): 0.72 (0.61 to 0.81) Elderly (2): 0.91 (0.91 to 0.92) Women of reproductive age (3): 0.79 (0.44 to 0.97) Pregnant women (1): 0.68
Measures based on the CBC and differential	Low	Please see the Results section for the test performance of various test combinations	—
Alvarado score (low-risk cutoff)	Moderate	Adults (3): 0.91 (0.89 to 0.93) Children (6): 0.99 (0.92 to 1.00) Women of reproductive age (2): 0.99 (0.98 to 1.00)	Adults (3): 0.31 (0.24 to 0.78) Children (6): 0.48 (0.24 to 0.74) Women of reproductive age (2): 0.24 (0.22 to 0.25)
Alvarado score (high-risk cutoff)	Moderate	Adults (16): 0.80 (0.60 to 0.93) Children (9): 0.83 (0.73 to 0.91) Women of reproductive age (5): 0.70 (0.35 to 0.92)	Adults (16): 0.71 (0.50 to 0.85) Children (9): 0.81 (0.63 to 0.92) Women of reproductive age (5): 0.91 (0.65 to 0.99)
PAS	Low	Children (5): 0.03 (0.00 to 0.13)	Children (5): 1.00 (0.99 to 1.00)
CT	Moderate–high	Adults (72): 0.96 (0.95 to 0.97) Children (34): 0.96 (0.94 to 0.98) Elderly (4): 1.00 (0.94 to 1.00) Women of reproductive age (11): 0.99 (0.96 to 1.00) Pregnant women (5): 0.99 (0.96 to 1.00)	Adults (72): 0.96 (0.93 to 0.97) Children (34): 0.92 (0.85 to 0.96) Elderly (4): 1.00 (0.94 to 1.00) Women of reproductive age (11): 0.91 (0.75 to 0.97) Pregnant women (5): 0.91 (0.75 to 0.97)
MRI	Low	Adults (7): 0.95 (0.88 to 0.98) Children (7): 0.97 (0.87 to 1.00) Women of reproductive age (1): 1.00 Pregnant women (11): 0.98 (0.92 to 1.00)	Adults (7): 0.92 (0.87 to 0.95) Children (7): 0.96 (0.84 to 0.99) Women of reproductive age (1): 0.86 Pregnant women (11): 0.98 (0.96 to 1.00)
US	Moderate	Adults (38): 0.85 (0.79 to 0.90) Children (85): 0.89 (0.86 to 0.92) Women of reproductive age (11): 0.72 (0.51 to 0.88) Pregnant women (13): 0.72 (0.45 to 0.92)	Adults (38): 0.90 (0.83 to 0.95) Children (85): 0.91 (0.89 to 0.94) Women of reproductive age (11): 0.92 (0.75 to 0.98) Pregnant women (13): 0.95 (0.84 to 0.99)
Laparoscopy	Moderate	Please see the Results section in the main report for a full description of results related to diagnostic laparoscopy	—

CBC = complete blood count; CrI = credible interval; CRP = C-reactive protein; CT = computed tomography; MRI = magnetic resonance imaging; PAS = Pediatric Appendicitis Score; US = ultrasound; WBC = white blood cell count

Comparisons among tests with respect to test performance relied on a small number of RCTs with moderate risk of bias, a relatively small number of direct comparisons among index tests in diagnostic cohort studies that were not designed to obtain comparative information, and indirect comparisons across single index test studies enrolling diverse populations in heterogeneous clinical settings. There was moderate-strength evidence that CT has superior overall test

performance compared with US and produces fewer nondiagnostic results. Similarly, MRI appeared to have better test performance than US, but the strength of evidence was deemed low. The strength of evidence on comparisons among other imaging tests and among multivariable diagnostic scores was deemed insufficient. The evidence regarding the effect of patient- and test-related characteristics on test performance was also deemed insufficient. There were indications that aspects of study design characteristics affect test performance, but the effects are often unpredictable in direction and do not have direct clinical relevance.

Patient-Relevant Outcomes

We based our assessment of the comparative effectiveness of alternative tests on randomized studies (with the exception of outcomes among pregnant women), because indirect (across studies) comparisons of outcomes other than test performance are susceptible to bias resulting from differences among the populations included. We found a few RCTs with moderate risk of bias that provided information on the comparative effectiveness of alternative testing strategies. These studies assessed various comparisons across different modalities (or different versions of the same modality) and therefore did not provide definitive evidence for any of the possible pairwise contrasts they evaluated.

Adverse Events of Testing

Information on harms was often incomplete and poorly reported. Only a minority of the included studies provided information on test-related harms, raising concerns about selective outcome and analysis reporting. The majority of the studies providing information on adverse events did not report the definitions or ascertainment methods they used. Importantly, no information was available from studies meeting our selection criteria regarding the effects of ionizing radiation. This is particularly important, as there is substantial variation in the levels of radiation delivered with newer multiphase CT scans performed for evaluation of appendicitis. Information was particularly limited on fetal and maternal outcomes of various diagnostic modalities applied during pregnancy for the investigation of acute appendicitis. Overall, we rated the strength of evidence on the harms of tests for acute appendicitis to be insufficient, primarily because of concerns about outcome reporting bias and the sparseness of available evidence.

Limitations of the Evidence Base

The evidence base regarding the diagnosis of acute appendicitis is limited in the following ways:

- Studies reporting information on test performance outcomes were at moderate to high risk of bias. Differential verification (the use of different reference-standard tests depending on the results of the index test) and partial verification (the failure to apply the reference standard to all of the included patients) were common, particularly in studies that were not surgical series (generally, studies with a lower prevalence of appendicitis). Studies with complete and nondifferential verification tended to be surgical cohorts reporting exclusively on patients undergoing appendectomy and so are not representative of all patients presenting with acute RLQ pain. In addition, poor reporting of information on study design hampered our risk-of-bias assessment.
- Studies provided limited information to assess the impact of various factors related to patients, technical implementation, operators, or systems on the performance of the tests of interest.

- Information on the comparative effectiveness of alternative testing strategies (e.g., sequential use of tests as part of a diagnostic algorithm) with respect to test performance, patient-relevant outcomes, and resource use was limited. Direct (within study) comparisons of test performance and the impact of testing strategies on clinical outcomes were scarce. Studies have not compared diagnostic algorithms (e.g., combinations of tests applied in sequence, such that the results of earlier tests determine the choice of subsequent tests). When two or more index tests were evaluated in the same study, the role of testing that was being examined (add-on, replacement, triage) was often unclear.
- In studies of diagnostic scores, multivariable models were often developed and evaluated in the same patient sample. The lack of separation between the training and testing datasets (or any attempt at internal validation of the model) generally leads to optimistic (too high) estimates of test performance. The lack of external validation (replication) also limited our ability to assess the generalizability of many diagnostic scores.
- Few RCTs compared alternative test strategies with respect to patient-relevant outcomes. The few trials reporting patient-relevant outcomes were fragmented across heterogeneous comparisons of alternative testing strategies. The trials often used suboptimal methods for randomized sequence generation, allocation concealment, and blinding, or they provided information that was too limited to assess these aspects of study design. Many had sample sizes that were too small to reliably detect small or moderate differences between the strategies being compared.
- In contrast to the RCTs, NRCSSs of alternative testing strategies attained large sample sizes but often reported unadjusted analyses (or analyses adjusted for only a small number of potential confounders) that do not allow strong conclusions about the comparative effectiveness of alternative test strategies to be drawn.

Strengths and Limitations of This Review

Previous reviews on this topic have focused on special patient populations, have almost exclusively focused on test performance outcomes, have not assessed harms systematically, or have focused on a very limited spectrum of study designs. Our work provides a comprehensive up-to-date summary of the evidence on the diagnosis of RLQ pain and suspected acute appendicitis. For many of the examined tests and patient populations, this review is the first to be conducted. For some important modalities that have been investigated to some extent in previous meta-analyses (e.g., CT, MRI, US, and multivariable diagnostic scores), our work includes a much larger number of studies (and a greater total number of patients) than previous reviews. This allows us to provide accurate estimates of test performance in different patient populations that can be used to inform clinical decisions (especially if used as inputs in decision and simulation models) and to identify evidence gaps to inform the planning of future research.

Nonetheless, several limitations, which to a large extent reflect the limitations of the underlying evidence base, must be considered when interpreting our results.

- The evidence base has a number of limitations, detailed in the preceding section: quality was often poor, patient-relevant outcomes and harms were incompletely and inconsistently reported, and information on study- or population-level characteristics that could modify test performance and patient-relevant outcomes was also incomplete.
- We assumed that pathological diagnosis and clinical followup have negligible error (i.e., that they represent a “gold” standard). It is unlikely that this assumption is exactly true. Consequently, it is likely that estimates of test performance are biased, and the direction

of this bias is hard to predict, particularly at the meta-analysis level. However, we believe that the error rate of these reference standards is low enough that its influence on our estimates is relatively small.

- Finally, we did not address contextual factors (e.g., availability of equipment, trained readers) that are important determinants of the adoption of specific diagnostic strategies in particular settings.

Applicability of Review Findings

In general, the existing evidence on alternative diagnostic tests for the diagnosis of acute RLQ pain and suspected acute appendicitis appears to be applicable to clinical practice in the United States. The included studies enrolled patients representative of the age and sex distribution of patients seeking care for RLQ abdominal pain in the United States, and evidence on test performance was available for all commonly used modalities. Information on adults and children was often separately reported, allowing the assessment of test performance in these patient subgroups. However, information was more limited for patients at the extremes of age (i.e., children younger than 5 years or the elderly), pregnant women, and women of reproductive age; in some cases, decisions for these will have to rely on extrapolation of results from population subgroups with more available information, and thus applicability assessments are not possible. Approximately one-third of the studies in this review were conducted in the United States, and the vast majority were carried out either in the United States or in industrialized European or Asian countries. Care settings varied across studies, including academic and nonacademic centers, and patient populations included those sampled at emergency departments, in surgical cohorts, or from mixed populations.

Assessing the applicability of studies on clinical symptoms and signs was challenging: the pathophysiologic rationale for many of these tests is well established, but many of the relevant studies were conducted before the widespread availability of imaging modalities, and thus their findings may reflect test performance in a population with more advanced disease or populations selected for a high probability of appendicitis (e.g., surgical cohorts). Studies of laboratory and imaging tests evaluated “stable” technologies (e.g., white blood cell count) or were conducted in recent years; for example, many studies of C-reactive protein, CT, and US were conducted from 2005 onward. In meta-regression analyses comparing test performance in the last decade against earlier years, there was no evidence that the performance of laboratory or imaging tests has changed significantly over time; however, the indirect nature of metaregression comparisons and the low precision of metaregression estimates limit the strength of these results. In contrast, the applicability of the evidence on most multivariable diagnostic scores may be somewhat limited because most were developed before the era of widespread availability of imaging. The lack of external validation for most diagnostic scores also limits the applicability of these results. The findings of studies on diagnostic laparoscopy may also be less applicable because many of the studies were conducted before the widespread availability of diagnostic imaging.

Future Research Needs

Studies of Diagnostic Test Performance

- Cohort studies of test performance would provide useful information, particularly for diagnostic tests that have not been studied adequately (e.g., MRI in all relevant patient populations) and to compare the performance of tests for which comparative information

is limited (e.g., direct comparisons of CT vs. US; comparisons between CT with contrast administered via alternative routes).

- Such diagnostic cohort studies (and comparative studies in particular) are also needed to evaluate the test performance of combinations of tests and testing strategies by estimating conditional test performance and by developing and validating multivariable diagnostic tools internally and in independent datasets. For example, they could examine the use of US as a triage test for CT or MRI, or the use of multivariable diagnostic scores to select patients who can be monitored without immediate imaging or treatment (e.g., low-risk patients who can be managed with wait-and-see strategies), those who need imaging, and those who need the initiation of treatment without imaging. They can also provide information to determine how patient- and test-related factors affect performance (i.e., to examine whether test performance depends on easily identifiable patient characteristics).
- Research is needed on the natural history of acute appendicitis, specifically on whether (and how often) cases of appendicitis resolve on their own and the rate of recurrence among such cases. Studies of natural history (e.g., among patients deemed to be appropriate candidates for medical management or wait-and-see strategies) are necessary for evaluating the impact of tests in decision and simulation modeling studies (discussed later) and also to inform the design of studies of alternative test-and-treatment strategies, including studies of the sequencing of multiple tests and the timing of examinations. Of note, the test performance of diagnostic tests may vary during different timepoints in the development of acute appendicitis; for instance, laboratory tests may be highly sensitive for cases associated with more severe inflammation.
- Paired test study designs, in which all index tests are applied to all enrolled patients (so that each patient has results from every test of interest), are generally more efficient than parallel-arm designs and should be considered when planning future studies.⁶⁵
- Cohort studies assessing the performance of tests that have been evaluated extensively (e.g., CT and US) are most needed for specific patient populations (e.g., pregnant women, young children, and the elderly); for other tests (e.g., MRI) further research is needed in all patient populations. Comparative studies are needed for all tests and all populations. Ideally, future studies of test performance will be large (powered to achieve adequate precision), prospectively designed, multicenter investigations enrolling patients representative of those seen in clinical practice. Studies should prespecify the criteria for a positive test, use standardized diagnostic criteria for the diagnosis of appendicitis, use followup for an adequate period of time (1–2 weeks) for patients who do not undergo surgery, and have as complete followup as possible. Studies that evaluate two or more index tests should provide a detailed description of the role of testing they are evaluating (triage, add-on, replacement) and report data in enough detail to allow statistical analyses appropriate for that evaluation.⁶⁶
- Multivariable diagnostic scores provide an appealing way to combine information from multiple clinical symptoms and signs, laboratory tests, and possibly US. Multivariable scores may be particularly useful in identifying patients who are at low risk for appendicitis and who may be candidates for wait-and-see strategies or less aggressive imaging strategies. Cohort studies for the development and validation of such scores should use state-of-the-science methods for model development and internal and external validation.

- Future research needs to be better reported and studies should adhere to established reporting guidelines (e.g., STAndards for the Reporting of Diagnostic accuracy studies; www.stard-statement.org/).

Studies of Patient-Relevant Outcomes and Resource Use

- Cohort studies of diagnostic test strategies can also be used to study the impact of tests on patient-relevant and resource use outcomes. For tests with well-understood performance characteristics, such studies may use randomized designs. In many cases, however, randomized comparisons of alternative test strategies are unlikely to be fruitful because existing studies indicate that many of the competing tests have sensitivities and specificities that are fairly similar and close to 1.⁶⁷ Under these conditions, RCTs comparing alternative test strategies would need to enroll very large numbers of participants to allow reliable comparisons. If randomized studies are deemed necessary, consideration should be given to paired randomized designs because they are more efficient than parallel-arm trials.
- Large-scale observational prospective studies could be used to evaluate the effectiveness of alternative test strategies with respect to short- and long-term patient-relevant outcomes and to explore factors that may modify the effect of tests on these outcomes. Such studies would need to collect detailed information on baseline factors that may be associated with the choice of test strategy and the outcomes of interest in order to attempt to address confounding bias. Comparisons across methods should be performed only among patients who would be candidates for assessment with all methods being compared.
- Decision and simulation modeling can be used to determine whether randomized or nonrandomized cohort studies assessing patient-relevant outcomes and resource use are necessary and to guide their design. Models can also be used to synthesize evidence on test performance, impact of tests on clinical decisions, treatment effectiveness, resource use (and, when relevant, economic costs), and patient preferences to guide clinical decisionmaking. We think that the results of the current review provide a solid basis for conducting such modeling studies.

Studies of Test-Related Adverse Events

- Future studies should report complete information on test-related adverse events, using prespecified criteria and careful ascertainment methods.
- Mathematical modeling studies can be used to combine data on the effective radiation dose received during alternative CT-based approaches with external information on long-term radiation effects.⁶⁷

Conclusions

The literature on the test performance of clinical symptoms and signs, laboratory and imaging tests, and multivariable diagnostic scores for the diagnosis of acute appendicitis is large, but it consists almost exclusively of studies at moderate risk of bias, primarily because of differential and incomplete verification. The few studies that assess multiple tests are typically not designed with the goal of providing comparative information. Thus, the available evidence supports fairly strong conclusions about the performance of individual tests, but it is largely insufficient to support conclusions about comparative effectiveness, especially with respect to

clinical outcomes. Clinical symptoms and signs and laboratory tests have relatively limited test performance when used in isolation. Their combination in multivariable scores is promising, but the best studied scores were developed before the widespread use of imaging modalities, and more recently developed scores have not yet been studied adequately. All three major imaging modalities have adequate test performance. Evidence on CT is mature for most patient populations of interest. In contrast, MRI has been investigated in fewer studies, many of which focus on its use for pregnant women. US produces nondiagnostic scans more often than CT or MRI, and when a diagnosis is possible, its performance appears to be somewhat worse than CT and MRI. Beyond test performance, information on patient-relevant outcomes and resource use is very limited. Information on test-related harms (e.g., adverse events due to radiation) is provided by only a minority of studies and is poorly reported. More research, much of which could be accomplished through nonrandomized studies, is needed to establish the performance in understudied patient populations (very young children, women of reproductive age, the elderly) and modalities (e.g., MRI, multivariable scores); compare competing tests; identify factors that affect performance; and evaluate the impact of testing strategies on patient-relevant outcomes, resource use, and harms. Perhaps most importantly, given the large volume of accumulated evidence on the performance of various tests, decision and simulation modeling (e.g., decision analysis, simulation modeling of the impact of radiation on long-term outcomes) should be used to guide decisionmaking and to inform the design of future studies.

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Background

Nature and Burden of the Condition

Abdominal pain is a common presenting complaint for patients seeking care at emergency departments, with approximately 3.4 million expected cases per year in the United States.¹ Appendicitis is a frequent cause of abdominal pain, caused by acute inflammation of the appendix, and occurs in approximately 8 to 10 percent of the population (over a lifetime).^{2,3} Appendicitis has its highest incidence between the ages of 10 and 30 years. The ratio of incidence in men and women is 3:2 through the mid-20s and then equalizes after age 30. Appendicitis is the most common abdominal surgical emergency, with over 250,000 appendectomies performed annually in the U.S. The risk of acute appendicitis in pregnant women is similar to that of the general population, making appendicitis the most common non-obstetric emergency during pregnancy.⁴⁻⁷ Untreated, appendicitis can lead to perforation of the appendix, which typically occurs within 24 to 36 hours of the onset of symptoms. Perforation of the appendix can cause intra-abdominal infection, sepsis, intraperitoneal abscesses, and rarely death.⁴ In order to avoid the sequelae of perforated appendicitis, a low percentage of “negative” appendectomies (i.e., removing a normal, non-inflamed appendix in patients mistakenly diagnosed with appendicitis) is generally accepted from a surgical standpoint.

Diagnosis of Suspected Acute Appendicitis

Guidelines suggest that when a diagnosis of acute appendicitis can be made on clinical grounds surgical consultation should be sought without delay for additional diagnostic testing.⁸ Clinical symptoms and signs suggestive of appendicitis include a history of central abdominal pain migrating to the right lower quadrant (RLQ), anorexia, fever, and nausea/vomiting. On examination, RLQ tenderness, along with “classical” signs of peritoneal irritation (e.g., rebound tenderness, guarding, rigidity, referred pain), may be present. Other signs (e.g., the psoas or obturator signs) may help the clinician localize the inflamed appendix.⁹⁻¹¹ The performance of clinical symptoms and signs for identifying acute appendicitis seems to be variable across studies, many patients present atypically, and few clinical findings appear to have adequate sensitivity and specificity when used in isolation.^{10,11}

For patients with right lower quadrant (RLQ) pain, when the diagnosis cannot be made on clinical grounds alone, laboratory or imaging tests are often used to attempt to establish a diagnosis and guide treatment. Laboratory evaluations potentially useful for the diagnosis of appendicitis include white blood cell count, granulocyte count, the proportion of polymorphonuclear blood cells, and C-reactive protein concentration.¹⁰⁻¹² Imaging tests, such as ultrasound (US), computed tomography (CT) with and without contrast, and magnetic resonance imaging (MRI), are also used extensively for the diagnosis of appendicitis.¹³⁻¹⁹ Imaging tests can be used alone or in combination. For example, US is sometimes used as a triage test to separate patients in whom sonography alone is adequate to establish a diagnosis from those who require further imaging with CT.⁸ Different factors may affect the performance of alternative tests and their impact on clinical outcomes. For example, US examination is considered to be operator dependent²⁰ and is technically challenging in obese patients or women in late pregnancy. CT scanning can be performed with or without the use of contrast agents, and contrast can be administered orally, rectally, intravenously, or via combinations of these routes.⁸ It has been suggested that low body mass index (BMI), a marker for lack of sufficient mesenteric fat (which

helps visualize periappendiceal fat stranding, a radiological sign of appendicitis), may affect the relative test performance of CT performed with or without contrast (contrast being more useful in individuals with low BMI and children).⁸

Clinical symptoms and signs, along with the results of laboratory or imaging tests, can be combined into multivariable diagnostic scores (sometimes referred to as “clinical prediction rules”), multivariable that synthesize the findings of different investigations to determine the most likely diagnosis.²¹ In adults, the most commonly used multivariable score for appendicitis is the Alvarado score,²² which separates patients into 3 groups of increasing probability of appendicitis (the score is based on 8 items: pain migration, anorexia, nausea, tenderness in RLQ, rebound pain, elevated temperature, leukocytosis, and shift of white blood cell count to the left).²³ Although the Alvarado score is also used in pediatric populations,^{24,25} the Pediatric Appendicitis Score has been developed and validated for use in children.²⁶ It is based on 9 items (migration of pain, anorexia, nausea/vomiting, fever, cough/percussion tenderness, hopping tenderness, RLQ tenderness, leukocytosis, polymorphonuclear neutrophilia) and classifies children into two groups (high vs. low probability of appendicitis).²⁶

Diagnostic laparoscopy is also used for the evaluation of patients with RLQ pain and suspected acute appendicitis, primarily when a diagnosis cannot be established via other means. Although diagnostic laparoscopy is generally considered safe, studies have reported variable rates of morbidity and mortality from the procedure.²⁷

In general the diagnostic tests discussed in this section are widely available in the U.S. Clinical symptoms and signs can be evaluated relatively easily and inexpensively. Evidence from the National Hospital Ambulatory Medical Care Survey suggested that CT and complete blood counts are obtained in the majority of patients presenting to the emergency department with abdominal pain. The survey also showed that over time (between 1992 and 2006) the use of CT for both adults and children has been increasing. Over the same period, the use of the complete blood count has increased in adults but decreased in children.^{28,29} Various other sources suggest that the use of US and MRI is increasing in populations where exposure to ionizing radiation is a particular concern (e.g., children and pregnant women).³⁰⁻³⁶

Importance of Accurate Diagnosis and Impact on Outcomes

As with all diagnostic tests, the modalities used in the diagnostic investigation of patients with RLQ pain/suspected appendicitis affect clinical outcomes indirectly, through their impact on clinicians’ diagnostic thinking and decisionmaking.³⁷ More accurate and timely diagnosis of appendicitis can minimize the time to the indicated intervention (e.g., surgery), thus reducing the time patients are in pain and improving clinical outcomes (e.g., reducing the rate of perforated appendicitis and its attendant complications).³⁸ Conversely, time-consuming or unnecessary diagnostic workup (an important, but hard to operationalize outcome) may delay the indicated treatment and increase the risk of complications or result in false positive results and more “negative” appendectomies. Furthermore, diagnostic testing can impact resource utilization for the management of patients with acute abdominal pain. For example, examination with CT may reduce length of stay by avoiding prolonged observation in cases where a diagnosis cannot be established clinically or by eliminating the need for additional diagnostic testing.¹⁸ In some cases, CT can also facilitate direct therapeutic intervention. For example, in patients with perforated appendicitis complicated by an abscess, the radiologist can not only detect but also treat the abscess by percutaneous drainage, thus avoiding the need for immediate operative intervention.

Special Considerations for the Diagnosis of RLQ Pain/Acute Appendicitis

The diagnostic workup of acute appendicitis is complex because patients with acute abdominal pain of different etiologies can present with similar symptoms. Diagnosis is particularly challenging in children, women of reproductive age, pregnant women, and frail or elderly patients.^{8,39,40}

Children

Acute appendicitis in children is often diagnosed after perforation has occurred.⁴¹⁻⁴³ Children have a thinner appendiceal wall and less developed omentum (the largest peritoneal fold), and thus may not readily wall off a perforation. In addition, many common childhood illnesses have symptoms similar to those of early acute appendicitis (e.g., fever, nausea, and vomiting), making the differential diagnosis more challenging. Young children may have difficulty communicating about their discomfort or describing their symptoms, making the clinical examination less informative and leading to diagnostic delays.¹¹ In addition, the use of modalities that involve ionizing radiation (e.g., CT) possibly entails greater radiation-related risks for children.⁸

Women of Reproductive Age

A large proportion of women of reproductive age with appendicitis are misdiagnosed.⁴⁴ Establishing a diagnosis in women of reproductive age with RLQ pain/suspected acute appendicitis can be particularly challenging because symptoms of acute appendicitis can mimic those of gynecologic disease (e.g., pelvic inflammatory disease, ectopic pregnancy, etc.).

Pregnant Women

Diagnosis of suspected acute appendicitis in pregnant women can also be challenging because some symptoms of appendicitis (nausea and vomiting) are common in normal pregnancies and because enlargement of the uterus can alter the location of the appendix, which often moves higher and to the back.⁴⁵ Anatomic changes induced by pregnancy make the clinical examination of pregnant patients with abdominal pain more challenging and result in technical difficulties when using US.^{36,46,47} Tests involving ionizing radiation (e.g., CT) are also generally avoided during pregnancy to prevent exposure of the fetus to radiation. Finally, obtaining a white blood cell count is generally not helpful in the diagnosis of acute appendicitis in pregnant women because leukocytosis is common during pregnancy. From a decisionmaking perspective, the management of suspected appendicitis in pregnant women is complicated by the need to balance the potential benefits and harms of testing for both the mother and the fetus.

Frail and Elderly Individuals

The elderly typically present with appendicitis in more advanced stage, when compared to younger patients.⁴⁸ Older patients may delay seeking care, and definitive diagnosis is sometimes delayed further because competing etiologies for abdominal pain (e.g., malignancy or diverticulitis) are considered more likely. Therefore, the performance of diagnostic tests may be modified by patient age (e.g., US has been reported to have higher diagnostic performance in older patients) and by the more advanced disease stage that is common in this age group. Elderly

and frail individuals with appendicitis have a higher complication rate and a higher risk of mortality, compared to younger/less-frail patients.

Rationale for Evidence Review

Accurate testing of patients with RLQ pain, or less typical presentations consistent with acute appendicitis, to identify those who need treatment can improve clinical outcomes and reduce resource utilization. Our review of guidelines and published systematic reviews indicated a lack of specific guidance for selecting diagnostic modalities, particularly in patient subgroups in whom the diagnosis is known to be particularly challenging (e.g., children, women of reproductive age, and pregnant women). Existing systematic reviews have not adequately investigated the comparative effectiveness of alternative diagnostic approaches (typically they assess a single diagnostic modality), have focused almost exclusively on test performance outcomes (without providing evidence on the impact of tests on intermediate or patient-relevant outcomes), and have not addressed factors that may modify the test performance (such as patients' age and sex, setting of care, or aspects of the test itself, e.g., the use of oral contrast, its administration via different routes, etc.). No review has comprehensively examined all tests of interest or focused on comparisons between alternative strategies.

Key Questions

This review addresses the following Key Questions:

Key Question 1: What is the performance of alternative diagnostic tests, alone or in combination, for patients with right lower quadrant (RLQ) pain and suspected acute appendicitis?

1. What is the performance and comparative performance of alternative diagnostic tests in the following patient populations: children, adults, nonpregnant women of reproductive age, the elderly (age ≥ 65 years)?
2. What factors modify the test performance and comparative test performance of available diagnostic tests in these populations?

Key Question 2: What is the comparative effectiveness of alternative diagnostic tests, alone or in combination, for patients with RLQ pain and suspected acute appendicitis?

1. For the populations listed under Key Question 1a, what is the effect of alternative testing strategies on diagnostic thinking, therapeutic decisionmaking, clinical outcomes, and resource utilization?
2. What factors modify the comparative effectiveness of testing for patients with RLQ pain and suspected acute appendicitis?

Key Question 3: What are the harms of diagnostic tests per se, and what are the treatment-related harms of test-directed treatment for tests used to diagnose RLQ pain and suspected acute appendicitis?

Methods

The methods for this systematic review follow the AHRQ “Methods Guide for Effectiveness and Comparative Effectiveness Reviews” (available at www.effectivehealthcare.ahrq.gov/); methods and results are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist.⁵⁰

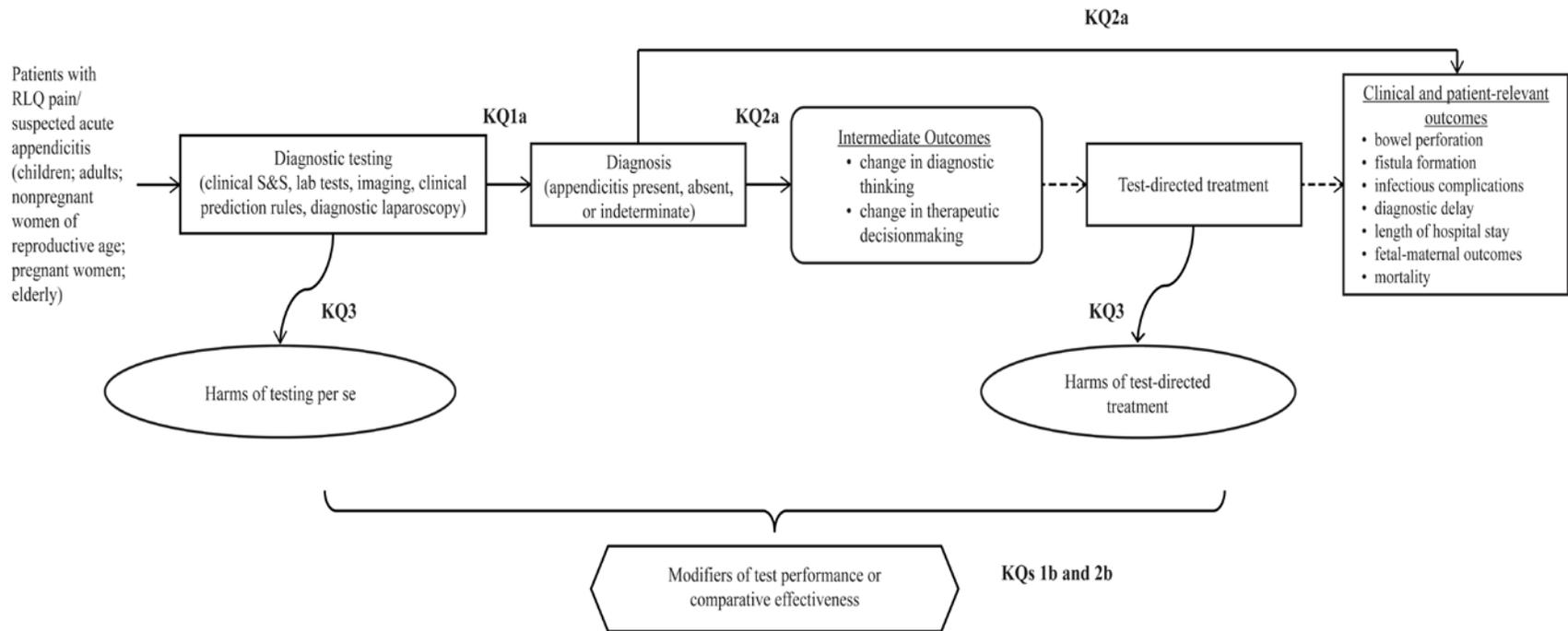
AHRQ Task Order Officer, Stakeholder Input, and Review Protocol

The AHRQ Task Order Officer (TOO) was responsible for overseeing all aspects of this project. A panel of key informants gave input on the key questions (KQs) to be examined; these KQs were posted on AHRQ’s EHC website for public comment from April 17 to May 14, 2013 and revised in response to comments. We then drafted a protocol for the systematic review and recruited a panel of technical experts to provide high-level content and methodological input throughout the development of the review. The TEP included representatives of professional societies, experts in the diagnosis and treatment of RLQ abdominal pain and appendicitis (including emergency physicians, radiologists, and surgeons), and a patient representative. The finalized protocol is posted on the EHC Web site at <http://effectivehealthcare.ahrq.gov/ehc/products/528/1827/Appendicitis-protocol-131209.pdf>. The PROSPERO registration number for this review is CRD42013006480.

Analytic Framework

We used an analytic framework (Figure 1) that maps the Key Questions within the context of populations, interventions, comparators, and outcomes of interest.

Figure 1. Analytic framework



KQ = Key Question; RLQ = right lower quadrant; S & S = symptoms and signs

Inclusion and Exclusion Criteria

Populations and Conditions of Interest

The population of interest for all Key Questions was patients with acute RLQ abdominal pain (≤ 7 days duration) for whom appendicitis is considered in the differential diagnosis. Separate analyses were performed for the following populations:

- Children (age < 18 years); we initially planned additional analyses for subgroups of very young children (< 2 years and 2-5 years of age); however, data were inadequate for examining these subgroups
- Adults (age ≥ 18 years)
- Nonpregnant women of reproductive age
- Pregnant women
- Elderly (age ≥ 65 years)

Interventions

For all Key Questions, the interventions of interest were diagnostic tests (alone or in combination) for diagnosing appendicitis, including clinical signs (e.g., psoas sign, obturator sign, Rovsing sign), clinical symptoms (e.g., fever, migrating pain, guarding), laboratory tests (e.g., white blood cell count, C-reactive protein concentration, left shift), multivariate diagnostic scores (including clinical prediction and decision rules, e.g., Alvarado score, Pediatric Appendicitis Score, other predictive models), imaging tests (e.g., US; multidetector or helical CT with or without contrast administered orally, rectally, or intravenously, MRI with or without contrast; abdominal X-ray); nuclear imaging studies; and diagnostic laparoscopy.

Comparators (Index and Reference Standard Tests)

For all Key Questions, the comparators were alternative tests or test combinations (as listed above) or clinical observation.

Outcomes

For Key Question 1, the outcome of interest was test performance, as assessed by sensitivity, specificity, or other measures of accuracy; using pathology or clinical followup as the reference standard. For Key Question 2, we looked for the following outcomes: impact on diagnostic thinking (e.g., change in diagnosis after testing; change in subsequent diagnostic approach after obtaining initial test results) and impact on therapeutic decisionmaking (e.g., change in treatment plan after testing; time from admission to surgery). We also looked at the following patient-centered and resource utilization outcomes: “negative” appendectomy rate, bowel perforation (ruptured appendix), fistula formation, infectious complications (abscess formation, peritonitis, sepsis, stump appendicitis), delay in diagnosis (time from presentation to definitive diagnosis; time from presentation to initiation of treatment; time from presentation to resolution of pain), length of hospital stay, fetal/maternal outcomes (for pregnant women; including premature labor, pregnancy loss, fetal morbidity, fetal mortality, maternal morbidity, maternal mortality), and mortality. For Key Question 3, we considered adverse effects of interventions, including direct harms of testing (e.g., harms from exposure to ionizing radiation, allergic reactions/kidney injury caused by contrast agents) harms of test-directed treatment (indirect).

When outcome definitions were not provided by the included studies, we adopted the terms used by the studies at face value.

Timing

Studies were considered regardless of duration of followup.

Setting

All health care settings were considered.

Study Design and Additional Criteria

Given the large expected number of potentially relevant studies to be reviewed in full text, the scope of the project had to be constrained operationally to ensure feasibility. Several approaches that could be used to achieve this aim were discussed with Key Informants during Topic Refinement and the TEP members (in preparation of this protocol). Based on these discussions and preliminary literature scans, we opted to use the following approach:

- For studies assessing test performance outcomes (i.e. for a subset of the studies pertaining to Key Question 1), we relied on previously completed systematic reviews (when available) to identify relevant studies and obtain specific data items (see following paragraph). We updated these reviews to include more recent studies identified through literature searches.
- For index tests where no relevant systematic review of test performance meeting our selection criteria (see following paragraph) could be identified, we performed a de novo systematic review.
- For studies that directly compare alternative tests (for all outcomes of interest) and for studies (comparative or noncomparative) reporting outcomes other than test performance (e.g., change in diagnostic thinking, impact on therapeutic decisionmaking, clinical outcomes, and harms) we performed a de novo review, because these topics were not addressed adequately by the reviews that were available when we designed our protocol.

We used existing systematic reviews to identify studies with test performance outcomes (Key Question 1). Systematic reviews were considered as potential sources of eligible studies if they met the following criteria:

- Reported the bibliographic databases searched and any additional sources of included studies.
- Used explicit criteria for selecting primary studies of the populations and index tests of interest (as described in section 2, above).
- Examined test performance outcomes.
- Provided a list of included studies that allowed the retrieval of the corresponding full text publications.

Literature Search and Abstract Screening

Appendix A describes our literature search strategies. Searches were conducted in PubMed[®], EMBASE[®], the Cochrane Central Register of Controlled Trials, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL[®]) databases to identify primary research studies meeting our criteria (last search on August 6, 2014, for PubMed; August 12, 2014, for all other

databases). We also used the PubMed[®] search results to identify systematic reviews of the tests of interest (last search July 31, 2013; the search for systematic reviews was not updated because our search for primary studies covered recent years adequately). We did not restrict searches by year of publication. A common set of 200 abstracts (in 2 pilot rounds, each with 100 abstracts) were screened by all reviewers, and discrepancies were discussed in order to standardize screening practices and ensure understanding of screening criteria by all team members. The remaining citations were split into nonoverlapping sets, each screened by two reviewers independently. Discrepancies were resolved by consensus involving a third investigator.

Study Selection and Eligibility Criteria

Potentially eligible citations (i.e., abstracts considered potentially relevant by consensus) were obtained in full text and reviewed for eligibility on the basis of the predefined inclusion criteria. A single reviewer examined all articles; a second reviewer examined a subset of 350 articles independently. Disagreements regarding article eligibility were resolved by consensus involving a third reviewer.

We included only English-language studies during full text review because our preliminary searches indicated that non-English-language studies had small sample sizes and represented a small proportion of the evidence for any given test modality; as such, their exclusion is unlikely to have affected our conclusions. We excluded studies published exclusively in abstract form (e.g., conference proceedings) because they are typically not peer reviewed, only partially report results, and may change substantially when fully published. The lists of included and excluded studies (organized by reason for exclusion) are in Appendix B.

We asked the TEP to provide citations of potentially relevant articles. Additional studies were identified through the perusal of reference lists of eligible studies, published clinical practice guidelines, relevant narrative and systematic reviews, conference proceedings, and Scientific Information Packages from manufacturers. All articles identified through these sources were screened for eligibility against the same criteria as for articles identified through literature searches. The final list of included studies was reviewed by the TEP to ensure that no key publications had been missed.

Data Abstraction and Management

Previously published reviews were used as sources of eligible single index test studies of test performance and as sources of data for objective data elements from these studies (bibliographic study information, characteristics of included populations, and counts of individuals stratified by diagnostic test result and disease status). For all studies, EPC investigators extracted data elements using standardized operational definitions (e.g., elements of study design, risk of bias assessment) from the full text of primary study publications.

Data was extracted into Word or Excel data extraction forms and will be uploaded to the Systematic Review Data Repository (SRDR, <http://srdr.ahrq.gov/home/index>) upon submission of the Final Report. The forms included elements that address population characteristics, sample size, study design, descriptions of the index and reference standard tests of interest, analytic details, and outcome data. We pilot tested the forms on several studies extracted by all team members to ensure consistency in operational definitions.

A single reviewer extracted data from each eligible study of test performance; one reviewer extracted and a second reviewer verified data from NRCSs and RCTs. For RCTs, when possible, data were extracted according to the intention-to-treat principle. We verified the data extraction

and risk of bias assessment in a random sample of 368 non-comparative test performance studies (reporting 1487 separate pairs of sensitivity and specificity). Overall, we found that agreement was excellent in capturing information about the index and reference standard tests and numerical information on test performance. Agreement was less good for some risk of bias items (complete and non-differential verification and inappropriate exclusions). These items were re-extracted for all included studies following a series of standardization exercises to ensure consistent application of our operational definitions.

We contacted authors (a) to clarify information reported in the papers that is hard to interpret (e.g., inconsistencies between tables and text); (b) to obtain missing data on key subgroups of interest when not available in the published reports (e.g., pregnant women, women of reproductive age, children); and (c) to verify suspected overlap between study populations in publications from the same group of investigators. Author contact was by email (to the corresponding author of each study), with a primary contact attempt (once all eligible studies had been identified) and up to two reminder emails (approximately 2 and 4 weeks after the first attempt).

Assessment of the Risk of Bias of Individual Studies

We assessed the risk of bias for each individual study using the assessment methods detailed by the AHRQ Methods Guide. We used items from the updated QUADAS 2 instrument to assess the risk of bias of the diagnostic test studies included in the review (these studies comprised the majority of the available studies).⁵¹⁻⁵⁴ The items we selected assessed four domains for risk of bias related to patient selection, use of the index test, use of the reference standard test, and patient flow and timing. For studies of other designs, we used appropriate sets of items to assess risk of bias: for NRCSs, we used items from the Newcastle-Ottawa scale;⁵⁵ for RCTs, we used items from the Cochrane Risk of Bias tool.⁵⁶

We did not calculate “composite” quality scores. Instead, we assessed and reported each methodological quality item (as Yes, No, or Unclear/Not Reported) for each eligible study. We rated each study as being of low, intermediate, or high risk of bias on the basis of adherence to accepted methodological principles. Generally, studies with low risk of bias have the following features: lowest likelihood of confounding due to comparison to a randomized controlled group; a clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting inconsistencies; clear reporting of dropouts, and a dropout rate less than 10 percent; and no other apparent source of bias. Studies with moderate risk of bias are susceptible to some bias but not sufficiently to invalidate results. They do not meet all the criteria for low risk of bias owing to some deficiencies, but none are likely to introduce major bias. Studies with moderate risk of bias may not be randomized or may be missing information, making it difficult to assess limitations and potential problems. Studies with high risk of bias are those with indications of bias that may invalidate the reported findings (e.g., observational studies not adjusting for any confounders, studies using historical controls, or studies with very high dropout rates). These studies have serious errors in design, analysis, or reporting and contain discrepancies in reporting or have large amounts of missing information. We discuss the handling of high risk of bias studies in the following sections.

In quantitative analyses, we performed subgroup analyses to assess the impact of each risk of bias item on the meta-analytic results. The grading was outcome specific, such that a given study that reports its primary outcome well but did an incomplete analysis of a secondary outcome was

graded of different quality for the two outcomes. Studies of different designs were graded within the context of their study design.

Evidence Synthesis

We summarized the included studies qualitatively and present important features of the study populations, designs, interventions, outcomes, and results in summary tables. Population characteristics of interest include age, sex, duration of symptoms, and clinical presentation at enrollment. Design characteristics include methods of population selection and sampling, and follow-up duration. Test characteristics include aspects specific to each diagnostic test of interest (e.g., the use and route of administration of contrast agents for imaging tests), the specific definitions of clinical signs, and the components and their weights for clinical prediction rules (the surgical approach for diagnostic laparoscopy, etc.). We present information on test performance, harms, intermediate and terminal outcomes, and resource utilization. Of note, all studies evaluating the test performance of the same single index test in a similar patient population were synthesized jointly, regardless of their source (our own literature searches or previously published reviews).

For each comparison of interest, we judged whether the eligible studies were sufficiently similar to be combined in a meta-analysis on the basis of clinical heterogeneity of patient populations and testing strategies, as well as methodological heterogeneity of study designs and outcomes reported. We performed analyses appropriate for the specific role of testing evaluated in each study (replacement, triage, add-on) whenever possible.⁵⁷ However, the complexity of the differential diagnosis of RLQ pain and limited reporting of relevant information in published studies limited our ability to distinguish between alternative test roles.

Studies employed a variety of different diagnostic methods (e.g., different imaging modalities, clinical symptoms and signs, laboratory measurements, and combinations thereof). We have based our judgments on the similarity of available tests on technical descriptions of the modalities used in each study (e.g., whether studies used similar imaging technologies or similar clinical examination protocols). We sought input from TEP members to define groups of “sufficiently similar” studies for synthesis (including meta-analysis) during later stages of the review as questions arose. Of note, the material used to solicit TEP input did not include any data on outcome results extracted from the studies (to limit the potential for bias). The determination on the appropriateness of meta-analysis was made before any data analysis. We did not base the decision to perform a meta-analysis on statistical criteria for heterogeneity. Such criteria are often inadequate (e.g., low power when the number of studies is small) and do not account for the ability to explore and explain heterogeneity by examining study-level characteristics. Instead, we used clinical criteria to assess study exchangeability (e.g., we considered whether studies enrolled populations selected using similar inclusion criteria, with comparable baseline risk of appendicitis, and assessed using similar imaging technologies or other tests). The main analyses include all relevant studies.

Analyses were performed separately for the following patient populations: children, women of reproductive age, pregnant women, and the elderly. Subgroup analyses (e.g., by clinical presentation at diagnosis, aspects of specific test modalities, etc.) were also performed. The concordance of findings across subgroup analyses was evaluated qualitatively (in all instances) and quantitatively (using meta-regression, when the data allowed). We considered the following potential modifiers of test performance or other outcomes in meta-regression analyses: patient characteristics (e.g., age, sex, clinical presentation at enrollment), test characteristics (e.g., extent

of imaging field, use of contrast agents and route of administration), clinician and facility factors (e.g., setting of test use), and date of publication (≥ 2005 vs. earlier). We also performed subgroup analyses by individual risk of bias items to assess the impact of each risk of bias item on the results of the meta-analysis. We evaluated the robustness of our findings in sensitivity analyses that exclude studies at high risk of bias. Some studies examining the test performance of imaging tests reported classification results from multiple raters. In our main analyses we used results from the rater that had the highest sum of sensitivity plus specificity (i.e., the rater that had a sum of estimated sensitivity and specificity closest to 2). As a worst-case sensitivity analysis we also repeated all analyses using results from the rater that had the lowest sum of sensitivity plus specificity. In addition, some studies of imaging tests reported information on indeterminate test results (in some cases separately by final diagnostic status, in other cases without any information on final diagnosis). In our main analyses, indeterminate test results were excluded. To explore the impact of indeterminate results on test performance we performed two “extreme case” sensitivity analyses, one where all indeterminate results with unknown (not reported) final diagnostic status were considered false positive and one where all were considered false negative. In these sensitivity analyses, all indeterminate results with known diagnostic status were considered in the corresponding false result category (i.e., indeterminate results in patients with a final diagnosis of appendicitis were considered false negative and indeterminate results in unaffected individuals were considered false positive).⁵⁸

When five or more sufficiently similar studies evaluated the test performance of the same test in the same population, we used a bivariate-bivariate normal meta-analysis model to obtain summary sensitivity and specificity estimates.^{59,60} We used the summary sensitivity and specificity estimates to calculate summary positive and negative likelihood ratios (LRs).⁶¹ We also used the estimates from the bivariate model to construct summary receiver operating characteristic (ROC) curves using the model proposed by Rutter and Gatsonis.^{62,63} For parallel arm studies comparing alternative test strategies with respect to clinical outcomes and resource utilization, we planned to perform meta-analyses when there were more than three unique, sufficiently similar studies evaluating the same intervention and comparator and reporting the same outcomes; however, no such instances were identified. All meta-analyses were conducted using Bayesian methods with flat (uninformative) priors;⁶⁴ models were fit with Markov chain Monte Carlo methods. Sensitivity analyses (including leave-one-out analyses, analyses assuming a fixed effects model, and reanalyses after excluding a group of studies) were undertaken where considered appropriate (e.g., in the presence of studies with outlying effect sizes or evidence of temporal changes in effect sizes). Heterogeneity was assessed visually by inspecting plots of study estimates in the ROC space and by examining the posterior distribution of the between-study heterogeneity parameters (for logit-sensitivity and logit-specificity). We explored between-study heterogeneity using subgroup and meta-regression analyses, by extending the binomial-bivariate normal model to include study-level covariates.

In cases when only a subset of the available studies could be quantitatively combined (e.g., when some studies are judged to be so clinically different from others as to be excluded from meta-analysis), we synthesized findings across all studies qualitatively by taking into account the magnitude and direction of effects and estimates of performance.

Grading the Strength of Evidence

We followed the Methods Guide⁴⁹ to evaluate the strength of the body of evidence for each Key Question with respect to the following domains: risk of bias, consistency, directness,

precision, and reporting bias.^{49,65} Briefly, we defined the risk of bias (low, medium, or high) on the basis of the study design and the methodological quality of the studies. Generally, lack of studies at low risk of bias or inconsistencies among groups of studies at different levels of risk of bias led to downgrading the strength of the evidence. We rated the consistency of the data as no inconsistency, inconsistency present, or not applicable (if there is only one study available). We did not use rigid counts of studies as standards of evaluation (e.g., four of five studies agree, therefore the data are consistent); instead, we assessed the direction, magnitude, and statistical significance of all studies and made a determination. We describe our logic where studies are not unanimous. We assessed directness of the evidence (“direct” vs. “indirect”) on the basis of the use of surrogate outcomes or the need for indirect comparisons. We assessed the precision of the evidence as precise or imprecise on the basis of the degree of certainty surrounding each effect estimate. A precise estimate is one that allows for a clinically useful conclusion. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions and that therefore precludes a conclusion.

The majority of studies to be included in this review are observational cohorts, reporting on outcomes of test performance, utilizing one or more index tests on all study participants. However, we found a small number of parallel group, randomized or non-randomized, comparative studies of alternative test strategies (e.g., reporting comparisons between alternative tests). We did not combine the results of randomized and non-randomized studies statistically. Instead, we qualitatively evaluated similarities and differences in study populations, diagnostic methods, and outcomes among study designs. These comparisons inform our judgments on applicability of study findings to clinical practice.

The potential for *reporting bias* (“suspected” vs. “not suspected”) was evaluated with respect to publication bias, selective outcome reporting bias, and selective analysis reporting bias. For reporting bias, we made qualitative dispositions rather than perform formal statistical tests to evaluate differences in the effect sizes between more precise (larger) and less precise (smaller) studies. Although these tests are often referred to as tests for publication bias; reasons other than publication bias can lead to a statistically significant result, including “true” heterogeneity between smaller and larger studies, other biases, and chance, rendering the interpretation of the tests nonspecific and the tests noninformative.^{66,67} Therefore, instead of relying on statistical tests, we evaluated the reported results across studies qualitatively, on the basis of completeness of reporting (separately for each outcome of interest), number of enrolled patients, and numbers of observed events. Judgment on the potential for selective outcome reporting bias was based on reporting patterns for each outcome of interest across studies. We acknowledge that both types of reporting bias are difficult to reliably detect on the basis of data available in published research studies (i.e., without access to study protocols and detailed analysis plans). Because such assessments are inherently subjective, we explicitly present all operational decisions and the rationale for our judgment on reporting bias in the Results and Discussion sections.

Finally, we rated the strength of the body of evidence using four levels: high, moderate, low, and insufficient.⁴⁹ These describe our level of confidence that the evidence reflects the true effect for the major comparisons of interest.

Assessing Applicability

We followed the Methods Guide⁴⁹ to evaluate the applicability of included studies to patient populations of interest. We evaluated studies separately by important clinical subgroups: children, women of reproductive age, pregnant women, and the elderly. Applicability to the

population of interest was also judged separately on the basis of duration of symptoms before enrollment, outcomes (e.g., test performance, impact on diagnostic thinking and clinical decisionmaking, clinical outcomes), and setting of care (e.g., whether patients were recruited in an academic, tertiary, or primary care setting).

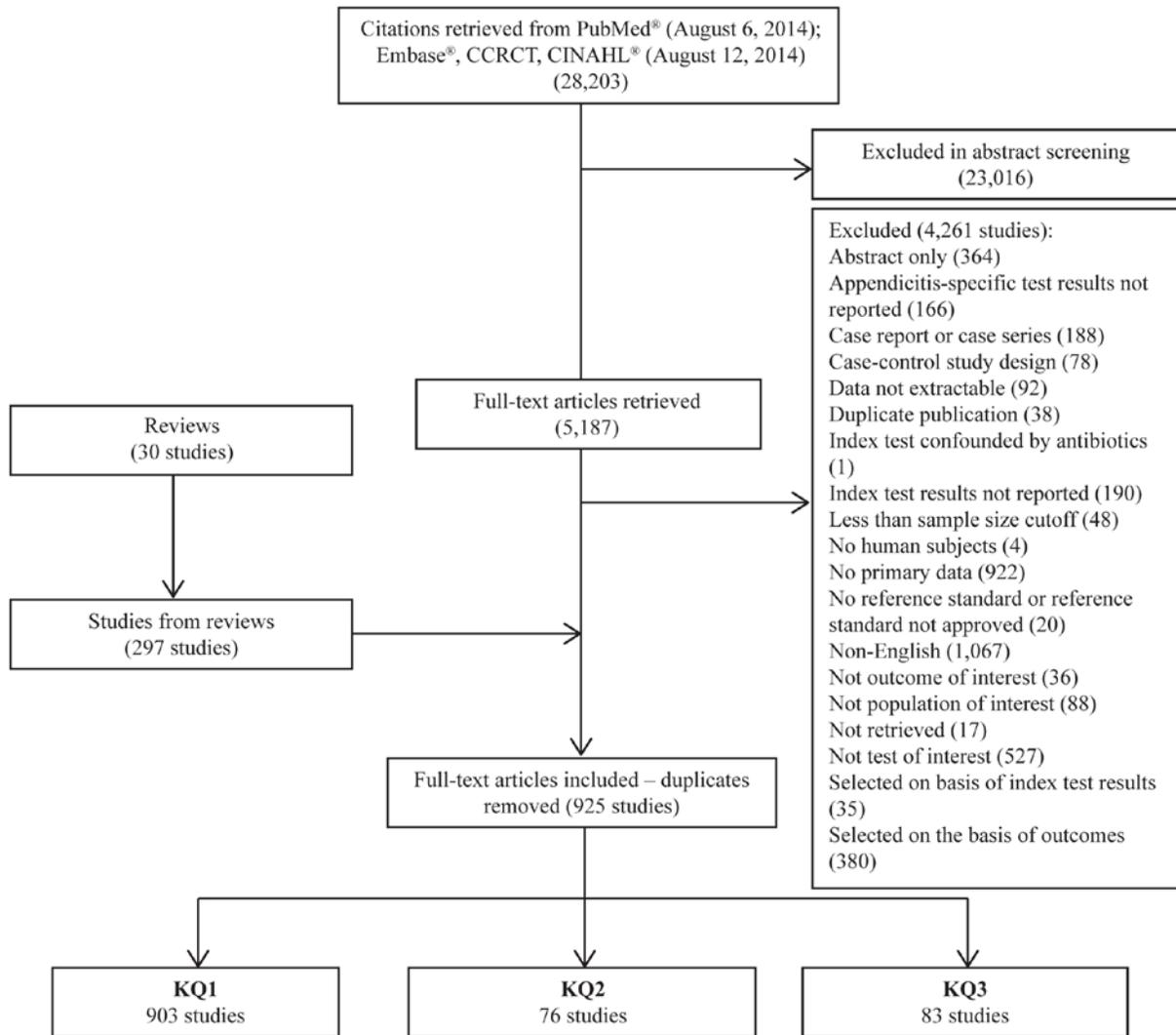
Peer Review

The initial draft report was pre-reviewed by the TOO and an AHRQ Associate Editor. Following revisions, the draft report was sent to invited peer reviewers and was simultaneously uploaded to the AHRQ Web site where it was available for public comment for 30 days. All reviewer comments (both invited and from the public) were collated and individually addressed. The revised report and the EPC's responses to invited and public reviewers' comments were again reviewed by the TOO and Associate Editor prior to completion of the report. The authors of the report had final discretion as to how the report was revised based on the reviewer comments, with oversight by the TOO and Associate Editor. A disposition of comments report will be made available online, 3 months after the Agency posts the final systematic review on the EHC Web site.

Results

Our searches for systematic reviews retrieved 699 citations. After review of abstracts, 58 of these citations were deemed potentially relevant and the corresponding full-length articles were obtained and examined in full text. After full-text review, 30 systematic reviews were considered eligible, and provided information on 297 potentially relevant primary studies on the diagnosis of acute appendicitis. Our literature searches for primary studies retrieved 28,203 citations. Based on abstract review, 5187 of these citations were considered potentially relevant and were retrieved in full text. Our search strategies for all databases are presented in Appendix A; the complete lists of included and excluded studies (organized by reason for exclusion) are presented in Appendix B. After full-text review, 925 primary studies were considered eligible (630 of which had not been included in previous reviews – mainly because they had been published after last search date of the reviews). Figure 2 presents the literature flow.

Figure 2. Flow chart of included studies



CCRCT = Cochrane Central Register of Controlled Trials; KQ = Key Question

Key Question 1: What is the performance of alternative diagnostic tests, alone or in combination, for patients with right lower quadrant (RLQ) pain and suspected acute appendicitis?

Included Studies With Information on Test Performance

In total, 903 studies, published between 1956 and 2014, met the inclusion criteria for Key Question 1. We organized studies into five categories based on the tests they evaluated: clinical symptoms and signs (137 studies), laboratory tests (217 studies), imaging tests (519 studies), multivariable diagnostic scores (127 studies), and diagnostic laparoscopy (55 studies). Appendix C contains a list of all included studies for this Key Question, with information on the tests examined in each study, test performance data, a summary of study characteristics, and details of our risk of bias assessment. In this section we summarize information on tests that were examined most often in the studies we reviewed and those that, based on our reading of the literature, and discussions with Key Informants and Technical Experts, were thought to be more clinically relevant.

Results for each test category (and each test) are presented separately for adults, children, women of reproductive age, pregnant women (some studies reported results for more than one of these subgroups), and mixed populations (typically including male and female patients of all ages). When five or more independent studies had evaluated the same test in the same population subgroup, we conducted meta-analyses of test performance using a binomial-bivariate normal random effects model. Results from these analyses are presented as summary sensitivity and specificity estimates, and corresponding positive and likelihood ratios (with 95% central CrIs).^a

Test Performance of Clinical Symptoms and Signs (in Isolation)

One hundred and thirty seven studies, published between 1976 and 2014, provided information on the performance of clinical symptoms and signs for the diagnosis of acute appendicitis. Commonly examined symptoms included right lower quadrant abdominal pain, anorexia, nausea and vomiting, and fever. Commonly examined signs included guarding, tenderness (including rebound tenderness), rigidity, and other signs indicative of peritoneal

^aTo aid in the interpretation of likelihood ratios we remind readers that these statistics can be used to convert pre-test probabilities to post-test probabilities. For example, before testing, assume that a patient has probability of disease

$$pre\text{-}test\ p = 0.1 \text{ and } pre\text{-}test\ odds = \frac{pre\text{-}test\ p}{1 - pre\text{-}test\ p} = \frac{0.1}{0.9} = 0.11 .$$

If the diagnostic test has a positive likelihood

ratio (LR^+) of 15 then the post-test odds are $post\text{-}test\ odds = pre\text{-}test\ odds \times LR^+ = 0.11 \times 15 = 1.67$. This

corresponds to a post-test probability of $post\text{-}test\ p = \frac{post\text{-}test\ odds}{post\text{-}test\ odds + 1} = \frac{1.67}{1.67 + 1} = 0.625$ (i.e. the post-test

probability is approximately 6 times greater than the pre-test value). If the test results had been negative and the test had a negative likelihood ratio (LR^-) of 0.1, the post-tests odds would be

$$post\text{-}test\ odds = pre\text{-}test\ odds \times LR^- = 0.11 \times 0.1 = 0.011 , \text{ which corresponds to } post\text{-}test\ p = \frac{0.011}{0.011 + 1} = 0.011$$

(i.e., the post-test probability is approximately 10 times lower than the pre-test value). As a rule of thumb,

$LR^+ > 10$ and $LR^- < 0.1$ are generally considered clinically meaningful.

inflammation. Table 1 presents a summary of the descriptive characteristics of the studies. Table 2 presents a summary of items related to study risk of bias. Studies were at moderate to high risk of bias. Blinding of index test and reference standard assessors were either not used or relevant information was not reported; the definition of a positive index test was often not provided; and most studies had differential verification. Table 3 presents a summary of the test performance results for clinical symptoms and signs. In general, their performance was limited. Almost all tests had positive likelihood ratios lower than 3 (no test had a positive likelihood ratio higher than 6) and most tests had negative likelihood ratios higher than 0.2. Figure 3 (parts 1 through 3) presents study results and summary ROC curves for selected clinical symptoms and signs. There was substantial heterogeneity in sensitivity and specificity for most tests; however, in most cases summary ROC lines appeared to fit the data relatively well (indicating that some of the heterogeneity may be due to threshold effects). Figure 4 shows the positive and negative predictive value for selected clinical symptoms and signs, over appendicitis prevalence.

Table 1. Descriptive characteristics for studies evaluating clinical symptoms and signs for the diagnosis of acute appendicitis

Patient Population	N Studies (Median N Patients/Affected/ Unaffected)	Median % of Women	Median of Average Age (Yrs)	Community Setting	Ambulatory Setting	Surgical Cohort	Clinical Presentation Consistent With Appendicitis	Median % of Patients With Perforation
Adults	21 (232/115/50)	52.5%	33.5	14.3%	38.1%	33.3%	85.7%	11.2%
Children	40 (156/69/69)	46.2%	10.9	2.5%	45.0%	12.5%	85.0%	12.5%
Children <5yrs	2 (136.5/98/38.5)	43.8%	3.8	0.0%	0.0%	100.0%	100.0%	35.4%
Elderly	0	NA	NA	NA	NA	NA	NA	NA
Women of reproductive age	5 (105/26/45)	100.0%	29.7	20.0%	60.0%	20.0%	100.0%	26.2%
Pregnant women	11 (37/29/14)	100.0%	25.0	18.2%	9.1%	81.8%	100.0%	13.2%
Mixed	66 (214.5/104.5/80)	53.3%	26.5	9.1%	33.3%	27.3%	80.3%	9.7%

N = number; NA = not applicable; yrs = years

Table 2. Assessment of risk of bias for studies evaluating clinical symptoms and signs for the diagnosis of acute appendicitis

Patient Population	Consecutive or Random Sample of Patients	Study Avoided Inappropriate Exclusions	Index Test Results Interpreted Without Knowledge of Ref. Std.	Were the Positivity Criteria Prespecified?	Ref. Std. Results Interpreted Without Knowledge of Index Test	All Patients Received a Ref. Std.	All Patients Received the Same Ref. Std.	All Patients Received Pathology for a Ref. Std.	All Patients Included in the Analysis
Adults	42.9%	0.0	38.1%	23.8%	14.3%	95.2%	47.6%	47.6%	76.2%
Children	50.0%	100.0	57.5%	27.5%	7.5%	85.0%	25.0%	20.0%	85.0%
Children <5yrs	100.0%	50.0	50.0%	0.0%	0.0%	100.0%	100.0%	100.0%	100.0%
Women of reproductive age	40.0%	100.0	80.0%	40.0%	0.0%	100.0%	40.0%	40.0%	100.0%
Pregnant women	81.8%	100.0	27.3%	9.1%	0.0%	100.0%	90.9%	90.9%	90.9%
Mixed	51.5%	100.0	57.6%	28.8%	16.7%	97.0%	37.9%	31.8%	75.8%

N = number; ref. std. = reference standard; yrs = years

Table 3. Summary estimates of test performance of clinical symptoms and signs for the diagnosis of acute appendicitis

Test	Population	N Studies [Affected/ Unaffected]	Sensitivity	Specificity	LR+	LR-
Anorexia	Adults	12 [1655/1553]	0.62 (0.50 to 0.73)	0.51 (0.34 to 0.67)	1.26 (0.94 to 1.78)	0.75 (0.53 to 1.10)
	Children	15 [2171/3891]	0.72 (0.58 to 0.83)	0.51 (0.40 to 0.62)	1.47 (1.15 to 1.88)	0.54 (0.34 to 0.82)
	Children <5yrs	1 [155/28]	0.68	0.50	1.35	0.65
	Women of reproductive age	1 [17/27]	0.71	0.48	1.36	0.61
	Pregnant women	6 [181/117]	0.50 (0.20 to 0.80)	0.67 (0.41 to 0.87)	1.50 (0.63 to 3.39)	0.75 (0.34 to 1.28)
	Mixed	23 [4266/4936]	0.70 (0.59 to 0.79)	0.54 (0.40 to 0.67)	1.49 (1.22 to 1.93)	0.57 (0.44 to 0.72)
Constipation	Adults	2 [295/461]	0.14 (0.11 to 0.18)	0.90 (0.89 to 0.91)	1.41 (1.22 to 1.59)	0.95 (0.93 to 0.98)
	Children	2 [165/57]	0.11 (0.02 to 0.19)	0.54 (0.23 to 0.84)	0.62 (0.03 to 1.21)	2.60 (0.96 to 4.23)
	Pregnant women	2 [83/37]	0.04 (0.03 to 0.04)	0.95 (0.90 to 1.00)	0.37 (0.37 to 0.37)	1.02 (0.97 to 1.07)
	Mixed	6 [2229/3155]	0.12 (0.04 to 0.32)	0.85 (0.63 to 0.96)	0.83 (0.34 to 2.59)	1.03 (0.86 to 1.25)
Diarrhea	Adults	5 [570/969]	0.07 (0.01 to 0.32)	0.82 (0.55 to 0.94)	0.41 (0.07 to 1.55)	1.12 (0.90 to 1.56)
	Children	10 [1963/1558]	0.22 (0.11 to 0.41)	0.77 (0.51 to 0.92)	0.97 (0.42 to 2.43)	1.01 (0.79 to 1.44)
	Children <5yrs	2 [196/77]	0.13 (0.10 to 0.15)	0.88 (0.86 to 0.90)	1.02 (0.96 to 1.08)	1.00 (0.99 to 1.00)
	Pregnant women	5 [153/79]	0.11 (0.02 to 0.35)	0.93 (0.77 to 0.99)	1.67 (0.28 to 13.34)	0.95 (0.74 to 1.14)
	Mixed	10 [3070/4119]	0.16 (0.06 to 0.37)	0.85 (0.65 to 0.95)	1.07 (0.70 to 1.76)	0.99 (0.88 to 1.08)
Fever	Adults	15 [2082/1796]	0.46 (0.29 to 0.64)	0.63 (0.47 to 0.77)	1.26 (0.83 to 1.93)	0.85 (0.61 to 1.14)
	Children	22 [3952/3845]	0.51 (0.41 to 0.61)	0.72 (0.66 to 0.77)	1.82 (1.37 to 2.37)	0.68 (0.54 to 0.83)
	Children <5yrs	2 [196/77]	0.88 (0.83 to 0.93)	0.34 (0.29 to 0.39)	1.35 (1.16 to 1.53)	0.39 (0.18 to 0.60)
	Women of reproductive age	2 [37/36]	0.36 (0.20 to 0.53)	0.94 (0.89 to 1.00)	4.76 (4.76 to 4.76)	0.66 (0.53 to 0.80)
	Pregnant women	10 [309/166]	0.33 (0.14 to 0.59)	0.65 (0.37 to 0.86)	0.96 (0.46 to 1.86)	1.02 (0.73 to 1.58)
	Mixed	33 [8766/5386]	0.50 (0.39 to 0.61)	0.72 (0.62 to 0.80)	1.76 (1.45 to 2.22)	0.70 (0.59 to 0.80)
Guarding	Adults	5 [771/1158]	0.67 (0.36 to 0.89)	0.69 (0.43 to 0.87)	2.14 (1.10 to 4.49)	0.48 (0.18 to 0.93)
	Children	8 [870/1554]	0.64 (0.49 to 0.77)	0.69 (0.54 to 0.81)	2.07 (1.46 to 3.14)	0.52 (0.36 to 0.70)
	Women of reproductive age	1 [17/27]	0.76	0.85	5.16	0.28
	Pregnant women	4 [144/103]	0.63 (0.14 to 0.76)	0.55 (0.43 to 0.74)	1.34 (0.32 to 2.44)	0.63 (0.50 to 1.53)
	Mixed	18 [3151/4231]	0.63 (0.47 to 0.78)	0.69 (0.53 to 0.81)	2.03 (1.50 to 2.89)	0.53 (0.37 to 0.71)

Table 3. Summary estimates of test performance of clinical symptoms and signs for the diagnosis of acute appendicitis (continued)

Test	Population	N Studies [Affected/ Unaffected]	Sensitivity	Specificity	LR+	LR-
Nausea	Adults	5 [406/790]	0.57 (0.32 to 0.77)	0.62 (0.47 to 0.75)	1.46 (0.81 to 2.39)	0.71 (0.37 to 1.15)
	Children	7 [652/1783]	0.70 (0.49 to 0.84)	0.43 (0.22 to 0.68)	1.23 (0.85 to 2.05)	0.70 (0.37 to 1.38)
	Children <5yrs	1 [155/28]	0.75	0.61	1.90	0.41
	Pregnant women	8 [281/190]	0.83 (0.69 to 0.93)	0.33 (0.20 to 0.46)	1.23 (1.00 to 1.51)	0.52 (0.24 to 0.99)
	Mixed	14 [3076/4603]	0.69 (0.53 to 0.82)	0.50 (0.32 to 0.69)	1.37 (1.01 to 2.07)	0.63 (0.38 to 0.98)
Nausea or vomiting	Adults	4 [415/115]	0.48 (0.35 to 0.79)	0.38 (0.00 to 0.73)	1.07 (0.48 to 1.33)	0.88 (0.87 to 1.24)
	Children	10 [1641/2252]	0.76 (0.66 to 0.84)	0.50 (0.33 to 0.67)	1.51 (1.11 to 2.31)	0.48 (0.31 to 0.81)
	Pregnant women	1 [21/1]	0.52	1.00	.	0.48
	Mixed	9 [1545/745]	0.66 (0.46 to 0.81)	0.38 (0.22 to 0.56)	1.07 (0.65 to 1.68)	0.89 (0.40 to 2.10)
Obturator sign	Children	3 [458/786]	0.29 (0.17 to 0.34)	0.90 (0.87 to 0.94)	2.84 (2.19 to 3.52)	0.82 (0.73 to 0.89)
	Pregnant women	1 [54/30]	0.13	0.73	0.49	1.19
	Mixed	6 [2035/999]	0.13 (0.04 to 0.36)	0.84 (0.37 to 0.98)	0.82 (0.19 to 5.21)	1.03 (0.81 to 2.14)
Pain	Adults	1 [54/363]	0.87	0.20	1.09	0.64
	Children <5yrs	1 [155/28]	1.00	0.00	1.00	.
	Mixed	9 [2172/1286]	0.93 (0.67 to 0.99)	0.24 (0.04 to 0.67)	1.20 (0.96 to 2.42)	0.32 (0.06 to 1.35)
Pain cough	Children	1 [87/13]	0.00	0.15	0.00	6.50
	Women of reproductive age	1 [17/27]	0.82	0.59	2.02	0.30
	Mixed	6 [1117/3621]	0.67 (0.36 to 0.88)	0.66 (0.35 to 0.87)	1.93 (1.28 to 3.21)	0.51 (0.30 to 0.77)
Pain duration	Adults	3 [145/519]	0.80 (0.74 to 0.93)	0.32 (0.22 to 0.37)	1.18 (1.17 to 1.19)	0.61 (0.34 to 0.70)
	Children	5 [1312/1126]	0.73 (0.44 to 0.90)	0.35 (0.16 to 0.58)	1.11 (0.72 to 1.61)	0.79 (0.33 to 1.77)
	Mixed	8 [1651/3789]	0.71 (0.49 to 0.86)	0.44 (0.25 to 0.65)	1.27 (0.94 to 1.81)	0.66 (0.36 to 1.11)
Pain migration	Adults	11 [1831/864]	0.56 (0.45 to 0.67)	0.65 (0.50 to 0.78)	1.62 (1.22 to 2.27)	0.67 (0.56 to 0.81)
	Children	15 [2049/3535]	0.57 (0.39 to 0.73)	0.74 (0.66 to 0.81)	2.19 (1.56 to 2.94)	0.58 (0.38 to 0.80)
	Women of reproductive age	1 [17/27]	0.53	0.67	1.59	0.71
	Pregnant women	1 [42/14]	0.57	0.86	4.00	0.50
	Mixed	23 [4475/6156]	0.61 (0.49 to 0.71)	0.67 (0.56 to 0.76)	1.81 (1.37 to 2.44)	0.59 (0.45 to 0.76)
Pain progression	Adults	3 [451/568]	0.70 (0.60 to 0.95)	0.38 (0.22 to 0.88)	1.21 (0.96 to 5.81)	0.34 (0.24 to 1.06)
	Children	1 [68/371]	0.66	0.65	1.89	0.52
	Mixed	6 [2253/4232]	0.43 (0.14 to 0.79)	0.72 (0.44 to 0.89)	1.49 (0.89 to 2.32)	0.80 (0.43 to 1.03)

Table 3. Summary estimates of test performance of clinical symptoms and signs for the diagnosis of acute appendicitis (continued)

Test	Population	N Studies [Affected/ Unaffected]	Sensitivity	Specificity	LR+	LR-
Pain RLQ	Adults	7 [551/747]	0.87 (0.68 to 0.97)	0.23 (0.05 to 0.62)	1.13 (0.88 to 2.11)	0.55 (0.15 to 2.38)
	Children	6 [1834/1123]	0.79 (0.43 to 0.95)	0.41 (0.15 to 0.73)	1.30 (0.89 to 2.28)	0.53 (0.19 to 1.23)
	Pregnant women	7 [278/156]	0.64 (0.33 to 0.86)	0.39 (0.14 to 0.73)	1.05 (0.61 to 2.06)	0.92 (0.40 to 2.30)
	Mixed	9 [1640/1649]	0.92 (0.73 to 0.98)	0.58 (0.20 to 0.89)	2.18 (1.07 to 8.36)	0.14 (0.02 to 0.77)
Pain RUQ	Adults	1 [26/33]	0.12	0.85	0.76	1.04
	Pregnant women	8 [297/165]	0.12 (0.06 to 0.20)	0.88 (0.70 to 0.97)	0.99 (0.38 to 4.43)	1.00 (0.88 to 1.23)
	Mixed	1 [234/614]	0.06	0.89	0.51	1.06
PSOAS Sign	Children	4 [501/873]	0.31 (0.22 to 0.38)	0.87 (0.86 to 0.92)	2.63 (1.95 to 3.15)	0.80 (0.70 to 0.86)
	Pregnant women	3 [101/42]	0.17 (0.15 to 0.62)	0.67 (0.29 to 1.00)	0.66 (0.44 to 0.87)	1.28 (0.83 to 1.33)
	Mixed	11 [2671/1893]	0.24 (0.12 to 0.41)	0.88 (0.61 to 0.97)	1.94 (0.71 to 6.57)	0.88 (0.72 to 1.15)
Rigidity	Adults	6 [513/1217]	0.28 (0.06 to 0.67)	0.89 (0.58 to 0.98)	2.38 (0.73 to 8.70)	0.83 (0.45 to 1.08)
	Children	1 [68/371]	0.04	0.99	4.09	0.97
	Pregnant women	1 [19/9]	0.32	0.89	2.84	0.77
	Mixed	5 [1397/3677]	0.19 (0.04 to 0.54)	0.97 (0.88 to 1.00)	6.70 (0.96 to 51.94)	0.84 (0.49 to 1.00)
Rovsing sign	Children	3 [614/1018]	0.32 (0.30 to 0.34)	0.84 (0.84 to 0.91)	2.01 (1.91 to 3.94)	0.81 (0.72 to 0.83)
	Pregnant women	4 [133/101]	0.34 (0.31 to 0.67)	0.74 (0.00 to 0.91)	1.22 (0.67 to 3.70)	0.91 (0.72 to 0.93)
	Mixed	10 [2564/2198]	0.38 (0.21 to 0.59)	0.84 (0.59 to 0.95)	2.42 (1.13 to 6.51)	0.74 (0.56 to 0.94)
Symptom duration	Adults	3 [389/353]	0.86 (0.84 to 1.00)	0.35 (0.04 to 0.52)	1.30 (1.04 to 1.79)	0.27 (0.00 to 0.46)
	Children	3 [206/321]	0.77 (0.72 to 0.86)	0.55 (0.41 to 0.82)	1.58 (1.31 to 4.89)	0.52 (0.17 to 0.56)
	Pregnant women	1 [21/1]	0.71	1.00	.	0.29
	Mixed	7 [1145/1607]	0.68 (0.42 to 0.85)	0.43 (0.17 to 0.74)	1.16 (0.86 to 2.05)	0.77 (0.45 to 1.37)
Tenderness	Children	2 [206/474]	0.63 (0.26 to 1.00)	0.57 (0.46 to 0.68)	1.33 (0.80 to 1.86)	0.55 (0.00 to 1.09)
	Children <5yrs	1 [155/28]	0.98	0.25	1.31	0.08
	Women of reproductive age	1 [17/27]	1.00	0.04	1.04	0.00
	Mixed	10 [1450/1510]	0.99 (0.95 to 1.00)	0.30 (0.08 to 0.67)	1.41 (1.08 to 2.94)	0.03 (0.00 to 0.21)

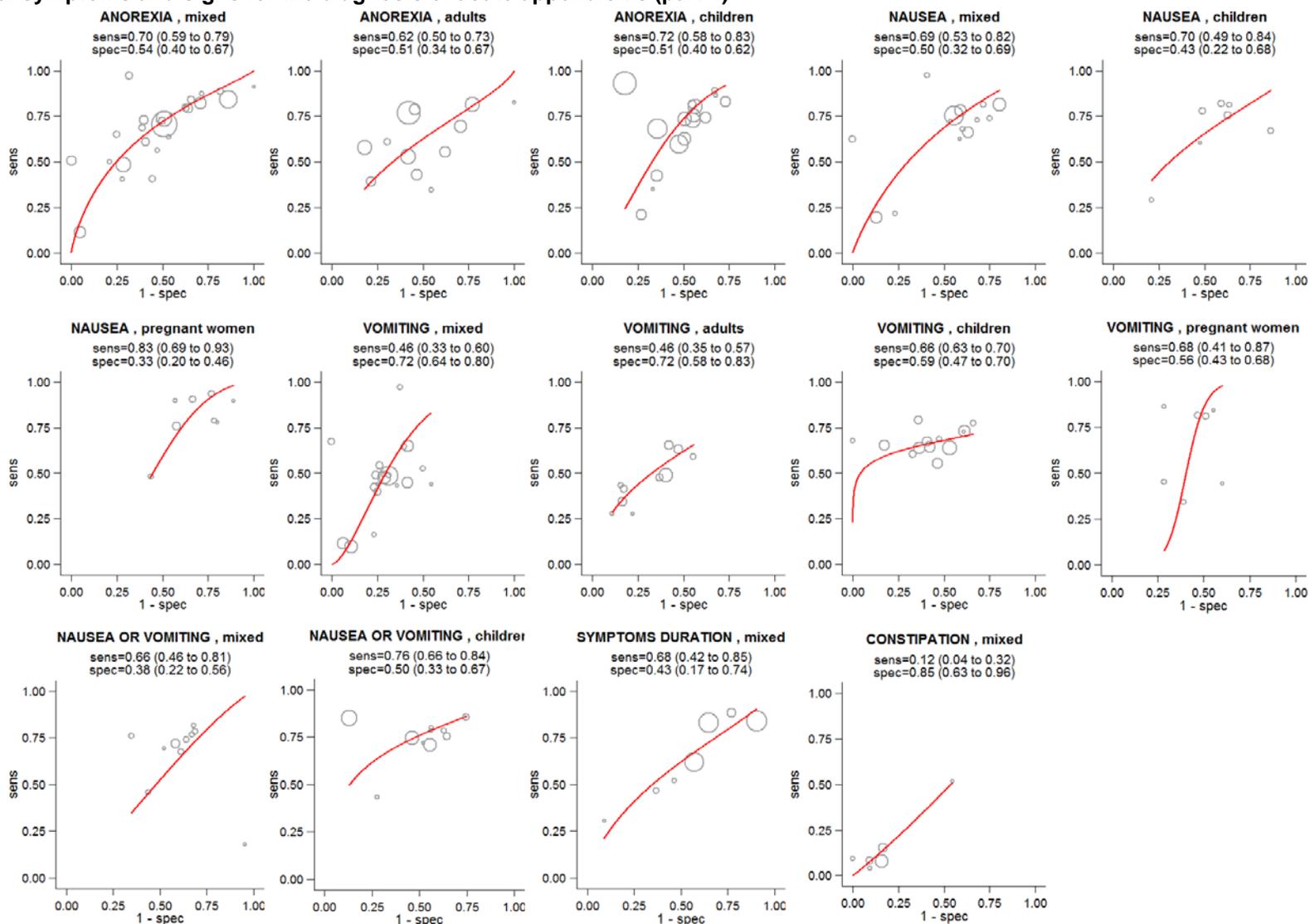
Table 3. Summary estimates of test performance of clinical symptoms and signs for the diagnosis of acute appendicitis (continued)

Test	Population	N Studies [Affected/ Unaffected]	Sensitivity	Specificity	LR+	LR-
Tenderness rebound	Adults	11 [1423/1540]	0.67 (0.50 to 0.81)	0.70 (0.51 to 0.83)	2.19 (1.38 to 3.76)	0.48 (0.29 to 0.72)
	Children	11 [1013/1895]	0.60 (0.43 to 0.77)	0.73 (0.57 to 0.84)	2.22 (1.39 to 3.44)	0.55 (0.34 to 0.78)
	Children <5yrs	1 [155/28]	0.85	0.86	5.92	0.18
	Women of reproductive age	1 [26/79]	0.42	0.65	1.19	0.89
	Pregnant women	5 [160/111]	0.71 (0.36 to 0.92)	0.58 (0.21 to 0.88)	1.63 (0.80 to 5.50)	0.52 (0.14 to 1.41)
	Mixed	30 [5859/6738]	0.74 (0.65 to 0.82)	0.60 (0.48 to 0.72)	1.87 (1.47 to 2.51)	0.43 (0.31 to 0.57)
Tenderness rectal	Adults	6 [896/1694]	0.36 (0.10 to 0.73)	0.83 (0.58 to 0.95)	2.10 (0.53 to 7.55)	0.78 (0.34 to 1.20)
	Children	7 [443/837]	0.42 (0.25 to 0.60)	0.90 (0.82 to 0.95)	4.09 (2.18 to 9.03)	0.65 (0.45 to 0.83)
	Women of reproductive age	1 [155/45]	0.45	0.42	0.78	1.30
	Pregnant women	2 [58/30]	0.33 (0.21 to 0.45)	0.48 (0.14 to 0.83)	0.86 (0.52 to 1.19)	2.41 (0.96 to 3.86)
	Mixed	15 [3753/4690]	0.33 (0.21 to 0.48)	0.61 (0.37 to 0.81)	0.86 (0.49 to 1.67)	1.09 (0.80 to 1.75)
Tenderness RLQ	Adults	7 [1077/1040]	0.92 (0.77 to 0.98)	0.38 (0.10 to 0.76)	1.47 (1.02 to 3.63)	0.21 (0.05 to 0.88)
	Children	14 [3506/2627]	0.92 (0.80 to 0.97)	0.50 (0.20 to 0.79)	1.81 (1.15 to 4.32)	0.17 (0.06 to 0.49)
	Children <5yrs	1 [41/49]	0.93	0.18	1.14	0.40
	Pregnant women	4 [133/101]	0.83 (0.50 to 0.97)	0.23 (0.05 to 0.33)	1.07 (0.63 to 1.25)	0.67 (0.50 to 2.50)
	Mixed	12 [3081/2969]	0.93 (0.80 to 0.98)	0.16 (0.07 to 0.30)	1.10 (1.00 to 1.24)	0.45 (0.19 to 1.02)
Vomiting	Adults	10 [1395/1667]	0.46 (0.35 to 0.57)	0.72 (0.58 to 0.83)	1.65 (1.24 to 2.36)	0.75 (0.65 to 0.86)
	Children	13 [2043/1994]	0.66 (0.63 to 0.70)	0.59 (0.47 to 0.70)	1.60 (1.25 to 2.21)	0.58 (0.47 to 0.72)
	Children <5yrs	2 [196/77]	0.75 (0.63 to 0.86)	0.54 (0.39 to 0.69)	1.74 (1.41 to 2.07)	0.44 (0.36 to 0.53)
	Women of reproductive age	1 [17/27]	0.35	0.81	1.91	0.79
	Pregnant women	7 [223/131]	0.68 (0.41 to 0.87)	0.56 (0.43 to 0.68)	1.53 (0.90 to 2.23)	0.57 (0.23 to 1.09)
	Mixed	19 [4264/6045]	0.46 (0.33 to 0.60)	0.72 (0.64 to 0.80)	1.67 (1.23 to 2.26)	0.74 (0.57 to 0.90)

LR = likelihood ratio; N = number; RLQ = right lower quadrant; RUQ = right upper quadrant; yrs = years.

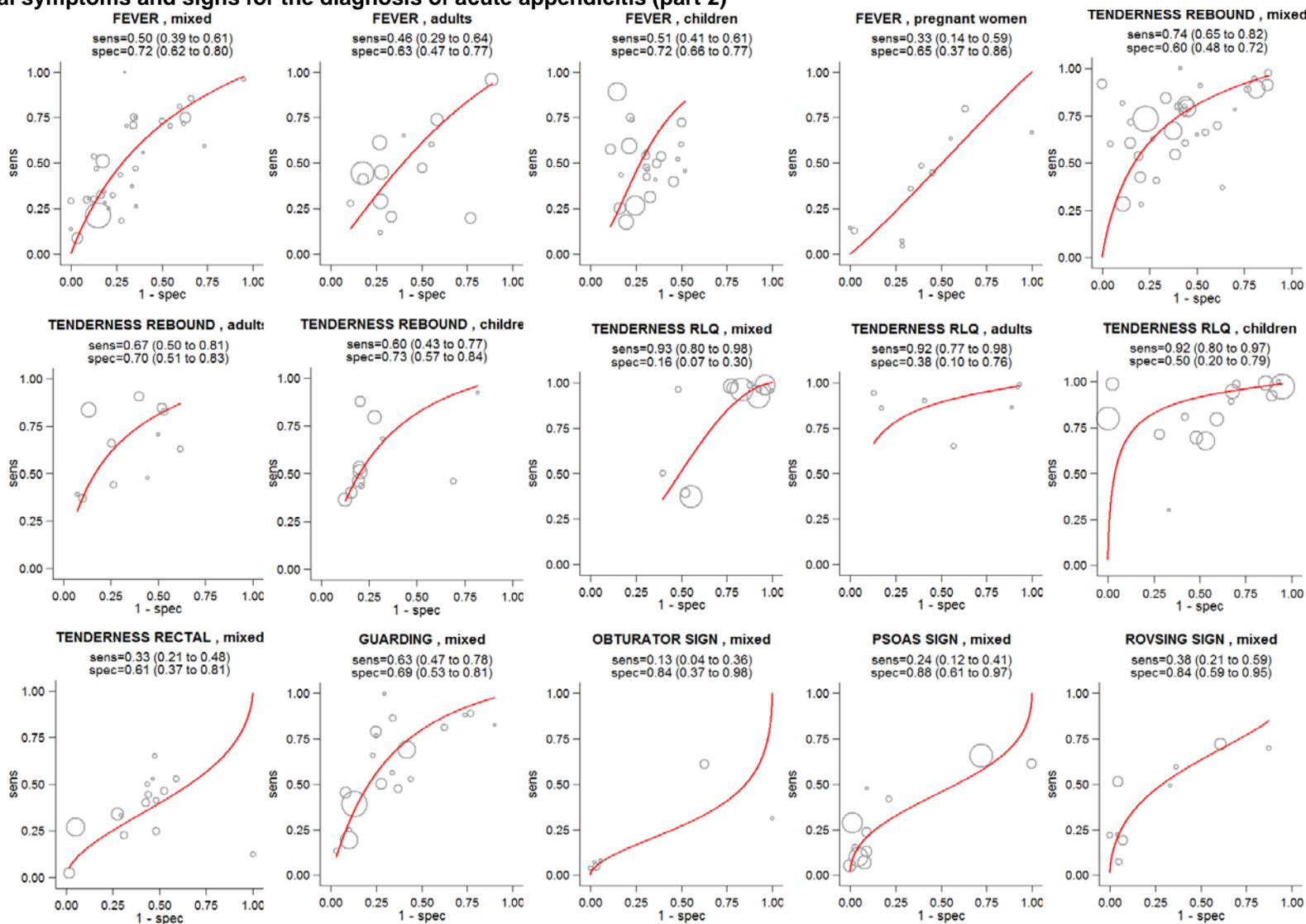
Sensitivity, specificity, and LR values are medians and 95% central credible intervals when 5 or more studies were available; medians and minimum to maximum values are reported when <5 studies were available; when a single study was available we report the estimate from that study.

Figure 3. Scatterplot of results in the receiver operating characteristic space and summary receiver operating characteristic curves of clinical symptoms and signs for the diagnosis of acute appendicitis (part 1)



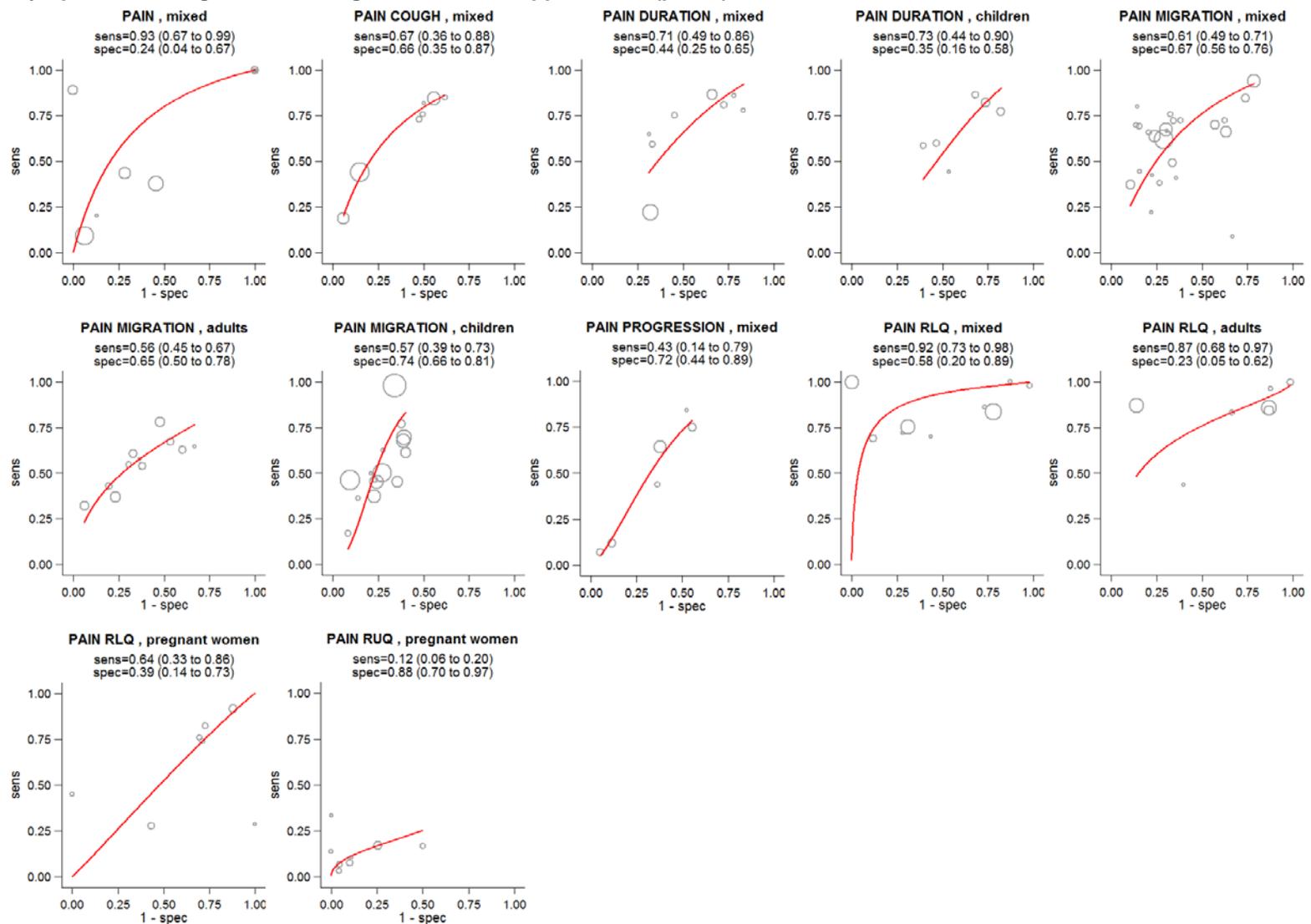
Sens. = sensitivity, spec.=specificity

Figure 3. Scatterplot of results in the receiver operating characteristic space and summary receiver operating characteristic curves of clinical symptoms and signs for the diagnosis of acute appendicitis (part 2)



sens.=sensitivity; spec.=specificity

Figure 3. Scatterplot of results in the receiver operating characteristic space and summary receiver operating characteristic curves of clinical symptoms and signs for the diagnosis of acute appendicitis (part 3)



Sens.=sensitivity; spec.=specificity; RLQ=right lower quadrant; RUQ=right upper quadrant

Figure 4. Positive and negative predictive value curves of clinical symptoms and signs for the diagnosis of acute appendicitis (part 1)

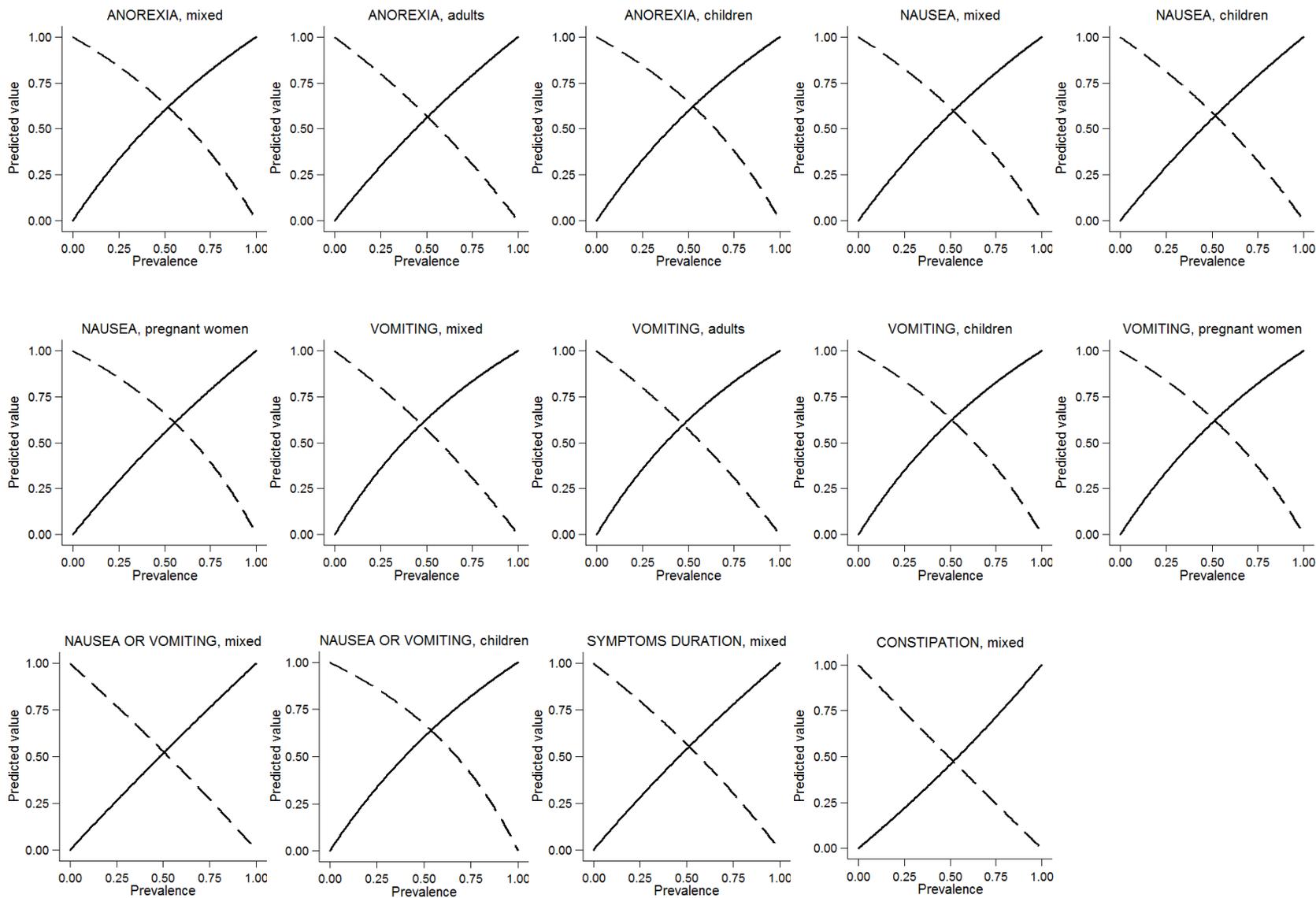
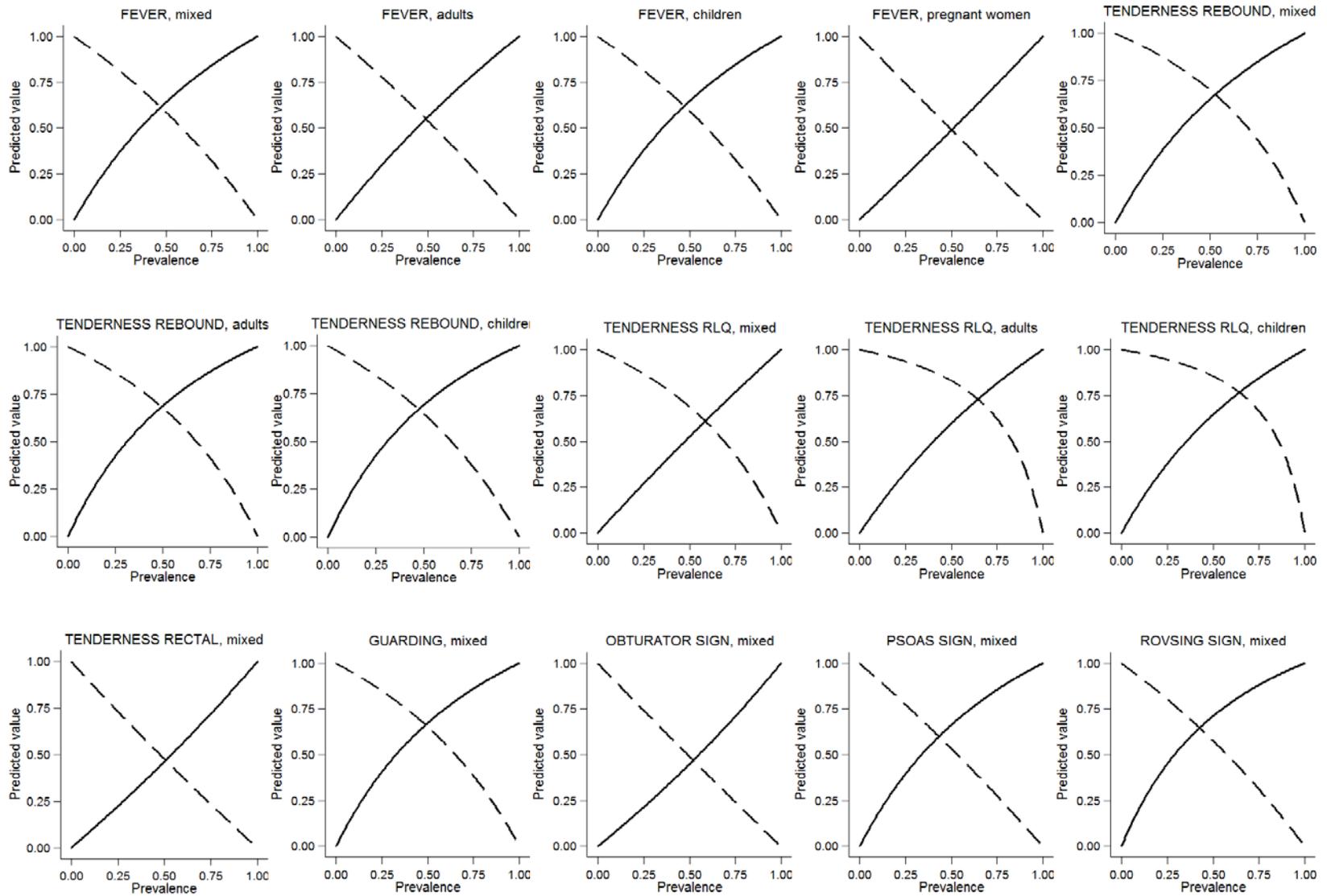
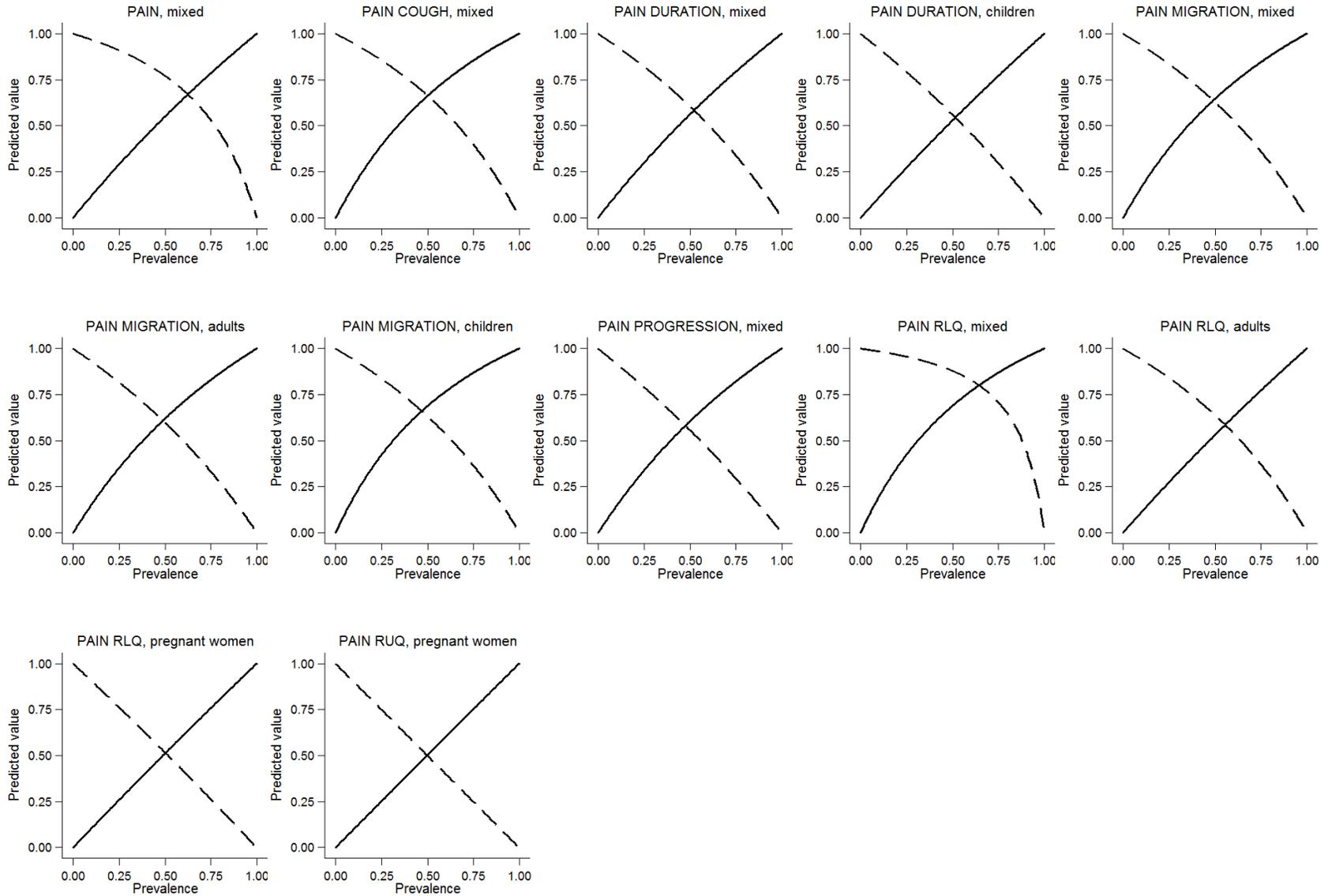


Figure 4. Positive and negative predictive value curves of clinical symptoms and signs for the diagnosis of acute appendicitis (part 2)



RLQ = right lower quadrant

Figure 4. Positive and negative predictive value curves of clinical symptoms and signs for the diagnosis of acute appendicitis (part 3)



RLQ = right lower quadrant; RUQ=right upper quadrant

Factors That Affect the Test Performance of Clinical Symptoms and Signs

The vast majority of studies did not report adequate data to assess factors that may affect test performance (i.e., based on within study comparisons); for this reason we relied on comparisons across studies (via meta-regression analyses) to identify factors that may affect test performance. Table 4 summarizes the results of meta-regression analyses for various factors that may affect the performance of clinical signs for the diagnosis of acute appendicitis. Overall, no distinct pattern emerged to establish a particular factor as a modifier of test performance. Recent studies tended to produce lower estimates of summary sensitivity (published from 2005 onwards), often but not always associated with higher estimates of specificity. Yet, for all factors examined but CrIs were wide, indicating substantial uncertainty regarding the relative test performance of tests over levels of the modifiers we examined.

Impact of Risk of Bias Items on Estimated Test Performance of Clinical Symptoms and Signs

Table 5 summarizes the results of meta-regression analyses for various factors that may affect the performance of clinical symptoms and signs tests for the diagnosis of acute appendicitis. In some cases items related to study risk of bias appeared to be associated with worse test performance of various clinical symptoms and signs. Specifically, nondifferential verification was associated with lower sensitivity in studies of fever in mixed populations; blinding of reference standard assessors was associated with lower specificity in studies of pain migration in mixed populations; complete verification was associated with lower sensitivity in studies of rebound tenderness in mixed populations; and blinding of index test assessors was associated with lower sensitivity in studies of rebound tenderness in mixed populations.

These results that study conduct may have affected estimates of test performance in meta-analyses of clinical symptoms and signs. However, our analyses relied on information that was often poorly reported in the primary studies and meta-regression results were often imprecise, indicating substantial uncertainty. The aforementioned differences were the only cases when CrIs did not include the null value among the large number of comparisons summarized in Table 5. Because each risk of bias item was examined individually, and because different items may be correlated between them and with other study characteristics that may affect performance estimates, we do not believe that definitive conclusions about specific items can be reached.

Table 4. Meta-regression results for factors that affect the performance of clinical signs and symptoms for the diagnosis of acute appendicitis

Test	Population	Subgroup		N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity
Anorexia	Adults	Study year	<2005	5	0.76 (0.66 to 0.85)	1.24 (0.63 to 2.42)	0.46 (0.22 to 0.69)	1.42 (0.43 to 5.29)
			>=2005	7	0.51 (0.40 to 0.62)		0.55 (0.34 to 0.74)	
		Ambulatory setting	no	7	0.59 (0.43 to 0.75)	1.82 (1.01 to 3.21)	0.50 (0.26 to 0.72)	1.01 (0.25 to 4.58)
			yes	5	0.66 (0.46 to 0.82)		0.51 (0.26 to 0.76)	
		Surgical cohorts	no	7	0.60 (0.43 to 0.76)	1.57 (0.85 to 2.92)	0.52 (0.30 to 0.73)	0.89 (0.19 to 3.55)
			yes	5	0.64 (0.45 to 0.81)		0.49 (0.22 to 0.74)	
	Children	Ambulatory setting	no	6	0.70 (0.45 to 0.87)	1.49 (0.59 to 3.82)	0.46 (0.31 to 0.63)	1.40 (0.57 to 2.96)
			yes	9	0.74 (0.55 to 0.87)		0.54 (0.40 to 0.66)	
	Mixed	Study year	<2005	14	0.73 (0.62 to 0.82)	1.60 (0.86 to 2.91)	0.45 (0.29 to 0.62)	1.82 (0.59 to 5.77)
			>=2005	8	0.70 (0.56 to 0.82)		0.60 (0.38 to 0.79)	
		Ambulatory setting	no	11	0.75 (0.64 to 0.84)	0.64 (0.36 to 1.15)	0.53 (0.36 to 0.72)	0.84 (0.25 to 2.09)
			yes	11	0.68 (0.56 to 0.79)		0.48 (0.29 to 0.65)	
		Surgical cohorts	no	17	0.70 (0.60 to 0.79)	1.11 (0.46 to 2.65)	0.55 (0.41 to 0.69)	0.43 (0.12 to 1.26)
			yes	5	0.79 (0.64 to 0.89)		0.35 (0.16 to 0.58)	
		Appendicitis presentation	atypical/other/unclear	7	0.71 (0.55 to 0.85)	1.57 (0.66 to 3.47)	0.52 (0.26 to 0.74)	0.90 (0.28 to 3.64)
			typical	15	0.73 (0.61 to 0.81)		0.50 (0.34 to 0.66)	

Table 4. Meta-regression results for factors that affect the performance of clinical signs and symptoms for the diagnosis of acute appendicitis (continued)

Test	Population	Subgroup		N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity
Fever	Adults	Study year	<2005	7	0.58 (0.35 to 0.78)	1.67 (0.62 to 4.53)	0.53 (0.30 to 0.76)	2.24 (0.55 to 7.95)
			>=2005	8	0.36 (0.18 to 0.58)		0.72 (0.50 to 0.86)	
		Ambulatory setting	no	10	0.45 (0.24 to 0.66)	3.22 (1.11 to 10.10)	0.58 (0.35 to 0.77)	1.82 (0.35 to 10.55)
			yes	5	0.49 (0.21 to 0.78)		0.72 (0.42 to 0.91)	
		Surgical cohorts	no	8	0.43 (0.22 to 0.67)	2.11 (0.74 to 6.49)	0.68 (0.46 to 0.84)	0.60 (0.15 to 2.35)
			yes	7	0.50 (0.26 to 0.74)		0.57 (0.32 to 0.79)	
	Children	Study year	<2005	7	0.65 (0.51 to 0.78)	3.53 (1.10 to 12.07)	0.74 (0.63 to 0.82)	0.86 (0.47 to 1.54)
			>=2005	15	0.44 (0.34 to 0.55)		0.71 (0.63 to 0.77)	
		Ambulatory setting	no	10	0.48 (0.34 to 0.63)	3.13 (1.16 to 9.34)	0.68 (0.60 to 0.76)	1.37 (0.81 to 2.21)
			yes	12	0.54 (0.40 to 0.67)		0.75 (0.67 to 0.80)	
	Mixed	Study year	<2005	24	0.54 (0.41 to 0.68)	0.75 (0.26 to 2.19)	0.66 (0.53 to 0.77)	2.92 (1.03 to 9.42)
			>=2005	8	0.40 (0.20 to 0.64)		0.85 (0.70 to 0.94)	
		Ambulatory setting	no	22	0.47 (0.34 to 0.60)	0.15 (0.01 to 2.91)	0.72 (0.60 to 0.83)	0.85 (0.29 to 2.21)
			yes	10	0.59 (0.39 to 0.76)		0.69 (0.48 to 0.84)	
Surgical cohorts		no	24	0.56 (0.43 to 0.69)	0.18 (0.01 to 3.78)	0.70 (0.56 to 0.81)	1.44 (0.42 to 4.19)	
		yes	8	0.35 (0.19 to 0.58)		0.77 (0.54 to 0.90)		
Guarding	Mixed	Ambulatory setting	no	12	0.66 (0.45 to 0.82)	0.24 (0.01 to 4.82)	0.66 (0.47 to 0.82)	1.57 (0.34 to 4.91)
			yes	6	0.58 (0.30 to 0.83)		0.75 (0.46 to 0.89)	
		Surgical cohort	no	13	0.65 (0.44 to 0.81)	3.21 (0.13 to 73.13)	0.70 (0.51 to 0.84)	0.86 (0.16 to 3.75)
			yes	5	0.61 (0.30 to 0.86)		0.66 (0.33 to 0.87)	
Nausea	Mixed	Study year	<2005	5	0.70 (0.41 to 0.89)	1.12 (0.68 to 1.90)	0.40 (0.16 to 0.67)	1.89 (0.56 to 9.28)
			>=2005	9	0.68 (0.47 to 0.84)		0.56 (0.35 to 0.77)	
		Appendicitis presentation	atypical/other/unclear	5	0.74 (0.48 to 0.90)	1.23 (0.67 to 2.25)	0.38 (0.14 to 0.67)	2.17 (0.50 to 14.78)
			typical	9	0.66 (0.45 to 0.83)		0.57 (0.35 to 0.79)	

Table 4. Meta-regression results for factors that affect the performance of clinical signs and symptoms for the diagnosis of acute appendicitis (continued)

Test	Population	Subgroup		N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity
Nausea or vomiting	Children	Ambulatory setting	no	5	0.74 (0.57 to 0.86)	1.49 (0.89 to 2.59)	0.46 (0.22 to 0.73)	1.39 (0.25 to 6.35)
			yes	5	0.78 (0.63 to 0.88)		0.54 (0.27 to 0.77)	
Pain migration	Children	Ambulatory setting	no	6	0.53 (0.38 to 0.69)	0.68 (0.31 to 1.49)	0.67 (0.44 to 0.83)	0.90 (0.24 to 3.44)
			yes	5	0.60 (0.43 to 0.74)		0.64 (0.39 to 0.83)	
	Mixed	Study year	no	6	0.42 (0.19 to 0.69)	0.99 (0.51 to 1.91)	0.78 (0.67 to 0.87)	0.70 (0.31 to 1.41)
			yes	9	0.66 (0.45 to 0.83)		0.71 (0.61 to 0.80)	
		Ambulatory setting	<2005	15	0.62 (0.48 to 0.74)	1.42 (0.81 to 2.59)	0.71 (0.60 to 0.80)	0.44 (0.19 to 0.92)
			>=2005	7	0.61 (0.40 to 0.79)		0.52 (0.34 to 0.67)	
Psoas sign	Mixed	Study year	no	9	0.67 (0.50 to 0.80)	1.41 (0.80 to 2.47)	0.57 (0.41 to 0.72)	1.84 (0.72 to 4.17)
			yes	13	0.58 (0.43 to 0.72)		0.70 (0.57 to 0.80)	
		Ambulatory setting	<2005	6	0.22 (0.09 to 0.47)	0.99 (0.54 to 1.85)	0.90 (0.55 to 0.99)	0.59 (0.03 to 9.40)
			>=2005	5	0.25 (0.10 to 0.52)		0.84 (0.37 to 0.98)	
Tenderness rebound	Adults	Study year	no	6	0.19 (0.07 to 0.41)	1.18 (0.64 to 2.19)	0.93 (0.66 to 0.99)	0.28 (0.02 to 3.36)
			yes	5	0.30 (0.11 to 0.60)		0.78 (0.30 to 0.97)	
		Ambulatory setting	<2005	5	0.72 (0.47 to 0.88)	0.83 (0.31 to 2.13)	0.73 (0.48 to 0.89)	0.70 (0.18 to 2.79)
			>=2005	6	0.62 (0.39 to 0.82)		0.66 (0.41 to 0.85)	
	Children	Ambulatory setting	no	6	0.63 (0.40 to 0.82)	0.38 (0.17 to 0.88)	0.65 (0.39 to 0.84)	1.54 (0.37 to 7.00)
			yes	5	0.72 (0.46 to 0.88)		0.74 (0.48 to 0.90)	
	Mixed	Study year	no	6	0.52 (0.32 to 0.74)	0.99 (0.38 to 2.77)	0.70 (0.48 to 0.85)	1.29 (0.36 to 4.66)
			yes	5	0.68 (0.45 to 0.85)		0.75 (0.51 to 0.89)	
		Ambulatory setting	<2005	21	0.74 (0.62 to 0.83)	1.93 (0.78 to 5.59)	0.61 (0.46 to 0.74)	0.86 (0.33 to 2.87)
			>=2005	9	0.75 (0.57 to 0.88)		0.58 (0.37 to 0.79)	
		Surgical cohorts	no	18	0.73 (0.59 to 0.83)	1.13 (0.62 to 2.20)	0.59 (0.42 to 0.73)	1.21 (0.43 to 3.36)
			yes	12	0.77 (0.62 to 0.88)		0.63 (0.43 to 0.79)	
		Appendicitis presentation	no	20	0.77 (0.66 to 0.85)	1.11 (0.59 to 2.09)	0.64 (0.50 to 0.76)	0.59 (0.23 to 1.48)
			yes	10	0.69 (0.52 to 0.82)		0.51 (0.32 to 0.70)	

Table 4. Meta-regression results for factors that affect the performance of clinical signs and symptoms for the diagnosis of acute appendicitis (continued)

Test	Population	Subgroup	N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity	
Tenderness rectal	Mixed	Surgical cohorts	atypical/other/unclear	7	0.64 (0.43 to 0.83)	1.02 (0.44 to 2.50)	0.71 (0.46 to 0.86)	0.53 (0.18 to 1.84)
			typical	23	0.77 (0.67 to 0.85)		0.57 (0.43 to 0.70)	
Tenderness RLQ	Children	Ambulatory setting	no	10	0.29 (0.17 to 0.46)	0.33 (0.14 to 0.87)	0.65 (0.34 to 0.86)	0.63 (0.09 to 4.96)
			yes	5	0.42 (0.21 to 0.64)		0.53 (0.17 to 0.86)	
	Mixed	Ambulatory setting	no	7	0.85 (0.59 to 0.96)	1.19 (0.68 to 1.97)	0.40 (0.11 to 0.82)	2.32 (0.15 to 18.40)
			yes	7	0.96 (0.85 to 0.99)		0.59 (0.17 to 0.90)	

N = number; RLQ = right lower quadrant; RUQ = right upper quadrant

Sensitivity, relative sensitivity, specificity, and relative specificity values are medians and 95% central credible intervals when 5 or more studies were available; medians and minimum to maximum values are reported when <5 studies were available; when a single study was available we report the estimate from that study.

Table 5. Meta-regression results for the impact of risk of bias items on the estimated test performance of clinical signs and symptoms for the diagnosis of acute appendicitis

Test	Population	Subgroup		N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity	
Anorexia	Adults	All pts. received same ref. std.	no	6	0.60 (0.40 to 0.76)	1.14 (0.40 to 3.59)	0.52 (0.30 to 0.76)	0.91 (0.16 to 3.14)	
			yes	6	0.64 (0.46 to 0.80)		0.49 (0.22 to 0.72)		
		Pathology (100%)	no	6	0.60 (0.40 to 0.76)	1.14 (0.40 to 3.59)	0.52 (0.30 to 0.76)	0.91 (0.16 to 3.14)	
			yes	6	0.64 (0.46 to 0.80)		0.49 (0.22 to 0.72)		
		Consecutive/random sample	no	5	0.55 (0.36 to 0.74)	1.66 (0.55 to 4.64)	0.56 (0.29 to 0.79)	0.69 (0.17 to 3.04)	
			yes	7	0.67 (0.51 to 0.80)		0.47 (0.24 to 0.70)		
		Blinding index tests	no	6	0.69 (0.53 to 0.82)	0.55 (0.20 to 1.44)	0.45 (0.22 to 0.70)	1.63 (0.33 to 6.06)	
			yes	6	0.54 (0.37 to 0.71)		0.56 (0.30 to 0.77)		
		Children	Consecutive/random sample	no	9	0.72 (0.53 to 0.86)	1.03 (0.27 to 3.90)	0.49 (0.35 to 0.63)	1.31 (0.47 to 3.36)
				yes	6	0.73 (0.49 to 0.88)		0.55 (0.36 to 0.72)	
			Blinding index tests	no	6	0.63 (0.38 to 0.81)	2.00 (0.64 to 8.29)	0.61 (0.46 to 0.75)	0.52 (0.20 to 1.12)
				yes	9	0.77 (0.61 to 0.89)		0.45 (0.32 to 0.57)	
	Mixed	All pts. received same ref. std.	no	17	0.71 (0.60 to 0.80)	1.34 (0.53 to 3.48)	0.53 (0.38 to 0.67)	0.67 (0.19 to 2.16)	
			yes	5	0.76 (0.59 to 0.88)		0.43 (0.20 to 0.69)		
		Pathology (100%)	no	17	0.71 (0.60 to 0.80)	1.34 (0.53 to 3.48)	0.53 (0.38 to 0.67)	0.67 (0.19 to 2.16)	
			yes	5	0.76 (0.59 to 0.88)		0.43 (0.20 to 0.69)		
		Consecutive/random sample	no	11	0.69 (0.56 to 0.80)	1.36 (0.61 to 3.26)	0.49 (0.31 to 0.67)	1.17 (0.37 to 3.19)	
			yes	11	0.75 (0.63 to 0.85)		0.53 (0.33 to 0.70)		
		Blinding index tests	no	7	0.78 (0.64 to 0.88)	0.62 (0.26 to 1.37)	0.49 (0.27 to 0.70)	1.09 (0.40 to 3.39)	
			yes	15	0.69 (0.58 to 0.78)		0.51 (0.36 to 0.67)		

Table 5. Meta-regression results for the impact of risk of bias items on the estimated test performance of clinical signs and symptoms for the diagnosis of acute appendicitis (continued)

Test	Population	Subgroup	N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity	Test
Fever	Adults	All pts. received same ref. std.	no	6	0.43 (0.19 to 0.71)	1.23 (0.28 to 5.13)	0.71 (0.47 to 0.87)	0.54 (0.14 to 2.03)
			yes	9	0.48 (0.26 to 0.70)		0.57 (0.35 to 0.76)	
		Pathology (100%)	no	6	0.43 (0.19 to 0.71)	1.23 (0.28 to 5.13)	0.71 (0.47 to 0.87)	0.54 (0.14 to 2.03)
			yes	9	0.48 (0.26 to 0.70)		0.57 (0.35 to 0.76)	
		Consecutive/random sample	no	7	0.44 (0.21 to 0.68)	1.21 (0.31 to 5.09)	0.69 (0.47 to 0.85)	0.61 (0.17 to 1.99)
			yes	8	0.48 (0.26 to 0.72)		0.58 (0.36 to 0.77)	
	Blinding index tests	no	9	0.43 (0.23 to 0.66)	1.32 (0.31 to 5.82)	0.65 (0.43 to 0.82)	0.86 (0.23 to 3.15)	
		yes	6	0.50 (0.24 to 0.77)		0.61 (0.35 to 0.82)		
	Children	Pre-specified positivity criteria	no	15	0.49 (0.37 to 0.61)	1.25 (0.53 to 3.05)	0.74 (0.67 to 0.79)	0.71 (0.41 to 1.25)
			yes	7	0.55 (0.38 to 0.71)		0.67 (0.56 to 0.76)	
		All pts. received same ref. std.	no	16	0.49 (0.38 to 0.61)	1.26 (0.57 to 2.87)	0.73 (0.66 to 0.78)	0.87 (0.47 to 1.67)
			yes	6	0.55 (0.38 to 0.72)		0.70 (0.58 to 0.80)	
		Pathology (100%)	no	17	0.51 (0.40 to 0.63)	1.00 (0.30 to 2.51)	0.73 (0.66 to 0.79)	0.77 (0.40 to 1.54)
			yes	5	0.51 (0.28 to 0.70)		0.68 (0.53 to 0.79)	
	Consecutive/random sample	no	14	0.44 (0.34 to 0.56)	2.08 (1.00 to 4.35)	0.71 (0.63 to 0.77)	1.20 (0.68 to 2.06)	
		yes	8	0.62 (0.48 to 0.75)		0.74 (0.64 to 0.82)		
	Blinding index tests	no	8	0.57 (0.42 to 0.72)	0.66 (0.29 to 1.43)	0.72 (0.62 to 0.80)	1.02 (0.55 to 1.79)	
		yes	14	0.47 (0.35 to 0.59)		0.72 (0.64 to 0.78)		

Table 5. Meta-regression results for the impact of risk of bias items on the estimated test performance of clinical signs and symptoms for the diagnosis of acute appendicitis (continued)

Test	Population	Subgroup	N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity	Test
Fever (continued)	Mixed	Pre-specified positivity criteria	no	24	0.52 (0.38 to 0.65)	0.83 (0.30 to 2.31)	0.68 (0.55 to 0.79)	2.12 (0.71 to 6.33)
			yes	8	0.47 (0.27 to 0.69)		0.82 (0.64 to 0.92)	
		Blinding ref. std. to index test results	no	27	0.49 (0.36 to 0.62)	1.62 (0.48 to 5.67)	0.73 (0.62 to 0.82)	0.54 (0.16 to 1.98)
			yes	5	0.61 (0.34 to 0.83)		0.60 (0.33 to 0.83)	
		All pts. received same ref. std.	no	23	0.55 (0.42 to 0.68)	0.53 (0.21 to 1.45)	0.68 (0.55 to 0.79)	1.72 (0.60 to 5.31)
			yes	9	0.39 (0.22 to 0.61)		0.79 (0.60 to 0.91)	
		All pts. included in the analysis	no	5	0.58 (0.31 to 0.80)	0.69 (0.23 to 2.30)	0.70 (0.43 to 0.89)	1.09 (0.29 to 3.69)
			yes	27	0.49 (0.37 to 0.62)		0.72 (0.60 to 0.81)	
		Pathology (100%)	no	24	0.58 (0.45 to 0.69)	0.32 (0.12 to 0.86)	0.68 (0.55 to 0.78)	1.95 (0.72 to 5.51)
			yes	8	0.31 (0.16 to 0.51)		0.80 (0.63 to 0.91)	
		Consecutive/random sample	no	13	0.55 (0.37 to 0.73)	0.73 (0.27 to 1.83)	0.71 (0.51 to 0.84)	1.06 (0.41 to 3.25)
			yes	19	0.48 (0.33 to 0.62)		0.72 (0.58 to 0.83)	
		Blinding index tests	no	13	0.55 (0.38 to 0.74)	0.74 (0.24 to 1.80)	0.68 (0.50 to 0.82)	1.27 (0.49 to 3.65)
			yes	19	0.47 (0.32 to 0.63)		0.73 (0.59 to 0.84)	
Guarding	Mixed	Pre-specified positivity criteria	no	13	0.59 (0.40 to 0.76)	2.01 (0.47 to 8.32)	0.73 (0.55 to 0.85)	0.50 (0.13 to 2.10)
			yes	5	0.74 (0.45 to 0.91)		0.58 (0.30 to 0.82)	
		All pts. received same ref. std.	no	13	0.59 (0.38 to 0.76)	1.99 (0.44 to 10.39)	0.71 (0.52 to 0.84)	0.76 (0.16 to 3.37)
			yes	5	0.74 (0.44 to 0.92)		0.65 (0.33 to 0.87)	
		Consecutive/random sample	no	9	0.64 (0.39 to 0.84)	0.95 (0.18 to 3.86)	0.72 (0.49 to 0.87)	0.69 (0.18 to 3.05)
			yes	9	0.63 (0.37 to 0.83)		0.65 (0.40 to 0.83)	

Table 5. Meta-regression results for the impact of risk of bias items on the estimated test performance of clinical signs and symptoms for the diagnosis of acute appendicitis (continued)

Test	Population	Subgroup	N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity	Test
		Blinding index tests	no	7	0.68 (0.43 to 0.88)	0.72 (0.16 to 2.43)	0.65 (0.39 to 0.84)	1.42 (0.37 to 5.19)
			yes	11	0.60 (0.38 to 0.79)		0.72 (0.51 to 0.86)	
Nausea	Mixed	Consecutive/random sample	no	6	0.74 (0.51 to 0.89)	0.63 (0.15 to 2.42)	0.36 (0.18 to 0.60)	2.71 (0.83 to 9.40)
			yes	8	0.65 (0.42 to 0.82)		0.61 (0.40 to 0.79)	
Nausea or vomiting	Children	Blinding index tests	no	5	0.76 (0.62 to 0.87)	0.95 (0.36 to 2.49)	0.57 (0.34 to 0.77)	0.56 (0.18 to 1.96)
			yes	5	0.76 (0.60 to 0.86)		0.43 (0.23 to 0.66)	
Pain migration	Adults	All pts. received same ref. std.	no	5	0.56 (0.39 to 0.72)	0.98 (0.38 to 2.36)	0.65 (0.41 to 0.83)	1.04 (0.29 to 4.17)
			yes	6	0.56 (0.40 to 0.70)		0.66 (0.43 to 0.83)	
		Pathology (100%)	no	5	0.56 (0.39 to 0.72)	0.98 (0.38 to 2.36)	0.65 (0.41 to 0.83)	1.04 (0.29 to 4.17)
			yes	6	0.56 (0.40 to 0.70)		0.66 (0.43 to 0.83)	
		Consecutive/random sample	no	6	0.60 (0.46 to 0.74)	0.70 (0.29 to 1.69)	0.62 (0.40 to 0.79)	1.40 (0.44 to 4.71)
			yes	5	0.52 (0.36 to 0.67)		0.70 (0.47 to 0.85)	
	Blinding index tests	no	6	0.58 (0.42 to 0.72)	0.88 (0.34 to 2.10)	0.60 (0.38 to 0.78)	1.76 (0.52 to 6.37)	
		yes	5	0.54 (0.38 to 0.70)		0.72 (0.50 to 0.87)		
	Children	Consecutive/random sample	no	10	0.51 (0.30 to 0.72)	2.13 (0.44 to 9.46)	0.75 (0.65 to 0.83)	0.87 (0.38 to 1.93)
			yes	5	0.69 (0.38 to 0.88)		0.72 (0.57 to 0.84)	
		Blinding index tests	no	6	0.63 (0.35 to 0.85)	0.67 (0.14 to 3.02)	0.74 (0.60 to 0.85)	1.01 (0.43 to 2.37)
			yes	9	0.54 (0.30 to 0.75)		0.74 (0.63 to 0.83)	
	Mixed	Blinding ref. std. to index test results	no	17	0.59 (0.46 to 0.72)	1.53 (0.52 to 4.51)	0.70 (0.59 to 0.79)	0.39 (0.15 to 1.02)
			yes	5	0.69 (0.46 to 0.85)		0.47 (0.29 to 0.68)	
Consecutive/random sample		no	15	0.62 (0.48 to 0.75)	0.95 (0.34 to 2.58)	0.61 (0.48 to 0.73)	1.67 (0.67 to 4.21)	

Table 5. Meta-regression results for the impact of risk of bias items on the estimated test performance of clinical signs and symptoms for the diagnosis of acute appendicitis (continued)

Test	Population	Subgroup	N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity	Test
			yes	7	0.61 (0.40 to 0.78)		0.73 (0.55 to 0.85)	
		Blinding index tests	no	7	0.70 (0.51 to 0.83)	0.59 (0.23 to 1.55)	0.72 (0.53 to 0.85)	0.61 (0.23 to 1.69)
			yes	15	0.58 (0.44 to 0.71)		0.61 (0.48 to 0.73)	
Psoas sign	Mixed	Consecutive/random sample	no	6	0.27 (0.11 to 0.52)	0.65 (0.14 to 2.80)	0.72 (0.29 to 0.94)	12.23 (0.93 to 163.99)
			yes	5	0.19 (0.07 to 0.45)		0.97 (0.79 to 1.00)	
		Blinding index tests	no	5	0.25 (0.09 to 0.54)	0.85 (0.17 to 5.01)	0.74 (0.26 to 0.96)	5.77 (0.26 to 77.32)
			yes	6	0.22 (0.09 to 0.48)		0.94 (0.67 to 0.99)	
Tenderness rebound	Adults	All pts. received same ref. std.	no	6	0.71 (0.47 to 0.86)	0.71 (0.20 to 2.72)	0.71 (0.46 to 0.88)	0.80 (0.19 to 3.73)
			yes	5	0.63 (0.38 to 0.83)		0.67 (0.38 to 0.87)	
		Pathology (100%)	no	6	0.71 (0.47 to 0.86)	0.71 (0.20 to 2.72)	0.71 (0.46 to 0.88)	0.80 (0.19 to 3.73)
			yes	5	0.63 (0.38 to 0.83)		0.67 (0.38 to 0.87)	
		Consecutive/random sample	no	6	0.75 (0.55 to 0.89)	0.42 (0.11 to 1.44)	0.49 (0.37 to 0.63)	6.02 (2.70 to 13.04)
			yes	5	0.56 (0.32 to 0.77)		0.85 (0.77 to 0.91)	
	Blinding index tests	no	6	0.75 (0.55 to 0.89)	0.42 (0.11 to 1.44)	0.49 (0.37 to 0.63)	6.02 (2.70 to 13.04)	
		yes	5	0.56 (0.32 to 0.77)		0.85 (0.77 to 0.91)		
	Mixed	Pre-specified positivity criteria	no	23	0.74 (0.63 to 0.83)	1.10 (0.36 to 3.34)	0.55 (0.42 to 0.68)	2.50 (0.82 to 7.58)
			yes	7	0.76 (0.54 to 0.90)		0.76 (0.53 to 0.89)	
		All pts. received same ref. std.	no	18	0.72 (0.59 to 0.83)	1.33 (0.48 to 3.35)	0.64 (0.48 to 0.77)	0.68 (0.29 to 1.98)
			yes	12	0.77 (0.62 to 0.88)		0.55 (0.37 to 0.73)	
Pathology (100%)		no	19	0.75 (0.63 to 0.84)	0.98 (0.42 to 2.27)	0.64 (0.49 to 0.76)	0.65 (0.26 to 1.67)	
		yes						

Table 5. Meta-regression results for the impact of risk of bias items on the estimated test performance of clinical signs and symptoms for the diagnosis of acute appendicitis (continued)

Test	Population	Subgroup	N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity	Test
			yes	11	0.74 (0.59 to 0.85)		0.54 (0.35 to 0.72)	
		Consecutive/random sample	no	15	0.70 (0.56 to 0.82)	1.50 (0.63 to 3.61)	0.67 (0.50 to 0.80)	0.53 (0.20 to 1.57)
			yes	15	0.78 (0.65 to 0.87)		0.52 (0.35 to 0.70)	
		Blinding index tests	no	14	0.80 (0.67 to 0.89)	0.58 (0.24 to 1.29)	0.58 (0.40 to 0.73)	1.22 (0.51 to 3.28)
			yes	16	0.69 (0.55 to 0.80)		0.63 (0.46 to 0.77)	
Tenderness rectal	Mixed	All pts. received same ref. std.	no	10	0.27 (0.15 to 0.43)	2.40 (0.71 to 8.85)	0.64 (0.36 to 0.85)	0.66 (0.09 to 3.83)
			yes	5	0.47 (0.24 to 0.71)		0.54 (0.18 to 0.85)	
		Pathology (100%)	no	10	0.27 (0.15 to 0.43)	2.40 (0.71 to 8.85)	0.64 (0.36 to 0.85)	0.66 (0.09 to 3.83)
			yes	5	0.47 (0.24 to 0.71)		0.54 (0.18 to 0.85)	
		Consecutive/random sample	no	9	0.35 (0.19 to 0.53)	0.87 (0.27 to 3.16)	0.56 (0.24 to 0.81)	1.60 (0.28 to 14.89)
			yes	6	0.32 (0.15 to 0.55)		0.68 (0.32 to 0.92)	
		Blinding index tests	no	6	0.34 (0.14 to 0.58)	0.95 (0.26 to 4.10)	0.47 (0.18 to 0.78)	2.52 (0.44 to 13.59)
			yes	9	0.33 (0.18 to 0.55)		0.69 (0.40 to 0.88)	

Table 5. Meta-regression results for the impact of risk of bias items on the estimated test performance of clinical signs and symptoms for the diagnosis of acute appendicitis (continued)

Test	Population	Subgroup	N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity	Test
Tenderness RLQ	Children	Consecutive/random sample	no	6	0.96 (0.85 to 0.99)	0.29 (0.03 to 1.41)	0.26 (0.05 to 0.71)	6.25 (0.52 to 71.67)
			yes	8	0.87 (0.64 to 0.96)		0.69 (0.29 to 0.92)	
		Blinding index tests	no	5	0.81 (0.50 to 0.95)	4.62 (0.65 to 26.22)	0.67 (0.20 to 0.94)	0.33 (0.03 to 3.96)
			yes	9	0.95 (0.86 to 0.99)		0.40 (0.12 to 0.77)	
	Mixed	Blinding index tests	no	5	0.93 (0.66 to 0.99)	0.79 (0.07 to 9.17)	0.14 (0.03 to 0.37)	1.13 (0.24 to 11.50)
			yes	6	0.91 (0.66 to 0.98)		0.16 (0.05 to 0.42)	

N = number; pts. = patients; ref. std. = reference standard; RLQ = right lower quadrant; RUQ = right upper quadrant
Sensitivity, relative sensitivity, specificity, and relative specificity values are medians and 95% central credible intervals when 5 or more studies were available; medians and minimum to maximum values are reported when <5 studies were available; when a single study was available we report the estimate from that study.

Test Performance of Laboratory Tests

Two hundred and seventeen studies, published between 1956 and 2014, provided information on the test performance of laboratory tests for the diagnosis of acute appendicitis. Commonly evaluated tests included the white blood cell count, measures based on the blood count and differential, and serum C-reactive protein concentration. Table 6 presents a summary of the descriptive characteristics of the studies reporting information on laboratory tests. Table 7 presents a summary of key items related to study risk of bias. Studies were at moderate to high risk of bias. Blinding of the reference standard assessors was either not used or relevant information was not reported; a large proportion of studies had differential verification. Table 8 presents a summary of the test performance results for clinical symptoms and signs. In general, the performance of individual laboratory tests was rather poor; however, it was better than that of clinical symptoms and signs. Almost all laboratory tests had positive likelihood ratios lower than 3 (no test had a summary positive likelihood ratio higher than 5) and most tests had negative likelihood ratios higher than 0.2. Figure 5 presents study results and summary ROC curves for selected laboratory tests. There was substantial heterogeneity in sensitivity and specificity for most tests; however, in most cases summary ROC lines appeared to fit the data relatively well. Figure 6 shows the positive and negative predictive value for selected laboratory tests, over appendicitis prevalence.

Table 6. Descriptive characteristics for studies evaluating laboratory tests for the diagnosis of acute appendicitis

Patient Population	N studies (Median N Patients/Affected/ Unaffected)	Median % of Women	Median of Average Age (Yrs)	Community Setting	Ambulatory Setting	Surgical Cohorts	Clinical Presentation Consistent With Appendicitis	Median % of Patients With Perforation
Adults	38 (134/73/29)	44.2%	29.4	10.5%	21.1%	52.6%	92.1%	11.9%
Children	55 (169/90.5/52.5)	44.4%	10.4	7.3%	25.5%	23.6%	94.5%	14.2%
Children <5yrs	1 (90/41/49)	41.1%	3.8	0.0%	0.0%	100.0%	100.0%	17.8%
Elderly	3 (85/77/10)	27.2%	55.1	0.0%	0.0%	100.0%	100.0%	38.9%
Women of reproductive age	4 (72/45.5/18.5)	100.0%	24.0	25.0%	0.0%	50.0%	100.0%	NR
Pregnant women	7 (39/29/9)	100.0%	24.5	14.3%	0.0%	85.7%	100.0%	12.0%
Mixed	123 (168/95/58.5)	50.6%	27.0	7.3%	17.9%	42.3%	93.5%	10.0%

N = number; NA = not applicable; NR = not reported; yrs = years

Table 7. Assessment of risk of bias for studies evaluating laboratory tests for the diagnosis of acute appendicitis

Patient Population	Consecutive or Random Sample of Patients	Study Avoided Inappropriate Exclusions	Index Test Results Interpreted Without Knowledge of Ref. Std.	Were the Positivity Criteria Prespecified?	Ref. Std. Results Interpreted Without Knowledge of Index Test	All Patients Received a Ref. Std.	All Patients Received the Same Ref. Std.	All Patients Received Pathology for Ref. Std.	All Patients Included in the Analysis
Adults	63.2%	100.0	42.1%	34.2%	7.9%	94.7%	68.4%	68.4%	73.7%
Children	50.9%	100.0	47.3%	45.5%	9.1%	90.9%	40.0%	41.8%	81.8%
Children <5yrs	100.0%	100.0	0.0%	0.0%	0.0%	100.0%	100.0%	100.0%	100.0%
Elderly	100.0%	100.0	66.7%	66.7%	0.0%	100.0%	100.0%	100.0%	33.3%
Women of reproductive age	75.0%	100.0	0.0%	25.0%	25.0%	100.0%	75.0%	75.0%	100.0%
Pregnant women	71.4%	100.0	42.9%	14.3%	0.0%	100.0%	100.0%	100.0%	100.0%
Mixed	56.9%	100.0	44.7%	41.5%	12.2%	93.5%	49.6%	48.0%	70.7%

ref. std. = reference standard; yrs = years

Table 8. Summary estimates of test performance of laboratory tests for the diagnosis of acute appendicitis

Test	Population	N Studies [Affected/Unaffected]	Sensitivity	Specificity	LR+	LR-
CRP	Adults	15 [1541/983]	0.84 (0.73 to 0.92)	0.67 (0.50 to 0.81)	2.53 (1.59 to 4.62)	0.23 (0.11 to 0.46)
	Children	22 [2226/1635]	0.73 (0.66 to 0.80)	0.72 (0.61 to 0.81)	2.62 (1.91 to 3.81)	0.37 (0.28 to 0.48)
	Elderly	2 [213/72]	0.91 (0.91 to 0.92)	0.21 (0.17 to 0.25)	1.16 (1.11 to 1.21)	0.42 (0.36 to 0.47)
	Women of reproductive age	3 [169/133]	0.79 (0.44 to 0.97)	0.70 (0.33 to 0.93)	1.44 (1.19 to 13.64)	0.62 (0.03 to 0.81)
	Pregnant women	1 [31/8]	0.68	0.50	1.35	0.65
	Mixed	52 [8742/5903]	0.79 (0.74 to 0.83)	0.65 (0.57 to 0.72)	2.23 (1.78 to 2.86)	0.33 (0.25 to 0.42)
ESR	Children	2 [121/88]	0.40 (0.39 to 0.41)	0.87 (0.85 to 0.90)	3.27 (2.72 to 3.82)	0.69 (0.68 to 0.70)
	Mixed	5 [565/466]	0.30 (0.20 to 0.43)	0.79 (0.60 to 0.90)	1.41 (0.73 to 2.89)	0.89 (0.73 to 1.15)
IL-6	Adults	2 [113/66]	0.59 (0.33 to 0.84)	0.65 (0.46 to 0.83)	1.74 (1.57 to 1.92)	0.57 (0.34 to 0.81)
	Children	6 [319/467]	0.90 (0.63 to 0.98)	0.85 (0.54 to 0.98)	5.99 (1.89 to 34.09)	0.12 (0.02 to 0.46)
	Mixed	4 [306/87]	0.73 (0.46 to 0.84)	0.63 (0.31 to 1.00)	1.58 (0.96 to 3.58)	0.48 (0.21 to 1.10)
Left shift	Adults	1 [243/15]	0.76	0.13	0.87	1.82
	Children	4 [270/420]	0.75 (0.60 to 0.88)	0.65 (0.22 to 0.90)	2.21 (1.13 to 5.92)	0.49 (0.26 to 0.53)
	Mixed	5 [1105/496]	0.77 (0.37 to 0.95)	0.64 (0.29 to 0.87)	2.05 (1.02 to 4.73)	0.38 (0.10 to 0.98)
Neutrophil%	Adults	5 [831/328]	0.79 (0.60 to 0.90)	0.59 (0.40 to 0.76)	1.90 (1.21 to 3.26)	0.36 (0.17 to 0.76)
	Children	6 [833/584]	0.78 (0.47 to 0.93)	0.70 (0.55 to 0.81)	2.52 (1.34 to 4.24)	0.32 (0.10 to 0.80)
	Elderly	1 [77/8]	0.88	0.25	1.18	0.47
	Mixed	15 [3328/1558]	0.80 (0.71 to 0.87)	0.61 (0.50 to 0.72)	2.06 (1.59 to 2.83)	0.33 (0.22 to 0.48)
PMNC count	Children	3 [863/697]	0.83 (0.81 to 0.96)	0.64 (0.56 to 0.72)	2.33 (2.20 to 2.90)	0.26 (0.06 to 0.26)
	Mixed	6 [1429/634]	0.85 (0.69 to 0.95)	0.71 (0.60 to 0.79)	2.91 (2.11 to 3.85)	0.21 (0.07 to 0.43)
WBC	Adults	26 [4070/2452]	0.81 (0.74 to 0.87)	0.54 (0.42 to 0.64)	1.74 (1.40 to 2.27)	0.35 (0.24 to 0.51)
	Children	41 [6595/4473]	0.80 (0.73 to 0.85)	0.65 (0.56 to 0.73)	2.29 (1.87 to 2.90)	0.31 (0.23 to 0.40)
	Elderly	3 [287/82]	0.71 (0.69 to 0.77)	0.50 (0.38 to 0.70)	1.54 (1.14 to 2.30)	0.46 (0.44 to 0.76)
	Women of reproductive age	2 [49/18]	0.64 (0.60 to 0.69)	0.67 (0.67 to 0.67)	1.93 (1.80 to 2.07)	0.53 (0.47 to 0.60)
	Pregnant women	6 [197/82]	0.63 (0.21 to 0.92)	0.75 (0.38 to 0.95)	2.41 (0.64 to 12.27)	0.51 (0.11 to 1.34)
	Mixed	84 [19074/10883]	0.78 (0.75 to 0.82)	0.62 (0.58 to 0.66)	2.07 (1.88 to 2.30)	0.35 (0.30 to 0.41)

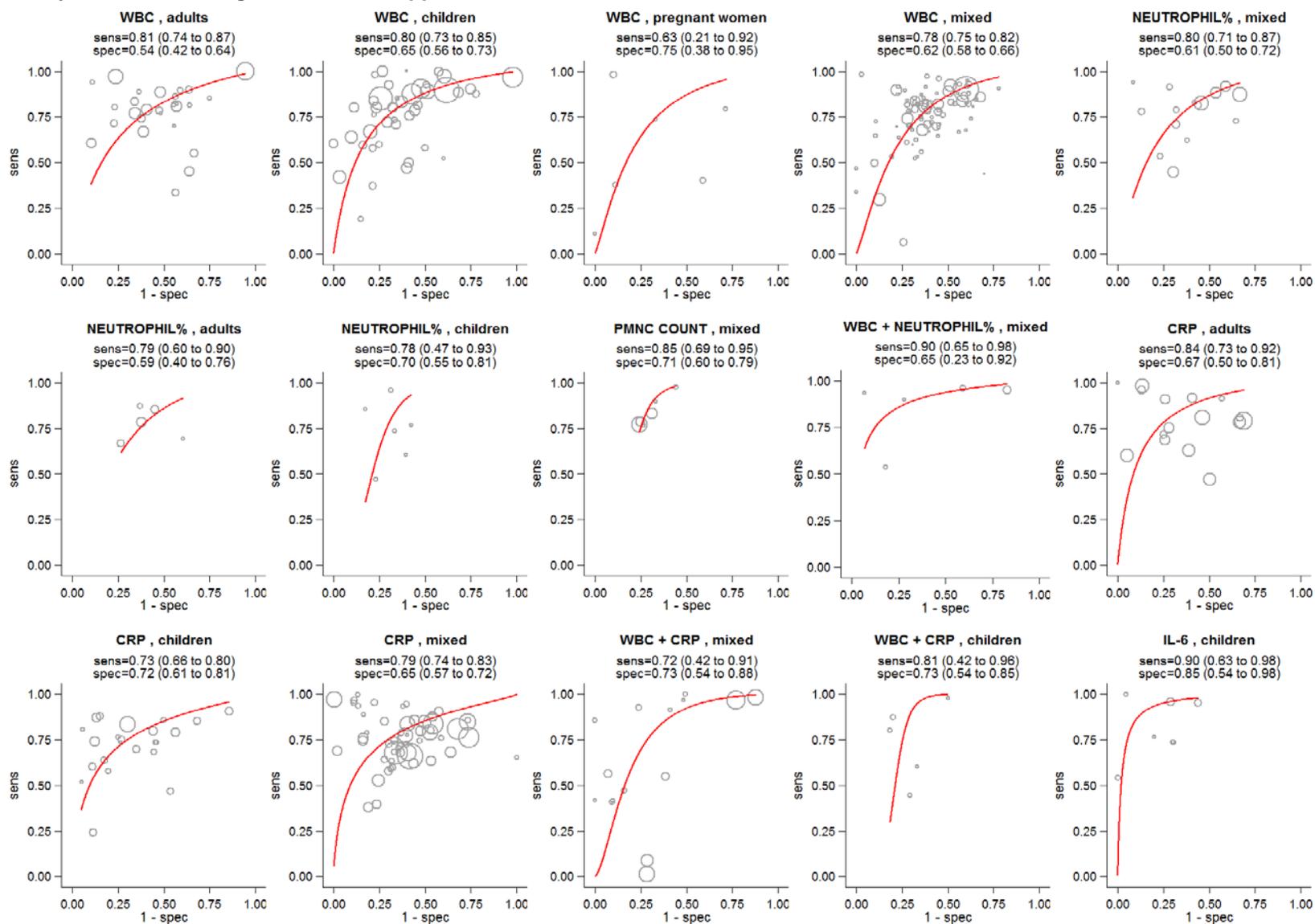
Table 8. Summary estimates of test performance of laboratory tests for the diagnosis of acute appendicitis (continued)

Test	Population	N Studies [Affected/Unaffected]	Sensitivity	Specificity	LR+	LR-
WBC + CRP	Adults	2 [194/68]	0.93 (0.86 to 1.00)	0.62 (0.37 to 0.86)	4.35 (1.37 to 7.33)	0.18 (0.00 to 0.37)
	Children	5 [566/132]	0.81 (0.42 to 0.96)	0.73 (0.54 to 0.85)	2.88 (1.35 to 5.51)	0.27 (0.05 to 0.82)
	Elderly	1 [77/8]	0.96	0.13	1.10	0.31
	Women of reproductive age	1 [29/9]	0.93	0.44	1.68	0.16
	Mixed	15 [4145/1734]	0.72 (0.42 to 0.91)	0.73 (0.54 to 0.88)	2.62 (1.48 to 5.49)	0.38 (0.14 to 0.77)
WBC + Neutrophil%	Adults	1 [438/102]	0.68	0.75	2.78	0.42
	Children	1 [212/48]	0.71	0.71	2.44	0.41
	Elderly	1 [77/8]	0.92	0.25	1.23	0.31
	Mixed	5 [1572/437]	0.90 (0.65 to 0.98)	0.65 (0.23 to 0.92)	2.54 (1.14 to 10.88)	0.16 (0.04 to 0.65)

CRP = c-reactive protein; ESR = erythrocyte sedimentation rate; IL-6 = interleukin 6; LR = likelihood ratio; N = number; PMNC = polymorphonuclear count; WBC = white blood cell count

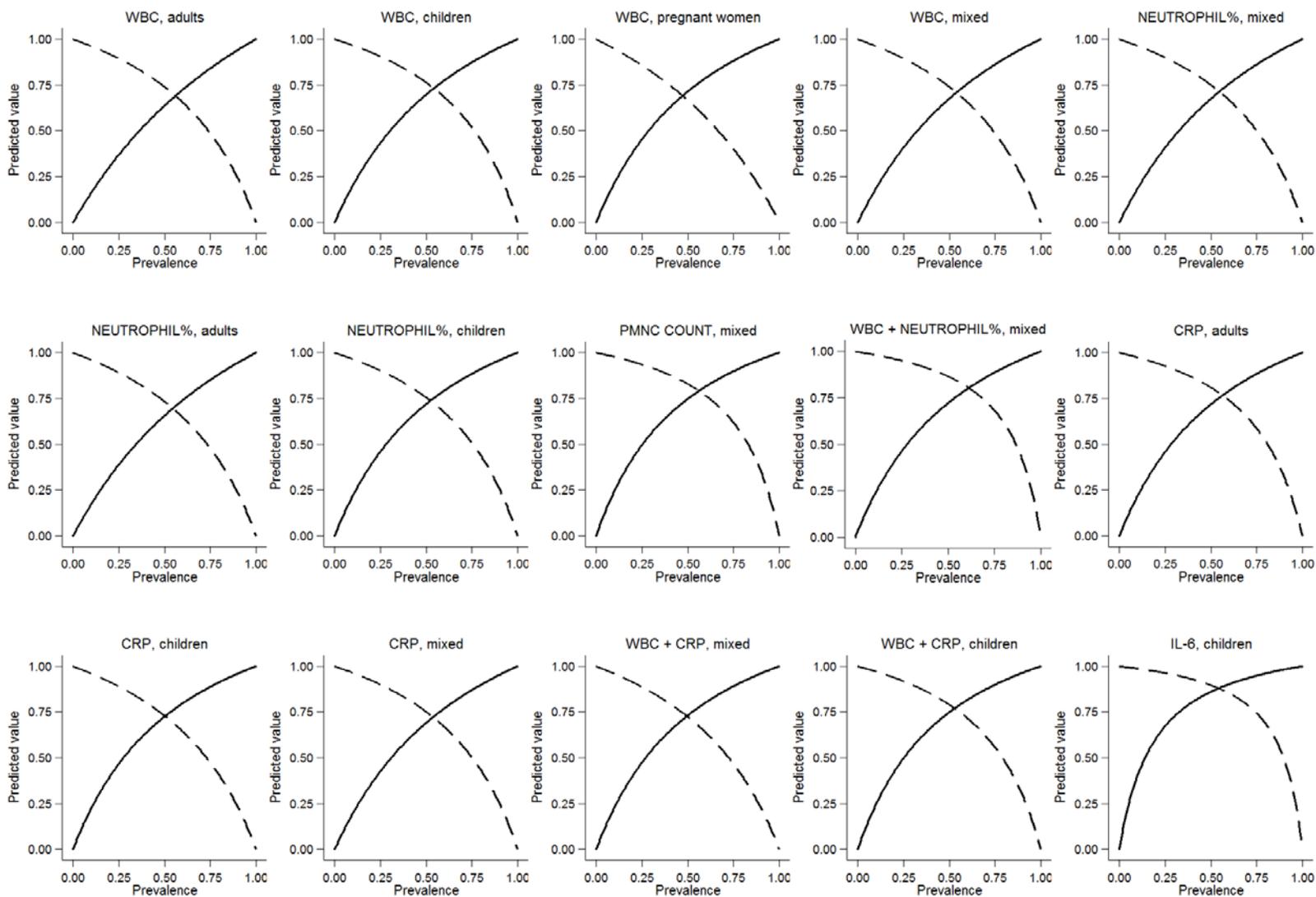
Sensitivity, specificity, and LR values are medians and 95% central credible intervals when 5 or more studies were available; medians and minimum to maximum values are reported when <5 studies were available; when a single study was available we report the estimate from that study.

Figure 5. Scatterplot of results in the receiver operating characteristic space and summary receiver operating characteristic curves of laboratory tests for the diagnosis of acute appendicitis



CRP = c-reactive protein; IL-6 = interleukin 6; PMNC = polymorphonuclear count; WBC = white blood cell count; sens.=sensitivity; spec.=specificity

Figure 6. Positive predictive value and negative predictive value curves of laboratory tests for the diagnosis of acute appendicitis



CRP = c-reactive protein; IL-6 = interleukin 6; PMNC = polymorphonuclear count; WBC = white blood cell count

Factors That Affect the Test Performance of Laboratory Tests

Table 9 summarizes the results of meta-regression analyses for various factors that may affect the performance of laboratory tests for the diagnosis of acute appendicitis. The vast majority of studies did not report adequate data to assess factors that may affect test performance (i.e., based on within study comparisons); for this reason we relied on comparisons across studies (via meta-regression analyses) to identify factors that may affect test performance. Overall, no distinct pattern emerged to establish a particular factor as a modifier of test performance. For all factors examined but CrIs were wide, indicating substantial uncertainty regarding the relative test performance of tests over levels of the modifiers we examined.

Impact of Study Risk of Bias Items on Estimated Test Performance

Table 10 summarizes the results of meta-regression analyses for various factors that may affect the performance of laboratory tests for the diagnosis of acute appendicitis. We only observed a single case where the 95% CrIs for a risk of bias item did not include the null value: studies of white blood cell count that had complete verification of index test results had lower specificity than studies with incomplete verification; these results were rather imprecise (i.e., CrIs were wide). More generally, these results should not be taken to mean that there is no potential for bias in studies of laboratory tests. Our analyses relied on information that was often poorly reported in the primary studies and meta-regression results were often imprecise, indicating substantial uncertainty. Because each risk of bias item was examined individually, and because different items may be correlated between them and with other study characteristics that may affect performance estimates, we do not believe that definitive conclusions about specific items can be reached.

Table 9. Meta-regression results for factors that affect the performance of laboratory tests for the diagnosis of acute appendicitis

Test	Population	Subgroup		N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity
CRP	Adults	Study year	<2005	6	0.82 (0.60 to 0.94)	1.37 (0.31 to 6.02)	0.65 (0.37 to 0.86)	1.14 (0.23 to 5.11)
			>=2005	9	0.86 (0.71 to 0.95)		0.68 (0.45 to 0.86)	
		Ambulatory setting	no	10	0.85 (0.70 to 0.94)	0.84 (0.18 to 4.74)	0.64 (0.42 to 0.82)	1.43 (0.34 to 7.16)
			yes	5	0.83 (0.58 to 0.96)		0.72 (0.44 to 0.91)	
		Surgical cohorts	no	9	0.86 (0.70 to 0.95)	0.82 (0.16 to 3.77)	0.63 (0.41 to 0.82)	1.58 (0.32 to 6.60)
			yes	6	0.83 (0.61 to 0.94)		0.72 (0.44 to 0.90)	
	Children	Study year	<2005	7	0.70 (0.54 to 0.81)	1.32 (0.61 to 3.10)	0.71 (0.51 to 0.86)	1.11 (0.34 to 3.01)
			>=2005	15	0.75 (0.66 to 0.83)		0.73 (0.58 to 0.83)	
		Surgical cohorts	no	13	0.76 (0.67 to 0.84)	0.69 (0.30 to 1.45)	0.77 (0.64 to 0.86)	0.52 (0.20 to 1.43)
			yes	9	0.69 (0.55 to 0.80)		0.63 (0.44 to 0.79)	
	Mixed	Study year	<2005	27	0.80 (0.74 to 0.85)	0.88 (0.51 to 1.43)	0.62 (0.51 to 0.72)	1.25 (0.65 to 2.53)
			>=2005	25	0.78 (0.71 to 0.83)		0.67 (0.56 to 0.77)	
		Ambulatory setting	no	45	0.78 (0.73 to 0.83)	1.20 (0.55 to 2.57)	0.61 (0.53 to 0.69)	2.90 (1.17 to 6.91)
			yes	7	0.81 (0.68 to 0.90)		0.82 (0.66 to 0.91)	
Surgical cohorts		no	27	0.78 (0.71 to 0.84)	1.13 (0.65 to 1.96)	0.66 (0.54 to 0.75)	0.91 (0.45 to 1.83)	
		yes	25	0.80 (0.73 to 0.85)		0.64 (0.51 to 0.75)		
Neutrophil %	Mixed	Study year	<2005	9	0.83 (0.74 to 0.90)	0.76 (0.30 to 1.85)	0.63 (0.47 to 0.77)	0.79 (0.28 to 2.30)
			>=2005	5	0.79 (0.64 to 0.89)		0.57 (0.37 to 0.77)	
		Surgical cohorts	no	6	0.84 (0.73 to 0.92)	0.74 (0.28 to 1.79)	0.70 (0.55 to 0.82)	0.47 (0.19 to 1.11)
			yes	8	0.80 (0.68 to 0.88)		0.52 (0.38 to 0.67)	

Table 9. Meta-regression results for factors that affect the performance of laboratory tests for the diagnosis of acute appendicitis (continued)

Test	Population	Subgroup	N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity	
WBC	Adults	Study year	<2005	15	0.85 (0.76 to 0.91)	0.56 (0.23 to 1.32)	0.47 (0.34 to 0.62)	1.78 (0.73 to 4.16)
			>=2005	11	0.76 (0.62 to 0.86)		0.62 (0.45 to 0.76)	
		Ambulatory setting	no	19	0.82 (0.74 to 0.88)	0.81 (0.31 to 2.30)	0.54 (0.41 to 0.66)	0.96 (0.36 to 2.53)
			yes	7	0.79 (0.62 to 0.90)		0.53 (0.33 to 0.72)	
		Surgical cohorts	no	14	0.81 (0.70 to 0.89)	1.02 (0.40 to 2.55)	0.56 (0.42 to 0.70)	0.77 (0.31 to 1.81)
			yes	12	0.81 (0.70 to 0.89)		0.50 (0.34 to 0.66)	
	Children	Study year	<2005	15	0.73 (0.60 to 0.82)	1.88 (1.01 to 3.77)	0.75 (0.63 to 0.85)	0.46 (0.22 to 0.95)
			>=2005	26	0.84 (0.77 to 0.89)		0.58 (0.47 to 0.69)	
		Ambulatory setting	no	31	0.80 (0.72 to 0.86)	0.94 (0.38 to 2.24)	0.65 (0.54 to 0.75)	1.01 (0.41 to 2.67)
			yes	10	0.79 (0.64 to 0.89)		0.65 (0.47 to 0.81)	
		Surgical cohorts	no	31	0.82 (0.74 to 0.87)	0.68 (0.29 to 1.64)	0.67 (0.56 to 0.75)	0.73 (0.30 to 1.82)
			yes	10	0.75 (0.59 to 0.86)		0.59 (0.40 to 0.76)	
	Mixed	Study year	<2005	49	0.80 (0.75 to 0.84)	0.80 (0.53 to 1.18)	0.60 (0.54 to 0.65)	1.31 (0.94 to 1.84)
			>=2005	35	0.76 (0.70 to 0.81)		0.66 (0.60 to 0.72)	
		Community setting	no	78	0.78 (0.74 to 0.82)	0.93 (0.42 to 2.10)	0.62 (0.58 to 0.67)	0.89 (0.45 to 1.76)
			Yes	6	0.77 (0.61 to 0.88)		0.60 (0.43 to 0.74)	
		Ambulatory setting	No	66	0.78 (0.74 to 0.82)	1.11 (0.67 to 1.85)	0.63 (0.58 to 0.67)	0.89 (0.58 to 1.36)
			yes	18	0.80 (0.71 to 0.86)		0.60 (0.51 to 0.69)	
		Surgical cohorts	No	50	0.80 (0.75 to 0.84)	0.79 (0.53 to 1.22)	0.62 (0.57 to 0.67)	1.04 (0.73 to 1.46)
			yes	34	0.76 (0.70 to 0.81)		0.63 (0.56 to 0.69)	
		Appendicitis presentation	atypical/other/unclear	7	0.83 (0.69 to 0.90)	0.72 (0.38 to 1.65)	0.55 (0.41 to 0.70)	1.36 (0.72 to 2.52)
typical			77	0.78 (0.74 to 0.81)		0.63 (0.59 to 0.67)		

CRP = c-reactive protein; N = number; WBC = white blood cell count

Sensitivity, relative sensitivity, specificity, and relative specificity values are medians and 95% central credible intervals when 5 or more studies were available; medians and minimum to maximum values are reported when <5 studies were available; when a single study was available we report the estimate from that study.

Table 10. Meta-regression results for the impact of risk of bias items on the estimated test performance of laboratory tests for the diagnosis of acute appendicitis

Test	Population	Subgroup		N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity
CRP	Adults	Pre-specified positivity criteria	no	10	0.83 (0.68 to 0.93)	1.41 (0.28 to 5.80)	0.74 (0.56 to 0.87)	0.39 (0.10 to 1.39)
			yes	5	0.87 (0.66 to 0.96)		0.52 (0.26 to 0.77)	
		All pts. received same ref. std.	no	6	0.87 (0.67 to 0.96)	0.75 (0.18 to 3.36)	0.75 (0.51 to 0.91)	0.52 (0.12 to 1.96)
			yes	9	0.83 (0.66 to 0.93)		0.61 (0.39 to 0.80)	
		Pathology (100%)	no	6	0.87 (0.67 to 0.96)	0.75 (0.18 to 3.36)	0.75 (0.51 to 0.91)	0.52 (0.12 to 1.96)
			yes	9	0.83 (0.66 to 0.93)		0.61 (0.39 to 0.80)	
		Blinding index tests	no	10	0.86 (0.72 to 0.94)	0.75 (0.16 to 3.02)	0.74 (0.58 to 0.87)	0.28 (0.07 to 1.01)
			yes	5	0.82 (0.57 to 0.94)		0.45 (0.22 to 0.72)	
	Children	Pre-specified positivity criteria	no	9	0.78 (0.67 to 0.87)	0.65 (0.31 to 1.37)	0.66 (0.47 to 0.80)	1.64 (0.65 to 4.13)
			yes	13	0.70 (0.59 to 0.79)		0.76 (0.63 to 0.85)	
		All pts. received same ref. std.	no	8	0.75 (0.60 to 0.85)	0.89 (0.42 to 2.27)	0.82 (0.68 to 0.92)	0.41 (0.13 to 1.03)
			yes	14	0.73 (0.63 to 0.82)		0.65 (0.50 to 0.77)	
		All pts. included in the analysis	no	6	0.78 (0.62 to 0.88)	0.71 (0.30 to 1.90)	0.66 (0.42 to 0.83)	1.47 (0.54 to 4.59)
			yes	16	0.72 (0.62 to 0.80)		0.74 (0.62 to 0.84)	
		Pathology (100%)	no	8	0.75 (0.60 to 0.85)	0.89 (0.42 to 2.27)	0.82 (0.68 to 0.92)	0.41 (0.13 to 1.03)
			yes	14	0.73 (0.63 to 0.82)		0.65 (0.50 to 0.77)	
		Consecutive/random sample	no	7	0.75 (0.59 to 0.86)	0.89 (0.39 to 2.22)	0.77 (0.57 to 0.90)	0.68 (0.22 to 2.13)
			yes	15	0.73 (0.63 to 0.82)		0.70 (0.56 to 0.81)	
Blinding index tests	no	14	0.77 (0.67 to 0.84)	0.63 (0.30 to 1.40)	0.71 (0.57 to 0.82)	1.10 (0.40 to 3.14)		
	yes	8	0.67 (0.54 to 0.79)		0.73 (0.55 to 0.87)			

Table 10. Meta-regression results for the impact of risk of bias items on the estimated test performance of laboratory tests for the diagnosis of acute appendicitis (continued)

Test	Population	Subgroup		N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity
CRP (continued)	Mixed	Pre-specified positivity criteria	no	30	0.80 (0.75 to 0.85)	0.80 (0.47 to 1.31)	0.65 (0.55 to 0.75)	0.95 (0.48 to 1.89)
			yes	22	0.76 (0.69 to 0.83)		0.64 (0.51 to 0.75)	
		Blinding ref. std. to index test results	no	46	0.77 (0.72 to 0.81)	2.75 (1.28 to 6.28)	0.64 (0.55 to 0.72)	1.48 (0.52 to 3.97)
			yes	6	0.90 (0.82 to 0.95)		0.72 (0.49 to 0.87)	
		All pts. received same ref. std.	no	24	0.79 (0.72 to 0.85)	0.96 (0.57 to 1.60)	0.65 (0.53 to 0.75)	0.99 (0.51 to 2.11)
			yes	28	0.78 (0.72 to 0.84)		0.65 (0.53 to 0.75)	
		All pts. included in the analysis	no	18	0.78 (0.70 to 0.85)	1.05 (0.60 to 1.75)	0.61 (0.48 to 0.74)	1.31 (0.60 to 2.46)
			yes	34	0.79 (0.73 to 0.84)		0.67 (0.57 to 0.75)	
		Pathology (100%)	no	24	0.79 (0.72 to 0.85)	0.96 (0.57 to 1.60)	0.65 (0.53 to 0.75)	0.99 (0.51 to 2.11)
			yes	28	0.78 (0.72 to 0.84)		0.65 (0.53 to 0.75)	
		Consecutive/random sample	no	21	0.83 (0.77 to 0.88)	0.63 (0.38 to 1.02)	0.71 (0.60 to 0.81)	0.59 (0.31 to 1.11)
			yes	31	0.75 (0.69 to 0.81)		0.60 (0.49 to 0.69)	
		Blinding index tests	no	31	0.75 (0.69 to 0.81)	1.71 (1.03 to 2.78)	0.61 (0.50 to 0.70)	1.55 (0.76 to 3.10)
			yes	21	0.84 (0.78 to 0.88)		0.70 (0.58 to 0.80)	
Neutrophil %	Mixed	All pts. received same ref. std.	no	5	0.82 (0.69 to 0.91)	0.95 (0.33 to 2.30)	0.68 (0.49 to 0.83)	0.59 (0.21 to 1.63)
			yes	9	0.81 (0.70 to 0.89)		0.56 (0.41 to 0.71)	
		All pts. included in the analysis	no	6	0.79 (0.65 to 0.88)	1.34 (0.53 to 3.27)	0.60 (0.39 to 0.78)	1.11 (0.36 to 3.23)
			yes	8	0.83 (0.73 to 0.90)		0.62 (0.44 to 0.78)	
		Pathology (100%)	no	5	0.82 (0.69 to 0.91)	0.95 (0.33 to 2.30)	0.68 (0.49 to 0.83)	0.59 (0.21 to 1.63)
			yes	9	0.81 (0.70 to 0.89)		0.56 (0.41 to 0.71)	
		Consecutive/random sample	no	6	0.81 (0.68 to 0.89)	1.07 (0.43 to 2.76)	0.49 (0.33 to 0.66)	2.31 (0.93 to 5.86)
			yes	8	0.82 (0.71 to 0.90)		0.69 (0.55 to 0.81)	
		Blinding index tests	no	8	0.83 (0.72 to 0.90)	0.86 (0.33 to 2.09)	0.60 (0.44 to 0.76)	1.07 (0.35 to 2.97)
			yes	6	0.80 (0.66 to 0.89)		0.62 (0.42 to 0.79)	

Table 10. Meta-regression results for the impact of risk of bias items on the estimated test performance of laboratory tests for the diagnosis of acute appendicitis (continued)

Test	Population	Subgroup		N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity	
WBC	Adults	Pre-specified positivity criteria	no	16	0.79 (0.69 to 0.87)	1.37 (0.58 to 3.18)	0.46 (0.33 to 0.59)	2.22 (1.01 to 5.08)	
			yes	10	0.84 (0.73 to 0.91)		0.65 (0.49 to 0.78)		
		All pts. received same ref. std.	no	10	0.82 (0.70 to 0.91)	0.99 (0.36 to 2.11)	0.58 (0.41 to 0.75)	0.71 (0.26 to 1.75)	
			yes	16	0.81 (0.71 to 0.88)		0.50 (0.35 to 0.64)		
		All pts. included in the analysis	no	7	0.85 (0.71 to 0.93)	0.73 (0.27 to 1.96)	0.67 (0.49 to 0.82)	0.45 (0.18 to 1.09)	
			yes	19	0.80 (0.71 to 0.87)		0.48 (0.36 to 0.60)		
		Pathology (100%)	no	10	0.82 (0.70 to 0.91)	0.99 (0.36 to 2.11)	0.58 (0.41 to 0.75)	0.71 (0.26 to 1.75)	
			yes	16	0.81 (0.71 to 0.88)		0.50 (0.35 to 0.64)		
		Consecutive/random sample	no	10	0.75 (0.58 to 0.85)	1.90 (0.80 to 5.04)	0.56 (0.39 to 0.72)	0.85 (0.34 to 2.01)	
			yes	16	0.85 (0.77 to 0.91)		0.52 (0.38 to 0.65)		
		Blinding index tests	no	15	0.80 (0.70 to 0.88)	1.25 (0.53 to 2.94)	0.55 (0.40 to 0.69)	0.88 (0.35 to 2.15)	
			yes	11	0.83 (0.72 to 0.91)		0.52 (0.34 to 0.68)		
		Children	Pre-specified positivity criteria	no	21	0.85 (0.78 to 0.90)	0.47 (0.23 to 0.95)	0.56 (0.43 to 0.67)	2.32 (1.15 to 4.80)
				yes	20	0.73 (0.62 to 0.82)		0.74 (0.63 to 0.83)	
	All pts. received same ref. std.		no	25	0.81 (0.72 to 0.88)	0.82 (0.34 to 1.89)	0.69 (0.58 to 0.78)	0.60 (0.27 to 1.36)	
			yes	16	0.78 (0.65 to 0.87)		0.57 (0.42 to 0.72)		
	All pts. included in the analysis		no	8	0.76 (0.58 to 0.87)	1.34 (0.58 to 3.39)	0.67 (0.47 to 0.83)	0.90 (0.33 to 2.19)	
			yes	33	0.81 (0.74 to 0.87)		0.65 (0.54 to 0.74)		
	Pathology (100%)		no	25	0.81 (0.72 to 0.88)	0.82 (0.34 to 1.89)	0.69 (0.58 to 0.78)	0.60 (0.27 to 1.36)	
			yes	16	0.78 (0.65 to 0.87)		0.57 (0.42 to 0.72)		
	Consecutive/random sample		no	20	0.83 (0.74 to 0.89)	0.67 (0.33 to 1.48)	0.61 (0.48 to 0.73)	1.38 (0.66 to 2.86)	
			yes	21	0.77 (0.66 to 0.85)		0.69 (0.56 to 0.79)		
	Blinding index tests		no	22	0.79 (0.69 to 0.86)	1.17 (0.52 to 2.55)	0.66 (0.53 to 0.77)	0.97 (0.43 to 2.16)	
			yes	19	0.81 (0.71 to 0.89)		0.65 (0.51 to 0.77)		

Table 10. Meta-regression results for the impact of risk of bias items on the estimated test performance of laboratory tests for the diagnosis of acute appendicitis (continued)

Test	Population	Subgroup	N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity	
WBC (continued)	Mixed	Pre-specified positivity criteria	no	48	0.77 (0.71 to 0.81)	1.25 (0.83 to 1.88)	0.60 (0.55 to 0.66)	1.22 (0.84 to 1.70)
			yes	36	0.80 (0.75 to 0.85)		0.65 (0.58 to 0.71)	
		Blinding ref. std. to index test results	no	75	0.78 (0.75 to 0.82)	0.90 (0.45 to 1.76)	0.62 (0.57 to 0.66)	1.28 (0.75 to 2.23)
			yes	9	0.77 (0.63 to 0.86)		0.67 (0.55 to 0.77)	
		All pts. received same ref. std.	no	46	0.79 (0.74 to 0.83)	0.94 (0.62 to 1.36)	0.64 (0.59 to 0.69)	0.84 (0.61 to 1.20)
			yes	38	0.78 (0.72 to 0.82)		0.60 (0.53 to 0.66)	
		All pts. included in the analysis	no	24	0.80 (0.74 to 0.86)	0.84 (0.51 to 1.30)	0.65 (0.57 to 0.72)	0.87 (0.59 to 1.25)
			yes	60	0.77 (0.73 to 0.81)		0.61 (0.56 to 0.66)	
		Pathology (100%)	no	46	0.79 (0.74 to 0.83)	0.94 (0.62 to 1.36)	0.64 (0.59 to 0.69)	0.84 (0.61 to 1.20)
			yes	38	0.78 (0.72 to 0.82)		0.60 (0.53 to 0.66)	
		Consecutive/random sample	no	37	0.77 (0.71 to 0.82)	1.18 (0.77 to 1.77)	0.62 (0.56 to 0.68)	1.00 (0.72 to 1.42)
			yes	47	0.79 (0.74 to 0.84)		0.62 (0.57 to 0.68)	
		Blinding index tests	no	44	0.78 (0.72 to 0.82)	1.10 (0.72 to 1.64)	0.62 (0.56 to 0.68)	1.00 (0.67 to 1.39)
			yes	40	0.79 (0.74 to 0.84)		0.62 (0.56 to 0.68)	

CRP = c-reactive protein; N = number; pts. = patients; ref. std. = reference standard; WBC = white blood cell count

Sensitivity, relative sensitivity, specificity, and relative specificity values are medians and 95% central credible intervals when 5 or more studies were available; medians and minimum to maximum values are reported when <5 studies were available; when a single study was available we report the estimate from that study.

Test Performance of Multivariable Diagnostic Scores

One hundred and twenty seven studies reported information on one or more multivariable diagnostic scores. The authors usually proposed two types of cut points for these scores: a low value, below which patients might be safely discharged or observed (we refer to this cut point as the “low-risk cutoff”), and a high value, above which patients could proceed to surgery without additional investigation (we refer to this cutoff as the “high-risk cutoff”). When studies reported results at multiple cut point, analyses were performed at a “low risk” and “high risk” cut points suggested by the original score developers or recommended in subsequent studies. For scores developed specifically for binary classification, we used a single cut point. The majority of multivariable diagnostic scores had been developed prior to the widespread use of diagnostic imaging with CT and US. However, more recently developed scores have been developed with the intention of identifying a low risk group in whom imaging can be omitted.

Fifty-six of the studies enrolled mixed populations; 36 enrolled exclusively adults and 31 enrolled exclusively children; two studies were conducted in women of reproductive age; no studies were conducted in pregnant women or the elderly. Table 11 summarizes the descriptive characteristics of studies assessing the test performance of multivariable diagnostic scores and Table 12 summarizes key elements related to study risk of bias.

Table 11. Descriptive characteristics for studies evaluating score tests for the diagnosis of acute appendicitis

Patient Population	N Studies (Median N Patients/Affected/ Unaffected)	Median % of Women	Median of Average Age (Yrs)	Community Setting	Ambulatory Setting	Surgical Cohort	Clinical Presentation Consistent With Appendicitis	Median % of Patients With Perforation
Adults	55 (201/87/67)	47.8%	30.1	0.0%	38.2%	32.7%	98.2%	11.6%
Children	43 (196/70/89)	46.6%	10.8	2.3%	65.1%	4.7%	97.7%	9.1%
Children <5yrs	1 (27/17/10)	NA	NA	0.0%	100.0%	0.0%	100.0%	NA
Elderly	1 (17/7/10)	NA	NA	0.0%	0.0%	100.0%	100.0%	94.1%
Women of reproductive age	15 (70/48/19)	100.0%	34.1	0.0%	13.3%	60.0%	100.0%	13.5%
Mixed	72 (211/113/72)	52.1%	26.5	2.8%	36.1%	23.6%	94.4%	6.9%

N = number; NA = not applicable; yrs = years

Table 12. Assessment of risk of bias for studies evaluating score tests for the diagnosis of acute appendicitis

Patient Population	Consecutive or Random Sample of Patients	Study Avoided Inappropriate Exclusions	Index Test Results Interpreted Without Knowledge of Ref. Std.	Were the Positivity Criteria Prespecified?	Ref. Std. Results Interpreted Without Knowledge of Index Test	All Patients Received a Ref. Std.	All Patients Received the Same Ref. Std.	All Patients Received Pathology for Ref. Std.	All Patients Included in the Analysis
Adults	67.3%	100.0	65.5%	49.1%	3.6%	92.7%	34.5%	30.9%	72.7%
Children	53.5%	100.0	58.1%	46.5%	16.3%	95.3%	11.6%	9.3%	65.1%
Children <5yrs	0.0%	100.0	100.0%	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%
Elderly	100.0%	0.0	100.0%	0.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Women of reproductive age	20.0%	0.0	60.0%	40.0%	6.7%	93.3%	66.7%	66.7%	40.0%
Mixed	67.3%	100.0	65.5%	49.1%	3.6%	92.7%	34.5%	30.9%	72.7%

ref. std. = reference standard; yrs = year

Table 13 summarizes the variables and scoring systems used in five or more of the included studies. The most commonly used score was the Alvarado score (n=77), developed from a cohort of patients who all underwent appendectomy, and includes three items created by dichotomizing continuous predictors, white blood cell count (10 or more), neutrophil percentage (75% or more) and increased temperature (≥ 37.3 Celsius). Studies often (n=11) assessed variants of the Alvarado score neutrophil percentage is not reported (or reported in a delayed fashion) by some laboratories. Thus, subsequent papers have frequently modified the original Alvarado score by omitting this element.

Table 13. Components and scoring methods for appendicitis scores evaluated in at least five studies

Score	Components	Scoring Rule and Item Weights	Interpretation of Results
Alvarado score	Migration of pain	+1	The score is obtained by summing the components using the weights. Higher values indicate higher probability of appendicitis. Maximum total score is 10. The modified Alvarado score omits <i>Shift to the Left</i> resulting in a total score of 9. For both scores, a low risk cutpoint of ≥ 5 and a high risk cutpoint ≥ 7 were evaluated.
	Anorexia/Acetone	+1	
	Nausea/Vomiting	+1	
	Tenderness in RLQ	+2	
	Rebound pain	+1	
	Elevated temperature	+1	
	Leukocytosis	+2	
	Shift to left	+1	
PAS	Pain with cough/percussion/hopping	+2	This score was developed for use in children. A low risk cutpoint of ≥ 6 and a high risk cutpoint ≥ 8 were evaluated.
	Anorexia	+1	
	Elevated temperature	+1	
	Nausea/Vomiting	+1	
	Tenderness over right iliac fossa	+2	
	Leukocytosis	+1	
	Shift to left	+1	
	Migration of pain	+1	

PAS = Pediatric Appendicitis Score

Tables 14 and 15 summarize information on the test performance of various multivariable diagnostic scores. In general, their test performance appeared to be better than that of their component clinical symptoms and signs, but still lower than that of imaging tests. Figure 7 presents study results and summary ROC curves for selected multivariable diagnostic scores. Figure 8 shows the positive and negative predictive value for selected multivariable diagnostic scores, over appendicitis prevalence.

Table 16 summarizes the results of meta-regression analyses. There was some indication that the sensitivity of the Alvarado score has been lower in more recent studies (published from 2005 onwards).

Table 14. Summary estimates of test performance of diagnostic score tests (low-risk cutoff) for the diagnosis of acute appendicitis

Test*	Population	N Studies [Affected/ Unaffected]	Sensitivity	Specificity	LR+	LR-
AIR	Adults	1 [392 / 437]	0.83	0.63	2.26	0.27
	Mixed	2 [422 / 748]	0.94 (0.93 to 0.96)	0.79 (0.73 to 0.85)	4.96 (3.58 to 6.34)	0.07 (0.05 to 0.08)
Alvarado	Adults	3 [407 / 264]	0.91 (0.89 to 0.93)	0.31 (0.24 to 0.78)	1.35 (1.17 to 4.15)	0.23 (0.11 to 0.45)
	Children	6 [674 / 898]	0.99 (0.92 to 1.00)	0.48 (0.24 to 0.74)	1.88 (1.28 to 3.74)	0.03 (0.00 to 0.20)
	Mixed	20 [3986 / 4073]	0.96 (0.92 to 0.98)	0.46 (0.34 to 0.58)	1.77 (1.42 to 2.30)	0.09 (0.04 to 0.21)
	Women of reproductive age	2 [89 / 50]	0.99 (0.98 to 1.00)	0.24 (0.22 to 0.25)	1.30 (1.26 to 1.33)	0.05 (0.00 to 0.09)
	Children <5yrs	1 [17 / 10]	1.00	0.20	1.25	0.00
Alvarado modified	Adults	1 [53 / 208]	0.55	0.76	2.28	0.60
	Children	1 [38 / 80]	0.87	0.49	1.69	0.27
	Women of reproductive age	1 [108 / 18]	0.58	0.67	1.75	0.63
Alvarado modified + tenesmus	Adults	1 [126 / 32]	0.83	0.66	2.42	0.25
	Women of reproductive age	1 [45 / 18]	0.84	0.67	2.53	0.23
Arnbjornsson	Adults	1 [84 / 26]	1.00	0.27	1.37	0.00
	Mixed	1 [84 / 26]	1.00	0.27	1.37	0.00
Bengezi	Mixed	2 [132 / 96]	0.99 (0.99 to 1.00)	0.74 (0.54 to 0.94)	8.99 (2.18 to 15.80)	0.01 (0.00 to 0.01)
Eskelinen	Adults	1 [87 / 114]	0.83	0.92	10.48	0.19
High-risk criteria	Children	1 [65 / 113]	0.75	0.75	3.04	0.33
Jearwattanakanok	Women of reproductive age	1 [197 / 105]	0.92	0.79	4.39	0.10
Kharbanda	Children	1 [929 / 1461]	0.95	0.36	1.50	0.12
Kharbanda refined	Children	1 [1018 / 1607]	0.98	0.24	1.29	0.08
Leeuwenburgh	Adults	2 [75 / 244]	0.77 (0.71 to 0.83)	0.73 (0.71 to 0.75)	2.84 (2.82 to 2.86)	0.31 (0.24 to 0.39)
Low-risk criteria	Children	1 [65 / 113]	0.97	0.41	1.63	0.08
Ohmann	Women of reproductive age	1 [108 / 18]	0.98	0.00	0.98	NA
Teicher	Adults	1 [87 / 114]	0.89	0.83	5.31	0.14
de Dombal	Adults	1 [87 / 114]	0.80	0.73	2.96	0.27

AIR = appendicitis inflammatory response score; LR = likelihood ratio; N = number; PAS = pediatric appendicitis score; yrs = years

*First author name used as test name when not otherwise specified.

Sensitivity, specificity, and LR values are medians and 95% central credible intervals when 5 or more studies were available; medians and minimum to maximum values are reported when <5 studies were available; when a single study was available we report the estimate from that study.

Table 15. Factors that affect the performance of multivariable diagnostic scores

Test	Population	Cutoff Type	Subgroup		N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity
Alvarado	Adults	HR	Surgical cohorts	no	8	0.67 (0.43 to 0.86)	2.31 (0.52 to 9.83)	0.86 (0.71 to 0.94)	0.24 (0.07 to 0.86)
				yes	8	0.82 (0.61 to 0.94)		0.60 (0.37 to 0.78)	
	Mixed	HR	Study year	<2005	9	0.86 (0.76 to 0.93)	0.41 (0.17 to 0.90)	0.75 (0.61 to 0.84)	1.46 (0.72 to 3.10)
				>=2005	21	0.72 (0.62 to 0.80)		0.81 (0.74 to 0.87)	
		LR	Study year	<2005	6	0.97 (0.91 to 0.99)	0.53 (0.12 to 2.23)	0.57 (0.37 to 0.75)	0.55 (0.21 to 1.25)
				>=2005	14	0.95 (0.89 to 0.98)		0.42 (0.29 to 0.55)	
		HR	Ambulatory setting	no	20	0.76 (0.65 to 0.84)	1.32 (0.54 to 3.19)	0.77 (0.69 to 0.83)	1.61 (0.84 to 3.13)
				yes	10	0.80 (0.66 to 0.90)		0.84 (0.75 to 0.90)	
		LR	Ambulatory setting	no	11	0.95 (0.87 to 0.98)	1.64 (0.42 to 8.56)	0.42 (0.26 to 0.58)	1.43 (0.57 to 3.92)
				yes	9	0.97 (0.91 to 0.99)		0.51 (0.34 to 0.68)	
	HR	Surgical cohorts	no	25	0.77 (0.67 to 0.84)	1.14 (0.35 to 3.46)	0.82 (0.77 to 0.86)	0.31 (0.14 to 0.69)	
			yes	5	0.79 (0.57 to 0.91)		0.59 (0.41 to 0.75)		

HR = high risk; N = number; LR = low risk

Sensitivity, relative sensitivity, specificity, and relative specificity values are medians and 95% central credible intervals when 5 or more studies were available; medians and minimum to maximum values are reported when <5 studies were available; when a single study was available we report the estimate from that study.

Table 16. Summary estimates of test performance of diagnostic score tests (high-risk cutoff) for the diagnosis of acute appendicitis

Test*	Population	N Studies [Affected/ Unaffected]	Sensitivity	Specificity	LR+	LR-
AIR	Adults	1 [392 / 437]	0.15	0.97	4.89	0.88
	Mixed	2 [422 / 748]	0.24 (0.10 to 0.37)	1.00 (0.99 to 1.00)	56.37 (56.37 to 56.37)	0.77 (0.64 to 0.90)
Alvarado	Adults	16 [2354 / 1212]	0.75 (0.59 to 0.87)	0.75 (0.57 to 0.87)	2.96 (1.85 to 5.09)	0.34 (0.19 to 0.52)
	Children	9 [855 / 1163]	0.85 (0.75 to 0.93)	0.84 (0.61 to 0.96)	5.44 (2.04 to 20.95)	0.18 (0.08 to 0.36)
	Mixed	30 [4475 / 4337]	0.77 (0.69 to 0.84)	0.79 (0.74 to 0.84)	3.71 (2.91 to 4.84)	0.29 (0.21 to 0.39)
	Women of reproductive age	5 [202 / 177]	0.70 (0.35 to 0.92)	0.91 (0.65 to 0.99)	7.22 (1.77 to 67.68)	0.33 (0.10 to 0.76)
	Children <5yrs	1 [17 / 10]	0.76	0.60	1.91	0.39
Alvarado modified	Adults	4 [254 / 126]	0.68 (0.54 to 0.89)	0.60 (0.14 to 0.89)	1.96 (1.04 to 5.91)	0.61 (0.42 to 0.78)
	Children	5 [109 / 110]	0.89 (0.71 to 0.98)	0.80 (0.37 to 0.97)	4.49 (1.40 to 29.49)	0.15 (0.03 to 0.44)
	Elderly	1 [7 / 10]	0.86	0.80	4.29	0.18
	Mixed	6 [412 / 139]	0.82 (0.63 to 0.93)	0.62 (0.24 to 0.89)	2.13 (1.01 to 7.66)	0.30 (0.11 to 0.96)
	Women of reproductive age	4 [186 / 69]	0.60 (0.17 to 0.91)	0.50 (0.17 to 1.00)	1.15 (1.09 to 1.28)	0.79 (0.55 to 0.83)
Alvarado modified + tenesmus	Adults	1 [126 / 32]	0.83	0.66	2.42	0.25
	Women of reproductive age	1 [45 / 18]	0.84	0.67	2.53	0.23
Arnbjornsson	Adults	1 [84 / 26]	0.24	0.96	6.19	0.79
	Mixed	1 [84 / 26]	0.24	0.96	6.19	0.79
Bengezi	Mixed	2 [132 / 96]	0.50 (0.20 to 0.81)	0.96 (0.92 to 1.00)	9.69 (9.69 to 9.69)	0.50 (0.21 to 0.80)
Garcia Pena	Children	1 [588 / 370]	0.97	0.35	1.49	0.07
High risk criteria	Children	1 [65 / 113]	0.75	0.75	3.04	0.33
Jearwattanakanok	Women of reproductive age	1 [197 / 105]	0.92	0.79	4.39	0.10
Kharbanda	Children	1 [929 / 1461]	0.95	0.36	1.50	0.12

Table 16. Summary estimates of test performance of diagnostic score tests (high-risk cutoff) for the diagnosis of acute appendicitis (continued)

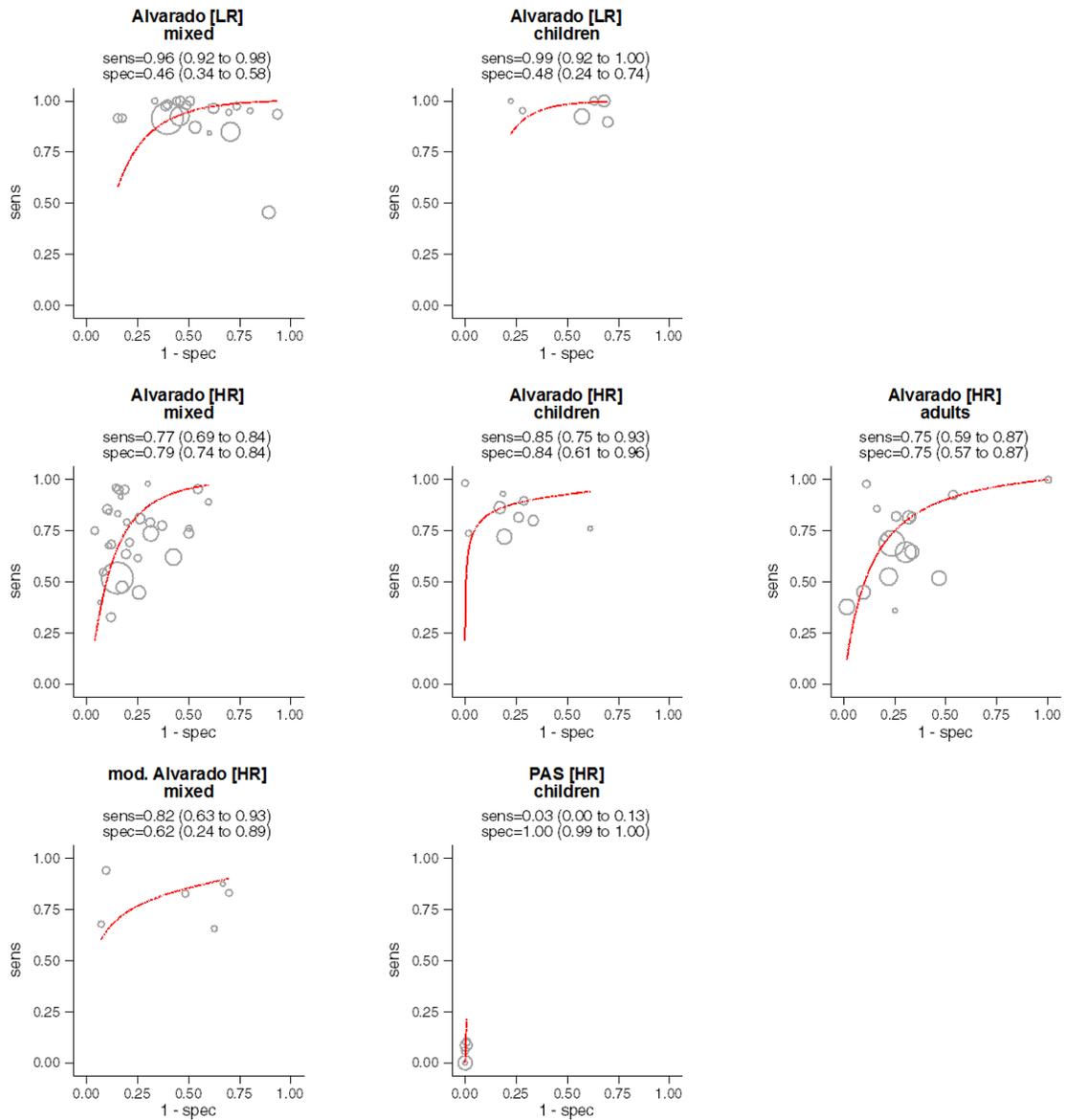
Test*	Population	N Studies [Affected/ Unaffected]	Sensitivity	Specificity	LR+	LR-
Leeuwenburgh	Adults	2 [75 / 244]	0.77 (0.71 to 0.83)	0.73 (0.71 to 0.75)	2.84 (2.82 to 2.86)	0.31 (0.24 to 0.39)
Ohmann	Mixed	1 [65 / 113]	0.97	0.41	1.63	0.08
	Women of reproductive age	1 [15 / 88]	1.00	0.06	1.06	0.00
PAS	Children	1 [108 / 18]	0.95	0.11	1.07	0.42
de Dombal	Adults	5 [600 / 1469]	0.03 (0.00 to 0.13)	1.00 (0.99 to 1.00)	22.85 (1.75 to 376.20)	0.97 (0.87 to 1.00)

AIR = appendicitis inflammatory response score; LR = likelihood ratio; N = number; PAS = pediatric appendicitis score; yrs = years

*First author name used as test name when not otherwise specified.

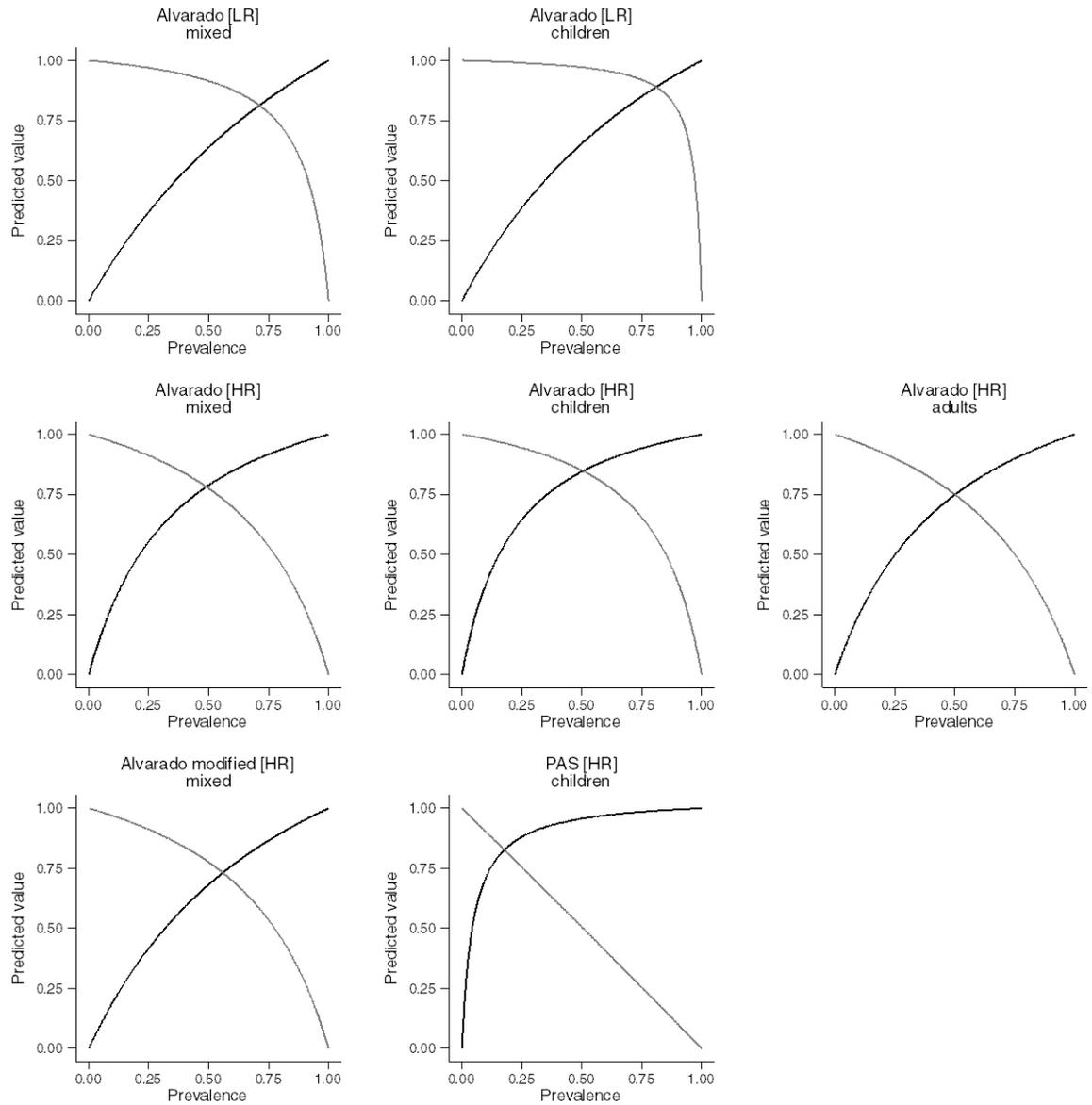
Sensitivity, specificity, and LR values are medians and 95% central credible intervals when 5 or more studies were available; medians and minimum to maximum values are reported when <5 studies were available; when a single study was available we report the estimate from that study.

Figure 7. Scatterplot of study results in the receiver operating characteristic space and summary receiver operating characteristic curves for appendicitis diagnostic scores for the diagnosis of acute appendicitis



HR = high-risk cutoff; mod. = modified; LR = low-risk cutoff; PAS = pediatric appendicitis score

Figure 8. Positive predictive value and negative predictive value for appendicitis diagnostic scores for the diagnosis of acute appendicitis



HR = high-risk cutoff; mod. = modified; LR = low-risk cutoff; PAS = pediatric appendicitis score

Test Performance of Imaging Tests

Five hundred and nineteen studies, published between 1965 and 2014, provided information on the test performance of imaging tests for the diagnosis of acute appendicitis. By far the most commonly evaluated tests included CT, US, and MRI.

Table 17 presents a summary of the descriptive characteristics of the studies. Table 18 presents a summary of key items related to study risk of bias. Studies of CT and MRI were at moderate risk of bias; studies of US and other imaging tests were at moderate to high risk of bias. In general, blinding of index test and reference standard assessors were either not used or relevant information was not reported; and most studies had differential verification.

Table 19 presents a summary of key test performance results for imaging tests. CT and MRI had high sensitivity and specificity in all populations for which data were available; US had lower sensitivity and comparable specificity. Positive and negative likelihood ratios were generally higher for CT and MRI, as compared to US, but all three tests had likelihood ratios that are clinically relevant. US also had substantially higher rates of non-diagnostic exams (the median percentage of non-diagnostic scans for CT was lower than 6% for all populations examined; the median proportion was substantially higher for US). However, the reporting of information on non-diagnostic scans was inconsistent across studies, raising concerns reporting bias. Computed tomography (CT) had high sensitivity (summary estimates ranging from 0.95 to 1) and specificity (ranging from 0.91 to 0.99) in all populations of interest to this report. MRI had high sensitivity (ranging from 0.91 to 1) but appeared to have variable specificity (ranging from 0.86 to 1), mainly due to the smaller number of available studies, which focused on its use for pregnant women. In adult populations, US had lower sensitivity (0.83) and specificity (0.89) than CT (0.96, both for sensitivity and specificity) and MRI, and produced more non-diagnostic scans. In children, the specificity of US was similar to that of CT (0.92 vs. 0.91), but CT had greater sensitivity (0.89 vs. 0.96); these results were based on a large number of studies (72 for US and 32 for US). In the same patient population, MRI had a specificity of 0.99 and sensitivity of 1, but data were derived from only 3 studies. Among pregnant women, CT, MRI, and US had similar specificity (0.98, 0.98, and 0.95, respectively), but CT and MRI had higher sensitivity than US (0.95, 0.98, and 0.73, respectively).

Figure 9 presents study results and summary ROC curves for selected imaging tests. Studies of CT exhibited low heterogeneity in sensitivity and moderate heterogeneity in specificity; studies of US exhibited more heterogeneity, both for sensitivity and specificity. Studies of MRI had relatively homogeneous sensitivity and specificity, but the number of available studies was too limited to draw conclusions about consistency. Studies of other tests showed moderate heterogeneity. For all imaging tests, in most cases, summary ROC lines appeared to fit the data relatively well. Figure 10 shows the positive and negative predictive value for selected imaging tests, over appendicitis prevalence.

Sensitivity analyses using test readings from worse performing raters (see methods section for a description of details of these analyses) produced results that were similar to our main analyses (which used test readings from the rater with the highest sum of sensitivity and specificity). Sensitivity analyses for the impact of indeterminate test results produced test performance estimates that were lower than the main analyses; the deterioration of performance was more pronounced for US (as compared to CT and MRI), reflecting the higher rate of indeterminate results. The complete sensitivity analyses are presented in Appendix D.

Table 17. Descriptive characteristics for studies evaluating imaging tests for the diagnosis of acute appendicitis

Patient Population	N Studies (Median N Patients/Affected/Unaffected)	Median % of Women	Median of Average Age (Yrs)	Community Setting	Ambulatory Setting	Surgical Cohort	Clinical Presentation Consistent With Appendicitis	Median % of Patients With Perforation
Adults	113	52.6%	37.0	3.5%	42.5%	19.5%	83.2%	9.0%
Children	137	49.3%	10.6	2.2%	35.0%	13.1%	86.9%	12.3%
Children <5yrs	0	NA	NA	NA	NA	NA	NA	NA
Elderly	4 (119/18.5/79)	78.4%	70.0	0.0%	25.0%	25.0%	100.0%	25.0%
Women of reproductive age	26 (64/27/27)	100.0%	28.5	3.8%	50.0%	19.2%	84.6%	25.0%
Pregnant women	26 (23/4/15)	100.0%	26.9	7.7%	30.8%	15.4%	84.6%	2.0%
Mixed	241	54.5%	30.6	6.6%	32.0%	19.1%	87.6%	6.9%

N = number; NA = not applicable; yrs = years

Table 18. Assessment of risk of bias for studies evaluating imaging tests for the diagnosis of acute appendicitis

Patient Population	Consecutive or Random Sample of Patients	Study Aavoided Inappropriate Exclusions	Index Test Results Interpreted Without Knowledge of Ref. Std.	Were the Positivity Criteria Prespecified?	Ref. Std. Results Interpreted Without Knowledge of Index Test	All Patients Received a Ref. Std.	All Patients Received the Same Ref. Std.	All Patients Received Pathology for Ref. Std.	All Patients Included in the Analysis
Adults	68.1%	100.0	62.8%	34.5%	20.4%	97.3%	26.5%	24.8%	79.6%
Children	52.6%	100.0	62.0%	42.3%	10.2%	92.0%	18.2%	19.0%	77.4%
Elderly	100.0%	100.0	75.0%	25.0%	25.0%	100.0%	25.0%	25.0%	75.0%
Women of reproductive age	65.4%	100.0	57.7%	26.9%	11.5%	96.2%	34.6%	34.6%	92.3%
Pregnant women	76.9%	100.0	73.1%	26.9%	15.4%	100.0%	23.1%	23.1%	84.6%
Mixed	55.6%	100.0	60.6%	41.1%	9.1%	91.7%	25.7%	23.2%	76.8%

ref. std. = reference standard

Table 19. Summary estimates of test performance of imaging tests for the diagnosis of acute appendicitis

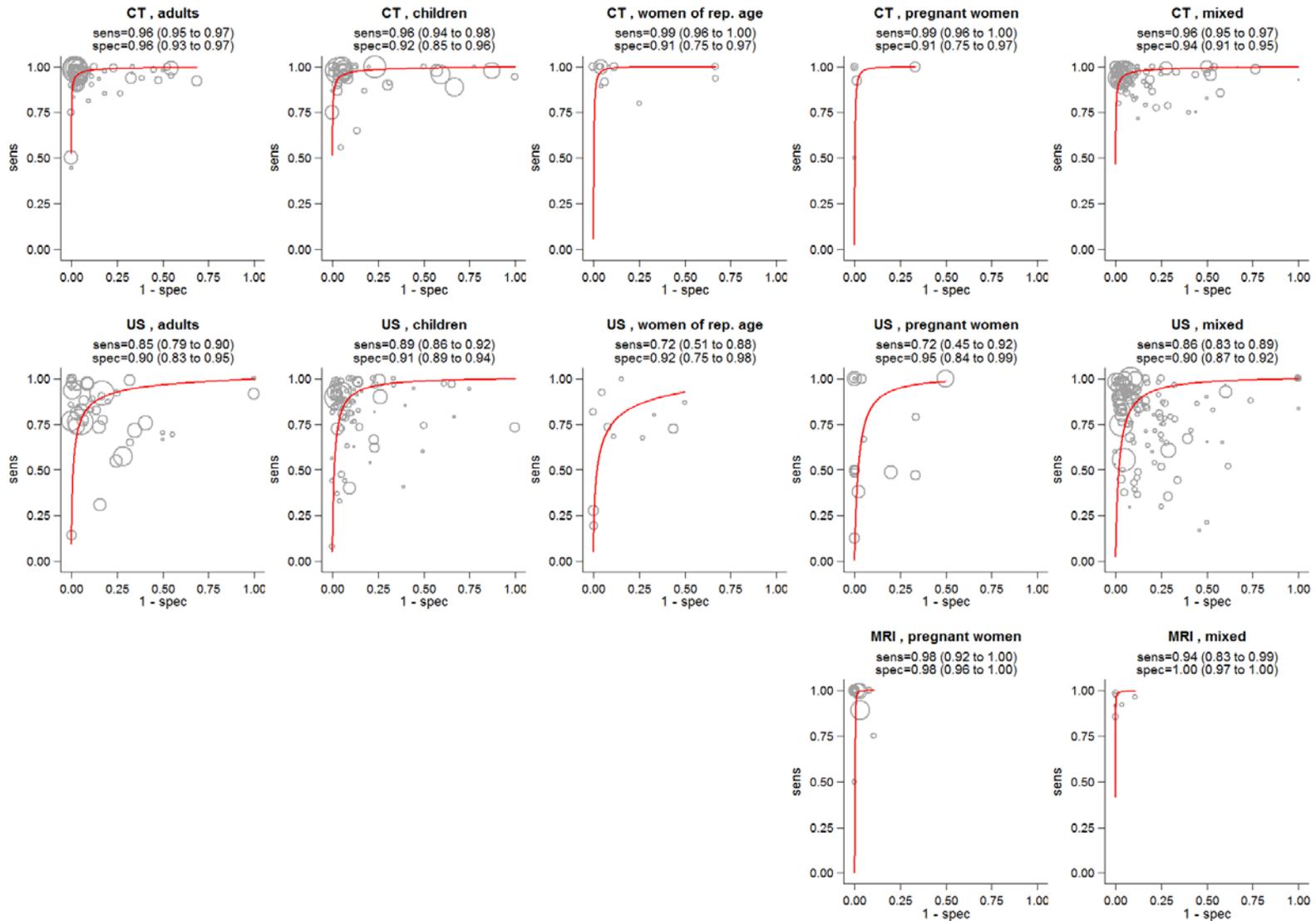
Test	Population	N Studies [Affected/ Unaffected]	Sensitivity	Specificity	LR+	LR-	Median % Nondiagnostic (Range)
Abdominal X x-ray	Adults	3 [29/1007]	0.38 (0.00 to 0.86)	1.00 (1.00 to 1.00)	NA	0.63 (0.14 to 1.00)	NA
	Children	6 [925/784]	0.68 (0.24 to 0.94)	0.83 (0.42 to 0.97)	3.79 (0.92 to 22.86)	0.41 (0.08 to 1.06)	31.3 (0.00 to 62.54)
	Mixed	9 [1096/994]	0.36 (0.10 to 0.75)	0.94 (0.82 to 0.98)	5.86 (1.47 to 23.17)	0.68 (0.28 to 0.96)	0.0 (0.00 to 0.00)
Barium enema	Children	5 [88/53]	0.91 (0.66 to 0.99)	0.77 (0.57 to 0.91)	3.87 (1.92 to 10.07)	0.12 (0.01 to 0.46)	20.5 (1.69 to 39.39)
	Mixed	5 [185/206]	0.97 (0.90 to 1.00)	0.87 (0.53 to 0.98)	7.70 (2.08 to 42.82)	0.03 (0.01 to 0.12)	11.2 (7.57 to 14.85)
CT	Adults	72 [7833/14469]	0.96 (0.95 to 0.97)	0.96 (0.93 to 0.97)	21.83 (14.77 to 33.46)	0.04 (0.03 to 0.05)	4.0 (0.00 to 43.95)
	Children	34 [3581/3122]	0.96 (0.94 to 0.98)	0.92 (0.85 to 0.96)	12.13 (6.57 to 24.47)	0.04 (0.02 to 0.06)	5.7 (0.00 to 43.62)
	Elderly	4 [144/582]	1.00 (0.94 to 1.00)	1.00 (0.43 to 1.00)	55.32 (1.64 to 109.00)	0.00 (0.00 to 0.15)	0.0 (0.00 to 0.00)
	Women of reproductive age	11 [596/652]	0.99 (0.96 to 1.00)	0.91 (0.75 to 0.97)	10.65 (3.95 to 34.31)	0.01 (0.00 to 0.05)	2.0 (0.00 to 17.53)
	Pregnant women	5 [26/84]	0.99 (0.96 to 1.00)	0.91 (0.75 to 0.97)	10.65 (3.95 to 34.31)	0.01 (0.00 to 0.05)	0.0 (0.00 to 9.09)
	Mixed	93 [9341/10357]	0.96 (0.95 to 0.97)	0.94 (0.91 to 0.95)	15.00 (11.02 to 20.75)	0.04 (0.03 to 0.05)	3.3 (0.00 to 28.28)
MRI	Adults	7 [512/467]	0.95 (0.88 to 0.98)	0.92 (0.87 to 0.95)	11.56 (7.08 to 19.98)	0.06 (0.02 to 0.14)	5.4 (0.00 to 5.83)
	Children	7 [359/665]	0.97 (0.87 to 1.00)	0.96 (0.84 to 0.99)	26.62 (5.94 to 123.70)	0.03 (0.00 to 0.13)	0.0 (0.00 to 0.48)
	Women of reproductive age	1 [50/88]	1.00	0.86	7.33	0.00	NA
	Pregnant women	11 [76/570]	0.98 (0.92 to 1.00)	0.98 (0.96 to 1.00)	52.55 (26.44 to 263.00)	0.02 (0.00 to 0.08)	3.5 (0.00 to 48.48)
	Mixed	5 [243/141]	0.94 (0.83 to 0.99)	1.00 (0.97 to 1.00)	311.70 (32.07 to 16750.00)	0.06 (0.01 to 0.17)	8.7 (0.00 to 41.79)
TC99M Nuclear	Adults	5 [110/113]	0.88 (0.76 to 0.96)	0.97 (0.88 to 1.00)	26.80 (7.46 to 228.90)	0.12 (0.04 to 0.25)	0.0 (0.00 to 0.00)
	Children	7 [141/185]	0.93 (0.78 to 0.99)	0.83 (0.63 to 0.94)	5.55 (2.31 to 15.80)	0.08 (0.02 to 0.29)	12.1 (0.00 to 24.24)
	Women of reproductive age	4 [57/73]	0.91 (0.75 to 0.93)	0.89 (0.86 to 1.00)	6.50 (6.00 to 9.33)	0.10 (0.07 to 0.29)	10.0 (0.00 to 20.00)
	Pregnant women	1 [2/11]	0.50	0.73	1.83	0.69	NA
	Mixed	11 [271/395]	0.92 (0.84 to 0.97)	0.89 (0.79 to 0.97)	8.72 (4.16 to 26.93)	0.09 (0.03 to 0.19)	0.0 (0.00 to 47.71)

Table 19. Summary estimates of test performance of imaging tests for the diagnosis of acute appendicitis (continued)

Test	Population	N Studies [Affected/ Unaffected]	Sensitivity	Specificity	LR+	LR-	Median % Nondiagnostic (Range)
US	Adults	38 [3560/3656]	0.85 (0.79 to 0.90)	0.90 (0.83 to 0.95)	8.49 (5.00 to 15.67)	0.17 (0.11 to 0.24)	29.6 (4.07 to 63.08)
	Children	85 [8539/15167]	0.89 (0.86 to 0.92)	0.91 (0.89 to 0.94)	10.35 (7.80 to 13.95)	0.12 (0.09 to 0.16)	9.8 (0.00 to 79.23)
	Women of reproductive age	11 [516/539]	0.72 (0.51 to 0.88)	0.92 (0.75 to 0.98)	8.67 (2.97 to 35.50)	0.31 (0.14 to 0.53)	0.0 (0.00 to 0.00)
	Pregnant women	13 [188/198]	0.72 (0.45 to 0.92)	0.95 (0.84 to 0.99)	13.10 (4.43 to 63.18)	0.30 (0.09 to 0.58)	77.3 (0.00 to 96.97)
	Mixed	125 [11902/14314]	0.86 (0.83 to 0.89)	0.90 (0.87 to 0.92)	8.24 (6.43 to 10.69)	0.15 (0.12 to 0.19)	8.9 (0.00 to 75.76)

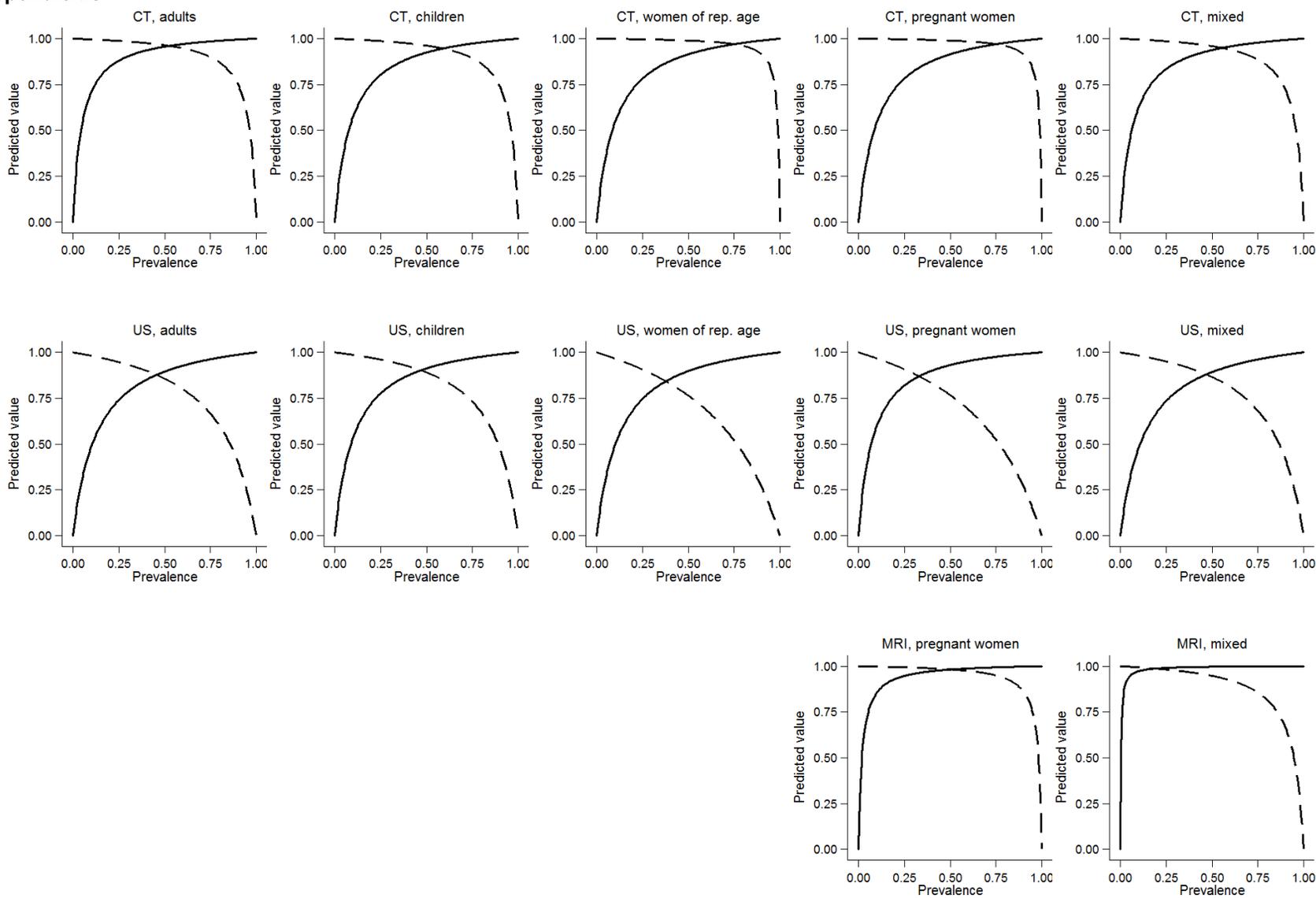
CT = computed tomography; LR = likelihood ratio; MRI = magnetic resonance imaging; N = number; NA = not applicable; TC99M = technetium-99m ; US = ultrasound
Sensitivity, specificity, and LR values are medians and 95% central credible intervals when 5 or more studies were available; medians and minimum to maximum values are reported when <5 studies were available; when a single study was available we report the estimate from that study.

Figure 9. Scatterplot of results in the receiver operating characteristic space and summary receiver operating characteristic curves for selected imaging tests for the diagnosis of acute appendicitis



CT = computed tomography; US = ultrasound; MRI = magnetic resonance imaging; rep. = reproductive; sens. = sensitivity; spec. = specificity

Figure 10. Positive predictive value and negative predictive value curves for selected imaging tests for the diagnosis of acute appendicitis



CT = computed tomography; US = ultrasound; MRI = magnetic resonance imaging; rep. = reproductive

Factors That Affect the Test Performance of Imaging Tests

Table 20 summarizes the results of meta-regression analyses for various factors that may affect the performance of imaging tests for the diagnosis of acute appendicitis.

The vast majority of studies did not report adequate data to assess factors that may affect test performance (i.e., based on within study comparisons); for this reason we relied on comparisons across studies (via meta-regression analyses) to identify factors that may affect test performance. Overall, no distinct pattern emerged to establish a particular factor as a modifier of test performance. For all factors examined but CrIs were wide, indicating substantial uncertainty regarding the relative test performance of tests over levels of the modifiers we examined.

Impact of Study Risk of Bias Items on Estimated Test Performance

Table 21 summarizes the results of meta-regression analyses for various factors that may affect the performance of imaging tests for the diagnosis of acute appendicitis. In some cases items related to study risk of bias appeared to be associated with worse test performance of various clinical symptoms and signs. Specifically, for CT in adult populations, differential verification and blinding of index test assessors were associated with higher specificity. For CT in children, incomplete verification was associated with higher sensitivity. For CT in mixed populations differential verification was associated with higher specificity and partial verification was associated with lower sensitivity. For US in adults, the use of prespecified positivity criteria were associated with higher sensitivity. For US in children complete verification was associated with higher sensitivity. For US in mixed populations differential verification was associated with higher sensitivity and specificity, partial verification was associated with lower sensitivity, and using a consecutive or random sample of patients was associated with higher sensitivity.

These results suggest that study conduct may have affected estimates of test performance in meta-analyses of imaging tests. However, our analyses relied on information that was often poorly reported in the primary studies and meta-regression results were often imprecise, indicating substantial uncertainty. Because each risk of bias item was examined individually, and because different items may be correlated between them and with other study characteristics that may affect performance estimates, we do not believe that definitive conclusions about specific items can be reached.

Table 20. Meta-regression results for factors that affect the performance of imaging tests for the diagnosis of acute appendicitis

Test	Population	Subgroup	N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity	
CT	Adults	Study year	<2005	25	0.96 (0.93 to 0.98)	1.24 (0.63 to 2.42)	0.94 (0.90 to 0.97)	1.44 (0.58 to 3.37)
			>=2005	47	0.97 (0.95 to 0.98)		0.96 (0.94 to 0.98)	
		Oral contrast	no	39	0.95 (0.93 to 0.97)	1.82 (1.01 to 3.21)	0.96 (0.93 to 0.98)	0.93 (0.40 to 2.11)
			yes	33	0.97 (0.96 to 0.98)		0.95 (0.92 to 0.98)	
		IV contrast	no	28	0.95 (0.93 to 0.97)	1.57 (0.85 to 2.92)	0.94 (0.89 to 0.97)	1.64 (0.71 to 4.00)
			yes	44	0.97 (0.96 to 0.98)		0.96 (0.94 to 0.98)	
		Rectal contrast	no	63	0.96 (0.95 to 0.97)	1.49 (0.59 to 3.82)	0.96 (0.94 to 0.98)	0.29 (0.08 to 1.01)
			yes	9	0.97 (0.94 to 0.99)		0.88 (0.69 to 0.96)	
		Multiple contrast (NOS)	no	42	0.96 (0.94 to 0.97)	1.60 (0.86 to 2.91)	0.96 (0.94 to 0.98)	0.62 (0.27 to 1.45)
			yes	30	0.97 (0.96 to 0.98)		0.94 (0.90 to 0.97)	
		Ambulatory setting	no	36	0.97 (0.96 to 0.98)	0.64 (0.36 to 1.15)	0.94 (0.89 to 0.96)	2.12 (0.91 to 4.74)
			yes	36	0.96 (0.93 to 0.97)		0.97 (0.95 to 0.98)	
		Surgical cohorts	no	62	0.96 (0.95 to 0.97)	1.11 (0.46 to 2.65)	0.96 (0.95 to 0.98)	0.16 (0.05 to 0.45)
			yes	10	0.97 (0.93 to 0.99)		0.80 (0.61 to 0.92)	
		Appendicitis presentation	atypical/other/ unclear	12	0.95 (0.90 to 0.98)	1.57 (0.66 to 3.47)	0.96 (0.92 to 0.99)	0.79 (0.25 to 2.05)
			typical	60	0.97 (0.95 to 0.98)		0.95 (0.93 to 0.97)	

Table 20. Meta-regression results for factors that affect the performance of imaging tests for the diagnosis of acute appendicitis (continued)

Test	Population	Subgroup	N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity	
CT (ctd.)	Children	Study year	<2005	14	0.95 (0.91 to 0.98)	1.67 (0.62 to 4.53)	0.92 (0.79 to 0.97)	1.05 (0.27 to 4.75)
			>=2005	20	0.97 (0.95 to 0.99)		0.92 (0.83 to 0.97)	
		Oral contrast	no	24	0.95 (0.92 to 0.97)	3.22 (1.11 to 10.10)	0.93 (0.85 to 0.97)	0.70 (0.17 to 3.21)
			yes	10	0.98 (0.96 to 0.99)		0.90 (0.73 to 0.97)	
		IV contrast	no	22	0.95 (0.92 to 0.98)	2.11 (0.74 to 6.49)	0.93 (0.85 to 0.97)	0.68 (0.16 to 2.85)
			yes	12	0.98 (0.95 to 0.99)		0.90 (0.74 to 0.97)	
		Rectal contrast	no	27	0.95 (0.93 to 0.97)	3.53 (1.10 to 12.07)	0.93 (0.86 to 0.97)	0.46 (0.09 to 2.37)
			yes	7	0.99 (0.96 to 1.00)		0.86 (0.59 to 0.97)	
		Multiple contrast (NOS)	no	23	0.95 (0.92 to 0.97)	3.13 (1.16 to 9.34)	0.93 (0.84 to 0.97)	0.81 (0.19 to 3.25)
			yes	11	0.98 (0.96 to 0.99)		0.91 (0.75 to 0.97)	
		Ambulatory setting	no	23	0.97 (0.94 to 0.98)	0.75 (0.26 to 2.19)	0.90 (0.79 to 0.95)	2.38 (0.58 to 9.79)
			yes	11	0.96 (0.91 to 0.98)		0.95 (0.87 to 0.99)	
	Women of reproductive age	Study year	<2005	5	1.00 (0.97 to 1.00)	0.15 (0.01 to 2.91)	0.85 (0.53 to 0.97)	2.61 (0.26 to 20.83)
			>=2005	6	0.98 (0.89 to 1.00)		0.93 (0.76 to 0.98)	
		IV contrast	no	5	1.00 (0.97 to 1.00)	0.18 (0.01 to 3.78)	0.90 (0.63 to 0.98)	1.13 (0.10 to 10.81)
			yes	6	0.98 (0.89 to 1.00)		0.91 (0.67 to 0.98)	
		Multiple contrast (NOS)	no	5	1.00 (0.96 to 1.00)	0.24 (0.01 to 4.82)	0.91 (0.63 to 0.98)	1.06 (0.10 to 10.92)
			yes	6	0.98 (0.90 to 1.00)		0.91 (0.66 to 0.98)	
Ambulatory setting	no	6	0.99 (0.91 to 1.00)	3.21 (0.13 to 73.13)	0.86 (0.59 to 0.97)	2.57 (0.26 to 18.29)		
	yes	5	1.00 (0.95 to 1.00)		0.94 (0.76 to 0.99)			

Table 20. Meta-regression results for factors that affect the performance of imaging tests for the diagnosis of acute appendicitis (continued)

Test	Population	Subgroup	N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity	
CT (ctd.)	Mixed	Study year	<2005	40	0.96 (0.94 to 0.97)	1.12 (0.68 to 1.90)	0.94 (0.90 to 0.96)	0.94 (0.48 to 1.80)
			>=2005	53	0.96 (0.95 to 0.97)		0.93 (0.90 to 0.96)	
		Oral contrast	no	70	0.96 (0.95 to 0.97)	1.23 (0.67 to 2.25)	0.93 (0.91 to 0.95)	1.16 (0.55 to 2.45)
			yes	23	0.97 (0.94 to 0.98)		0.94 (0.89 to 0.97)	
		IV contrast	no	57	0.95 (0.94 to 0.97)	1.49 (0.89 to 2.59)	0.93 (0.89 to 0.95)	1.46 (0.73 to 2.84)
			yes	36	0.97 (0.95 to 0.98)		0.95 (0.92 to 0.97)	
		Community setting	no	85	0.96 (0.95 to 0.97)	0.68 (0.31 to 1.49)	0.94 (0.91 to 0.96)	0.85 (0.28 to 2.80)
			>=2005	8	0.94 (0.89 to 0.97)		0.93 (0.81 to 0.98)	
		Rectal contrast	no	76	0.96 (0.95 to 0.97)	0.99 (0.51 to 1.91)	0.94 (0.91 to 0.96)	1.00 (0.43 to 2.41)
			yes	17	0.96 (0.93 to 0.98)		0.94 (0.87 to 0.97)	
		Multiple contrast (NOS)	no	67	0.96 (0.94 to 0.97)	1.42 (0.81 to 2.59)	0.93 (0.90 to 0.95)	1.17 (0.53 to 2.50)
			yes	26	0.97 (0.95 to 0.98)		0.94 (0.90 to 0.97)	
		Ambulatory setting	no	67	0.96 (0.94 to 0.97)	1.41 (0.80 to 2.47)	0.90 (0.87 to 0.93)	4.16 (2.05 to 8.32)
			yes	26	0.97 (0.95 to 0.98)		0.98 (0.96 to 0.99)	
		Surgical cohorts	no	73	0.96 (0.95 to 0.97)	0.99 (0.54 to 1.85)	0.95 (0.93 to 0.97)	0.20 (0.09 to 0.45)
			yes	20	0.96 (0.93 to 0.98)		0.80 (0.67 to 0.89)	
		Appendicitis presentation	atypical/other/ unclear	15	0.95 (0.92 to 0.97)	1.18 (0.64 to 2.19)	0.97 (0.93 to 0.98)	0.45 (0.20 to 1.11)
			typical	78	0.96 (0.95 to 0.97)		0.93 (0.90 to 0.95)	

Table 20. Meta-regression results for factors that affect the performance of imaging tests for the diagnosis of acute appendicitis (continued)

Test	Population	Subgroup	N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity	
US	Adults	Study year	<2005	13	0.87 (0.75 to 0.93)	0.83 (0.31 to 2.13)	0.88 (0.70 to 0.96)	1.48 (0.39 to 6.05)
			>=2005	25	0.84 (0.76 to 0.90)		0.91 (0.83 to 0.96)	
		Ambulatory setting	no	24	0.89 (0.83 to 0.93)	0.38 (0.17 to 0.88)	0.89 (0.79 to 0.95)	1.31 (0.32 to 4.73)
			yes	14	0.75 (0.61 to 0.86)		0.91 (0.79 to 0.97)	
		Surgical cohorts	no	27	0.85 (0.77 to 0.91)	0.99 (0.38 to 2.77)	0.92 (0.86 to 0.96)	0.35 (0.10 to 1.26)
			yes	11	0.85 (0.72 to 0.93)		0.81 (0.58 to 0.93)	
		Appendicitis presentation	atypical/other/ unclear	8	0.77 (0.56 to 0.89)	1.93 (0.78 to 5.59)	0.94 (0.83 to 0.98)	0.53 (0.10 to 1.78)
			typical	30	0.87 (0.80 to 0.92)		0.89 (0.80 to 0.94)	
	Children	Study year	<2005	39	0.88 (0.82 to 0.92)	1.13 (0.62 to 2.20)	0.94 (0.90 to 0.96)	0.56 (0.32 to 1.11)
			>=2005	46	0.89 (0.85 to 0.93)		0.89 (0.85 to 0.93)	
		Ambulatory setting	no	57	0.88 (0.84 to 0.92)	1.11 (0.59 to 2.09)	0.90 (0.86 to 0.93)	1.85 (0.99 to 3.55)
			yes	28	0.90 (0.84 to 0.94)		0.94 (0.91 to 0.96)	
		Surgical cohorts	no	74	0.89 (0.85 to 0.92)	1.02 (0.44 to 2.50)	0.92 (0.90 to 0.94)	0.28 (0.12 to 0.76)
			yes	11	0.89 (0.79 to 0.95)		0.78 (0.60 to 0.90)	
Appendicitis presentation		atypical/other/ unclear	10	0.96 (0.90 to 0.98)	0.33 (0.14 to 0.87)	0.90 (0.79 to 0.96)	1.16 (0.46 to 3.22)	
		typical	75	0.88 (0.84 to 0.91)		0.92 (0.89 to 0.94)		

Table 20. Meta-regression results for factors that affect the performance of imaging tests for the diagnosis of acute appendicitis (continued)

Test	Population	Subgroup	N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity	
US (ctd.)	Mixed	Study year	<2005	67	0.85 (0.80 to 0.89)	1.19 (0.68 to 1.97)	0.90 (0.86 to 0.93)	0.90 (0.51 to 1.58)
			>=2005	58	0.87 (0.82 to 0.91)		0.89 (0.84 to 0.92)	
		Community setting	no	118	0.87 (0.83 to 0.90)	0.56 (0.18 to 1.77)	0.89 (0.86 to 0.92)	1.82 (0.59 to 5.58)
			>=2005	7	0.78 (0.55 to 0.92)		0.94 (0.83 to 0.98)	
		Ambulatory setting	no	87	0.83 (0.79 to 0.87)	2.12 (1.20 to 3.82)	0.88 (0.84 to 0.91)	1.68 (0.94 to 3.05)
			yes	38	0.91 (0.87 to 0.95)		0.92 (0.88 to 0.95)	
		Surgical cohorts	no	104	0.88 (0.84 to 0.91)	0.47 (0.24 to 0.95)	0.91 (0.88 to 0.93)	0.49 (0.23 to 1.01)
			yes	21	0.77 (0.64 to 0.86)		0.82 (0.70 to 0.90)	
		Appendicitis presentation	atypical/other/unclear	13	0.93 (0.83 to 0.97)	0.46 (0.18 to 1.27)	0.95 (0.88 to 0.98)	0.46 (0.16 to 1.12)
			typical	112	0.85 (0.82 to 0.89)		0.89 (0.86 to 0.91)	

CT = computed tomography; IV = intravenous; N = number; NOS = not otherwise specified; US = ultrasound

Sensitivity, relative sensitivity, specificity, and relative specificity values are medians and 95% central credible intervals when 5 or more studies were available; medians and minimum to maximum values are reported when <5 studies were available; when a single study was available we report the estimate from that study.

Table 21. Meta-regression results for the impact of risk of bias items on the estimated test performance of imaging tests for the diagnosis of acute appendicitis

Test	Population	Subgroup	N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity	
CT	Adults	Pre-specified positivity criteria	no	48	0.96 (0.94 to 0.97)	1.55 (0.81 to 3.08)	0.95 (0.92 to 0.97)	1.25 (0.51 to 3.03)
			yes	24	0.97 (0.96 to 0.99)		0.96 (0.92 to 0.98)	
		Blinding ref. std. to index test results	no	59	0.97 (0.95 to 0.98)	0.74 (0.35 to 1.60)	0.96 (0.94 to 0.97)	0.79 (0.25 to 2.34)
			yes	13	0.96 (0.92 to 0.98)		0.95 (0.87 to 0.98)	
		All pts. received same ref. std.	no	56	0.96 (0.95 to 0.97)	1.23 (0.59 to 2.71)	0.97 (0.96 to 0.98)	0.13 (0.06 to 0.30)
			yes	16	0.97 (0.94 to 0.99)		0.80 (0.66 to 0.89)	
		All pts. included in the analysis	no	13	0.94 (0.89 to 0.97)	1.86 (0.80 to 4.03)	0.96 (0.90 to 0.98)	0.89 (0.31 to 2.52)
			yes	59	0.97 (0.96 to 0.98)		0.96 (0.93 to 0.97)	
		Pathology (100%)	no	56	0.96 (0.95 to 0.98)	1.14 (0.57 to 2.37)	0.97 (0.95 to 0.98)	0.16 (0.07 to 0.38)
			yes	16	0.97 (0.94 to 0.98)		0.83 (0.71 to 0.92)	
		Consecutive/random sample	no	19	0.98 (0.95 to 0.99)	0.62 (0.32 to 1.32)	0.95 (0.89 to 0.98)	1.12 (0.43 to 3.05)
			yes	53	0.96 (0.95 to 0.97)		0.96 (0.93 to 0.97)	
		Blinding index tests	no	31	0.96 (0.94 to 0.97)	1.32 (0.71 to 2.46)	0.93 (0.88 to 0.96)	2.66 (1.17 to 5.89)
			yes	41	0.97 (0.95 to 0.98)		0.97 (0.95 to 0.98)	
	Children	Pre-specified positivity criteria	no	23	0.96 (0.94 to 0.98)	0.93 (0.32 to 2.86)	0.89 (0.79 to 0.95)	2.64 (0.59 to 11.55)
			yes	11	0.96 (0.92 to 0.99)		0.96 (0.87 to 0.99)	
		All pts. received same ref. std.	no	28	0.96 (0.94 to 0.98)	0.85 (0.26 to 2.95)	0.94 (0.89 to 0.97)	0.12 (0.03 to 0.56)
			yes	6	0.96 (0.89 to 0.99)		0.67 (0.33 to 0.90)	
		All pts. included in the analysis	no	7	0.98 (0.96 to 0.99)	0.36 (0.11 to 1.14)	0.92 (0.75 to 0.98)	0.94 (0.21 to 4.78)
			yes	27	0.95 (0.92 to 0.97)		0.92 (0.84 to 0.96)	
		Pathology (100%)	no	28	0.96 (0.94 to 0.98)	1.03 (0.29 to 3.67)	0.95 (0.91 to 0.97)	0.07 (0.02 to 0.30)
			yes	6	0.96 (0.90 to 0.99)		0.56 (0.27 to 0.82)	
		Consecutive/random sample	no	15	0.97 (0.95 to 0.99)	0.58 (0.19 to 1.58)	0.90 (0.76 to 0.96)	1.78 (0.40 to 6.63)
			yes	19	0.96 (0.92 to 0.98)		0.94 (0.85 to 0.98)	
Blinding index tests	no	15	0.97 (0.95 to 0.99)	0.61 (0.18 to 1.59)	0.93 (0.82 to 0.97)	0.81 (0.21 to 3.54)		
	yes	19	0.96 (0.92 to 0.98)		0.91 (0.81 to 0.97)			

Table 21. Meta-regression results for the impact of risk of bias items on the estimated test performance of imaging tests for the diagnosis of acute appendicitis (continued)

Test	Population	Subgroup	N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity	Test
CT (ctd.)	Women of reproductive age	All pts. received same ref. std.	no	6	0.99 (0.93 to 1.00)	1.15 (0.05 to 22.91)	0.96 (0.87 to 0.99)	0.15 (0.03 to 0.92)
			yes	5	0.99 (0.93 to 1.00)			
		Pathology (100%)	no	6	0.99 (0.93 to 1.00)	1.15 (0.05 to 22.91)	0.96 (0.87 to 0.99)	0.15 (0.03 to 0.92)
			yes	5	0.99 (0.93 to 1.00)			
	Mixed	Pre-specified positivity criteria	no	49	0.96 (0.95 to 0.98)	0.78 (0.47 to 1.28)	0.93 (0.89 to 0.95)	1.29 (0.65 to 2.47)
			yes	44	0.95 (0.94 to 0.97)			
		Blinding ref. std. to index test results	no	83	0.96 (0.95 to 0.97)	0.96 (0.43 to 2.10)	0.93 (0.91 to 0.95)	1.71 (0.60 to 4.74)
			yes	10	0.96 (0.92 to 0.98)			
		All pts. received a ref. std.	no	6	0.95 (0.89 to 0.98)	1.23 (0.50 to 3.10)	0.92 (0.78 to 0.97)	1.32 (0.37 to 4.43)
			yes	87	0.96 (0.95 to 0.97)			
		All pts. received same ref. std.	no	65	0.96 (0.95 to 0.97)	0.74 (0.43 to 1.26)	0.96 (0.95 to 0.97)	0.15 (0.08 to 0.27)
			yes	28	0.95 (0.93 to 0.97)			
		All pts. included in the analysis	no	26	0.94 (0.91 to 0.96)	1.84 (1.06 to 3.15)	0.92 (0.86 to 0.96)	1.28 (0.57 to 2.78)
			yes	67	0.97 (0.96 to 0.97)			
		Pathology (100%)	no	67	0.96 (0.95 to 0.97)	0.92 (0.53 to 1.57)	0.96 (0.95 to 0.97)	0.14 (0.07 to 0.25)
			yes	26	0.96 (0.94 to 0.97)			
		Consecutive/random sample	no	35	0.96 (0.94 to 0.97)	0.96 (0.57 to 1.60)	0.92 (0.88 to 0.95)	1.33 (0.67 to 2.58)
			yes	58	0.96 (0.95 to 0.97)			
Blinding index tests	no	39	0.96 (0.95 to 0.98)	0.82 (0.49 to 1.37)	0.92 (0.87 to 0.95)	1.52 (0.74 to 2.98)		
	yes	54	0.96 (0.94 to 0.97)					

Table 21. Meta-regression results for the impact of risk of bias items on the estimated test performance of imaging tests for the diagnosis of acute appendicitis (continued)

Test	Population	Subgroup	N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity	Test	
US	Adults	Pre-specified positivity criteria	no	26	0.80 (0.71 to 0.87)	2.99 (1.21 to 6.81)	0.89 (0.79 to 0.95)	1.59 (0.44 to 5.13)	
			yes	12	0.92 (0.85 to 0.96)		0.92 (0.81 to 0.97)		
		All pts. received same ref. std.	no	23	0.85 (0.76 to 0.91)	0.93 (0.37 to 2.39)	0.93 (0.87 to 0.97)	0.31 (0.09 to 1.03)	
			yes	15	0.84 (0.73 to 0.92)		0.81 (0.63 to 0.92)		
		All pts. included in the analysis	no	7	0.90 (0.76 to 0.96)	0.59 (0.18 to 1.83)	0.80 (0.47 to 0.95)	2.66 (0.49 to 16.28)	
			yes	31	0.84 (0.76 to 0.90)		0.92 (0.85 to 0.96)		
		Pathology (100%)	no	24	0.87 (0.79 to 0.92)	0.72 (0.30 to 1.83)	0.93 (0.87 to 0.97)	0.31 (0.09 to 1.04)	
			yes	14	0.82 (0.69 to 0.91)		0.80 (0.61 to 0.92)		
		Consecutive/random sample	no	13	0.85 (0.73 to 0.92)	0.96 (0.42 to 2.49)	0.81 (0.63 to 0.92)	3.04 (0.91 to 10.30)	
			yes	25	0.85 (0.77 to 0.91)		0.93 (0.87 to 0.97)		
		Blinding index tests	no	14	0.80 (0.67 to 0.90)	1.64 (0.62 to 3.86)	0.89 (0.76 to 0.96)	1.28 (0.38 to 3.85)	
			yes	24	0.87 (0.80 to 0.92)		0.91 (0.82 to 0.95)		
		Children	Pre-specified positivity criteria	no	50	0.87 (0.83 to 0.91)	1.43 (0.79 to 2.62)	0.90 (0.86 to 0.93)	1.48 (0.82 to 2.88)
				yes	35	0.91 (0.86 to 0.94)		0.93 (0.89 to 0.96)	
	Blinding ref. std. to index test results		no	78	0.88 (0.85 to 0.91)	1.68 (0.57 to 5.51)	0.92 (0.89 to 0.94)	0.84 (0.29 to 2.56)	
			yes	7	0.93 (0.82 to 0.98)		0.90 (0.77 to 0.96)		
	All pts. received same ref. std.		no	68	0.88 (0.84 to 0.91)	1.84 (0.88 to 3.89)	0.93 (0.91 to 0.95)	0.17 (0.08 to 0.35)	
			yes	17	0.93 (0.87 to 0.96)		0.71 (0.56 to 0.82)		
	All pts. included in the analysis		no	22	0.88 (0.80 to 0.93)	1.17 (0.58 to 2.28)	0.92 (0.86 to 0.96)	0.90 (0.44 to 1.89)	
			yes	63	0.89 (0.85 to 0.92)		0.91 (0.88 to 0.94)		
	Pathology (100%)		no	66	0.88 (0.84 to 0.91)	1.46 (0.73 to 2.82)	0.93 (0.91 to 0.95)	0.24 (0.12 to 0.48)	
			yes	19	0.91 (0.85 to 0.95)		0.77 (0.64 to 0.86)		
	Consecutive/random sample		no	39	0.87 (0.81 to 0.91)	1.50 (0.82 to 2.70)	0.94 (0.91 to 0.96)	0.53 (0.28 to 0.98)	
			yes	46	0.91 (0.86 to 0.94)		0.89 (0.84 to 0.92)		
	Blinding index tests		no	32	0.86 (0.79 to 0.91)	1.53 (0.86 to 2.97)	0.91 (0.86 to 0.94)	1.17 (0.62 to 2.15)	
			yes	53	0.90 (0.87 to 0.93)		0.92 (0.88 to 0.94)		

Table 21. Meta-regression results for the impact of risk of bias items on the estimated test performance of imaging tests for the diagnosis of acute appendicitis (continued)

Test	Population	Subgroup	N Studies	Sensitivity	Relative Sensitivity	Specificity	Relative Specificity	Test
US (ctd.)	Mixed	Pre-specified positivity criteria	no	73	0.85 (0.80 to 0.89)	1.29 (0.78 to 2.23)	0.87 (0.82 to 0.90)	1.91 (1.13 to 3.25)
			yes	52	0.88 (0.83 to 0.92)		0.93 (0.89 to 0.95)	
		Blinding ref. std. to index test results	no	116	0.86 (0.82 to 0.89)	1.37 (0.52 to 3.88)	0.89 (0.86 to 0.92)	1.20 (0.43 to 3.42)
			yes	9	0.89 (0.77 to 0.96)		0.91 (0.79 to 0.97)	
		All pts. received a ref. std.	no	11	0.87 (0.74 to 0.95)	0.89 (0.34 to 2.23)	0.91 (0.80 to 0.97)	0.78 (0.28 to 2.26)
			yes	114	0.86 (0.83 to 0.89)		0.89 (0.86 to 0.92)	
		All pts. received same ref. std.	no	95	0.89 (0.86 to 0.92)	0.38 (0.21 to 0.67)	0.91 (0.89 to 0.93)	0.39 (0.21 to 0.72)
			yes	30	0.75 (0.65 to 0.83)		0.80 (0.70 to 0.88)	
		All pts. included in the analysis	no	34	0.78 (0.68 to 0.85)	2.15 (1.24 to 4.14)	0.88 (0.81 to 0.93)	1.28 (0.67 to 2.31)
			yes	91	0.89 (0.85 to 0.91)		0.90 (0.87 to 0.93)	
		Pathology (100%)	no	99	0.89 (0.86 to 0.91)	0.35 (0.19 to 0.62)	0.91 (0.88 to 0.93)	0.43 (0.22 to 0.83)
			yes	26	0.73 (0.61 to 0.82)		0.81 (0.71 to 0.89)	
		Consecutive/random sample	no	53	0.83 (0.76 to 0.88)	1.58 (0.90 to 2.71)	0.88 (0.83 to 0.92)	1.24 (0.71 to 2.28)
			yes	72	0.88 (0.84 to 0.92)		0.90 (0.87 to 0.93)	
		Blinding index tests	no	52	0.85 (0.79 to 0.90)	1.18 (0.70 to 2.06)	0.89 (0.85 to 0.93)	1.05 (0.60 to 1.80)
			yes	73	0.87 (0.83 to 0.91)		0.90 (0.86 to 0.93)	

CT = computed tomography; MRI = magnetic resonance imaging; N = number; pts. = patients; US = ultrasound Sensitivity, relative sensitivity, specificity, and relative specificity values are medians and 95% central credible intervals when 5 or more studies were available; medians and minimum to maximum values are reported when <5 studies were available; when a single study was available we report the estimate from that study.

Classifiers and Computer-Aided Diagnosis

We also identified 52 studies of various multivariable classifiers (other than diagnostic scores). We did not extract detailed information from these studies because they generally did not report results in a way that would allow the use of the classifiers in current practice or described software that is not currently applicable. For completeness, a list of these studies is provided in Appendix E.

Test Performance of Diagnostic Laparoscopy

Fifty-five studies, published between 1974 and 2014, reported information on the test performance of diagnostic laparoscopy. The sample sizes ranged from 23 to 1899, and prevalence of appendicitis ranged from 3 to 95 percent, with a median of 65 percent.

The reporting of methods and test performance outcomes in these studies was less complete than that of studies of other tests. In addition, studies had heterogeneous (and often incompletely reported) policies for the management of cases when laparoscopy did not reveal an inflamed appendix or no other pathology. Such differences can influence the estimates of test performance and for this reason we did not perform any quantitative synthesis for the test performance of diagnostic laparoscopy. It is important to note that patients included in studies of diagnostic laparoscopy (e.g., have more severe symptoms, or have atypical findings in other) are different from patients included in studies of non-invasive tests (even if the selection criteria are not clearly presented). Thus, indirect comparisons among test categories are not likely to be meaningful.

Because of the generally poor reporting, quality assessment of these studies was challenging. Most reported their criteria for a positive laparoscopic examination, but did not discuss how and when it was established. The reference standard varied across studies and populations. Generally, more than 90 percent of enrolled patients were included in the analysis and received a reference standard, but in approximately half of the studies there was differential verification.

Sixteen studies looked at laparoscopy in women of reproductive age. This was the only subgroup reported on in more than two studies. Mean and median ages ranged from 21 to 30. Prevalence ranged from 39 to 92 percent of the population (median 59%). These results are reported along with the others below.

Tests Positive for Appendicitis

Generally, tests were reported as positive for appendicitis when the appendix appeared inflamed, though the precise definition varied across studies. Forty-two studies reported on this outcome. The median total positive diagnoses in those receiving diagnostic laparoscopy was 64 percent (min 23%, max 100%, 25th percentile 51%, 75th percentile 78%). The median correct diagnoses of appendicitis in those receiving diagnostic laparoscopy was 57 percent (min 16%, max 100%, 25th percentile 47%, 75th percentile 75%). The median incorrect diagnoses of appendicitis in those receiving diagnostic laparoscopy was 0 percent (min 0%, max 21%, 25th percentile 0%, 75th percentile 6%).

In 16 studies of women of reproductive age, the median total positive diagnoses in those receiving diagnostic laparoscopy was 64 percent (min 22%, max 92%, 25th percentile 56%, 75th percentile 74%). The median correct diagnoses of appendicitis in

those receiving diagnostic laparoscopy was 57 percent (min 16%, max 92%, 25th percentile 53%, 75th percentile 68%). The median proportion of incorrect diagnoses of appendicitis in those receiving diagnostic laparoscopy was 3 percent (min 0%, max 1%, 25th percentile 0%, 75th percentile 6.5%).

Sensitivity and Specificity

For the 54 studies for which they could be calculated, the median sensitivity and specificity were 100 and 89 percent, respectively. However, there was a wide range with sensitivity ranging from 37 to 100 percent (25th percentile 95%, 75th percentile 100%) and specificity ranging from 0 to 100 percent (25th percentile 73%, 75th percentile 100%). This variability likely reflects the heterogeneous populations evaluated in these studies (which often do not describe the details of patient selection).

In the 16 studies that reported on women of reproductive age, the median sensitivity was 100 percent (min 90%, max 100%, 25th percentile 100%, 75th percentile 100%), and the median specificity was 89 percent (min 73%, max 100%, 25th percentile 79%, 75th percentile 100%).

Tests Positive for Other Pathology

Forty-one studies reported some information on other pathology diagnosed at laparoscopy. The median proportion of patients with non-appendiceal pathology identified was 22 percent (min 0%, max 71%, 25th percentile 11.5%, 75th percentile 34%). Only six small studies reported that other pathology was found when appendicitis was also present. The median was 5 percent (min 0.5%, max 20%, 25th percentile 2%, 75th percentile 13%). In nine studies of women of reproductive age, the median proportion of patients with non-appendiceal pathology identified was 23 percent (min 6%, max 40%, 25th percentile 18%, 75th percentile 26%), none were in patients who also had appendicitis.

Appendix not Visualized (Indeterminate Findings)

Twenty-six studies reported at least partially on inability to visualize the appendix. The median was 6 percent (min 1%, max 51%, 25th percentile 3%, 75th percentile 10%). These were slightly more likely to be negative than positive. Median proportions were 2.6 percent and 1 percent, respectively. The range for patients without appendicitis was 0 to 51 percent (25th percentile 1%, 75th percentile 6%). The range for those with appendicitis was 0 to 30 percent (25th percentile 0%, 75th percentile 7%). In ten studies of women of reproductive age, the median was 5 percent (min 3%, max 17%, 25th percentile 4.5%, 75th percentile 8%). In this population, there was little difference between those with and without appendicitis. The median proportion with appendicitis was 3.5 percent (min 0%, max 10%, 25th percentile 0%, 75th percentile 6%). The median proportion without appendicitis was 3 percent (min 1%, max 19%, 25th percentile 2%, 75th percentile 6%).

No Cause Found

Thirty-five studies gave information on cases in which the appendix appeared normal and no other pathology was found. The median percentage of patients who had diagnostic laparoscopy with no pathology found was 11 percent (min 5%, max 26%, 25th percentile

8%, 75th percentile 18%). Again, these were more likely to be patient without appendicitis. The median was 4 percent with appendicitis and 9 percent without. The range for patients without appendicitis was 2 to 29 percent (25th percentile 5%, 75th percentile 14%). The range for those with appendicitis was 1 to 9 percent (25th percentile 1%, 75th percentile 5%), but these were less likely to be reported (9 studies).

In ten studies of women of reproductive age, the percentage of patients who had diagnostic laparoscopy with no pathology found was only reported for those without appendicitis. The median was 13 percent (min 2%, max 29%, 25th percentile 8%, 75th percentile 19%).

Risk of Bias in Studies of Diagnostic Laparoscopy

Most studies enrolled patients using a consecutive or random sampling method, one explicitly stated that the authors used a convenience sample, and the sampling method was unclear in 25. Thirty-one studies avoided inappropriate exclusions, but this could not be assessed in 24.

In 46 studies it was clear that the index test results were interpreted without knowledge of the results of the reference standard, but this was unclear in nine. Only two studies reported that the criterion for a positive diagnostic laparoscopy was prespecified, 52 were unclear, and one clearly did not use a prespecified threshold. Only four studies clearly stated that the reference standard results were interpreted without knowledge of the results of the index test; 51 were unclear.

The reference standard varied widely among studies from all receiving pathologic diagnosis to some receiving pathologic diagnosis and others receiving some sort of followup. In 40 studies the reference standard was deemed likely to correctly classify the target condition, one clearly was not, and in 14 studies it was unclear. Fifteen studies reported an appropriate interval between index tests and reference standard, six clearly did not have an appropriate interval, 13 were unclear, and in 21 this was not applicable because all patients had verification by pathology. Fifty studies had all patients receiving a reference standard, one had partial verification, and four were unclear. Nearly all studies (53) included all patients in the analysis, one did not, and the other as unclear. However, because of the fact that the reference standard varied based on index test in some studies, 24 studies had all patients receive the same reference standard, 28 had patients receiving different reference standards, and three were unclear.

Comparative Assessments of Test Performance

Information on comparative test performance was sparse. The majority of included studies assessed a single index test; thus allowing only *indirect* comparisons among tests of interest (i.e., comparisons based on the test specific estimates presented in the preceding sections of this chapter). Because studies differ in many ways, including the patient populations they sample, the selection criteria they use, and the specific implementation of the various test strategies, cross-study comparisons provide only weak evidence regarding comparative test performance (because any differences in test performance may be attributable to cross-study differences in factors other than specific test assessed). For this reason, our assessment of comparative test performance relied primarily on randomized and non-randomized *direct comparisons* (i.e., within-study) of tests.

Randomized Comparisons of Alternative Tests

Thirty-six RCTs reported information on comparative test performance; all studies had a parallel arm design (i.e., none used a paired design). Overall, on the basis of items from the Cochrane risk of bias tool, RCTs were deemed to be at moderate risk of bias. Details on the risk of bias of individual studies are presented in the next chapter of this report (Key Question 2) because the studies assessed outcomes beyond test performance. Results on selected test performance comparison are summarized in Tables 22 to 25; additional extracted data are presented in Appendix F. Data were sparse because each possible contrast (between alternative test strategies or versions of a test strategy) were typically examined by one or two trials and because not all trials reported information on the same outcomes. Studies were small, produced imprecise results, therefore we could not make any definitive conclusions about the relative test performance of the strategies compared based on RCTs.

Nonrandomized Comparisons of Alternative Tests

Non-randomized studies of test performance were not synthesized with RCTs because the latter were deemed to be at substantial risk of bias (confounding and selection bias) and often provided inadequate information to understand their design (see below).

Nonrandomized Comparisons of CT and US

Fifty-three studies reported results in cohorts using both CT and US as index tests, potentially permitting direct (within-study) nonrandomized comparisons of these modalities. Ten studies investigated CT as a replacement for US, 13 investigated US as a triage test for CT, and 30 studies were unclear about the actual role of testing that was being evaluated (studies often used convenience samples of patients that were selected using criteria that were often not reported; results from these studies are presented in Figure 11 for completeness; though these studies suggested that CT generally has better test performance than US, the strength of this evidence was itself weakened by the lack of information on the exact study design).

Nine of the studies had a paired design (both tests applied to the same patient group) and 44 had a parallel group design (separate groups of patients received each test). Figure 11 presents diagnostic ORs from these studies (higher values indicate better performance) and relative diagnostic ORs (comparing CT vs. US; values higher than 1 indicate that CT had better test performance than US). In general, CT had better test performance than US, when used as a replacement test. In the triage context, CT had high test performance (diagnostic odds ratios higher than 10 and often higher than 100) in patient populations selected on the basis of US results (typically, nondiagnostic US findings, or negative findings in the presence of symptoms suggestive of appendicitis).

Nonrandomized Comparisons of MRI and US

Eight studies reported results in cohorts using both MRI and US as index tests, potentially permitting direct (within-study) nonrandomized comparisons of these modalities. Four studies investigated MRI as a replacement for US, one investigated US as a triage test for MRI, and three studies were unclear about the actual role of testing that was being evaluated (these studies tended to use convenience samples of patients that were selected for a specific test using criteria that were often not reported; this studies

were included in the review for completeness; however, the strength of the evidence they provide is weakened by the lack of information on the exact study design). Four of the studies had a paired design (both tests applied to the same patient group) and four had a parallel group design (separate groups of patients received each test). Studies investigating MRI as a replacement test suggested that MRI, when used as a replacement test for US has greater test performance, however the available studies are few and have produced rather imprecise results.

Table 22. Test performance comparisons in randomized trials – CT versus standard of care

Author, Year [PMID]	Contrast	Sensitivity Group 1	Sensitivity Group 2	Difference in Sensitivity	Specificity Group 1	Specificity Group 2	Difference in Specificity	Accuracy Group 1	Accuracy Group 2	Difference in Accuracy
Hong, 2003 [14588157]	Clinical observation and abdominal/pelvic CT vs. clinical observation alone (women of reproductive age)	5/5	11/11	(-0.25 to 0.25); p = 1.000	22/24	7/8	0.04 (-0.21 to 0.30); p = 0.748	27/29	18/19	-0.02 (-0.15 to 0.12); p = 0.814
	Clinical observation and abdominal/pelvic CT vs. Clinical observation alone (total study population)	30/33	42/42	-0.09 (-0.20 to 0.02); p = 0.096	42/45	19/26	0.20 (0.02 to 0.39); p = 0.032	72/78	61/68	0.03 (-0.07 to 0.12); p = 0.585
Lopez, 2007 [18186378]	Clinical observation and abdominal/pelvic CT vs. clinical observation alone	17/19	22/22	-0.11 (-0.26 to 0.05); p = 0.188	22/23	21/24	0.08 (-0.07 to 0.24); p = 0.307	39/42	43/46	-0.01 (-0.11 to 0.10); p = 0.908
Walker, 2000 [11182396]	Limited CT scan with colorectal contrast vs. standard management	30/32	29/29	-0.06 (-0.16 to 0.04); p = 0.226	25/25	27/34	0.21 (0.06 to 0.35); p = 0.006	55/57	56/63	0.08 (-0.02 to 0.17); p = 0.102

CI = confidence interval; CT = computed tomography

Trial groups are numbered in the order they are described in the corresponding “Contrast”. Differences between groups are calculated by subtracting group 2 values from group 1 values and are presented with corresponding 95% CIs.

Table 23. Test performance comparisons in randomized trials – alternative CT strategies

Author, Year [PMID]	Contrast	Sensitivity Group 1	Sensitivity Group 2	Difference in Sensitivity	Specificity Group 1	Specificity Group 2	Difference in Specificity	Accuracy Group 1	Accuracy Group 2	Difference in Accuracy
Hekimoglu, 2011 [22191292]	IV and oral contrast enhanced CT vs. IV contrast-enhanced CT (Radiologist 1)	31/32	21/25	0.13 (-0.03 to 0.28); p = 0.105	67/68	71/75	0.04 (-0.02 to 0.10); p = 0.194	98/100	92/100	0.06 (0.00 to 0.12); p = 0.049
	IV and oral contrast enhanced CT vs. IV contrast-enhanced CT (Radiologist 2)	30/32	18/25	0.22 (0.02 to 0.41); p = 0.029	66/68	67/75	0.08 (0.00 to 0.16); p = 0.060	96/100	85/100	0.11 (0.03 to 0.19); p = 0.007
Hershko, 2007 [17566826]	IV and oral contrast-enhanced CT vs. nonenhanced CT (Radiologist 1)	43/43	19/21	0.10 (-0.04 to 0.23); p = 0.171	36/41	30/35	0.02 (-0.13 to 0.17); p = 0.789	79/84	49/56	0.07 (-0.03 to 0.17); p = 0.201
	IV and oral contrast-enhanced CT vs. rectal contrast-enhanced CT (Radiologist 1)	43/43	37/39	0.05 (-0.03 to 0.13); p = 0.216	36/41	36/39	-0.05 (-0.18 to 0.09); p = 0.499	79/84	73/78	(-0.07 to 0.08); p = 0.904
Kepner, 2012 [22633722]	IV contrast-enhanced CT vs. IV and oral contrast-enhanced CT	41/41	35/35	(-0.05 to 0.05); p = 1.000	72/73	75/78	0.02 (-0.03 to 0.08); p = 0.335	113/114	110/113	0.02 (-0.02 to 0.05); p = 0.309
Hershko, 2007 [17566826]	Rectal contrast-enhanced CT vs. nonenhanced CT (Radiologist 1)	37/39	19/21	0.04 (-0.10 to 0.19); p = 0.548	36/39	30/35	0.07 (-0.08 to 0.21); p = 0.366	73/78	49/56	0.06 (-0.04 to 0.16); p = 0.243
Mittal, 2004 [15136349]	Standard triple-contrast abdominopelvic CT scan vs. focused pelvic scan with rectal contrast only	43/44	36/36	-0.02 (-0.09 to 0.04); p = 0.488	4/8	3/3	-0.50 (-0.96 to -0.04); p = 0.033	47/52	39/39	-0.10 (-0.19 to -0.01); p = 0.034
Kim, 2012 [22533576]	Standard-dose CT vs. low-dose CT	171/180	156/165	(-0.04 to 0.05); p = 0.850	244/260	250/268	(-0.04 to 0.05); p = 0.792	415/440	406/433	(-0.03 to 0.04); p = 0.730

CI = confidence interval; CT = computed tomography; IV = intravenous

Trial groups are numbered in the order they are described in the corresponding "Contrast". Differences between groups are calculated by subtracting group 2 values from group 1 values and are presented with corresponding 95% CIs.

Table 24. Test performance comparisons in randomized trials – CT versus US

Author, Year [PMID]	Contrast	Sensitivity Group 1	Sensitivity Group 2	Difference in Sensitivity	Specificity Group 1	Specificity Group 2	Difference in Specificity	Accuracy Group 1	Accuracy Group 2	Difference in Accuracy
Horton, 2000 [10930484]	CT vs. US	36/37	23/25	0.05 (-0.07 to 0.17); p = 0.381	9/12	1/3	0.42 (-0.17 to 1.00); p = 0.164	45/49	24/28	0.06 (-0.09 to 0.21); p = 0.426
Kaiser, 2002 [12034928]	US + CT vs. US only	133/135	94/109	0.12 (0.05 to 0.19); p < 0.001	162/182	165/174	-0.06 (-0.11 to 0.00); p = 0.042	295/317	259/283	0.02 (-0.03 to 0.06); p = 0.481

CI = confidence interval; CT = computed tomography; US = ultrasound

Trial groups are numbered in the order they are described in the corresponding “Contrast”. Differences between groups are calculated by subtracting group 2 values from group 1 values and are presented with corresponding 95% CIs.

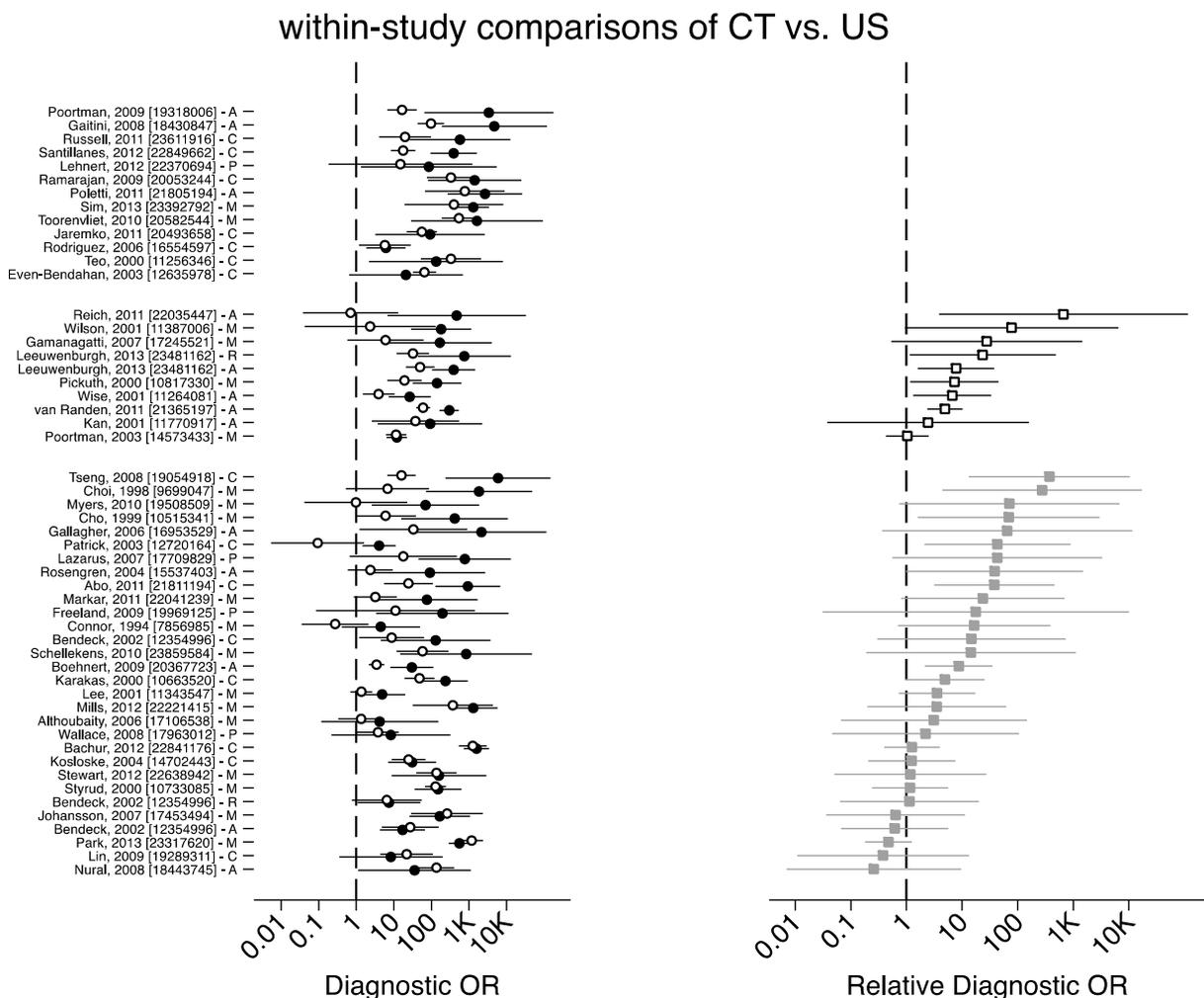
Table 25. Test performance comparisons in randomized trials – multivariable diagnostic scores versus no scores

Author, Year [PMID]	Contrast	Sensitivity Group 1	Sensitivity Group 2	Difference in Sensitivity	Specificity Group 1	Specificity Group 2	Difference in Specificity	Accuracy Group 1	Accuracy Group 2	Difference in Accuracy
Lintula, 2009 [18841382]	Management based on a diagnostic scoring system for children vs. standard clinical assessment and management	24/24	26/27	(-0.06 to 0.14); p = 0.467	37/42	23/33	0.18 (0.00 to 0.37); p = 0.051	61/66	49/60	0.11 (-0.01 to 0.22); p = 0.071
Lintula, 2010 [20379739]	Management based on a diagnostic scoring system for children vs. standard clinical assessment and management	45/52	32/36	-0.02 (-0.16 to 0.11); p = 0.739	26/44	36/45	-0.21 (-0.40 to -0.02); p = 0.028	71/96	68/81	-0.10 (-0.22 to 0.02); p = 0.099

CI = confidence interval

Trial groups are numbered in the order they are described in the corresponding “Contrast”. Differences between groups are calculated by subtracting group 2 values from group 1 values and are presented with corresponding 95% CIs.

Figure 11. Test performance results in studies evaluating both CT and US as index tests



CT = computed tomography; OR = odds ratio; PMID = PubMed identification number; US = ultrasound

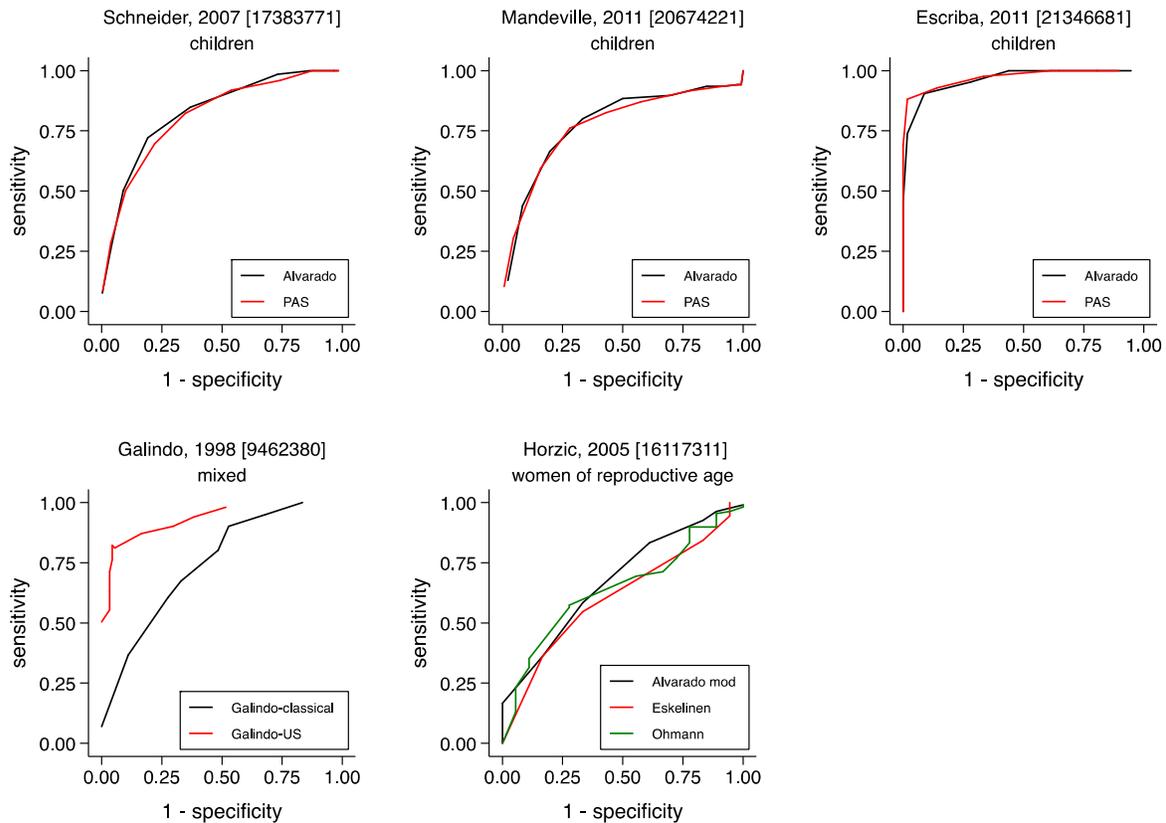
Forest plot of results from studies assessing CT and US as index tests. Studies are ordered by the magnitude of the difference between the diagnostic OR of CT and US and are labeled by their first author, year of publication, and PMID. Both panels: top group of studies = studies evaluating US as a triage test for CT; middle group of studies = studies evaluating CT as a replacement test for US, bottom = studies where the role of testing evaluated was unclear. Capital letters in the y-axis label denote the population enrolled: A = adults; C = children; M = mixed; R = women of reproductive age; P = pregnant women. Left panel: diagnostic ORs for CT (black circles) and US (white circles), with corresponding confidence intervals; greater values denote better test performance. Right panel relative ORs comparing the test performance of CT and US (relative ORs are not shown for studies evaluating US as a triage test); values > 1 denote better test performance by CT (as compared to US). X-axis scale is logarithmic on both panels. For paired designs we have assumed that the correlation between the diagnostic ORs of the tests being compared is 0 (this correlation was not reported in the primary studies). This is a conservative assumption (i.e., it leads to wide confidence intervals) because the correlation is generally expected to be positive, and accounting for it would result in narrower confidence intervals compared to those depicted in the graph.

Nonrandomized Comparisons of Diagnostic Scores

Eight studies reported direct comparisons among alternative diagnostic scores for appendicitis.^{68-70, 25,71-74} Three studies included children, one included women of reproductive age, and four included mixed populations. Five of the studies reported results on three or more score cutoffs, and their results are shown in Figure 12. Across all eight studies, differences in test performance between scores were small; this was particularly true for the comparison of the Alvarado and PAS scores applied to children with suspected acute appendicitis. The one exception was a study that compared a multivariable diagnostic score based on clinical symptoms and signs versus a score combining the same clinical variables with the addition of US: incorporation of US information improved test performance substantially, with respect to both sensitivity and specificity.⁷⁴

Figure 12. Receiver operating characteristic curves from studies comparing two or more appendicitis diagnostic scores

7



Mod. = modified; PAS = pediatric appendicitis score; US = ultrasound

Each panel represents a within-study comparison among two or more diagnostic scores. Study results were used to reconstruct the empirical receiver operating characteristic curves. In the study by Galindo et al. the empirical ROC curve appears to not be monotonic; we have verified our data extraction against the paper and we believe that this may be the results of a reporting or typographical error in the publication.

Key Question 2: What is the comparative effectiveness of alternative diagnostic tests, alone or in combination, for patients with RLQ pain and suspected acute appendicitis?

Included Studies With Information on the Comparative Effectiveness of Alternative Test Strategies

Fifty-four studies provided information on the comparative effectiveness of alternative test strategies (36 RCTs and 18 NRCSs) in patients with RLQ pain. We only considered RCTs and NRCSs for the assessment of comparative effectiveness. Indirect (cross-study) comparisons for such outcomes are likely to be confounded by factors that differ across studies. We only considered NRCSs that enrolled at least 1000 patients because comparative effectiveness outcomes are relatively rare; as such, a large sample is needed to obtain reliable estimates of effect – especially if statistical adjustments for possible confounders are to be performed. Detailed information from the included RCTs and NRCS is presented in Appendix F; key study characteristics and findings are summarized below. Because pregnant women are underrepresented in RCTs and NRCSs of alternative test strategies, we collected information on fetal and maternal outcomes from non-comparative cohort studies that enrolled at least 10 patients. Many of the included studies were small and may have produced unstable estimates of event rates, as well as treatment effects. Furthermore, selection criteria differed substantially among trials (as would be expected by the very different nature of the compared test modalities), rendering indirect comparisons uninformative.

Computed Tomography Versus Routine Management or Clinical Assessment

Seven RCTs⁷⁵⁻⁸³ (described in 9 publications) with a total of 1177 participants compared the use of CT imaging to routine management in the diagnosis of appendicitis and reported comparative effectiveness outcomes (Table 26). Four studies reported details of adequate random sequence generation,^{76,78-80,82} and two studies described adequate allocation concealment procedures.⁷⁶ Two studies described blinding of outcome assessors to group assignment^{76,82} Loss to followup was greater than 10% in three studies.^{75,76,78}

Hong et al. (2003) reported no significant difference between clinical observation alone versus clinical observation and abdominopelvic CT in terms of perforations ($p = 0.4$) among adults evaluated for possible acute appendicitis. In the clinical observation group, there were four perforations in 68 patients, while in the clinical observation plus CT group, there were seven perforations in 78 patients. The mean length of hospital stay was also not significant ($p = 0.55$) at 2.4 (± 3.2) days in the clinical observation group and 2.2 (± 2.2) days in the clinical observation and CT group. However, the mean time from presentation to surgery was significantly less in the clinical observation group ($P < 0.01$), at 10.6 hours as compared to 18.7 hours in the clinical observation and CT group.⁷⁵

Lopez et al. (2007) also compared clinical observation alone versus clinical observation and abdominopelvic CT among women of childbearing age with possible acute appendicitis. There were no perforations in either group, and both groups reported a median days of hospital stay at 1 day (range: clinical observation alone 0 to 7 days, clinical observation plus CT 0 to 6 days; $p = 0.22$).⁷⁸

Walker et al. (2000) reported a higher negative appendectomy rate in the standard care group (7 of 36), as compared to the group that had a limited CT scan versus colorectal contrast (2 of 38; $p = 0.08$), among adult patients receiving surgical consultation for appendicitis.⁸³

Lee et al. (2007) compared selective versus mandatory CT imaging in adult patients presenting with acute right lower quadrant pain and suspected acute appendicitis. They reported a difference of 8.2 percent (95% CI, -8.0, 24.4) for perforations, with a rate of 18.4 percent (7 of 38) in the selective imaging group and 10.3% (4 of 39) in the mandatory imaging group. The difference in negative appendectomy rates was 11.3 percent (95% CI, -3.5, 26.3), with a rate of 13.9 percent (6 of 43) in the selective imaging group and 2.6 percent (1 of 39 patients) in the mandatory imaging group. The mandatory CT group had 0.9 hour longer mean time from ED triage to surgery, 10.9 (± 6.9) hours as compared to 10 (± 7) hours in the selective imaging group.⁷⁶

Lehtimaki et al. (2013) compared selective and mandatory CT imaging among patients presenting to a surgical emergency department with acute abdominal pain lasting more than 2 hours and less than 7 days. There was one negative appendectomy in 111 patients in the selective group, and one negative appendectomy in 143 patients in the mandatory group ($p > 0.99$). The mean length of hospital stay was significantly shorter ($p = .01$) in the selective group (2.5 days, min 0, max 21) as compared to the mandatory group (3.7 days, min 0, max 32).⁷⁷

Three publications presenting results from the study by Ng et al. (original publication 2002; additional information presented in 2007 and 2010) reported outcomes for the same cohort of adult patients with acute abdominopelvic pain admitted under the care of the surgical team in a single academic hospital and randomized to either current standard practice versus early CT (within 24 hours). Both groups had a median five days' hospital stay ($p = 0.2$), but there were significantly more deaths in the standard care group (7 of 63) than in the early CT group (0 of 55; $p = 0.014$).⁷⁹⁻⁸¹ Of note, mortality was not an a priori endpoint for this study. Two of these studies also reported information on the impact of testing on diagnostic confidence. Both reported that diagnostic confidence increased between admission and 24 hours after admission in both groups, but that the increase was not significantly greater in the CT group (25.2%) than in the standard care group (24.9%; $p = 0.098$).^{79,81}

Sala et al. (2009) randomized patients presenting to the "on-call" surgeons with acute "nonspecific" abdominal pain to current standard practice versus CT within one hour. This study also reported length of stay and mortality. The median length of hospital stay for the standard care group was 5.3 days (25th percentile 2 days, 75th percentile 9.5 days), and the median for the early CT group was 4.2 days (25th percentile 1.1 days, 75th percentile 7.6 days). There were 11 deaths within 6 months in the standard care group, as compared to six of 99 in the early CT group ($p = 0.31$).⁸²

Seven large NRCS with a total of 149,422 participants compared the use of CT imaging to routine management in the diagnosis of appendicitis and reported comparative effectiveness outcomes.⁸⁴⁻⁹⁰ One study was prospective, with more than 90 percent follow-up;⁸⁶ the others were retrospective.

McGory et al. reported a non-significant difference in negative appendectomy rate in 4731 patients with a CT scan (8%) versus 70721 patients who did not have a CT scan (9.4%; $p = 0.36$). However, there were statistically significantly more cases of appendicitis with abscess in the CT group (18.6%) compared to the non-CT group (9.3%). ($p < 0.001$), and mean and median length of stay was statistically significantly longer in the CT group (mean 5.46 ± 5.21 days;

median 4, min 0, max 83) than the non-CT group (mean 3.28 ± 4.04 days; median 2, min 0, max 289) ($p < 0.001$).⁸⁴

Raja et al. and Wagner et al. found significant differences in the negative appendectomy rate between patients with and without CT before surgery. Raja et al. reported a negative appendectomy rate of 1.7 percent in a group of 637 patients, 97.5 percent of whom had a CT scan and 23 percent in a group of 971 patients only one percent of whom had a CT scan ($p < 0.001$).⁸⁶ Wagner et al. also found a lower negative appendectomy rate in 1070 patients who had CT scan (7.2%) compared to 129 patients who did not (14%; $p = 0.007$).⁸⁹ Bachur et. al reported on 55,227 children based on age. For children under five, they found that CT reduced the negative appendectomy rate significantly ($p < 0.001$; boys: OR 0.18; 95% CI 0.12 to 0.28; girls: OR 0.11; 95% CI 0.07 to 0.18) from approximately 22 percent without CT to approximately 5 percent with CT, but for children between five and ten (boys: $p = 0.123$; OR 0.68; 95% CI 0.42 to 1.11; girls: $p = 0.236$; OR 0.78; 95% CI 0.51 to 1.18) and children over ten (boys: $p = 0.556$; OR 1.10; 95%CI 0.79 to 1.57; girls: $p = 0.598$; OR 1.07; 95%CI 0.83 to 1.38) the reduction was not significant.⁹⁰ Petrosyan et al. reported similar overall negative appendectomy rates between the groups (with CT 6%, 31 of 546; without CT 6%; 23 of 383), but in to patients with an Alvarado scores of 5 to 7, the CT group had a lower negative appendectomy rate (3.3%; 12 of 357) than the non-CT group (6.2%; 20 of 321) (mean difference 2.9%, 95% CI: 0.3% to 6%).⁸⁵ Tsao et al. reported a lower perforated appendix rate in children who had a CT scan (24.6%, 159 of 646) than those who did not (33.8%, 117 of 346).⁸⁸

Shalligram et al. reported significant differences between 11,340 men (18 to 55 years old) who had a CT scan as part of their diagnostic workup and 1888 who did not. Mean length of stay was statistically significantly longer for those with CT scan (1.66 ± 1.63 days) than those who did not (1.37 ± 0.6 days) ($p < 0.001$). However, readmission within 30 days, morbidity, and ICU admission were lower in the CT group. Readmission within 30 days was 1.8 percent in the CT group compared to 5.13% in the non-CT group ($p < 0.001$). Morbidity was 0.86 percent in the CT group, compared to 2.2 percent in the non-CT group ($p < 0.001$). The rate of ICU admissions was also lower in the CT group (1.38%) compared to the non-CT group (1.8%), but this was not significant ($p = 0.19$).

Table 26. Randomized comparisons of CT versus routine management with respect to clinical outcomes and resource utilization

Comparison	Outcome	Author, Year [PMID]	Outcome Rate or Mean in Group 1	Outcome Rate or Mean in Group 2	Between-Group Difference*
CT vs. routine management	Deaths	Ng, 2002 [12480851]	0/57 (0.0%)	7/63 (11.1%)	-0.11 (-0.19 to -0.03); p = 0.008
		Sala, 2007 [17901913]	6/99 (6.1%)	11/99 (11.1%)	-0.05 (-0.13 to 0.03); p = 0.203
	Length of Stay	Hong, 2003 [14588157]	2.00 days (2.10)	2.30 days (2.30)	-0.30 days (-1.59 to 0.99); p = 0.648 (women of reproductive age)
		Hong, 2003 [14588157]	2.20 days (2.20)	2.40 days (3.20)	-0.20 days (-1.10 to 0.70); p = 0.664 (all patients)
		Ng, 2002 [12480851]	5.30 days	6.40 days	-1.10 days
	Negative appendectomy	Walker, 2000 [11182396]	2/65 (3.1%)	7/63 (11.1%)	-0.14 (-0.29 to 0.01); p = 0.060
	Perforations	Hong, 2003 [14588157]	7/78 (9.0%)	4/68 (5.9%)	0.03 (-0.05 to 0.12); p = 0.474
		Ng, 2002 [12480851]	1/57 (1.8%)	5/63 (7.9%)	-0.06 (-0.14 to 0.01); p = 0.106
	Time to Surgery	Hong, 2003 [14588157]	27.40 hours (34.10)	10.80 hours (6.40)	16.60 hours (3.86 to 29.34); p = 0.011 (women of reproductive age)
		Hong, 2003 [14588157]	18.70 hours (18.80)	10.60 hours (8.40)	8.10 hours (3.47 to 12.73); p = 0.001 (all patients)

CT=computed tomography

*Risk difference for binary outcomes; mean difference for continuous outcomes. For continuous outcomes, p-values are missing when studies did not report adequate data to calculate them.

Alternative Types of Computed Tomography

Four RCTs,⁹¹⁻⁹⁴ with a total of 1,441 participants, compared different types of CT imaging for the diagnosis of appendicitis and reported comparative effectiveness outcomes (Table 27). One study reported details of random sequence generation, adequate allocation concealment procedures, and blinding of outcome assessors to group assignment.⁹³ All studies had loss to follow-up of less than 10 percent. Three of these studies looked at differing contrast regimens for CT. Mittal et al. (2004) compared CT scans with rectal contrast only versus scans using oral, rectal, and intravenous contrast among patients with an “uncertain” diagnosis of appendicitis aged 6 years of age or older. They reported similar negative appendectomy rates in the two groups, 7.7 percent (3 of 39) in the rectal contrast group and 8 percent (4 of 48; p > 0.99) in the triple contrast group. The perforation rate was lower in the rectal contrast group (3%, 1 of 36) than in the triple contrast group (30%, 13 of 44; p = 0.002); one patient in each group died of sepsis due to perforated appendicitis (p > 0.99). However, the mean time from emergency department presentation to operation was lower in the triple contrast group (8.3 hours) than the rectal contrast group (12.2 hours).⁹⁴ Hersko et al. (2007), in a randomized study of a mixed patient population (16 to 83 years of age) with suspected acute appendicitis found that with no contrast, the negative appendectomy rate of CT was 25 percent (7 of 28), while with intravenous and oral contrast it was lower at 10 percent (5 of 48; p = 0.112 vs. no contrast) and with rectal contrast even lower at 7 percent (3 of 42; p = 0.08 vs. no contrast; omnibus p = 0.07 across all 3 groups).⁹¹ Kepner et al. (2012) reported a shorter mean time from emergency department

presentation to disposition in the group with intravenous contrast enhanced CT alone (6:41; 25th percentile 5:03, 75th percentile 8:49) as compared to the group that had both oral and intravenous contrast (8:12; 25th percentile 6:40, 75th percentile 9:44).

Kim et al. randomized patients with suspected acute appendicitis (15 to 44 years of age) to low-dose versus standard-dose CT and examined perforation and negative appendectomy rates, median time from CT to appendectomy, and median number of days of hospital stay. Only median time from CT to appendectomy showed a statistically significant difference ($p = 0.02$) with standard dose CT shorter (5.6 hours, 25th percentile 3.4, 75th percentile 9.2) than low-dose CT (7.1 hours, 25th percentile 4.3, 75th percentile 11.7). Median length of hospital stay was not significantly shorter ($p = 0.54$) in the standard dose group (3.2 days; 25th percentile 2.5, 75th percentile 4.1) than in the low-dose group (3.4 days; 25th percentile 2.7, 75th percentile 4.1). The standard dose CT group had a perforation rate of 23.3 percent (42 of 180) and the low-dose CT group had a rate of 26.5 percent (44 of 166), but this difference was not statistically significant ($p = 0.46$). The negative appendectomy rate was also similar between the two groups (6 of 186, 3.2% standard-dose CT; 6 of 172, 3.5% low-dose CT; $p > 0.99$).⁹³

Table 27. Randomized comparisons of alternative types of CT with respect to clinical outcomes and resource utilization

Comparison	Outcome	Author, Year [PMID]	Outcome Rate or Mean in Group 1	Outcome Rate or Mean in Group 2	Between-Group Difference*
IV and oral contrast-enhanced CT vs. Nonenhanced CT	Negative appendectomy	Hershko, 2007 [17566826]	5/84 (6.0%)	7/56 (12.5%)	-0.15 (-0.33 to 0.04); p = 0.117
Mandatory CT vs. Selective CT	Length of Stay	Lehtimaki, 2013 [23715771]	3.70 days	2.50 days	1.20 days
	Negative appendectomy	Lee, 2007 [17192450]	1/72 (1.4%)	6/80 (7.5%)	-0.11 (-0.23 to 0.00); p = 0.052
		Lehtimaki, 2013 [23715771]	1/143 (0.7%)	1/111 (0.9%)	0.00 (-0.02 to 0.02); p = 0.859
	Perforations	Lee, 2007 [17192450]	4/39 (10.3%)	7/38 (18.4%)	-0.08 (-0.24 to 0.07); p = 0.304
Rectal contrast-enhanced CT vs. nonenhanced CT	Negative appendectomy	Hershko, 2007 [17566826]	3/78 (3.8%)	7/56 (12.5%)	-0.18 (-0.36 to -0.00); p = 0.050
Standard triple-contrast abdominopelvic CT scan vs. Focused pelvic scan with rectal contrast only	Negative appendectomy	Mittal, 2004 [15136349]	4/52 (7.7%)	3/39 (7.7%)	0.01 (-0.11 to 0.12); 0.02 p = 0.913
Standard triple-contrast abdominopelvic CT scan vs. Focused pelvic scan with rectal contrast only	Perforations	Mittal, 2004 [15136349]	13/52 (25.0%)	1/39 (2.6%)	0.22 (0.10 to 0.35); p = 0.001
	Time to Surgery	Mittal, 2004 [15136349]	8.30 hours (0.40)	12.20 hours (0.30)	-3.90 hours (-4.04 to -3.76); p < 0.001
Standard-dose CT vs. Low-dose CT	Negative appendectomy	Kim, 2012 [22533576]	6/447 (1.3%)	6/444 (1.4%)	0.00 (-0.04 to 0.03); p = 0.890
	Perforations	Kim, 2012 [22533576]	42/447 (9.4%)	44/444 (9.9%)	-0.01 (-0.04 to 0.03); p = 0.795
IV + oral contrast CT vs. rectal contrast CT	Negative appendectomy	Hershko, 2007 [17566826]	5/84 (6.0%)	3/78 (3.8%)	0.03 (-0.08 to 0.15); 0.04 p = 0.581

CT=computed tomography; IV=intravenous

*Risk difference for binary outcomes; mean difference for continuous outcomes. For continuous outcomes, p-values are missing when studies did not report adequate data to calculate them.

One NRCS⁹⁵ of 3764 patients examined patients receiving abdominopelvic CT during a 12 month period to compare non-oral contrast examination (2668 patients) versus traditional CT (with IV and oral contrast; 1096 patients). The authors found that the median turn-around time from test order to complete examination was 1.82 hours versus 2.36 hours ($p < 0.001$); the median turn-around time from order to final interpretation was 2.9 and 3.5 hours ($p < 0.001$); and the overall emergency department length of stay was 7.46 hours versus 8.18 hours ($p = 0.003$), for the non-oral contrast group versus the traditional CT group, respectively.

Computed Tomography Versus US

Two RCTs (reported in 3 publications⁹⁶⁻⁹⁸) with a total of 689 participants compared CT imaging to US for the diagnosis of appendicitis and reported comparative effectiveness outcomes (Table 28). Neither trial reported details of random sequence generation, adequate allocation concealment procedures, or blinding of outcome assessors to group assignment. One trial followed less than 90% of participants for appendicitis outcomes⁹⁶ and the second trial restricted its examination of changes in diagnostic decision-making to those participants who had received both initial and final diagnoses from physicians with similar levels of expertise (209 of 600; 35% of enrolled participants).⁹⁸

These studies reported outcomes for both groups for negative appendectomy rates. Horton et al. (2000) reported the same rate for both the US and CT groups (6%; 4 of 70) among patients 18 to 65 years old who presented to an emergency department with a diagnosis of possible appendicitis but had an atypical presentation after initial evaluation.⁹⁶ Kaiser et al. reported an overall negative appendectomy rate of 3.7 percent (9 of 244), of which four were in the US only group and five were in the US plus CT group, in a RCT of children with clinically suspected acute appendicitis admitted to the emergency department of a single academic hospital.⁹⁷ Kaiser et al. (2004) also reported on the impact of testing on change in management outcomes. Because the difference in impact on surgeon decisionmaking between the groups was not significant ($z = 0.89$), the groups were analyzed together. In total 347 of 600 children had their management changed after imaging, including 11 unnecessary operations possibly avoided, and 28 missed appendicitis avoided. In 18 cases, the imaging was false negative, but 17 of these children had appendectomy based on clinical diagnosis.⁹⁸

Three NRCS^{30,99,100} with a total of more than 11,419 participants compared CT imaging to US for the diagnosis of appendicitis and reported comparative effectiveness outcomes. Only two reported on other outcomes. The SCOAP Collaborative reported a significantly higher negative appendectomy rate in the group that had US (10.4%) compared to the group that had CT (4.1%) ($p < 0.001$).³⁰ Raval et al. reported a significantly lower negative appendectomy rate in children who had only CT scans (3.6%) compared to those who had only US (6.5%) or those who had US and CT (6.6%) ($p < 0.001$ for CT vs. US and for CT vs. US and CT). The perforation rate was significantly lower in children who had US only (29.8%) than those who had CT only (31.8%) or US and CT (36.3%) ($p = 0.004$ for US vs. CT and US vs. US and CT). Time from admission to surgery was also significantly longer in children who had US and CT (15.4 hours) compared to US only (7.4 hours) or CT only (9.6 hours) ($p < 0.01$ for US and CT vs. CT and US and CT vs. US), although it was not stated whether these were mean or median times.⁹⁹

Table 28. Randomized comparisons of CT versus US with respect to clinical outcomes and resource utilization

Comparison	Author, Year [PMID]	Outcome	Outcome Rate or Mean in Group 1	Outcome Rate or Mean in Group 2	Between-Group Difference*
CT + US vs. US	Kaiser, 2002 [12034928]	Negative appendectomy	5/317 (1.6%)	4/283 (1.4%)	(-0.02 to 0.02); p = 0.867
CT vs. US	Horton, 2000 [10930484]	Negative appendectomy	4/70 (5.7%)	4/70 (5.7%)	(-0.08 to 0.08); p = 1.000

CT=computed tomography; US=ultrasound

*Risk difference for binary outcomes; mean difference for continuous outcomes. For continuous outcomes, p-values are missing when studies did not report adequate data to calculate them.

US Versus Routine Management or Clinical Assessment

Two RCTs¹⁰¹⁻¹⁰⁵ with a total of 1102 participants compared the use of US to routine management in the diagnosis of appendicitis and reported comparative effectiveness outcomes (Table 29). One trial described random sequence generation by coin toss and did not report adequate allocation concealment procedures¹⁰¹ and the second trial did not describe random sequence generation or adequate allocation concealment procedures.¹⁰²⁻¹⁰⁵ Both trials followed more than 90% of participants for some outcomes, but fewer than 90% of participants for other outcomes.

Douglas et al. (2000) compared US and clinical assessment in 302 patients older than 6 years old, referred to the surgical service of a single academic hospital with suspected appendicitis. The only significant difference between the groups was for time to therapeutic operation (p = 0.016). The mean time to operation was shorter in the US group (7 hours; 95% CI: 5.9 to 8.1) than in the clinical assessment group (10.2 hours; 95% CI: 7.9 to 13). Duration of hospital stay was not significantly different between the groups (p = 0.99). The mean length of stay was similar in the two groups (53.4 hours, 95% CI: 47 to 60 in the US group; 54.5 hours; 95% CI: 46 to 63 in the clinical assessment group). The perforation rate was similar between the two groups (14 of 160, 8.8% with US; 10 of 142, 7% with clinical assessment; p = 0.58). Both groups had a single readmission for complications. In the US group, one patient was readmitted for drainage of an abscess, while in the clinical assessment group, one patient was readmitted for an early small bowel obstruction.¹⁰¹

Lindelius et al. compared routine management with routine management plus US. They reported a non-significant difference for mean length of hospital stay (p = 0.964). The US group had a slightly lower mean length of stay (4.3 ± 5.7 days) than routine management (5.4 ± 5.7 days). The US group also had a not statistically significant (p = 0.733) lower number of total hospital days over 2 years followup (mean 6 ± 26.3 days; median 0, min 0, max 462 days) than routine management (mean 8.7 ± 35.6 days; median 0, min 0, max 470 days). Two patients in the US group died within 7 days and a third died within 6 weeks. No patients in the routine management group died.^{103,104} They also reported that US helped in making the diagnosis in 49.5 percent of patients and was considered misleading in 10.2 percent.¹⁰⁵

Two NRCS^{90,106} with a total of 57,553 participants compared US to no imaging for the diagnosis of appendicitis and reported comparative effectiveness outcomes. Even-Bendahan et al. reported a 6.5 percent negative appendectomy rate in the 1069 children who had US if they were equivocal followed by CT as needed and 13.2 percent in those who had no diagnostic imaging.¹⁰⁶ Bachur et al. reported that for boys under five, US increased the negative appendectomy rate significantly (p < 0.008; OR 2.07; 95% CI 1.21 to 3.54), but for girls under

five ($p < 0.13$; OR 1.54; 95% CI 0.88 to 2.68) and all children between five and ten (boys: $p = 0.61$; OR 0.87; 95% CI 0.52 to 1.47; girls: $p = 0.636$; OR 0.87; 95% CI 0.49 to 1.55) and children over ten (boys: $p = 0.122$; OR 0.56; 95% CI 0.27 to 1.17; girls: $p = 0.897$; OR 1.03; 95% CI 0.64 to 1.67) US resulted in a nonsignificantly lower negative appendectomy rate.⁹⁰

Table 29. Randomized comparisons of US versus no imaging with respect to clinical outcomes and resource utilization

Comparison	Author, Year [PMID]	Outcome	Outcome Rate or Mean in Group 1	Outcome Rate or Mean in Group 2	Between-Group Difference*
Routine management and US vs. Routine management alone	Lindelius, 2009 [19625549]	Length of Stay	4.30 days (2.40)	5.40 days (5.70)	-1.10 days (-1.98 to -0.22); $p = 0.014$
US informed by Alvarado score vs. clinical assessment and management	Douglas, 2000 [11030676]	Duration of hospitalization	53.40 hours	54.50 hours	-1.10 hours
		Duration of hospitalization	45.00 hours	40.50 hours	4.50 hours
		Perforations	14/160 (8.8%)	10/142 (7.0%)	0.02 (-0.04 to 0.08); $p = 0.582$
		Time to Surgery	7.00 hours	10.20 hours	-3.20 hours (total population)
		Time to Surgery	7.00 hours	13.10 hours	-6.10 hours (children)

US=ultrasound

*Risk difference for binary outcomes; mean difference for continuous outcomes. For continuous outcomes, p-values are missing when studies did not report adequate data to calculate them.

Any Imaging Versus No Imaging

Two NRCS^{30,90} with an approximate total of 74,554 participants compared US, CT, and/or MRI to no imaging for the diagnosis of appendicitis and reported comparative effectiveness outcomes. The SCOAP Collaborative reported a significantly lower negative appendectomy rate in the group that had CT, US, or MRI (4.5%) compared to the group that had no imaging (15.4%; $p < 0.001$). Perforation rates were slightly lower in the CT, US, or MRI group (15.8%) compared to the non-imaging group (15.6%), but this difference was not significant ($p = 0.16$).³⁰ Bachur et al reported that for children under five, US or CT decreased the negative appendectomy rate significantly for girls under five ($p = 0.011$; OR = 0.24; 95% CI 0.08 to 0.72), but not significantly for boys under five ($p < 0.125$; OR = 0.56; 95% CI 0.27 to 1.17). For children between five and ten (boys: $p = 0.36$; OR = 1.55; 95% CI 0.60 to 3.98; girls: $p = 0.14$; OR = 1.83; 95% CI 0.83 to 4.02) and boys over ten (boys: $p = 0.97$; OR = 0.98; 95% CI 0.34 to 2.85), CT or US resulted in a non-significantly higher negative appendectomy rate. In girls over 10, CT or US resulted in a significantly higher negative appendectomy rate ($p < 0.001$; OR = 1.97; 95% CI 1.42 to 2.74)⁹⁰

Score-Based Managements Versus Routine Management or Non-Score-Based Clinical Assessment

Four RCTs with a total of 657 participants compared the use of scores to routine management in the diagnosis of appendicitis and reported comparative effectiveness outcomes (Table 30).¹⁰⁷⁻¹¹⁰ One trial described both details of random sequence generation and an adequate

allocation concealment procedure,¹⁰⁸ and two trials described only details of random sequence generation.^{107,110} The third did not describe randomization or allocation procedures.¹⁰⁹ No trial described blinding of outcome assessors and no trial described any loss to follow-up for any outcome.

Farahnak et al. (2007) randomized patients referred to the emergency service with an “impermanent” diagnosis of acute appendicitis to standard clinical management versus management according to the Alvarado score. They found significant differences in mean time to surgery and duration of hospitalization between patients randomized to either standard clinical management or management according to the Alvarado score. The mean time from randomization to surgery was statistically significantly less ($p = 0.03$) in 10 patients in the Alvarado group (6.39 ± 9.93 hours; median 2.05, min 0.4, max 32.4, IQR 7.39) than in 10 patients in the standard care group (11.09 ± 10.04 hours; median 8.35, min 2.4, max 37.1, IQR 5.55). Mean length of stay was also shorter in the 21 patients in the Alvarado group (42.61 ± 62.48 hours; median 37 hours, min 0.3, max 290.5, IQR 58.4) than in the 21 patients in the standard care group (66.27 ± 61.89 hours; median 60.40, min 0.3, max 280.2, IQR 40.7) ($p = 0.034$). The perforation rate was similar in the two groups (1 of 21, 4.8% in the Alvarado group; 0 of 21, 0% in the standard care group; $p > 0.99$).¹⁰⁷

In two separate trials, Lintula et al. evaluated the Lintula score in pediatric (2009) and adult (2010) populations. In the pediatric population, the negative appendectomy rate was lower in the Lintula score group (17%; 5 of 29) than in the standard clinical assessment group (29%; 11 of 38; $p = 0.05$). Perforation rates were similar (21 of 66, 32% in the score group; 24 of 60, 40% in the standard clinical assessment group; $p = 0.36$). The score group had a perforation rate of 88 percent (21 of 24) and an abscess rate of 8.3 percent (2 of 24), and the standard clinical assessment group had a perforation rate of 89 percent (24 of 27) and an abscess rate of 8.3 percent (2 of 27). Mean length of hospital stay was also reported as not significant. The mean length of stay in the score group was 2.7 (± 1.8) days, and the mean length of stay in the standard clinical assessment group was 2.9 (± 1.1) days. There were no deaths in either group, but one patient in each group had a post-surgical wound infection.¹⁰⁸ In adults, they also found non-significant differences between the groups in terms of negative appendectomy rate, number of perforations or abscesses, and length of stay. The negative appendectomy rate (8 of 60, 13% in the score group vs. 7 of 43, 16% in the standard assessment group; $p = 0.78$), the perforation rate (3 of 60, 5% in the score group; 3 of 43, 7% in the standard assessment group; $p = 0.69$), and the abscess rate (2 of 60, 3% in the score group; 0 of 43, 0% in the standard assessment group; $p = 0.51$). The mean length of stay was 2.2 (± 1.8) days in the score group as compared to 2.3 (± 2.6) days in the standard clinical assessment group.¹⁰⁹

Shah et al. (2008) randomized a group of 308 patients (both adults and children) who had a provisional diagnosis of appendicitis to an intervention group (Alvarado score and US based on the results of the score assessment) versus a control group of “clinical diagnosis”. In the intervention group patients with an Alvarado score of 3 or less did not undergo ultrasound, those with a score of 4 to 8 underwent US, and those with a score of 9 or 10 were deemed candidates for surgery and US was optional. Patients in the control group were not evaluated with the Alvarado score and did not undergo US. The authors found that average length of stay (61.3 hours in the intervention group and 62.5 hours in the control group), the rate of non-therapeutic operations (1.3% vs. 4.4%), the rate of delayed treatment and perforation (3.3% vs. 1.9%), and the rate of all adverse outcomes (delayed treatment in association with perforation and non-

therapeutic operations, 4.7% vs. 6.3%) were not statistically significantly different between groups.

One NRCS¹¹¹ with 1,484 participants reported comparative effectiveness outcomes. They reported that the negative appendectomy rate was higher in patients who had a diagnostic score as part of their workup (10.2%; 13 of 127) compared to those who did not (8.4%; 18 of 214), but the difference was not significant ($p = 0.57$). The negative laparotomy rate was lower in patients who had a diagnostic score as part of their workup (3.4%; 8 of 233) compared to those who did not (3.9%; 14 of 358), but again the difference was not significant ($p = 0.83$). There were fewer perforated appendixes in the scores group (14.9%; 17 of 114) than in the non-scores group (19.4%; 38 of 196) ($p = 0.32$). The scores group had a significantly lower delayed appendectomy (≥ 2 days) rate (1.8%; 2 of 114 vs. 7.7%; 15 of 196 in the non-scores group; $p = 0.03$), as well as a significantly lower delayed discharge (≥ 10 days) rate (11.4%; 13 of 114 vs. 21.6%; 43 of 199 in the non-scores group; $p = 0.02$).¹¹¹

Table 30. Randomized comparisons of scores versus no scores with respect to clinical outcomes and resource utilization

Comparison	Author, Year [PMID]	Outcome	Outcome Rate or Mean in Group 1	Outcome Rate or Mean in Group 2	Between-Group Difference*
Alvarado vs. standard practice	Farahnak, 2007 [17870498]	Duration of hospitalization	42.61 hours (62.48)	66.27 hours (61.89)	-23.66 hours (-61.27 to 13.95); p = 0.218
		Perforations	0/21 (0.0%)	1/21 (4.8%)	-0.05 (-0.17 to 0.07); p = 0.446
		Time to Surgery	6.39 hours (9.93)	11.09 hours (10.04)	-4.70 hours (-12.23 to 2.83); p = 0.221
Pediatric score vs. standard practice	Lintula, 2009 [18841382]	Deaths	0/66 (0.0%)	0/60 (0.0%)	0 (-0.03 to 0.03); p = 1.00
		Length of Stay	2.70 days (1.80)	2.90 days (1.10)	-0.20 days (-0.72 to 0.32); p = 0.447
		Negative appendectomy	5/66 (7.6%)	11/60 (18.3%)	-0.12 (-0.32 to 0.08); p = 0.249
		Perforations	21/66 (31.8%)	24/60 (40.0%)	-0.08 (-0.25 to 0.09); p = 0.338
Pediatric score vs. standard practice	Lintula, 2010 [20379739]	Negative appendectomy	8/96 (8.3%)	7/81 (8.6%)	-0.03 (-0.17 to 0.11); p = 0.680
		Perforations	3/96 (3.1%)	3/81 (3.7%)	-0.01 (-0.06 to 0.05); p = 0.833
Alvarado + US depending on the score value vs. standard practice	Shah, 2008 [not indexed]	Length of stay	61.3 hours (NR)	62.5 hours (NR)	0.9 hours (no additional information reported)
		Delayed treatment and perforation	5/150 (3.3%)	3/158 (1.9%; this percentage was reported as 11.91% in the paper but that number was inconsistent with the count of events provided in tables and in the text)	0.014 (-0.0 to 0.05); p = 0.432
		Non-therapeutic operations	2/150 (1.3%)	7/158 (4.4%)	-0.031 (-0.06 to 0.006); p=0.101
		Delayed treatment in association with perforation and non-therapeutic operations	7/150 (4.6%)	10/158 (6.3%)	-0.017 (-0.067 to 0.034); p=0.521

NR = not reported

*Risk difference for binary outcomes; mean difference for continuous outcomes. Values in parentheses are 95% confidence intervals. For continuous outcomes, p-values are missing when studies did not report adequate data to calculate them.

Diagnostic Laparoscopy Versus Open Diagnostic Exploration

Bruwer (2003) compared the use of diagnostic laparoscopy to open diagnostic exploration in a RCT of 34 premenopausal women (15 to 45 years old) in whom a decision to perform surgical exploration made.¹¹² The trial described random sequence generation procedures, but did not describe procedures for allocation concealment or blinding of outcome assessors. No participants were lost for any other outcomes. They found that there were fewer negative appendectomies in the diagnostic laparoscopy group (2 of 11) than in the open appendectomy group (7 of 16), but the difference was not statistically significant ($p=0.23$). The difference in length of stay was reported not to be significant, though the laparoscopy group had a slightly shorter mean length of stay (3 ± 1.6 days) than the open group (3.7 ± 1.1 days).

One NRCS¹¹³ of 1899 patients compared the diagnostic performance (see Key Question 1) and complications of laparoscopic (1043 patients) versus open (856) approaches for patients with presumed acute appendicitis. The authors found that the laparoscopic approach had a higher rate of intra-abdominal abscess formation (3.9% vs. 2.2%; $p=0.055$) and lower rate of wound infection (1.5% vs. 7%; $p<0.001$) compared to the open approach.

Diagnostic Laparoscopy Versus No Laparoscopy

Three RCTs¹¹⁴⁻¹¹⁶ with a total of 334 participants compared the use of diagnostic laparoscopy to routine management in the diagnosis of appendicitis and reported comparative effectiveness outcomes. Two of the trials did not describe random sequence generation procedures, procedures for allocation concealment, or blinding of outcome assessors.^{114,116} The other described adequate random sequence and allocation concealment procedures, but did not describe blinding.¹¹⁵ One study reported fewer than 90% of participants were followed for well-being outcomes, but no participants were described as lost for any other outcomes.¹¹⁴ The others reported no participants lost for any outcomes extracted in this review.^{115 116}

Decadt et al. reported that participants randomized to early laparoscopy had a median time to operation of 10 hours (min 2, max 39), while those randomized to active observation and noninvasive investigation had a median time to operation of 39 hours (min 15, max 119). Length of hospital stay was two days (min 1, max 13) in each group ($p = 0.87$).¹¹⁴ Gaitan et al. reported that the time to diagnosis was shorter in the group that had laparoscopy within 24 hours of admission (1.41 ± 1.06 days) than in the group that had clinical observation and conventional diagnosis (2.32 ± 2.3 days).¹¹⁵ Morino et al. reported that the mean time to operation was 7.5 hours in the immediate laparoscopy group compared to 69.1 (± 50.9 hours) the observation group, and the mean duration of hospital stay was shorter (3.7 ± 0.8 days) in the immediate laparoscopy group when compared to the observation group (4.7 ± 2.4 days).¹¹⁶

Diagnostic Laparoscopy Versus Immediate Appendectomy

Six RCTs, all enrolling women of reproductive age, with a total of 461 participants compared the use of diagnostic laparoscopy to immediate appendectomy and reported comparative effectiveness outcomes.¹¹⁷⁻¹²² No trial described random sequence generation procedures, procedures for allocation concealment, or blinding of outcome assessors. All outcomes were reported for greater than 90% of participants in each trial.

All five studies that reported negative appendectomy rates found them to be lower in the diagnostic laparoscopy group compared to the immediate appendectomy group. Jadallah et al. (1994) reported a rate of 13.3 percent (4 of 30) in the diagnostic laparoscopy group compared to

36 percent (18 of 50) in the immediate open appendectomy group.¹¹⁷ Laine et al. (1997) reported a rate of 5.9 percent (1 of 17) in the diagnostic laparoscopy group compared to 44 percent (11 of 25) in the immediate open appendectomy group.¹¹⁸ Larsson et al. (2001) reported a rate of 9 percent (4 of 44) in the diagnostic laparoscopy group compared to 34 percent (18 of 55) in the immediate open appendectomy group. They reported that the relative risk of removing a healthy appendix was 6.6 (95% CI 2 to 21) for open compared to laparoscopic group.¹¹⁹ Olsen et al. (1993) reported a rate of 7 percent (2 of 30) in the diagnostic laparoscopy group compared to 37 percent (11 of 30) in the immediate appendectomy group.¹²⁰ van Dalen et al. (2003) reported a rate of 4 percent (1 of 25) in the diagnostic laparoscopy group compared to 26 percent (8 of 31) in the immediate appendectomy group.¹²¹

Five studies also reported on length of stay. Jadallah et al. reported a slightly shorter median length of stay (2 days, min <1, max 7) in the diagnostic laparoscopy group compared to the immediate open appendectomy group (3 days, min 1, max 18). Mean length of stay was 2.33 and 3.1 days, respectively. The p-value was <0.001 when comparing laparoscopy alone (no appendectomy) to appendectomy without laparoscopy.¹¹⁷ Laine et al. reported a slightly longer length of stay for diagnostic laparoscopy (2.7 ± 0.3 days) compared to immediate open appendectomy (2.3 ± 0.1 days).¹¹⁸ Olsen et al. also reported a slightly longer length of stay for diagnostic laparoscopy (3.8 days; min 1, max 8) compared to immediate appendectomy (3.2 days; min 1, max 7; $p = 0.25$).¹²⁰ van Dalen et al. reported a statistically significantly shorter mean length of stay for diagnostic laparoscopy (4 days; min 1, max 9) than immediate appendectomy (4.9 days; min 2, max 11; $p = 0.01$).¹²¹ Tzovaras et al. reported that both groups had a mean length of stay of two days, but the range for diagnostic laparoscopy was one to nine days, while it was one to seven days for open appendectomy.¹²²

Four NRCS^{89,123-125} with 5497 participants reported comparative effectiveness outcomes for diagnostic laparoscopy versus open appendectomy. All four studies reported on negative appendectomy rates. Barrat et al. reported that the negative appendectomy rate was significantly lower for those who had laparoscopy (8.2%; 24 of 290) than those who had open appendectomy (25.4%; 236 of 930) ($p = 0.015$).¹²⁵ Wagner et al. also reported that the negative appendectomy rate was lower for those who had laparoscopy (7.3%) than those who had open appendectomy (8.4%), but it was not significant ($p = 0.53$).⁸⁹ Akbar et al. reported a higher negative appendectomy rate in diagnostic laparoscopy participants (24.5%; 63 of 256) than in those that had open appendectomy (13% 178 of 1357).¹²³ Ekeh et al. also reported a significantly higher negative appendectomy rate in laparoscopy patients (23.3%) than in those that had open appendectomy (14%) ($p < 0.001$).¹²⁴ Only one study reported on time from ED to surgery, which was significantly longer for laparoscopy participants (mean 10.8 ± 9 hours) than for open appendectomy patients (9.75 ± 8.5 hours; $p = 0.0333$).¹²⁴

Clinical Outcomes and Resource Utilization in Pregnant Women With Suspected Acute Appendicitis

Eight studies^{126-132,133} reported information on clinical outcomes and resource utilization for pregnant women. These studies were mostly small and only a few gave comparative results.

Three studies reported negative appendectomy rates for pregnant women. One reported a negative appendectomy rate with MRI of 8 of 27.¹³⁰ A second reported a negative appendectomy rate of 1 of 20 in patients who first had US then MRI.¹³³ The third reported negative appendectomy rates of 7 of 13 for clinical evaluation, 20 of 55 for US, 1 of 13 for US and CT,

and 3 of 5 for CT alone.¹²⁶ Only one study reported that repeat imaging was necessary; two MRI patients required repeat imaging to visualize contrast material in the cecum.¹³¹

Four studies reported information on delay in diagnosis. Two studies, one of MRI and the other of laboratory findings, reported that there were no delays caused by the diagnostic process or test findings.^{127,128} A third study reported that operative delay due to diagnostic delay was significantly correlated with maternal morbidity.¹³² and a fourth reported that there were three perforations due to diagnostic delay in a cohort of 36 patients.¹²⁹

Key Question 3: What are the harms of diagnostic tests per se, and what are the treatment-related harms of test-directed treatment for tests used to diagnose RLQ pain and suspected acute appendicitis?

Included Studies With Information on Adverse Events

Of 925 included studies, only 82 mentioned harms related to diagnostic tests: 17 RCTs^{76,78,82,83,91,93,94,97,110,112,114,116-118,120-122}; 12 NRCS^{100,113,125,134-142}; and 53 diagnostic cohort studies.^{129,132,143-193} Eight (3 RCTs^{78,91,94} and 5 diagnostic cohort studies^{159,162,165-167}) reported an absence of adverse events for all tests except diagnostic laparoscopy (see Table 31). The fact that so few studies reported harms raises concerns about selective outcome reporting. The studies that mentioned at least one harm are included in Tables 32 to 35 and are discussed briefly below.

Contrast-Related Adverse Events

Eight studies (3 RCTs^{76,83,97} and 5 diagnostic cohort^{152,155,161,163,164}) reported on adverse events related to contrast administration. Of these, three reported that the contrast was well tolerated.^{83,155,164} Twelve studies of CT (of 247 included for Key Question 1), two of MRI (of 35), two of nuclear medicine (of 31), and one of US (of 301) reported data on contrast related harms. Full results by study are in Table 32.

Of the two RCTs that reported contrast-related harms, one reported five cases of vomiting after oral contrast in 152 patients, one in the group that got selective CT imaging (n=80) and four in the group that got CT imaging standard (n=72).⁷⁶ A second reported a mild skin rash after intravenous contrast administration that resolved spontaneously within 10 minutes in the CT group (n=317; n total = 600).⁹⁷

In the diagnostic cohort studies, one reported that a single patient of 308 had Gastrografin-induced chemical pneumonitis; this patient required mechanical ventilation for three days and recovered completely.¹⁶³ Another reported that of 100 patients, there was leakage of colonic contrast material in 12 cases, nausea or vomiting three cases, and extravasation of intravenous contrast material one case.¹⁶¹ A third reported that of 1561 patients given oral contrast before CT, 243 vomited at least once, 84 required nasogastric intubation, and the average wait time before CT scan was an hour longer (2 hours) than for those who did not have contrast.¹⁵²

Table 31. Studies that reported that no adverse events occurred

Study Design	Study	Test	Contrast Route of Administration	N	Population	Summary
RCT	Mittal et al., 2004, 15136349 ⁹⁴	Standard vs. focused CT	IV, oral, rectal vs. rectal only	91	mixed	There were no complications as a result of the procedures in either group. No morbidities due to the CT scans were reported in either group.
	Lopez et al., 2007, 18186378 ⁷⁸	CT vs. clinical observation	oral, IV	95	women of childbearing age	No complications were associated with this radiologic protocol.
	Hersko et al., 2007, 17566826 ⁹¹	Unenhanced vs. rectal contrast enhanced vs. IV and oral contrast enhanced CT	none used vs. rectal vs. IV and oral	232	adults	"CT-related complications, such as contrast material sensitivity reactions, aspiration, or renal failure, were not observed in any of the study groups." "All techniques were found to be safe and no CT-related complications were observed."
Diagnostic cohort studies	Brandt et al., 2003, 14509318 ¹⁵⁹	CT	oral, IV contrast	330	adults	There were no complications attributable to the CT scans obtained
	Johnson et al., 2012, 22623558 ¹⁶⁵	MRI	NR	42	children	All patients enrolled in the study were able to complete the examination.
	Leeuwenburgh et al., 2013, 23481162 ¹⁶²	CT and/or MRI	none used	230	adults	No adverse events occurred during imaging.
	Kipper et al., 2000, 10716317 ¹⁶⁶	Tc-99m	NR	49	mixed	No serious adverse events were attributable to LeuTech injection, and vital signs did not significantly change after injection. One patient with a history of asthma had a brief episode of shortness of breath 1 hour after injection that completely resolved without intervention. This occurrence was believed to be unrelated to the LeuTech injection because of timing and the manner in which it resolved.
	Wong et al., 1997, 9404876 ¹⁶⁷	Tc-99m	NR	51	mixed	No patients developed any side effects, adverse reactions, or complications.

CT = computed tomography; IV = intravenous; MRI = magnetic resonance imaging

Table 32. Reported contrast-related adverse events

Study Design	Study	Test	Contrast Route of Administration	N	Population	Summary
RCT	Lee et al., 2007, 17192450 ⁷⁶	CT	oral and IV	152	adults	Selective CT imaging: 1 case of recurrent vomiting secondary to oral contrast ingestion. Routine CT imaging 4 cases of recurrent vomiting secondary to oral contrast ingestion.
	Walker et al., 2000, 11182396 ⁸³	CT	rectal	65	adults	"Rectal contrast for the CT scan was well tolerated by the majority of patients. One patient refused more than 200 cc of rectal contrast and other received no contrast at all."
	Kaiser et al., 2002, 12034928 ⁹⁷	CT	IV	600	children	No severe adverse drug reactions. 1/600 = mild skin rash limited to the chest that resolved spontaneously within 10 minutes.
Diagnostic cohort studies	Hershko et al., 2002, 12455796 ¹⁶³	CT	oral and IV	308	adults	One case of Gastrografin-induced chemical pneumonitis. The patient required mechanical ventilation for three days and recovered completely.
	Kan et al., 2001, 11770917 ¹⁶⁴	CT or US, Hydrocolonic	rectal	31	adults	"All 31 patients were able to hold the rectally administered contrast material until completion of both hydrocolonic US and appendiceal CT."
	Laituri et al., 2011, 21470628 ¹⁵²	CT	oral	1561	children	Vomiting in 243, nasogastric intubation in 84, time to scan average 2 hours (estimated time to scan without contrast 1 hour).
	Rao et al., 1997, 8988203 ¹⁵⁵	CT	rectal	99	mixed	This bowel contrast medium regimen was well tolerated by our patients.
	Wise et al., 2001, 11264081 ¹⁶¹	CT	oral, IV, rectal	100	adults	Leakage of rectal contrast in 12 cases, nausea or vomiting in 3 cases, extravasation of IV contrast material in 1 case

CT = computed tomography; IV = intravenous

Exposure to Ionizing Radiation

No studies reported direct evidence on the effect of ionizing radiation on patient relevant outcomes.

Twelve studies (3 RCTs,^{82,93,116} 4 NRCS,^{135,140-142} and 5 cohort studies^{150,151,153,154,157} reported radiation doses, and two of these^{154,157} discussed strategies to reduce CT-related radiation exposure in a population (of a total of 247 CT studies included for Key Question 1). Reported mean CT radiation doses ranged from 7.2 to 15 mSv in adults;^{82,151,153,154} in children, the mean reported dose was 4 mSv; and in a mixed-age population, the mean reported dose was 8 mSv.¹⁵⁷ Reported mean low-dose computed tomography (LDCT) radiation doses ranged from 1.2 to 4.2 mSv in adult and mixed populations.^{93,154,157} Specific results for each study are in Table 33.

Both of the RCTs that reported evidence for this outcome in terms of CT compared standard CT radiation doses with radiation doses from another diagnostic modality. One RCT looked at the difference between low- and standard-dose CT in 891 participants and reported a median dose-length product for radiation from standard CT at 521 mGy x cm (IQR = 448-564); for LDCT, the median dose-length product for LDCT was about a quarter as much, at 116 mGy x cm (IQR = 94-124).⁹³ The second RCT compared current standard practice (plain radiography of the supine abdomen and erect chest, as well as CT if it was deemed necessary) with an early CT protocol that used abdominopelvic scans on a 16 detector scanner with intravenous contrast. The authors reported that the CT protocol had a mean radiation dose of 9 mSv, while the dose for the plain radiography was only 0.82 mSv.⁸² The third RCT reported mean radiation dose for patients who either received immediate laparoscopy (1.1±1 mSv) or underwent observation before laparoscopy (2.2±5.1 mSv).¹¹⁶

Three retrospective NRCS and one prospective NRCS reported radiation doses between different arms of CT in mixed and pediatric populations. In 2011, Kim et al. reported the same radiation doses for CT and LDCT as in their 2012 RCT (standard CT: median dose-length product = 544 mGy x cm; LDCT: median dose-length product = 122 mGy x cm).¹³⁵ In a prospective NRCS, Karabulut et al. compared low-dose dual slice CT versus multidetector row CT in a mixed population. They found similar calculated mean effective radiation doses between low-dose CT (1.2 and 2.2 mSv for male and female patients, respectively) and multidetector CT (1.5 and 2.0 mSv for male and female patients, respectively).¹⁴²

In 2014, Didier et al. reported lower radiation doses in a pediatric population with a change in CT protocol in 2010. The mean size-specific dose estimate and volume CT dose index with the standard protocol between 2008 and October 18, 2010 were 12.6 mGy (SD 2.5 mGy) and 7.3 mGy (SD 2.3 mGy), respectively. Between October 19, 2010 and 2012, the scans were performed using iterative reconstruction technique software, and the mean size-specific dose estimate and volume CT dose indexes dropped to 6.8 mGy (SD 2.6 mGy) and 4 mGy (SD 2 mGy), respectively (p<0.0001).¹⁴⁰ Sharp et al. reported lower CT radiation doses in children in children's versus outside hospitals. The mean dose length product was 143.54 mGycm (SD 41.19 mGycm) in the children's hospital as compared to 586.25 mGycm (SD 521.59 mGycm) in the outside hospital (p<0.001); the mean volume computed tomography dose length index was 4.89 mGy (SD 2.64 mGy) in the children's hospital and 16.98 mGy (SD 15.58 mGy) in the outside hospital (p<0.001); and the mean size-specific dose estimate was 3.81 mGy (SD 2.02 mGy), in the children's hospital and 26.71mGy (SD 23.1 mGy) in the outside hospital (p<0.001).¹⁴¹

There were five diagnostic cohort studies reporting on this outcome. One study in which everyone first had a LDCT then a standard CT reported a total radiation dose of 12.2 mSv (8

mSv from the standard CT plus 4.2 mSv from the low-dose CT).¹⁵⁷ A second study reported on the evaluation of an algorithm, in which patients were first evaluated by US then, in the case of indeterminate US findings or negative US findings with high clinical suspicion of appendicitis, the patient received a low-dose CT exam. If the low-dose CT exam was indeterminate, the patient had a standard CT. The authors of this study reported an actual mean dose with the algorithm of 3.23 mSv, which was significantly lower ($p < 0.0001$) than the hypothetical mean dose if a standard CT had been systematically performed at admission (9.02 mSv).¹⁵⁴ One study of pregnant women reported a mean radiation dose of 16 mGy (range 4 to 45 mGy) for CT.¹⁹¹

Table 33. Reported radiation dose

Study Design	Study	Test	Contrast Route of Administration	N	Population	Radiation Dose (Mean)
RCT	Kim et al., 2012, 22533576 ⁹³	CT vs. LDCT	IV	891	mixed	Standard CT: median dose-length product = 521 mGy x cm (IQR = 448-564); low-dose CT: median dose-length product = 116 mGy x cm (IQR = 94-124)
	Sala et al. ⁸²	CT vs. XRAY	IV	99	adults	CT = 9 mSv; XRAY = 0.82 mSv
	Morino et al. ¹¹⁶	Immediate laparoscopy vs. observation	NR	104	adults	Immediate lap: 1.1 ± 1 mSv (range 0.1-2.1 mSv); observation: 2.2 ± 5.1 mSv (range 0-22 mSv)
NRCS	Kim et al., 2011, 21633052 ¹³⁵	CT vs. LDCT	IV contrast	257	adults	Standard CT: median dose-length product = 544 mGy · cm (range, 303–672 mGy · cm; IQR = 518–578 mGy · cm); low dose: median dose-length product = 122 mGy · cm (range, 76–145 mGy · cm; IQR = 118–126 mGy · cm)
	Didier et al., 2014, 24996812 ¹⁴⁰	CT (2008-2010) vs. iDose CT (2010-2012)	oral, IV	386	children	Mean size-specific dose estimate: CT = 12.6 +- 2.5 mGy, iDose CT = 6.8 +- 2.6 mGy; mean volume CT dose index: CT = 7.3 +- 2.3 mGy, iDose CT = 4.0 +- 2.0 mGy
	Sharp et al., 2014, 24888854 ¹⁴¹	CT Children's Hospital (CH) vs CT Outside Hospital (OH)	oral, IV	263	children	Mean dose length product (mGycm) CH: 143.54 +- 41.19, OH: 586.25 +- 521.59; mean volume computed tomography dose length index (mGy) CH: 4.89 +- 2.64, OH: 16.98 +- 15.58; mean size specific dose estimate (mGy) CH: 3.81 +- 2.02, OH: 26.71 +- 23.1
	Karabulut et al., 2014, 24513314 ¹⁴²	LD CT vs. CT	none	104	mixed	LDCT calculated mean effective radiation doses: males 1.2 mSv, females 2.2 mSv; CT calculated mean effective radiation doses: males 1.5 mSv, females 2.0 mSv

Table 33. Reported radiation dose (continued)

Study Design	Study	Test	Contrast Route of Administration	N	Population	Radiation Dose (Mean)
Diagnostic cohort studies	Ghotbi et al., 2006, 17041792 ¹⁵⁰	CT	NR	24	children	4 mGy
	Pickhardt, 2011, 21690593 ¹⁵³	CT	oral and IV in the majority of patients	2871	adults	10-15 mSv
	Poletti, 2011, 21805194 ¹⁵⁴	US + LDCT + CT protocol	oral	183	adults	Algorithm = 3.23 mSv; LDCT = 1.7 mSv (women), 1.2 mSv (men); CT = 10.2 mSv (women), and 7.2 mSv (men)
	Keyzer, 2004, 15155894 ¹⁵¹	CT	none	95	adults	mean dose at 100 effective mAs: 5.2 mSv for males and 7.1 mSv for females, mean dose at 30 effective mAs: 1.4 mSv for males and 2.2 mSv for females
	Lazarus, 2000, 17709829 ¹⁹¹	CT	various	80	pregnant women	The mean radiation dose delivered was 16 mGy (1.6 rad) (range, 4–45 mGy [0.4–4.5 rad]).
	Seo, 2009, 19542400 ¹⁵⁷	LDCT + CT	none for LDCT, IV for standard CT	207	mixed	LDCT = 4.2 mSv; CT = 8 mSv; Combined = 12.2 mSv

CT = computed tomography; IV = intravenous; LDCT = low-dose CT; MRI = magnetic resonance imaging

Maternal/Fetal Adverse Events

Six studies (3 studies of US, of 301 included for Key Question 1); 3 of MRI (of 35); and 2 of multiple clinical and lab tests (of 217); some studies evaluated more than one test) reported information on maternal outcomes. One study of MRI reported that 17 patients without appendicitis progressed to uneventful labor and delivery.¹⁸⁸ A second study of MRI reported that not using oral contrast sped up the imaging process.¹⁸⁹ Four reported that there was no maternal mortality.^{129,185-187}

Seven studies (5 studies of US (of 301); 2 of MRI (of 35); 1 of CT (of 247); and 1 of clinical symptoms and signs (of 137); some studies evaluated more than one test) reported information on fetal outcomes. Barloon et al. in a study of US reported that 18 of 22 patients had a normal term delivery; there were two spontaneous abortions (in patients with no clinical or sonographic evidence of acute appendicitis) and two elective abortions.¹⁸⁵ Kapan et al. in a study of US and several clinical and laboratory tests reported that all 20 women delivered healthy infants.¹⁸⁶ Lim et al. in a study of US only reported fetal outcomes for two of the 45 participants. One was a spontaneous abortion in a case of surgically confirmed acute appendicitis without perforation, and the other was a premature delivery in a patient with no evidence of appendicitis at followup through delivery.¹⁸⁷ Fonseca et al. reported on a clinical/US pathway versus MRI in 75 patients. They reported a total of nine adverse fetal outcomes (5/31 who had MRI and 4/44 in the US or clinical group), none were in the perioperative period (OR 1.09, 95% CI 0.90-1.31; p = 0.47).¹⁹⁴

Freeland et al. reported outcomes for US, MRI, and CT. In the US group, one patient, who had an open appendectomy in the first trimester, developed severe preeclampsia and had a premature delivery at 33 weeks (this patient also had a diagnostic CT), there was one fetal demise after a negative open appendectomy, but neither the fetal demise nor the early delivery was related directly to the appendectomy, and one patient with perforated appendicitis had abruptio-placentae and vaginal hemorrhage. Only one patient had MRI, and she delivered a healthy baby at term. Among thirteen patients who had a diagnostic CT, nine delivered healthy infants, one who had an open appendectomy in the first trimester developed severe preeclampsia and had a premature delivery at 33 weeks (see above), and three were lost to followup.¹⁹⁰ Lazarus et al. reported fetal outcomes for 55 of 80 patients who had CT. Fifty-one had a live infant at or near term, one had a premature delivery of a live 30-week infant three days after CT-diagnosed gastric cancer, two had spontaneous vaginal delivery of a nonviable fetus (one at 18 weeks with sepsis after normal CT and normal laparotomy, and one at 22 weeks with chorioamnionitis, 5 days after normal CT). There was one fetal demise at 26 weeks (four weeks after a CT examination with normal findings).¹⁹¹ Tamir et al. reported that on a group evaluated on symptoms and signs, there were seven therapeutic abortions, two perioperative spontaneous abortions (first trimester), and four without appendicitis had severe perinatal morbidity or mortality.¹³² Two studies of MRI reported on other harms in pregnant women. One reported that “all 12 patients and fetuses were exposed to unknown bioeffects of MRI.”¹²⁷ The other reported that patient tolerance of the MRI environment represents an additional concern in terms of successful implementation, but noted that only one patient refused to complete the MRI protocol.¹³⁰

Other Adverse Events of Imaging Tests

One RCT¹¹⁰ and six diagnostic cohort studies^{156,158,160-162,193} reported on a variety of other adverse events. For details by study, see Table 34.

In an RCT of standard clinical management versus an Alvarado/US pathway, Shah et al. found that a delay of over 10 hours from randomization to operation was associated with perforation in 5 of 100 patients in the US/Alvarado group and 3 of 110 patients in the clinical management group. They also noted two complications: a subcutaneous abscess in the scar in the intervention group and a subacute intestinal obstruction in the control group.

One reported that one child in a sample of 94 was unable to tolerate the CT procedure;¹⁵⁸ they did not give any further details. A second study measured discomfort in 100 patients who underwent US and CT on a scale of 0-10, where 10 was the most discomfort. The imaging pathway for half of the patients was oral contrast administration, then US, then unenhanced CT, then CT with intravenous contrast, then CT with colonic contrast material, then US; in the other half of patients, this order was reversed. They found that in general US produced more discomfort (average scores of 6.1 with oral contrast and 6.7 with oral, intravenous, and rectal contrast) than CT (average score 4.2 in focused scans with oral contrast, 6.7 in focused scans with oral, IV, and rectal contrast, and 5.3 in abdominopelvic scans with oral and intravenous contrast).¹⁶¹ A study of Tc-99m labeled white blood cells reported that “of the 203 patients injected with LeuTech, 17 (8%) reported 20 mild and 4 moderate adverse events. None of these events were reported as definitely drug related. The most commonly reported adverse events were vasodilation (n=8), dyspnea (n=3), syncope (n=2), headache (n=2), and dizziness (n=2). Nine (4.4%) patients experienced significant changes in vital signs; however, none was assessed as drug related.”¹⁵⁶ In a study of rectal examinations, a rectal examination proved impossible on five of 328 occasions. Eighty children experienced severe and 121 minor discomfort during rectal examination at the time of hospital admission; at the examination before hospital discharge, severe discomfort was found in 34 and minor discomfort in 88 children.”¹⁶⁰ Leeuwenburgh et al. reported that seven patients could not complete the MRI procedure because of claustrophobia or unexpected technical failure;¹⁶² they did not report how many of them had a claustrophobic reaction or give any further details. A final study reported on the results of a survey sent to 104 children after US and MRI. Of the total 52 that responded, 52 percent reported that MRI had a long duration, 10 percent found it painful, 53 percent reported tolerance, 32.7 percent found lying on the MRI gantry as burdensome, and 55.8 percent reported a preference for MRI over US immediately following the procedure; that number dropped to 51.8 percent after 3 months.¹⁹³

Table 34. Other adverse events

Study Design	Study	Test	Contrast Route of Administration	N	Population	Summary
RCT	Shah et al., 2008 [not indexed in PubMed] ¹¹⁰	US/Alvarado vs. clinical	N/A	308	mixed	Delayed treatment (operated after 10 hours from randomization) in association with perforation: 5 perforations in Alvarado/US vs, 3 in clinical group. Intervention group: 1 subcutaneous abscess; clinical group: 1 intestinal obstruction.
Diagnostic cohort studies	Acosta et al., 2005, 15633057 ¹⁵⁸	CT	rectal	94	children	One child was unable to tolerate the procedure.
	Dickson et al., 1985, 4026364 ¹⁶⁰	rectal exam	NR	201	children	A rectal examination was impossible in 5/328 exams. Admission examination: severe discomfort in 80, minor discomfort in 121. Discharge examination: severe discomfort in 34, minor discomfort in 88.
	Rypins et al., 2002, 11807363 ¹⁵⁶	Tc-99m	NR	248	mixed	No serious or severe adverse events were reported. 17/203 reported 20 mild and 4 moderate adverse events (none definitely drug related). The most commonly reported adverse events were vasodilation (8), dyspnea (3), syncope (2), headache (2), and dizziness (2). Nine patients experienced significant changes in vital signs (none drug related).
	Leeuwenburgh et al., 2013, 23481162 ¹⁶²	MRI	none used	223	adults	"In seven patients, an MR examination could not be performed because of claustrophobia or unexpected technical failure."
	Wise et al., 2001, 11264081 ¹⁶¹	oral contrast administration, then US, then unenhanced CT, then CT with IV contrast, then CT with colonic contrast material, then US – in the other half of patients, this order was reversed	oral, IV, rectal	100	adults	Average discomfort score: CT: 4.2 in focused scans with oral contrast, 6.7 in focused scans with oral, IV, and rectal contrast, and 5.3 in abdominopelvic scans with oral and IV contrast. US: 6.1 with oral contrast and 6.7 with oral, IV, and rectal contrast.
	Cobben, 2004, 15333354 ¹²⁷	MRI	no contrast	12	pregnant women	All 12 patients and fetuses were exposed to unknown bioeffects of MRI.
	Pedrosa, 2009, 19244044 ¹³⁰	MRI	oral	148	pregnant women	One patient refused to complete the MRI protocol
Thieme, 2014, 24135892 ¹⁹³	MRI	none used	104	children	Patients returning the survey reported on the following parameters: long duration = 58% (30/52), painful = 10% (5/52), tolerance = 53% (28/52), lying on the MRI gantry as burdensome = 32.7% (17/52), preference for MRI over US = 55.8% (29/52) immediate and 51.8% (27/52) after 3 months	

CT = computed tomography; IV = intravenous; MRI = magnetic resonance imaging; RCT = randomized controlled trial

Surgical Complications Related to Diagnostic Laparoscopy

Thirty-four studies of diagnostic laparoscopy (of 55 included for Key Question 1) mentioned surgery related harms. Eight RCTs (469 patients) and eight NRCSs (4084 patients) described complications related to laparoscopy as compared to open appendectomy; twenty-five diagnostic cohort studies (5553 patients) reported on complications of diagnostic laparoscopy. In general the rates of specific complications were low (generally less than 10% and in most cases less than 2%); however, few studies attributed specific adverse events to diagnostic laparoscopy (as opposed to additional surgical intervention). Nine studies, including five RCTs, reported that there were no complications related to the diagnostic laparoscopic procedure.

Four RCTs reported no complications or adverse events in the study group that had diagnostic laparoscopy.^{117,118,120,121} Two of these studies reported harms that were not caused by the laparoscopic part of the operation: one postoperative ileus and two wound infections.^{117,118} One RCT compared immediate laparoscopy with observation. Morino et al. reported that in the immediate laparoscopy group there was no mortality, one urinary tract infection, and one trocar site infection. In the observation group, there was also no mortality, and adverse events were limited to a single case of severe anemia.¹¹⁶ Three RCTs compared laparoscopic versus open surgery. One RCT reported that in the laparoscopy group, one patient of 18 had spillage of purulent matter into the lower abdomen; in the open appendectomy group there were two wound infections and one adhesive small bowel obstruction in 16 patients.¹¹² Another RCT reported laparoscopy complications in 14 of 59 patients, including abdominal pain that persisted for at least one month after discharge (n=7), wound infection (n=5), wound dehiscence after laparotomy (n=1), readmission with respiratory symptoms and shoulder tip pain (n=1), and death from a massive pulmonary embolus 5 days after laparotomy despite full thromboprophylaxis. In the open group, 19 of 61 patients had complications, including abdominal pain persisting for at least 1 month (n=15), wound infection (n=4), and one death seven days after discharge from a presumed pulmonary embolism.¹¹⁴ The third RCT reported more harms with laparoscopic surgery than open, including wound infections (4 of 59 in the early laparoscopic group and 3 of 61 in the open group), one trocar site hematoma, three pelvic collections, and one case of DVT in the laparoscopic group and 1 urinary retention in the open group.¹²²

Eight NRCS described complications related to laparoscopy as compared to open appendectomy. One reported only that there was no mortality in either group.¹²⁵ The second reported that there were no intraoperative complications in either group, but that in the diagnostic laparoscopy group the complication rate was 6.6 percent (n=376). In the group that got an operation immediately, the complication rate was higher, 12.3 (n=124) percent. Specifically, the superficial wound infection rate was significantly lower in the diagnostic laparoscopy group than in the primary open surgery group ($p = 0.020$), while the intra-abdominal infection rate did not differ between the groups ($t9 = 0.15$). One patient in the laparoscopic appendectomy group required reoperation for mesoappendix bleeding, three were readmitted within 30 days after surgery because of intra-abdominal infection and three were converted to open appendectomy group because of subileus (no operation needed), prolonged pyrexia, or intestinal fistula. One patient in the laparoscopy group died, a 93-year-old woman who was discharged in good condition 6 days after a laparoscopic appendectomy but died in her home 12 days after surgery for unknown reasons.¹³⁹ A third study reported no complications of any type in the six patients who had diagnostic laparoscopy alone. In the 54 patients who had open appendectomy, there were five wound complications and one death. In the 47 patients who had diagnostic laparoscopy followed by laparoscopic appendectomy there were two wound complications. In the 15 patients

who had laparoscopy and open appendectomy there were two wound complications.¹⁸³ A recent comparative study of 1043 patients reported that the laparoscopic approach had a higher rate of intra-abdominal abscess (3.9% compared with 2.2% in the open group; $p=0.055$), but a lower rate of wound infections (1.5% versus 7% for the open group; $p < 0.0001$).¹¹³ Another NRCS comparing diagnostic laparoscopy and open appendectomy reported that among the 93 diagnostic laparoscopy patients, there were three wound infections, one ileus, one hemolytic anemia, one case of aspiration pneumonia, and one infected hydrocele. In the open appendectomy group ($n=74$), there were four wound infections, two ileus, and one UTI.¹³⁶ Two other NRCS reported perforations, one of the small bowel,¹³⁸ and one of the transverse colon with the pneumoneedle.¹³⁷

Twenty-five diagnostic cohort studies^{143-149,168-184,192} reported on complications of diagnostic laparoscopy in 5469 patients. Five studies reported that there were no complications.^{143,146,173,175,184} Two studies reported a total four deaths^{145,147}. Others reported 37 wound infections,^{145,147-149,170-172,176-179,182} 27 cases of ileus,^{145,171,172,177,182} 23 deep venous thromboses,¹⁴⁵ 22 cases of fever (one with acute abdominal pain),^{145,147,172} 18 intrabdominal infections,¹⁴⁵ 17 hematomas (4 wound, 2 intraabdominal, 2 abdominal wall, 1 parietal, and 8 unspecified),^{145,147,179,181} 14 abscess,^{144,147,148,171,177,182} 13 chest or respiratory infections,^{145,147,168,176,177,182} six perforations (3 bowel and 3 bladder),^{170,171,177,180} six fluid collection,^{174,176,178} six bleeding or hemorrhage,^{145,168,177,181} six intestinal obstructions,^{147,177} five coronary related complications,¹⁴⁵ three inferior epigastric artery injury,^{172,180} three appendix ruptured on removal,¹⁷² two intestinal lesions,¹⁴⁵ two cases of cecal leakage,¹⁷⁷ one cecal dehiscence,¹⁷⁷ one insufflation in cecal wall,¹⁸¹ one cecal phlegmon,¹⁴⁷ one appendiceal artery hemorrhage,¹⁴⁷ a perioperative arrhythmia and a pneumothorax,¹⁷⁶ one case of pancreatitis,¹⁴⁷ one case of intraabdominal sepsis,¹⁴⁷ a laryngeal spasm post-intubation,¹⁸² a reaction to the abdominal sutures,¹⁷⁴ one tertiary peritonitis and enterocutaneous fistula,¹⁴⁸ a minor abdominal wall cellulitis,¹⁴⁴ one case of mesoappendiceal bleeding,¹⁴⁵ one pseudomembranous enterocolitis,¹⁴⁵ one pulmonary embolism,¹⁴⁵ one ruptured aortic aneurysm,¹⁴⁵ and one reoperation to repair the appendix stump.¹⁹² Further details are presented in Table 35.

Table 35. Reported surgical complications of diagnostic laparoscopy

Study Design	Study	N	Population	Summary of Surgical Complications
RCTs	Laine et al., 1997, 9069134 ¹¹⁸	25	women of childbearing age	No complications related to laparoscopy. 1 postoperative ileus (not caused by the laparoscopic part of the operation).
	Olsen et al., 1992, 8369940 ¹²⁰	30	women of childbearing age	No complications related to laparoscopy.
	Jadallah et al., 1994, 8186313 ¹¹⁷	100	women of childbearing age	No complications related to laparoscopy; 2 wound infections in laparoscopic appendectomy group.
	Van Dalen et al., 2003, 12739123 ¹²¹	63	women of childbearing age	No complications related to laparoscopy.
	Bruwer et al., 2003, 14768141 ¹¹²	34	women of childbearing age	Laparoscopy: 1 spillage of purulent matter into the lower abdomen. Open appendectomy: 2 wound infections, 1 adhesive small bowel obstruction.
	Decadt et al., 1999, 10583282 ¹¹⁴	59	adults	Laparoscopy: 7 abdominal pain that persisted for at least 1 month after discharge, 5 wound infections, 1 wound dehiscence after laparotomy, 1 readmission with respiratory symptoms and shoulder tip pain, and 1 death from a massive pulmonary embolus 5 days after laparotomy. Open appendectomy: 15 abdominal pain persisting for at least 1 month, 4 wound infections, and 1 death 7 days after discharge from a presumed pulmonary embolism.
	Tzovaras et al., 2007, 17219281 ¹²²	54	mixed	Laparoscopy: 4 wound infections, 1 trocar site hematoma, 3 pelvic collections, 1 DVT. Open: 3 wound infections, 1 urinary retention
	Morino et al., 2006, 17122613 ¹¹⁶	104	adults	Immediate laparoscopy: 1 urinary tract infection, 1 trocar site infection; observation 1 severe anemia.
NRCSSs	Ragland et al., 1988, 2792080 ¹³⁷	21	women of childbearing age	1 perforation of the transverse colon with the pneumoneedle
	Tronin et al., 1996, 9050636 ¹³⁸	1000	mixed	1 perforation of the small bowel
	Moberg et al., 2000, 1180408 ¹³⁹	500	adults	No intraoperative complications were seen in either group. Laparoscopy: complication rate = 6.6%, 1 reoperation for mesoappendix bleeding, 3 readmitted within 30 days because of intra-abdominal infection, 3 converted to open appendectomy, 1 death. Primary open appendectomy: complication rate = 12.3%.
	Schirmer et al., 1992, 8506965 ¹³⁹	68	mixed	No complications of any type with diagnostic laparoscopy alone (n=6); open appendectomy (n=54): 1 death, 5 wound complications, 18.9% complication rate; diagnostic laparoscopy + laparoscopic appendectomy (n=47): 2 wound complications, 10.6% complication rate; laparoscopy + open appendectomy (n=15): 2 wound complications, 46.7% complication rate.
	Barrat et al., 1999, 9950123 ¹²⁵	1285	adults	No mortality in either group.
	Kollias et al., 1994, 7980256 ¹³⁶	167	mixed	Laparoscopy (n=93): 3 wound infections, 1 ileus, 1 hemolytic anemia, 1 aspiration pneumonia, 1 infected hydrocele. Open (n=74) 4 wound infections, 2 ileus, 1 UTI.
	Sadot et al., 2013, 24016703 ¹¹³	1899	mixed	Laparoscopy (n=1043): 41 intra-abdominal abscess, 16 wound infections; Open and laparoscopy (n=1899) 9 small bowel obstructions, 1 inadvertent enterotomy, 1 required reoperation for leakage from the cecum resection line, 1 small bowel obstruction, 1 intractable abdominal pain

Table 35. Reported surgical complications of diagnostic laparoscopy (continued)

Study Design	Study	N	Population	Summary of Surgical Complications
Diagnostic cohort studies	Ng et al., 2008, 18259838 ¹⁸²	787	mixed	1 wound infection, 1 intra-abdominal abscess, 1 ileus, 1 respiratory tract infection, 1 laryngeal spasm post-intubation
	Clarke et al., 1986, 2937361 ¹⁷⁰	46	adults	1 wound infection and 1 minor tear of the small bowel
	Cristalli et al., 1991, 1839575 ¹⁷³	31	mixed	No post-operative complications
	Spirtos et al., 1987, 2948388 ¹⁸⁴	86	women of childbearing age	No complications from laparoscopy; laparotomy: 4 wound infections, 2 pelvic abscess, 1 pulmonary embolism, 1 ileus
	Diehl et al., 1981, 6457704 ¹⁷⁵	25	mixed	no complications resulted directly from the procedure
	Cox et al., 1993, 8216060 ¹⁷²	81	mixed	5 operative complications: 3 appendix ruptured during manipulation, 1 left inferior epigastric artery was ruptured by the 5 mm LIF port, 1 extra peritoneal insufflation; 5 post-operative complications: 3 prolonged ileus, 1 fever, 1 wound infection
	Graham et al., 1999, 10615200 ¹⁷⁶	85	mixed	2 small intraperitoneal collections, 1 umbilical wound infection, 1 perioperative arrhythmia, 1 pneumothorax secondary to a patent pleuroperitoneal canal, 1 chest infection
	Borgstein et al., 1997, 9294274 ¹⁶⁹	161	women of childbearing age	1 bleeding from the trocar site, which required abdominal wall exploration
	Mutter et al., 1998, 9817258 ¹⁸¹	36	mixed	No major complications. Minor complications: 1 insufflation in cecal wall, 1 preoperative hemorrhage on 2mm port site, 1 postoperative parietal hematoma required reoperation for removal
	in't Hof et al., 2004, 15386320 ¹⁴⁸	103	adults	3 wound infections, 2 intra-abdominal abscesses, 1 tertiary peritonitis and enterocutaneous fistula
	Lee et al., 2001, 11343547 ¹⁴⁹	76	mixed	1 wound infection
	DeCou et al., 2004, 14745576 ¹⁷⁴	30	children	1 suture reaction at the umbilical incision, 1 pelvic fluid collection
	Konstantinidis et al., 2008, 18373452 ¹⁷⁹	1024	mixed	Complication rate was 5.7% (52 patients), consisting mostly of minor complications. There were no major intraoperative complications. There were no intra-abdominal abscesses postoperatively. Wound-infection rate was 1.1%. We had 3 patients with an abdominal-wall hematoma at the trocar sites. Two of them were managed intraoperatively. The 3rd patient was treated conservatively after surgery. There was no mortality.
	Jones et al., 2011, 21688285 ¹⁷⁸	146	mixed	1 wound infection, 3 intra-abdominal collection
	Gurrado et al., 2009, 20334502 ¹⁷⁷	1024	Mixed	Minor: 1 wound infection, 1 pneumonia, 1 ilium. Major: 4 intraabdominal abscesses, 5 intestinal obstructions, 1 hemorrhage, 2 bowel perforation, 1 bladder perforation, 1 cecal dehiscence, 2 cecal leakage
Linos et al., 1999, 10194691 ¹⁸⁰	121	women of childbearing age	2 injury to inferior epigastric artery, 1 bladder injury caused by suprapubic trocar	

Table 35. Reported surgical complications of diagnostic laparoscopy (continued)

Study Design	Study	N	Population	Summary of Surgical Complications
Diagnostic cohort studies (continued)	Ates et al., 2008, 18373441 ¹⁶⁸	74	mixed	Other than a chest infection observed in 1 patient, there was no operative complication; no death and, postoperatively, none of our patients had a leak or residual intra-abdominal abscess in this study.
	Moberg, 1998, 9845129 ¹⁴⁵	1043	mixed	Perioperative complications: 2 intestinal lesions, 1 mesoappendiceal bleeding. Postoperative complications: 12 wound infections, 20 prolonged fever, 8 hematoma, 21 ileus, 23 DVT, 5 lung complications, 1 pseudomembranous enterocolitis, 18 intrabdominal infections, 3 bleeding, 1 pulmonary embolism, 5 coronary related complications, 3 deaths, 1 ruptured aortic aneurism
	Thorell, 1999, 10494640 ¹⁴³	77	women of childbearing age	No complications developed during the hospital stay
	Wagner, 1996, 8703146 ¹⁴⁷	267	mixed	4 wound infections, 4 wound hematoma, 4 pneumonia, 1 early obstruction, 1 pancreatitis, 1 intraabdominal hematoma, 5 abscess, 1 bleeding from appendiceal artery, 1 acute abdominal pain and fever, 1 cecal phlegmon, 1 intraabdominal sepsis, 1, death
	Bagnato et al., 1992, 1387169 ¹⁴⁴	23	mixed	1 postoperative pelvic abscess, 1 minor abdominal wall cellulitis
	Kuster, 1992, 1416436 ¹⁴⁶	38	adults	No morbidity or mortality
	Connor et al., 1994, 7856985 ¹⁷¹	85	mixed	1 bladder perforation, 1 postoperative abscess, 1 prolonged ileus, 1 wound infection
	Ilce et al., 2013, 24353684 ¹⁹²	84	children	1 appendix stump was opened postoperatively and repaired by laparotomy 3 days after the first operation. No postoperative mortalities.

NRCS = nonrandomized comparative study; RCT = randomized controlled trial

Discussion

Key Findings and Strength of Evidence Assessment

This Comparative Effectiveness Review synthesizes evidence from more than 900 studies on the diagnosis of RLQ pain and suspected acute appendicitis to answer Key Questions related to test performance, patient-relevant outcomes, and test-related harms. The literature on the test performance of various clinical symptoms and signs, laboratory and imaging tests, and multivariable diagnostic scores is vast, but consists almost exclusively of studies assessing the test performance of individual index tests. Information on test performance of multiple tests applied jointly and conditional test performance (i.e., test performance among patients already examined with other tests) was very limited. The few studies that provided information on more than one index tests were typically not designed with the goal of providing comparative information and cross-study comparisons cannot provide reliable evidence on relative performance. We found very limited information on the test performance or comparative effectiveness of diagnostic pathways (i.e., well-defined sequences of diagnostic and treatment steps). Comparisons of the test performance of alternative test strategies had to rely on indirect (cross-study) evidence. We believe that the available evidence can support fairly strong conclusions about the test performance of individual tests, but is often insufficient to support conclusions about their comparative effectiveness. In this section we briefly summarize our assessment of the strength of evidence for key outcomes (Table 36). Of note, strength of evidence grades reflect our confidence in the evidence underlying the report's conclusions and should not be interpreted as clinical recommendations. For example, "insufficient" strength of evidence for a comparison between two tests means that the available evidence does not allow us to confidently estimate the difference in test performance between the two tests; it does not mean that we believe the tests to have (or not have) similar performance.

Test Performance

Clinical symptoms and signs, including classical signs of peritoneal irritation, fever, and various assessments of abdominal pain, appeared to have limited test performance when used in isolation (positive likelihood ratios smaller than 5; negative likelihood ratios larger than 0.2) in all the populations of interest to this report. Among laboratory tests WBC, CRP, and tests derived from combinations of measurements on the complete blood count and differential had test performance that was generally higher compared to that of clinical symptoms and signs (especially with respect to sensitivity using a low risk threshold) but still rather limited (e.g., in terms of summary LRs). Because studies did not allow an examination of the performance of multiple tests applied jointly, and because conditional test performance was not reported uniformly across studies, the clinical implications of the relatively limited test performance of many non-imaging tests are not clear. Furthermore, signs and symptoms are variable within patient (over the course of disease) and among patients, and it is hard to assess their performance based on test performance. Importantly, the clinical examination forms the basis of the investigation of acute abdominal pain and suspected acute appendicitis and – even if poorly reported – all studies of imaging tests use some form of clinical examination for patient selection.

Multivariable diagnostic scores appeared to have test performance that was superior to the individual clinical signs, symptoms, or laboratory tests they included, but still rather limited

(e.g., in terms of summary likelihood ratios). Of note, the majority of studies assessed scores that had been developed before the widespread availability of CT and US imaging, suggesting that their results may be less applicable to current clinical practice.

Among imaging tests, CT and MRI had high sensitivity and specificity, resulting in clinically relevant summary likelihood ratios. CT had been investigated by a large number of diagnostic cohort studies, leading to precise estimates of test performance in all populations of interest to this report. Although there were no reported short-term harms from ionizing radiation, it does present a long-term risk, particularly in children and pregnant women. In contrast, MRI had been investigated in a relatively small number of studies mainly focused on pregnant women. US had lower test performance and resulted in substantially greater proportion of non-diagnostic examinations, compared to both CT and MRI, across populations of interest. US was investigated by a large number of studies and results were somewhat heterogeneous, suggesting that the average estimate of test performance may not apply to all populations for which US is considered. A possible explanation for this heterogeneity is the operator dependence of the test performance of US and the fact that studies had been conducted in different settings.

Diagnostic laparoscopy appeared to have good test performance; however, studies were poorly reported and differed in their policies regarding removal of the appendix when no pathology was macroscopically visible, which may bias test performance results. Furthermore, patients included in studies of diagnostic laparoscopy are different from patients included in studies of non-invasive tests. Therefore, our results for the test performance of laparoscopy should not be compared with the other diagnostic tests reviewed in this report.

For all diagnostic tests, we emphasize that test performance is not directly related to clinical outcomes, and high sensitivity and specificity do not necessarily imply improvements in outcomes, such as perforations, abscesses, or other infectious complications.

Comparative Test Performance

Comparisons among tests with respect to test performance relied on a small number of RCTs of moderate risk of bias, a relatively small number of direct comparisons among index tests in diagnostic cohort studies that were not designed to obtain comparative information, and indirect comparisons across single index test studies enrolling diverse populations in heterogeneous clinical settings. There was evidence of moderate strength that CT has superior overall test performance compared to US and produces fewer non-diagnostic results. Similarly, MRI appeared to have better test performance than US, but the strength of evidence was deemed low. The strength of the evidence on comparisons among other imaging tests and among multivariable diagnostic scores was deemed insufficient.

Patient-Relevant Outcomes

The evidence is insufficient for patient relevant outcomes. We based our assessment of the comparative effectiveness of alternative tests primarily on RCTs because indirect (across studies) comparisons of outcomes other than test performance are susceptible to bias due to differences among the populations included. We found only a few RCTs, which assessed a range of comparisons across different modalities (or different versions of the same modality), and as such did not provide definitive evidence for any of the possible pairwise contrasts they evaluated.

Adverse Events of Testing

The evidence is insufficient for adverse events. Information on harms was often incomplete and poorly reported. Only a minority of the included studies provided information on test-related harms, raising concerns about selective outcome and analysis reporting. The majority of the studies providing information on adverse events did not report the definitions or ascertainment methods they used. Importantly, no information was available from studies meeting our selection criteria regarding the effects of ionizing radiation. Information was particularly limited on fetal and maternal outcomes of various diagnostic modalities applied during pregnancy for the investigation of acute appendicitis.

Table 36. Assessment of the strength of evidence for test performance and modifiers of test performance

Test or Comparison Between Tests	Strength of Evidence	Risk of Bias	Precision	Directness	Consistency	Adults	Children	Elderly	Women of Reproductive Age	Pregnant Women
Diagnostic test performance										
WBC count	Moderate	Intermediate-high	Somewhat imprecise	Direct	Somewhat inconsistent	26 studies Sens: 0.81 (0.74 to 0.87) Spec: 0.54 (0.42 to 0.64)	41 studies Sens: 0.80 (0.73 to 0.85) Spec: 0.65 (0.56 to 0.73)	3 studies Sens: 0.71 (0.69 to 0.77) Spec: 0.50 (0.38 to 0.70)	2 studies Sens: 0.64 (0.60 to 0.69) Spec: 0.67 (0.67 to 0.67)	6 studies Sens: 0.63 (0.21 to 0.92) Spec: 0.75 (0.38 to 0.95)
CRP	Low	Intermediate-high	Imprecise	Direct	Somewhat inconsistent	15 studies Sens: 0.84 (0.73 to 0.92) Spec: 0.67 (0.50 to 0.81)	22 studies Sens: 0.73 (0.66 to 0.80) Spec: 0.72 (0.61 to 0.81)	2 studies Sens: 0.91 (0.91 to 0.92) Spec: 0.21 (0.17 to 0.25)	3 studies Sens: 0.79 (0.44 to 0.97) Spec: 0.70 (0.33 to 0.93)	1 study Sens: 0.68 Spec: 0.50
Measures based on the CBC and differential	Low	Intermediate-high	Imprecise	Direct	Somewhat inconsistent; but available data limit our ability to assess consistency	Please see the Results section for the test performance of various test combinations				
Alvarado score (low risk cut-off)	Moderate	Intermediate	Somewhat imprecise	Direct	Somewhat inconsistent	3 studies Sens: 0.91 (0.89 to 0.93) Spec: 0.31 (0.24 to 0.78)	6 studies Sens: 0.99 (0.92 to 1.00) Spec: 0.48 (0.24 to 0.74)	No studies	2 studies Sens: 0.99 (0.98 to 1.00) Spec: 0.24 (0.22 to 0.25)	No studies
Alvarado score (high risk cut-off)	Moderate	Intermediate	Somewhat imprecise	Direct	Somewhat inconsistent	16 studies Sens: 0.80 (0.60 to 0.93) Spec: 0.71 (0.50 to 0.85)	9 studies Sens: 0.83 (0.73 to 0.91) Spec: 0.81 (0.63 to 0.92)	No studies	5 studies Sens: 0.70 (0.35 to 0.92) Spec: 0.91 (0.65 to 0.99)	No studies
PAS	Low	Intermediate	Imprecise	Direct	Consistent	No studies	5 studies Sens: 0.03 (0.00 to 0.13) Spec: 1.00 (0.99 to 1.00)	No studies	No studies	No studies

Table 36. Assessment of the strength of evidence for test performance and modifiers of test performance (continued)

Test or Comparison Between Tests	Strength of Evidence	Risk of Bias	Precision	Directness	Consistency	Adults	Children	Elderly	Women of Reproductive Age	Pregnant Women
CT	Moderate-High	Intermediate	Precise	Direct	Consistent	72 studies Sens: 0.96 (0.95 to 0.97) Spec: 0.96 (0.93 to 0.97)	34 studies Sens: 0.96 (0.94 to 0.98) Spec: 0.92 (0.85 to 0.96)	4 studies Sens: 1.00 (0.94 to 1.00) Spec: 1.00 (0.43 to 1.00)	11 studies Sens: 0.99 (0.96 to 1.00) Spec: 0.91 (0.75 to 0.97)	5 studies Sens: 0.99 (0.96 to 1.00) Spec: 0.91 (0.75 to 0.97)
MRI	Low	Intermediate	Imprecise	Direct	Consistent	7 studies Sens: 0.95 (0.88 to 0.98) Spec: 0.92 (0.87 to 0.95)	7 studies Sens: 0.97 (0.87 to 1.00) Spec: 0.96 (0.84 to 0.99)	No studies	1 study Sens: 1.00 Spec: 0.86	11 studies Sens: 0.98 (0.92 to 1.00) Spec: 0.98 (0.96 to 1.00)
US	Moderate	Intermediate-high	Precise	Direct	Somewhat inconsistent	38 studies Sens: 0.85 (0.79 to 0.90) Spec: 0.90 (0.83 to 0.95)	85 studies Sens: 0.89 (0.86 to 0.92) Spec: 0.91 (0.89 to 0.94)	No studies	11 studies Sens: 0.72 (0.51 to 0.88) Spec: 0.92 (0.75 to 0.98)	13 studies Sens: 0.72 (0.45 to 0.92) Spec: 0.95 (0.84 to 0.99)
Laparoscopy	Moderate	Intermediate-high	Somewhat imprecise	Direct	Somewhat inconsistent	Please see the Results section for a complete description of results related to diagnostic laparoscopy				
Modification of test performance										
All factors	Insufficient	Intermediate or high	Typically imprecise	Indirect (meta-regression)	Not possible to assess consistency on the basis of available data (assessments relied on cross-study comparisons)	The evidence on the effect of patient- and test-related characteristics on test performance was limited and exclusively derived from indirect comparisons. There were indications that aspects of study design characteristics affect test performance but the effects are often unpredictable in direction and do not have direct clinical relevance.				

CT = computed tomography; MRI = magnetic resonance imaging; PAS = Pediatric Appendicitis Score; Sens = sensitivity; Spec = specificity; US = ultrasound; WBC = white blood cell

Ratings reflect our trust in the estimates of test performance (from individual studies or meta-analyses) and should not be construed as clinical recommendations.

Limitations of the Evidence Base

The evidence base regarding the diagnosis of acute appendicitis is limited in the following ways:

- *Studies reporting information on test performance outcomes were at moderate to high risk of bias.* Differential verification (the use of a different reference standard test depending on the results of the index test) and partial verification (the failure to apply the reference standard on the included patients) were common, particularly in studies that were not surgical series (generally, studies with a lower prevalence of appendicitis). Studies with complete and non-differential verification tended to be surgical cohorts reporting exclusively on patients undergoing appendectomy that are not representative of all patients with acute RLQ pain. In addition, poor reporting of information on study design hampered our risk of bias assessment.
- *Studies provided limited information to assess the impact of various patient-, technical implementation-, operator-, or system-related factors on the test performance of the tests of interest.* For example, the impact of patient age, sex, contrast use (for CT), operator experience, and setting of care on test performance and patient-relevant outcomes could not be fully explored.
- *Information on the comparative effectiveness of alternative testing strategies (e.g., sequential use of tests as part of a diagnostic algorithm) with respect to test performance, patient-relevant outcomes, and resource use was limited.* Direct (within study) comparisons of test performance and impact of testing strategies on clinical outcomes were scarce. Studies have not compared diagnostic algorithms (e.g., combinations of tests applied in sequence such that the results of earlier tests determine the choice of subsequent tests). When two or more index tests were evaluated in the same study, the role of testing that was being examined (add-on, replacement, triage) was often unclear.
- *In studies of diagnostic scores, multivariable models were often developed and evaluated in the same patient sample.* The lack of separation between the training and testing datasets (or any attempt at internal validation of the model) generally leads to optimistic (too high) estimates of test performance. The lack of external validation (replication) also limited our ability to assess the generalizability of many diagnostic scores.
- *Few RCTs compared alternative test strategies with respect to patient-relevant outcomes.* The few trials reporting patient-relevant outcomes were fragmented across heterogeneous comparisons of alternative testing strategies. The trials often used suboptimal methods for randomized sequence generation, allocation concealment, and blinding, or they provided information that was too limited to assess these aspects of study design. Many had sample sizes that were too small to reliably detect small or moderate differences between the strategies being compared.
- *In contrast to the RCTs, NRCSSs of alternative testing strategies attained large sample sizes but often reported unadjusted analyses (or analyses adjusted only for a small number of potential confounders) that do not allow drawing strong conclusions about the comparative effectiveness of alternative test strategies.*

Strengths and Limitations of This Review

Previous reviews on this topic have focused on special patients populations (e.g., children only or pregnant women only), have largely focused on test performance outcomes, have not

assessed harms systematically, or have focused on a very limited spectrum of study designs (e.g., comparative prospective cohort studies only). Our work provides a comprehensive, up-to-date summary of the evidence on the diagnosis of RLQ pain and suspected acute appendicitis. For many of the examined tests and patient populations, this review is the first to be conducted; for some important modalities that have been to some extent investigated in previous meta-analyses (e.g., CT, MRI, US, and multivariable diagnostic scores), our work includes a much larger number of studies (and a greater total number of patients) compared to previous reviews. This allows us to provide accurate estimates of test performance in different patient populations that can be used to inform clinical decisions (especially if used as inputs in decision and simulation modeling studies) and to identify evidence gaps to inform the planning of future research.

Nonetheless, several limitations—which to some extent reflect the limitations of the underlying evidence base—need to be considered when interpreting our results. The body of evidence consisted of studies that we deemed to be of moderate to high risk of bias on the basis of aspects of their design and conduct. In some cases, methodological shortcomings and poor reporting limited our ability to draw strong conclusions, despite the availability of a large number of relevant studies.

Information for several outcomes of interest was not reported from all available studies. We were most concerned about selective outcome and analysis reporting for patient-relevant outcomes and harms. Furthermore, the selective publication of favorable or unfavorable evidence on any given test (i.e., publication bias) may have affected our results. Statistical methods for the detection of publication bias have general limitations that limit their usefulness; empirical studies in diagnostic test meta-analyses have demonstrated that existing methods are inadequate.

Information on study- or population-level characteristics that could be modifiers of test performance, patient-relevant outcomes, and adverse events was incomplete or poorly reported in the included studies. Thus, our ability to explore between-study heterogeneity using meta-regression was limited. Furthermore, because we relied on published information and did not obtain individual patient data from any of the included studies, we were unable to evaluate the impact of patient- or lesion-level factors on outcomes of interest. Although worthwhile, individual patient meta-analysis of diagnostic studies in acute appendicitis would be very challenging to undertake given the large number of available studies, each reporting findings for different test modalities, and employing alternative definitions of positive index and reference standard tests.

The reference standard in the reviewed studies was a combination of pathologic examination following appendectomy (for index test positive patients) and clinical followup (for index test negative patients); in many studies a substantial proportion of included patients were not assessed with a reference standard. Differential and incomplete verification can bias the estimation of test performance measures.

We assumed that pathological diagnosis and clinical followup have negligible measurement error (i.e., that they represent a “gold” standard). It is unlikely that this assumption is exactly true (e.g., pathologic examination may have some diagnostic error, and clinical followup provides less than perfectly accurate information). Consequently, it is likely that estimates of test performance are biased, and the direction of this bias is hard to predict, particularly at the meta-analysis level. However, we believe that the error rate of this reference standard is low enough that its influence on our estimates is relatively small.

Finally, we did not address contextual factors (e.g., availability of equipment, trained readers) that are important determinants of the adoption of specific diagnostic strategies in particular settings.

Applicability of Review Findings

In general, the existing evidence on alternative diagnostic tests for the diagnosis of acute RLQ pain and suspected acute appendicitis appears to be applicable to clinical practice in the U.S. The included studies enrolled patients representative of the age and sex distribution of patients seeking care for right lower quadrant abdominal pain in the U.S. and evidence on test performance was available for all commonly used modalities. Information on adults and children was often separately reported allowing the assessment of test performance in these patient subgroups. However, information was more limited for patients at the extremes of age (i.e., children younger than 5 years or the elderly), pregnant women, and women of reproductive age; in some cases decisions for these will have to rely on extrapolation of results from population subgroups with more available information (and thus applicability assessments are not possible). Approximately one third of the studies in this review were conducted in the U.S, and the vast majority was carried out in either the U.S. or in industrialized European or Asian countries. Care settings varied across studies and included academic and non-academic centers, and patient populations were sampled at emergency departments, from surgical cohorts, or from mixed populations.

Assessing the applicability of studies on clinical symptoms and signs was challenging: the pathophysiologic rationale for many of these tests is well established. However, many of the relevant studies were conducted before the widespread availability of imaging modalities, and thus their findings may reflect test performance in a population with more advanced disease or populations selected for a high probability of appendicitis (e.g., surgical cohorts). Studies of laboratory and imaging tests evaluated “stable” technologies (e.g., white blood cell count) or had been conducted in recent years (e.g., many studies of CRP, CT, and US had been conducted from 2005 onwards). In meta-regression analyses comparing test performance in the last decade against earlier years there was no evidence that the performance of laboratory or imaging tests has changed significantly over time; however, the indirect nature of meta-regression comparisons and the low precision of meta-regression estimates limits the strength of these findings. In contrast, the applicability of the evidence on most multivariable diagnostic scores may be somewhat limited because most were developed before the era of widespread availability of imaging. The lack of external validation for most diagnostic scores also limits the applicability of these results. The findings of studies on diagnostic laparoscopy may also be less applicable because they were conducted before the widespread availability of diagnostic imaging.

Evidence Gaps and Ongoing Research

Table 37 summarizes the evidence gaps with regards to the Key Questions of diagnostic test performance, patient-relevant outcomes, and adverse events.

Table 37. Evidence gaps for the diagnosis of right lower quadrant abdominal pain and suspected acute appendicitis

Key Question	Category	Evidence Gap
Test performance	Population	Limited information on all populations for MRI Relatively limited information on women of reproductive age, pregnant women, and the elderly for tests other than MRI
	Interventions & Comparators	Limited information on MRI Limited information on combinations of tests and alternative test algorithms
	Outcomes	Test performance outcomes (sensitivity, specificity, area under the ROC curve, etc.)
	Modifiers of test performance	Optimal imaging method for specific subgroups of patients, different presentations of patients with right lower quadrant pain, and physician- or system-level factors
Comparative test performance	Population	All populations of interest
	Interventions & Comparators	All tests of interest to this report; particularly imaging modalities in common use (CT, MRI) and emerging technologies (e.g., MRI, novel multivariable diagnostic scores) Combinations of tests, especially alternative test algorithms combining more than one tests, in sequence or in parallel
	Outcomes	Test performance outcomes (sensitivity, specificity, area under the ROC curve, etc.)
	Modifiers of test performance	Preferred imaging method for specific subgroups of patients, different presentations of patients with right lower quadrant pain, and physician- or system-level factors
Patient-centered outcomes and resource utilization	Population	All populations of interest
	Interventions & Comparators	All tests of interest to this report; particularly imaging modalities in common use (e.g., CT, MRI) and emerging technologies (e.g., MRI, novel multivariable diagnostic scores) Combinations of tests, especially alternative test algorithms combining more than one tests, in sequence or in parallel
	Outcomes	Impact on diagnostic thinking and therapeutic decisionmaking; bowel perforation (ruptured appendix), fistula formation, infectious complications (abscess formation, peritonitis, sepsis, stump appendicitis), delay in diagnosis (time from presentation to definitive diagnosis; time from presentation to initiation of treatment; time from presentation to resolution of pain), length of hospital stay, and mortality.
	Modifiers of comparative effectiveness	Information on factors that affect the incidence of adverse events is sparse. Unclear what subgroups of patients and lesions may be most likely to experience adverse events
Test-related harms	Population	All populations of interest; particularly individuals at the extremes of age and pregnant women
	Interventions & Comparators	All tests of interest to this report; particularly imaging modalities in common use (e.g., CT, MRI) and emerging technologies (e.g., MRI, new multivariable diagnostic scores) Combinations of tests, especially alternative test algorithms combining more than one tests, in sequence or in parallel
	Outcomes	Direct harms of testing (e.g., harms from exposure to ionizing radiation, allergic reactions/kidney injury caused by contrast agents); fetal/maternal outcomes (for pregnant women; including premature labor, pregnancy loss, fetal morbidity, fetal mortality, maternal morbidity, maternal mortality); harms of test-directed treatment
	Modifiers of adverse events	Limited information was available for key adverse events of interest. Reporting in existing studies was inconsistent and potentially selective. Outcome ascertainment was not standardized.

CT = computed tomography; MRI = magnetic resonance imaging; ROC = receiver operating characteristic curve; US = ultrasound

Future Research Needs

Studies of Diagnostic Test Performance

- Cohort studies of test performance would provide useful information particularly for diagnostic tests that have not been studied adequately (e.g., MRI in all relevant patient populations), and to compare the performance of tests for which comparative information is limited (e.g., direct comparisons of CT vs. US; comparisons between CT with contrast administered via alternative routes).
- Such diagnostic cohort studies (and comparative studies in particular) are also needed to evaluate the test performance of combinations of tests and testing strategies by estimating conditional test performance and by developing and validating (internally and in independent datasets) multivariable diagnostic tools. For example, they could examine the use of US as a triage test for CT or MRI, or the use of multivariable diagnostic scores to select patients who can be monitored without immediate imaging or treatment (e.g., low risk patients who can be managed with wait-and-see strategies), those who need imaging, and those who need the initiation of treatment without imaging. They can also provide information to determine how patient- and test-related factors affect performance (i.e., to examine whether test performance depends on easily identifiable patient characteristics).
- Research on the natural history of acute appendicitis, specifically on whether (and how often) cases of appendicitis can resolve on their own and the rate of recurrence among such cases is needed. Studies of natural history (e.g., among patients deemed to be appropriate candidates for medical management or wait-and-see strategies) are necessary for evaluating the impact of tests in decision and simulation modeling studies (see below) and also to inform the design of studies of alternative test-and-treatment strategies (including studies of the sequencing of multiple tests and the timing of examinations). Of note, the test performance of diagnostic tests may vary during different time-points in the development of acute appendicitis (e.g., laboratory tests may be highly sensitive for cases associated with more severe inflammation).
- Paired test study designs, in which all index tests are applied to all enrolled patients (so that each patient has results from every test of interest), are generally more efficient than parallel arm designs and should be considered when planning future studies.¹⁹⁵
- Cohort studies assessing the performance of tests that have been evaluated extensively (e.g., CT and US) are most needed for specific patient populations (e.g., pregnant women, young children, and the elderly); for other tests (e.g., MRI) further research is needed in all patient populations. Comparative studies are needed for all tests and all populations. Ideally, future studies of test performance will be large (powered to achieve adequate precision), prospectively designed, multicenter investigations enrolling patients representative of those seen in clinical practice. Studies should prespecify the criteria for a positive test, use standardized diagnostic criteria for the diagnosis of appendicitis and use followup for an adequate period of time (1-2 weeks) for patients who do not undergo surgery, and have as complete a followup as possible. Studies that evaluate two or more index tests should provide a detailed description of the role of testing they are evaluating (triage, add-on, replacement) and report data in enough detail to allow statistical analyses appropriate for that evaluation.⁵⁷

- Multivariable diagnostic scores provide an appealing way to combine information from multiple clinical symptoms and signs, laboratory tests, and (possibly) US. Multivariable scores may be particularly useful in identifying the subgroup of patients who are at low risk for appendicitis and who may be candidates for wait-and-see strategies or less aggressive imaging strategies. Cohort studies for the development and validation of such scores should use state-of-the-science methods for model development and internal and external validation.
- Future research needs to be better reported and studies should adhere to established reporting guidelines (e.g., Standards for the Reporting of Diagnostic accuracy studies; www.stard-statement.org/).

Studies of Patient-Relevant Outcomes and Resource Utilization

- Cohort studies of diagnostic test strategies can also be used to study the impact of tests on patient-relevant and resource utilization outcomes. For tests with well-understood performance characteristics such studies may use randomized designs. For example randomized trials may be used to identify the preferred route of administration of contrast for CT scanning or to compare strategies of US triage followed by CT versus CT for all patients. In many cases, however, randomized comparisons of alternative test strategies are unlikely to be fruitful because existing studies indicate that many of the competing tests have sensitivities and specificities that are fairly similar and close to 1. Under these conditions RCTs comparing alternative test strategies would need to enroll very large numbers of participants to allow reliable comparisons. If randomized studies are deemed necessary, consideration should be given to paired randomized designs, because they are more efficient than parallel arm trials.
- Large-scale observational prospective studies could be used to evaluate the effectiveness of alternative test strategies with respect to short and long-term patient-relevant outcomes and to explore factors that may modify the effect of tests on these outcomes. Such studies would need to collect detailed information on baseline factors that may be associated with the choice of test strategy and the outcomes of interest (e.g., duration of pain, signs, symptoms and laboratory test results before imaging, patient characteristics, etc.), in order to attempt to address confounding bias. Comparisons across methods should be performed only among patients that would be candidates for assessment with all methods being compared.
- Decision and simulation modeling can be used to determine whether randomized or non-randomized cohort studies assessing patient-relevant outcomes and resource utilization are necessary and to guide their design. Models can also be used to synthesize evidence on test performance, impact of tests on clinical decisions, treatment effectiveness, resource utilization (and when relevant, economic costs), and patient preferences to guide clinical decisionmaking. We think that the results of the current review provide a solid basis for conducting such modeling studies.

Studies of Test-Related Adverse Events

- *Future studies should report complete information on test-related adverse events, using pre-specified criteria and careful ascertainment methods. Research is particularly needed*

among special populations (e.g., young children, pregnant women, the elderly) and tests that have been less commonly examined (e.g., MRI with gadolinium).

- *Mathematical modeling studies can be used to combine data on the effective radiation dose received during alternative CT-based approaches (e.g., abdominopelvic vs. focused CT; low-dose vs. standard-dose CT, etc.) with external information on long-term radiation effects. Such studies appear to represent the most feasible approach to investigate the impact of testing on long-term cancer risk.*¹⁹⁶

Conclusions

The literature on the test performance of clinical symptoms and signs, laboratory and imaging tests, and multivariable diagnostic scores for the diagnosis of acute appendicitis is large, but consists almost exclusively of studies at moderate risk of bias (primarily due to differential and incomplete verification). The few studies that assess multiple tests are typically not designed with the goal of providing comparative information. Thus, the available evidence supports fairly strong conclusions about the performance of individual tests, but is largely insufficient to support conclusions about comparative effectiveness, especially with respect to clinical outcomes. Clinical symptoms and signs and laboratory tests have relatively limited test performance when used in isolation. Their combination in multivariable scores is promising, but the best-studied scores had been developed before the widespread use of imaging modalities and more recently developed scores have not yet been studied adequately. All three major imaging modalities have adequate test performance. Evidence on CT is mature for most patient populations of interest. In contrast, MRI has been investigated by fewer studies, many of which focus on its use for pregnant women. US produces non-diagnostic scans more often than CT or MRI, and, when a diagnosis is possible, its performance appears to be somewhat worse than CT and MRI. Beyond test performance, information on patient-relevant outcomes and resource utilization is very limited. Information on test-related harms (e.g., adverse events due to radiation) is provided only by a minority of studies and is poorly reported. More research, much of which could be accomplished through non-randomized studies, is needed to establish the performance of understudied patient populations (very young children, women of reproductive age, the elderly) and modalities (e.g., MRI, multivariable scores), compare competing tests, identify factors that affect performance, and to evaluate the impact of testing strategies on patient-relevant outcomes, resource utilization, and harms. Perhaps most importantly, given the large volume of accumulated evidence on the test performance of various tests, decision and simulation modeling (e.g., decision analysis, simulation modeling of the impact of radiation on long term outcomes) should be used to guide decisionmaking and to inform the design of future studies.

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Abbreviations

AHRQ	Agency for Healthcare Research and Quality
CI	Confidence interval
CrI	Credible interval
CT	Computed tomography
EPC	Evidence-based Practice Center
FN	False negative
FP	False positive
MRI	Magnetic resonance imaging
NRCS	Nonrandomized comparative study
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
ROC	Received operating characteristic
SRDR	Systematic Review Data Repository
STARD	Standards for Reporting of Diagnostic Accuracy
TEP	Technical Expert Panel
TOO	Task Order Officer
TN	True negative
TP	True positive
US	Ultrasound

Appendix A. Search Strategies

A-1. PubMed/MEDLINE[®]

Date run 7/31/2013), citations retrieved 21,650.

1. ("0001/01/01"[PDAT] : "2013/07/31"[PDAT])
AND
2. (("Computerized tomography" OR "Computed tomography" OR "CT" or enhancement*)
OR (Ultrasonography OR Sonography OR US OR ultrasound OR ultra-sound) OR
("MR" OR magnetic resonance OR MRI OR "magnetic resonance imaging"[MeSH]) OR
(Radiography[MeSH] OR Tomography, x-ray computed[MeSH] OR Tomography
scanners, x-ray computed[MeSH] OR Tomography, spiral computed[MeSH]) OR
("radionuclide imaging"[Subheading] OR (radionuclide* AND imaging)) OR
laparoscop* OR "laparoscopy"[MeSH Terms] OR skin temperature OR fever OR
temperature OR ((McBurney OR obturator OR psoas OR rovsing*) AND (sign OR point)
) OR (rectal AND exam*) OR "acute-phase proteins"[MeSH Terms] OR ("c reactive
protein" OR crp) OR (urine test OR white blood cell count OR WBC OR leukocyte* OR
acute phase proteins) OR (DT OR decision* tools OR decision* support system OR
algorithm OR scoring system) OR ((Alvarado OR Mantrels) AND (test OR tests OR
score OR scores)) OR checklist* OR algorith* OR (slide rule*) OR calculator* OR
(score OR scores) OR (practice AND guideline*) OR (progno* AND (model OR
modeling OR models)) OR (decision support system*) OR computer* OR (decision
tree*) OR (decision analy*) OR (decision aid*) OR (decision tool*) OR (advisory AND
(system OR systems)) OR nomogram* OR expert system\$ OR neural network* OR
artificial intellig* OR machine learning OR Bayes* OR "decision support systems,
clinical"[MeSH] OR "decision support systems, management"[MeSH] OR "decision
support techniques"[MeSH] OR "artificial intelligence"[MeSH] OR "decision making,
computer assisted"[MeSH] OR "medical informatics"[MeSH] OR "information
systems"[MeSH] OR "decision making"[MeSH] OR "Reminder Systems"[MeSH] OR
"Hospital Information Systems"[MeSH] OR "Management Information Systems"[MeSH]
OR "Medical Records Systems, Computerized"[MeSH] OR "Computers"[MeSH] OR
(information system*) OR informatic* OR (predict*[tiab] OR predictive value of
tests[mh] OR (score[tiab] OR scores[tiab] OR scoring[tiab])) OR "clinical prediction"
OR "clinical model*" OR "clinical score*" OR "decision rule*" OR "diagnostic
accuracy" OR "diagnostic rule*" OR "diagnostic score*" OR "diagnostic value" OR
"predictive outcome*" OR "predictive rule*" OR "predictive score*" OR "predictive
value" OR "predictive risk*" OR "prediction outcome*" OR "prediction rule*" OR
"prediction score*" OR "prediction value*" OR "prediction risk*" OR "risk assessment"
OR "risk score*" OR (clinical[tiab] AND predict*[tiab]) OR (clinical[tiab] AND
model*[tiab]) OR (clinical[tiab] AND (score [tiab] OR scores[tiab] OR scoring[tiab]))
OR (decision [tiab] AND rule*[tiab]) OR (derive*[tiab] AND validat*[tiab]) OR (
(diagnosi*[tiab] OR diagnost*[tiab] OR diagnose*[tiab]) AND accura*[tiab]) OR

((diagnosi*[tiab] OR diagnost*[tiab] OR diagnose*[tiab]) AND rule*[tiab]) OR ((diagnosi*[tiab] OR diagnost*[tiab] OR diagnose*[tiab]) AND (score [tiab] OR scores[tiab] OR scoring[tiab])) OR ((diagnosi*[tiab] OR diagnost*[tiab] OR diagnose*[tiab]) AND value[tiab]) OR (predict*[tiab] AND outcome*[tiab]) OR (predict*[tiab] AND rule*[tiab]) OR (predict*[tiab] AND (score[tiab] OR scores[tiab] OR scoring[tiab])) OR (risk*[tiab] AND assessment*[tiab]) OR (risk[tiab] AND (score[tiab] OR scores[tiab] OR scoring[tiab])))

AND

3. ("abdomen, acute"[MeSH] OR "appendicitis"[MeSH] OR "appendectomy"[MeSH] OR "appendix"[MeSH] OR (acute AND (abdome* OR abdomi*) AND pain) OR appendic* OR appendec* OR appendicec* OR appendix OR ((non?specific) AND (abdome* OR abdomi*) AND pain) OR nsap OR RLQ pain OR (right AND lower AND (quarter OR quadrant) AND pain) OR (acute AND abdominal AND pain) OR AAP)

A-2. Embase[®]

Because the search strategy developed for MEDLINE, initially retrieved an overwhelming number of citations, it was decided in consultation with the TEP to limit that strategy to the years 2008-present and develop a less sensitive strategy for the older articles. The two strategies are listed below.

EMBASE search 1 (more sensitive and limited to 2008-present, run 8/23/13; citations retrieved: 7200):

1. #13: #11 NOT 'case report'/de AND [humans]/lim AND [embase]/lim AND [2008-2013]/py
2. #11: #8 AND #10
3. #10: sensitivity OR specificity OR (predictive AND value) OR 'diagnosis'/exp OR (roc AND curve) OR diagnostic OR (reference AND values) OR (false AND (negative OR positive)) OR (diagnostic AND errors) OR 'accuracy'/exp OR 'screening'/exp OR 'prediction'/exp OR identify OR identification OR tests OR outcome
4. #8: #1 AND #6 and #7
5. #7: #2 OR #5
6. #6: 'accuracy'/exp OR accurate OR 'diagnosis'/exp OR diagnostic OR diagnose
7. #5: 'checklist'/exp OR 'algorithm'/exp OR (slide AND rule) OR 'calculator'/exp OR score OR scores OR (practice AND guideline) OR ('prognosis'/exp AND 'model'/exp) OR (decision AND (support AND system OR 'tree'/exp OR 'analysis'/exp OR aid OR tool OR support AND 'technique'/exp OR making)) OR 'nomogram'/exp OR 'nomograms'/exp OR (expert OR experts OR advisory AND (system OR systems)) OR (neural AND (network OR networks)) OR (artificial AND 'intelligence'/exp) OR 'machine'/exp AND 'learning'/exp OR bayes OR bayesian OR (predictive AND (value OR outcome)) OR (decision AND support AND systems) OR (diagnostic AND ('accuracy'/exp OR rule OR score OR value)) OR (clinical AND prediction) OR ('risk'/exp AND (predicton OR assesment OR score))

8. #2: 'tomography'/exp OR 'ultrasonography'/exp OR
(magnetic AND resonance AND 'imaging'/exp) OR 'laparoscopy'/exp
OR laparoscopic OR 'ultrasound'/exp OR 'ultra sound'/exp OR 'sonography'/exp
OR 'mri'/exp OR 'x ray'/exp OR ('radionuclide'/exp AND 'imaging'/exp)
OR 'radiography'/exp OR ('skin'/exp AND 'temperature'/exp) OR 'fever'/exp
OR mcburney OR 'obturator'/exp OR psoas OR rovsing OR ('rectal'/exp AND
(exam OR exams)) OR ('acute phase' AND 'proteins'/exp) OR
(c AND reactive AND 'protein'/exp) OR 'crp'/exp OR 'leukocytes'/exp OR
(acute AND phase AND 'proteins'/exp) OR ('urine'/exp AND test) OR
(white AND 'blood'/exp AND 'cell'/exp AND count) OR 'wbc'/exp OR 'leukocyte'/exp
OR alvarado OR mantrels
9. #1: 'appendicitis'/exp OR 'appendix'/exp OR ('abdomen'/exp AND acute)
OR 'appendectomy'/exp OR (acute AND (abdominal OR abdominal) AND 'pain'/exp)
OR (nonspecific OR 'non specific' OR non AND specific AND
(abdominal OR abdominal) AND 'pain'/exp) OR (rlq OR
(right AND lower AND quadrant) AND 'pain'/exp) OR aap OR nsap AND [humans]/lim
AND [embase]/lim

EMBASE search 2 (less sensitive no date limit, run 9/4/13; citations retrieved: 1213):

1. #4 #1 AND #3
2. #3 abdomen, AND acute OR 'appendicitis'/exp OR 'appendectomy'/exp OR (acute AND
(abdome* OR abdomi*) AND 'pain'/exp)
OR appendic* OR appendec* OR appendicec* OR 'appendix'/exp OR (non?specific AND
(abdome* OR abdomi*) AND 'pain'/exp) OR nsap OR rlq AND 'pain'/exp OR
(right AND lower AND (quarter OR quadrant) AND 'pain'/exp) OR
(acute AND abdominal AND 'pain'/exp) OR aap AND [humans]/lim AND [embase]/lim
3. #1 'computerized tomography'/exp OR 'computed tomography'/exp
OR 'ct' OR enhancement* OR 'ultrasonography'/exp OR 'sonography'/exp
OR us OR 'ultrasound'/exp OR 'ultra sound'/exp OR ('mr'/exp
OR magnetic AND resonance) OR 'mri'/exp OR 'magnetic resonance imaging'/exp OR
('radiography'/exp OR tomography, AND 'x ray'/exp
AND computed OR 'tomography'/exp AND scanners, AND 'x ray'/exp
AND computed OR tomography, AND spiral AND computed) OR 'radionuclide
imaging'/exp OR (radionuclide* AND 'imaging'/exp)
OR laparoscop* OR 'laparoscopy'/exp OR 'skin'/exp AND 'temperature'/exp
OR 'fever'/exp OR 'temperature'/exp OR (mcburney OR 'obturator'/exp
OR psoas OR rovsing* AND (sign OR point)) OR ('rectal'/exp AND exam*) OR 'acute
phase' AND 'proteins'/exp OR 'c reactive protein'/exp OR 'crp'/exp OR ('urine'/exp
AND test OR white AND 'blood'/exp AND 'cell'/exp AND count OR 'wbc'/exp
OR leukocyte* OR acute AND phase AND 'proteins'/exp) OR
(dt OR decision* AND tools OR decision* AND support AND system OR 'algorithm'/exp
OR scoring AND system) OR (alvarado OR mantrels AND
(test OR tests OR score OR scores)) AND [humans]/lim AND [embase]/lim

A-3. Cochrane Central Register of Controlled Trials

(run 8/23/13; citations retrieved 1127)

1. (abdomen, acute OR appendicitis OR appendectomy OR appendix OR (acute AND (abdome* OR abdomi*) AND pain) OR appendic* OR appendec* OR appendicec* OR appendix OR ((non?specific) AND (abdome* OR abdomi*) AND pain) OR nsap OR RLQ pain OR (right AND lower AND (quarter OR quadrant) AND pain) OR (acute AND abdominal AND pain) OR AAP)
AND
2. (("Computerized tomography" OR "Computed tomography" OR CT or enhancement*) OR (Ultrasonography OR Sonography OR US OR ultrasound OR ultra-sound) OR ("MR" OR magnetic resonance OR MRI OR magnetic resonance imaging) OR (Radiography OR Tomography, x-ray computed OR Tomography scanners, x-ray computed OR Tomography, spiral computed) OR (radionuclide imaging OR (radionuclide* AND imaging)) OR laparoscop* OR laparoscopy OR skin temperature OR fever OR temperature OR ((McBurney OR obturator OR psoas OR rovsing*) AND (sign OR point)) OR (rectal AND exam*) OR acute-phase proteins OR ("c reactive protein" OR crp) OR (urine test OR white blood cell count OR WBC OR leukocyte* OR acute phase proteins) OR (DT OR decision* tools OR decision* support system OR algorithm OR scoring system) OR ((Alvarado OR Mantrels) AND (test OR tests OR score OR scores)) OR checklist* OR algorith* OR (slide rule*) OR calculator* OR (score OR scores) OR (practice AND guideline*) OR (progno* AND (model OR modeling OR models)) OR (decision support system*) OR computer* OR (decision tree*) OR (decision analy*) OR (decision aid*) OR (decision tool*) OR (advisory AND (system OR systems)) OR nomogram* OR expert system\$ OR neural network* OR artificial intellig* OR machine learning OR Bayes* OR "decision support systems, clinical" OR "decision support systems, management" OR "decision support techniques" OR "artificial intelligence" OR "decision making, computer assisted" OR "medical informatics" OR "information systems" OR "decision making" OR "Reminder Systems" OR "Hospital Information Systems" OR "Management Information Systems" OR "Medical Records Systems, Computerized" OR "Computers" OR (information system*) OR informatic* OR (predict* OR predictive value of tests OR (score OR scores OR scoring)) OR "clinical prediction" OR "clinical model*" OR "clinical score*" OR "decision rule*" OR "diagnostic accuracy" OR "diagnostic rule*" OR "diagnostic score*" OR "diagnostic value" OR "predictive outcome*" OR "predictive rule*" OR "predictive score*" OR "predictive value" OR "predictive risk*" OR "prediction outcome*" OR "prediction rule*" OR "prediction score*" OR "prediction value*" OR "prediction risk*" OR "risk assessment" OR "risk score*" OR (clinical AND predict*) OR (clinical AND model*) OR (clinical AND (score OR scores OR scoring)) OR (decision AND rule*) OR (derive* AND validat*) OR ((diagnosi* OR diagnost* OR diagnose*) AND accura*) OR ((diagnosi* OR diagnost* OR diagnose*) AND rule*) OR ((diagnosi* OR diagnost* OR diagnose*) AND (score OR scores OR scoring)) OR ((diagnosi* OR diagnost* OR diagnose*) AND value) OR (predict* AND outcome*) OR (predict* AND rule*) OR (predict* AND (score OR scores OR scoring))OR (risk* AND assessment*) OR (risk AND (score OR scores OR scoring)))

A-4. Cumulative Index to Nursing and Allied Health Literature (CINAHL®)

(run 8/23/13; citations retrieved: 93)

1. S105: S102 AND S103
2. S104: S102 AND S103
3. S103: ((MH "Tomography, Spiral Computed") OR (MH "Tomography, Emission-Computed") OR (MH "Tomography, X-Ray Computed") OR (MH "Multidetector Computed Tomography") or (MH "Radiography") OR (MH "Ultrasonography") OR (MH "Magnetic Resonance Imaging") OR (MH "Laparoscopy") OR (MH "Surgery, Laparoscopic") OR (MH "Fever") OR Computerized tomography OR Computed tomography OR CT OR ultrasonography or ultrasound or ultra-sound or sonography OR mri or magnetic resonance OR x-ray computed OR (MH "Tomography, X-Ray Computed") OR (MH "Tomography, X-Ray") OR (MH "X-Ray Film") OR radionuclide imaging or radiography or tomography scanners or tomography spiral computed OR laparoscopic or laparoscopy OR laparoscopic or laparoscopy OR skin temperature or fever or temperature OR McBurney OR obturator or psoas OR rovsing OR rectal and (exam or exams) OR acute-phase proteins OR (MH "Acute-Phase Proteins") OR c reactive protein or crp OR urine test OR white blood cell count OR WBC OR leukocyte or leukocytes OR acute phase proteins OR Alvarado OR Mantrels or computer OR checklist or algorithm or slide rule or calculator or score or scores or practice guideline or prognosis model OR decision and (support system or tree or analysis or aid or tool or support technique or making) OR nomogram or nomograms OR expert system or expert systems or advisory system or advisory systems OR neural network OR neural networks OR artificial intelligence OR machine learning OR Bayes OR Bayesian OR medical informatics or information systems or reminder systems or hospital information systems or management information systems or medical records or information system OR (MH "Predictive Value of Tests") OR (MH "Predictive Validity") OR (MH "Decision Support Systems, Clinical") OR (MH "Clinical Assessment Tools") OR predictive outcome or predictive value or clinical prediction or clinical model or clinical score or decision rule or diagnostic accuracy or diagnosis or diagnostic rule or diagnostic score or diagnostic value OR predictive risk or prediction value or prediction risk OR risk assessment OR risk score OR accuracy or accurate or diagnosis or diagnostic or diagnose)
4. S102: (MH "Appendicitis") OR (MH "Appendix")OR (MH "Appendectomy")OR (MH "Abdomen, Acute") OR acute abdomenOR appendicitisOR appendectomyOR appendix or (MH "appendix") OR acute abdominal pain or acute abdominal pain OR (nonspecific or non-specific or non specific) and (abdominal or abdominal) and pain OR RLQ pain OR right lower quadrant pain OR right lower quarter pain OR AAP or nsap
5. S52: S50 AND S51
6. S51: ((MH "Tomography, Spiral Computed") OR (MH "Tomography, Emission-Computed") OR (MH "Tomography, X-Ray Computed") OR (MH "Multidetector Computed Tomography") or (MH "Radiography")OR (MH "Ultrasonography") OR (MH "Magnetic Resonance Imaging") OR (MH "Laparoscopy") OR (MH "Surgery, Laparoscopic") OR (MH "Fever") OR Computerized tomography OR Computed tomography OR CT OR ultrasonography or ultrasound or ultra-sound or sonography OR mri or magnetic resonance OR x-ray computed OR (MH "Tomography, X-Ray

Computed") OR (MH "Tomography, X-Ray") OR (MH "X-Ray Film") OR radionuclide imaging or radiography or tomography scanners or tomography spiral computed OR laparoscopic or laparoscopy OR laparoscopic or laparoscopy OR skin temperature or fever or temperature OR McBurney OR obturator or psoas OR rovsing OR rectal and (exam or exams) OR acute-phase proteins OR (MH "Acute-Phase Proteins") OR c reactive protein or crp OR urine test OR white blood cell count OR WBC OR leukocyte or leukocytes OR acute phase proteins OR Alvarado OR Mantrels or computerOR checklist or algorithm or slide rule or calculator or score or scores or practice guideline or prognosis model OR decision and (support system or tree or analysis or aid or tool or support technique or making) OR nomogram or nomograms OR expert system or expert systems or advisory system or advisory systems OR neural network OR neural networks OR artificial intelligence OR machine learning OR Bayes OR Bayesian OR medical informatics or information systems or reminder systems or hospital information systems or management information systems or medical records or information system OR (MH "Predictive Value of Tests") OR (MH "Predictive Validity") OR (MH "Decision Support Systems, Clinical") OR (MH "Clinical Assessment Tools") OR predictive outcome or predictive value or clinical prediction or clinical model or clinical score or decision rule or diagnostic accuracy or diagnosis or diagnostic rule or diagnostic score or diagnostic value OR predictive risk or prediction value or prediction risk OR risk assessment OR risk score OR accuracy or accurate or diagnosis or diagnostic or diagnose)

7. S50: (MH "Appendicitis") OR (MH "Appendix") OR (MH "Appendectomy") OR (MH "Abdomen, Acute") OR acute abdomen OR appendicitis OR appendectomy OR appendix or (MH "appendix") OR acute abdominal pain or acute abdominal pain OR (nonspecific or non-specific or non specific) and (abdominal or abdominal) and pain OR RLQ pain OR right lower quadrant pain OR right lower quarter pain OR AAP or nsap

Appendix B. List of Included and Excluded Studies

B-1. Included Studies

1. Abbas MH and Choudhry MN and Hamza N and Ali B and Amin AA and Ammori BJ. Admission Levels of Serum Amyloid A and Procalcitonin are More Predictive of the Diagnosis of Acute Appendicitis Compared With C-reactive Protein. PMID: 24910938.
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B-2. Rejection Reason: Abstract Only

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B-3. Rejection Reason: Appendicitis Specific Test Results Not Reported

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B-4. Rejection Reason: Case Report or Case Series

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B-5. Rejection Reason: Case-Control Study Design

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B-10. Rejection Reason: Less Than Sample Size CutOff

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Appendix C. Studies Assessing the Test Performance of Clinical Signs and Symptoms, Laboratory and Imaging Tests, and Multivariable Diagnostic Scores

Table C1. Test performance of clinical signs and symptoms

Author	Year	PMID	Country	Population	Test	TP	FN	FP	TN
Abo	2011	21811194	USA	children	CT	9	1	0	14
Abo	2011	21811194	USA	children	US	2	9	1	14
Abo	2011	21811194	USA	children	US	23	39	2	83
Abo	2011	21811194	USA	children	CT	52	2	2	72
Abo	2011	21811194	USA	children	US	17	20	1	51
Abo	2011	21811194	USA	children	US	5	8	2	17
Abo	2011	21811194	USA	children	CT	13	0	1	16
Abo	2011	21811194	USA	children	CT	30	1	1	42
Abu-Yousef	1987	3296711	USA	mixed	PAIN RLO	18	7	12	31
Abu-Yousef	1987	3296711	USA	mixed	US	20	5	9	34
Abu-Yousef	1987	3296711	USA	mixed	FEVER	14	11	17	26
Abu-Yousef	1987	3296711	USA	mixed	NAUSEA + VOMITING	10	15	27	16
Abu-Yousef	1987	3296711	USA	mixed	SYMPTOMS DURATION	13	12	20	23
Abu-Yousef	1987	3296711	USA	mixed	WBC	22	3	19	24
Acar	2012	21641156	Turkey	adults	SERUM CHITOTRIOSIDASE	13	11	1	9
Acar	2012	21641156	Turkey	adults	SERUM CHITOTRIOSIDASE	16	8	4	6
Acar	2012	21641156	Turkey	adults	SERUM CHITOTRIOSIDASE	12	12	1	9
Acosta	2005	15633057	USA	children	CT	9	0	1	43
Adams	1988	3277469	USA	mixed	US	16	2	3	18
Adams	1988	3277469	USA	mixed	US	11	1	2	11
Adesunkanmi AR.	1993	8199059	Ibadan	mixed	TENDERNESS REBOUND	37	0	7	10
Adesunkanmi AR.	1993	8199059	Ibadan	mixed	GUARDING	37	0	5	12
Adesunkanmi AR.	1993	8199059	Ibadan	mixed	FEVER	37	0	5	12
Adesunkanmi AR.	1993	8199059	Ibadan	mixed	LOSS OF APPETITE	37	0	4	13
Adesunkanmi AR.	1993	8199059	Ibadan	mixed	TENDERNESS ABDOMINAL	37	0	17	0
Adesunkanmi AR.	1993	8199059	Ibadan	mixed	PAIN ABDOMINAL	37	0	17	0
Agrawal	2008	18700623	Nepal	mixed	WBC	81	22	19	23
Agrawal	2008	18700623	Nepal	mixed	WBC + CRP	42	61	4	38
Agrawal	2008	18700623	Nepal	mixed	CRP	77	26	14	28
Ahmed	2006	17044228	UK	women of reproductive age	PERIUMBILICAL PIERCING	10	25	22	50
Ahn	2002	12355000	USA	adults	ABD XRAY	0	14	0	857

Ahn	2002	12355000	USA	adults	CT	1	1	0	185
Akhtar	2011	22204183	Pakistan	children	CT	21	2	15	33
Al Hilli	2009	19350346	Ireland	adults	PAIN RIF	67	109	4	16
Al Hilli	2009	19350346	Ireland	adults	PAIN RIF LOCALIZED	63	113	13	7
Al-Ajerami	2012	22360013	Palestine	mixed	US	2	2	4	0
Al-Ajerami	2012	22360013	Palestine	mixed	US	14	4	0	10
Al-Ajerami	2012	22360013	Palestine	mixed	US	22	16	4	10
Al-Ajerami	2012	22360013	Palestine	mixed	US	2	2	2	22
Al-Ajerami	2012	22360013	Palestine	mixed	US	6	10	0	0
Al-Ajerami	2012	22360013	Palestine	mixed	US	8	2	1	5
Al-Ajerami	2012	22360013	Palestine	mixed	US	90	4	4	30
Al-Ajerami	2012	22360013	Palestine	mixed	US	112	20	8	40
Al-Ajerami	2012	22360013	Palestine	mixed	US	80	0	1	3
Al-Gaithy	2012	23031349	Saudi Arabia	adults	NEUTROPHIL COUNT	303	124	10	19
Al-Gaithy	2012	23031349	Saudi Arabia	adults	WBC	328	99	10	19
Al-Mulhim	1996	9028994	Saudi Arabia	pregnant women	NAUSEA	14	15	10	13
Al-Mulhim	1996	9028994	Saudi Arabia	pregnant women	ANOREXIA	7	22	4	19
Al-Mulhim	1996	9028994	Saudi Arabia	pregnant women	TENDERNESS RLO	24	5	17	6
Al-Mulhim	1996	9028994	Saudi Arabia	pregnant women	GUARDING	4	25	10	13
Al-Mulhim	1996	9028994	Saudi Arabia	pregnant women	PAIN RLO	26	3	22	1
Al-Mulhim	1996	9028994	Saudi Arabia	pregnant women	TENDERNESS RLO	26	3	19	4
Al-Mulhim	1996	9028994	Saudi Arabia	pregnant women	PULSE	10	19	8	15
Al-Mulhim	1996	9028994	Saudi Arabia	pregnant women	FEVER	11	18	8	15
Al-Mulhim	1996	9028994	Saudi Arabia	pregnant women	VOMITING	10	19	9	14
Al-Mulhim	1996	9028994	Saudi Arabia	pregnant women	PAIN RLO	22	7	16	7
Al-Mulhim	1996	9028994	Saudi Arabia	pregnant women	ABNORMAL URINATION	2	27	5	18
Al-Mulhim	1996	9028994	Saudi Arabia	pregnant women	PAIN RUQ	1	28	1	22
Al-Mulhim	1996	9028994	Saudi Arabia	pregnant women	DIARRHEA	2	27	1	22
Al-Mulhim	1996	9028994	Saudi Arabia	pregnant women	DISTENTION	3	26	2	21
Al-Mulhim	1996	9028994	Saudi Arabia	pregnant women	FEVER	14	15	9	14
Al-Mulhim	1996	9028994	Saudi Arabia	pregnant women	TENDERNESS RECTAL	6	23	4	19
Al-Mulhim	1996	9028994	Saudi Arabia	pregnant women	TENDERNESS PELVIC	9	20	5	18
Al-Mulhim	1996	9028994	Saudi Arabia	pregnant women	TENDERNESS REBOUND	22	7	16	7
Al-Mulhim	1996	9028994	Saudi Arabia	pregnant women	CHILLS	10	19	7	16
Al-Mulhim	1996	9028994	Saudi Arabia	pregnant women	ROVSING SIGN	9	20	6	17
Al-Mulhim	1996	9028994	Saudi Arabia	pregnant women	CONTRACTIONS UTARINE	3	26	3	20
Al-Saigh	1992	1383518	Saudi Arabia	mixed	CRP	60	91	9	29
Albano	2001	11724048	USA	mixed	CT	32	0	1	65
Albano	2001	11724048	USA	mixed	CT	32	0	1	65
Albu	1994	8287747	USA	mixed	CRP	26	0	4	26
Alleman	1999	10574106	Switzerland	adults	US	89	6	2	399

Allister	2009	20097375	USA	children	GCSF SERUM LEVELS	21	2	4	5
Alobaidi	2003	12490503	USA	mixed	CT	120	19	3	12
Alshehri	1995	7588144	Saudi Arabia	mixed	RIGIDITY	3	54	2	64
Alshehri	1995	7588144	Saudi Arabia	mixed	TENDERNESS REBOUND	23	2	22	11
Alshehri	1995	7588144	Saudi Arabia	mixed	TENDERNESS REBOUND	31	1	31	2
Alshehri	1995	7588144	Saudi Arabia	mixed	GUARDING	30	27	29	37
Alshehri	1995	7588144	Saudi Arabia	children	TENDERNESS REBOUND	12	1	18	4
Alshehri	1995	7588144	Saudi Arabia	mixed	ROVSING SIGN	28	29	22	44
Alshehri	1995	7588144	Saudi Arabia	mixed	TENDERNESS REBOUND	54	3	53	13
Althoubaity	2006	17106538	Saudi Arabia	mixed	US	17	9	7	5
Althoubaity	2006	17106538	Saudi Arabia	mixed	CT	3	0	2	1
Alvarado	1986	3963537	USA	mixed	TENDERNESS	227	0	69	9
Alvarado	1986	3963537	USA	mixed	PAIN REBOUND	125	102	17	61
Alvarado	1986	3963537	USA	mixed	WBC	211	16	48	30
Alvarado	1986	3963537	USA	mixed	TENDERNESS RECTAL	120	107	46	32
Alvarado	1986	3963537	USA	mixed	FEVER	166	61	39	39
Alvarado	1986	3963537	USA	mixed	NEUTROPHIL%	161	66	25	53
Alvarado	1986	3963537	USA	mixed	PAIN MIGRATION	157	70	12	66
Alvarado	1986	3963537	USA	mixed	ANOREXIA OR ACETONE	138	89	22	56
Alvarado	1986	3963537	USA	mixed	NAUSEA OR VOMITING	168	59	50	28
Amalesh	2004	17462226	India	mixed	CRP	144	15	19	14
Amland	1989	2662692	Norway	mixed	WBC	19	9	25	57
Amland	1989	2662692	Norway	mixed	FEVER	21	7	29	53
Amland	1989	2662692	Norway	mixed	ESR	9	19	29	53
Amland	1989	2662692	Norway	mixed	US	24	4	9	73
Amland	1989	2662692	Norway	mixed	CRP	20	8	30	53
Andersen	1980	7376784	Sweden	mixed	VOMITING	165	140	30	84
Andersen	1999	10535336	Sweden	pregnant women	PAIN RUQ	7	35	7	7
Andersen	1999	10535336	Sweden	pregnant women	PAIN RLQ	31	11	10	4
Andersen	1999	10535336	Sweden	pregnant women	WBC	12	20	1	8
Andersen	1999	10535336	Sweden	pregnant women	FEVER	14	25	4	8
Andersen	1980	7376784	Sweden	mixed	PAIN DURATION	151	50	35	42
Andersen	1999	10535336	Sweden	pregnant women	CRP	21	10	4	4
Andersen	1999	10535336	Sweden	pregnant women	CONTRACTIONS UTARINE	6	12	0	10
Andersen	1980	7376784	Sweden	mixed	PAIN DURATION	76	125	19	58
Andersen	1980	7376784	Sweden	mixed	TENDERNESS REBOUND	130	175	23	91
Andersen	1999	10535336	Sweden	pregnant women	NAUSEA	33	9	11	3
Andersen	1999	10535336	Sweden	pregnant women	VOMITING	19	23	4	10
Andersen	1999	10535336	Sweden	pregnant women	PAIN MIGRATION	24	18	2	12
Anderson	2009	19843742	USA	adults	CT	12	1	3	136
Anderson	2009	19843742	USA	adults	CT	14	0	4	133

Andersson	2000	11071167	Sweden	mixed	VOMITING	82	112	71	231
Andersson	2000	11071167	Sweden	mixed	TENDERNESS RECTAL	44	150	94	208
Andersson	1999	9880421	Sweden	mixed	WBC	237	22	144	153
Andersson	1999	9880421	Sweden	mixed	PAIN MIGRATION	128	109	102	175
Andersson	1999	9880421	Sweden	mixed	CRP	106	150	52	242
Andersson	2000	11071167	Sweden	mixed	PAIN MIGRATION	95	99	102	200
Andersson	2000	11071167	Sweden	mixed	WBC	96	98	30	272
Andersson	1999	9880421	Sweden	mixed	WBC	161	98	46	251
Andersson	1999	9880421	Sweden	mixed	TENDERNESS	196	65	76	225
Andersson	1999	9880421	Sweden	mixed	FEVER	196	65	104	196
Andersson	1999	9880421	Sweden	mixed	PMNC RATE	125	101	236	31
Andersson	1999	9880421	Sweden	mixed	PAIN DURATION	118	142	130	171
Andersson	2000	11071167	Sweden	mixed	PAIN	84	110	86	216
Andersson	1999	9880421	Sweden	mixed	PMNC COUNT	117	109	22	244
Andersson	1999	9880421	Sweden	mixed	TENDERNESS	255	5	240	61
Andersson	1999	9880421	Sweden	mixed	CRP	173	83	90	204
Andersson	2000	11071167	Sweden	mixed	GUARDING	88	106	25	277
Andersson	1999	9880421	Sweden	mixed	CRP	214	42	119	175
Andersson	1999	9880421	Sweden	mixed	PMNC RATE	213	13	135	132
Andersson	2000	11071167	Sweden	mixed	PMNC RATE	139	55	96	206
Andersson	2000	11071167	Sweden	mixed	TENDERNESS REBOUND	117	77	45	257
Andersson	1999	9880421	Sweden	mixed	FEVER	190	63	162	121
Andersson	1999	9880421	Sweden	mixed	GUARDING	205	55	75	226
Andersson	1999	9880421	Sweden	mixed	PMNC COUNT	77	149	10	256
Andersson	1999	9880421	Sweden	mixed	TENDERNESS PERITONEAL	192	51	63	206
Andersson	2000	11071167	Sweden	mixed	FEVER	137	57	104	198
Andersson	1999	9880421	Sweden	mixed	PAIN DURATION	210	50	218	83
Andersson	1999	9880421	Sweden	mixed	PMNC COUNT	155	71	49	217
Andersson	1999	9880421	Sweden	mixed	WBC	205	54	95	202
Andersson	1999	9880421	Sweden	mixed	TENDERNESS REBOUND	220	41	105	206
Andersson	1999	9880421	Sweden	mixed	PMNC RATE	164	62	68	199
Andersson	1999	9880421	Sweden	mixed	PAIN MIGRATION	209	38	213	75
Andersson	1999	9880421	Sweden	mixed	VOMITING	123	128	71	222
Andersson	1999	9880421	Sweden	mixed	PAIN DURATION	232	28	256	45
Andersson	2000	11071167	Sweden	mixed	CRP	150	44	119	183
Andersson	1999	9880421	Sweden	mixed	PAIN DURATION	8	252	14	287
Andersson	2000	11071167	Sweden	mixed	PAIN PROGRESSION	85	109	110	192
Andersson	2000	11071167	Sweden	mixed	TENDERNESS	168	26	104	198
Andersson	1999	9880421	Sweden	mixed	PMNC COUNT	188	38	83	183
Andersson	1999	9880421	Sweden	mixed	WBC	90	169	14	283
Andersson	1999	9880421	Sweden	mixed	PAIN DURATION	50	210	48	253

Ang	2001	11673709	Canada	children	US	145	34	13	125
Anielski	2010	19924436	Poland	mixed	IL-6	41	48	0	43
Anielski	2010	19924436	Poland	mixed	IL-6	64	25	16	27
Anielski	2010	19924436	Poland	mixed	PROCALCITONIN	69	20	14	29
Anielski	2010	19924436	Poland	mixed	WBC	30	59	0	43
Anielski	2010	19924436	Poland	mixed	PROCALCITONIN	51	38	16	27
Anielski	2010	19924436	Poland	mixed	WBC	77	12	30	13
Anielski	2010	19924436	Poland	mixed	LYMPHOCYTE COUNT:NEUTROPHIL COUNT	56	33	0	43
Anielski	2010	19924436	Poland	mixed	LYMPHOCYTE COUNT:NEUTROPHIL COUNT	68	21	24	19
Anielski	2010	19924436	Poland	mixed	CRP	65	24	13	30
Anielski	2010	19924436	Poland	mixed	CRP	59	30	15	28
Antevil	2004	15529835	USA	adults	CT	123	15	14	469
Antevil	2006	17116553	USA	mixed	CT	92	3	5	429
Antevil	2006	17116553	USA	mixed	CT	96	7	6	196
Applegate	2001	11425980	USA	children	US	75	26	10	10
Applegate	2001	11425980	USA	children	CT	87	2	4	3
Arnbjornsson	1985	3909908	Sweden	adults	TENDERNESS RECTAL	198	43	22	76
Arnbjornsson	1985	3909908	Sweden	adults	VOMITING	99	142	17	81
Arnbjornsson	1985	3909908	Sweden	adults	NAUSEA OR ANOREXIA	224	17	63	35
Arnbjornsson	1985	3909908	Sweden	adults	WBC	108	133	63	35
Arnbjornsson	1985	3909908	Sweden	adults	FEVER	94	147	71	27
Arnbjornsson	1985	3909908	Sweden	adults	PAIN PERIUMBILICAL	142	99	37	61
Arnbjornsson	1985	3909908	Sweden	adults	RIGIDITY + GUARDING	80	161	6	92
Arnbjornsson	1985	3909908	Sweden	adults	PAIN MIGRATION	77	164	6	92
Arnbjornsson	1985	3909908	Sweden	adults	MASS ABDOMINAL	60	181	4	94
Arnbjornsson	1985	3909908	Sweden	adults	TENDERNESS REBOUND	89	152	10	89
Arnbjornsson	1985	3909908	Sweden	adults	PREVIOUS SIMILAR SYMPTOMS	19	221	19	79
Arnbjornsson	1985	3909908	Sweden	adults	TENDERNESS RECTAL	67	174	6	92
Arnbjornsson	1985	3909908	Sweden	adults	TENDERNESS RLO	207	34	17	81
Arnbjornsson	1985	3909908	Sweden	adults	PAIN RIF	77	164	11	87
Arnbjornsson	1985	3909908	Sweden	adults	CONSTIPATION	43	198	11	87
Arnbjornsson	1985	3909908	Sweden	adults	ABNORMAL URINATION	7	234	8	90
Arnbjornsson	1985	3909908	Sweden	adults	SYMPTOMS DURATION	207	34	47	51
Arnbjornsson	1985	3909908	Sweden	adults	FEVER	231	10	87	11
Arnbjornsson	1985	3909908	Sweden	adults	DIARRHEA	17	224	24	74
Artiko	2009	19760940	Serbia	mixed	TC99M NUCLEAR	4	0	0	30
Asadi	2011	21553201	Iran	mixed	TC99M NUCLEAR	13	8	6	13
Asadi	2011	21553201	Iran	mixed	TC99M NUCLEAR	4	17	0	19
Asfar	2000	10815376	Kuwait	mixed	CRP	59	4	2	13

Ashdown	2012	23247977	UK	adults	TENDERNESS REBOUND	24	10	15	15
Ashdown	2012	23247977	UK	adults	PAIN MIGRATION	22	12	20	10
Ashdown	2012	23247977	UK	adults	NAUSEA OR VOMITING	27	7	25	5
Ashdown	2012	23247977	UK	adults	PAIN SPEED BUMPS	33	1	21	9
Ashindoitiang	2008	19062484	Lagos	adults	ABD XRAY	3	5	0	92
Ashraf	2006	16767943	Pakistan	mixed	CT	21	2	0	35
Assefa	2006	17447365	Ethiopia	mixed	US	51	7	12	77
Avcu	2013	23266968	Turkey	mixed	MRI	39	1	0	40
Bachur	2012	22841176	USA	children	US	288	12	10	522
Bachur	2012	22841176	USA	children	US	267	33	26	506
Bachur	2012	22841176	USA	children	US	273	24	80	455
Bachur	2012	22841176	USA	children	CT	432	18	31	735
Bachur	2012	22841176	USA	children	US	237	63	15	517
Bachur	2012	22841176	USA	children	CT	445	9	76	686
Bachur	2012	22841176	USA	children	CT	436	18	30	732
Bachur	2012	22841176	USA	children	US	241	56	107	428
Bachur	2012	22841176	USA	children	US	216	47	15	453
Bachur	2012	22841176	USA	children	CT	432	18	23	738
Bachur	2012	22841176	USA	children	CT	441	9	23	743
Bachur	2012	22841176	USA	children	US	237	63	21	511
Bachur	2012	22841176	USA	children	CT	445	9	61	701
Bachur	2012	22841176	USA	children	CT	436	18	76	686
Bachur	2012	22841176	USA	children	CT	427	27	69	693
Bachur	2012	22841176	USA	children	CT	423	27	23	743
Bachur	2012	22841176	USA	children	US	241	56	102	433
Bachur	2012	22841176	USA	children	US	258	39	75	460
Bachur	2012	22841176	USA	children	US	285	12	86	449
Bachur	2012	22841176	USA	children	US	255	45	5	527
Bachur	2012	22841176	USA	children	CT	441	9	31	735
Bachur	2012	22841176	USA	children	CT	432	18	23	743
Baldisserotto	2000	11044049	Brazil	children	US	196	3	4	222
Baldisserotto	2007	17331831	Brazil	children	US	24	1	0	25
Balthazar	1994	8259423	USA	mixed	US	41	13	4	42
Balthazar	1994	8259423	USA	mixed	CT	52	2	5	41
Balthazar	1991	2052696	USA	mixed	CT	60	1	4	30
Balthazar	1994	8259423	USA	mixed	US	19	1	2	27
Balthazar	1998	9625125	USA	mixed	CT	111	4	1	30
Balthazar	1994	8259423	USA	mixed	US	12	8	1	28
Barbee	1975	1138636	USA	mixed	PERITONEAL LAVAGE	6	2	2	23
Barloon	1995	7787719	USA	pregnant women	US	2	1	1	18
Barron	1999	10076613	USA	mixed	TC99M NUCLEAR	29	3	11	92

Bealer	2010	20370768	USA	mixed	WBC	25	15	45	93
Bealer	2010	20370768	USA	mixed	S100A8 OR S100A9	38	3	65	75
Becker	2007	17192449	USA	children	TENDERNESS PERCUSSION	187	83	189	296
Becker	2007	17192449	USA	children	NEUTROPHIL COUNT	214	56	199	286
Becker	2007	17192449	USA	children	ROVSING SIGN	86	184	77	408
Becker	2007	17192449	USA	children	FEVER	47	223	96	389
Becker	2007	17192449	USA	children	PAIN MIGRATION	136	134	133	352
Becker	2007	17192449	USA	children	PAIN REBOUND	131	139	120	365
Becker	2007	17192449	USA	children	DIARRHEA	224	46	380	105
Becker	2007	17192449	USA	children	WBC	244	26	232	253
Becker	2007	17192449	USA	children	BOWEL SOUNDS	98	172	69	416
Becker	2007	17192449	USA	children	GUARDING	172	98	205	280
Becker	2007	17192449	USA	children	TENDERNESS RLO	183	87	259	226
Becker	2007	17192449	USA	children	NAUSEA OR VOMITING	192	78	270	215
Becker	2007	17192449	USA	children	PAIN DURATION	222	48	359	126
Becker	2007	17192449	USA	children	ANOREXIA	161	109	230	255
Becker	2007	17192449	USA	children	PAIN GRADUAL	149	121	269	216
Beltran	2007	17618882	Chile	children	WBC + CRP	51	120	3	24
Beltran	2007	17618882	Chile	children	WBC	68	103	3	24
Beltran	2007	17618882	Chile	children	WBC + CRP	86	85	3	24
Beltran	2007	17618882	Chile	children	CRP	34	137	3	24
Beltran	2007	17618882	Chile	children	WBC + CRP	120	51	3	24
Beltran	2007	17618882	Chile	children	WBC	103	68	3	24
Beltran	2007	17618882	Chile	children	CRP	120	51	8	19
Beltran	2007	17618882	Chile	children	CRP	68	103	3	24
Beltran	2007	17618882	Chile	children	CRP	103	68	3	24
Beltran	2007	17618882	Chile	children	WBC	137	34	3	24
Beltran	2007	17618882	Chile	children	WBC	120	51	3	24
Beltran	2007	17618882	Chile	children	WBC + CRP	137	34	5	22
Bendeck	2002	12354996	USA	children	US	35	6	2	3
Bendeck	2002	12354996	USA	children	CT	21	0	1	4
Bendeck	2002	12354996	USA	women of reproductive age	CT	74	5	4	2
Bendeck	2002	12354996	USA	adults	US	48	7	2	8
Bendeck	2002	12354996	USA	women of reproductive age	US	39	6	2	2
Bendeck	2002	12354996	USA	adults	CT	163	8	6	5
Bendeck	2002	12354996	USA	mixed	CT	184	8	7	9
Bendeck	2002	12354996	USA	mixed	US	83	13	4	5
Berry	1984	6385879	USA	mixed	FEVER	44	202	15	39
Berry	1984	6385879	USA	mixed	NAUSEA OR VOMITING	166	80	33	21
Berry	1984	6385879	USA	mixed	PSOAS SIGN	31	215	5	49
Berry	1984	6385879	USA	mixed	TENDERNESS REBOUND	171	75	33	21

Berry	1984	6385879	USA	mixed	GUARDING	117	129	20	34
Berry	1984	6385879	USA	mixed	ABNORMAL URINATION	26	220	1	53
Berry	1984	6385879	USA	mixed	CHILLS	17	229	2	52
Berry	1984	6385879	USA	mixed	ANOREXIA	150	96	22	32
Berry	1984	6385879	USA	mixed	MASS ABDOMINAL	26	220	6	48
Berry	1984	6385879	USA	mixed	PAIN PELVIC	83	163	18	36
Berry	1984	6385879	USA	mixed	TENDERNESS RECTAL	102	144	26	28
Berry	1984	6385879	USA	mixed	CONSTIPATION	10	236	5	49
Berry	1984	6385879	USA	mixed	OBTURATOR SIGN	19	227	3	51
Berry	1984	6385879	USA	mixed	TENDERNESS RLO	236	10	52	2
Berry	1984	6385879	USA	mixed	MENSES	60	186	15	39
Berry	1984	6385879	USA	mixed	DIARRHEA	27	219	8	46
Berry	1984	6385879	USA	mixed	PAIN ABDOMINAL	246	0	54	0
Biersack	1993	8508569	Germany	mixed	TC99M NUCLEAR	12	5	4	11
Bilbey	1989	2647214	Canada	mixed	US	13	0	1	0
Birchard	2005	15671363	USA	pregnant women	MRI	1	0	2	22
Birchley	2006	16460636	UK	mixed	NEUTROPHIL COUNT	50	8	7	10
Birchley	2006	16460636	UK	women of reproductive age	WBC	20	9	3	6
Birchley	2006	16460636	UK	mixed	WBC + NEUTROPHIL COUNT	49	9	6	11
Birchley	2006	16460636	UK	mixed	WBC	45	13	5	12
Birchley	2009	19723423	UK	mixed	WBC	29	7	7	4
Birchley	2006	16460636	UK	mixed	CRP + NEUTROPHIL COUNT	54	4	8	9
Birchley	2006	16460636	UK	mixed	CRP	44	14	10	7
Birchley	2006	16460636	UK	women of reproductive age	WBC + CRP	27	2	5	4
Birchley	2006	16460636	UK	women of reproductive age	CRP + NEUTROPHIL COUNT	28	1	5	4
Birchley	2006	16460636	UK	women of reproductive age	NEUTROPHIL COUNT	24	5	4	5
Birchley	2006	16460636	UK	women of reproductive age	CRP	23	6	6	3
Birchley	2006	16460636	UK	mixed	WBC + CRP + NEUTROPHIL COUNT	54	4	7	10
Birchley	2006	16460636	UK	mixed	WBC + CRP	53	5	7	10
Birchley	2009	19723423	UK	mixed	CRP	30	8	2	9
Birchley	2006	16460636	UK	women of reproductive age	WBC + CRP + NEUTROPHIL COUNT	27	2	5	4
Birchley	2006	16460636	UK	women of reproductive age	WBC + NEUTROPHIL COUNT	23	6	4	5
Blalock	1989	2610191	USA	mixed	WBC	74	7	16	26
Blalock	1989	2610191	USA	mixed	TENDERNESS RLO	80	1	37	5
Blalock	1989	2610191	USA	mixed	FEVER	21	60	15	27
Blalock	1989	2610191	USA	mixed	ABNORMAL URINATION	19	56	4	35
Blalock	1989	2610191	USA	mixed	PERITONISM RLO	68	13	28	14
Boehnert	2009	20367723	Switzerland	adults	CT	44	3	15	31

Boehnert	2009	20367723	Switzerland	adults	US	77	57	52	133
Bolton	1975	1191953	UK	mixed	WBC	24	22	17	36
Bondi	2012	22273324	Israel	adults	US	140	4	13	135
Bondi	2012	22273324	Israel	adults	CT + US	12	4	1	9
Bonello	1979	428284	USA	mixed	TENDERNESS RECTAL	188	219	38	34
Bonello	1979	428284	USA	women of reproductive age	TENDERNESS RECTAL	70	85	26	19
Bonello	1979	428284	USA	mixed	TENDERNESS RECTAL	140	180	36	28
Bonello	1979	428284	USA	children	TENDERNESS RECTAL	48	39	2	6
Bower	1981	7209769	USA	mixed	NEUTROPHIL%	351	31	42	29
Bower	1981	7209769	USA	mixed	WBC OR NEUTROPHIL%	315	67	42	29
Bower	1981	7209769	USA	mixed	WBC	331	51	42	29
Bower	1981	7209769	USA	mixed	WBC + NEUTROPHIL%	367	15	42	29
Brandt	2003	14509318	USA	adults	CT	165	1	3	10
Brandt	2003	14509318	USA	women of reproductive age	CT	132	0	0	18
Brewer	1976	1251963	USA	adults	ANOREXIA	33	10	223	304
Brewer	1976	1251963	USA	adults	DIARRHEA	5	38	104	423
Brewer	1976	1251963	USA	adults	RIGIDITY	3	40	7	520
Brewer	1976	1251963	USA	adults	FEVER	7	36	13	514
Brewer	1976	1251963	USA	adults	GUARDING	27	16	97	430
Brewer	1976	1251963	USA	adults	VOMITING	21	22	213	314
Brewer	1976	1251963	USA	adults	BOWEL SOUNDS	32	11	301	226
Brewer	1976	1251963	USA	adults	WBC	39	3	220	307
Brewer	1976	1251963	USA	adults	TENDERNESS RECTAL	13	30	20	507
Brewer	1976	1251963	USA	adults	WBC	43	0	498	29
Brewer	1976	1251963	USA	adults	TENDERNESS REBOUND	36	7	70	457
Brewer	1976	1251963	USA	adults	OBSTIPATION	5	38	28	499
Brewer	1976	1251963	USA	adults	WBC	2	40	5	522
Brewer	1976	1251963	USA	adults	FEVER	19	24	93	434
Brooks	1965	14261578	USA	mixed	ABD XRAY	2	157	0	41
Brooks	1965	14261578	USA	mixed	ABD XRAY	96	63	15	26
Brooks	1965	14261578	USA	mixed	ABD XRAY	2	157	0	41
Brooks	1965	14261578	USA	mixed	ABD XRAY	11	148	0	41
Brooks	1965	14261578	USA	mixed	ABD XRAY	36	142	1	40
Brooks	1965	14261578	USA	mixed	ABD XRAY	52	107	8	33
Brooks	1965	14261578	USA	mixed	ABD XRAY	3	156	0	41
Brooks	1965	14261578	USA	mixed	ABD XRAY	11	148	0	41
Brooks	1965	14261578	USA	mixed	ABD XRAY	17	142	1	40
Brooks	1965	14261578	USA	mixed	ABD XRAY	51	108	7	34
Bullard	1999	17659136	Canada	adults	US	138	33	78	91
Bullard	1999	17659136	Canada	adults	US	122	49	59	110
Burford	2011	21683208	USA	children	US	23	6	1	24

Burford	2011	21683208	USA	children	US	3	3	1	14
Burford	2011	21683208	USA	children	US	27	2	4	21
Burford	2011	21683208	USA	children	US	5	1	1	14
Butler	1987	3586627	USA	mixed	TC99M NUCLEAR	10	0	2	26
Caglayan	2010	21038123	Turkey	mixed	CT	31	3	3	15
Cakirer	2002	15290575	Turkey	adults	CT	89	5	3	24
Campbell	1988	3395821	UK	mixed	ABD XRAY	6	0	9	140
Cannon	1956	13157341	USA	mixed	NEUTROPHIL%	107	40	11	6
Cannon	1956	13157341	USA	mixed	WBC	112	37	6	11
Cannon	1956	13157341	USA	mixed	WBC	86	60	9	8
Cardall	2004	15466143	USA	mixed	WBC	66	21	89	98
Cardall	2004	15466143	USA	mixed	FEVER	43	49	72	129
Cavusoglu	2009	19184052	Turkey	children	US	82	50	35	117
Ceres	1990	2186346	Spain	children	US	332	10	17	9
Ceydeli	2006	17084779	USA	mixed	CT	68	3	1	3
Ceydeli	2006	17084779	USA	mixed	NAUSEA OR VOMITING OR ANOREXIA	75	14	1	10
Ceydeli	2006	17084779	USA	mixed	TENDERNESS REBOUND	33	56	7	4
Cha	1996	8875877	Korea	mixed	US	10	1	0	15
Chabanova	2011	20347539	Denmark	adults	MRI	28	2	9	9
Chabanova	2011	20347539	Denmark	adults	MRI	26	4	7	11
Chabanova	2011	20347539	Denmark	adults	MRI	25	5	3	15
Chakhunashvili	2005	16444038	Georgia	children	WBC	12	11	3	2
Chakhunashvili	2005	16444038	Georgia	children	PROCALCITONIN	23	0	0	5
Chakhunashvili	2005	16444038	Georgia	children	LEFT SHIFT	15	7	2	3
Chan	2005	15908535	Canada	mixed	US	145	29	23	470
Chang	2003	12749239	Taiwan	children	US	26	4	2	18
Chang	2003	12749239	Taiwan	children	TC99M NUCLEAR	29	1	4	16
Chang	2007	17460492	Taiwan	children	US	38	2	3	28
Chee	1982	7157006	Malaysia	mixed	TENDERNESS RECTAL	120	150	44	56
Chee	1982	7157006	Malaysia	mixed	TENDERNESS RECTAL	42	66	22	38
Chen	1996	8630133	Taiwan	adults	CRP	55	13	8	4
Chen	2000	10919537	Taiwan	mixed	US	106	4	12	25
Chen	1996	8630133	Taiwan	adults	CRP	28	6	3	2
Chen	1998	9564286	China	adults	US	143	1	15	32
Chen	1998	10668876	Taiwan	mixed	US	11	1	1	89
Chen	1996	8630133	Taiwan	adults	CRP	27	7	5	2
Cheng	2003	12630009	Taiwan	women of reproductive age	TC99M NUCLEAR	28	2	2	18
Cheng	2003	12630009	Taiwan	mixed	US	25	5	1	19
Chesbrough	1993	8475271	USA	mixed	US	128	14	10	84
Chi	1996	8639195	USA	mixed	CRP	41	11	14	24
Chi	1996	8639195	USA	mixed	WBC + CRP	25	35	3	27

Chi	1996	8639195	USA	mixed	WBC	32	28	10	20
Chi	1996	8639195	USA	mixed	WBC OR CRP	53	6	20	11
Chin	2012	22919012	UK	mixed	CT	4	1	2	113
Chiu	2013	22951113	Taiwan	adults	CT	38	4	0	58
Chiu	2013	22951113	Taiwan	adults	CT	42	0	3	55
Cho	1999	10515341	Australia	mixed	CT	21	0	1	14
Cho	1999	10515341	Australia	mixed	US	9	6	2	8
Choi	2003	14616200	Korea	mixed	CT	11	60	0	167
Choi	2003	14616200	Korea	mixed	CT	66	5	13	154
Choi	2003	14616200	Korea	mixed	CT	12	59	0	167
Choi	2003	14616200	Korea	mixed	CT	5	66	3	164
Choi	2003	14616200	Korea	mixed	CT	29	42	70	97
Choi	2012	22067287	South Korea	mixed	CT	52	3	7	37
Choi	2003	14616200	Korea	mixed	CT	53	18	25	142
Choi	2003	14616200	Korea	mixed	CT	12	59	8	159
Choi	1998	9699047	USA	mixed	CT	7	0	0	0
Choi	2003	14616200	Korea	mixed	CT	0	71	8	159
Choi	1998	9699047	USA	mixed	CT	104	0	1	12
Choi	1998	9699047	USA	mixed	CT	111	0	1	12
Choi	2003	14616200	Korea	mixed	CT	4	67	32	135
Choi	2012	22067287	South Korea	mixed	CT	49	6	1	43
Choi	2003	14616200	Korea	mixed	CT	62	9	43	124
Choi	2012	22067287	South Korea	mixed	CT	50	5	0	44
Choi	2012	22067287	South Korea	mixed	CT	46	9	0	44
Choi	2003	14616200	Korea	mixed	CT	1	70	22	145
Choi	2012	22067287	South Korea	mixed	CT	48	7	6	38
Choi	2012	22067287	South Korea	mixed	CT	52	3	3	41
Choi	2003	14616200	Korea	mixed	CT	3	68	0	167
Choi	2003	14616200	Korea	mixed	CT	47	24	7	160
Choi	2003	14616200	Korea	mixed	CT	15	56	57	110
Choi	2003	14616200	Korea	mixed	CT	12	59	37	130
Choi	2012	22067287	South Korea	mixed	CT	47	8	0	44
Choi	2012	22067287	South Korea	mixed	CT	52	3	1	43
Choi	2003	14616200	Korea	mixed	CT	6	65	12	155
Choi	2003	14616200	Korea	mixed	CT	11	60	10	157
Choi	1998	9699047	USA	mixed	US	9	4	1	3
Choudhary	1980	7410859	India	mixed	WBC	50	25	14	11
Choudhri	2012	22146833	USA	adults	CT	15	0	0	10
Choudhri	2012	22146833	USA	adults	CT	14	1	0	10
Christopher	2002	12217464	USA	mixed	CT	27	4	4	66
Cobben	2009	19137303	Netherlands	mixed	US	57	0	1	48

Cobben	2009	19137303	Netherlands	mixed	MRI	62	1	0	41
Cobben	2004	15333354	Netherlands	pregnant women	MRI	3	0	0	7
Cobben	2009	19137303	Netherlands	mixed	MRI	18	0	0	12
Cobben	2009	19137303	Netherlands	mixed	MRI	2	0	0	3
Colak	2001	11383861	Turkey	mixed	TC99M NUCLEAR	16	0	0	25
Colvin	2007	18091591	USA	children	GUARDING	12	3	32	37
Colvin	2007	18091591	USA	children	PSOAS SIGN	7	8	4	65
Colvin	2007	18091591	USA	children	DIARRHEA	16	105	45	213
Colvin	2007	18091591	USA	children	UNABLE TO WALK OR LIMPING	11	4	30	39
Colvin	2007	18091591	USA	children	VOMITING	67	54	120	138
Colvin	2007	18091591	USA	children	GUARDING	68	53	99	159
Colvin	2007	18091591	USA	children	OBTURATOR SIGN	20	101	15	243
Colvin	2007	18091591	USA	children	TENDERNESS REBOUND	8	7	8	61
Colvin	2007	18091591	USA	children	ROVSING SIGN	24	97	21	237
Colvin	2007	18091591	USA	children	PSOAS SIGN	27	94	21	237
Colvin	2007	18091591	USA	children	VOMITING	11	4	38	31
Colvin	2007	18091591	USA	children	TENDERNESS RLO	13	2	32	37
Colvin	2007	18091591	USA	children	PAIN COUGH PERCUSSION HOPPING	12	3	21	48
Colvin	2007	18091591	USA	children	PAIN DURATION	12	3	25	44
Colvin	2007	18091591	USA	children	FEVER	12	3	49	20
Colvin	2007	18091591	USA	children	OBTURATOR SIGN	5	10	1	68
Colvin	2007	18091591	USA	children	ANOREXIA	76	45	130	128
Colvin	2007	18091591	USA	children	TENDERNESS REBOUND	56	65	51	207
Colvin	2007	18091591	USA	children	NAUSEA	81	40	223	35
Colvin	2007	18091591	USA	children	TENDERNESS RLO	84	37	124	134
Colvin	2007	18091591	USA	children	ROVSING SIGN	5	10	7	62
Colvin	2007	18091591	USA	children	PAIN COUGH PERCUSSION HOPPING	81	40	94	164
Colvin	2007	18091591	USA	children	PAIN MIGRATION	5	10	9	60
Colvin	2007	18091591	USA	children	PAIN DURATION	71	50	102	156
Colvin	2007	18091591	USA	children	PAIN RLO	90	31	126	132
Colvin	2007	18091591	USA	children	BOWEL SOUNDS	31	90	24	234
Colvin	2007	18091591	USA	children	ANOREXIA	14	1	41	28
Colvin	2007	18091591	USA	children	PAIN RLO	11	4	22	47
Colvin	2007	18091591	USA	children	DIARRHEA	1	14	4	65
Colvin	2007	18091591	USA	children	NAUSEA	11	4	37	32
Colvin	2007	18091591	USA	children	BOWEL SOUNDS	6	9	10	59
Colvin	2007	18091591	USA	children	PAIN MIGRATION	45	76	59	199
Colvin	2007	18091591	USA	children	UNABLE TO WALK OR LIMPING	93	28	107	151
Colvin	2007	18091591	USA	children	FEVER	48	73	118	140
Connor	1994	7856985	USA	mixed	CT	6	2	2	3

Connor	1994	7856985	USA	mixed	WBC	44	21	12	8
Connor	1994	7856985	USA	mixed	US	3	11	3	3
Corey	1984	6702761	USA	mixed	NEUTROPHIL% OR BANDS%	47	2	2	10
Corey	1984	6702761	USA	mixed	NEUTROPHIL%	46	3	1	11
Corey	1984	6702761	USA	mixed	NEUTROPHIL% + BANDS%	17	32	0	12
Corey	1984	6702761	USA	mixed	BAND%	11	38	0	12
Corey	1984	6702761	USA	mixed	BAND%	19	30	1	11
Corey	1984	6702761	USA	mixed	PMNC COUNT	44	5	4	8
Coursey	2010	20093517	USA	adults	CT	349	3	19	16
Coursey	2010	20093517	USA	adults	CT	390	4	21	18
Coursey	2010	20093517	USA	adults	CT	421	5	24	19
Coursey	2010	20093517	USA	adults	CT	27	2	4	1
Coursey	2010	20093517	USA	adults	CT	1	0	0	0
Coursey	2010	20093517	USA	adults	CT	107	0	7	3
Coursey	2010	20093517	USA	adults	CT	6	2	2	2
Coursey	2010	20093517	USA	adults	CT	0	0	0	1
Coursey	2010	20093517	USA	adults	CT	0	0	0	1
Coursey	2011	21679558	USA	adults	CT	122	6	9	8
Coursey	2010	20093517	USA	adults	CT	35	1	3	2
Coursey	2010	20093517	USA	adults	CT	87	2	2	6
Coursey	2010	20093517	USA	adults	CT	47	0	1	3
Coursey	2011	21679558	USA	adults	CT	8	0	1	2
Coursey	2011	21679558	USA	adults	CT	98	0	6	3
Coursey	2011	21679558	USA	adults	CT	167	3	9	11
Coursey	2010	20093517	USA	adults	CT	0	0	0	1
Coursey	2010	20093517	USA	adults	CT	5	2	1	2
Coursey	2010	20093517	USA	adults	CT	111	3	7	7
Coursey	2010	20093517	USA	adults	CT	1	0	1	0
Coursey	2010	20093517	USA	adults	CT	95	0	3	2
Coursey	2010	20093517	USA	adults	CT	453	4	24	20
Coursey	2010	20093517	USA	adults	CT	57	1	3	4
Coursey	2011	21679558	USA	adults	CT	18	1	1	0
Coursey	2010	20093517	USA	adults	CT	52	1	1	2
Coursey	2010	20093517	USA	adults	CT	17	3	1	5
Coursey	2010	20093517	USA	adults	CT	63	0	3	2
Coursey	2010	20093517	USA	adults	CT	23	2	1	2
Coursey	2010	20093517	USA	adults	CT	60	1	6	4
Coursey	2010	20093517	USA	adults	CT	1	0	0	0
Coursey	2010	20093517	USA	adults	CT	85	2	5	6
Coursey	2010	20093517	USA	adults	CT	16	0	0	1
Coursey	2010	20093517	USA	adults	CT	25	0	1	3

Coursey	2010	20093517	USA	adults	CT	23	1	2	2
Coursey	2010	20093517	USA	adults	CT	276	2	15	10
Coursey	2010	20093517	USA	adults	CT	5	2	1	2
Crady	1993	8517561	USA	children	US	22	4	4	68
Daly	2005	15908536	USA	adults	CT	266	2	36	864
Davidson	1999	9914351	Australia	children	FEVER	35	30	53	122
Davidson	1999	9914351	Australia	children	NEUTROPHIL%	23	26	31	103
Davidson	1999	9914351	Australia	children	PAIN MIGRATION	43	27	73	108
Davidson	1999	9914351	Australia	children	TENDERNESS RIF	69	1	161	22
Davidson	1999	9914351	Australia	children	GUARDING RLO	28	42	10	170
Davidson	1999	9914351	Australia	children	US	62	8	9	174
Davidson	1999	9914351	Australia	children	NAUSEA OR VOMITING	60	10	136	46
Davidson	1999	9914351	Australia	children	WBC	23	26	55	82
Davidson	1999	9914351	Australia	children	ANOREXIA	58	12	133	49
Davies	1991	1941740	UK	mixed	CRP	29	2	11	18
Davies	1991	1958978	UK	mixed	US	21	2	1	17
Davies	1991	1941740	UK	mixed	WBC	22	9	12	17
Davies	1991	1941740	UK	mixed	WBC + CRP	30	1	14	15
De Oliveira Peixoto	2011	21710048	Brazil	mixed	US	56	30	5	10
De Oliveira Peixoto	2011	21710048	Brazil	mixed	US	36	21	5	12
De Oliveira Peixoto	2011	21710048	Brazil	mixed	US	29	16	2	8
De Oliveira Peixoto	2011	21710048	Brazil	mixed	US	49	25	2	6
De Oliveira Peixoto	2011	21710048	Brazil	mixed	US	85	46	7	18
DeLaney	1989	2802977	USA	mixed	LAST MENSTRUAL PERIOD	6	26	22	46
DeLaney	1989	2802977	USA	mixed	INDIUM-111 NUCLEAR	29	3	2	66
DeLaney	1989	2802977	USA	mixed	PREVIOUS ABDOMINAL SURGERY	4	28	18	50
DeLaney	1989	2802977	USA	mixed	TENDERNESS BILATERAL ADEXINAL	2	30	5	63
DeLaney	1989	2802977	USA	mixed	ANOREXIA	18	14	32	36
DeLaney	1989	2802977	USA	mixed	DIARRHEA OR CONSTIPATION	10	22	32	36
DeLaney	1989	2802977	USA	mixed	VOMITING	14	18	37	31
DeLaney	1989	2802977	USA	mixed	BOWEL SOUNDS	9	23	22	46
DeLaney	1989	2802977	USA	mixed	TENDERNESS RECTAL OR MASS RECTAL	4	28	9	59
DeLaney	1989	2802977	USA	mixed	GUARDING	18	14	23	45
DeLaney	1989	2802977	USA	mixed	ABD XRAY	5	27	7	61
DeLaney	1989	2802977	USA	mixed	FEVER	19	13	50	18
DeLaney	1989	2802977	USA	mixed	ABNORMAL URINALYSIS	7	25	18	50
DeLaney	1989	2802977	USA	mixed	GENITOURINARY SYMPTOMS	1	31	16	52
DeLaney	1989	2802977	USA	mixed	TENDERNESS RLO	16	16	27	41

DeLaney	1989	2802977	USA	mixed	MASS ABDOMINAL	4	28	0	68
DeLaney	1989	2802977	USA	mixed	SYMPTOMS DURATION	15	17	25	43
DeLaney	1989	2802977	USA	mixed	PAIN MIGRATION	7	25	15	53
DeLaney	1989	2802977	USA	mixed	TENDERNESS RIGHT ADEXINAL	11	21	9	59
DeLaney	1989	2802977	USA	mixed	PERITONISM	14	18	28	40
DeLaney	1989	2802977	USA	mixed	PREVIOUS SIMILAR SYMPTOMS	6	26	25	43
DeLaney	1989	2802977	USA	mixed	WBC	29	3	53	15
Dearing	2008	18942613	USA	mixed	CT	115	13	2	115
Dearing	2008	18942613	USA	mixed	CT	6	3	0	14
Dearing	2008	18942613	USA	mixed	CT	12	3	1	10
Dearing	2008	18942613	USA	mixed	CT	85	6	1	85
Deibener	2011	21421538	France	mixed	NEUTROPHIL COUNT	25	28	263	125
Deibener	2011	21421538	France	mixed	LYMPHOCYTE COUNT	39	14	125	263
Deibener	2011	21421538	France	mixed	EOSINOPHILS	30	23	75	313
Deniszbasi	2003	14676508	Turkey	mixed	US	154	21	29	148
Di Cesare	2013	23860049	Italy	children	US	18	0	2	20
Dickson	1985	4026364	Scotland	children	TENDERNESS RECTAL	61	42	12	86 134
Dilley	2001	11172421	USA	children	US	491	37	78	6
Dixon	1991	2004144	Scotland	mixed	TENDERNESS RECTAL	6	389	14	619
Dixon	1991	2004144	Scotland	mixed	TENDERNESS RECTAL	134	261	175	458
Dixon	1991	2004144	Scotland	mixed	TENDERNESS RECTAL	34	361	53	580
Dixon	1991	2004144	Scotland	mixed	GUARDING	272	123	265	368
Dixon	1991	2004144	Scotland	mixed	TENDERNESS RLO	380	15	527	106
Dixon	1991	2004144	Scotland	mixed	TENDERNESS REBOUND	264	131	238	395
Dixon	1991	2004144	Scotland	mixed	TENDERNESS RECTAL	3	392	3	630
Dixon	1991	2004144	Scotland	mixed	RIGIDITY ABDOMINAL	43	352	15	618
Doraiswamy	1979	519164	Kuwait	children	NEUTROPHIL%	216	9	47	103
Doraiswamy	1979	519164	Kuwait	children	WBC	94	131	5	145
Douglas	2000	11030676	Australia	mixed	US	54	3	8	74
Dueholm	1989	2676422	Denmark	mixed	BAND%	4	55	42	103
Dueholm	1989	2676422	Denmark	mixed	WBC + CRP + NEUTROPHIL% + BAND%	59	0	0	145
Dueholm	1989	2676422	Denmark	mixed	WBC	58	1	4	141
Dueholm	1989	2676422	Denmark	mixed	WBC	45	14	19	126
Dueholm	1989	2676422	Denmark	mixed	WBC	49	10	17	128
Dueholm	1989	2676422	Denmark	mixed	WBC	9	50	38	107
Dueholm	1989	2676422	Denmark	mixed	NEUTROPHIL%	46	13	19	126
Dueholm	1989	2676422	Denmark	mixed	NEUTROPHIL%	3	56	41	104
Dueholm	1989	2676422	Denmark	mixed	NEUTROPHIL%	26	33	32	113
Dueholm	1989	2676422	Denmark	mixed	WBC	17	42	35	110
Dueholm	1989	2676422	Denmark	mixed	WBC + NEUTROPHIL%	55	4	10	135

Dueholm	1989	2676422	Denmark	mixed	WBC	5	54	41	104
Dueholm	1989	2676422	Denmark	mixed	WBC	23	36	33	112
Dueholm	1989	2676422	Denmark	mixed	WBC + CRP + NEUTROPHIL%	59	0	0	145
Dueholm	1989	2676422	Denmark	mixed	CRP	44	15	23	122
Dunning	1991	1863045	UK	children	TENDERNESS RECTAL	4	5	2	22
Durakbasa	2006	16456751	Turkey	children	ABD XRAY	182	150	11	35
Durakbasa	2006	16456751	Turkey	children	ABD XRAY	58	320	6	40
Durakbasa	2006	16456751	Turkey	children	ABD XRAY	109	269	5	41
Durakbasa	2006	16456751	Turkey	children	ABD XRAY	289	89	0	0
Durakbasa	2006	16456751	Turkey	children	ABD XRAY	18	360	1	45
Durakbasa	2006	16456751	Turkey	children	ABD XRAY	199	133	13	33
Durakbasa	2006	16456751	Turkey	children	ABD XRAY	11	367	1	45
Durakbasa	2006	16456751	Turkey	children	ABD XRAY	32	346	0	46
Durakbasa	2006	16456751	Turkey	children	ABD XRAY	6	372	0	46
Duzgun	2007	17708281	Turkey	mixed	US + WBC + D-LACTATE	23	4	2	3
Duzgun	2007	17708281	Turkey	mixed	US	26	1	3	2
Duzgun	2007	17708281	Turkey	mixed	WBC	18	9	2	3
Duzgun	2007	17708281	Turkey	mixed	WBC + D-LACTATE	18	9	0	5
Duzgun	2007	17708281	Turkey	mixed	US + D-LACTATE	25	2	1	4
Duzgun	2007	17708281	Turkey	mixed	D-LACTATE	26	1	2	3
Duzgun	2007	17708281	Turkey	mixed	CRP + D-LACTATE	20	7	2	3
Duzgun	2007	17708281	Turkey	mixed	WBC + CRP + D-LACTATE	20	7	1	4
Duzgun	2007	17708281	Turkey	mixed	CRP	21	6	2	3
D'Ippolito	1998	10349191	Brazil	mixed	CT	40	4	0	8
Ege	2002	12200239	Turkey	adults	CT	104	4	3	185
Elangovan	1996	8659268	USA	adults	FEVER	39	26	5	4
Elangovan	1996	8659268	USA	adults	PAIN RLQ	54	11	6	3
Elangovan	1996	8659268	USA	adults	VOMITING	18	47	2	7
Elangovan	1996	8659268	USA	adults	FEVER	15	50	2	7
Elangovan	1996	8659268	USA	adults	BAND%	31	34	0	9
Elangovan	1996	8659268	USA	adults	WBC	53	12	5	4
Elangovan	1996	8659268	USA	adults	WBC	30	35	3	6
Elangovan	1996	8659268	USA	adults	RIGIDITY	2	63	0	9
Elangovan	1996	8659268	USA	adults	TENDERNESS REBOUND TEMPERATURE DIFFERENCE RLQ AND LLO	31	34	4	5
Emery	1994	8285972	USA	mixed		0	25	3	58
Emil	2001	11329589	Canada	children	US	149	4	14	9
Emmanuel	2011	21477433	Ireland	mixed	WBC	285	62	32	47
Emmanuel	2011	21477433	Ireland	mixed	SERUM BILIRUBIN	102	239	10	75
Emmanuel	2011	21477433	Ireland	mixed	CRP	69	39	5	13
English	1977	869331	USA	mixed	WBC	19	1	37	24
English	1977	869331	USA	mixed	WBC	11	2	15	24

Eriksson	1994	7886405	Sweden	adults	WBC	45	1	8	12
Eriksson	1989	2741614	Sweden	adults	NEUTROPHIL%	75	11	10	17
Eriksson	1989	2741614	Sweden	adults	CRP	59	27	7	20
Eriksson	1995	8775633	Sweden	adults	WBC	52	33	8	6
Eriksson	1995	7727605	Sweden	mixed	CRP	21	3	4	0
Eriksson	1994	7886405	Sweden	adults	WBC	94	76	38	19
Eriksson	1995	8775633	Sweden	adults	LEUKOCYTE ELASTASE	18	7	2	2
Eriksson	1994	7886405	Sweden	adults	CRP	102	68	3	54
Eriksson	1995	7727605	Sweden	mixed	WBC	71	15	9	6
Eriksson	1995	8775633	Sweden	adults	WBC	69	16	9	5
Eriksson	1994	7886405	Sweden	adults	CRP	40	6	9	11
Eriksson	1995	8775633	Sweden	adults	LEUKOCYTE ELASTASE	14	11	1	3
Eriksson	1995	7727605	Sweden	mixed	WBC	18	6	2	2
Eriksson	1989	2741614	Sweden	adults	WBC	77	9	16	11
Eriksson	1995	7727605	Sweden	mixed	IL-6	55	28	9	4
Eriksson	1995	7727605	Sweden	mixed	CRP	65	11	11	4
Eriksson	1995	7727605	Sweden	mixed	IL-6	16	8	1	3
Erkasap	2000	10967943	Turkey	adults	WBC OR CRP	49	0	12	41
Erkasap	2000	10967943	Turkey	adults	WBC OR CRP OR IL-6	49	0	18	35
Erkasap	2000	10967943	Turkey	adults	WBC OR CRP OR IL-6	16	33	1	52
Erkasap	2000	10967943	Turkey	adults	CRP	47	2	7	46
Erkasap	2000	10967943	Turkey	adults	WBC OR CRP	44	5	2	51
Erkasap	2000	10967943	Turkey	adults	WBC	46	3	6	47
Erkasap	2000	10967943	Turkey	adults	IL-6	16	33	9	44
Escriba	2011	21346681	Spain	children	US	35	7	3	54
Eskelinen	1995	7610351	Finland	adults	FEVER	33	21	98	265
Eskelinen	1995	7610351	Finland	adults	TENDERNESS RLO	51	3	47	316
Eskelinen	1995	7610351	Finland	adults	DISTENTION	50	4	294	69
Eskelinen	1995	7610351	Finland	adults	PREVIOUS ABDOMINAL SURGERY	182	181	44	10
Eskelinen	1995	7610351	Finland	adults	PAIN	47	7	290	73
Eskelinen	1995	7610351	Finland	adults	PAIN DURATION	40	14	229	134
Eskelinen	1995	7610351	Finland	adults	VERTIGO	54	0	345	18
Eskelinen	1995	7610351	Finland	adults	NORMAL BOWELS	46	8	240	123
Eskelinen	1995	7610351	Finland	adults	NORMAL MICTURATION	51	3	327	36
Eskelinen	1995	7610351	Finland	adults	PAIN PROGRESSION	38	16	44	319
Eskelinen	1995	7610351	Finland	adults	WBC	36	18	142	221
Eskelinen	1995	7610351	Finland	adults	PREVIOUS SIMILAR PAIN	214	149	46	8
Eskelinen	1995	7610351	Finland	adults	BOWEL SOUNDS	52	2	272	91
Eskelinen	1995	7610351	Finland	adults	RELIEVING FACTORS	53	1	309	54
Eskelinen	1995	7610351	Finland	adults	PAIN NO MEDICATION	54	0	334	29
Eskelinen	1995	7610351	Finland	adults	PAIN RLO	47	7	51	312

Eskelinen	1995	7610351	Finland	adults	PAIN MUQ	18	36	134	229
Eskelinen	1995	7610351	Finland	adults	PAIN INTERMITTENT	7	47	36	327
Eskelinen	1995	7610351	Finland	adults	TENDERNESS RENAL	38	16	240	123
Eskelinen	1995	7610351	Finland	adults	CONSTIPATION	6	48	33	330
Eskelinen	1995	7610351	Finland	adults	MURPHY SIGN	51	3	290	73
Eskelinen	1995	7610351	Finland	adults	NO INDIGESTION	45	9	232	131
Eskelinen	1995	7610351	Finland	adults	NO PREVIOUS ABDOMINAL DISEASE	46	8	247	116
Eskelinen	1995	7610351	Finland	adults	GUARDING	50	4	200	163
Eskelinen	1995	7610351	Finland	adults	ANOREXIA	44	10	280	83
Eskelinen	1995	7610351	Finland	adults	NO USE OF ALCOHOL	54	0	352	11
Eskelinen	1995	7610351	Finland	adults	RIGIDITY	40	14	76	287
Eskelinen	1995	7610351	Finland	adults	VOMITING	34	20	171	192
Eskelinen	1995	7610351	Finland	adults	NAUSEA	27	27	124	239
Eskelinen	1995	7610351	Finland	adults	MASS ABDOMINAL	54	0	338	25
Eskelinen	1995	7610351	Finland	adults	URINE	54	0	338	25
Eskelinen	1995	7610351	Finland	adults	TENDERNESS REBOUND	49	5	145	218
Eskelinen	1995	7610351	Finland	adults	NORMAL MOOD	48	6	294	69
Eskelinen	1995	7610351	Finland	adults	NO SCAR	43	11	178	185
Eskelinen	1995	7610351	Finland	adults	TENDERNESS RECTAL	27	27	44	319
Eskelinen	1995	7610351	Finland	adults	NO AGGRAVATING FACTORS	49	5	236	127
Eskelinen	1995	7610351	Finland	adults	NORMAL COLOR	53	1	327	36
Estey	2013	23528502	Canada	children	US	0	2	0	0
Estey	2013	23528502	Canada	children	US	0	2	0	4
Estey	2013	23528502	Canada	children	US	4	2	38	32
Estey	2013	23528502	Canada	children	US	0	2	0	2
Estey	2013	23528502	Canada	children	US	4	2	39	32
Estey	2013	23528502	Canada	children	US	1	2	14	35
Estey	2013	23528502	Canada	children	US	1	4	26	39
Estey	2013	23528502	Canada	children	US	2	4	15	36
Estey	2013	23528502	Canada	children	US	6	4	44	45
Estey	2013	23528502	Canada	children	US	0	1	0	3
Estey	2013	23528502	Canada	children	US	1	1	0	3
Estey	2013	23528502	Canada	children	US	1	4	6	23
Estey	2013	23528502	Canada	children	US	3	4	41	45
Estey	2013	23528502	Canada	children	US	2	2	7	11
Estey	2013	23528502	Canada	children	US	1	4	4	23
Estey	2013	23528502	Canada	children	US	0	2	6	26
Estey	2013	23528502	Canada	children	US	0	0	0	1
Estey	2013	23528502	Canada	children	US	1	1	5	10
Even-Bendahan	2003	12635978	Israel	children	CT	3	1	0	4
Even-Bendahan	2003	12635978	Israel	children	US	86	23	14	245

Evetts	1994	8044391	USA	mixed	US	12	4	8	24
Evetts	1994	8044391	USA	women of reproductive age	TC99M NUCLEAR	13	1	2	12
Evetts	1994	8044391	USA	women of reproductive age	US	8	2	7	14
Evetts	1994	8044391	USA	mixed	TC99M NUCLEAR	23	2	4	27
Exadaktylos	2008	18842129	Switzerland	adults	US	79	11	5	66
Fa	1989	2675357	USA	children	US	1	0	0	6
Fa	1989	2675357	USA	women of reproductive age	US	5	0	2	33
Fa	1989	2675357	USA	women of reproductive age	US	5	0	6	33
Fa	1989	2675357	USA	children	US	0	1	0	6
Fa	1989	2675357	USA	mixed	US	8	4	6	58
Fa	1989	2675357	USA	mixed	US	8	2	3	57
Fefferman	2001	11526268	USA	children	CT	6	1	2	8
Fefferman	2001	11526268	USA	children	CT	34	1	4	54
Fefferman	2001	11526268	USA	children	CT	28	0	2	46
Fente	2009	20120145	Nigeria	mixed	NAUSEA	59	21	36	12
Fente	2009	20120145	Nigeria	mixed	ANOREXIA	58	22	24	24
Fente	2009	20120145	Nigeria	mixed	FEVER	43	37	6	42
Fente	2009	20120145	Nigeria	mixed	GUARDING OR RIGIDITY	56	24	48	0
Fente	2009	20120145	Nigeria	mixed	PSOAS SIGN	49	31	48	0
Fente	2009	20120145	Nigeria	mixed	TENDERNESS RECTAL	5	75	48	0
Fente	2009	20120145	Nigeria	mixed	TENDERNESS	80	0	0	48
Fente	2009	20120145	Nigeria	mixed	TENDERNESS COUGH	55	25	42	6
Fente	2009	20120145	Nigeria	mixed	VOMITING	42	38	24	24
Fente	2009	20120145	Nigeria	mixed	OBTURATOR SIGN	25	55	48	0
Fente	2009	20120145	Nigeria	mixed	TENDERNESS REBOUND	78	2	42	6
Fente	2009	20120145	Nigeria	mixed	TENDERNESS RECTAL	10	70	48	0
Fente	2009	20120145	Nigeria	mixed	ROVSING SIGN	56	24	42	6
Fente	2009	20120145	Nigeria	mixed	PAIN MIGRATION	58	22	30	18
Fenyo	1997	9414043	Sweden	mixed	TENDERNESS REBOUND	310	82	347	428
Fenyo	1997	9414043	Sweden	mixed	WBC	362	30	398	377
Fenyo	1997	9414043	Sweden	mixed	RIGIDITY	158	234	111	664
Fenyo	1997	9414043	Sweden	mixed	VOMITING	187	205	224	551
Fenyo	1997	9414043	Sweden	mixed	PAIN DURATION	340	52	513	262
Fenyo	1997	9414043	Sweden	mixed	PAIN COUGH	331	61	433	342
Fenyo	1997	9414043	Sweden	mixed	PAIN DURATION	292	100	425	350
Fenyo	1997	9414043	Sweden	mixed	WBC	181	211	116	659
Fenyo	1997	9414043	Sweden	mixed	PAIN MIGRATION	265	127	233	542
Fenyo	1997	9414043	Sweden	mixed	PAIN PROGRESSION	293	99	430	345
Fenyo	1997	9414043	Sweden	mixed	TENDERNESS RLQ	146	246	430	345
Fergusson	2002	12437687	Australia	mixed	US	62	40	11	27

Fergusson	2002	12437687	Australia	mixed	PMNC COUNT	559	166	54	168
Fergusson	2002	12437687	Australia	mixed	PMNC COUNT	427	298	27	195
Fergusson	2002	12437687	Australia	mixed	PMNC COUNT	288	437	18	204
Fergusson	2002	12437687	Australia	mixed	LEFT SHIFT	203	522	28	194
Fergusson	2002	12437687	Australia	mixed	WBC	628	97	104	118
Fergusson	2002	12437687	Australia	mixed	WBC	683	42	149	73
Fergusson	2002	12437687	Australia	mixed	PMNC COUNT	645	80	92	130
Fergusson	2002	12437687	Australia	mixed	PMNC RATE	234	491	23	199
Fergusson	2002	12437687	Australia	mixed	WBC	537	188	62	160
Fergusson	2002	12437687	Australia	mixed	LYMPHOCYTE COUNT	194	531	112	110
Fergusson	2002	12437687	Australia	mixed	PMNC RATE	415	310	43	179
Fergusson	2002	12437687	Australia	mixed	WBC	350	375	23	199
Fergusson	2002	12437687	Australia	mixed	LYMPHOCYTE COUNT	547	178	194	28
Fergusson	2002	12437687	Australia	mixed	PMNC RATE	629	96	86	136
Filiz	2010	20690847	Turkey	mixed	D-LACTATE	39	1	3	37
Filiz	2010	20690847	Turkey	mixed	WBC	35	5	9	31
Foley	1992	1456603	USA	mixed	TC99M NUCLEAR	13	3	0	8
Ford	1994	7978690	USA	mixed	US	39	48	8	230
Fox	2007	20440399	USA	mixed	US	27	42	9	77
Fox	2008	18446069	USA	mixed	US	37	20	7	62
Franke	1999	9880422	Germany	mixed	US	5	212	1	599
Franke	1999	9880422	Germany	mixed	US	120	97	29	571
Franke	1999	9880422	Germany	mixed	US	11	206	7	593
Franke	1999	9880422	Germany	mixed	US	5	212	2	598
Franke	1999	9880422	Germany	mixed	US	31	186	5	595
Franke	1999	9880422	Germany	mixed	US	96	121	17	583
Freeland	2009	19969125	USA	pregnant women	US	5	0	0	0
Freeland	2009	19969125	USA	pregnant women	CT	7	0	0	6
Freeland	2009	19969125	USA	pregnant women	MRI	1	0	0	0
Frisenda	1979	507547	USA	pregnant women	GUARDING AND TENDERNESS REBOUND	15	8	7	7
Frisenda	1979	507547	USA	pregnant women	URINARY SYMPTOMS NOS	1	22	4	10
Frisenda	1979	507547	USA	pregnant women	DIARRHEA	6	17	3	11
Frisenda	1979	507547	USA	pregnant women	FEVER	1	22	4	10
Frisenda	1979	507547	USA	pregnant women	NAUSEA OR VOMITING OR ANOREXIA	21	2	13	1
Fuchs	2002	12127818	USA	mixed	CT	73	1	4	104
Fujii	2000	10841063	Japan	mixed	US	47	3	7	143
Funaki	1998	9762983	USA	mixed	CT	29	1	4	66
Gai	1988	3051464	Germany	mixed	US	19	6	8	227
Gaitini	2008	18430847	Israel	adults	CT	38	0	1	92
Gaitini	2008	18430847	Israel	adults	US	66	23	9	303
Galindo	1998	9462380	Spain	mixed	WBC	83	18	49	42

Galindo	1998	9462380	Spain	mixed	GUARDING	82	19	57	34
Galindo	1998	9462380	Spain	mixed	ABD XRAY	21	80	1	99
Galindo	1998	9462380	Spain	mixed	LEFT SHIFT	82	19	44	47
Galindo	1998	9462380	Spain	mixed	US	83	18	4	87
Galindo	1998	9462380	Spain	mixed	TENDERNESS REBOUND	61	40	40	51
Gallagher	2006	16953529	USA	adults	US	2	3	0	70
Gallagher	2006	16953529	USA	adults	CT	7	0	0	71
Gallagher	2006	16953529	USA	adults	US	1	6	0	71
Gallagher	2006	16953529	USA	adults	CT	5	0	0	70
Gamanagatti	2007	17245521	India	mixed	CT	46	2	0	4
Gamanagatti	2007	17245521	India	mixed	US	32	16	1	3
Ganguli	2006	16928971	USA	mixed	CT	70	4	6	261
Garcia	1987	3687874	USA	children	BARIUM ENEMA	3	11	1	3
Garcia	1987	3687874	USA	children	BARIUM ENEMA	3	11	0	4
Garcia	1987	3687874	USA	children	BARIUM ENEMA	11	3	2	2
Garcia	1987	3687874	USA	children	BARIUM ENEMA	10	4	1	3
Garcia	1987	3687874	USA	children	BARIUM ENEMA	3	11	1	3
Garcia	1987	3687874	USA	children	BARIUM ENEMA	4	10	1	3
Garcia	1987	3687874	USA	children	BARIUM ENEMA	4	10	1	3
Garcia	1987	3687874	USA	children	BARIUM ENEMA	13	1	2	2
Garcia	1987	3687874	USA	children	BARIUM ENEMA	12	0	1	1
Garcia Pena	2004	14702442	USA	children	CT + US	553	35	22	348
Garcia Pena	1999	10469767	USA	mixed	CT	41	1	1	31
Garcia-Aguayo	2000	11305565	Spain	mixed	US	83	7	4	5
Garcia-Aguayo	2000	11305565	Spain	mixed	US	150	13	12	185
Garcia-Aguayo	2000	11305565	Spain	mixed	US	67	6	8	180
Gendel	2011	21480165	Israel	children	VOMITING	417	235	18	16
Gendel	2011	21480165	Israel	children	DIARRHEA	59	593	4	30
Gendel	2011	21480165	Israel	children	PAIN DURATION	502	150	28	6
Gendel	2011	21480165	Israel	children	PERITONISM	541	111	26	8
Ghotbi	2006	17041792	Japan	children	CT	13	2	0	6
Giuliano	2005	16133622	USA	mixed	CT	21	0	0	446
Goldin	2011	21409546	USA	children	US	26	52	5	124
Goldin	2011	21409546	USA	children	US	44	34	2	127
Goldin	2011	21409546	USA	children	US	55	23	0	129
Goldin	2011	21409546	USA	children	US	71	6	0	127
Goldin	2011	21409546	USA	children	US	16	62	1	128
Goldin	2011	21409546	USA	children	US	77	0	57	70
Goldin	2011	21409546	USA	children	US	76	1	6	124
Goldin	2011	21409546	USA	children	US	69	9	7	122
Goldin	2011	21409546	USA	children	US	71	7	26	103

Goldin	2011	21409546	USA	children	US	70	8	6	123
Goldin	2011	21409546	USA	children	US	60	18	4	125
Goldin	2011	21409546	USA	children	US	71	7	11	118
Goldman	2008	18534219	Canada	children	PAIN MIGRATION	57	66	70	656
Goldman	2008	18534219	Canada	children	TENDERNESS RLO COUGH PERCUSSION HOPPING	88	35	68	658
Goldman	2008	18534219	Canada	children	PMNC COUNT	84	17	67	121
Goldman	2008	18534219	Canada	children	ANOREXIA	84	39	258	468
Goldman	2008	18534219	Canada	children	TENDERNESS RIF	98	25	122	604
Goldman	2008	18534219	Canada	children	WBC	98	14	84	112
Goldman	2008	18534219	Canada	children	NAUSEA OR VOMITING	92	31	335	391
Goldman	2008	18534219	Canada	children	FEVER	73	50	154	572
Golledge	1996	8659965	UK	mixed	TENDERNESS REBOUND	36	8	6	50
Golledge	1996	8659965	UK	women of reproductive age	PAIN MIGRATION	9	8	9	18
Golledge	1996	8659965	UK	mixed	ANOREXIA	28	16	30	26
Golledge	1996	8659965	UK	women of reproductive age	BOWEL DYSFUNCTION	3	14	11	16
Golledge	1996	8659965	UK	mixed	BOWEL DYSFUNCTION	12	32	26	30
Golledge	1996	8659965	UK	mixed	PAIN COUGH	36	8	28	28
Golledge	1996	8659965	UK	women of reproductive age	TENDERNESS PERCUSSION	9	8	5	22
Golledge	1996	8659965	UK	mixed	FEVER	31	13	17	39
Golledge	1996	8659965	UK	mixed	GUARDING	29	15	13	43
Golledge	1996	8659965	UK	mixed	CATS EYE IMAGING	35	9	27	29
Golledge	1996	8659965	UK	women of reproductive age	VOMITING	6	11	5	22
Golledge	1996	8659965	UK	women of reproductive age	TENDERNESS	17	0	26	1
Golledge	1996	8659965	UK	women of reproductive age	GUARDING	13	4	4	23
Golledge	1996	8659965	UK	mixed	TENDERNESS PERCUSSION	25	19	8	48
Golledge	1996	8659965	UK	women of reproductive age	PAIN COUGH	14	3	11	16
Golledge	1996	8659965	UK	mixed	TENDERNESS	44	0	52	4
Golledge	1996	8659965	UK	mixed	PAIN MIGRATION	18	26	20	36
Golledge	1996	8659965	UK	women of reproductive age	TENDERNESS RIF	15	2	2	25
Golledge	1996	8659965	UK	mixed	VOMITING	19	25	20	36
Golledge	1996	8659965	UK	women of reproductive age	CATS EYE IMAGING	14	3	10	17
Golledge	1996	8659965	UK	women of reproductive age	ANOREXIA	12	5	14	13
Golledge	1996	8659965	UK	women of reproductive age	FEVER	9	8	3	24
Goodman	1995	7887542	USA	adults	WBC	290	77	9	13
Goodman	1995	7887542	USA	adults	NEUTROPHIL:LYMPH	324	43	11	11
Gracey	2007	17467395	UK	mixed	US	102	6	19	200
Graham	1980	7356110	USA	young children	NAUSEA	116	39	11	17

Graham	1980	7356110	USA	young children	VOMITING	133	22	17	11
Graham	1980	7356110	USA	young children	TENDERNESS	152	3	21	7
Graham	1980	7356110	USA	young children	FEVER	144	11	17	11
Graham	1980	7356110	USA	young children	MASS ABDOMINAL	18	137	0	28
Graham	1980	7356110	USA	young children	DISTENTION	36	191	1	27
Graham	1980	7356110	USA	young children	DIARRHEA	24	131	4	24
Graham	1980	7356110	USA	young children	ANOREXIA	105	50	14	14
Graham	1980	7356110	USA	young children	TENDERNESS REBOUND	131	24	4	24
Graham	1980	7356110	USA	young children	PAIN	155	0	28	0
Graham	1991	1836403	USA	mixed	FEVER	7	18	10	44
Graham	1991	1836403	USA	mixed	WBC	22	3	30	24
Graham	1991	1836403	USA	mixed	TENDERNESS LOCALIZED	22	3	50	4
Graham	1991	1836403	USA	mixed	BOWEL SOUNDS	12	13	22	32
Graham	1991	1836403	USA	mixed	GUARDING	22	3	40	14
Gray	1988	2970820	UK	mixed	PAIN ABDOMINAL	5	48	19	86
Gronroos	1999	10552288	Finland	adults	WBC	90	10	64	36
Gronroos	1999	10552288	Finland	adults	WBC OR CRP	100	0	76	24
Gronroos	1999	10552288	Finland	adults	CRP	63	37	39	61
Gronroos	1999	10340286	Finland	adults	CRP OR PMNC COUNT	73	0	8	2
Groselj-Grenc	2007	17589979	Slovenia	children	WBC	36	13	11	22
Groselj-Grenc	2007	17589979	Slovenia	children	COMBINATION OF SIGNS + SYMPTOMS	46	3	22	11
Groselj-Grenc	2007	17589979	Slovenia	children	US	32	3	1	20
Groselj-Grenc	2007	17365999	Slovenia	children	IL-6	36	13	12	27
Groselj-Grenc	2007	17589979	Slovenia	children	IL-6	36	13	10	23
Groselj-Grenc	2007	17589979	Slovenia	children	CRP	36	13	15	18
Groselj-Grenc	2007	17365999	Slovenia	children	WBC	36	13	13	26
Groselj-Grenc	2007	17365999	Slovenia	children	CRP	36	13	18	21
Groselj-Grenc	2007	17365999	Slovenia	children	LBP	41	8	19	20
Gurian	2011	22040784	USA	mixed	CT	356	2	5	10
Gurian	2011	22040784	USA	mixed	CT	720	7	10	26
Gurian	2011	22040784	USA	mixed	CT	364	5	5	16
Gurleyik	1995	7497838	Turkey	mixed	CRP	87	3	2	16
Gurleyik	2002	12269920	Turkey	adults	IL-6	54	10	7	6
Gutierrez	1999	10551747	USA	mixed	US	18	0	1	4
Gutierrez	1999	10551747	USA	mixed	US	10	5	2	100
Gutierrez	1999	10551747	USA	mixed	US	18	2	13	92
Gwynn	2001	11489398	USA	mixed	TENDERNESS	143	0	53	19
Gwynn	2001	11489398	USA	mixed	TENDERNESS REBOUND	102	41	11	61
Gwynn	2001	11489398	USA	mixed	FEVER	116	27	43	29
Gwynn	2002	12217465	USA	mixed	CT	150	17	4	19
Gwynn	2001	11489398	USA	mixed	ANOREXIA	93	50	18	54

Gwynn	2001	11489398	USA	mixed	CT	129	14	4	68
Gwynn	2001	11489398	USA	mixed	LEFT SHIFT	133	10	24	48
Gwynn	2001	11489398	USA	mixed	WBC	139	4	28	44
Gwynn	2001	11489398	USA	mixed	PAIN MIGRATION	100	43	10	62
Gwynn	2001	11489398	USA	mixed	NAUSEA OR VOMITING	109	34	25	47
Hahn	1998	9561531	Germany	children	US	444	50	97	326
Hale	1997	9060580	USA	mixed	WBC	3867	430	392	261
Hale	1997	9060580	USA	mixed	FEVER	903	339	4	98
Hallan	1997	9248988	Norway	mixed	WBC	94	4	72	87
Hallan	1997	9231854	Norway	mixed	PAIN COUGH	81	30	92	101
Hallan	1997	9248988	Norway	mixed	GUARDING OR RIGIDITY	46	52	33	126
Hallan	1997	9248988	Norway	mixed	PREVIOUS ABDOMINAL SURGERY	7	17	91	142
Hallan	1997	9248988	Norway	mixed	NEUTROPHIL%	80	18	70	89
Hallan	1997	9231854	Norway	mixed	TENDERNESS REBOUND	86	25	83	110
Hallan	1997	9231854	Norway	mixed	PAIN MIGRATION	80	31	102	91
Hallan	1997	9248988	Norway	mixed	ANOREXIA	78	20	100	59
Hallan	1997	9248988	Norway	mixed	PAIN MIGRATION	74	24	84	75
Hallan	1997	9231854	Norway	mixed	ANOREXIA	88	23	124	69
Hallan	1997	9248988	Norway	mixed	PAIN MIGRATION	74	24	52	107
Hallan	1997	9248988	Norway	mixed	ESR	23	75	22	137
Hallan	1997	9248988	Norway	mixed	TENDERNESS	98	0	122	37
Hallan	1997	9231854	Norway	mixed	PAIN MIGRATION	80	31	66	127
Hallan	1997	9248988	Norway	mixed	CRP	78	20	76	83
Hallan	1997	9248988	Norway	mixed	TENDERNESS REBOUND	78	20	64	95
Hallan	1997	9231854	Norway	mixed	ABNORMAL URINATION	16	95	23	170
Hallan	1997	9248988	Norway	mixed	PAIN COUGH	74	24	79	80
Hallan	1997	9231854	Norway	mixed	NAUSEA OR VOMITING	87	24	133	60
Hallan	1997	9231854	Norway	mixed	GUARDING OR RIGIDITY	51	60	43	150
Hallan	1997	9248988	Norway	mixed	NAUSEA OR VOMITING	75	23	107	52
Hallan	1997	9248988	Norway	mixed	MICTURITION ABNORMAL	14	84	19	140
Hallan	1997	9231854	Norway	mixed	TENDERNESS RLQ	108	3	151	42
Haller	2010	19878040	Sweden	adults	ABD XRAY	0	0	0	42
Haller	2010	19878040	Sweden	adults	CT	2	0	0	74
Hallfeldt	1994	7934421	Germany	mixed	US	61	101	1	19
Hambidge	1990	2182159	UK	mixed	TEMPERATURE DIFFERENCE RLQ AND LLQ	14	8	0	3
Hansen	2004	15611455	USA	adults	CT	102	0	1	2
Harland	1991	2051426	UK	children	WBC	133	11	13	30
Hatch	1981	7252733	USA	children	BARIUM ENEMA	31	3	1	5
Hayden	1992	1588691	USA	children	US	53	1	2	77
Hebert	2005	17056904	USA	adults	CT	20	0	1	19

Hebert	2005	17056904	USA	adults	CT	11	0	3	26
Hee	1999	10405056	Denmark	pregnant women	PAIN RUQ	10	48	15	44
Hee	1999	10405056	Denmark	pregnant women	PAIN RLO	53	5	52	7
Hee	1999	10405056	Denmark	pregnant women	NAUSEA	44	14	34	25
Hee	1999	10405056	Denmark	pregnant women	PAIN WITH SUBJECTIVE CONTRACTION	7	48	2	55
Hekimoglu	2011	22191292	Turkey	adults	CT	30	2	2	66
Hekimoglu	2011	22191292	Turkey	adults	CT	52	5	5	138
Hekimoglu	2011	22191292	Turkey	adults	CT	31	1	1	67
Hekimoglu	2011	22191292	Turkey	adults	CT	48	10	9	133
Hekimoglu	2011	22191292	Turkey	adults	CT	21	4	4	71
Hekimoglu	2011	22191292	Turkey	adults	CT	18	8	7	67
Henneman	1990	2206141	USA	women of reproductive age	TENDERNESS REBOUND	11	15	28	51
Henneman	1988	3276246	USA	mixed	TENDERNESS REBOUND	17	10	20	55
Henneman	1988	3276246	USA	mixed	FEVER	10	17	25	50
Henneman	1990	2206141	USA	mixed	TENDERNESS CERVICAL MOTION	3	17	21	51
Henneman	1988	3276246	USA	mixed	WBC	20	7	47	28
Henneman	1990	2206141	USA	mixed	ANOREXIA	21	3	53	21
Henneman	1990	2206141	USA	mixed	TENDERNESS RECTAL	8	16	21	51
Henneman	1990	2330248	USA	children	TC99M NUCLEAR	7	0	2	16
Henneman	1988	3276246	USA	mixed	TC99M NUCLEAR	17	2	5	61
Henneman	1988	3276246	USA	mixed	TENDERNESS RLO	26	1	70	75
Henneman	1988	3276246	USA	women of reproductive age	TC99M NUCLEAR	3	1	4	28
Henneman	1990	2330248	USA	children	TENDERNESS RLO REBOUND	6	4	4	19
Henneman	1990	2206141	USA	mixed	PAIN MIGRATION	11	15	17	59
Henneman	1990	2330248	USA	children	ANOREXIA	8	15	2	4
Henneman	1990	2330248	USA	children	PAIN MIGRATION	6	6	4	15
Henneman	1990	2330248	USA	children	TENDERNESS RECTAL	6	5	4	19
Henneman	1990	2206141	USA	mixed	TC99M NUCLEAR	16	1	5	36
Henneman	1990	2330248	USA	children	TENDERNESS RLO	9	21	1	2
Henneman	1988	3276246	USA	mixed	PAIN MIGRATION	18	9	23	52
Henneman	1990	2206141	USA	mixed	TENDERNESS RLO	25	1	77	6
Herliczek	2012	23617477	USA	children	MRI	10	0	2	48
Hernandez	2005	15635471	USA	children	CT OR US	133	0	4	42
Hernandez	2005	15635471	USA	children	ABD XRAY	65	0	16	152
Hernandez	2008	18358937	USA	adults	U-5-HIAA	28	35	3	6
Hernandez	2008	18358937	USA	adults	U-5-HIAA	28	34	11	19
Hernandez	2008	18358937	USA	adults	U-5-HIAA	40	24	19	9
Hernandez	2008	18358937	USA	adults	U-5-HIAA	23	13	11	5
Hernandez	2008	18358937	USA	adults	U-5-HIAA	15	21	6	10

Hernandez	2008	18358937	USA	adults	U-5-HIAA	42	21	5	4
Hernandez	2008	18358937	USA	adults	U-5-HIAA	42	22	17	11
Hernandez	2008	18358937	USA	adults	U-5-HIAA	64	0	8	28
Hernandez	2008	18358937	USA	adults	U-5-HIAA	26	38	10	18
Hershko	2007	17566826	Israel	adults	CT	43	0	5	36
Hershko	2007	17566826	Israel	adults	CT	19	2	5	30
Hershko	2002	12455796	Israel	adults	CT	67	5	7	118
Hershko	2007	17566826	Israel	adults	CT	37	2	3	36
Heverhagen	2012	22033948	Germany	adults	MRI	10	3	1	38
Heverhagen	2012	22033948	Germany	adults	MRI	11	2	1	38
Himeno	2003	12880303	Japan	mixed	US	83	2	10	47
Hoecker and Billman	2005	15837022	USA	children	CT	42	4	2	59
Holloway	2003	14672779	USA	mixed	CT	188	3	6	226
Hong	2003	14588157	USA	women of reproductive age	CT	5	0	2	22
Hong	2003	14588157	USA	adults	CT	30	3	3	42
Hormann	2003	12764662	Austria	children	US	17	3	6	44
Hormann	1998	9694477	Austria	children	MRI	20	0	0	0
Hormann	2003	12764662	Austria	children	US	0	0	1	2
Hormann	2003	12764662	Austria	children	US	19	4	8	48
Hormann	2003	12764662	Austria	children	US	2	1	1	2
Horton	2000	10930484	USA	adults	US	23	2	1	3
Horton	2000	10930484	USA	adults	CT	37	1	2	9
Howie	1984	6481676	Scotland	mixed	FEVER	93	90	222	104 8
Hsieh	2010	20466403	Taiwan	adults	ANOREXIA	45	70	14	51
Hsieh	2010	20466403	Taiwan	adults	NAUSEA OR VOMITING	55	60	26	39
Hsieh	2010	20466403	Taiwan	adults	DIARRHEA	0	115	3	62
Hsieh	2010	20466403	Taiwan	adults	CT	8	0	0	2
Hsieh	2010	20466403	Taiwan	adults	TENDERNESS RLO	112	3	60	5
Hsieh	2010	20466403	Taiwan	adults	PAIN REBOUND	84	31	17	48
Hsieh	2010	20466403	Taiwan	adults	PAIN RIGHT FLANK	0	115	3	62
Hsieh	2010	20466403	Taiwan	adults	PAIN MIGRATION	63	52	20	45
Hsieh	2010	20466403	Taiwan	adults	PAIN PROGRESSION	109	6	51	14
Huynh	2007	17983068	USA	mixed	CT	207	35	19	14
Incesu	2004	15081132	Turkey	mixed	US	35	0	1	14
Incesu	1997	9057512	Turkey	mixed	US	26	8	3	23
Incesu	1997	9057512	Turkey	mixed	US	33	1	2	24
Incesu	2004	15081132	Turkey	mixed	US	26	9	1	11
Inci	2011	20655156	Turkey	mixed	MRI	55	2	3	25
Inci	2011	20924585	Turkey	mixed	MRI	78	13	0	27
Isman	2010	20172058	Turkey	adults	VISTAFIN	20	4	1	9

Israel	2008	18666160	USA	pregnant women	MRI	4	0	0	13
Israel	2008	18666160	USA	pregnant women	US	1	1	0	2
Ives	2008	18620120	USA	mixed	CT	40	1	14	12
Ives	2008	18620120	USA	mixed	CT	34	7	3	23
Izbicki	1992	1352137a	Germany	mixed	GUARDING	7	47	3	93
Izbicki	1992	1352137a	Germany	mixed	TENDERNESS REBOUND	43	11	42	54
Izbicki	1992	1352137b	Germany	mixed	VOMITING	110	167	46	138
Izbicki	1992	1352137b	Germany	mixed	GUARDING	139	138	51	133
Izbicki	1992	1352137b	Germany	mixed	ROVSING SIGN	14	180	7	136
Izbicki	1992	1352137b	Germany	mixed	WBC	17	260	55	159
Izbicki	1992	1352137a	Germany	mixed	PAIN RLQ	53	1	94	2
Izbicki	1992	1352137b	Germany	mixed	RECTAL TEMPERATURE	113	164	25	159
Izbicki	1992	1352137a	Germany	mixed	PAIN DURATION	35	19	30	66
Izbicki	1992	1352137b	Germany	mixed	WBC	210	67	74	110
Izbicki	1992	1352137b	Germany	mixed	PAIN DURATION	164	113	61	123
Izbicki	1992	1352137a	Germany	mixed	ROVSING SIGN	12	42	4	92
Izbicki	1992	1352137b	Germany	mixed	TENDERNESS RECTAL TEMPERATURE DIFFERENCE AXILLARY AND RECTAL	136	413	89	95
Izbicki	1992	1352137b	Germany	mixed		69	208	29	155
Izbicki	1992	1352137a	Germany	mixed	PSOAS SIGN	8	46	3	93
Izbicki	1992	1352137b	Germany	mixed	PSOAS SIGN	12	159	10	113
Izbicki	1992	1352137a	Germany	mixed	GUARDING LOCALIZED	24	30	15	81
Izbicki	1992	1352137a	Germany	mixed	PAIN MIGRATION	24	30	15	81
Izbicki	1992	1352137b	Germany	mixed	FEVER	83	194	16	168
Izbicki	1992	1352137b	Germany	mixed	MCBURNEY SIGN	268	9	177	7
Izbicki	1992	1352137b	Germany	mixed	TENDERNESS REBOUND	151	126	71	113
Izbicki	1992	1352137a	Germany	mixed	WBC	40	14	34	62
Jacobs	2001	11526267	USA	mixed	CT	43	8	11	148
Jacobs	2001	11526267	USA	mixed	CT	45	6	6	153
Jacobs	2001	11526267	USA	mixed	CT	47	4	10	149
Jacobs	2001	11526267	USA	mixed	CT	36	15	3	156
Jacobs	2001	11526267	USA	mixed	CT	38	13	12	147
Jacobs	2001	11526267	USA	mixed	CT	47	4	8	151
Jahn	1997	9231855	Denmark	mixed	FEVER	66	28	70	58
Jahn	1997	9231855	Denmark	mixed	CHILLS	36	58	45	83
Jahn	1997	9231855	Denmark	mixed	PAIN MIGRATION	83	11	87	41
Jahn	1997	9231855	Denmark	mixed	ANOREXIA	79	15	84	44
Jahn	1997	9231855	Denmark	mixed	FEVER	9	85	12	116
Jahn	1997	9231855	Denmark	mixed	PAIN DURATION	81	13	100	28
Jahn	1997	9231855	Denmark	mixed	WBC	78	16	41	87
Jahn	1997	9231855	Denmark	mixed	PAIN ABRUPT	11	83	32	96

Jahn	1997	9231855	Denmark	mixed	NAUSEA	64	30	77	51
Jahn	1997	9231855	Denmark	mixed	TENDERNESS RECTAL	47	47	56	72
Jahn	1997	9231855	Denmark	mixed	PULSE	29	65	31	97
Jahn	1997	9231855	Denmark	mixed	TENDERNESS RLQ	37	57	67	61
Jahn	1997	9231855	Denmark	mixed	TENDERNESS	64	30	54	74
Jahn	1997	9231855	Denmark	mixed	PAIN PROGRESSION	79	15	67	61
Jahn	1997	9231855	Denmark	mixed	PAIN COUGH	80	14	79	49
Jahn	1997	9231855	Denmark	mixed	US	38	40	14	101
Jahn	1997	9231855	Denmark	mixed	FEVER	52	42	58	70
Jahn	1997	9231855	Denmark	mixed	DIARRHEA	19	75	35	93
Jahn	1997	9231855	Denmark	mixed	VOMITING	46	48	40	88
Jahn	1997	9231855	Denmark	mixed	PAIN MIGRATION	68	26	49	79
Jahn	1997	9231855	Denmark	mixed	PAIN DURATION	14	80	24	104
Jahn	1997	9231855	Denmark	mixed	GUARDING OR RIGIDITY	37	57	20	108
Jang	2010	19144480	Korea	mixed	US	39	0	1	62
Jang	2011	21835887	Korea	pregnant women	MRI	5	0	0	13
Jang	2010	19144480	Korea	mixed	CT	26	7	9	45
Jangjoo	2012	21450436	Iran	mixed	U-5-HIAA	26	33	2	9
Jangjoo	2011	21954737	Iran	mixed	NEUTROPHIL%	69	14	8	11
Jangjoo	2011	21954737	Iran	mixed	WBC	71	12	7	12
Jangjoo	2011	21954737	Iran	mixed	CRP	49	34	6	13
Jaremko	2011	20493658	Canada	children	US	41	0	5	35
Jaremko	2011	20493658	Canada	children	US	30	5	8	60
Jaremko	2011	20493658	Canada	children	US	23	6	3	54
Jaremko	2011	20493658	Canada	children	US	43	21	5	120
Jaremko	2011	20493658	Canada	children	CT	5	0	1	12
Jaremko	2011	20493658	Canada	children	US	56	8	14	111
Jaremko	2011	20493658	Canada	children	US	20	15	2	66
Jaremko	2011	20493658	Canada	children	US	26	3	6	51
Jawaid	1999	10647233	Pakistan	adults	ANOREXIA	203	148	9	41
Jawaid	1999	10647233	Pakistan	adults	TENDERNESS REBOUND	298	53	26	24
Jawaid	1999	10647233	Pakistan	adults	PAIN MIGRATION	274	77	24	26
Jawaid	1999	10647233	Pakistan	adults	FEVER	157	194	14	36
Jawaid	1999	10647233	Pakistan	adults	VOMITING	229	122	21	29
Jawaid	1999	10647233	Pakistan	adults	GUARDING	236	115	15	35
Jawaid	1999	10647233	Pakistan	adults	NEUTROPHIL%	275	76	19	31
Jawaid	1999	10647233	Pakistan	adults	PAIN EPIGASTRIC	78	273	2	48
Jawaid	1999	10647233	Pakistan	adults	WBC	311	40	24	26
Je	2009	19533813	South Korea	children	US	41	7	5	116
Je	2009	19533813	South Korea	children	US	39	4	8	113
Jeffrey	1988	3282253	USA	mixed	US	80	9	6	150

Jeffrey	1987	3547490	USA	mixed	US	25	0	3	0
Jeffrey	1988	3282253	USA	mixed	US	78	2	6	5
Jeffrey	1987	3547490	USA	women of reproductive age	US	6	1	0	0
Johansson	2007	17453494	Sweden	mixed	US	24	5	1	54
Johansson	2007	17453494	Sweden	mixed	CT	32	3	2	31
John	2011	21786842	India	adults	TENDERNESS RIF	193	107	45	0
John	1993	8511921	Switzerland	mixed	PAIN PERCUSSION	36	19	15	41
John	1993	8511921	Switzerland	mixed	US	43	12	15	41
John	2011	21786842	India	adults	PAIN ABDOMINAL	193	0	45	0
John	1993	8511921	Switzerland	mixed	HYPOECHOIC PERIAPPENDICULAR ZONE	26	29	4	51
John	2011	21786842	India	adults	PAIN MIGRATION	104	89	17	28
John	2011	21786842	India	adults	CRP	190	3	6	39
John	1993	8511921	Switzerland	mixed	BOWEL DYSFUNCTION	10	45	13	43
John	2011	21786842	India	adults	WBC	143	50	17	28
John	2011	21786842	India	adults	PULSE	131	62	6	39
John	1993	8511921	Switzerland	mixed	TENDERNESS RECTAL	29	26	26	30
John	2011	21786842	India	adults	US	106	87	11	34
John	2011	21786842	India	adults	MURPHY SIGN	64	129	5	40
John	2011	21786842	India	women of reproductive age	CRP	76	2	2	26
John	1993	8511921	Switzerland	mixed	PAIN MIGRATION	44	11	8	48
John	1993	8511921	Switzerland	mixed	GUARDING	42	13	14	42
John	1993	8511921	Switzerland	mixed	US	34	21	17	39
John	2011	21786842	India	adults	VOMITING	114	79	25	20
John	1993	8511921	Switzerland	mixed	NAUSEA	40	15	30	26
John	1993	8511921	Switzerland	mixed	GRANULOCYTE%	24	31	30	26
John	1993	8511921	Switzerland	mixed	IMMATURE CELLS	27	28	16	40
John	1993	8511921	Switzerland	mixed	TENDERNESS REBOUND	50	5	29	27
John	2011	21786842	India	adults	ANOREXIA	107	86	28	17
John	2011	21786842	India	adults	FEVER	79	114	8	37
John	2011	21786842	India	adults	GUARDING	105	88	19	26
John	2011	21786842	India	adults	FEVER	79	114	8	37
John	2011	21786842	India	adults	NEUTROPHIL%	159	79	12	33
John	2011	21786842	India	adults	TENDERNESS REBOUND	159	34	24	21
John	1993	8511921	Switzerland	mixed	PSOAS SIGN	23	32	12	44
Johnson	2009	19304692	USA	adults	CT	13	4	0	194
Johnson	2009	19304692	USA	adults	CT	14	3	5	189
Johnson	2009	19304692	USA	adults	CT	14	3	0	194
Johnson	2012	22623558	USA	children	MRI	48	0	1	119
Johnson	2012	22623558	USA	children	CT OR US	48	0	2	118
Johnson	2009	19304692	USA	adults	CT	13	4	1	193

Johnson	2009	19304692	USA	adults	CT	15	2	6	188
Johnson	2009	19304692	USA	adults	CT	14	3	3	191
Jones	2004	15619494	USA	women of reproductive age	CT	68	0	8	4
Jones	2004	15619494	USA	adults	CT	231	0	11	10
Jorulf	1996	8796514	Sweden	children	US	20	4	1	49
Josephson	2000	11016772	Sweden	mixed	US	46	14	13	69
Josephson	2000	11016772	Sweden	mixed	US	50	10	10	72
Josephson	2000	11016772	Sweden	mixed	US	7	12	0	20
Josephson	2000	11016772	Sweden	mixed	US	31	10	7	55
Kafetzis	2005	15995845	Greece	children	FEVER	65	88	18	40
Kafetzis	2005	15995845	Greece	children	NEUTROPHIL%	92	60	21	32
Kafetzis	2005	15995845	Greece	children	PROCALCITONIN	49	105	6	52
Kafetzis	2005	15995845	Greece	children	US	154	0	13	45
Kafetzis	2005	15995845	Greece	children	RIGIDITY ABDOMINAL	84	70	9	44
Kafetzis	2005	15995845	Greece	children	VOMITING	93	61	19	39
Kafetzis	2005	15995845	Greece	children	CRP	36	113	6	46
Kafetzis	2005	15995845	Greece	children	WBC	115	37	22	31
Kafetzis	2005	15995845	Greece	children	DIARRHEA	24	130	11	47
Kaidu	2008	18301980	Japan	mixed	CT	86	1	3	9
Kailidou	2006	16612913	Greece	adults	CT	69	3	2	75
Kaiser	2004	15031433	Sweden	children	CT	124	5	11	166
Kaiser	2004	15031433	Sweden	children	CT	108	21	16	161
Kaiser	2002	12034928	Sweden	children	CT	131	4	12	170
Kaiser	2004	15031433	Sweden	children	CT	88	41	11	166
Kaiser	2004	15031433	Sweden	children	CT	107	22	15	162
Kaiser	2002	12034928	Sweden	children	US	196	48	20	336
Kaiser	2004	15031433	Sweden	children	CT	126	3	11	166
Kaiser	2004	15031433	Sweden	children	CT	116	13	3	174
Kaiser	2004	15031433	Sweden	children	CT	93	36	6	171
Kaiser	2004	15031433	Sweden	children	CT	74	55	6	171
Kaiser	2004	15031433	Sweden	children	CT	116	13	7	170
Kamel	2000	11012439	USA	adults	CT	23	1	0	76
Kamran	2008	19610521	Pakistan	mixed	PMNC COUNT	62	19	5	14
Kan	2001	11770917	USA	adults	US	3	1	2	25
Kan	2001	11770917	USA	adults	CT	4	0	2	25
Kan	2001	11770917	USA	adults	US	2	2	1	26
Kaneko	2004	15359383	Japan	children	US	31	63	3	69
Kang	1989	2644718	Taiwan	adults	US	36	6	0	20
Kangegaye	1995	8570450	USA	children	TC99M NUCLEAR	4	3	10	6
Kangegaye	1995	8570450	USA	children	TC99M NUCLEAR	2	5	7	9
Kao	1996	8896923	China	mixed	TC99M NUCLEAR	28	2	2	18

Kapan	2013	23588974	Turkey	pregnant women	US	7	0	0	0
Kapoor	2010	20498461	India	mixed	US	22	3	0	15
Kapoor	2010	20498461	India	mixed	ELASTOGRAPHY	25	0	0	15
Karakas	2000	10663520	USA	children	US	32	12	10	180
Karakas	2000	10663520	USA	children	CT	53	8	3	107
Karstrup	1986	3533202	Denmark	mixed	US	24	5	1	16
Karstrup	1986	3533202	Denmark	adults	US	24	0	1	0
Kaya	2012	23236260	Turkey	adults	D-dimer	21	53	1	3
Kaya	2012	23236260	Turkey	adults	CRP	53	21	1	3
Kaya	2012	23236260	Turkey	adults	PROCALCITONIN	18	56	2	2
Kaya	2012	23236260	Turkey	adults	WBC	63	11	3	1
									40.0
Kentsis	2010	19556024	USA	children	CT	14	5	1.98	108
Kentsis	2012	22305331	USA	children	NAUSEA + VOMITING	13	11	9	16
Kentsis	2012	22305331	USA	children	US	15	9	3	22
Kentsis	2010	19556024	USA	children	PAIN RLO OR TENDERNESS RLO	25	0	39.9	2.1
								20.1	21.8
Kentsis	2010	19556024	USA	children	FEVER	13	12	6	4
Kentsis	2012	22305331	USA	children	CT	24	0	3	22
Kentsis	2012	22305331	USA	children	FEVER	11	13	13	12
Kentsis	2012	22305331	USA	children	PAIN RLO FOCAL	20	4	12	13
								10.9	
Kentsis	2010	19556024	USA	children	US	14.08	2	0	42
Kentsis	2012	22305331	USA	children	PAIN MIGRATION	15	9	7	18
									36.1
Kentsis	2010	19556024	USA	children	PAIN MIGRATION	9	16	5.88	2
								21.8	20.1
Kentsis	2010	19556024	USA	children	NAUSEA OR VOMITING	18	7	4	6
Kepner	2012	22633722	USA	adults	CT	41	0	1	72
Kepner	2012	22633722	USA	adults	CT	38	0	4	74
Keskek	2008	18774040	Turkey	adults	WBC + NEUTROPHIL%	342	96	38	64
Keskek	2008	18774040	Turkey	adults	WBC + NEUTROPHIL%	248	190	19	83
Keskek	2008	18774040	Turkey	adults	WBC + NEUTROPHIL%	298	140	25	77
Keskek	2008	18774040	Turkey	adults	WBC + NEUTROPHIL%	368	70	48	54
Keskek	2008	18774040	Turkey	adults	WBC + NEUTROPHIL%	269	169	22	80
Kessler	2004	14688403	France	mixed	WBC	44	25	13	43
Kessler	2004	14688403	France	mixed	WBC OR CRP	51	6	36	32
Kessler	2004	14688403	France	mixed	US	54	1	1	48
Kessler	2004	14688403	France	mixed	US	14	43	8	60
Kessler	2004	14688403	France	mixed	US	29	28	20	48
Kessler	2004	14688403	France	mixed	CRP	34	23	22	46
Kessler	2004	14688403	France	mixed	WBC + CRP	27	30	11	57
Kessler	2004	14688403	France	mixed	US	53	2	2	47

Kessler	2004	14688403	France	mixed	US	18	39	26	42
Kessler	2004	14688403	France	mixed	US	52	5	16	52
Kessler	2004	14688403	France	mixed	US	29	26	4	45
Kessler	2004	14688403	France	mixed	US	28	26	2	47
Keyzer	2009	19843741	Belgium	adults	CT	13	0	2	50
Keyzer	2005	16040910	Belgium	mixed	CT	8	22	14	50
Keyzer	2004	15155894	Belgium	mixed	CT	28	1	5	61
Keyzer	2005	16040910	Belgium	mixed	US	24	6	21	43
Keyzer	2004	15155894	Belgium	mixed	CT	7	22	9	57
Keyzer	2004	15155894	Belgium	mixed	CT	10	19	6	60
Keyzer	2009	19843741	Belgium	adults	CT	17	3	1	45
Keyzer	2004	15155894	Belgium	mixed	CT	8	21	45	21
Keyzer	2005	16040910	Belgium	mixed	CT	2	28	8	56
Keyzer	2004	15155894	Belgium	mixed	CT	4	25	39	27
Keyzer	2004	15155894	Belgium	mixed	CT	28	1	15	51
Keyzer	2005	16040910	Belgium	mixed	CT	22	8	4	60
Keyzer	2004	15155894	Belgium	mixed	CT	29	0	55	11
Keyzer	2009	19843741	Belgium	adults	CT	17	3	4	42
Keyzer	2004	15155894	Belgium	mixed	CT	4	25	1	65
Keyzer	2005	16040910	Belgium	mixed	US	16	14	14	50
Keyzer	2004	15155894	Belgium	mixed	CT	10	19	8	58
Keyzer	2004	15155894	Belgium	mixed	CT	9	20	2	64
Keyzer	2005	16040910	Belgium	mixed	US	25	5	8	56
Keyzer	2009	19843741	Belgium	adults	CT	11	2	1	51
Keyzer	2005	16040910	Belgium	mixed	CT	27	3	6	58
Keyzer	2009	19843741	Belgium	adults	CT	11	2	2	50
Keyzer	2004	15155894	Belgium	mixed	CT	9	20	4	62
Keyzer	2005	16040910	Belgium	mixed	US	22	8	8	56
Keyzer	2009	19843741	Belgium	adults	CT	11	2	2	50
Keyzer	2005	16040910	Belgium	mixed	US	5	25	2	62
Keyzer	2005	16040910	Belgium	mixed	US	17	13	4	60
Keyzer	2009	19843741	Belgium	adults	CT	13	0	0	52
Keyzer	2009	19843741	Belgium	adults	CT	13	0	6	46
Keyzer	2004	15155894	Belgium	mixed	CT	28	1	17	49
Keyzer	2004	15155894	Belgium	mixed	CT	28	1	15	51
Keyzer	2005	16040910	Belgium	mixed	CT	25	5	4	60
Keyzer	2004	15155894	Belgium	mixed	CT	4	25	2	64
Keyzer	2004	15155894	Belgium	mixed	CT	29	0	55	11
Keyzer	2004	15155894	Belgium	mixed	CT	4	25	1	65
Keyzer	2005	16040910	Belgium	mixed	US	0	30	2	62
Keyzer	2004	15155894	Belgium	mixed	CT	4	25	1	65

Keyzer	2005	16040910	Belgium	mixed	US	25	5	26	38
Keyzer	2005	16040910	Belgium	mixed	CT	27	3	10	54
Keyzer	2005	16040910	Belgium	mixed	US	2	28	2	62
Keyzer	2004	15155894	Belgium	mixed	CT	29	0	52	14
Keyzer	2009	19843741	Belgium	adults	CT	13	0	2	50
Keyzer	2009	19843741	Belgium	adults	CT	16	20	0	46
Keyzer	2005	16040910	Belgium	mixed	US	23	7	8	56
Keyzer	2005	16040910	Belgium	mixed	CT	3	27	37	27
Keyzer	2005	16040910	Belgium	mixed	US	24	6	34	30
Keyzer	2009	19843741	Belgium	adults	CT	16	4	3	43
Keyzer	2004	15155894	Belgium	mixed	CT	29	0	12	54
Keyzer	2004	15155894	Belgium	mixed	CT	28	1	5	61
Keyzer	2005	16040910	Belgium	mixed	CT	0	30	2	62
Keyzer	2005	16040910	Belgium	mixed	US	22	8	10	54
Keyzer	2005	16040910	Belgium	mixed	US	0	30	0	64
Keyzer	2004	15155894	Belgium	mixed	CT	10	19	10	56
Keyzer	2004	15155894	Belgium	mixed	CT	29	0	13	53
Keyzer	2005	16040910	Belgium	mixed	CT	10	20	4	60
Keyzer	2005	16040910	Belgium	mixed	US	17	13	14	50
Keyzer	2005	16040910	Belgium	mixed	US	5	25	0	64
Keyzer	2009	19843741	Belgium	adults	CT	14	6	0	46
Keyzer	2005	16040910	Belgium	mixed	US	27	3	0	64
Keyzer	2005	16040910	Belgium	mixed	US	4	26	0	64
Keyzer	2009	19843741	Belgium	adults	CT	12	1	2	50
Keyzer	2004	15155894	Belgium	mixed	CT	28	1	14	52
Keyzer	2009	19843741	Belgium	adults	CT	17	3	1	45
Keyzer	2004	15155894	Belgium	mixed	CT	5	24	40	26
Keyzer	2005	16040910	Belgium	mixed	CT	26	4	5	59
Keyzer	2004	15155894	Belgium	mixed	CT	6	23	5	61
Keyzer	2004	15155894	Belgium	mixed	CT	6	23	5	61
Keyzer	2004	15155894	Belgium	mixed	CT	8	21	46	20
Keyzer	2009	19843741	Belgium	adults	CT	15	5	3	43
Keyzer	2004	15155894	Belgium	mixed	CT	29	0	57	9
Keyzer	2005	16040910	Belgium	mixed	US	5	25	2	62
Keyzer	2009	19843741	Belgium	adults	CT	15	5	3	43
Keyzer	2005	16040910	Belgium	mixed	CT	10	20	53	11
Keyzer	2005	16040910	Belgium	mixed	CT	3	27	0	64
Keyzer	2005	16040910	Belgium	mixed	US	30	0	14	50
Keyzer	2005	16040910	Belgium	mixed	CT	3	27	8	56
Khan	2012	23304513	USA	children	BOWEL SOUNDS	19	3	28	0
Khan	2012	23304513	USA	children	TENDERNESS REBOUND	15	7	9	19

Khan	2012	23304513	USA	children	PROCALCITONIN	6	16	2	26
Khan	2012	23304513	USA	children	FEVER	9	13	10	18
Khan	2006	18603920	Nepal	mixed	ALT + SGPT	11	33	0	1
Khan	2008	18769079	Nepal	mixed	SERUM BILIRUBIN	87	19	0	4
Khan	2012	23304513	USA	children	ANOREXIA	19	3	19	9
Khan	2004	15631364	Scotland	mixed	CRP	168	54	6	31
Khan	2006	18603920	Nepal	mixed	AST + SGOT	16	28	0	1
Khan	2006	18603920	Nepal	mixed	SERUM BILIRUBIN	39	3	0	1
Khan	2012	23304513	USA	children	GUARDING	13	9	10	18
Khan	2012	23304513	USA	children	VOMITING	16	6	17	11
Khan	2006	18603920	Nepal	mixed	ALP	22	22	0	1
Khan	2004	15631364	Scotland	mixed	WBC	185	37	14	23
Khan	2012	23304513	USA	children	CT	21	1	1	17
Khan	2012	23304513	USA	children	TENDERNESS RLQ	22	0	26	2
Khanal	2008	18604118	Nepal	mixed	US	102	17	0	1
Kharbanda	2012	22221321	USA	children	S100A9	58	0	86	32
Kharbanda	2005	16140712	USA	children	PAIN COUGH PERCUSSION HOPPING	122	35	103	165
Kharbanda	2005	16140712	USA	children	VOMITING	101	56	113	155
Kharbanda	2005	16140712	USA	children	TENDERNESS REBOUND	83	74	54	214
Kharbanda	2011	21676053	USA	children	NEUTROPHIL COUNT	85	9	34	134
Kharbanda	2005	16140712	USA	children	TENDERNESS RECTAL	42	115	25	243
Kharbanda	2011	21676053	USA	children	CRP	82	12	22	144
Kharbanda	2011	21676053	USA	children	IL-6	77	17	52	113
Kharbanda	2005	16140712	USA	children	NEUTROPHIL COUNT	152	5	131	137
Kharbanda	2011	21676053	USA	children	CRP	87	7	119	47
Kharbanda	2005	16140712	USA	children	PAIN INTERMITTENT	32	125	113	155
Kharbanda	2011	21676053	USA	children	IL-8	39	55	22	143
Kharbanda	2012	22221321	USA	children	URINE LRG	58	0	91	27
Kharbanda	2011	21676053	USA	children	CRP	94	0	73	93
Kharbanda	2012	22221321	USA	children	SERUM LRG	58	0	77	41
Kharbanda	2005	16140712	USA	children	PAIN MIGRATION	71	86	65	203
Kharbanda	2005	16140712	USA	children	OBTURATOR SIGN	45	112	35	233
Kharbanda	2005	16140712	USA	children	WBC	153	4	162	106
Kharbanda	2005	16140712	USA	children	TENDERNESS RLQ	125	32	159	109
Kharbanda	2005	16140712	USA	children	PSOAS SIGN	56	101	38	230
Kharbanda	2011	21676053	USA	children	WBC	90	4	52	130
Kharbanda	2005	16140712	USA	children	UNABLE TO WALK OR LIMPING	125	32	126	142
Kharbanda	2005	16140712	USA	children	ROVSING SIGN	47	110	42	226
Kharbanda	2007	17456874	USA	children	CT	87	6	10	112
Kharbanda	2011	21676053	USA	children	IL-6	90	4	48	117
Kharbanda	2005	16140712	USA	children	BOWEL SOUNDS	106	51	232	36

Kharbanda	2005	16140712	USA	children	ANOREXIA	118	39	149	119
Kharbanda	2007	17456874	USA	children	CT	66	4	4	112
Kharbanda	2011	21676053	USA	children	NEUTROPHIL COUNT	86	8	56	112
Kharbanda	2011	21676053	USA	children	IL-6	86	8	68	97
Kharbanda	2011	21676053	USA	children	NEUTROPHIL COUNT	65	29	43	125
Kharbanda	2005	16140712	USA	children	PAIN ABRUPT	69	88	114	154
Kharbanda	2011	21676053	USA	children	IL-8	5	89	30	135
Kharbanda	2005	16140712	USA	children	TENDERNESS CVA	14	143	27	241
Kharbanda	2005	16140712	USA	children	PAIN DURATION	94	63	125	143
Kharbanda	2005	16140712	USA	children	NAUSEA	129	28	159	109
Kharbanda	2005	16140712	USA	children	DIARRHEA	24	133	58	210
Kharbanda	2012	22221321	USA	children	WBC	58	0	68	50
Kharbanda	2005	16140712	USA	children	PAIN RLO	121	36	150	118
Kharbanda	2011	21676053	USA	children	IL-8	61	33	61	104
Kharbanda	2011	21676053	USA	children	WBC	64	30	36	146
Kharbanda	2011	21676053	USA	children	WBC	94	0	49	133
Kharbanda	2005	16140712	USA	children	GUARDING	97	60	100	168
Kim	2009	19098194	Korea	children	CT	30	2	3	26
Kim	2011	21123307	Korea	adults	CRP	97	9	9	13
Kim	2008	18660392	Korea	adults	CT	88	2	3	64
Kim	2011	21123307	Korea	adults	WBC + CRP	106	0	3	19
Kim	2011	21633052	Korea	adults	CT	80	10	2	150
Kim	2011	21123307	Korea	adults	WBC	79	27		
Kim	2011	21633052	Korea	adults	CT	44	6	0	74
Kim	2009	19070557	USA	children	WBC	106	15	7	2
Kim	2012	22533576	South Korea	mixed	CT	171	9	16	244
Kim	2009	19070557	USA	children	WBC + CRP	73	48	3	6
Kim	2008	18022782	Korea	mixed	CT	210	16	3	13
Kim	2009	19098194	Korea	children	CT	31	1	2	27
Kim	2009	19070557	USA	children	CRP	83	38	4	5
Kim	2012	22533576	South Korea	mixed	CT	156	9	18	250
Kim	2011	21633052	Korea	adults	CT	36	4	2	76
Kipper	2000	10716317	USA	mixed	TC99M NUCLEAR	26	0	4	19
Kirkil	2013	23588973	Turkey	mixed	US	3	3	1	15
Kirkil	2013	23588973	Turkey	mixed	US	40	13	16	45
Kirshenbaum	2003	12592478	USA	mixed	CT	48	0	1	4
Kitagawa	2009	22470667	Japan	mixed	CT	45	0	14	12
Kitagawa	2009	22470667	Japan	mixed	CT	10	0	1	3
Klein	2001	11528609	USA	children	GUARDING + ANOREXIA	5	10	0	47
Klein	2001	11528609	USA	children	GUARDING	8	13	5	57
Klein	2001	11528609	USA	children	GUARDING	8	20	21	203

Klein	2001	11528609	USA	children	TENDERNESS + VOMITING	17	5	38	73
Klein	2001	11528609	USA	children	TENDERNESS	22	0	111	95
Klein	2001	11528609	USA	children	GUARDING + FEVER	20	1	4	199
Kniskern	1985	3513683	USA	mixed	US	3	2	0	15
Ko	1995	8592927	Taiwan	children	CRP	19	8	7	13
Ko	1995	8592927	Taiwan	children	LEFT SHIFT	22	5	6	14
Ko	1995	8592927	Taiwan	children	CRP	14	13	1	19
Ko	1995	8592927	Taiwan	children	ESR	11	16	3	17
Ko	1995	8592927	Taiwan	children	US	23	4	0	20
Ko	1995	8592927	Taiwan	children	WBC	23	4	7	13
Kokki	2005	15809382	Finland	children	GUARDING	18	3	11	31
Korner	1999	10452263	Norway	mixed	CRP	343	91	58	52
Korner	2000	11053944	Norway	mixed	PAIN ABDOMINAL OR ANOREXIA OR VOMITING	312	122	68	42
Korner	1999	10452263	Norway	mixed	RECTAL TEMPERATURE	239	195	46	64
Korner	2000	11053944	Norway	mixed	ANOREXIA	356	78	78	32
Korner	2000	11053944	Norway	mixed	RIGIDITY LOCALIZED	369	65	89	21
Korner	2000	11053944	Norway	mixed	NORMAL COLOR	204	230	44	66
Korner	2000	11053944	Norway	mixed	PAIN MIGRATION	304	130	63	47
Korner	2000	11053944	Norway	mixed	TENDERNESS RECTAL	174	260	47	63
Korner	1999	10452263	Norway	mixed	WBC	308	126	43	67
Korner	2000	11053944	Norway	mixed	NAUSEA OR VOMITING	312	122	64	46
Korner	2000	11053944	Norway	mixed	MCBURNEY SIGN	399	35	101	10
Korner	2000	10452263	Norway	mixed	NEUTROPHIL%	382	52	59	51
Korner	2000	11053944	Norway	mixed	TENDERNESS REBOUND	395	39	96	14
Kosloske	2004	14702443	USA	children	PROTOCOL OF IMAGING SIGNS SYMPTOMS LABS	208	1	11	136
Kosloske	2004	14702443	USA	children	CT	46	7	3	14
Kosloske	2004	14702443	USA	children	US	46	14	6	45
Kouame	2011	22421290	Cote d'Ivoire	adults	US	11	11	13	17
Kouame	2011	22421290	Cote d'Ivoire	adults	US	115	22	5	20
Kouame	2011	22421290	Cote d'Ivoire	adults	US	2	2	6	10
Kouame	2011	22421290	Cote d'Ivoire	adults	US	448	137	0	35
Kouame	2011	22421290	Cote d'Ivoire	adults	US	7	15	1	29
Krishnamoorthi	2011	21324843	USA	children	CT + US				
Krishnamoorthi	2011	21324843	USA	children	CT + US				
Krishnamoorthi	2011	21324843	USA	children	CT + US				
Krishnamoorthi	2011	21324843	USA	children	CT + US				
Krishnamoorthi	2011	21324843	USA	children	CT + US				
Krishnamoorthi	2011	21324843	USA	children	US	152	2	24	155
Krishnamoorthi	2011	21324843	USA	children	CT	62	1	15	220
Krishnamoorthi	2011	21324843	USA	children	CT + US	214	3	39	375
Kumar	2011	23508483	India	mixed	CRP	38	52	0	10

Kumar	2011	23508483	India	mixed	CRP	85	5	4	6
Kumar	2011	23508483	India	mixed	WBC + CRP	77	13	0	10
Kurane	2008	23133039	India	adults	US	19	4	4	33
Kutasy	2010	19855981	Ireland	children	CRP	71	14	212	486
Kutasy	2010	19855981	Ireland	children	CRP	35	7	61	61
Kutasy	2010	20640856	Ireland	children	US	655	420	103	51
Kutasy	2010	20640856	Ireland	children	US	967	108	40	114
Kwan and Nager	2010	20825931	USA	children	CRP	80.465	34.4	85	61.1
Kwan and Nager	2010	20825931	USA	children	CRP	80.465	85	33	325
Kwan and Nager	2010	20825931	USA	children	WBC	81.6145	33.3	31.9	62.0
Kwan and Nager	2010	20825931	USA	children	WBC	81.6145	355	77	73
Lai	2012	22226440	Hong Kong	mixed	CT	37	4	5	54
Lai	2012	22226440	Hong Kong	mixed	CT	26	15	5	54
Lai	2012	22226440	Hong Kong	mixed	CT	22	19	3	56
Lai	2012	22226440	Hong Kong	mixed	CT	9	32	0	59
Lai	2012	22226440	Hong Kong	mixed	CT	20	21	4	55
Laituri	2011	21470628	USA	children	CT, CONTRAST PRESENT IN TERMINAL ILEUM	437	215	693	216
Lameris	2009	19689484	Netherlands	adults	CRP	196	52	120	54
Lameris	2009	19689484	Netherlands	adults	ANOREXIA	139	123	67	93
Lameris	2009	19689484	Netherlands	adults	TENDERNESS RLO	51	7	324	40
Lameris	2009	19689484	Netherlands	adults	PAIN PROGRESSION	169	113	87	53
Lameris	2009	19689484	Netherlands	adults	RIGIDITY	78	182	26	136
Lameris	2009	19689484	Netherlands	adults	FEVER	73	180	46	123
Lameris	2009	19689484	Netherlands	adults	PAIN RLO	270	44	94	14
Lameris	2009	19689484	Netherlands	adults	TENDERNESS ABDOMINAL	345	11	65	1
Lameris	2009	19689484	Netherlands	adults	WBC	204	48	97	73
Lameris	2009	19689484	Netherlands	adults	TENDERNESS RLO	158	85	102	77
Lameris	2009	19689484	Netherlands	adults	VOMITING	85	164	29	144
Lameris	2009	19689484	Netherlands	adults	TENDERNESS RECTAL	11	215	18	159
Lameris	2009	19689484	Netherlands	adults	DIARRHEA	25	123	44	230
Lameris	2009	19689484	Netherlands	adults	PAIN MIGRATION	92	157	40	133
Lameris	2009	19689484	Netherlands	adults	NAUSEA	157	100	79	86
Lameris	2009	19689484	Netherlands	adults	PAIN MIGRATION	212	124	53	33
Lander	2007	17102959	UK	children	US	3	6	6	21
Lander	2007	17102959	UK	children	US	1	6	6	22
Lander	2007	17102959	UK	children	US	4	0	0	2
Lander	2007	17102959	UK	children	US	1	6	0	22
Lander	2007	17102959	UK	children	US	7	6	6	23
Lane	1997	9016216	USA	adults	CT	37	4	2	66
Lane	1999	10551210	USA	mixed	CT	110	5	4	181
Langenscheidt	1999	10231659	Madagascar	mixed	WBC	8	7	17	71
Langenscheidt	1999	10231659	Madagascar	mixed	TENDERNESS REBOUND	9	6	4	84

Larson	1989	2672728	USA	mixed	US	26	8	2	5
Larson	1989	2672728	USA	mixed	US	49	2	7	107
Larson	1989	2672728	USA	mixed	US	75	10	9	112
Larson	1989	2672728	USA	women of reproductive age	US	25	2	4	80
Latifi	2011	21406706	Sweden	adults	CT	26	1	1	87
Latifi	2011	21406706	Sweden	adults	CT	8	1	0	12
Latifi	2011	21406706	Sweden	adults	CT	22	0	1	51
Latifi	2011	21406706	Sweden	adults	CT	11	0	0	25
Lau	1989	2730458	Hong Kong	elderly	WBC	51	23	3	7
Lau	1989	2730458	Hong Kong	elderly	WBC OR NEUTROPHIL%	68	6	6	4
Lau	1989	2730458	Hong Kong	mixed	WBC OR NEUTROPHIL%	846	89	185	331
Lau	1989	2730458	Hong Kong	children	WBC OR NEUTROPHIL%	138	34	4	3
Lau	1989	2730458	Hong Kong	adults	WBC	670	19	19	61
Lau	1989	2730458	Hong Kong	adults	WBC OR NEUTROPHIL%	659	30	30	50
Lau	1989	2730458	Hong Kong	mixed	WBC	774	87	19	68
Lau	1989	2730458	Hong Kong	mixed	WBC OR NEUTROPHIL%	846	89	79	80
Lau	1989	2730458	Hong Kong	children	WBC	104	68	0	7
Laurell	2013	23838773	Sweden	mixed	TENDERNESS RECTAL	74	200	110	209
Laurell	2013	23838773	Sweden	mixed	PAIN IMPROVEMENT	164	110	661	4
Laurell	2013	23838773	Sweden	mixed	CONSTIPATION	22	252	349	154
Laurell	2013	23838773	Sweden	mixed	PAIN COUGH	120	154	331	185
Laurell	2013	23838773	Sweden	mixed	ANOREXIA	193	81	9	5
Laurell	2013	23838773	Sweden	mixed	PAIN FLUCTUATING	81	193	8	112
Laurell	2013	23838773	Sweden	children	ANOREXIA	50	18	189	107
Laurell	2013	23838773	Sweden	children	PAIN PROGRESSION	45	23	130	9
Laurell	2013	23838773	Sweden	children	TENDERNESS RECTAL	22	46	41	114
Laurell	2013	23838773	Sweden	mixed	VOMITING	133	141	686	105
Laurell	2013	23838773	Sweden	mixed	PAIN PROGRESSION	176	98	838	114
Laurell	2013	23838773	Sweden	mixed	PAIN GRADUAL	184	90	8	8
Laurell	2013	23838773	Sweden	mixed	TENDERNESS REBOUND	201	73	507	136
Laurell	2013	23838773	Sweden	mixed	GUARDING	107	167	287	127
Laurell	2013	23838773	Sweden	mixed	DIARRHEA	49	225	307	8
Laurell	2013	23838773	Sweden	mixed	PAIN FREE INTERVALS	32	242	639	156
Laurell	2013	23838773	Sweden	mixed	PAIN IMPROVEMENT	26	248	507	7
Laurell	2013	23838773	Sweden	children	NAUSEA	53	15	182	169
Laurell	2013	23838773	Sweden	mixed	PAIN COLIC	48	226	705	7

									9
									178
Laurell	2013	23838773	Sweden	mixed	TENDERNESS ABDOMINAL	36	238	419	5
Laurell	2013	23838773	Sweden	children	RIGIDITY	3	65	4	367
									127
Laurell	2013	23838773	Sweden	mixed	PAIN DULL	161	113	926	8
									156
Laurell	2013	23838773	Sweden	mixed	PAIN MIGRATION	170	104	639	5
Laurell	2013	23838773	Sweden	children	TENDERNESS REBOUND	54	14	104	267
Laurell	2013	23838773	Sweden	children	TENDERNESS RIF	44	24	104	267
Laurell	2013	23838773	Sweden	children	PAIN MIGRATION	10	58	37	334
									138
Laurell	2013	23838773	Sweden	mixed	PREVIOUS SIMILAR PAIN	42	232	815	9
									180
Laurell	2013	23838773	Sweden	mixed	TENDERNESS RIF	194	80	397	7
									147
Laurell	2013	23838773	Sweden	mixed	PAIN ABRUPT	75	199	727	7
									216
Laurell	2013	23838773	Sweden	mixed	RIGIDITY	15	259	44	0
									122
Laurell	2013	23838773	Sweden	mixed	NAUSEA	206	68	1	983
									147
Laurell	2013	23838773	Sweden	mixed	PAIN CONTINUOUS	61	213	727	7
Laurell	2013	23838773	Sweden	children	GUARDING LOCALIZED	20	48	30	341
									149
Laurell	2013	23838773	Sweden	mixed	PAIN DURATION	60	214	705	9
									101
Laurell	2013	23838773	Sweden	mixed	PAIN CONTINUOUS	184	90	4	0
Laurell	2013	23838773	Sweden	children	PAIN MIGRATION	46	22	145	226
Laurell	2013	23838773	Sweden	children	PAIN CONTINUOUS	48	20	134	237
									213
Laurell	2013	23838773	Sweden	mixed	PAIN MIGRATION	43	231	66	8
Laurell	2013	23838773	Sweden	children	PAIN GRADUAL	50	18	230	141
									196
Laurell	2013	23838773	Sweden	mixed	PAIN BURNING	27	247	242	2
Lazarus	2007	17709829	USA	pregnant women	US	1	7	0	44
Lazarus	2007	17709829	USA	pregnant women	CT	12	1	1	64
Lee	2005	15615956	South Korea	mixed	US	319	2	4	350
Lee	2006	16772851	Korea	mixed	CT	131	9	16	184
Lee	2006	16772851	Korea	mixed	CT	34	1	2	48
Lee	2008	18704462	Korea	mixed	NAUSEA OR VOMITING	12	55	21	1
Lee	2008	18704462	Korea	mixed	PAIN ABDOMINAL	14	8	5	62
Lee	2006	16772851	Korea	mixed	CT	34	1	1	49
Lee	2006	16799269	Korea	mixed	CT	46	0	10	54
Lee	2006	16772851	Korea	mixed	CT	35	0	2	48
Lee	2006	16799269	Korea	mixed	CT	43	3	3	61
Lee	2006	16799269	Korea	mixed	CT	44	2	36	28
Lee	2006	16772851	Korea	mixed	CT	138	2	5	195
Lee	2006	16799269	Korea	mixed	CT	44	2	5	59
Lee	2001	11343547	USA	mixed	US	65	118	15	37

Lee	2002	11906864	Korea	mixed	US	302	5	10	225
Lee	2006	16799269	Korea	mixed	CT	41	5	5	59
Lee	2006	16799269	Korea	mixed	CT	42	4	21	43
Lee	2006	16799269	Korea	mixed	CT	46	0	0	64
Lee	2006	16772851	Korea	mixed	CT	35	0	2	48
Lee	2008	18704462	Korea	mixed	WBC	16	6	7	60
Lee	2006	16772851	Korea	mixed	CT	33	2	9	41
Lee	2008	18704462	Korea	mixed	PAIN MIGRATION	6	62	14	7
Lee	2002	11906864	Korea	mixed	US	292	5	9	179
Lee	2001	11343547	USA	mixed	CT	29	6	6	6
Lee	2006	16772851	Korea	mixed	CT	29	6	1	49
Lee	2006	16772851	Korea	mixed	CT	34	1	4	46
Lee	2006	16799269	Korea	mixed	CT	45	1	1	63
Lee	2006	16772851	Korea	mixed	CT	35	0	0	50
Leeuwenburgh	2013	23481162	Netherlands	adults	MRI	116	2	13	99
Leeuwenburgh	2013	23481162	Netherlands	women of reproductive age	MRI	50	0	12	76
Leeuwenburgh	2013	23481162	Netherlands	women of reproductive age	MRI	48	2	6	76
Leeuwenburgh	2013	23481162	Netherlands	women of reproductive age	US	36	13	7	81
Leeuwenburgh	2013	23481162	Netherlands	adults	CT	115	3	10	102
Leeuwenburgh	2013	23481162	Netherlands	women of reproductive age	CT	50	0	10	78
Leeuwenburgh	2013	23481162	Netherlands	adults	MRI	113	4	7	99
Leeuwenburgh	2013	23481162	Netherlands	adults	US	90	27	7	105
Lehnert	2012	22370694	USA	pregnant women	US	2	0	0	1
Lehnert	2012	22370694	USA	pregnant women	MRI	0	0	0	6
Lehnert	2012	22370694	USA	pregnant women	CT	2	0	0	8
Lemieux	2009	19057956	Canada	pregnant women	US	13	14	0	15
Lessin	1999	10219853	USA	children	US	28	4	3	64
Levy	1997	9540398	South Africa	mixed	ANOREXIA	149	19	36	8
Levy	1997	9540398	South Africa	mixed	DIARRHEA	11	157	6	38
Levy	1997	9540398	South Africa	mixed	FEVER	73	95	12	32
Levy	1997	9540398	South Africa	mixed	OBTURATOR SIGN	12	156	1	43
Levy	1997	9540398	South Africa	mixed	TENDERNESS	70	98	21	23
Levy	1997	9540398	South Africa	mixed	CONSTIPATION	87	81	24	20
Levy	1997	9540398	South Africa	mixed	NAUSEA OR VOMITING	137	31	30	14
Levy	1997	9540398	South Africa	mixed	MENSES	15	153	19	25
Levy	1997	9540398	South Africa	mixed	TENDERNESS RIF	168	0	43	1
Levy	1997	9540398	South Africa	mixed	TENDERNESS RECTAL	109	59	21	23
Levy	1997	9540398	South Africa	mixed	ABNORMAL URINATION	23	145	15	29
Levy	1997	9540398	South Africa	mixed	PAIN	168	0	44	0
Levy	1997	9540398	South Africa	mixed	TENDERNESS REBOUND	139	71	24	20

Levy	1997	9540398	South Africa	mixed	PSOAS SIGN	40	128	4	40
Levy	1997	9540398	South Africa	mixed	ROVSING SIGN	100	68	16	28
Levy	1997	9540398	South Africa	mixed	GUARDING	145	23	15	29
Li	2012	22186150	Taiwan	children	CRP CHANGE	40	0	24	8
Li	2012	22186150	Taiwan	children	BANDS CHANGE	31	25	0	19
Li	2012	22186150	Taiwan	children	NEUTROPHIL% CHANGE	47	23	5	36
Li	2012	22186150	Taiwan	children	BANDS CHANGE	56	0	17	2
Li	2012	22186150	Taiwan	children	CRP CHANGE	50	6	2	17
Li	2012	22186150	Taiwan	children	CRP CHANGE	35	21	0	19
Li	2012	22186150	Taiwan	children	CRP CHANGE	30	10	0	32
Li	2012	22186150	Taiwan	children	NEUTROPHIL% CHANGE	70	0	30	11
Li	2012	22186150	Taiwan	children	CRP CHANGE	33	7	0	32
Li	2012	22186150	Taiwan	children	BANDS CHANGE	31	25	0	19
Li	2012	22186150	Taiwan	children	CRP CHANGE	56	0	4	15
Li	2012	22186150	Taiwan	children	NEUTROPHIL% CHANGE	5	65	0	41
Lim	1992	1503019	Korea	pregnant women	US	15	0	1	26
Lin	2009	19289311	China	children	CT	12	0	7	2
Lin	2009	19289311	China	children	US	35	2	12	15
Lin	1997	9061706	Taiwan	adults	TC99M NUCLEAR	23	2	2	22
Lin	2009	19289311	China	children	ABD XRAY	18	35	14	33
Lin	2008	18299362	Taiwan	mixed	CT	66	2	4	29
Lin	2013	23724179	Taiwan	children	US	108	4	41	134
Lin	2009	19289311	China	children	DIARRHEA	5	48	3	44
Lin	2009	19289311	China	children	NAUSEA OR VOMITING	23	30	13	34
Lin	2009	19289311	China	children	FEVER	23	30	8	39
Lin	2009	19289311	China	children	TENDERNESS REBOUND	23	30	10	37
Lin	2009	19289311	China	children	PAIN MIGRATION	9	44	4	43
Lindelius	2008	18660395	Sweden	adults	US				
Lintula	2005	15723233	Finland	children	COUGH	3	40	72	12
Lintula	2005	15723233	Finland	children	PAIN MICTRUIITION OR HAEMATURIA	3	40	7	77
Lintula	2005	15723233	Finland	children	DIARRHEA OR CONSTIPATION OR BLOOD OR MUCUS IN STOOL	8	35	18	66
Lintula	2005	15723233	Finland	children	PAIN MUQ	9	34	14	70
Lintula	2005	15723233	Finland	children	HEMATURIA	0	43	6	78
Lintula	2005	15723233	Finland	children	DISTENTION	7	36	6	78
Lintula	2005	15723233	Finland	children	PAIN DURATION	19	24	45	39
Lintula	2005	15723233	Finland	children	PSOAS SIGN	11	32	11	73
Lintula	2005	15723233	Finland	children	NAUSEA	26	17	40	44
Lintula	2005	15723233	Finland	children	PAIN CONTINUOUS	26	17	40	44
Lintula	2005	15723233	Finland	children	TENDERNESS TESTICULAR	0	27	1	35
Lintula	2005	15723233	Finland	children	WBC	16	27	18	66

Lintula	2005	15723233	Finland	children	COLD	4	39	15	69
Loke	2012	22862759	Australia	children	US	30	2	5	37
Lopez	2007	18186378	USA	women of reproductive age	CT	17	2	1	22
Lowe	2001	11719672	USA	children	CT	18	1	1	55
Lowe	2001	11133533	USA	children	US	20	0	7	51
Lowe	2001	11133533	USA	children	CT	35	0	36	36
Lowe	2000	11000148	USA	children	CT	39	21	6	38
Lowe	2001	11719672	USA	children	CT	12	7	2	54
Lycopoulou	2005	15653442	Greece	children	CRP	26	16	1	17
Lycopoulou	2005	15653442	Greece	children	CRP	34	8	1	17
Lycopoulou	2005	15653442	Greece	children	SAA-1 PLASMA MARKER	42	0	7	11
Lycopoulou	2005	15653442	Greece	children	WBC	36	6	6	12
Lycopoulou	2005	15653442	Greece	children	SAA-1 PLASMA MARKER	36	6	3	15
Lycopoulou	2006	15653442	Greece	children	WBC	32	10	4	14
Lyons	1987	3446277	Ireland	mixed	WBC	74	16	6	12
Lyons	1987	3446277	Ireland	mixed	NEUTROPHIL% CHANGE	31	59	6	12
Mahadevan	2000	11103723	Singapore	mixed	TENDERNESS PERCUSSION	13	7	18	28
Mahadevan	2000	11103723	Singapore	mixed	PAIN DEEP	20	0	44	2
Mahadevan	2000	11103723	Singapore	mixed	PAIN RLQ	14	6	20	26
Mahadevan	2000	11103723	Singapore	mixed	PAIN	4	16	6	40
Mahadevan	2000	11103723	Singapore	mixed	PAIN LIGHT	11	8	36	11
Mahadevan	2000	11103723	Singapore	mixed	TENDERNESS REBOUND	13	7	23	23
Mahadevan	2000	11103723	Singapore	mixed	TENDERNESS COUGH	10	10	12	34
Makanjuola	1998	9715110	Saudi Arabia	mixed	US	33	1	0	88
Mallick	2008	18675602	Saudi Arabia	children	WBC	59	43	2	2
Malone	1993	8456661	USA	mixed	CT	65	10	4	132
Maluccio	2001	12593710	USA	adults	CT	33	2	3	66
Maluccio	2001	12593710	USA	adults	CT	28	7	6	63
Mandeville	2011	20674221	USA	children	FEVER	77	78	48	84
Mandeville	2011	20674221	USA	children	PAIN REBOUND	73	82	39	93
Mandeville	2011	20674221	USA	children	WBC	129	26	49	83
Mandeville	2011	20674221	USA	children	TENDERNESS RLQ COUGH PERCUSSION HOPPING	129	26	71	61
Mandeville	2011	20674221	USA	children	ANOREXIA	115	40	82	50
Mandeville	2011	20674221	USA	children	TENDERNESS RLQ	143	12	118	14
Mandeville	2011	20674221	USA	children	PAIN MIGRATION	70	85	47	85
Mandeville	2011	20674221	USA	children	NAUSEA OR VOMITING	117	38	85	47
Mandeville	2011	20674221	USA	children	WBC:LYMPHOCYTE	119	36	48	84
Marchand	1983	6881101	USA	mixed	WBC OR CRP OR NEUTROPHIL COUNT	45	40	10	11
Marchand	1983	6881101	USA	mixed	CRP	58	27	7	14
Marchand	1983	6881101	USA	mixed	NEUTROPHIL%	53	32	8	13

Marchand	1983	6881101	USA	mixed	WBC OR CRP OR BAND%	40	45	11	10
Marchand	1983	6881101	USA	mixed	BAND%	69	16	4	17
Marchand	1983	6881101	USA	mixed	WBC OR CRP OR BAND	40	45	11	10
Marchand	1983	6881101	USA	mixed	WBC	60	25	6	15
Marchand	1983	6881101	USA	mixed	BAND COUNT	65	20	5	16
Marchand	1983	6881101	USA	mixed	WBC OR CRP OR NEUTROPHIL%	36	49	12	9
Marchand	1983	6881101	USA	mixed	NEUTROPHIL COUNT	65	20	5	16
Mardan	2007	18444596	Saudi Arabia	mixed	US	54	12	6	128
Mariadason	2012	22943328	USA	mixed	CT	376	5	13	4
Markar	2011	22041239	UK	mixed	US	5	9	1	7
Markar	2010	21158332	UK	mixed	NEUTROPHIL:LYMPH	2	876	237	2
Markar	2010	21158332	UK	mixed	NEUTROPHIL:LYMPH	6	872	237	2
Markar	2010	21158332	UK	mixed	CT	1	143	59	0
Markar	2011	22041239	UK	mixed	CT	38	1	1	2
Markar	2011	22041239	UK	mixed	US	17	16	4	12
Masselli	2011	21052664	Italy	pregnant women	MRI	5	0	0	35
Masters	1984	6507749	USA	pregnant women	PAIN RUQ	4	25	0	7
Masters	1984	6507749	USA	pregnant women	PSOAS SIGN	18	11	5	2
Masters	1984	6507749	USA	pregnant women	GRANULOCYTE%	17	12	3	4
Masters	1984	6507749	USA	pregnant women	CONSTIPATION	1	28	0	7
Masters	1984	6507749	USA	pregnant women	GRANULOCYTE%	23	6	6	1
Masters	1984	6507749	USA	pregnant women	FEVER	9	20	4	3
Masters	1984	6507749	USA	pregnant women	FEVER	2	27	2	5
Masters	1984	6507749	USA	pregnant women	DIARRHEA	1	28	0	7
Masters	1984	6507749	USA	pregnant women	ABNORMAL URINATION	1	28	0	7
Masters	1984	6507749	USA	pregnant women	PAIN ABDOMINAL DIFFUSE	2	27	3	4
Masters	1984	6507749	USA	pregnant women	PAIN RLQ	4	25	2	5
Masters	1984	6507749	USA	pregnant women	TENDERNESS REBOUND	16	13	2	5
Masters	1984	6507749	USA	pregnant women	WBC	12	17	4	3
Masters	1984	6507749	USA	pregnant women	GUARDING	22	7	4	3
Masters	1984	6507749	USA	pregnant women	PAIN RIGHT FLANK	3	26	2	5
Masters	1984	6507749	USA	pregnant women	ANOREXIA	19	10	4	3
Masters	1984	6507749	USA	pregnant women	PAIN RLQ	13	16	0	7
Masters	1984	6507749	USA	pregnant women	WBC	23	6	5	2
Masters	1984	6507749	USA	pregnant women	VOMITING	25	4	2	5
Masters	1984	6507749	USA	pregnant women	NAUSEA	26	3	4	3
Masters	1984	6507749	USA	pregnant women	BOWEL SOUNDS	14	15	3	4
Masters	1984	6507749	USA	pregnant women	URINARY INFECTION	7	22	0	7
Masters	1984	6507749	USA	pregnant women	TENDERNESS RECTAL	13	16	6	1
Masters	1984	6507749	USA	pregnant women	PAIN EPIGASTRIC	3	26	0	7
McCOMBE	1991	1773162	UK	mixed	WBC	146	41	93	146

McCartan	2010	20569941	Ireland	mixed	TENDERNESS REBOUND	64	55	35	148
McCartan	2010	20569941	Ireland	mixed	NAUSEA	97	22	131	52
McCartan	2010	20569941	Ireland	mixed	WBC	96	23	68	115
McCartan	2010	20569941	Ireland	mixed	VOMITING	77	42	72	111
McCartan	2010	20569941	Ireland	mixed	ANOREXIA	87	32	73	110
McCartan	2010	20569941	Ireland	mixed	PULSE	45	74	24	159
McCartan	2010	20569941	Ireland	mixed	FEVER	36	83	23	160
McCloskey	2013	22345311	Australia	children	FEVER	51	44	86	135
McCloskey	2013	22345311	Australia	children	CRP	57	20	7	49
McCloskey	2013	22345311	Australia	children	SYMPTOMS DURATION	3	92	43	178
McCloskey	2013	22345311	Australia	children	VOMITING	64	31	90	131
McCloskey	2013	22345311	Australia	children	NAUSEA	77	18	141	80
McCloskey	2013	22345311	Australia	children	GUARDING	62	33	61	160
McCloskey	2013	22345311	Australia	children	WBC	55	31	7	65
McCloskey	2013	22345311	Australia	children	SYMPTOMS DURATION	82	13	39	182
McCloskey	2013	22345311	Australia	children	ANOREXIA	40	55	78	143
McCloskey	2013	22345311	Australia	children	MASS ABDOMINAL	3	92	19	202
McCloskey	2013	22345311	Australia	children	SYMPTOMS DURATION	4	90	8	213
McCloskey	2013	22345311	Australia	children	TENDERNESS REBOUND	38	57	35	186
McDonald	2001	11730216	USA	mixed	CT	187	7	16	16
McDonough	2002	12412726	USA	mixed	CT	9	2	2	18
McKay	2007	17543650	USA	mixed	CT	51	3	3	42
Mekhail	2013	22248897	UK	children	CRP	92	23	15	19
Mekhail	2013	22248897	UK	children	WBC + CRP	70	10	4	16
Mekhail	2013	22248897	UK	children	WBC	107	29	16	20
Memisoglu	2010	20181221	Turkey	mixed	US	116	46	14	20
Mendelson	1987	3555679	UK	children	US	9	2	3	10
Mentes	2012	23188598	Turkey	adults	FIBRINOGEN	126	53	11	11
Mentes	2009	19683101	Turkey	adults	RIGIDITY	32	8	7	2
Mentes	2012	23188598	Turkey	adults	WBC	128	51	5	17
Mentes	2009	19683101	Turkey	adults	WBC	28	12	5	4
Mentes	2012	23188598	Turkey	adults	WBC + FIBRINOGEN	152	27	5	17
Mentes	2009	19683101	Turkey	adults	PAIN DURATION	25	15	6	3
Mentes	2009	19683101	Turkey	adults	US	34	15	5	4
Mentes	2009	19683101	Turkey	adults	PAIN DURATION	37	3	7	2
Mihmanli	2004	15286888	Turkey	mixed	U-5-HIAA	5	17	1	20
Mikaelsson	1984	6524861	Sweden	children	CRP	53	60	23	20
Mills	2012	22221415	USA	mixed	PAIN RUQ	13	221	67	547
Mills	2012	22221415	USA	mixed	PSOAS SIGN	23	211	29	585
Mills	2012	22221415	USA	mixed	DYSURIA	10	224	50	564
Mills	2012	22221415	USA	mixed	PAIN	88	146	281	333

Mills	2012	22221415	USA	mixed	ROVSING SIGN	45	189	44	570
Mills	2012	22221415	USA	mixed	TENDERNESS	228	3	582	28
Mills	2012	22221415	USA	mixed	SYMPTOMS DURATION	145	89	350	264
Mills	2012	22221415	USA	mixed	PAIN EPIGASTRIC	14	220	39	575
Mills	2012	22221415	USA	mixed	CT	154	2	15	253
Mills	2012	22221415	USA	mixed	ANOREXIA	113	121	175	439
Mills	2012	22221415	USA	mixed	PAIN PELVIC	1	233	12	602
Mills	2012	22221415	USA	mixed	US	23	1	2	32
Mills	2012	22221415	USA	mixed	PAIN MIGRATION	155	79	389	225
Mills	2012	22221415	USA	mixed	PAIN LLO	24	210	97	517
Mills	2012	22221415	USA	mixed	PAIN RLQ	234	0	0	614
Mills	2012	22221415	USA	mixed	PAIN LUQ	4	230	24	590
Mills	2012	22221415	USA	mixed	CONSTIPATION	19	215	57	557
Mills	2012	22221415	USA	mixed	VOMITING	105	129	254	360
Mills	2012	22221415	USA	mixed	DIARRHEA	37	197	127	487
Mills	2012	22221415	USA	mixed	RIGIDITY + GUARDING	81	153	90	524
Mills	2012	22221415	USA	mixed	NAUSEA	155	79	389	225
Mills	2012	22221415	USA	mixed	S100A8 OR S100A9	225	9	516	98
Mills	2012	22221415	USA	mixed	TENDERNESS REBOUND	66	168	67	547
Mills	2012	22221415	USA	mixed	NEUTROPHIL%	179	38	252	298
Mills	2012	22221415	USA	mixed	WBC	195	38	190	400
Mills	2012	22221415	USA	mixed	OBTURATOR SIGN	11	223	20	594
Mishra	2003	12619946	India	children	US	12	1	1	36
Miskowiak	1982	7105849	Denmark	mixed	WBC	70	30	62	150
Miskowiak	1982	7105849	Denmark	adults	WBC	66	13	54	105
Miskowiak	1982	7105849	Denmark	children	WBC	4	17	8	45
Mittal	2013	23859583	USA	children	US	7	0	1	23
Mittal	2013	23859583	USA	children	US	235	89	19	622
Mittal	2013	23859583	USA	children	US	99	0	4	87
Mittal	2013	23859583	USA	children	US	45	20	7	177
Mittal	2013	23859583	USA	children	US	67	25	5	128
Mittal	2013	23859583	USA	children	US	7	13	1	97
Mittal	2004	15136349	USA	adults	CT	36	0	0	3
Mittal	2013	23859583	USA	children	US	68	2	5	31
Mittal	2013	23859583	USA	children	US	16	1	2	9
Mittal	2013	23859583	USA	children	US	45	2	7	60
Mittal	2004	15136349	USA	adults	CT	43	1	4	4
Mittal	2013	23859583	USA	children	US	16	15	2	81
Mittal	2013	23859583	USA	children	US	98	16	4	141
Mohammed	2004	15448768	Libya	children	WBC + CRP + NEUTROPHIL%	112	18	8	78
Mohammed	2004	15448768	Libya	children	NEUTROPHIL%	111	19	15	71

Mohammed	2004	15448768	Libya	children	CRP	114	16	13	73
Mohammed	2004	15448768	Libya	children	WBC	109	21	19	67
Mohebbi	2008	18289949	Iran	mixed	VOMITING	440	526	109	106
Mohebbi	2008	18289949	Iran	mixed	PAIN CONTINUOUS	623	343	130	85
Mohebbi	2008	18289949	Iran	mixed	ABNORMAL URINATION	826	140	161	54
Mohebbi	2008	18289949	Iran	mixed	PAIN SUPRAPUBIC	16	950	6	209
Mohebbi	2008	18289949	Iran	mixed	CONSTIPATION	146	820	36	179
Mohebbi	2008	18289949	Iran	mixed	GUARDING	186	780	22	193
Mohebbi	2008	18289949	Iran	mixed	VOMITING	93	873	23	192
Mohebbi	2008	18289949	Iran	mixed	TENDERNESS SUPRAPUBIC	21	945	6	209
Mohebbi	2008	18289949	Iran	mixed	TENDERNESS LLO	13	953	2	213
Mohebbi	2008	18289949	Iran	mixed	PAIN EPIGASTRIC	156	810	24	191
Mohebbi	2008	18289949	Iran	mixed	NAUSEA	787	179	173	42
Mohebbi	2008	18289949	Iran	mixed	PAIN PERIUMBILICAL	304	662	60	155
Mohebbi	2008	18289949	Iran	mixed	PAIN COLIC INTERMITTENT	121	845	35	180
Mohebbi	2008	18289949	Iran	mixed	PAIN IMPROVEMENT	14	952	4	211
Mohebbi	2008	18289949	Iran	mixed	PAIN SUPRAPUBIC	48	918	19	196
Mohebbi	2008	18289949	Iran	mixed	TENDERNESS PERIUMBILICAL	18	948	5	210
Mohebbi	2008	18289949	Iran	mixed	ANOREXIA	813	153	185	30
Mohebbi	2008	18289949	Iran	mixed	DIARRHEA	179	787	36	179
Mohebbi	2008	18289949	Iran	mixed	PAIN RLO	807	159	168	47
Mohebbi	2008	18289949	Iran	mixed	PAIN PROGRESSION	113	853	25	190
Mohebbi	2008	18289949	Iran	mixed	PAIN PERIUMBILICAL	15	951	4	211
Mohebbi	2008	18289949	Iran	mixed	PAIN	87	879	13	202
Mohebbi	2008	18289949	Iran	mixed	PAIN	12	954	4	211
Mohebbi	2008	18289949	Iran	mixed	PAIN MIGRATION	908	58	169	46
Mohebbi	2008	18289949	Iran	mixed	DISCHARGE VAGINAL	26	940	6	209
Mohebbi	2008	18289949	Iran	mixed	ROVSING SIGN	696	270	131	84
Mohebbi	2008	18289949	Iran	mixed	WBC	284	682	27	188
Mohebbi	2008	18289949	Iran	mixed	PAIN RLO	215	751	68	147
Mohebbi	2008	18289949	Iran	mixed	TENDERNESS COUGH	850	116	188	27
Mohebbi	2008	18289949	Iran	mixed	TENDERNESS RLO	893	73	199	16
Mohebbi	2008	18289949	Iran	mixed	OBTURATOR SIGN	590	376	135	80
Mohebbi	2008	18289949	Iran	mixed	PSOAS SIGN	635	331	155	60
Mohebbi	2008	18289949	Iran	mixed	TENDERNESS REBOUND	858	108	175	40
Monib	2013	23458936	Saudi Arabia	mixed	US	328	15	0	33
Moore	2012	22677910	USA	children	MRI	40	5	1	162
Moore	1995	7786263	Australia	adults	TC99M NUCLEAR	9	1	1	23
Morris	2002	12034390	USA	adults	CT	38	1	8	82
Moteki	2009	19478631	Japan	adults	CT	81	31	65	103
Moteki	2009	19478631	Japan	adults	CT	64	22	32	136

Moteki	2009	19478631	Japan	adults	CT	107	5	116	52
Moteki	2009	19478631	Japan	adults	CT	109	3	36	132
Moteki	2009	19478631	Japan	adults	CT	77	35	32	136
Moteki	2009	19478631	Japan	adults	CT	62	24	30	138
Moteki	2009	19478631	Japan	adults	CT	74	38	0	168
Moteki	2009	19478631	Japan	adults	CT	62	24	0	168
Moteki	2009	19478631	Japan	adults	CT	84	2	116	52
Moteki	2009	19478631	Japan	adults	CT	74	38	30	138
Moteki	2009	19478631	Japan	adults	CT	61	25	65	103
Moteki	2009	19478631	Japan	adults	CT	77	9	5	163
Moteki	2009	19478631	Japan	adults	CT	86	0	36	132
Moteki	2009	19478631	Japan	adults	CT	81	5	1	167
Moteki	2009	19478631	Japan	adults	CT	109	3	0	168
Moteki	2009	19478631	Japan	adults	CT	97	15	5	163
Moteki	2009	19478631	Japan	adults	CT	86	0	0	168
Moteki	2009	19478631	Japan	adults	CT	103	9	1	167
Mourad	2000	10819817	USA	pregnant women	PAIN RLO	37	8	16	6
Mourad	2000	10819817	USA	pregnant women	FEVER	20	25	10	12
Mourad	2000	10819817	USA	pregnant women	WBC	18	27	13	9
Mourad	2000	10819817	USA	pregnant women	PAIN RUQ	3	42	1	21
Mullins	2001	11133535	USA	children	CT	64	2	1	128
Mun	2006	16362812	USA	adults	CT	56	0	3	114
Mun	2006	16362812	USA	women of reproductive age	CT	17	0	3	78
Musunuru	2007	17701439	USA	adults	CT	208	17	19	21
Myers	2010	19508509	Ireland	mixed	CT	1	0	0	0
Myers	2010	19508509	Ireland	mixed	US	3	0	1	0
Myers	2010	19508509	Ireland	mixed	CT	34	2	0	2
Myers	2010	19508509	Ireland	mixed	US	31	6	2	0
Naffaa	2005	15967316	Lebanon	mixed	CT	35	0	4	36
Naffaa	2005	15967316	Lebanon	mixed	CT	31.02	1.98	1.9	0.1
Naffaa	2005	15967316	Lebanon	mixed	CT	17.75	7.25	2.76	0.24
Naffaa	2005	15967316	Lebanon	mixed	CT	32.98	1.02	0	0
Naffaa	2005	15967316	Lebanon	mixed	CT	35	0	8.16	3.84
Naffaa	2005	15967316	Lebanon	mixed	CT	1.52	6.48	5.74	1.26
Nana	2007	17629058	Belgium	mixed	US	277	136	23	35
Nana	2007	17629058	Belgium	mixed	WBC + CRP	124	407	13	58
Nana	2007	17629058	Belgium	mixed	CT	152	41	6	15
Nana	2007	17629058	Belgium	mixed	CRP	361	170	29	42
Nana	2007	17629058	Belgium	mixed	WBC	414	117	32	39
Nana	2007	17629058	Belgium	mixed	WBC + CRP	46	485	29	72
Nana	2007	17629058	Belgium	mixed	WBC + CRP	289	242	19	53

Nana	2007	17629058	Belgium	mixed	WBC + CRP	72	459	10	61
Naoum	2002	12488178	USA	mixed	CT	61	1	1	4
Naoum	2002	12488178	USA	mixed	CT	26	3	5	2
Nasri	2012	22673121	Iran	mixed	US	37	15	1	5
Nathan	2008	18806151	USA	adults	TENDERNESS REBOUND	7	11	6	76
Nathan	2008	18806151	USA	adults	CT	17	0	0	79
Nathan	2008	18806151	USA	adults	FEVER	5	13	9	73
Nathan	2008	18806151	USA	adults	PAIN RLO	18	0	81	1
Nathan	2008	18806151	USA	adults	WBC	16	2	30	52
Nathan	2008	18806151	USA	adults	GUARDING RLO	7	11	3	79
Nathan	2008	18806151	USA	adults	NAUSEA	12	6	23	59
Nathan	2008	18806151	USA	adults	CT	10	0	0	65
Nathan	2008	18806151	USA	adults	ANOREXIA	11	7	25	57
Nathan	2008	18806151	USA	adults	SYMPTOMS DURATION	18	0	79	3
Nathan	2008	18806151	USA	adults	VOMITING	5	13	9	73
Nautiyal	2010	23133203	India	mixed	US	31	4	2	13
Navarro	1989	2516745	USA	mixed	INDIUM-111 NUCLEAR	53	4	4	83
Navarro	1987	3493655	USA	adults	INDIUM-111 NUCLEAR	12	2	1	17
Navarro-Fernandez	2009	19803663	Spain	mixed	PAIN RLO	49	22	26	195
Navarro-Fernandez	2009	19803663	Spain	mixed	WBC	58	13	85	221
Nelson	2013	23388421	USA	mixed	CT	624	0	20	20
Neufeld	2010	19844725	Israel	children	US	343	33	13	560
Ng	2002	12074480	Taiwan	mixed	WBC	199	44	24	15
Ng	2002	12074480	Taiwan	mixed	FEVER	78	165	9	30
Ng	2002	12074480	Taiwan	mixed	NEUTROPHIL:WBC	146	97	9	30
Ng	2002	12074480	Taiwan	mixed	CRP + NEUTROPHIL%	103	140	6	33
Ng	2002	12074480	Taiwan	mixed	WBC + CRP	133	110	15	24
Ng	2002	12074480	Taiwan	mixed	WBC + NEUTROPHIL%	130	113	7	32
Ng	2002	12074480	Taiwan	mixed	CRP	166	77	25	14
Ng	2002	12074480	Taiwan	mixed	WBC + CRP + NEUTROPHIL%	90	153	5	34
Niekel	1986	3022347	Netherlands	mixed	US	0	0	0	4
Niekel	1986	3022347	Netherlands	mixed	US	0	0	1	7
Niekel	1986	3022347	Netherlands	mixed	US	15	8	2	2
Nordback	1988	3354283	Finland	mixed	CRP	135	121	24	73
Nordback	1988	3354283	Finland	mixed	ESR	61	195	15	82
Nordback	1988	3354283	Finland	mixed	PMNC COUNT	201	55	24	73
Nordback	1988	3354283	Finland	mixed	FEVER	219	37	64	33
Nordback	1988	3354283	Finland	mixed	LYMPHOCYTE%	216	40	47	50
Nural	2008	18443745	Turkey	adults	US	30	7	8	255
Nural	2008	18443745	Turkey	adults	CT	1	0	2	29

Oncel	2003	14972260	Turkey	mixed	ABD XRAY	0	143	0	19
Oncel	2003	14972260	Turkey	mixed	ABD XRAY	53	90	7	12
Oncel	2003	14972260	Turkey	mixed	ABD XRAY	30	113	3	16
Oncel	2003	14972260	Turkey	mixed	ABD XRAY	9	134	0	19
Oncel	2003	14972260	Turkey	mixed	ABD XRAY	12	131	0	19
Oncel	2003	14972260	Turkey	mixed	ABD XRAY	1	142	0	19
Oncel	2003	14972260	Turkey	mixed	ABD XRAY	8	135	0	19
Oncel	2003	14972260	Turkey	mixed	ABD XRAY	0	143	0	19
Ooms	1991	2021847	Netherlands	mixed	US	163	30	42	290
Oosterhuis	1993	8098625	Netherlands	mixed	ESR	34	53	6	13
Oosterhuis	1993	8098625	Netherlands	mixed	ANOREXIA	63	29	7	11
Oosterhuis	1993	8098625	Netherlands	mixed	CRP	88	12	59	50
Oosterhuis	1993	8098625	Netherlands	mixed	PAIN DURATION	77	22	20	4
Oosterhuis	1993	8098625	Netherlands	mixed	WBC	92	7	13	10
Oosterhuis	1993	8098625	Netherlands	mixed	VOMITING	48	50	6	15
Oosterhuis	1993	8098625	Netherlands	mixed	FEVER	72	28	13	8
Oosterhuis	1993	8098625	Netherlands	mixed	NAUSEA	72	27	15	7
Ortega-Deballon	2008	18484138	Spain	adults	WBC + CRP	76	12	29	17
Ortega-Deballon	2008	18484138	Spain	adults	WBC	76	12	26	20
Ortega-Deballon	2008	18484138	Spain	adults	CRP	80	8	12	34
Ortega-Deballon	2008	18484138	Spain	adults	GRANULOCYTE%	73	15	25	21
Oto	2005	15591434	USA	pregnant women	MRI	3	1	2	17
Oto	2009	18330616	USA	pregnant women	MRI	9	0	2	105
Ozguner	2013	23757034	Turkey	children	CRP	25	9	4	11
Ozguner	2013	23757034	Turkey	children	IL-6	26	8	3	12
Ozguner	2013	23757034	Turkey	children	LEUKOCYTE CD64	28	6	3	12
Ozturk	2008	18723708	Turkey	mixed	ADENOSINE DEAMINASE	23	7	3	19
O'Shea	1988	3186519	USA	children	DIARRHEA	8	16	29	193
O'Shea	1988	3186519	USA	children	NAUSEA	7	17	47	175
O'Shea	1988	3186519	USA	children	LETHARGY	1	23	11	211
O'Shea	1988	3186519	USA	children	ANOREXIA	5	19	60	162
O'Shea	1988	3186519	USA	children	FEVER	18	6	49	173
O'Shea	1988	3186519	USA	children	VOMITING	19	5	80	142
O'Shea	1988	3186519	USA	children	ABNORMAL URINATION	0	0	7	215
Paajanen	2002	12564616	Finland	mixed	IL-6	53	10	4	13
Paajanen	2002	12564616	Finland	mixed	CRP	47	16	8	9
Paajanen	1997	9060929	Finland	adults	WBC	124	34	20	22
Paajanen	1997	9060929	Finland	mixed	WBC	291	127	84	108
Paajanen	1996	8740305	Finland	young children	TENDERNESS RLQ	38	3	40	9
Paajanen	1996	8740305	Finland	young children	PERITONITIS DIFFUSE	10	31	0	49
Paajanen	1997	9060929	Finland	mixed	CRP	355	63	133	49

Paajanen	1997	9060929	Finland	children	CRP	41	7	35	17
Paajanen	1996	8740305	Finland	young children	FEVER	34	7	35	14
Paajanen	1997	9060929	Finland	children	CRP	65	11	17	7
Paajanen	1997	9060929	Finland	children	CRP	106	18	52	24
Paajanen	1997	9060929	Finland	children	WBC	27	21	29	23
Paajanen	1996	8740305	Finland	young children	CRP	15	1	23	26
Paajanen	1996	8740305	Finland	young children	HEMATURIA	2	39	5	44
Paajanen	1996	8740305	Finland	young children	DIARRHEA	4	37	5	44
Paajanen	2002	12564616	Finland	mixed	WBC	47	16	6	11
Paajanen	1996	8740305	Finland	young children	WBC	24	17	29	20
Paajanen	1997	9060929	Finland	elderly	CRP	125	11	53	11
Paajanen	1996	8740305	Finland	young children	PYURIA	11	30	5	44
Paajanen	1996	8740305	Finland	young children	VOMITING	26	15	15	34
Paajanen	1997	9060929	Finland	adults	CRP	124	34	28	14
Paajanen	1997	9060929	Finland	children	WBC	35	41	3	21
Paajanen	1997	9060929	Finland	children	WBC	62	62	32	46
Paajanen	1996	8740305	Finland	young children	BACTERIURIA	1	40	0	49
Paajanen	1997	9060929	Finland	elderly	WBC	105	31	32	32
Pacharn	2010	21098847	USA	children	US	30	7	16	140
Panagiotopoulou	2013	23827295	UK	mixed	CRP	498	234	135	261
Panagiotopoulou	2013	23827295	UK	mixed	WBC OR CRP	644	88	158	238
Panagiotopoulou	2013	23827295	UK	mixed	WBC	615	117	230	166
Panagiotopoulou	2013	23827295	UK	mixed	WBC OR CRP OR BILIRUBIN	703	29	265	131
Panagiotopoulou	2013	23827295	UK	mixed	SERUM BILIRUBIN	366	366	127	269
Paranjape	2007	17285390	USA	elderly	CT	75	5	4	3
Park	2013	23317620	Korea	mixed	CT	452	17	21	440
Park	2013	23317620	Korea	mixed	US	1063	10	38	419
Park	2010	20336903	Korea	mixed	WBC	56	44	17	31
Passalaqua	2004	15359387	USA	mixed	TC99M NUCLEAR	19	1	2	18
Patrick	2003	12720164	USA	children	US	79	29	14	0
Patrick	2003	12720164	USA	children	CT	161	20	14	7
Paulson	2005	15833993	USA	adults	CT	24	0	6	70
Paulson	2005	15833993	USA	adults	CT	23	1	3	73
Paulson	2005	15833993	USA	adults	CT	24	1	4	72
Paulson	2005	15833993	USA	adults	CT	22	2	5	71
Paulson	2005	15833993	USA	adults	CT	22	2	3	73
Paulson	2005	15833993	USA	adults	CT	23	1	4	72
Pearl	1995	7738734	USA	children	WBC	1087	122	97	60
Pearl	1995	7738734	USA	children	PAIN RLQ	1164	45	149	8
Pearl	1995	7738734	USA	children	TENDERNESS RLQ	1176	33	149	8
Pearl	1995	7738734	USA	children	FEVER	320	889	39	118

Peck	2000	11044529	USA	mixed	CT	103	8	1	252
Pedrosa	2009	19244044	USA	pregnant women	US	7	0	1	1
Pedrosa	2006	16505393	USA	pregnant women	MRI	4	0	0	44
Pedrosa	2009	19244044	USA	pregnant women	MRI	13	0	3	125
Pedrosa	2006	16505393	USA	pregnant women	US	2	2	0	44
Peletti	2006	17004079	Brazil	children	US	56	0	1	43
Peltola	1986	3953219	Finland	children	WBC + CRP	42	52	20	48
Peltola	1986	3953219	Finland	children	CRP	60	34	12	56
Peltola	1986	3953219	Finland	children	CRP + ESR	34	60	15	53
Peltola	1986	3953219	Finland	children	ESR	37	57	7	61
Peltola	1986	3953219	Finland	children	WBC	56	38	11	57
Pena	1999	10493202	USA	children	CT	28	1	2	74
Pena	1999	10493202	USA	children	US	22	28	0	83
Pena	2002	12456904	USA	children	CT	174	0	40	302
Pena	1999	10882249	USA	children	CT	28	1	5	74
Pena	2002	12456904	USA	children	CT	328	0	14	76
Pena	2002	12456904	USA	children	CT	212	0	7	212
Pena	2002	12456904	USA	children	CT	526	0	91	303
Pena	1999	10882249	USA	children	US	22	28	6	83
Pesonen	1994	8057950	Finland	adults	COMBINATION OF SIGNS + SYMPTOMS	135	135	18	104 5
Pesonen	1994	8057950	Finland	adults	COMBINATION OF SIGNS + SYMPTOMS	203	67	59	100 4
Pesonen	1994	8057950	Finland	adults	COMBINATION OF SIGNS + SYMPTOMS	231	39	38	102 5
Petroianu	2012	22574093	Brazil	mixed	ABD XRAY	165	5	44	256 144
Pickhardt	2011	21690593	USA	adults	CT	344	27	8	7
Pickhardt	2011	21690593	USA	adults	CT	321	2	16	706 215
Pickhardt	2011	21690593	USA	adults	CT	655	10	43	3
Pickth and Spielman	2001	11268950	Germany	adults	CT	88	5	3	24
Pickuth	2000	10817330	Germany	mixed	CT	88	5	3	24
Pickuth	2000	10817330	Germany	mixed	US	81	12	7	20
Platon	2009	18797875	Switzerland	adults	CT	35	2	2	47
Platon	2009	18797875	Switzerland	adults	CT	33	0	1	45
Platon	2009	18797875	Switzerland	adults	CT	4	0	1	2
Platon	2009	18797875	Switzerland	adults	CT	33	0	1	45
Platon	2009	18797875	Switzerland	adults	CT	2	2	1	2
Platon	2009	18797875	Switzerland	adults	CT	37	0	2	47
Poh	2004	15284932	Singapore	adults	CT	36	4	0	127
Pohl	1998	9544604	USA	mixed	US	30	30	4	99
Poletti	2011	21805194	Switzerland	adults	US	50	2	1	31
Poletti	2011	21805194	Switzerland	adults	CT	85	3	1	94

Poletti	2011	21805194	Switzerland	adults	CT	76	3	1	85
									119
Pooler	2012	23023965	UK	adults	CT	346	4	25	6
									131
Pooler	2012	22131057	USA	adults	CT	324	8	25	8
Pooler	2012	22131057	USA	elderly	CT	44	0	2	216
Pooler	2012	22131057	USA	elderly	CT	24	0	0	87
									193
Pooler	2012	22131057	USA	adults	CT	621	10	41	7
Pooler	2012	22131057	USA	elderly	CT	20	0	2	129
Pooler	2012	22131057	USA	adults	CT	297	2	16	619
Poortman	2009	19390196	USA	mixed	US	101	12	27	28
Poortman	2009	19390196	USA	mixed	US	6	5	3	52
Poortman	2003	14573433	Netherlands	mixed	CT	110	32	21	73
Poortman	2009	19318006	Netherlands	adults	CT	21	0	0	39
Poortman	2010	19185439	Netherlands	children	CT	100	11	32	74
Poortman	2003	14573433	Netherlands	mixed	US	104	28	23	71
Poortman	2009	19390196	USA	mixed	US	107	17	30	80
Poortman	2009	19318006	Netherlands	adults	US	71	21	8	39
Prasannan	2005	16234073	Malaysia	mixed	ABD XRAY	1	15	5	20
Pruekprasert	2004	15117047	Thailand	mixed	CRP	109	67	18	23
Puig	2003	12511675	Austria	mixed	US	538	42	38	25
Puylaert	1987	3306375	USA	mixed	US	39	0	4	0
Puylaert	1986	2934762	Netherlands	mixed	US	25	3	0	32
Quillin	1994	8153340	USA	children	US	34	5	5	56
Quillin	1994	8153340	USA	children	US	34	5	2	59
Raftery	1976	1252716	UK	children	WBC	13	0	2	3
Raftery	1976	1252716	UK	mixed	WBC	97	9	6	20
Raftery	1976	1252716	UK	mixed	NEUTROPHIL%	97	9	6	15
Rajagopalan	1977	849164b	USA	mixed	BARIUM ENEMA	68	2	6	105
Rajagopalan	1977	849164a	USA	mixed	BARIUM ENEMA	68	2	6	9
Ramachandran	1996	8632272b	USA	children	US	46	6	5	123
Ramachandran	1996	8632272a	USA	children	US	55	5	6	206
Raman	2003	12886148	USA	adults	CT	137	5	8	402
Raman	2003	12886148	USA	adults	CT	63	0	5	130
Raman	2002	12034591	USA	adults	CT	137	5	8	402
Raman	2003	12886148	USA	adults	CT	74	5	3	272
Ramarajan	2009	20053244	USA	children	CT	43	0	9	155
Ramarajan	2009	20053244	USA	children	US	109	2	19	115
Ramarajan	2009	20053244	USA	children	CT + US	134	1	24	248
					PAIN ABDOMINOPELVIC OR TENDERNESS ABDOMINOPELVIC				
Rao	1999	10074991	USA	mixed	ABDOMINOPELVIC	32	0	0	68
Rao	1999	10074991	USA	mixed	WBC	24	8	28	40

Rao	1999	10074991	USA	women of reproductive age	CT	32	0	2	66
Rao	1997	9353441	USA	mixed	CT	52	1	1	46
Rao	1999	10074991	USA	mixed	PAIN RLQ	32	0	68	10
Rao	1999	10452424	USA	mixed	ABD XRAY	19	377	4	242
Rao	1999	10074991	USA	mixed	TENDERNESS REBOUND	9	23	14	54
Rao	1999	10074991	USA	mixed	PAIN RUQ	0	0	1	99
Rao	1997	8988203	USA	mixed	CT	56	0	2	41
Rao	1999	10074991	USA	mixed	GUARDING	8	24	7	61
Rao	1999	10077046	USA	mixed	CT	114	1	3	211
Rao	1999	10074991	USA	mixed	DIARRHEA	2	30	2	66
Rao	1996	9428814	USA	mixed	CT	53	1	1	45
Rao	1999	10074991	USA	mixed	NAUSEA	20	12	40	28
Rao	1999	10074991	USA	mixed	ANOREXIA	13	19	19	49
Rao	1997	9015058	USA	children	CT	17	39	0	43
Rao	1999	10074991	USA	mixed	PAIN BLQ	0	0	4	96
Rao	1999	10074991	USA	mixed	PAIN ABDOMINOPELVIC DIFFUSE	0	0	5	95
Rao	1997	9015058	USA	children	CT	52	4	2	41
Rao	1999	10074991	USA	mixed	FEVER	8	24	14	54
Rao	1999	10074991	USA	mixed	VOMITING	14	18	17	51
Rapp	2013	23360736	USA	pregnant women	MRI	17	2	6	187
Regimbeau	2003	12548414	France	mixed	CT	56	7	7	30
Regimbeau	2003	12548414	France	mixed	ABD XRAY	19	11	6	10
Regimbeau	2003	12548414	France	mixed	ABD XRAY	42	12	23	23
Regimbeau	2003	12548414	France	mixed	ABD XRAY	35	6	4	9
Regimbeau	2003	12548414	France	mixed	CT	18	9	6	13
Regimbeau	2003	12548414	France	mixed	CT	39	2	2	11
Reich	2011	22035447	USA	adults	CT	78	0	0	1
Reich	2011	22035447	Israel	adults	US	121	11	7	0
Rettenbacher	2003	12511674	Austria	mixed	US	108	0	109	65
Rettenbacher	2003	12511674	Austria	mixed	US	87	21	42	132
Rettenbacher	2002	12360459	Austria	mixed	US	126	2	5	217
Rettenbacher	2001	11230651	Austria	mixed	US	98	0	57	123
Rettenbacher	2001	11230651	Austria	mixed	US	92	6	22	158
Rettenbacher	2000	10644120	Austria	mixed	US	86	109	15	29
Rhea	2005	15908534	USA	women of reproductive age	CT	92	0	9	222
Rhea	2005	15908534	USA	mixed	CT	252	3	19	367
Rhea	2005	15908534	USA	elderly	CT	17	0	0	27
Rhea	2005	15908534	USA	children	CT	58	2	4	62
Rice	1999	10359177	USA	children	US	36	5	7	55
Rioux	1992	1546592	Canada	mixed	US	42	3	4	101

Rodriguez	2006	16554597	USA	children	CT	471	11	28	4
Rodriguez	2006	16554597	USA	children	US	13	0	1	0
Rodriguez	2006	16554597	USA	children	CT	113	2	19	4
Rodriguez	2006	16554597	USA	children	US	86	5	9	3
Rodriguez	2006	16554597	USA	children	CT	29	0	5	1
Rodriguez	2006	16554597	USA	children	CT	15	0	3	0
Rodriguez-Sanjuan	1999	10528772	Spain	children	CRP	60	44	4	16
Rompel	2006	17021716	Germany	children	US	42	1	1	6
Rordam	1987	3673452	Denmark	mixed	SEROTONIN	9	11	1	10
Rosengren	2004	15537403	Australia	adults	PAIN RIF	178	20	2	33
Rosengren	2004	15537403	Australia	adults	TENDERNESS RIF	19	75	12	0
Rosengren	2004	15537403	Australia	adults	GUARDING RIF	126	73	14	21
Rosengren	2004	15537403	Australia	adults	TENDERNESS RIF	194	5	0	35
Rosengren	2004	15537403	Australia	adults	ABD XRAY	6	1	0	58
Rosengren	2004	15537403	Australia	adults	US	15	34	3	16
Rosengren	2004	15537403	Australia	adults	CT	3	1	0	19
Rosengren	2004	15537403	Australia	adults	PAIN MIGRATION	124	74	21	14
Rosengren	2004	15537403	Australia	adults	FEVER	39	159	27	8
Rosengren	2004	15537403	Australia	adults	ANOREXIA	155	42	16	19
Rosengren	2004	15537403	Australia	adults	TENDERNESS REBOUND RIF	118	80	24	11
Rossi	1996	8662398	Italy	mixed	US	19	0	0	19
Rothrck	1991	1754487	USA	children	ABD XRAY	4	12	1	414
Rubin	1990	2199659	Canada	children	FEVER	25	20	20	45
Rubin	1990	2199659	Canada	children	PAIN RLO + TENDERNESS RLO	25	20	50	15
Rubin	1990	2199659	Canada	children	US	40	5	5	84
Rubin	1990	2199659	Canada	children	VOMITING	31	14	31	34
Rubin	1990	2199659	Canada	children	PULSE	29	16	31	34
Rubin	1990	2199659	Canada	children	WBC	26	19	14	51
Rubin	1990	2199659	Canada	children	SYMPTOMS DURATION	33	13	30	36
Russell	2011	23611916	USA	children	CT	46	0	2	15
Russell	2011	23611916	USA	children	US	24	14	2	23
Rypins	2000	10993624	USA	mixed	TC99M NUCLEAR	39	1	9	50
Rypins	2002	11807363	USA	children	TC99M NUCLEAR	10	1	5	32
Rypins	1997	9242338	USA	mixed	TC99M NUCLEAR	50	1	11	62
Rypins	2002	11807363	USA	mixed	TC99M NUCLEAR	53	6	19	122
Rypins	1997	9322663	USA	children	TC99M NUCLEAR	36	1	4	59
SCOAP Collaborative	2008	18936568	USA	mixed	CT + US	2578	198	96	15
Sack	2006	17132173	Germany	children	IL-6	21	1	83	106
Sakhri	2001	11910692	Tunesia	pregnant women	VOMITING	8	10	3	2
Sakhri	2001	11910692	Tunesia	pregnant women	ANOREXIA	2	16	1	4

Sakhri	2001	11910692	Tunesia	pregnant women	CONTRACTIONS UTARINE	3	15	0	5
Sakhri	2001	11910692	Tunesia	pregnant women	DISTENTION ABDOMINAL	1	17	0	5
Sakhri	2001	11910692	Tunesia	pregnant women	TENDERNESS RLO	9	9	4	1
Sakhri	2001	11910692	Tunesia	pregnant women	BLEEDING VAGINAL	0	18	2	3
Sakhri	2001	11910692	Tunesia	pregnant women	ROVSING SIGN	12	6	5	0
Sakhri	2001	11910692	Tunesia	pregnant women	PULSE	18	0	5	0
Sakhri	2001	11910692	Tunesia	pregnant women	TENDERNESS RUQ	3	15	0	5
Sakhri	2001	11910692	Tunesia	pregnant women	TENDERNESS ABDOMINAL DIFFUSE	2	16	0	5
Sakhri	2001	11910692	Tunesia	pregnant women	FEVER	12	6	5	0
Sakhri	2001	11910692	Tunesia	pregnant women	TENDERNESS RECTAL PELVIC ADNEXIAL	6	12	3	2
Sakhri	2001	11910692	Tunesia	pregnant women	WBC	18	0	5	0
Sakhri	2001	11910692	Tunesia	pregnant women	ABNORMAL URINATION	3	15	3	2
Sakhri	2001	11910692	Tunesia	pregnant women	DIARRHEA	1	17	0	5
Sakhri	2001	11910692	Tunesia	pregnant women	WBC	2	16	0	5
Sakhri	2001	11910692	Tunesia	pregnant women	NAUSEA	14	4	4	1
Sakhri	2001	11910692	Tunesia	pregnant women	PSOAS SIGN	3	15	0	5
Sakhri	2001	11910692	Tunesia	pregnant women	ABNORMAL URINALYSIS	4	14	2	3
Sakhri	2001	11910692	Tunesia	pregnant women	WBC	12	6	3	2
Sakover	1974	4846555	USA	mixed	BARIUM ENEMA	5	0	1	19
Salem	2005	16108882	UK	adults	CT	5	1	1	74
Samuel	2002	12037754	UK	children	WBC	624	110	113	323
Samuel	2002	12037754	UK	children	PAIN MIGRATION	719	15	148	288
Samuel	2002	12037754	UK	children	NAUSEA OR VOMITING	624	110	57	379
Samuel	2002	12037754	UK	children	TENDERNESS HOPPING	683	51	0	436
Samuel	2002	12037754	UK	children	TENDERNESS RLO	587	147	0	436
Samuel	2002	12037754	UK	children	ANOREXIA	683	51	78	358
Samuel	2002	12037754	UK	children	FEVER	653	81	65	371
Samuel	2002	12037754	UK	children	PMNC COUNT	595	139	122	314
Samuel	2002	12037754	UK	children	TENDERNESS COUGH PERCUSSION	683	51	0	436
Sand	2009	19672084	Germany	mixed	CRP	71	27	2	3
Sand	2009	19672084	Germany	mixed	WBC	46	52	0	5
Sand	2009	19672084	Germany	mixed	PROCALCITONIN	14	84	0	5
Santillanes	2012	22849662	USA	children	PMNC RATE	185	8	168	108
Santillanes	2012	22849662	USA	children	BOWEL SOUNDS	72	110	35	236
Santillanes	2012	22849662	USA	children	OBSTIPATION	30	151	22	238
Santillanes	2012	22849662	USA	children	CT	59	6	3	119
Santillanes	2012	22849662	USA	children	TENDERNESS RLO	182	10	187	89
Santillanes	2012	22849662	USA	children	GUARDING	133	57	85	188
Santillanes	2012	22849662	USA	children	TENDERNESS PERIUMBILICAL	80	112	100	170
Santillanes	2012	22849662	USA	children	PSOAS SIGN	69	111	32	231

Santillanes	2012	22849662	USA	children	PAIN DURATION	164	26	174	81
Santillanes	2012	22849662	USA	children	PAIN ABDOMINAL	39	141	84	177
Santillanes	2012	22849662	USA	children	US	44	49	10	196
Santillanes	2012	22849662	USA	children	ROVSING SIGN	64	123	23	242
Santillanes	2012	22849662	USA	children	OBTURATOR SIGN	61	119	25	235
Santillanes	2012	22849662	USA	children	TENDERNESS	48	136	87	181
Santillanes	2012	22849662	USA	children	WBC	172	21	142	134
Santillanes	2012	22849662	USA	children	TENDERNESS REBOUND	68	120	35	239
Santillanes	2012	22849662	USA	children	PAIN RLO	172	17	173	97
Santillanes	2012	22849662	USA	children	VOMITING	141	52	168	106
Santillanes	2012	22849662	USA	children	PAIN PERIUMBILICAL	95	95	133	135
Santillanes	2012	22849662	USA	children	DIARRHEA	42	150	49	222
Santillanes	2012	22849662	USA	children	ANOREXIA	155	38	152	117
Santillanes	2012	22849662	USA	children	TENDERNESS DIFFUSE	51	138	59	208
Santillanes	2012	22849662	USA	children	FEVER	60	132	90	184
Santillanes	2012	22849662	USA	children	PAIN ABDOMINAL DIFFUSE	56	130	73	190
Santos	2009	19886134	USA	mixed	CT	29	0	1	26
Savar	2006	16556158	USA	mixed	CT	13	1	2	0
Schellekens	2010	23859584	Netherlands	mixed	WBC	60	17	45	111
Schellekens	2010	23859584	Netherlands	mixed	WBC	75	2	105	51
Schellekens	2010	23859584	Netherlands	mixed	CP PLASMA MARKER	35	42	27	129
Schellekens	2010	23859584	Netherlands	mixed	SAA-1 PLASMA MARKER	59	18	48	108
Schellekens	2010	23859584	Netherlands	mixed	CRP	66	11	69	87
Schellekens	2010	23859584	Netherlands	mixed	SAA-1 PLASMA MARKER	75	2	97	59
Schellekens	2010	23859584	Netherlands	mixed	CRP	66	11	69	87
Schellekens	2010	23859584	Netherlands	mixed	CT	46	0	0	4
Schellekens	2010	23859584	Netherlands	mixed	CP PLASMA MARKER	75	2	120	36
Schellekens	2010	23859584	Netherlands	mixed	US	24	4	3	29
Schey	1973	4704036	USA	children	BARIUM ENEMA	9	0	3	13
Scholar	1998	9597298	USA	children	TENDERNESS RECTAL	2	6	0	45
Schuh	2011	20828717	Canada	children	US	86	0	9	76
Schuler	1998	9565116	USA	adults	CT	49	1	1	43
Schulte	1998	9971899	Germany	children	US	110	9	12	115 4
Schupp	2010	20490812	Germany	children	US	11	16	16	25
Schwerk	1989	2666252	Germany	pregnant women	US	1	0	0	6
Schwerk	1989	2666252	Germany	mixed	US	115	15	8	394
Schwerk	1989	2666252	Germany	women of reproductive age	US	12	3	0	13
Schwerk	1989	2666252	Germany	women of reproductive age	US	2	1	0	61
Schwerk	1989	2666252	Germany	women of reproductive age	US	18	4	0	92
Schwerk	1990	2183487	Germany	mixed	US	174	20	12	651

Schwerk	1989	2666252	Germany	mixed	US	11	1	0	237
Schwerk	1989	2666252	Germany	women of reproductive age	US	4	0	0	18
Schwerk	1989	2666252	Germany	mixed	US	73	12	4	42
Schwerk	1989	2666252	Germany	mixed	US	31	2	4	115
Sedlak	2008	18358949	Switzerland	adults	TENDERNESS RECTAL	85	117	148	208
Sengupta	2009	19102827	UK	mixed	WBC + CRP	10	9	8	71
Sengupta	2009	19102827	UK	mixed	WBC	16	3	22	57
Sengupta	2009	19102827	UK	mixed	CRP	12	7	25	54
Sengupta	2009	19102827	UK	mixed	WBC + CRP	19	0	39	40
Seo	2009	19542400	South Korea	mixed	CT	77	1	6	116
Seo	2009	19542400	South Korea	mixed	CT	78	0	4	122
Seo	2009	19542400	South Korea	mixed	CT	78	0	9	115
Seo	2009	19542400	South Korea	mixed	CT	78	0	4	120
Sezer	2012	23356200	Turkey	mixed	US	55	22	3	11
Shafi	2009	19568576	India	mixed	PMNC COUNT	90	2	8	10
Shafi	2009	19568576	India	mixed	CRP + PMNC COUNT	77	15	2	16
Shafi	2009	19568576	India	mixed	CRP + NEUTROPHIL% + PMNC COUNT	81	11	1	17
Shafi	2009	19568576	India	mixed	CRP	88	4	4	14
Shakhatreh	2000	10934841	Jordan	mixed	CRP	85	4	1	8
Sharma	2007	23132981	India	mixed	US	57	33	5	23
Shinbrot	1992	1559861	USA	mixed	US	9	8	0	4
Shirazi	2010	20437687	Iran	mixed	US	51	4	3	52
Shung-Shung	2002	11917347	Taiwan	mixed	TC99M NUCLEAR	36	3	13	28
Siddique	2011	21847441	UK	children	WBC	134	33	12	25
Siddique	2011	21847441	UK	children	CRP	125	42	10	27
Siegel	1991	1895479	USA	children	US	31	7	0	140
Sim	2013	23392792	Korea	mixed	CT	67	307	0	495
Sim	2013	23392792	Korea	mixed	CT	348	0	5	445
Sim	2013	23392792	Korea	mixed	US	12	0	3	55
Sim	2013	23392792	Korea	mixed	CT	277	97	2	493
Sim	2013	23392792	Korea	mixed	CT	374	0	50	445
Sim	2013	23392792	Korea	mixed	CT	349	25	12	483
Sim	2013	23392792	Korea	mixed	CT	153	221	1	494
Sim	1990	2674464	USA	mixed	US	26	0	0	0
Sim	2013	23392792	Korea	mixed	CT	366	8	41	454
Sim	2013	23392792	Korea	mixed	CT	348	26	5	490
Simonovsky	1999	10484221	Czech Republic	mixed	US	143	11	36	849
Simonovsky	1995	7489627	Czech Republic	mixed	US	105	10	15	426
Singh	2009	18649091	USA	mixed	MRI	12	1	1	27
Singh	2009	18649091	USA	pregnant women	MRI	4	0	0	14

Singh-Ranger	2010	20626973	UK	mixed	WBC	53	29	8	10
Singh-Ranger	2010	20626973	UK	mixed	WBC + FEVER	11	71	0	18
Singh-Ranger	2010	20626973	UK	mixed	FEVER	11	71	0	18
Singh-Ranger	2010	20626973	UK	women of reproductive age	WBC + FEVER	4	16	0	9
Singh-Ranger	2010	20626973	UK	women of reproductive age	FEVER	4	16	0	9
Singh-Ranger	2010	20626973	UK	women of reproductive age	WBC	12	8	3	6
Singh-Ranger	2010	20626973	UK	women of reproductive age	WBC OR FEVER	12	8	3	6
Singh-Ranger	2010	20626973	UK	mixed	WBC OR FEVER	53	29	8	10
Sivit	1992	1410371	USA	children	US	46	6	5	123
Sivit	2000	11000147	USA	children	US	65	18	17	215
Sivit	2000	10924565	USA	children	CT	58	3	6	87
Sivit	2000	11000147	USA	children	CT	58	3	6	86
Skaane	1997	9358775	Norway	mixed	US	35	61	13	96
Skaane	1997	9358775	Norway	mixed	CRP	61	35	58	51
Skaane	1990	2242476	Norway	mixed	US	67	0	13	0
Skaane	1997	9358775	Norway	mixed	ESR	33	63	21	88
Skaane	1997	9358775	Norway	mixed	WBC	69	27	45	64
Smink	2004	15017570	USA	children	PROTOCOL OF IMAGING SIGNS SYMPTOMS LABS	254	3	15	299
Soda	2001	11585505	Japan	mixed	US	52	8	3	26
Soda	2001	11585505	Japan	mixed	US	47	13	1	28
Sohail	2009	19260568	Pakistan	adults	US	53	41	3	3
Sohail	2009	19260568	Pakistan	adults	US	85	9	1	5
Sondenaa	1992	1455149	Norway	mixed	CRP	36	26	29	67
Sondenaa	1992	1455149	Norway	mixed	CRP	26	36	20	76
Sondenaa	1992	1455149	Norway	mixed	CRP	31	31	26	70
Sondenaa	1992	1455149	Norway	mixed	CRP	18	44	14	82
Sondenaa	1992	1455149	Norway	mixed	CRP	17	45	14	82
Sondenaa	1992	1455149	Norway	women of reproductive age	CRP	27	35	29	67
Sondenaa	1992	1455149	Norway	mixed	CRP	27	35	23	73
Sondenaa	1992	1455149	Norway	women of reproductive age	CRP	23	39	25	71
Sood	1977	615255	India	mixed	WBC	176	16	17	11
Staniland	1980	7011161	UK, Norway	mixed	PAIN MIGRATION	129	73	64	201
Staniland	1980	7011161	UK, Norway	mixed	ANOREXIA	149	53	135	130
Staniland	1980	7011161	UK, Norway	mixed	PAIN COUGH	38	164	16	249
Staniland	1980	7011161	UK, Norway	mixed	NAUSEA	158	44	156	109
Staniland	1980	7011161	UK, Norway	mixed	VOMITING	131	71	110	155
Staniland	1980	7011161	UK, Norway	mixed	PAIN RLO	152	50	82	183
Steele	1986	3563460	Scotland	mixed	THERMOGRAPHY ABDOMINAL	20	12	3	5

Stefanutti	2007	17502181	Italy	children	CRP	86	14	4	4
Stefanutti	2007	17502181	Italy	children	WBC + CRP	98	2	4	4
Stefanutti	2007	17502181	Italy	children	WBC	60	40	2	6
Stephen	2003	12632351	USA	women of reproductive age	CT				
Stephen	2003	12632351	USA	children	CT	87	5	4	0
Stephens	1999	10218289	USA	mixed	US	62	7	3	3
Stewart	2012	22638942	USA	mixed	US	55	6	5	74
Stewart	2006	17058729	USA	pregnant women	CT	1	1	0	2
Stewart	1986	2878273	New Zealand	adults	PERITONEAL CELL SAMPLE	9	1	0	17
Stewart	2012	22638942	USA	mixed	CT	11	0	11	79
Stewart	2006	17058729	USA	pregnant women	TC99M NUCLEAR	1	1	3	8
Stroman	1999	10670858	USA	mixed	CT	33	3	11	60
Stroman	1999	10670858	USA	mixed	WBC	25	11	32	39
Stroman	1999	10670858	USA	mixed	US	3	7	8	24
Stroman	1999	10670858	USA	mixed	PAIN RLQ	31	5	52	19
Stroman	1999	10670858	USA	mixed	ANOREXIA	18	18	15	56
Stroman	1999	10670858	USA	mixed	FEVER	11	25	7	64
Stroman	1999	10670858	USA	mixed	WBC:LYMPHOCYTE	32	4	42	29
Stroman	1999	10670858	USA	mixed	NAUSEA OR VOMITING	25	11	37	34
Stromberg	2007	17896131	Sweden	mixed	CT	313	21	41	181
Stunnell	2008	18807813	Ireland	women of reproductive age	US	5	21	0	9
Styrud	2000	10733085	Sweden	mixed	CT	25	2	0	12
Styrud	2000	10733085	Sweden	mixed	CT	19	4	3	20
Styrud	1999	9949266	Sweden	mixed	WBC + CRP	1571	49	320	41
Styrud	2000	10733085	Sweden	mixed	US	72	23	11	95
Styrud	2000	10733085	Sweden	mixed	US	194	42	13	236
Styrud	2000	10733085	Sweden	mixed	CT	44	6	3	361
Styrud	2000	10733085	Sweden	mixed	US	122	19	2	61
Summa	2007	23396678	Italy	mixed	US	369	7	7	125
Summa	2007	23396678	Italy	mixed	WBC	298	70	410	106
Summa	2007	23396678	Italy	mixed	CRP	243	125	453	4
Sun	2008	18520542	Korea	adults	CT	201	12	10	669
Sun	2002	12395266	Taiwan	adults	US	21	4	1	23
Sun	2008	18520542	Korea	women of reproductive age	CT	66	6	5	76
Sun	2002	12395266	Taiwan	adults	TC99M NUCLEAR	23	2	2	22
Tabbara	2012	22496979	Switzerland	women of reproductive age	US	55	142	0	27
Tamanna	2012	23588904	Saudi Arabia	mixed	WBC	47	1	45	23
Tamanna	2012	23588904	Saudi Arabia	mixed	WBC	21	27	6	62
Tamanna	2012	23588904	Saudi Arabia	mixed	WBC	43	5	18	50

Tamanna	2012	23588904	Saudi Arabia	mixed	WBC	43	5	24	44
Tamanna	2012	23588904	Saudi Arabia	mixed	WBC	35	13	15	53
Tamburrini	2007	17180324	USA	adults	CT	73	8	13	310
Tamburrini	2007	17180324	USA	adults	CT	22	1	8	95
Tamir	1990	2252115	USA	pregnant women	FEVER	43	11	19	11
Tamir	1990	2252115	USA	pregnant women	TENDERNESS BLO	3	51	4	26
Tamir	1990	2252115	USA	pregnant women	DIARRHEA	17	37	5	25
Tamir	1990	2252115	USA	pregnant women	ANOREXIA	38	16	18	12
Tamir	1990	2252115	USA	pregnant women	CONSTIPATION	2	52	3	27
Tamir	1990	2252115	USA	pregnant women	WBC	53	1	3	27
Tamir	1990	2252115	USA	pregnant women	ABNORMAL URINATION	4	50	5	25
Tamir	1990	2252115	USA	pregnant women	TENDERNESS RIGHT FLANK COSTOVERTERBRAL	14	40	9	21
Tamir	1990	2252115	USA	pregnant women	PAIN RLO PERIUMBILICAL DIFFUSE	26	28	9	21
Tamir	1990	2252115	USA	pregnant women	DISTENTION ABDOMINAL	7	47	1	29
Tamir	1990	2252115	USA	pregnant women	BOWEL SOUNDS	35	19	14	16
Tamir	1990	2252115	USA	pregnant women	PMNC RATE	22	7	18	12
Tamir	1990	2252115	USA	pregnant women	TENDERNESS MID- EPIGASTRIC	5	49	1	29
Tamir	1990	2252115	USA	pregnant women	FEVER	18	36	10	20
Tamir	1990	2252115	USA	pregnant women	OBTURATOR SIGN	7	47	8	22
Tamir	1990	2252115	USA	pregnant women	CONTRACTIONS UTAINE	8	46	6	24
Tamir	1990	2252115	USA	pregnant women	CHILLS	20	34	12	18
Tamir	1990	2252115	USA	pregnant women	PAIN MID-EPIGASTRIC	6	48	1	29
Tamir	1990	2252115	USA	pregnant women	ROVSING SIGN	18	36	8	22
Tamir	1990	2252115	USA	pregnant women	BACTERIURIA	12	42	2	28
Tamir	1990	2252115	USA	pregnant women	WBC	25	29	10	20
Tamir	1990	2252115	USA	pregnant women	NAUSEA	49	5	20	10
Tamir	1990	2252115	USA	pregnant women	PSOAS SIGN	8	46	10	20
Tamir	1990	2252115	USA	pregnant women	PAIN RIGHT FLANK	4	50	3	27
Tamir	1990	2252115	USA	pregnant women	PAIN RMQ	5	49	0	30
Tamir	1990	2252115	USA	pregnant women	PULSE	19	35	13	17
Tamir	1990	2252115	USA	pregnant women	PAIN RLO	15	39	13	17
Tamir	1990	2252115	USA	pregnant women	FEVER	9	45	8	22
Tamir	1990	2252115	USA	pregnant women	GUARDING	34	20	14	16
Tamir	1990	2252115	USA	pregnant women	TENDERNESS DIFFUSE	4	50	6	24
Tamir	1990	2252115	USA	pregnant women	PAIN RUQ	4	50	3	27
Tamir	1990	2252115	USA	pregnant women	PAIN ABDOMINAL	1	53	1	29
Tamir	1990	2252115	USA	pregnant women	TENDERNESS RLO	45	9	20	10
Tamir	1990	2252115	USA	pregnant women	TENDERNESS RMQ	5	49	1	29
Tamir	1990	2252115	USA	pregnant women	PAIN BLO	4	50	6	24
Tamir	1990	2252115	USA	pregnant women	TENDERNESS REBOUND	45	9	23	7

Tamir	1990	2252115	USA	pregnant women	TENDERNESS RECTAL PELVIC ADNEXIAL	23	31	20	10
Tamir	1990	2252115	USA	pregnant women	BLEEDING VAGINAL	3	51	4	26
Tamir	1990	2252115	USA	pregnant women	PYURIA	12	42	10	20
Tamir	1990	2252115	USA	pregnant women	VOMITING	44	10	14	16
Tamir	1990	2252115	USA	pregnant women	TENDERNESS RUO	10	44	6	24
Tan	2013	23351046	Singapore	mixed	CT	77	6	4	127
Teo	2000	11256346	Singapore	children	CT	3	0	0	9
Teo	2000	11256346	Singapore	children	US	21	2	3	95
Tepel	2004	14634825	Germany	mixed	WBC	93	20	109	178
Tepel	2004	14634825	Germany	mixed	RECTAL TEMPERATURE	78	35	112	175
Tepel	2004	14634825	Germany	mixed	US	71	34	21	244
Tepel	2004	14634825	Germany	mixed	CRP	96	17	143	144
Terzi	2010	21104201	Turkey	pregnant women	US	15	17	2	4
Thakur	2001	11388572	USA	adults	TC99M NUCLEAR	13	2	0	31
Thimsen	1989	2742230	USA	mixed	CRP	17	9	20	0
Thirumoorthi	2012	23217887	USA	children	CT + US	254	16	0	5
Thompson	1992	1393485	UK	mixed	CRP CHANGE	25	11	4	14
Thompson	1992	1393485	UK	mixed	WBC CHANGE	33	3	0	18
Thompson	1992	1393485	UK	mixed	CRP	25	11	3	15
Thompson	1992	1393485	UK	mixed	WBC	25	11	4	14
Thompson	1992	1393485	UK	mixed	CRP	32	4	3	15
Thompson	1992	1393485	UK	mixed	WBC	17	19	4	14
Thompson	1992	1393485	UK	mixed	WBC + CRP	15	21	0	18
Togawa	2005	15783013	Japan	adults	CT	47	11	4	38
Togawa	2005	15783013	Japan	adults	CRP	11	0	0	8
Togawa	2005	15783013	Japan	adults	CT + CRP	58	0	0	8
Tomizawa	2011	21937369	Japan	mixed	US	7	0	0	31
Toorenvliet	2010	20582544	Netherlands	mixed	CT + US	113	9	6	471
Toorenvliet	2010	20582544	Netherlands	mixed	CT	4	0	0	90
Toorenvliet	2010	20582544	Netherlands	mixed	US	94	9	6	310
Torbati	2003	12896881	USA	mixed	CT	43	4	5	166
Tracey	2000	10888131	USA	pregnant women	FEVER	3	18	0	1
Tracey	2000	10888131	USA	pregnant women	PAIN ABDOMINAL DIFFUSE	6	15	0	1
Tracey	2000	10888131	USA	pregnant women	GUARDING AND TENDERNESS REBOUND	16	5	1	0
Tracey	2000	10888131	USA	pregnant women	PAIN RUO	7	14	0	1
Tracey	2000	10888131	USA	pregnant women	PAIN RIGHT FLANK	2	19	0	1
Tracey	2000	10888131	USA	pregnant women	CONTRACTIONS UTARINE	1	20	0	1
Tracey	2000	10888131	USA	pregnant women	US	3	0	0	0
Tracey	2000	10888131	USA	pregnant women	SYMPTOMS DURATION	15	6	0	1
Tracey	2000	10888131	USA	pregnant women	PAIN RLO	6	15	1	0
Tracey	2000	10888131	USA	pregnant women	NAUSEA OR VOMITING	11	10	0	1

Trout	2012	22947273	USA	children	US	72	31	10	107
Trout	2012	22947273	USA	children	US	94	9	18	110
Trout	2012	22947273	USA	children	US	68	36	67	59
Trout	2012	22947273	USA	children	US	56	47	9	108
Trout	2012	22947273	USA	children	US	8	96	0	129
Trout	2012	22947273	USA	children	US	21	36	5	44
Trout	2012	22947273	USA	children	US	98	5	68	49
Trout	2012	22947273	USA	children	US	89	14	91	26
Trout	2012	22947273	USA	children	US	5	99	0	129
Trout	2012	22947273	USA	children	US	28	40	1	65
Trout	2012	22947273	USA	children	US	57	47	49	77
Trout	2012	22947273	USA	children	US	101	2	97	20
Trout	2012	22947273	USA	children	US	61	42	6	116
Trout	2012	22947273	USA	children	US	29	74	3	115
Trout	2012	22947273	USA	children	US	100	15	33	84
Trout	2012	22402833	USA	children	US	109	1	35	101
Trout	2012	22947273	USA	children	US	81	22	15	102
Trout	2012	22947273	USA	children	US	94	10	15	110
Trout	2012	22947273	USA	children	US	74	29	8	109
Trout	2012	22947273	USA	children	US	100	3	60	57
Trout	2012	22947273	USA	children	US	35	68	3	114
Trout	2012	22947273	USA	children	US	88	5	68	49
Trout	2012	22947273	USA	children	US	97	6	82	36
Trout	2012	22947273	USA	children	US	77	26	21	96
Trout	2012	22947273	USA	children	US	102	1	93	24
Tsao	2008	18498874	USA	children	CT	593	27	22	15
Tseng	2008	19054918	Taiwan	children	TENDERNESS REBOUND RLQ	246	10	17	127
Tseng	2008	19054918	Taiwan	children	DIARRHEA	56	200	14	130
Tseng	2008	19054918	Taiwan	children	TENDERNESS RLQ	253	3	4	140
Tseng	2008	19054918	Taiwan	children	US	41	15	11	64
Tseng	2008	19054918	Taiwan	children	FULLNESS ABDOMINAL TENDERNESS RLQ	5	251	10	134
Tseng	2008	19054918	Taiwan	children	ITERMITTENT	0	256	24	120
Tseng	2008	19054918	Taiwan	children	ABD XRAY	142	101	42	23
Tseng	2008	19054918	Taiwan	children	VOMITING	167	89	25	119
Tseng	2008	19054918	Taiwan	children	TENDERNESS RLQ DIFFUSE TENDERNESS RLQ + GUARDING	3	253	17	127
Tseng	2008	19054918	Taiwan	children	CT	9	247	4	140
Tseng	2008	19054918	Taiwan	children	CT	60	1	0	73
Tseng	2008	19054918	Taiwan	children	FEVER	147	109	16	128
Tsushima	2002	12069469	Japan	adults	CT	44	3	4	74
Turan	1999	10466611	Turkey	children	TC99M NUCLEAR	15	4	1	10

Turkyilmaz	2006	17101565	Turkey	children	IL-6	39	22	21	23
Turkyilmaz	2006	17101565	Turkey	children	IL-6	54	7	36	8
Turkyilmaz	2006	17101565	Turkey	children	TNF-ALPHA	33	28	20	24
Turkyilmaz	2006	17101565	Turkey	children	TNF-ALPHA	46	15	36	8
Turkyilmaz	2006	17101565	Turkey	children	WBC	58	3	32	12
Turkyilmaz	2006	17101565	Turkey	children	WBC	47	14	14	30
Turkyilmaz	2006	17101565	Turkey	children	WBC OR IL-6	60	1	13	31
Turkyilmaz	2006	17101565	Turkey	children	IL-6 OR TNF-ALPHA	60	1	34	10
Turkyilmaz	2006	17101565	Turkey	children	TNF-ALPHA	28	33	16	28
Turkyilmaz	2006	17101565	Turkey	children	WBC	60	1	10	34
Turkyilmaz	2006	17101565	Turkey	children	IL-6	33	28	17	27
Turkyilmaz	2006	17101565	Turkey	children	IL-6	28	33	14	30
Turkyilmaz	2006	17101565	Turkey	children	IL-6	28	33	10	34
Turkyilmaz	2006	17101565	Turkey	children	TNF-ALPHA	45	16	12	32
Turkyilmaz	2006	17101565	Turkey	children	IL-6	31	30	16	28
Turkyilmaz	2006	17101565	Turkey	children	IL-6	5	56	4	40
Turkyilmaz	2006	17101565	Turkey	children	TNF-ALPHA	47	14	28	16
Turkyilmaz	2006	17101565	Turkey	children	TNF-ALPHA	57	4	39	5
Turkyilmaz	2006	17101565	Turkey	children	TNF-ALPHA	43	18	9	35
Turkyilmaz	2004	15125095	Turkey	children	ABD XRAY	129	52	20	12
Turkyilmaz	2004	15125095	Turkey	children	ABD XRAY	51	130	12	20
Turkyilmaz	2006	17101565	Turkey	children	IL-6	54	7	30	14
Turkyilmaz	2006	17101565	Turkey	children	WBC	31	30	10	34
Turkyilmaz	2006	17101565	Turkey	children	IL-6	31	30	10	34
Turkyilmaz	2006	17101565	Turkey	children	TNF-ALPHA	40	21	3	41
Turkyilmaz	2006	17101565	Turkey	children	TNF-ALPHA	55	6	36	8
Turkyilmaz	2006	17101565	Turkey	children	IL-6 OR TNF-ALPHA	60	1	10	34
Turkyilmaz	2006	17101565	Turkey	children	TNF-ALPHA	40	21	29	15
Turkyilmaz	2006	17101565	Turkey	children	WBC OR TNF-ALPHA	52	9	3	41
Turkyilmaz	2006	17101565	Turkey	children	WBC	41	20	10	34
Turkyilmaz	2006	17101565	Turkey	children	WBC OR IL-6 OR TNF-ALPHA	60	1	36	8
Turkyilmaz	2006	17101565	Turkey	children	WBC	59	2	31	13
Turkyilmaz	2006	17101565	Turkey	children	WBC	54	7	26	18
Turkyilmaz	2006	17101565	Turkey	children	WBC	48	13	16	28
Turkyilmaz	2006	17101565	Turkey	children	WBC OR IL-6 OR TNF-ALPHA	60	1	12	32
Turkyilmaz	2006	17101565	Turkey	children	IL-6	33	28	0	44
Turkyilmaz	2006	17101565	Turkey	children	WBC	58	3	35	9
Turkyilmaz	2004	15125095	Turkey	children	ABD XRAY	152	18	29	14
Turkyilmaz	2006	17101565	Turkey	children	TNF-ALPHA	27	34	17	27
Turkyilmaz	2006	17101565	Turkey	children	IL-6	55	6	38	6
Turkyilmaz	2006	17101565	Turkey	children	TNF-ALPHA	33	28	20	24

Turkyilmaz	2006	17101565	Turkey	children	TNF-ALPHA	56	5	43	1
Turkyilmaz	2006	17101565	Turkey	children	WBC	52	9	24	20
Turkyilmaz	2006	17101565	Turkey	children	WBC	60	1	37	7
Turkyilmaz	2006	17101565	Turkey	children	WBC	28	33	5	39
Turkyilmaz	2006	17101565	Turkey	children	IL-6	59	2	39	5
Turkyilmaz	2006	17101565	Turkey	children	WBC OR IL-6	60	1	36	8
Tzanakis	2005	16088420	Greece	adults	WBC	79	51	18	155
Tzanakis	2005	16088420	Greece	adults	ANOREXIA	90	40	122	51
Tzanakis	2005	16088420	Greece	adults	US	107	23	9	164
Tzanakis	2005	16088420	Greece	adults	VOMITING	62	68	64	109
Tzanakis	2005	16088420	Greece	adults	TENDERNESS RLO	117	13	71	102
Tzanakis	2005	16088420	Greece	adults	CRP	105	25	80	93
Tzanakis	2005	16088420	Greece	adults	GUARDING	64	66	33	140
Tzanakis	2005	16088420	Greece	adults	TENDERNESS REBOUND	86	44	44	129
Tzanakis	2005	16088420	Greece	adults	FEVER	96	34	101	72
Tzanakis	2005	16088420	Greece	adults	PAIN MIGRATION	79	51	57	116
Tzanakis	2005	16088420	Greece	adults	SYMPTOMS DURATION	109	21	112	61
Tzanakis	2005	16088420	Greece	adults	TENDERNESS RECTAL	35	95	55	118
Tzanakis	2005	16088420	Greece	adults	NEUTROPHIL%	111	19	78	95
Ujiki	2002	12121697	USA	adults	CT	26	5	8	64
Ujiki	2002	12121697	USA	adults	CT	28	3	8	64
Ujiki	2002	12121697	USA	adults	CT	14	2	4	49
Unal	2011	21831513	Turkey	adults	US	4	2	7	7
Unal	2011	21831513	Turkey	adults	MRI	2	0	1	3
Unlu	2009	19559106	Netherlands	mixed	RIGIDITY	95	238	8	600
Unlu	2009	19559106	Netherlands	mixed	TENDERNESS RLO	329	4	585	23
Unlu	2009	19559106	Netherlands	mixed	NAUSEA	65	268	79	529
Unlu	2009	19559106	Netherlands	mixed	DIARRHEA	19	314	19	589
Unlu	2009	19559106	Netherlands	mixed	SYMPTOMS DURATION TENDERNESS RLO	280	53	549	59
Unlu	2009	19559106	Netherlands	mixed	REBOUND	263	70	58	550
Unlu	2009	19559106	Netherlands	mixed	CRP	279	54	331	277
Unlu	2009	19559106	Netherlands	mixed	TENDERNESS RECTAL	8	328	10	595
Unlu	2009	19559106	Netherlands	mixed	VOMITING	38	295	39	569
Unlu	2009	19559106	Netherlands	mixed	PAIN VAGINAL EXAM	18	119	89	305
Unlu	2009	19559106	Netherlands	mixed	WBC + CRP	4	329	174	434
Unlu	2009	19559106	Netherlands	mixed	PAIN PROGRESSION	23	310	33	575
Unlu	2009	19559106	Netherlands	mixed	WBC	296	37	307	301
Unlu	2009	19559106	Netherlands	mixed	PSOAS SIGN	96	237	7	601
Unlu	2009	19559106	Netherlands	mixed	ROVSING SIGN	171	162	27	581
Unlu	2009	19559106	Netherlands	mixed	FEVER	29	304	22	586
Van den Broek	2002	12428873	Netherlands	mixed	WBC	268	59	112	138

Van den Broek	2002	12428873	Netherlands	mixed	SYMPTOMS DURATION	271	56	162	88
Van den Broek	2002	12428873	Netherlands	mixed	TENDERNESS REBOUND	265	62	110	140
Van den Broek	2004	15065030	Netherlands	children	FEVER	47	18	17	17
Van den Broek	2004	15065030	Netherlands	children	TENDERNESS REBOUND	57	8	7	27
Van den Broek	2002	12428873	Netherlands	mixed	FEVER	245	82	157	93
Van den Broek	2004	15065030	Netherlands	children	SYMPTOMS DURATION	50	15	20	14
Van den Broek	2004	15065030	Netherlands	children	WBC	52	13	8	26
Vaughan-Shaw	2011	21637404	UK	mixed	WBC + CRP + NEUTROPHIL COUNT	86	76	5	17
Vaughan-Shaw	2011	21637404	UK	mixed	WBC	115	47	10	12
Vaughan-Shaw	2011	21637404	UK	mixed	CRP	110	52	8	14
Vaughan-Shaw	2011	21637404	UK	mixed	NEUTROPHIL COUNT	51	13	10	39
Vaughan-Shaw	2011	21637404	UK	mixed	WBC	45	19	9	40
Vaughan-Shaw	2011	21637404	UK	mixed	WBC OR CRP OR NEUTROPHIL COUNT	149	13	8	14
Vaughan-Shaw	2011	21637404	UK	mixed	WBC + CRP + NEUTROPHIL COUNT	29	35	5	44
Vaughan-Shaw	2011	21637404	UK	mixed	WBC OR CRP OR NEUTROPHIL COUNT	60	4	20	29
Vaughan-Shaw	2011	21637404	UK	mixed	NEUTROPHIL COUNT	126	36	11	11
Vaughan-Shaw	2011	21637404	UK	mixed	CRP	42	22	13	36
Vermeulen	1999	10207461	Switzerland	adults	US	58	14	43	50
Vermeulen	1999	10207461	Switzerland	women of reproductive age	US	48	18	56	72
Vermeulen	1999	10207461	Switzerland	women of reproductive age	US	21	4	32	35
Vermeulen	1999	10207461	Switzerland	adults	US	117	38	75	110
Vermeulen	1999	10207461	Switzerland	women of reproductive age	US	27	14	24	37
Vermeulen	1999	10207461	Switzerland	adults	US	59	24	32	60
Verroken	1996	8830871	Belgium	mixed	US	55	7	7	75
Verroken	1996	8830871	Belgium	mixed	US	115	22	14	68
Vignault	1990	2195594	Canada	children	US	30	3	5	32
Vu	2009	19560166	Canada	pregnant women	MRI	1	1	0	17
Wade	1993	8368922	USA	mixed	US	53	9	7	38
Wade	1993	8368922	USA	adults	US	40	5	3	23
Wade	1993	8368922	USA	adults	US	7	4	3	14
Walker	2000	11182396	USA	adults	CT	30	2	0	25
Wallace	2008	17963012	USA	pregnant women	CT	2	0	1	2
Wallace	2008	17963012	USA	pregnant women	CT + US	9	3	0	1
Wallace	2008	17963012	USA	pregnant women	US	17	18	4	16
Wang	2012	22205003	Taiwan	adults	CT	26	0	1	32
Wang	2012	22205003	Taiwan	adults	PAIN RLQ	25	1	29	4
Wang	2007	17351404	USA	children	WBC + LEFT SHIFT	25	17	22	346
Wang	2012	22205003	Taiwan	adults	PAIN DULL	20	6	22	11
Wang	2012	22205003	Taiwan	adults	PAIN LLQ	6	20	7	26

Wang	2012	22205003	Taiwan	adults	WBC	20	6	16	17
Wang	2012	22205003	Taiwan	adults	PAIN RUQ	3	23	5	28
Wang	2012	22205003	Taiwan	adults	PAIN SHARP	4	22	7	26
Wang	2012	22205003	Taiwan	adults	PAIN REBOUND	10	16	14	19
Wang	2012	22205003	Taiwan	adults	PAIN RLQ	4	22	6	27
Wang	2012	22205003	Taiwan	adults	PAIN LUQ	4	22	6	27
Wang	2012	22205003	Taiwan	adults	FEVER	3	23	9	24
Wang	2007	17351404	USA	children	WBC OR LEFT SHIFT	33	9	74	294
Wang	2012	22205003	Taiwan	adults	ANOREXIA	9	17	18	15
Wang	2012	22205003	Taiwan	adults	NAUSEA	8	18	12	21
Wang	2007	17351404	USA	children	WBC	28	14	74	294
Wang	2007	17351404	USA	children	LEFT SHIFT	25	17	37	331
Wang	2012	22205003	Taiwan	adults	PAIN CRAMPING	2	24	4	29
Wang	2012	22205003	Taiwan	adults	MCBURNEY SIGN	16	10	22	11
Wang	2003	12749236	Taiwan	adults	TC99M NUCLEAR	28	7	0	10
Wang	2012	22205003	Taiwan	adults	PAIN MIGRATION	15	11	12	21
Wang	2012	22205003	Taiwan	adults	NEUTROPHIL%	18	8	20	13
Webb	2011	21940573	USA	adults	CT	180	22	16	10
Webb	2011	21940573	USA	adults	CT	399	34	22	10
Webb	2011	21940573	USA	adults	CT	180	22	6	10
Webb	2011	21940573	USA	adults	CT	401	32	10	12
Weltman	2000	10887244	USA	mixed	CT	40	8	2	50
Weltman	2000	10887244	USA	mixed	CT	39	9	3	49
Weltman	2000	10887244	USA	mixed	CT	48	0	1	51
Weltman	2000	10887244	USA	mixed	CT	47	1	1	51
West	2006	16921703	Jamaica	mixed	US	5	12	1	12
West	2006	16921703	Jamaica	mixed	WBC	9	6	4	9
Weyant	2000	10922984	USA	mixed	CT	183	9	26	24
Weyant	2001	12594877	USA	children	US	6	4	2	2
Whitney	1992	1332523	USA	adults	ANOREXIA	19	4	5	0
Whitney	1992	1332523	USA	adults	FEVER	15	8	2	3
Whitney	1992	1332523	USA	adults	PERITONITIS DIFFUSE	7	16	4	1
Whitney	1992	1332523	USA	adults	DIARRHEA	6	17	3	2
Whitney	1992	1332523	USA	adults	CHILLS	6	17	1	4
Whitney	1992	1332523	USA	adults	PAIN RLQ	10	13	2	3
Whitney	1992	1332523	USA	adults	NAUSEA OR VOMITING	11	12	5	0
Wiersma	2009	18815791	Netherlands	children	US	70	1	5	95
Wiersma	2009	18815791	Netherlands	children	US	59	1	3	95
Wijetunga	2001	11719671	Australia	mixed	CT	28	2	2	68
Wild	1985	4026076	USA	mixed	TENDERNESS REBOUND	18	5	7	3
Wild	1985	4026076	USA	mixed	ANOREXIA	21	2	11	0

Wild	1985	4026076	USA	mixed	GUARDING	19	4	9	1
Wild	1985	4026076	USA	mixed	PSOAS SIGN	11	12	1	10
Wild	1985	4026076	USA	mixed	TENDERNESS RLO	22	1	10	0
Wild	1985	4026076	USA	mixed	LEFT SHIFT	21	2	8	2
Wild	1985	4026076	USA	mixed	WBC	10	13	7	3
Wild	1985	4026076	USA	mixed	NAUSEA + VOMITING	18	5	11	0
Wild	1985	4026076	USA	mixed	SYMPTOMS DURATION	7	16	1	10
Wild	1985	4026076	USA	mixed	SYMPTOMS DURATION	9	14	2	9
Wild	1985	4026076	USA	mixed	BARIUM ENEMA	23	0	5	5
Wild	1985	4026076	USA	mixed	PYURIA OR HEMATURIA	3	20	5	5
Williams	2009	19476843	USA	children	TENDERNESS RLO	108	43	27	69
Williams	2009	19476843	USA	children	TENDERNESS DIFFUSE	42	109	16	80
Wilson	1994	8658993	Belgium	children	PAIN CHEST	0	87	11	2
Wilson	1994	8658993	Belgium	children	GUARDING	67	20	7	6
Wilson	1994	8658993	Belgium	children	TENDERNESS REBOUND	40	47	9	4
Wilson	1994	8658993	Belgium	children	HEADACHE	0	87	12	1
Wilson	1994	8658993	Belgium	children	PAIN RIF	63	24	10	3
Wilson	1994	8658993	Belgium	children	PAIN COUGH	0	87	11	2
Wilson	1994	8658993	Belgium	children	SORE THROAT	3	84	9	4
Wilson	1994	8658993	Belgium	children	CONSTIPATION	2	85	10	3
Wilson	1994	8658993	Belgium	children	FEVER	64	23	3	10
Wilson	1994	8658993	Belgium	children	DIARRHEA	13	74	12	1
Wilson	1994	8658993	Belgium	children	VOMITING	59	28	0	13
Wilson	1994	8658993	Belgium	children	COMBINATION OF SIGNS + SYMPTOMS	78	9	3	10
Wilson	1994	8658993	Belgium	children	ABNORMAL URINATION	2	85	12	1
Wilson	2001	11387006	USA	mixed	US	17	0	7	0
Wilson	1994	8658993	Belgium	children	RHONCHI OR CREPITATIONS	0	87	11	2
Wilson	1994	8658993	Belgium	children	PAIN ABDOMINAL	14	73	10	3
Wilson	2001	11387006	USA	mixed	CT	33	2	3	33
Wise	2001	11264081	USA	adults	US	1	1	4	8
Wise	2001	11264081	USA	adults	CT	20	4	13	63
Wise	2001	11264081	USA	adults	CT	17.04	6.84	6.96	69.1
Wise	2001	11264081	USA	adults	CT		0.70	6.12	
Wise	2001	11264081	USA	adults	CT	23.04	626	455	69.9
Wise	2001	11264081	USA	adults	CT		3	7	2
Wise	2001	11264081	USA	adults	US		9.31	16.0	
Wise	2001	11264081	USA	adults	US	13.68	218	591	62.3
Wise	2001	11264081	USA	adults	CT	18	4	3	2
Wise	2001	11264081	USA	adults	CT		15.3	11.2	
Wise	2001	11264081	USA	adults	US	8.16	313	685	65.3
Wise	2001	11264081	USA	adults	CT		6	7	6
Wise	2001	11264081	USA	adults	CT	17.76	7.34	7.61	66.1
Wise	2001	11264081	USA	adults	CT		666	142	2

							7	9	
							15.8	8.66	
							661	042	67.6
Wise	2001	11264081	USA	adults	US	7.68	7	5	4
Wise	2001	11264081	USA	adults	CT	19	5	9	68
Wise	2001	11264081	USA	adults	CT	18	6	10	66.1
								14.4	
								248	
Wise	2001	11264081	USA	adults	CT	19.92	3.4	3	64.6
							8.06	25.3	
							298	362	53.9
Wise	2001	11264081	USA	adults	US	14.88	8	2	6
Wong	1997	9404876	USA	mixed	US	8	1	0	5
Wong	1994	7807325	USA	children	US	25	4	1	61
Wong	1997	9404876	USA	women of reproductive age	TC99M NUCLEAR	8	1	0	7
Wong	1997	9404876	USA	mixed	TC99M NUCLEAR	21	2	0	12
Wong	1997	9404876	USA	mixed	US	18	3	0	10
Wong	2002	12169286	Singapore	mixed	CT	35	2	1	12
Worrell	1990	2407861	USA	mixed	US	29	15	14	142
Worrell	1990	2407861	USA	mixed	US	29	15	11	145
Worrell	1990	2407861	USA	mixed	US	5	39	0	156
Worrell	1990	2407861	USA	mixed	US	26	18	3	153
Worrell	1990	2407861	USA	mixed	US	33	11	14	142
Worrell	1990	2407861	USA	mixed	US	33	11	11	145
Worrell	1990	2407861	USA	mixed	US	30	14	3	153
Wu	2003	14674227	Taiwan	children	NEUTROPHIL%	156	56	16	32
Wu	2003	14674227	Taiwan	children	CRP	168	44	27	21
Wu	2003	14674227	Taiwan	children	WBC + NEUTROPHIL%	151	61	14	34
Wu	2006	16782436	Taiwan	mixed	CRP				
Wu	2012	22491817	Taiwan	mixed	CRP	78	35	2	99
Wu	2006	16782436	Taiwan	mixed	US				
Wu	2003	14674227	Taiwan	children	WBC + CRP + NEUTROPHIL% + BAND%	14	198	3	45
Wu	2003	14674227	Taiwan	children	NEUTROPHIL%	97	115	6	42
Wu	2003	14674227	Taiwan	children	WBC	196	16	34	14
Wu	2012	22491817	Taiwan	mixed	NAUSEA OR VOMITING	52	61	44	57
Wu	2006	16782436	Taiwan	mixed	CRP + NEUTROPHIL COUNT	80	27	9	109
Wu	2006	16782436	Taiwan	mixed	CT				
Wu	2012	22491817	Taiwan	mixed	TENDERNESS REBOUND	46	67	29	72
Wu	2005	16032609	Taiwan	mixed	CRP	84	33	4	19
Wu	2012	22491817	Taiwan	mixed	LEFT SHIFT	69	44	29	72
Wu	2003	14674227	Taiwan	children	BAND%	31	181	7	41
Wu	2003	14674227	Taiwan	children	NEUTROPHIL%	51	161	3	45
Wu	2003	14674227	Taiwan	children	WBC	67	145	8	40

Wu	2006	16782436	Taiwan	mixed	CRP				
Wu	2012	22491817	Taiwan	mixed	MCBURNEY SIGN	104	9	94	7
Wu	2003	14674227	Taiwan	children	WBC + CRP + NEUTROPHIL%	84	128	8	40
Wu	2012	22491817	Taiwan	mixed	FEVER	53	60	14	87
Wu	2003	14674227	Taiwan	children	WBC	153	59	14	34
Wu	2012	22491817	Taiwan	mixed	CRP	96	17	74	27
Wu	2003	14674227	Taiwan	children	WBC	105	107	10	38
Wu	2003	14674227	Taiwan	children	WBC	203	9	42	6
Wu	2005	16032609	Taiwan	mixed	CRP	68	112	7	30
Wu	2012	22491817	Taiwan	mixed	PROCALCITONIN	108	5	84	17
Wu	2012	22491817	Taiwan	mixed	WBC	69	44	28	73
Wu	2005	16032609	Taiwan	mixed	CRP	91	54	9	31
Wu	2006	16782436	Taiwan	mixed	NEUTROPHIL%				
Wu	2003	14674227	Taiwan	children	WBC	181	31	26	22
Wu	2012	22491817	Taiwan	mixed	ANOREXIA	46	67	45	56
Wu	2012	22491817	Taiwan	mixed	PROCALCITONIN	35	78	10	91
Wu	2012	22491817	Taiwan	mixed	PAIN MIGRATION	43	70	27	74
Xharra	2012	22866907	Kosovo	mixed	NEUTROPHIL%	117	31	8	17
Xharra	2012	22866907	Kosovo	mixed	WBC + CRP	137	11	6	19
Xharra	2012	22866907	Kosovo	mixed	WBC	126	22	8	17
Xharra	2012	22866907	Kosovo	mixed	CRP	126	22	7	18
Xharra	2012	22866907	Kosovo	mixed	WBC + CRP + NEUTROPHIL%	141	7	2	23
Xharra	2012	22866907	Kosovo	mixed	WBC + NEUTROPHIL%	133	15	7	18
Xharra	2012	22866907	Kosovo	mixed	CRP + NEUTROPHIL%	140	8	7	18
Yan	2002	12195306	Taiwan	children	TC99M NUCLEAR	29	1	4	16
Yang	2005	15943411	Taiwan	elderly	WBC + CRP + NEUTROPHIL%	75	2	7	1
Yang	2005	15943411	Taiwan	elderly	NEUTROPHIL%	68	9	6	2
Yang	2006	16483301	China	mixed	WBC + NEUTROPHIL%	702	38	130	27
Yang	2005	15943411	Taiwan	elderly	WBC + CRP	74	3	7	1
Yang	2006	16483301	China	mixed	WBC + CRP	727	13	138	19
Yang	2006	16483301	China	mixed	CRP	566	174	116	41
Yang	2005	15943411	Taiwan	elderly	WBC + NEUTROPHIL%	71	6	6	2
Yang	2006	16483301	China	mixed	WBC	635	105	107	50
Yang	2006	16483301	China	mixed	NEUTROPHIL%	645	95	105	52
Yang	2006	16483301	China	mixed	WBC + CRP + NEUTROPHIL%	734	6	147	10
Yang	2005	15943411	Taiwan	elderly	CRP	70	7	6	2
Yang	2005	15943411	Taiwan	elderly	WBC	55	22	5	3
Yazici	2010	21043386	Turkey	children	NEUTROPHIL:WBC	159	24	5	52
Yazici	2010	21043386	Turkey	children	NEUTROPHIL:WBC	165	18	7	50
Yazici	2010	21043386	Turkey	children	NEUTROPHIL:WBC	148	35	3	54

Yazici	2010	21043386	Turkey	children	WBC	162	21	39	18
Yazici	2010	21043386	Turkey	children	NEUTROPHIL:WBC	167	16	16	41
Yazici	2010	21043386	Turkey	children	NEUTROPHIL:WBC	154	29	5	52
Yetkin	2002	12471766	Turkey	adults	CT	42	3	3	17
Yigiter	2011	21480284	Turkey	children	US	14	5	0	1
Yigiter	2011	21480284	Turkey	children	US	99	19	0	4
Yigiter	2011	21480284	Turkey	children	US	14	5	0	1
Yildirim	2006	17101603	Turkey	mixed	WBC OR CRP OR IL-6 OR IL-10	71	0	8	6
Yildirim	2006	17101603	Turkey	mixed	WBC OR CRP OR IL-6 OR IL-10	28	43	5	9
Yildirim	2006	17101603	Turkey	mixed	WBC OR CRP OR IL-6 OR IL-10	8	63	2	12
Yildirim	2006	17101603	Turkey	mixed	CRP	50	21	5	9
Yildirim	2006	17101603	Turkey	mixed	IL-10	29	42	1	13
Yildirim	2006	17101603	Turkey	mixed	IL-6	56	15	7	7
Yildirim	2006	17101603	Turkey	mixed	WBC OR CRP OR IL-6 OR IL-10	51	20	7	7
Yildirim	2008	18306139	Turkey	adults	CT	122	8	5	8
Yildirim	2006	17101603	Turkey	mixed	WBC	62	9	5	9
Zaki	1994	7945068	Australia	children	US	16	2	0	6
Zeidan	1997	9046139	USA	mixed	US	23	8	4	59
Zhu	2012	23289088	China	mixed	MRI	33	3	0	5
Zielke	2001	11369983	Germany	mixed	US	13	5	3	79
Zielke	2001	11369983	Germany	mixed	US	10	5	3	82
Zielke	2001	11369983	Germany	mixed	US	78	16	3	303
Zielke	1997	9094278	Germany	mixed	US	7	6	2	222
Zielke	1998	9562281	Germany	mixed	US	114	29	17	509
Zielke	2001	11369983	Germany	mixed	US	267	40	40	653
Zielke	1997	9094278	Germany	mixed	US	94	19	13	378
Zielke	2001	11369983	Germany	mixed	US	168	36	29	567
Zielke	2001	11369983	Germany	mixed	US	55	18	9	318
Zielke	1997	9094278	Germany	mixed	US	51	7	4	17
Zielke	2001	11369983	Germany	mixed	US	403	137	53	1616
Zielke	1997	9094278	Germany	mixed	US	36	6	7	139
Zona	1985	1188426	USA	children	BARIUM ENEMA	14	0	7	16
Zuniga	2012	22653450	Spain	children	WBC	26	2	37	36
Zuniga	2012	22653450	Spain	children	PMNC COUNT	27	1	32	41
Zuniga	2012	22653450	Spain	children	TENDERNESS COUGH PERCUSSION	20	8	38	35
Zuniga	2012	22653450	Spain	children	TENDERNESS RLO	25	3	49	24
Zuniga	2012	22653450	Spain	children	NAUSEA OR VOMITING	22	6	41	32
Zuniga	2012	22653450	Spain	children	ANOREXIA	25	3	49	24
Zuniga	2012	22653450	Spain	children	PAIN MIGRATION	13	15	17	56

Zuniga	2012	22653450	Spain	children	BLUMBERG SIGN	14	14	21	52
Zuniga	2012	22653450	Spain	children	FEVER	13	15	23	50
el Ferzli	1990	2360147	USA	mixed	BARIUM ENEMA	15	2	2	48
in't Hof	2004	15386320	Netherlands	adults	CT	83	4	0	16
in't Hoff	2009	19164615	Netherlands	adults	CT	79	8	1	15
in't Hoff	2009	19164615	Netherlands	adults	CT	71	16	1	15
in't Hoff	2009	19164615	Netherlands	adults	CT	83	4	0	15
van Breda Vriesman	2003	12845461	Netherlands	mixed	CT + US	208	4	8	1
van Dieijen- Visser	1991	1782282	Netherlands	mixed	WBC OR CRP OR SEGMENTED GRANULOCYTES %	75	1	48	48
van Dieijen- Visser	1991	1782282	Netherlands	mixed	WBC + CRP + SEGMENTED GRANULOCYTES %	17	59	1	95
van Dieijen- Visser	1991	1782282	Netherlands	mixed	WBC OR CRP	74	2	43	53
van Dieijen- Visser	1991	1782282	Netherlands	mixed	WBC + CRP	43	33	7	89
van Randen	2011	21365197	Netherlands	adults	CT	267	17	37	700
van Randen	2010	20119730	Netherlands	adults	CT	271	12	33	626
van Randen	2010	20119730	Netherlands	adults	US	260	23	112	547
van Randen	2011	21365197	Netherlands	adults	US	216	68	37	700

Table C2. Risk of bias, studies of the test performance of clinical signs and symptoms, laboratory tests, and imaging tests

Author	Year	PMID	Quality Item 1	Quality Item 2	Quality Item 3	Quality Item 4	Quality Item 5	Quality Item 6	Quality Item 7	Quality Item 8
Abo	2011	21811194	no	no	yes	no	no	no	no	yes
Abu-Yousef	1987	3296711	yes	yes	no	yes	yes	no	no	yes
Acar	2012	21641156	yes	no	no	yes	no	yes	yes	no
Acosta	2005	15633057	no	yes	yes	yes	no	yes	no	yes
Adams	1988	3277469	no	no	yes	yes	no	no	no	no
Adesunkanmi AR.	1993	8199059	yes	no	yes	yes	no	no	no	yes
Agrawal	2008	18700623	no	no	no	yes	no	yes	yes	yes
Ahmed	2006	17044228	yes	yes	no	no	no	yes	no	yes
Ahn	2002	12355000	yes	no	no	no	no	yes	yes	yes
Akhtar	2011	22204183	no	yes	no	no	no	yes	no	yes
Al Hilli	2009	19350346	no	no	yes	yes	yes	yes	yes	yes
Al-Ajerami	2012	22360013	no	no	yes	yes	no	no	no	no
Al-Gaithy	2012	23031349	no	yes	yes	yes	no	yes	yes	yes
Al-Mulhim	1996	9028994	no	no	no	yes	no	yes	yes	yes
Al-Saigh	1992	1383518	yes	no	yes	yes	no	yes	yes	yes
Albano	2001	11724048	yes	no	no	no	no	no	no	yes
Albu	1994	8287747	no	yes	yes	no	yes	no	no	no
Alleman	1999	10574106	yes	yes	yes	no	no	yes	no	yes
Allister	2009	20097375	no	no	no	yes	no	yes	no	yes
Alobaidi	2003	12490503	no	yes	no	yes	no	yes	yes	yes
Alshehri	1995	7588144	yes	no	yes	no	no	no	no	no
Althoubaily	2006	17106538	no	no	yes	no	no	no	no	no
Alvarado	1986	3963537	yes	yes	yes	no	no	no	yes	no
Amalesh	2004	17462226	no	no	no	yes	no	yes	yes	yes
Amland	1989	2662692	no	yes	no	no	no	yes	no	yes
Andersen	1980	7376784	no	no	no	yes	no	yes	yes	yes
Andersen	1999	10535336	yes	no	no	yes	no	yes	yes	yes
Anderson	2009	19843742	yes	yes	yes	yes	yes	yes	yes	yes
Andersson	2000	11071167	no	yes	no	no	yes	no	yes	no
Andersson	1999	9880421	no	yes	no	no	yes	yes	no	yes
Ang	2001	11673709	no	yes	yes	yes	no	yes	no	no
Anielski	2010	19924436	yes	no	yes	no	no	no	no	yes
Antevil	2004	15529835	no	yes	no	no	no	yes	no	yes
Antevil	2006	17116553	yes	yes	no	no	no	yes	no	yes
Applegate	2001	11425980	no	yes	no	yes	no	yes	no	no
Arnbjornsson	1985	3909908	yes	yes	no	yes	no	yes	yes	yes
Artiko	2009	19760940	no	yes	no	no	no	yes	yes	yes
Asadi	2011	21553201	yes	yes	yes	yes	no	yes	no	yes

Asfar	2000	10815376	yes	yes	yes	yes	yes	yes	yes	yes
Ashdown	2012	23247977	no	no	yes	no	no	no	no	no
Ashindoitiang	2008	19062484	yes	no	no	no	no	yes	yes	yes
Ashraf	2006	16767943	no	yes	no	yes	no	yes	no	yes
Assefa	2006	17447365	no	yes	yes	yes	no	yes	yes	no
Avcu	2013	23266968	yes	no	no	no	no	no	no	no
Bachur	2012	22841176	no	no	yes	yes	no	no	yes	no
Baldisserotto	2000	11044049	yes	no	yes	yes	no	yes	no	yes
Baldisserotto	2007	17331831	yes	yes	yes	yes	no	yes	yes	yes
Balthazar	1994	8259423	yes	no	yes	yes	no	no	no	yes
Balthazar	1991	2052696	yes	yes	no	no	no	no	no	yes
Balthazar	1998	9625125	yes	yes	no	no	no	yes	no	yes
Barbee	1975	1138636	no	no	yes	no	no	yes	no	yes
Barloon	1995	7787719	no	yes	no	yes	yes	yes	no	yes
Barron	1999	10076613	no	no	yes	yes	no	yes	no	yes
Bealer	2010	20370768	no	no	no	no	yes	no	yes	no
Becker	2007	17192449	no	yes	no	yes	no	yes	no	yes
Beltran	2007	17618882	yes	yes	yes	yes	no	yes	yes	yes
Bendeck	2002	12354996	yes	no	yes	no	no	no	no	yes
Berry	1984	6385879	yes	no	no	yes	no	yes	yes	yes
Biersack	1993	8508569	no	no	no	yes	no	yes	no	yes
Bilbey	1989	2647214	yes	no	no	no	no	yes	no	yes
Birchard	2005	15671363	yes	yes	no	yes	no	yes	no	yes
Birchley	2006	16460636	yes	no	no	yes	no	yes	yes	yes
Birchley	2009	19723423	no	no	yes	no	no	no	no	no
Blalock	1989	2610191	no	no	no	no	no	yes	yes	yes
Boehnert	2009	20367723	yes	no	no	no	no	no	no	no
Bolton	1975	1191953	yes	yes	yes	no	no	yes	no	yes
Bondi	2012	22273324	no	no	yes	yes	no	yes	no	yes
Bonello	1979	428284	no	yes	no	yes	no	yes	yes	yes
Bower	1981	7209769	no	no	yes	yes	no	yes	yes	yes
Brandt	2003	14509318	yes	yes	no	yes	no	yes	yes	yes
Brewer	1976	1251963	yes	yes	no	no	no	yes	no	yes
Brooks	1965	14261578	yes	yes	yes	yes	yes	yes	yes	yes
Bullard	1999	17659136	yes	yes	no	yes	no	yes	no	yes
Burford	2011	21683208	yes	no	yes	yes	yes	yes	no	no
Butler	1987	3586627	no	yes	no	no	no	yes	no	yes
Caglayan	2010	21038123	no	yes	yes	yes	no	yes	yes	yes
Cakirer	2002	15290575	yes	yes	yes	no	no	no	yes	no
Campbell	1988	3395821	yes	no	yes	no	no	no	no	yes
Cannon	1956	13157341	no	no	yes	yes	no	yes	yes	yes

Cardall	2004	15466143	yes	no	no	no	no	yes	no	yes
Cavusoglu	2009	19184052	no	no	no	no	no	yes	no	yes
Ceres	1990	2186346	yes	no	no	no	no	no	no	yes
Ceydeli	2006	17084779	yes	yes	no	yes	no	yes	yes	yes
Cha	1996	8875877	no	no	yes	yes	no	yes	no	yes
Chabanova	2011	20347539	yes	yes	yes	yes	yes	yes	yes	no
Chakhunashvili	2005	16444038	no	no	yes	yes	no	yes	no	no
Chan	2005	15908535	no	no	no	no	no	yes	no	yes
Chang	2003	12749239	no	yes	yes	yes	no	yes	yes	yes
Chang	2007	17460492	no	yes	no	no	yes	yes	no	yes
Chee	1982	7157006	no	no	no	no	no	no	no	no
Chen	1996	8630133	yes	yes	yes	yes	no	yes	yes	yes
Chen	2000	10919537	no	no	yes	yes	no	no	no	yes
Chen	1998	9564286	yes	yes	yes	yes	yes	yes	yes	yes
Chen	1998	10668876	yes	yes	no	no	no	yes	yes	yes
Cheng	2003	12630009	no	no	no	no	no	yes	no	yes
Chesbrough	1993	8475271	yes	yes	yes	yes	no	no	yes	no
Chi	1996	8639195	no	yes	no	yes	no	yes	yes	no
Chin	2012	22919012	yes	yes	no	no	no	no	yes	no
Chiu	2013	22951113	no	yes	no	yes	no	yes	no	yes
Cho	1999	10515341	yes	yes	yes	no	no	no	yes	no
Choi	2003	14616200	yes	yes	no	no	no	yes	no	yes
Choi	2012	22067287	yes	yes	yes	no	yes	yes	no	yes
Choi	1998	9699047	no	yes	no	yes	no	yes	yes	yes
Choudhary	1980	7410859	yes	no	no	no	no	yes	yes	yes
Choudhri	2012	22146833	no	yes	no	no	no	yes	no	yes
Christopher	2002	12217464	no	yes	no	yes	no	no	yes	no
Cobben	2009	19137303	yes	yes	yes	yes	no	yes	no	yes
Cobben	2004	15333354	yes	yes	no	yes	no	yes	no	yes
Colak	2001	11383861	yes	no	yes	yes	no	yes	no	yes
Colvin	2007	18091591	no	yes	no	no	no	yes	no	yes
Connor	1994	7856985	yes	yes	no	yes	no	yes	yes	yes
Corey	1984	6702761	yes	no	yes	yes	no	no	yes	yes
Coursey	2010	20093517	no	no	no	yes	no	yes	yes	yes
Coursey	2011	21679558	yes	no	no	no	no	no	no	no
Crady	1993	8517561	yes	yes	yes	yes	no	yes	no	yes
Daly	2005	15908536	yes	no	no	no	no	no	no	yes
Davidson	1999	9914351	yes	no	yes	no	no	no	no	yes
Davies	1991	1941740	no	yes	yes	no	no	yes	no	yes
Davies	1991	1958978	yes	yes	no	no	no	no	no	yes
De Oliveira Peixoto	2011	21710048	no	no	no	yes	no	no	yes	yes

DeLaney	1989	2802977	yes	yes	no	no	no	yes	no	yes
Dearing	2008	18942613	yes	no	yes	yes	no	no	no	yes
Deibener	2011	21421538	yes	no	no	no	no	no	no	no
Deniszbası	2003	14676508	yes	yes	no	no	no	no	no	yes
Di Cesare	2013	23860049	yes	yes	no	no	no	yes	no	yes
Dickson	1985	4026364	no	yes	no	no	no	no	no	no
Dilley	2001	11172421	yes	yes	yes	yes	no	yes	yes	no
Dixon	1991	2004144	yes	yes	no	no	no	yes	no	yes
Doraiswamy	1979	519164	no	no	yes	no	no	no	no	yes
Douglas	2000	11030676	no	yes	no	yes	no	yes	no	yes
Dueholm	1989	2676422	yes	no	yes	yes	no	no	no	yes
Dunning	1991	1863045	yes	no	no	no	no	no	no	yes
Durakbasa	2006	16456751	no	yes	yes	yes	yes	yes	yes	yes
Duzgun	2007	17708281	yes	yes	no	yes	no	yes	yes	yes
D'ippolito	1998	10349191	no	no	yes	yes	no	yes	yes	no
Ege	2002	12200239	no	no	no	no	no	no	yes	no
Elangovan	1996	8659268	no	no	no	yes	no	yes	no	no
Emery	1994	8285972	no	no	yes	yes	no	no	yes	no
Emil	2001	11329589	yes	yes	no	yes	no	yes	yes	yes
Emmanuel	2011	21477433	yes	no	yes	yes	no	no	no	no
English	1977	869331	no	no	no	no	no	no	no	no
Eriksson	1994	7886405	yes	no	no	yes	no	yes	yes	yes
Eriksson	1989	2741614	yes	no	no	yes	no	yes	yes	yes
Eriksson	1995	8775633	yes	no	yes	yes	no	yes	yes	yes
Eriksson	1995	7727605	yes	no	yes	yes	no	yes	yes	no
Erkasap	2000	10967943	yes	no	yes	no	no	no	yes	no
Escriba	2011	21346681	no	yes	no	no	no	yes	no	yes
Eskelinen	1995	7610351	no	no	no	no	no	no	no	no
Estey	2013	23528502	yes	no	yes	yes	no	no	no	yes
Even-Bendahan	2003	12635978	yes	yes	no	no	no	yes	no	yes
Evetts	1994	8044391	no	no	no	yes	no	yes	no	yes
Exadaktylos	2008	18842129	no	yes	no	yes	yes	yes	no	no
Fa	1989	2675357	yes	yes	yes	yes	no	yes	no	yes
Fefferman	2001	11526268	yes	yes	yes	no	yes	no	no	yes
Fente	2009	20120145	no	no	no	yes	no	yes	no	yes
Fenyo	1997	9414043	no	no	no	no	no	no	no	yes
Fergusson	2002	12437687	no	yes	no	yes	no	yes	yes	yes
Filiz	2010	20690847	yes	yes	no	yes	no	no	no	no
Foley	1992	1456603	no	yes	no	yes	yes	yes	yes	yes
Ford	1994	7978690	yes	yes	no	no	no	no	yes	no
Fox	2007	20440399	yes	yes	no	yes	no	yes	yes	yes

Fox	2008	18446069	yes	no	yes	yes	no	yes	no	no
Franke	1999	9880422	no	yes	yes	yes	no	yes	no	yes
Freeland	2009	19969125	yes	yes	no	no	no	yes	no	yes
Frisenda R, Roty AR Jr, Kilway JB, Brown AL 2nd, Peelen M.	1979	507547	yes	no	no	yes	no	yes	yes	no
Fuchs	2002	12127818	no	no	yes	yes	no	no	yes	yes
Fujii	2000	10841063	yes	no	yes	no	no	no	yes	no
Funaki	1998	9762983	no	yes	yes	yes	no	no	yes	no
Gai	1988	3051464	no	no	no	no	no	no	no	no
Gaitini	2008	18430847	yes	yes	yes	yes	no	yes	no	yes
Galindo	1998	9462380	no	yes	yes	no	no	yes	no	yes
Gallagher	2006	16953529	yes	yes	no	yes	no	yes	no	yes
Gamanagatti	2007	17245521	yes	no	yes	yes	no	no	yes	yes
Ganguli	2006	16928971	no	no	yes	yes	no	yes	no	yes
Garcia	1987	3687874	yes	yes	yes	no	no	yes	yes	yes
Garcia Pena	2004	14702442	yes	yes	no	no	no	yes	no	yes
Garcia Pena	1999	10469767	yes	no	yes	yes	no	yes	no	no
Garcia-Aguayo	2000	11305565	yes	no	no	yes	no	yes	no	yes
Gendel	2011	21480165	yes	yes	no	yes	no	yes	yes	yes
Ghotbi	2006	17041792	yes	no	no	no	no	yes	no	yes
Giuliano	2005	16133622	no	yes	no	yes	no	yes	no	yes
Goldin	2011	21409546	no	yes	no	yes	no	yes	no	yes
Goldman	2008	18534219	no	yes	no	no	no	yes	no	yes
Golledge	1996	8659965	no	yes	no	yes	no	yes	no	yes
Goodman	1995	7887542	no	yes	yes	yes	no	yes	yes	no
Gracey	2007	17467395	yes	no	yes	yes	no	yes	yes	yes
Graham	1980	7356110	yes	yes	no	no	no	yes	yes	yes
Graham	1991	1836403	no	yes	yes	yes	no	yes	no	yes
Gray	1988	2970820	no	no	yes	yes	no	yes	no	no
Gronroos	1999	10552288	yes	no	no	yes	no	yes	yes	yes
Gronroos	1999	10340286	yes	no	yes	yes	no	no	yes	yes
Groselj-Grenc	2007	17589979	yes	yes	no	yes	no	no	no	no
Groselj-Grenc	2007	17365999	yes	no	no	yes	no	no	no	yes
Gurian	2011	22040784	no	no	no	yes	no	no	yes	yes
Gurleyik	1995	7497838	yes	yes	no	yes	yes	yes	yes	yes
Gurleyik	2002	12269920	yes	no	no	yes	no	yes	yes	yes
Gutierrez	1999	10551747	no	no	no	no	no	no	yes	no
Gwynn	2001	11489398	no	no	no	no	no	yes	no	yes
Gwynn	2002	12217465	no	no	yes	yes	no	no	no	no
Hahn	1998	9561531	no	no	yes	no	no	no	no	yes
Hale	1997	9060580	yes	yes	no	yes	no	yes	yes	yes

Hallan	1997	9248988	yes	no	yes	no	no	no	no	no
Hallan	1997	9231854	yes	no	no	no	no	yes	no	yes
Haller	2010	19878040	yes	no	no	no	no	no	no	yes
Hallfeldt	1994	7934421	no	no	no	no	no	no	no	no
Hambidge	1990	2182159	yes	yes	no	yes	yes	yes	yes	no
Hansen	2004	15611455	yes	yes	yes	yes	yes	yes	yes	yes
Harland	1991	2051426	no	no	no	yes	no	yes	yes	yes
Hatch	1981	7252733	no	yes	no	yes	no	yes	yes	yes
Hayden	1992	1588691	yes	no	no	no	no	no	yes	no
Hebert	2005	17056904	no	no	yes	no	no	yes	no	yes
Hee	1999	10405056	yes	no	no	yes	no	yes	yes	yes
Hekimoglu	2011	22191292	no	yes	no	no	no	yes	no	yes
Henneman	1990	2206141	no	yes	yes	no	no	yes	no	yes
Henneman	1988	3276246	no	yes	no	no	no	yes	no	yes
Henneman	1990	2330248	yes	no	no	yes	yes	yes	no	yes
Herliczek	2012	23617477	no	yes	yes	yes	no	no	no	yes
Hernandez	2005	15635471	no	yes	yes	no	no	yes	no	yes
Hernandez	2008	18358937	no	no	no	yes	no	no	yes	yes
Hershko	2007	17566826	yes	yes	yes	yes	no	yes	no	yes
Hershko	2002	12455796	yes	yes	no	yes	yes	yes	yes	no
Heverhagen	2012	22033948	yes	yes	no	yes	no	yes	no	yes
Himeno	2003	12880303	no	no	no	no	no	yes	no	yes
Hoecker and Billman	2005	15837022	yes	yes	no	yes	yes	no	no	yes
Holloway	2003	14672779	no	yes	yes	no	no	yes	no	yes
Hong	2003	14588157	yes	no	no	yes	no	yes	yes	no
Hormann	2003	12764662	no	yes	yes	no	no	yes	no	yes
Hormann	1998	9694477	no	no	no	yes	no	yes	yes	no
Horton	2000	10930484	no	no	yes	no	no	no	yes	no
Howie	1984	6481676	yes	no	no	no	no	yes	no	yes
Hsieh	2010	20466403	no	yes	no	no	no	yes	no	yes
Huynh	2007	17983068	no	yes	yes	yes	no	no	no	no
Incesu	2004	15081132	yes	yes	no	no	no	yes	no	yes
Incesu	1997	9057512	yes	no	yes	yes	no	no	no	yes
Inci	2011	20655156	yes	yes	no	yes	no	yes	no	yes
Inci	2011	20924585	no	yes	no	yes	no	yes	no	yes
Isman	2010	20172058	no	no	no	yes	no	no	yes	yes
Israel	2008	18666160	yes	yes	yes	no	no	no	no	yes
Ives	2008	18620120	no	yes	yes	yes	yes	yes	yes	yes
Izbicki	1992	1352137a	yes	yes	no	yes	no	yes	no	yes
Izbicki	1992	1352137b	no	no	no	yes	no	yes	no	yes
Jacobs	2001	11526267	yes	no	yes	no	no	no	no	no

Jahn	1997	9231855	yes	yes	no	yes	yes	yes	no	yes
Jang	2010	19144480	yes	no	no	no	no	no	no	yes
Jang	2011	21835887	yes	no	yes	no	no	no	no	yes
Jangjoo	2012	21450436	no	yes	yes	yes	no	no	no	no
Jangjoo	2011	21954737	yes	yes	yes	no	no	yes	yes	no
Jaremko	2011	20493658	no	no	yes	yes	no	yes	no	yes
Jawaid	1999	10647233	no	no	no	yes	no	yes	yes	yes
Je	2009	19533813	no	no	no	no	no	no	yes	no
Jeffrey	1988	3282253	yes	yes	no	yes	no	yes	no	yes
Jeffrey	1987	3547490	no	no	no	yes	no	yes	no	yes
Johansson	2007	17453494	yes	yes	no	yes	no	yes	no	no
John	2011	21786842	no	no	no	yes	yes	yes	yes	yes
John	1993	8511921	no	no	no	no	no	yes	no	yes
Johnson	2009	19304692	no	yes	no	no	no	yes	no	yes
Johnson	2012	22623558	no	yes	yes	yes	no	yes	no	yes
Jones	2004	15619494	yes	no	yes	yes	no	yes	yes	yes
Jorulf	1996	8796514	yes	no	no	no	no	no	no	yes
Josephson	2000	11016772	yes	yes	no	no	no	yes	no	yes
Kafetzis	2005	15995845	no	yes	yes	yes	no	yes	yes	yes
Kaidu	2008	18301980	no	yes	yes	yes	no	yes	yes	no
Kailidou	2006	16612913	yes	no	yes	yes	no	yes	no	yes
Kaiser	2004	15031433	no	yes	no	yes	no	yes	no	yes
Kaiser	2002	12034928	yes	yes	yes	yes	no	yes	no	yes
Kamel	2000	11012439	yes	yes	yes	yes	no	yes	no	yes
Kamran	2008	19610521	no	yes	yes	no	no	no	no	yes
Kan	2001	11770917	no	yes	no	no	no	yes	no	yes
Kaneko	2004	15359383	yes	yes	yes	no	no	no	no	yes
Kang	1989	2644718	yes	no	no	no	no	yes	no	yes
Kangegaye	1995	8570450	no	yes	no	yes	yes	yes	no	yes
Kao	1996	8896923	yes	yes	no	yes	no	yes	no	yes
Kapan	2013	23588974	no	yes	no	yes	no	yes	yes	yes
Kapoor	2010	20498461	yes	yes	no	no	no	yes	no	yes
Karakas	2000	10663520	yes	no	yes	no	no	no	yes	no
Karstrup	1986	3533202	no	yes	no	yes	no	yes	yes	yes
Kaya	2012	23236260	yes	yes	no	yes	no	yes	yes	yes
Kentsis	2010	19556024	no	no	no	yes	no	yes	yes	yes
Kentsis	2012	22305331	no	yes	no	yes	yes	no	no	yes
Kepner	2012	22633722	no	yes	no	no	no	yes	no	yes
Keskek	2008	18774040	no	yes	yes	yes	no	yes	yes	no
Kessler	2004	14688403	yes	no	yes	yes	no	yes	yes	yes
Keyzer	2009	19843741	yes	yes	no	no	yes	yes	no	yes

Keyzer	2005	16040910	yes	no	yes	yes	no	no	no	yes
Keyzer	2004	15155894	yes	no	yes	yes	yes	no	no	yes
Khan	2012	23304513	no	yes	no	yes	no	yes	no	yes
Khan	2006	18603920	yes	yes	yes	yes	no	yes	yes	yes
Khan	2008	18769079	yes	no	yes	yes	no	yes	yes	no
Khan	2004	15631364	yes	yes	yes	yes	no	yes	yes	yes
Khanal	2008	18604118	yes	no	yes	yes	no	no	no	yes
Kharbanda	2012	22221321	no	yes	no	yes	yes	yes	no	yes
Kharbanda	2005	16140712	yes	yes	no	yes	no	yes	yes	yes
Kharbanda	2011	21676053	no	no	yes	yes	no	no	no	yes
Kharbanda	2007	17456874	yes	yes	yes	yes	no	no	yes	no
Kim	2009	19098194	no	no	no	no	no	no	no	no
Kim	2011	21123307	yes	no	no	yes	no	yes	yes	yes
Kim	2008	18660392	yes	yes	no	yes	no	yes	no	yes
Kim	2011	21633052	yes	yes	yes	yes	no	no	yes	no
Kim	2009	19070557	no	no	yes	yes	no	no	yes	yes
Kim	2012	22533576	no	yes	no	yes	no	yes	no	yes
Kim	2008	18022782	no	yes	no	yes	no	yes	yes	no
Kipper	2000	10716317	yes	yes	no	yes	yes	yes	no	yes
Kirkil	2013	23588973	yes	yes	no	no	no	no	yes	no
Kirshenbaum	2003	12592478	no	no	yes	no	no	no	no	yes
Kitagawa	2009	22470667	no	no	no	yes	no	yes	no	yes
Klein	2001	11528609	yes	no	no	yes	no	yes	yes	no
Kniskern	1985	3513683	yes	no	no	no	no	no	no	yes
Ko	1995	8592927	yes	yes	no	no	no	yes	no	yes
Kokki	2005	15809382	yes	yes	yes	yes	no	yes	no	yes
Korner	1999	10452263	yes	yes	no	yes	no	yes	yes	no
Korner	2000	11053944	yes	yes	no	yes	yes	yes	yes	yes
Kosloske	2004	14702443	no	no	no	no	no	no	no	yes
Kouame	2011	22421290	yes	yes	no	yes	no	yes	yes	yes
Krishnamoorthi	2011	21324843	yes	no	yes	yes	no	no	no	yes
Kumar	2011	23508483	yes	yes	no	yes	no	yes	yes	yes
Kurane	2008	23133039	no	yes	no	yes	no	yes	yes	yes
Kutasy	2010	19855981	yes	no	yes	yes	no	no	yes	yes
Kutasy	2010	20640856	yes	no	no	yes	no	yes	yes	yes
Kwan and Nager	2010	20825931	yes	no	yes	yes	yes	yes	no	yes
Lai	2012	22226440	no	no	no	yes	no	yes	no	yes
Laituri	2011	21470628	no	yes	yes	no	no	no	no	no
Lameris	2009	19689484	yes	no	yes	yes	no	no	no	no
Lander	2007	17102959	no	yes	no	no	no	yes	no	yes
Lane	1997	9016216	no	yes	yes	no	no	no	no	yes

Lane	1999	10551210	yes	no	no	no	no	yes	no	yes
Langenscheidt	1999	10231659	no	no	yes	yes	yes	no	no	no
Larson	1989	2672728	no	no	no	yes	no	yes	no	yes
Latifi	2011	21406706	yes	no	no	no	no	no	yes	no
Lau	1989	2730458	yes	yes	yes	yes	no	no	no	no
Laurell	2013	23838773	no	no	no	yes	no	yes	no	yes
Lazarus	2007	17709829	yes	yes	yes	no	no	no	yes	no
Lee	2005	15615956	yes	no	yes	yes	no	yes	no	yes
Lee	2006	16772851	no	yes	yes	yes	yes	yes	yes	yes
Lee	2008	18704462	no	yes	yes	yes	no	no	no	yes
Lee	2006	16799269	yes	yes	yes	yes	no	no	no	yes
Lee	2001	11343547	yes	no	no	no	no	no	no	no
Lee	2002	11906864	yes	no	no	no	no	yes	no	yes
Leeuwenburgh	2013	23481162	yes	yes	no	yes	yes	yes	yes	yes
Lehnert	2012	22370694	yes	yes	no	no	no	yes	yes	yes
Lemieux	2009	19057956	yes	no	no	yes	yes	yes	yes	yes
Lessin	1999	10219853	yes	yes	no	no	no	yes	no	yes
Levy	1997	9540398	no	yes	no	yes	no	yes	yes	yes
Li	2012	22186150	no	no	no	yes	no	no	no	yes
Lim	1992	1503019	no	yes	no	no	no	yes	no	yes
Lin	2009	19289311	no	no	no	yes	no	yes	no	yes
Lin	1997	9061706	no	no	no	no	no	yes	no	yes
Lin	2008	18299362	yes	no	no	no	no	no	no	yes
Lin	2013	23724179	yes	no	yes	no	no	yes	no	no
Lindelius	2008	18660395	yes	yes	no	no	yes	yes	yes	no
Lintula	2005	15723233	no	yes	no	no	no	yes	no	yes
Loke	2012	22862759	no	no	no	no	no	no	no	no
Lopez	2007	18186378	yes	yes	no	yes	yes	yes	yes	no
Lowe	2001	11719672	yes	no	no	yes	no	no	no	yes
Lowe	2001	11133533	no	yes	yes	yes	yes	no	no	yes
Lowe	2000	11000148	yes	yes	no	yes	no	yes	no	yes
Lycopoulou	2005	15653442	no	no	no	no	no	no	yes	no
Lyons	1987	3446277	yes	no	no	yes	no	yes	yes	yes
Mahadevan	2000	11103723	yes	no	no	no	no	yes	yes	yes
Makanjuola	1998	9715110	no	no	no	no	no	no	yes	no
Mallick	2008	18675602	yes	no	yes	yes	no	no	no	yes
Malone	1993	8456661	yes	yes	yes	yes	no	yes	no	yes
Maluccio	2001	12593710	yes	yes	yes	no	no	yes	no	yes
Mandeville	2011	20674221	no	yes	no	yes	no	yes	no	yes
Marchand	1983	6881101	no	no	yes	yes	no	yes	yes	no
Mardan	2007	18444596	no	yes	no	yes	no	yes	no	yes

Mariadason	2012	22943328	yes	yes	no	yes	no	yes	yes	yes
Markar	2011	22041239	yes	yes	no	yes	no	yes	yes	yes
Markar	2010	21158332	yes	no	no	yes	no	yes	yes	no
Masselli	2011	21052664	no	no	no	no	no	yes	no	yes
Masters	1984	6507749	no	no	no	yes	no	yes	yes	yes
McCOMBE	1991	1773162	no	no	yes	no	no	no	no	yes
McCartan	2010	20569941	yes	yes	no	no	no	yes	no	yes
McCloskey	2013	22345311	no	no	yes	no	no	yes	yes	yes
McDonald	2001	11730216	no	yes	no	yes	no	yes	yes	no
McDonough	2002	12412726	no	no	no	no	no	yes	no	yes
McKay	2007	17543650	yes	no	no	yes	no	no	no	no
Mekhail	2013	22248897	yes	yes	no	yes	no	yes	yes	yes
Memisoglu	2010	20181221	no	no	no	yes	no	yes	yes	yes
Mendelson	1987	3555679	yes	yes	no	no	no	yes	yes	yes
Mentes	2012	23188598	no	no	no	yes	no	yes	yes	no
Mentes	2009	19683101	no	yes	no	yes	no	yes	yes	yes
Mihmanli	2004	15286888	no	no	no	no	no	no	no	no
Mikaelsson	1984	6524861	yes	no	yes	yes	no	yes	yes	no
Mills	2012	22221415	no	yes	yes	yes	yes	yes	no	yes
Mishra	2003	12619946	no	no	no	yes	no	yes	yes	yes
Miskowiak	1982	7105849	yes	no	yes	yes	yes	no	no	yes
Mittal	2013	23859583	no	no	no	yes	no	no	no	yes
Mittal	2004	15136349	yes	yes	yes	yes	no	yes	no	yes
Mohammed	2004	15448768	yes	no	yes	no	no	no	yes	no
Mohebbi	2008	18289949	no	yes	no	yes	no	yes	yes	yes
Monib	2013	23458936	yes	yes	yes	no	no	yes	yes	yes
Moore	2012	22677910	no	no	no	yes	no	yes	yes	yes
Moore	1995	7786263	yes	yes	no	yes	yes	yes	no	yes
Morris	2002	12034390	yes	no	no	no	no	yes	no	yes
Moteki	2009	19478631	yes	yes	no	no	no	yes	no	yes
Mourad	2000	10819817	yes	no	yes	yes	no	yes	no	yes
Mullins	2001	11133535	yes	yes	no	no	no	no	yes	no
Mun	2006	16362812	yes	no	yes	no	no	yes	no	yes
Musunuru	2007	17701439	yes	no	no	yes	no	yes	yes	yes
Myers	2010	19508509	no	no	no	yes	no	no	yes	no
Naffaa	2005	15967316	yes	no	yes	yes	no	yes	no	yes
Nana	2007	17629058	no	no	no	yes	no	no	yes	no
Naoum	2002	12488178	no	no	no	yes	no	yes	yes	yes
Nasri	2012	22673121	yes	yes	no	yes	no	yes	yes	yes
Nathan	2008	18806151	yes	yes	no	no	no	yes	no	yes
Nautiyal	2010	23133203	no	no	yes	no	no	no	no	no

Navarro	1989	2516745	no	yes	no	no	no	yes	no	yes
Navarro	1987	3493655	no	yes	no	no	yes	yes	no	yes
Navarro-Fernandez	2009	19803663	yes	yes	no	no	no	yes	no	yes
Nelson	2013	23388421	yes	no	no	yes	no	no	yes	yes
Neufeld	2010	19844725	yes	no	no	no	no	no	no	no
Ng	2002	12074480	yes	no	no	yes	no	yes	yes	yes
Niekel	1986	3022347	no	no	yes	no	no	no	no	yes
Nordback	1988	3354283	yes	no	yes	yes	no	no	yes	yes
Nural	2008	18443745	no	yes	no	no	no	no	no	yes
Oncel	2003	14972260	yes	yes	yes	yes	yes	yes	yes	yes
Ooms	1991	2021847	yes	yes	yes	yes	yes	yes	no	yes
Oosterhuis	1993	8098625	yes	yes	no	yes	no	yes	no	no
Ortega-Deballon	2008	18484138	yes	no	no	no	no	yes	no	yes
Oto	2005	15591434	yes	yes	yes	yes	yes	no	yes	yes
Oto	2009	18330616	yes	yes	yes	yes	no	yes	no	yes
Ozguner	2013	23757034	yes	no	no	no	no	no	yes	no
Ozturk	2008	18723708	no	no	no	no	no	no	no	yes
O'Shea	1988	3186519	yes	no	no	no	no	yes	yes	yes
Paajanen	2002	12564616	yes	yes	yes	yes	no	yes	yes	yes
Paajanen	1997	9060929	yes	yes	no	yes	no	yes	yes	yes
Paajanen	1996	8740305	yes	no	no	yes	no	yes	yes	yes
Pacharn	2010	21098847	yes	yes	no	yes	no	no	no	no
Panagiotopoulou	2013	23827295	yes	no	no	yes	no	yes	yes	yes
Paranjape	2007	17285390	yes	yes	no	yes	no	yes	yes	yes
Park	2013	23317620	yes	yes	no	no	no	yes	no	yes
Park	2010	20336903	yes	no	yes	yes	no	yes	yes	yes
Passalacqua	2004	15359387	yes	no	no	yes	no	yes	no	yes
Patrick	2003	12720164	yes	yes	no	yes	no	yes	yes	yes
Paulson	2005	15833993	yes	yes	no	yes	no	yes	no	yes
Pearl	1995	7738734	yes	no	no	yes	no	yes	yes	yes
Peck	2000	11044529	yes	yes	yes	yes	yes	no	no	no
Pedrosa	2009	19244044	yes	yes	no	no	no	no	yes	no
Pedrosa	2006	16505393	yes	yes	yes	yes	yes	yes	no	yes
Peletti	2006	17004079	no	yes	yes	no	no	yes	no	yes
Peltola	1986	3953219	yes	no	yes	no	no	yes	no	yes
Pena	1999	10493202	yes	yes	yes	yes	no	yes	no	yes
Pena	2002	12456904	no	no	no	yes	no	yes	no	no
Pena	1999	10882249	no	yes	no	yes	no	yes	no	yes
Pesonen	1994	8057950	no	no	no	no	no	no	no	no
Petroianu	2012	22574093	yes	yes	no	no	no	no	no	yes
Pickhardt	2011	21690593	no	yes	no	yes	yes	yes	no	yes

Pickth and Spielman	2001	11268950	yes	no	yes	no	no	no	no	yes
Pickuth	2000	10817330	yes	yes	yes	yes	no	yes	no	yes
Platon	2009	18797875	yes	yes	yes	no	no	yes	no	yes
Poh	2004	15284932	yes	no	yes	yes	no	no	no	no
Pohl	1998	9544604	no	yes	no	no	no	yes	no	yes
Poletti	2011	21805194	yes	yes	yes	yes	no	yes	no	yes
Pooler	2012	23023965	no	no	no	yes	no	no	no	yes
Pooler	2012	22131057	yes	yes	no	yes	yes	yes	no	yes
Poortman	2009	19390196	yes	no	yes	yes	no	yes	no	yes
Poortman	2003	14573433	yes	yes	yes	yes	no	no	yes	no
Poortman	2009	19318006	no	yes	yes	no	no	yes	no	yes
Poortman	2010	19185439	no	no	yes	yes	yes	no	yes	yes
Prasannan	2005	16234073	yes	yes	no	no	no	yes	no	yes
Pruekprasert	2004	15117047	no	yes	no	no	no	no	yes	no
Puig	2003	12511675	no	yes	no	yes	no	yes	yes	yes
Puylaert	1987	3306375	yes	yes	yes	no	no	no	yes	no
Puylaert	1986	2934762	yes	yes	yes	no	no	yes	no	yes
Quillin	1994	8153340	yes	no	no	no	no	yes	no	yes
Raftery	1976	1252716	yes	yes	yes	no	no	yes	no	yes
Rajagopalan	1977	849164b	no	yes	no	no	no	no	no	yes
Rajagopalan	1977	849164a	no	yes	no	yes	no	yes	yes	yes
Ramachandran	1996	8632272b	no	no	no	no	no	yes	no	yes
Ramachandran	1996	8632272a	no	yes	no	no	no	yes	no	yes
Raman	2003	12886148	yes	no	yes	yes	no	no	no	yes
Raman	2002	12034591	yes	yes	yes	yes	yes	yes	no	no
Ramarajan	2009	20053244	yes	yes	no	no	no	yes	no	yes
Rao	1999	10074991	yes	yes	yes	yes	no	yes	no	yes
Rao	1997	9353441	no	yes	yes	yes	no	no	yes	no
Rao	1999	10452424	yes	yes	no	no	no	yes	no	yes
Rao	1997	8988203	yes	yes	no	yes	no	yes	no	yes
Rao	1999	10077046	yes	yes	no	no	no	yes	no	yes
Rao	1996	9428814	yes	no	yes	yes	no	yes	no	yes
Rao	1997	9015058	yes	no	yes	yes	no	no	no	yes
Rapp	2013	23360736	no	yes	yes	yes	yes	no	yes	no
Regimbeau	2003	12548414	no	yes	yes	yes	yes	no	yes	yes
Reich	2011	22035447	yes	yes	no	yes	no	yes	yes	no
Rettenbacher	2003	12511674	no	no	yes	yes	no	no	no	yes
Rettenbacher	2002	12360459	yes	yes	yes	no	yes	no	no	yes
Rettenbacher	2001	11230651	no	yes	no	no	no	yes	no	yes
Rettenbacher	2000	10644120	yes	no	yes	yes	no	no	no	yes
Rhea	2005	15908534	yes	yes	yes	no	no	yes	no	yes

Rice	1999	10359177	yes	yes	yes	yes	no	yes	no	yes
Rioux	1992	1546592	yes	yes	yes	yes	no	yes	no	yes
Rodriguez	2006	16554597	yes	yes	no	yes	no	yes	no	yes
Rodriguez-Sanjuan	1999	10528772	yes	no	yes	yes	no	no	yes	yes
Rompel	2006	17021716	yes	yes	yes	yes	no	yes	yes	yes
Rordam	1987	3673452	yes	yes	yes	yes	yes	yes	yes	no
Rosengren	2004	15537403	yes	no	no	yes	no	yes	yes	yes
Rossi	1996	8662398	yes	yes	no	yes	no	yes	no	yes
Rothrck	1991	1754487	yes	yes	no	no	no	yes	yes	yes
Rubin	1990	2199659	no	yes	no	yes	no	yes	no	no
Russell	2011	23611916	no	no	no	no	no	no	no	no
Rypins	2000	10993624	no	yes	no	yes	yes	yes	no	yes
Rypins	2002	11807363	no	yes	no	yes	yes	yes	no	yes
Rypins	1997	9242338	yes	yes	no	yes	no	yes	no	yes
Rypins	1997	9322663	yes	yes	no	yes	no	yes	no	yes
SCOAP Collaborative	2008	18936568	no	no	no	yes	no	no	yes	yes
Sack	2006	17132173	no	yes	yes	no	no	yes	no	yes
Sakhri	2001	11910692	yes	yes	no	yes	no	yes	yes	yes
Sakover	1974	4846555	yes	no	yes	no	no	no	no	no
Salem	2005	16108882	no	yes	no	yes	no	yes	no	yes
Samuel	2002	12037754	yes	no	no	no	no	yes	no	yes
Sand	2009	19672084	yes	no	no	yes	no	yes	yes	yes
Santillanes	2012	22849662	no	yes	no	yes	no	no	no	yes
Santos	2009	19886134	no	yes	yes	no	no	yes	no	yes
Savar	2006	16556158	yes	no	yes	yes	no	no	yes	yes
Schellekens	2010	23859584	yes	no	no	yes	no	no	no	yes
Schey	1973	4704036	no	no	yes	no	no	yes	no	yes
Scholar	1998	9597298	yes	yes	no	no	no	no	no	yes
Schuh	2011	20828717	yes	yes	yes	yes	yes	yes	no	yes
Schuler	1998	9565116	yes	yes	yes	yes	yes	yes	no	yes
Schulte	1998	9971899	no	yes	no	no	no	no	yes	yes
Schupp	2010	20490812	no	no	yes	no	no	no	no	no
Schwerk	1989	2666252	yes	yes	no	no	no	yes	no	yes
Schwerk	1990	2183487	no	no	yes	no	no	no	no	no
Sedlak	2008	18358949	no	no	no	no	no	yes	no	yes
Sengupta	2009	19102827	yes	no	no	no	no	no	no	no
Seo	2009	19542400	no	yes	no	yes	yes	yes	no	yes
Sezer	2012	23356200	yes	yes	no	yes	no	yes	yes	yes
Shafi	2009	19568576	no	no	yes	yes	no	yes	yes	no
Shakhatreh	2000	10934841	no	no	yes	yes	no	yes	yes	no
Sharma	2007	23132981	no	yes	no	yes	no	yes	yes	yes

Shinbrot	1992	1559861	no	no	no	yes	yes	yes	yes	yes
Shirazi	2010	20437687	yes	yes	no	no	no	no	no	yes
Shung-Shung	2002	11917347	yes	yes	yes	yes	no	yes	no	yes
Siddique	2011	21847441	yes	yes	no	yes	no	yes	yes	yes
Siegel	1991	1895479	yes	no	yes	yes	no	yes	yes	yes
Sim	2013	23392792	yes	yes	yes	no	no	yes	no	yes
Sim	1990	2674464	no	no	no	yes	no	yes	no	yes
Simonovsky	1999	10484221	no	yes	yes	no	no	yes	no	yes
Simonovsky	1995	7489627	no	no	yes	yes	no	yes	no	yes
Singh	2009	18649091	yes	yes	no	no	no	no	no	no
Singh-Ranger	2010	20626973	yes	no	yes	yes	no	yes	yes	yes
Sivit	1992	1410371	yes	yes	no	no	no	yes	no	yes
Sivit	2000	11000147	no	yes	yes	no	no	no	yes	no
Sivit	2000	10924565	no	no	yes	no	no	no	no	yes
Skaane	1997	9358775	no	yes	yes	no	no	no	yes	no
Skaane	1990	2242476	yes	yes	no	no	no	yes	no	yes
Smink	2004	15017570	yes	yes	yes	no	no	no	yes	no
Soda	2001	11585505	no	yes	no	no	no	yes	no	yes
Sohail	2009	19260568	no	yes	yes	no	no	yes	yes	yes
Sondenaa	1992	1455149	yes	no	no	no	no	yes	no	yes
Sood	1977	615255	no	no	yes	yes	no	no	no	yes
Staniland	1980	7011161	no	yes	no	no	no	yes	no	yes
Steele	1986	3563460	no	no	no	yes	no	no	no	no
Stefanutti	2007	17502181	no	no	yes	yes	no	no	yes	yes
Stephen	2003	12632351	yes	no	no	yes	no	no	no	yes
Stephens	1999	10218289	no	no	no	yes	no	yes	yes	no
Stewart	2012	22638942	yes	no	yes	yes	no	yes	no	yes
Stewart	2006	17058729	yes	no	no	no	no	yes	no	yes
Stewart	1986	2878273	no	yes	no	no	no	yes	no	yes
Stroman	1999	10670858	no	yes	no	no	no	yes	no	yes
Stromberg	2007	17896131	no	yes	no	yes	no	yes	no	yes
Stunnell	2008	18807813	yes	no	no	yes	no	yes	yes	yes
Styrud	2000	10733085	yes	no	yes	no	no	no	no	no
Styrud	1999	9949266	yes	no	no	yes	no	yes	no	no
Summa	2007	23396678	yes	yes	yes	yes	no	yes	no	yes
Sun	2008	18520542	yes	yes	no	yes	yes	yes	no	yes
Sun	2002	12395266	yes	no	no	yes	no	yes	no	yes
Tabbara	2012	22496979	no	yes	no	no	no	yes	no	yes
Tamanna	2012	23588904	no	no	no	no	no	no	yes	no
Tamburrini	2007	17180324	yes	no	yes	yes	no	yes	no	yes
Tamir	1990	2252115	yes	yes	no	yes	no	yes	yes	yes

Tan	2013	23351046	yes	no	no	no	no	no	yes	no
Teo	2000	11256346	no	yes	yes	no	no	yes	no	yes
Tepel	2004	14634825	no	yes	yes	no	no	no	yes	no
Terzi	2010	21104201	no	yes	no	yes	no	yes	yes	yes
Thakur	2001	11388572	no	no	no	no	no	yes	no	yes
Thimsen	1989	2742230	yes	no	yes	yes	no	yes	yes	yes
Thirumoorthi	2012	23217887	no	no	no	no	no	no	no	no
Thompson	1992	1393485	no	no	no	yes	no	yes	yes	yes
Togawa	2005	15783013	yes	no	no	no	no	no	yes	no
Tomizawa	2011	21937369	no	yes	yes	no	no	yes	no	yes
Toorenvliet	2010	20582544	yes	no	no	no	no	no	no	no
Torbati	2003	12896881	yes	yes	no	yes	no	yes	no	yes
Tracey	2000	10888131	yes	no	no	yes	no	yes	yes	yes
Trout	2012	22947273	no	yes	yes	no	no	yes	no	no
Trout	2012	22402833	yes	yes	no	no	no	yes	no	yes
Tsao	2008	18498874	yes	yes	no	yes	no	yes	yes	yes
Tseng	2008	19054918	yes	yes	no	no	no	yes	no	yes
Tsushima	2002	12069469	yes	no	no	yes	no	yes	no	yes
Turan	1999	10466611	no	yes	no	no	no	no	no	yes
Turkyilmaz	2006	17101565	no	no	no	no	no	yes	no	yes
Turkyilmaz	2004	15125095	no	no	yes	no	no	no	no	no
Tzanakis	2005	16088420	yes	yes	yes	no	no	yes	no	yes
Ujiki	2002	12121697	yes	no	yes	no	no	yes	no	no
Unal	2011	21831513	no	yes	no	no	no	yes	no	yes
Unlu	2009	19559106	yes	yes	yes	yes	yes	yes	no	yes
Van den Broek	2002	12428873	yes	yes	no	no	no	yes	no	yes
Van den Broek	2004	15065030	yes	yes	no	no	no	yes	no	yes
Vaughan-Shaw	2011	21637404	yes	no	yes	yes	no	no	yes	no
Vermeulen	1999	10207461	no	yes	no	yes	no	yes	no	yes
Verroken	1996	8830871	no	yes	yes	yes	no	no	yes	no
Vignault	1990	2195594	no	no	yes	yes	no	no	no	yes
Vu	2009	19560166	yes	yes	no	yes	no	yes	yes	yes
Wade	1993	8368922	no	yes	yes	no	no	no	yes	no
Walker	2000	11182396	no	yes	no	no	no	yes	no	yes
Wallace	2008	17963012	yes	no	no	yes	no	yes	yes	yes
Wang	2012	22205003	no	yes	yes	yes	yes	yes	no	yes
Wang	2007	17351404	yes	no	yes	no	no	no	no	yes
Wang	2003	12749236	no	yes	no	yes	no	yes	no	yes
Webb	2011	21940573	no	no	no	yes	yes	yes	yes	yes
Weltman	2000	10887244	yes	yes	no	yes	no	yes	no	yes
West	2006	16921703	no	no	no	yes	no	no	yes	no

Weyant	2000	10922984	yes	yes	yes	yes	no	yes	yes	yes
Weyant	2001	12594877	yes	yes	no	yes	no	yes	yes	yes
Whitney	1992	1332523	yes	no	no	yes	no	yes	yes	yes
Wiersma	2009	18815791	yes	yes	yes	yes	no	no	yes	no
Wijetunga	2001	11719671	yes	yes	yes	yes	no	yes	no	yes
Wild	1985	4026076	yes	no	no	no	no	yes	no	yes
Williams	2009	19476843	yes	no	yes	no	no	no	no	yes
Wilson	1994	8658993	no	yes	yes	yes	no	no	no	yes
Wilson	2001	11387006	yes	yes	no	no	no	yes	no	yes
Wise	2001	11264081	yes	no	no	yes	no	yes	no	yes
Wong	1997	9404876	no	yes	no	no	no	yes	no	yes
Wong	1994	7807325	no	no	no	no	no	yes	no	yes
Wong	2002	12169286	no	no	yes	yes	no	no	yes	yes
Worrell	1990	2407861	yes	no	yes	no	no	no	yes	no
Wu	2003	14674227	yes	no	yes	no	no	no	no	yes
Wu	2006	16782436	no	no	no	yes	no	no	no	yes
Wu	2012	22491817	no	yes	no	no	no	yes	no	yes
Wu	2005	16032609	yes	no	no	yes	no	yes	yes	yes
Xharra	2012	22866907	no	no	yes	yes	no	yes	yes	no
Yan	2002	12195306	no	no	yes	yes	no	yes	no	yes
Yang	2005	15943411	yes	no	yes	yes	no	yes	yes	no
Yang	2006	16483301	no	no	no	yes	no	yes	yes	yes
Yazici	2010	21043386	no	no	no	no	no	yes	no	yes
Yetkin	2002	12471766	no	no	yes	no	no	no	yes	no
Yigiter	2011	21480284	yes	no	no	yes	no	yes	yes	yes
Yildirim	2006	17101603	no	no	no	yes	no	yes	yes	yes
Yildirim	2008	18306139	yes	no	no	yes	no	yes	yes	yes
Zaki	1994	7945068	no	yes	no	no	no	yes	no	yes
Zeidan	1997	9046139	no	no	no	no	no	yes	no	yes
Zhu	2012	23289088	yes	yes	yes	yes	no	yes	yes	yes
Zielke	2001	11369983	yes	yes	yes	no	no	yes	no	yes
Zielke	1997	9094278	yes	yes	no	no	no	yes	no	yes
Zielke	1998	9562281	yes	yes	yes	no	no	yes	no	yes
Zona	1985	1188426	yes	no	no	no	no	yes	no	yes
Zuniga	2012	22653450	yes	yes	yes	yes	no	yes	no	no
el Ferzli	1990	2360147	no	no	no	yes	no	yes	no	yes
in't Hof	2004	15386320	yes	yes	no	yes	yes	yes	yes	yes
in't Hoff	2009	19164615	yes	yes	no	no	yes	yes	yes	yes
van Breda Vriesman	2003	12845461	no	no	yes	yes	no	yes	yes	yes
van Diejjen- Visser	1991	1782282	no	no	no	no	no	yes	no	no
van Randen	2011	21365197	yes	yes	no	yes	no	yes	no	yes

van Randen	2010	20119730	no	yes	yes	yes	yes	yes	yes	yes
Quality Item 1 = Was a consecutive or random sample of patients enrolled?										
Quality Item 2 = Were the index test results interpreted without knowledge of the results of the reference standard?										
Quality Item 3 = If a threshold was used, was it prespecified?										
Quality Item 4 = Is the reference standard likely to correctly classify the target condition?										
Quality Item 5 = Were the reference standard results interpreted without knowledge of the results of the index test?										
Quality Item 6 = Did all patients receive a reference standard?										
Quality Item 7 = Did all patients receive the same reference standard?										
Quality Item 8 = Were all patients included in the analysis?										

Table C3. Test performance of multivariable diagnostic scores

Author	Year	PMID	Country	Population	Test	Cut-off	TP	FN	FP	TN
Abdeldaim	2011	17380927	Ireland	mixed	Alvarado	≥ 7	106	18	12	106
Abdeldaim	2011	17380927	Ireland	mixed	Alvarado	≥ 9	56	68	0	118
Abdeldaim	2011	17380927	Ireland	mixed	Alvarado	≥ 5	124	0	54	64
Al Hashemy	2004	15448772	Saudi Arabia	women of reproductive age	Alvarado modified	≥ 7	12	13	9	15
Al Hashemy	2004	15448772	Saudi Arabia	adults	Alvarado modified	≥ 7	43	37	9	36
Al Qahtani	2004	19861831	Saudi Arabia	mixed	Alvarado	≥ 1	122	0	89	0
Al Qahtani	2004	19861831	Saudi Arabia	mixed	Alvarado	≥ 7	116	6	14	75
Al Qahtani	2004	19861831	Saudi Arabia	mixed	Alvarado	≥ 6	120	2	27	62
Al Qahtani	2004	19861831	Saudi Arabia	mixed	Alvarado	≥ 2	122	0	88	1
Al Qahtani	2004	19861831	Saudi Arabia	mixed	Alvarado	≥ 3	122	0	80	9
Al Qahtani	2004	19861831	Saudi Arabia	mixed	Alvarado	≥ 5	122	0	45	44
Al Qahtani	2004	19861831	Saudi Arabia	mixed	Alvarado	≥ 8	100	22	9	80
Al Qahtani	2004	19861831	Saudi Arabia	mixed	Alvarado	≥ 9	75	47	4	85
Al Qahtani	2004	19861831	Saudi Arabia	mixed	Alvarado	≥ 10	36	86	1	88
Al Qahtani	2004	19861831	Saudi Arabia	Mixed	Alvarado	≥ 4	122	0	62	27
Althoubaity	2006	17106538	Saudi Arabia	Mixed	Alvarado	≥ 7	41	5	34	23
Alvarado	1986	3963537	USA	Mixed	Alvarado	≥ 9	73	154	3	47
Alvarado	1986	3963537	USA	Mixed	Alvarado	≥ 10	30	197	0	50
Alvarado	1986	3963537	USA	Mixed	Alvarado	≥ 8	129	98	7	43
Alvarado	1986	3963537	USA	Mixed	Alvarado	≥ 7	184	43	13	37
Alvarado	1986	3963537	USA	Mixed	Alvarado	≥ 0	227	0	50	0
Alvarado	1986	3963537	USA	Mixed	Alvarado	≥ 2	227	0	47	3
Alvarado	1986	3963537	USA	Mixed	Alvarado	≥ 5	219	8	31	19
Alvarado	1986	3963537	USA	Mixed	Alvarado	≥ 6	211	16	24	26
Alvarado	1986	3963537	USA	Mixed	Alvarado	≥ 3	227	0	47	3

Alvarado	1986	3963537	USA	Mixed	Alvarado	>=4	224	3	40	10
Alvarado	1986	3963537	USA	Mixed	Alvarado	>=1	227	0	50	0
Andersson	2008	18553045	Sweden	Mixed	AIR	>=9	28	48	1	152
Andersson	2008	18553045	Sweden	Mixed	Alvarado	>=9	21	55	2	151
Andersson	2008	18553045	Sweden	Mixed	AIR	>=5	73	3	41	112
Andersson	2008	18553045	Sweden	mixed	Alvarado	>=5	80	2	59	94
Arnbjornsson	1985	3909908	Sweden	mixed	Arnbjornsson	>=-55	84	0	26	0
Arnbjornsson	1985	3909908	Sweden	adults	Arnbjornsson	>=20	20	64	1	25
Arnbjornsson	1985	3909908	Sweden	adults	Arnbjornsson	>=-10	84	0	19	7
Arnbjornsson	1985	3909908	Sweden	mixed	Arnbjornsson	>=20	20	64	1	25
Arnbjornsson	1985	3909908	Sweden	mixed	Arnbjornsson	>=-10	84	0	19	7
Bhatt	2009	19549016	Canada	children	PAS	>=8	46	37	8	155
Bhatt	2009	19549016	Canada	children	PAS	>=10	5	78	0	163
Bhatt	2009	19549016	Canada	children	PAS	>=3	83	0	130	33
Bhatt	2009	19549016	Canada	children	PAS	>=1	83	0	163	0
Bhatt	2009	19549016	Canada	children	PAS	>=9	26	57	1	162
Bhatt	2009	19549016	Canada	children	PAS	>=4	82	1	109	54
Bhatt	2009	19549016	Canada	children	PAS	>=5	81	2	78	85
Bhatt	2009	19549016	Canada	children	PAS	>=7	61	22	24	139
Bhatt	2009	19549016	Canada	children	PAS	>=2	83	0	147	16
Bhatt	2009	19549016	Canada	children	PAS	>=6	77	6	50	113
Bhattacharjee	2002	12418631	India	mixed	Alvarado modified	>=7	67	14	14	15
Bhattacharjee	2002	12418631	India	children	Alvarado modified	>=7	12	0	3	1
Bond	1990	2393167	USA	children	Alvarado	>=7	104	12	21	52
Bond	1990	2393167	USA	children	Alvarado	>=6	110	6	34	39
Bond	1990	2393167	USA	young children	Alvarado	>=6	14	3	6	4
Bond	1990	2393167	USA	children	Alvarado	>=8	83	33	12	61

Bond	1990	2393167	USA	young children	Alvarado	>=9	8	9	0	10
Bond	1990	2393167	USA	children	Alvarado	>=4	116	0	52	21
Bond	1990	2393167	USA	young children	Alvarado	>=8	11	6	2	8
Bond	1990	2393167	USA	young children	Alvarado	>=5	17	0	8	2
Bond	1990	2393167	USA	young children	Alvarado	>=7	13	4	4	6
Bond	1990	2393167	USA	children	Alvarado	>=5	116	0	46	27
Bond	1990	2393167	USA	children	Alvarado	>=9	49	67	5	68
Bond	1990	2393167	USA	young children	Alvarado	>=3	17	0	10	0
Bond	1990	2393167	USA	children	Alvarado	>=10	16	100	0	73
Bond	1990	2393167	USA	young children	Alvarado	>=1	17	0	10	0
Bond	1990	2393167	USA	young children	Alvarado	>=2	17	0	10	0
Bond	1990	2393167	USA	children	Alvarado	>=2	116	0	66	7
Bond	1990	2393167	USA	children	Alvarado	>=0	116	0	73	0
Bond	1990	2393167	USA	young children	Alvarado	>=10	2	15	0	10
Bond	1990	2393167	USA	children	Alvarado	>=3	116	0	59	14
Bond	1990	2393167	USA	young children	Alvarado	>=4	17	0	10	0
Bond	1990	2393167	USA	young children	Alvarado	>=0	17	0	10	0
Bond	1990	2393167	USA	children	Alvarado	>=1	116	0	71	2
Bulus	2013	23292641	Turkey	adults	Alvarado modified	>=7	82	28	29	19
Bulus	2013	23292641	Turkey	women of reproductive age	Alvarado modified	>=7	30	12	13	8
Bulus	2013	23292641	Turkey	adults	Alvarado modified + tenesmus	UNCLEAR	105	21	11	21
Bulus	2013	23292641	Turkey	women of reproductive age	Alvarado modified + tenesmus	UNCLEAR	38	7	6	12
Chan	2003	15568423	Ireland	mixed	Alvarado	>=1	75	0	100	0
Chan	2003	15568423	Ireland	mixed	Alvarado	>=10	0	75	0	100
Chan	2003	15568423	Ireland	mixed	Alvarado	>=9	10	65	4	96
Chan	2003	15568423	Ireland	mixed	Alvarado	>=7	52	23	21	79

Chan	2001	11603135	Singapore	mixed	Alvarado	>=7	48	2	14	84
Chan	2003	15568423	Ireland	mixed	Alvarado	>=2	75	0	99	1
Chan	2003	15568423	Ireland	mixed	Alvarado	>=4	75	0	66	34
Chan	2003	15568423	Ireland	mixed	Alvarado	>=3	75	0	82	18
Chan	2003	15568423	Ireland	mixed	Alvarado	>=8	25	50	11	89
Chan	2003	15568423	Ireland	mixed	Alvarado	>=5	75	0	44	56
Chan	2003	15568423	Ireland	mixed	Alvarado	>=6	66	9	30	70
Chong	2012	21633767	Brunei	mixed	Alvarado	>=7	69	32	11	80
Chong	2011	21633767	Brunei	mixed	RIPASA	>=7.5	99	2	17	74
Chong	2010	20428744	Brunei	mixed	RIPASA	>=7.5	230	31	17	34
Davidson	1999	9914351	Australia	children	Alvarado	>=7	57	13	48	135
Davidson	1999	9914351	Australia	children	Alvarado	>=8	42	28	24	159
Deniszbasi	2003	14676508	Turkey	adults	Alvarado	>=7	75	6	15	13
Deniszbasi	2003	14676508	Turkey	mixed	Alvarado	>=7	167	8	25	21
Dey	2010	21938190	India	women of reproductive age	Alvarado	>=7	31	9	0	32
Dey	2010	21938190	India	mixed	Alvarado	>=1	80	0	75	0
Dey	2010	21938190	India	mixed	Alvarado	>=5	78	2	55	20
Dey	2010	21938190	India	women of reproductive age	Alvarado	>=1	40	0	32	0
Dey	2010	21938190	India	mixed	Alvarado	>=7	60	20	3	72
Dey	2010	21938190	India	women of reproductive age	Alvarado	>=5	40	0	24	8
Enochsson	2004	15791379	Sweden	adults	Fenyo	>=-2	257	77	28	64
Enochsson	2004	15791379	Sweden	women of reproductive age	Fenyo	>=-2	95	19	58	47
Ergul	2008	19024138	Turkey	mixed	Alvarado	>=5	485	45	845	1295
Ergul	2008	19024138	Turkey	mixed	Alvarado	>=7	275	255	321	1819
Escriba	2011	21346681	Spain	children	Alvarado	>=8	19	23	0	57
Escriba	2011	21346681	Spain	children	Alvarado	>=1	42	0	54	3

Escriba	2011	21346681	Spain	children	Alvarado	>=7	31	11	1	56
Escriba	2011	21346681	Spain	children	Alvarado	>=5	40	2	16	41
Escriba	2011	21346681	Spain	children	PAS	>=2	42	0	46	11
Escriba	2011	21346681	Spain	children	Alvarado	>=6	38	4	5	52
Escriba	2011	21346681	Spain	children	Alvarado	>=3	42	0	37	20
Escriba	2011	21346681	Spain	children	Alvarado	>=10	0	42	0	57
Escriba	2011	21346681	Spain	children	PAS	>=3	42	0	35	22
Escriba	2011	21346681	Spain	children	Alvarado	>=2	42	0	46	11
Escriba	2011	21346681	Spain	children	PAS	>=8	18	24	0	57
Escriba	2011	21346681	Spain	children	Alvarado	>=9	4	38	0	57
Escriba	2011	21346681	Spain	children	PAS	>=1	42	0	51	6
Escriba	2011	21346681	Spain	children	PAS	>=10	0	42	0	57
Escriba	2011	21346681	Spain	children	PAS	>=9	3	39	0	57
Escriba	2011	21346681	Spain	children	Alvarado	>=4	42	0	25	32
Escriba	2011	21346681	Spain	children	PAS	>=4	41	1	19	38
Escriba	2011	21346681	Spain	children	PAS	>=7	29	13	0	57
Escriba	2011	21346681	Spain	children	PAS	>=5	39	3	8	49
Escriba	2011	21346681	Spain	children	PAS	>=6	37	5	1	56
Fente	2009	20120145	Nigeria	mixed	Bengezi	>=5	79	1	3	45
Fente	2009	20120145	Nigeria	mixed	Bengezi	>=8	16	64	0	48
Fenyo	1987	3321809	Sweden	adults	Fenyo	>=12	231	25	49	525
Fenyo	1997	9414043	Sweden	mixed	Fenyo	>=-2	286	106	101	674
Galindo	1998	9462380	Spain	mixed	Galindo-classical	>=-12	91	10	48	43
Galindo	1998	9462380	Spain	mixed	Galindo-classical	>=0	68	33	30	61
Galindo	1998	9462380	Spain	mixed	Galindo-US	>=-6	88	13	15	76
Galindo	1998	9462380	Spain	mixed	Galindo-US	>=30	56	45	3	88
Galindo	1998	9462380	Spain	mixed	Galindo-classical	>=12	37	64	10	81

Galindo	1998	9462380	Spain	mixed	Galindo-US	>=18	72	29	3	88
Galindo	1998	9462380	Spain	mixed	Galindo-US	>=30	101	0	52	39
Galindo	1998	9462380	Spain	mixed	Galindo-US	>=-24	99	2	47	44
Galindo	1998	9462380	Spain	mixed	Galindo-US	>=36	51	50	0	91
Galindo	1998	9462380	Spain	mixed	Galindo-US	>=-18	95	6	35	56
Galindo	1998	9462380	Spain	mixed	Galindo-classical	>=-6	81	20	44	47
Galindo	1998	9462380	Spain	mixed	Galindo-US	>=-12	91	10	27	64
Galindo	1998	9462380	Spain	mixed	Galindo-classical	>=-18	96	5	62	29
Galindo	1998	9462380	Spain	mixed	Galindo-US	>=12	77	24	4	87
Galindo	1998	9462380	Spain	mixed	Galindo-US	>=24	64	37	3	88
Galindo	1998	9462380	Spain	mixed	Galindo-classical	>=18	7	94	0	91
Galindo	1998	9462380	Spain	mixed	Galindo-US	>=6	83	18	4	87
Galindo	1998	9462380	Spain	mixed	Galindo-classical	>=6	61	40	25	66
Galindo	1998	9462380	Spain	mixed	Galindo-US	>=0	82	19	5	86
Galindo	1998	9462380	Spain	mixed	Galindo-classical	>=-24	101	0	76	15
Garcia Pena	2004	14702442	USA	children	Garcia Pena	yes high risk	202	386	23	347
Garcia Pena	2004	14702442	USA	children	Garcia Pena	yes not low risk	573	15	242	128
Goldman	2008	18534219	Canada	children	PAS	>=7	7	116	15	711
Goldman	2008	18534219	Canada	children	PAS	>=9	0	123	0	726
Goldman	2008	18534219	Canada	children	PAS	>=0	123	0	530	196
Goldman	2008	18534219	Canada	children	PAS	>=6	20	103	29	697
Goldman	2008	18534219	Canada	children	PAS	>=8	2	121	7	719
Goldman	2008	18534219	Canada	children	PAS	>=2	84	39	196	530
Goldman	2008	18534219	Canada	children	PAS	>=3	62	61	123	603
Goldman	2008	18534219	Canada	children	PAS	>=1	107	16	327	399
Goldman	2008	18534219	Canada	children	PAS	>=10	0	123	0	726
Goldman	2008	18534219	Canada	children	PAS	>=5	34	89	44	682

Goldman	2008	18534219	Canada	children	PAS	>=4	49	74	73	653
Gough	1988	3075891	Australia	mixed	Gough	>=4	134	31	34	77
Gough	1988	3075891	Australia	mixed	Gough	>=8.1	99	66	21	90
Goulder	2008	20011493	UK	children	PAS	>=6	34	5	7	10
Gwynn	2002	12217465	USA	mixed	Alvarado	>=5	153	14	4	19
Gwynn	2001	11489398	USA	mixed	Alvarado	>=5	131	12	11	61
Hong	2003	14588157	USA	adults	Alvarado	>=9	132	75	2	71
Hong	2003	14588157	USA	adults	Alvarado	>=3	207	0	73	0
Horzic	2005	16117311	Croatia	women of reproductive age	Eskelinen	>=57.45	59	49	6	12
Horzic	2005	16117311	Croatia	women of reproductive age	Ohmann	>=6.02	106	2	18	0
Horzic	2005	16117311	Croatia	women of reproductive age	Alvarado modified	>=1	107	1	18	0
Horzic	2005	16117311	Croatia	women of reproductive age	Ohmann	>=14.5	25	83	1	17
Horzic	2005	16117311	Croatia	women of reproductive age	Ohmann	>=14.02	34	74	2	16
Horzic	2005	16117311	Croatia	women of reproductive age	Alvarado modified	>=7	18	90	0	18
Horzic	2005	16117311	Croatia	women of reproductive age	Ohmann	>=12.99	61	47	5	13
Horzic	2005	16117311	Croatia	women of reproductive age	Ohmann	>=10.5	90	18	14	4
Horzic	2005	16117311	Croatia	women of reproductive age	Alvarado modified	>=6	39	69	3	15
Horzic	2005	16117311	Croatia	women of reproductive age	Ohmann	>=9.98	95	13	14	4
Horzic	2005	16117311	Croatia	women of reproductive age	Eskelinen	>=40.4	108	0	17	1
Horzic	2005	16117311	Croatia	women of reproductive age	Ohmann	>=12	75	33	10	8
Horzic	2005	16117311	Croatia	women of reproductive age	Ohmann	>=13.5	38	70	2	16
Horzic	2005	16117311	Croatia	women of reproductive age	Ohmann	>=8.51	102	6	16	2

Horzic	2005	16117311	Croatia	women of reproductive age	Eskelinen	>=61.7	0	108	0	18
Horzic	2005	16117311	Croatia	women of reproductive age	Ohmann	>=16	0	108	0	18
Horzic	2005	16117311	Croatia	women of reproductive age	Alvarado modified	>=9	0	108	0	18
Horzic	2005	16117311	Croatia	women of reproductive age	Ohmann	>=15.01	14	94	1	17
Horzic	2005	16117311	Croatia	women of reproductive age	Ohmann	>=7.01	104	4	17	1
Horzic	2005	16117311	Croatia	women of reproductive age	Alvarado modified	>=2	104	4	16	2
Horzic	2005	16117311	Croatia	women of reproductive age	Alvarado modified	>=5	63	45	6	12
Horzic	2005	16117311	Croatia	women of reproductive age	Eskelinen	>=44.65	102	6	17	1
Horzic	2005	16117311	Croatia	women of reproductive age	Alvarado modified	>=8	1	107	0	18
Horzic	2005	16117311	Croatia	women of reproductive age	Ohmann	>=9.5	97	11	14	4
Horzic	2005	16117311	Croatia	women of reproductive age	Eskelinen	>=59.6	39	69	3	15
Horzic	2005	16117311	Croatia	women of reproductive age	Eskelinen	>=55.35	91	17	15	3
Horzic	2005	16117311	Croatia	women of reproductive age	Ohmann	>=8	103	5	16	2
Horzic	2005	16117311	Croatia	women of reproductive age	Alvarado modified	>=3	100	8	15	3
Horzic	2005	16117311	Croatia	women of reproductive age	Ohmann	>=12.51	62	46	5	13
Horzic	2005	16117311	Croatia	women of reproductive age	Alvarado modified	>=4	90	18	11	7
Horzic	2005	16117311	Croatia	women of reproductive age	Ohmann	>=8.99	97	11	16	2
Horzic	2005	16117311	Croatia	women of reproductive age	Ohmann	>=11.01	83	25	13	5
Horzic	2005	16117311	Croatia	women of reproductive age	Ohmann	>=11.49	77	31	12	6
Horzic	2005	16117311	Croatia	women of reproductive age	Ohmann	>=4.51	107	1	18	0

Horzic	2005	16117311	Croatia	women of reproductive age	Eskelinen	>=42.55	104	4	17	1
Inci	2011	20655156	Turkey	mixed	Alvarado	>=7	48	9	3	25
Jawaid	1999	10647233	Pakistan	adults	Jawaid	>=-7	63	18	2	16
John	2011	21786842	India	adults	Alvarado	>=7	125	68	15	30
Kalan	1994	7702329	UK	children	Alvarado modified	>=7	11	0	0	0
Kalan	1994	7702329	UK	mixed	Alvarado modified	>=7	35	5	6	3
Kalan	1994	7702329	UK	women of reproductive age	Alvarado modified	>=7	10	1	5	1
Kamran	2010	22455259	Pakistan	mixed	Bengezi	>=8	42	10	4	44
Kamran	2010	22455259	Pakistan	mixed	Bengezi	>=5	52	0	22	26
Kang	1989	2644718	Taiwan	adults	Alvarado	>=7	30	12	4	16
Kanumba	2011	21329493	Tanzania	elderly	Alvarado modified	>=7	6	1	2	8
Kanumba	2011	21329493	Tanzania	mixed	Alvarado modified	>=7	80	5	4	38
Kanumba	2011	21329493	Tanzania	children	Alvarado modified	>=7	28	2	1	14
Kell	2003	12930054	Ireland	mixed	Alvarado	>=7	87	54	2	6
Khan	2005	16320795	Pakistan	mixed	Alvarado	>=5	51	3	32	14
Khan	2005	16320795	Pakistan	mixed	Alvarado	>=7	45	9	7	39
Kharbanda	2005	16140712	USA	children	Kharbanda logistic	>=6	207	4	240	150
Kharbanda	2012	22869405	USA	children	Kharbanda validated	yes not low risk	887	42	930	531
Kharbanda	2012	22869405	USA	children	Kharbanda refined	yes not low risk	999	19	1226	381
Kharbanda	2005	16140712	USA	children	Kharbanda validated	yes not low risk	210	1	260	130
Kim	2008	18660392	Korea	adults	Alvarado	>=8	38	52	14	53
Kim	2008	18660392	Korea	adults	Alvarado	>=5	79	11	44	23
Kirkil	2013	23588973	Turkey	mixed	Lintula	>=16	48	5	8	53
Kirkil	2013	23588973	Turkey	mixed	Lintula	>=21	26	27	2	59
Kirkil	2013	23588973	Turkey	mixed	Alvarado	>=4	51	2	36	25

Kirkil	2013	23588973	Turkey	mixed	Alvarado	>=7	42	11	12	49
Kurane	2008	23133039	India	adults	Alvarado	>=7	18	3	6	31
Lamparelli	2000	10858683	UK	children	Alvarado modified	>=7	15	4	0	9
Lamparelli	2000	10858683	UK	mixed	Alvarado modified	>=7	38	18	2	26
Lamparelli	2000	10858683	UK	adults	Alvarado modified	>=7	23	14	2	17
Langenscheidt	1999	10231659	Madagascar	mixed	Ohmann	>=8	15	0	83	5
Langenscheidt	1999	10231659	Madagascar	mixed	Ohmann	>=14	5	10	2	86
Langenscheidt	1999	10231659	Madagascar	mixed	Ohmann	>=12	8	7	17	71
Langenscheidt	1999	10231659	Madagascar	mixed	Ohmann	>=10	11	4	73	15
Limpawattanasiri	2011	21591529	Thailand	mixed	Alvarado	>=3	123	160	123	2
Limpawattanasiri	2011	21591529	Thailand	mixed	Alvarado	>=2	123	162	123	0
Limpawattanasiri	2011	21591529	Thailand	mixed	Alvarado	>=8	51	241	51	234
Limpawattanasiri	2011	21591529	Thailand	mixed	Alvarado	>=4	123	156	123	6
Limpawattanasiri	2011	21591529	Thailand	mixed	Alvarado	>=6	106	134	106	77
Limpawattanasiri	2011	21591529	Thailand	mixed	Alvarado	>=10	9	616	9	276
Limpawattanasiri	2011	21591529	Thailand	mixed	Alvarado	>=7	73	90	73	212
Limpawattanasiri	2011	21591529	Thailand	mixed	Alvarado	>=5	123	147	123	15
Limpawattanasiri	2011	21591529	Thailand	mixed	Alvarado	>=9	22	515	22	184
Lintula	2006	15723233	Finland	children	Lintula	>=21	16	11	4	75
Lintula	2005	15723233	Finland	children	Lintula	>=16	23	4	21	58
Lintula	2008	18841382	Finland	children	Lintula	>=21	24	0	5	37
Macklin	1997	9196342	UK	children	Alvarado modified	>=7	29	9	17	63
Macklin	1997	9196342	UK	children	Alvarado modified	>=1	38	0	80	0
Macklin	1997	9196342	UK	children	Alvarado modified	>=5	33	5	41	39
Malik	1998	9669364	India	children	Alvarado modified	>=7	9	1	1	1
Malik	1998	9669364	India	adults	Alvarado modified	>=7	24	3	12	2
Malik	1998	9669364	India	mixed	Alvarado modified	>=7	69	14	16	7

Mandeville	2011	20674221	USA	children	PAS	>=7	118	37	37	95
Mandeville	2011	20674221	USA	children	Alvarado	>=8	103	52	26	106
Mandeville	2011	20674221	USA	children	Alvarado	>=9	68	87	11	121
Mandeville	2011	20674221	USA	children	Alvarado	>=3	145	10	121	11
Mandeville	2011	20674221	USA	children	PAS	>=1	146	9	131	1
Mandeville	2011	20674221	USA	children	Alvarado	>=4	145	10	112	20
Mandeville	2011	20674221	USA	children	Alvarado	>=1	146	9	131	1
Mandeville	2011	20674221	USA	children	PAS	>=6	128	27	57	75
Mandeville	2011	20674221	USA	children	Alvarado	>=6	137	18	66	66
Mandeville	2011	20674221	USA	children	PAS	>=10	16	139	1	131
Mandeville	2011	20674221	USA	children	Alvarado	>=2	146	9	129	3
Mandeville	2011	20674221	USA	children	PAS	>=4	142	13	103	29
Mandeville	2011	20674221	USA	children	PAS	>=5	135	20	76	56
Mandeville	2011	20674221	USA	children	PAS	>=3	145	10	121	11
Mandeville	2011	20674221	USA	children	PAS	>=8	92	63	21	111
Mandeville	2011	20674221	USA	children	Alvarado	>=0	155	0	132	0
Mandeville	2011	20674221	USA	children	PAS	>=0	155	0	132	0
Mandeville	2011	20674221	USA	children	Alvarado	>=7	124	31	44	88
Mandeville	2011	20674221	USA	children	PAS	>=9	47	108	6	126
Mandeville	2011	20674221	USA	children	Alvarado	>=10	20	135	3	129
Mandeville	2011	20674221	USA	children	PAS	>=2	146	9	130	2
Mandeville	2011	20674221	USA	children	Alvarado	>=5	139	16	92	40
Mardan	2007	18444596	Pakistan	mixed	Alvarado	>=6	120	8	40	32
McKay	2007	17543650	USA	mixed	Alvarado	>=4	49	2	46	53
McKay	2007	17543650	USA	mixed	Alvarado	>=7	28	23	8	91
Meltzer	2013	23623557	USA	adults	Alvarado modified	>=4	38	15	96	112
Meltzer	2013	23623557	USA	adults	Alvarado modified	>=6	19	34	25	183

Meltzer	2013	23623557	USA	adults	Alvarado modified	>=5	29	24	50	158
Memon	2013	23726829	Pakistan	mixed	Alvarado	>=6	72	5	7	26
Mentes	2012	23188598	Turkey	adults	Alvarado	>=7	146	33	7	15
Mentes	2009	19683101	Turkey	adults	Alvarado	>=8	27	13	4	5
Nasri	2012	22673121	Iran	mixed	Alvarado modified	>=7	44	23	5	3
Nautiyal	2010	23133203	India	adults	Alvarado	>=7	9	16	1	3
Nautiyal	2010	23133203	India	women of reproductive age	Alvarado	>=7	3	5	0	9
Nautiyal	2010	23133203	India	mixed	Alvarado	>=7	14	21	1	14
Nelson	2013	23388421	USA	mixed	Alvarado	>=7	388	236	17	23
Nelson	2013	23388421	USA	mixed	Alvarado	>=4	598	26	36	4
Owen	1992	1489366	UK	children	Alvarado	>=7	40	3	5	22
Owen	1992	1489366	UK	mixed	Alvarado	>=7	118	6	17	74
Owen	1992	1489366	UK	women of reproductive age	Alvarado	>=7	31	2	9	28
Owen	1992	1489366	UK	adults	Alvarado	>=7	47	1	3	24
Petrosyan	2008	17998781	USA	mixed	Alvarado	>=5	743	132	38	16
Petrosyan	2008	17998781	USA	mixed	Alvarado	>=8	97	778	6	58
Pouget-Baudry	2010	20692636	France	adults	Alvarado	>=4	148	23	30	32
Pouget-Baudry	2010	20692636	France	adults	Alvarado	>=7	77	94	6	56
Prabhudesai	2008	18043966	UK	mixed	Alvarado	>=6	23	1	10	26
Prabhudesai	2008	18043966	UK	mixed	Alvarado	>=7	22	2	6	30
Pruekprasert	2004	15117047	Thailand	mixed	Alvarado	>=7	147	39	14	31
Ramirez	1994	8044545b	Spain	women of reproductive age	Ramirez	>=10	37	11	3	16
Ramirez	1994	8044545a	Spain	adults	Ramirez	>=-15	293	0	28	39
Ramirez	1994	8044545a	Spain	adults	Ramirez	>=0	255	38	19	48
Ramirez	1994	8044545a	Spain	adults	Ramirez	>=-10	281	12	21	46
Ramirez	1994	8044545a	Spain	adults	Ramirez	>=5	234	59	15	52

Ramirez	1994	8044545a	Spain	adults	Ramirez	>=-5	272	21	21	46
Ramirez	1994	8044545a	Spain	adults	Ramirez	>=15	164	129	0	67
Ramirez	1994	8044545a	Spain	adults	Ramirez	>=10	226	67	9	58
Rezak	2011	21242447	USA	children	Alvarado	>=5	32	0	6	21
Rezak	2011	21242447	USA	children	Alvarado	>=8	16	16	0	27
Rezak	2011	21242447	USA	children	Alvarado	>=1	32	0	27	0
Saidi	2003	14601782	Kenya	mixed	Saidi	>=5	127	30	28	4
Saidi	2003	14601782	Kenya	mixed	Saidi	>=1	157	0	32	0
Saidi	2003	14601782	Kenya	mixed	Saidi	>=7	61	96	15	17
Samuel	2002	12037754	UK	children	PAS	>=6	734	0	35	401
Schellekens	2010	23859584	Netherlands	mixed	Alvarado	>=3	75	2	129	27
Schellekens	2010	23859584	Netherlands	mixed	Alvarado	>=7	49	28	30	126
Schneider	2007	17383771	USA	children	PAS	>=4	189	8	290	101
Schneider	2007	17383771	USA	children	Alvarado	>=6	167	30	144	247
Schneider	2007	17383771	USA	children	PAS	>=8	99	98	39	352
Schneider	2007	17383771	USA	children	Alvarado	>=8	99	98	35	356
Schneider	2007	17383771	USA	children	Alvarado	>=1	197	0	385	6
Schneider	2007	17383771	USA	children	PAS	>=7	137	60	86	305
Schneider	2007	17383771	USA	children	PAS	>=9	56	141	15	376
Schneider	2007	17383771	USA	children	PAS	>=1	197	0	385	6
Schneider	2007	17383771	USA	children	Alvarado	>=10	15	182	1	390
Schneider	2007	17383771	USA	children	Alvarado	>=4	194	3	286	105
Schneider	2007	17383771	USA	children	Alvarado	>=2	197	0	378	13
Schneider	2007	17383771	USA	children	PAS	>=10	17	180	2	389
Schneider	2007	17383771	USA	children	Alvarado	>=7	142	55	75	316
Schneider	2007	17383771	USA	children	PAS	>=2	197	0	377	14
Schneider	2007	17383771	USA	children	Alvarado	>=9	51	146	15	376

Schneider	2007	17383771	USA	children	Alvarado	>=3	197	0	338	53
Schneider	2007	17383771	USA	children	PAS	>=6	162	35	136	255
Schneider	2007	17383771	USA	children	PAS	>=5	181	16	210	181
Schneider	2007	17383771	USA	children	PAS	>=3	197	0	342	49
Schneider	2007	17383771	USA	children	Alvarado	>=5	182	15	223	168
Shera	2011	21046287	India	children	Shera	>=7	66	2	6	16
Shreef	2010	20859021	Egypt	children	Alvarado	>=6	132	0	78	140
Shreef	2010	20859021	Egypt	children	Alvarado	>=7	114	18	37	181
Shreef	2010	20859021	Egypt	children	Alvarado	>=2	132	0	218	0
Shreef	2010	20859021	Egypt	children	Alvarado	>=8	81	51	19	199
Shreef	2010	20859021	Egypt	children	Alvarado	>=3	132	0	215	3
Shreef	2010	20859021	Egypt	children	Alvarado	>=4	132	0	190	28
Shreef	2010	20859021	Egypt	children	Alvarado	>=10	5	127	0	218
Shreef	2010	20859021	Egypt	children	Alvarado	>=1	132	0	218	0
Shreef	2010	20859021	Egypt	children	Alvarado	>=9	32	100	5	213
Shreef	2010	20859021	Egypt	children	Alvarado	>=5	132	0	148	70
Shrivastava	2004	15912982	Serbia	adults	Alvarado	>=7	48	0	9	0
Shrivastava	2004	15912982	Serbia	adults	Alvarado	>=8	38	10	7	2
Shrivastava	2004	15912982	Serbia	adults	Alvarado	>=9	28	20	3	6
Shrivastava	2004	15912982	Serbia	adults	Alvarado	>=10	14	34	0	9
Sigdel	2010	21485591	Nepal	adults	Alvarado	>=7	77	17	2	4
Sitter	2004	14624293	Germany	mixed	Eskelinen	>=55	522	140	249	1448
Sitter	2004	14624293	Germany	mixed	Eskelinen	>=57	479	183	150	1547
Stephens	1999	10218289	USA	mixed	Alvarado	>=7	64	20	5	5
Stephens	1999	10218289	USA	mixed	Alvarado	>=5	80	4	8	2
Sun	2008	18520542	Korea	adults	Alvarado	>=6	155	58	61	98
Sun	2008	18520542	Korea	women of reproductive age	Alvarado	>=7	43	29	13	68

Sun	2008	18520542	Korea	adults	Alvarado	>=7	112	101	35	124
Sun	2008	18520542	Korea	women of reproductive age	Alvarado	>=6	53	19	28	53
Tade	2007	18399336	Nigeria	mixed	Alvarado	>=8	17	17	4	62
Tade	2007	18399336	Nigeria	mixed	Alvarado	>=5	34	0	22	44
Tade	2007	18399336	Nigeria	mixed	Alvarado	>=6	30	4	13	53
Tade	2007	18399336	Nigeria	mixed	Alvarado	>=10	1	33	0	66
Tade	2007	18399336	Nigeria	mixed	Alvarado	>=9	8	26	1	65
Tade	2007	18399336	Nigeria	mixed	Alvarado	>=2	34	0	65	1
Tade	2007	18399336	Nigeria	mixed	Alvarado	>=7	23	11	7	59
Tade	2007	18399336	Nigeria	mixed	Alvarado	>=4	34	0	35	31
Tade	2007	18399336	Nigeria	mixed	Alvarado	>=1	34	0	66	0
Tade	2007	18399336	Nigeria	mixed	Alvarado	>=3	34	0	56	10
Tan	2013	23351046	Singapore	mixed	Alvarado	>=8	44	135	13	166
Tan	2013	23351046	Singapore	mixed	Alvarado	>=3	176	3	153	26
Tan	2013	23351046	Singapore	mixed	Alvarado	>=9	14	165	0	179
Tan	2013	23351046	Singapore	mixed	Alvarado	>=7	85	94	31	148
Tan	2013	23351046	Singapore	mixed	Alvarado	>=6	122	57	59	120
Tan	2013	23351046	Singapore	mixed	Alvarado	>=4	171	8	133	46
Tan	2013	23351046	Singapore	mixed	Alvarado	>=5	156	23	95	84
Tan	2013	23351046	Singapore	mixed	Alvarado	>=2	178	1	174	5
Tepel	2004	14634825	Germany	mixed	Ohmann	>=12.5	69	44	43	244
Ting	2011	20728850	Taiwan	adults	Ting	yes high risk	397	23	22	90
Ting	2010	20728850	Taiwan	adults	Alvarado	>=7	271	149	34	78
Tzanakis	2005	16088420	Greece	adults	Tzanakis	>=8	83	4	3	111
Tzanakis	2005	16088420	Greece	adults	van Way	NR	71	16	29	85
Tzanakis	2005	16088420	Greece	adults	Ohmann	NR	81	6	19	95
Tzanakis	2005	16088420	Greece	adults	Christian	NR	74	13	17	97

Tzanakis	2005	16088420	Greece	adults	de Dombal	NR	70	17	31	83
Tzanakis	2005	16088420	Greece	adults	Tzanakis	>=5	87	0	104	10
Tzanakis	2005	16088420	Greece	adults	Teicher	NR	77	10	19	95
Tzanakis	2005	16088420	Greece	adults	Alvarado	NR	78	9	27	87
Tzanakis	2005	16088420	Greece	adults	Arnbjornsson	NR	71	16	33	81
Tzanakis	2005	16088420	Greece	adults	Eskelinen	NR	72	15	9	105
Tzanakis	2005	16088420	Greece	adults	Lindberg	NR	74	13	14	100
Tzanakis	2005	16088420	Greece	adults	Izbicki	NR	70	17	34	80
Tzanakis	2005	16088420	Greece	adults	Fenyo	NR	79	8	17	97
Van Way	1982	6753199	USA	mixed	van Way	>=28	138	31	35	23
Wu	2012	22009520	Taiwan	children	PAS	>=6	760	121	155	359
Wu	2012	22491817	Taiwan	mixed	Alvarado	>=7	37	76	12	89
Wu	2012	22491817	Taiwan	mixed	Alvarado	>=4	105	8	59	42
Wu	2012	22009520	Taiwan	children	Alvarado	>=6	806	75	137	377
Wu	2012	21529827	Taiwan	children	Alvarado	>=7	220	86	49	239
Wu	2012	21529827	Taiwan	children	Alvarado	>=6	266	40	89	199
Yildirim	2008	18306139	Turkey	adults	Alvarado	>=5	109	13	16	5
Yildirim	2008	18306139	Turkey	adults	Alvarado	>=8	50	72	5	16
Yoldas	2012	22155381	Turkey	mixed	Lintula	>=16	120	12	2	22
Yoldas	2012	22155381	Turkey	mixed	Lintula	>=21	89	43	2	22
Zakaria	2011	22087573	Egypt	children	Zakaria	>=8	179	0	8	78
Zielke	2001	11369983	Germany	mixed	Eskelinen	>=57	379	161	137	1532
Zielke	2001	11369983	Germany	mixed	Ohmann	>=12	332	208	109	1560
de Castro	2012	22447205	Netherlands	mixed	AIR	>=9	36	310	0	595
de Castro	2012	22447205	Netherlands	mixed	AIR	>=5	321	25	87	508
de Castro	2012	22447205	Netherlands	mixed	Alvarado	>=5	311	25	271	324
de Castro	2012	22447205	Netherlands	mixed	Alvarado	>=9	100	236	30	565

van den Broek	2002	12428873	Netherlands	mixed	van den Broek (adult)	>=4	469	36	190	167
van den Broek	2004	15065030	Netherlands	children	van den Broek (pediatric)	>=4	116	32	16	73
van den Broek	2002	12428873	Netherlands	mixed	van den Broek (adult)	>=7	296	209	59	298
van den Broek	2004	15065030	Netherlands	children	van den Broek (pediatric)	>=1	147	1	55	34
van den Broek	2004	15065030	Netherlands	children	van den Broek (pediatric)	>=5	78	70	7	82
van den Broek	2004	15065030	Netherlands	children	van den Broek (pediatric)	>=3	136	12	29	60
van den Broek	2004	15065030	Netherlands	children	van den Broek (pediatric)	>=2	146	2	39	50
van den Broek	2002	12428873	Netherlands	mixed	van den Broek (adult)	>=0	505	0	357	0

Table C4. Risk of bias, studies of multivariable diagnostic scores

Author	Year	PMID	Quality Item 1	Quality Item 2	Quality Item 3	Quality Item 4	Quality Item 5	Quality Item 6	Quality Item 7	Quality Item 8
Abdeldaim	2011	17380927	yes	no	no	yes	no	no	no	yes
Al Hashemy	2004	15448772	no	yes	yes	no	no	no	yes	no
Al Qahtani	2004	19861831	yes	yes	no	no	no	no	yes	no
Althoubaity	2006	17106538	no	no	yes	no	no	no	no	no
Alvarado	1986	3963537	yes	yes	yes	no	no	no	yes	no
Andersson	2008	18553045	yes	no	no	yes	no	yes	no	yes
Arnbjornsson	1985	3909908	yes	yes	no	yes	no	yes	yes	yes
Bhatt	2009	19549016	yes	no	no	yes	no	no	no	yes
Bhattacharjee	2002	12418631	no	yes	yes	no	no	no	no	no
Bond	1990	2393167	no	yes	no	yes	no	no	yes	no
Bulus	2013	23292641	no	yes	no	yes	no	yes	yes	yes
Chan	2003	15568423	yes	no	no	yes	no	no	no	yes
Chan	2001	11603135	yes	no	no	yes	yes	yes	no	yes
Chong	2012	21633767	yes	yes	yes	yes	no	no	yes	no
Chong	2010	20428744	no	no	no	yes	no	yes	yes	no
Davidson	1999	9914351	yes	no	yes	no	no	no	no	yes
Deniszbas	2003	14676508	yes	yes	no	no	no	no	no	yes
Dey	2010	21938190	yes	no	no	no	no	no	yes	no
Enochsson	2004	15791379	no	no	yes	yes	no	yes	yes	no
Ergul	2008	19024138	yes	no	no	yes	no	no	no	yes
Escriba	2011	21346681	no	yes	no	no	no	yes	no	yes
Fente	2009	20120145	no	no	no	yes	no	yes	no	yes
Fenyo	1987	3321809	no	no	yes	no	no	no	yes	no
Fenyo	1997	9414043	no	no	no	no	no	no	no	yes
Galindo	1998	9462380	no	yes	yes	no	no	yes	no	yes
Garcia Pena	2004	14702442	yes	yes	no	no	no	yes	no	yes
Goldman	2008	18534219	no	yes	no	no	no	yes	no	yes
Gough	1988	3075891	no	no	no	no	no	no	no	no
Goulder	2008	20011493	yes	no	no	yes	no	yes	yes	yes
Gwynn	2002	12217465	no	no	yes	yes	no	no	no	no
Gwynn	2001	11489398	no	no	no	no	no	yes	no	yes
Hong	2003	14588157	yes	no	no	yes	no	yes	yes	no
Horzic	2005	16117311	no	yes	no	yes	no	yes	no	no
Inci	2011	20655156	yes	yes	no	yes	no	yes	no	yes
Jawaid	1999	10647233	no	no	no	yes	no	yes	yes	yes
John	2011	21786842	no	no	no	yes	yes	yes	yes	yes
Kalan	1994	7702329	no	no	no	yes	no	yes	yes	yes
Kamran	2010	22455259	yes	yes	no	no	no	no	yes	no
Kang	1989	2644718	yes	no	no	no	no	yes	no	yes

Kanumba	2011	21329493	yes	yes	no	yes	yes	yes	yes	yes	yes
Kell	2003	12930054	yes	no	no	yes	no	no	no	no	yes
Khan	2005	16320795	no	no	yes	yes	no	yes	no	no	yes
Kharbanda	2005	16140712	yes	yes	no	yes	no	yes	yes	yes	yes
Kharbanda	2012	22869405	no	yes	yes	yes	yes	no	yes	yes	no
Kim	2008	18660392	yes	yes	no	yes	no	yes	no	no	yes
Kirkil	2013	23588973	yes	yes	no	no	no	no	no	yes	no
Kurane	2008	23133039	no	yes	no	yes	no	yes	yes	yes	yes
Lamparelli	2000	10858683	yes	yes	yes	no	no	no	no	yes	no
Langenscheidt	1999	10231659	no	no	yes	yes	yes	yes	no	no	no
Limpawattanasiri	2011	21591529	no	yes	yes	no	no	no	no	yes	no
Lintula	2006	15723233	no	yes	no	no	no	no	yes	no	yes
Lintula	2008	18841382	yes	no	yes	yes	no	yes	yes	no	yes
Macklin	1997	9196342	yes	no	yes	no	no	no	no	yes	no
Malik	1998	9669364	no	no	no	yes	no	yes	yes	yes	yes
Mandeville	2011	20674221	no	yes	no	yes	no	yes	no	no	yes
Mardan	2007	18444596	no	yes	no	yes	no	yes	no	no	yes
McKay	2007	17543650	yes	no	no	yes	no	no	no	no	no
Meltzer	2013	23623557	no	yes	yes	no	no	no	no	yes	no
Memon	2013	23726829	yes	yes	no	yes	no	yes	yes	yes	yes
Mentes	2012	23188598	no	no	no	yes	no	yes	yes	yes	no
Mentes	2009	19683101	no	yes	no	yes	no	yes	yes	yes	yes
Nasri	2012	22673121	yes	yes	no	yes	no	yes	yes	yes	yes
Nautiyal	2010	23133203	no	no	yes	no	no	no	no	no	no
Nelson	2013	23388421	yes	no	no	yes	no	no	no	yes	yes
Owen	1992	1489366	yes	yes	yes	no	no	no	no	yes	no
Petrosyan	2008	17998781	yes	no	no	yes	no	yes	yes	yes	no
Pouget-Baudry	2010	20692636	yes	yes	yes	no	no	no	no	yes	no
Prabhudesai	2008	18043966	yes	yes	no	no	no	yes	no	no	yes
Pruekprasert	2004	15117047	no	yes	no	no	no	no	no	yes	no
Ramirez	1994	8044545b	no	no	yes	yes	no	yes	yes	yes	no
Ramirez	1994	8044545a	no	no	no	yes	no	yes	yes	yes	no
Rezak	2011	21242447	yes	yes	yes	no	no	no	no	yes	no
Saidi	2003	14601782	no	no	no	yes	no	yes	yes	yes	no
Samuel	2002	12037754	yes	no	no	no	no	yes	no	no	yes
Schellekens	2010	23859584	yes	no	no	yes	no	no	no	no	yes
Schneider	2007	17383771	yes	no	yes	yes	no	no	no	yes	no
Shera	2011	21046287	yes	yes	yes	no	no	no	no	yes	no
Shreef	2010	20859021	yes	no	no	yes	no	no	no	no	yes
Shrivastava	2004	15912982	no	yes	no	yes	no	yes	yes	yes	no
Sigdel	2010	21485591	yes	yes	yes	yes	no	yes	yes	yes	no

Sitter	2004	14624293	yes	yes	yes	no	no	no	yes	no
Stephens	1999	10218289	no	no	no	yes	no	yes	yes	no
Sun	2008	18520542	yes	yes	no	yes	yes	yes	no	yes
Tade	2007	18399336	yes	yes	no	yes	no	no	no	yes
Tan	2013	23351046	yes	no	no	no	no	no	yes	no
Tepel	2004	14634825	no	yes	yes	no	no	no	yes	no
Ting	2011	20728850	yes	yes	no	yes	no	yes	yes	no
Tzanakis	2005	16088420	yes	yes	yes	no	no	yes	no	yes
Van Way	1982	6753199	no	no	no	no	no	no	no	yes
Wu	2012	22009520	yes	no	no	yes	no	no	no	no
Wu	2012	22491817	no	yes	no	no	no	yes	no	yes
Wu	2012	21529827	no	yes	no	no	no	no	yes	no
Yildirim	2008	18306139	yes	no	no	yes	no	yes	yes	yes
Yoldas	2012	22155381	no	no	yes	yes	no	yes	yes	yes
Zakaria	2011	22087573	no	no	no	no	no	no	no	yes
Zielke	2001	11369983	yes	yes	yes	no	no	yes	no	yes
de Castro	2012	22447205	yes	yes	no	no	no	no	yes	no
van den Broek	2002	12428873	yes	yes	no	no	no	yes	no	yes
van den Broek	2004	15065030	yes	yes	no	no	no	yes	no	yes

Quality Item 1 = Was a consecutive or random sample of patients enrolled?

Quality Item 2 = Were the index test results interpreted without knowledge of the results of the reference standard?

Quality Item 3 = If a threshold was used, was it prespecified?

Quality Item 4 = Is the reference standard likely to correctly classify the target condition?

Quality Item 5 = Were the reference standard results interpreted without knowledge of the results of the index test?

Quality Item 6 = Did all patients receive a reference standard?

Quality Item 7 = Did all patients receive the same reference standard?

Quality Item 8 = Were all patients included in the analysis?

Table C5. RCT study design

Comparison of CT and routine management									
Study	Population selection criteria	Randomized interventions	Enrolment period	# centers	Power calculations?	Enrolment goal met?	Duration and method of follow-up	Loss to follow-up	Cluster trial, non-inferiority?
Hong et al. 2003 (United States) PMID: 14588157 ³³⁵	Patients at least 18 years old presenting to the emergency department with a possible diagnosis of acute appendicitis and an Alvarado score of 2-8. Exclusion criteria were awaiting interval appendectomy, unable to receive IV contrast, pregnancy, or unreliable clinical exams (e.g., taking steroids, known IBD, sickle cell disease).	1) Clinical observation alone, consisting of admission to the surgical service and monitoring with serial physical examinations and laboratory studies until there is resolution of symptoms, another diagnosis is confirmed, or appendectomy is performed for high clinical suspicion. 2) Clinical observation and abdominal/ pelvic CT. CT scans performed on a helical scanner with oral and iv contrast. Scans interpreted by a senior radiology resident or a radiology attending.	November 1998 through October 1999	1	Yes	Yes	1 week phone call post discharge	19.8% (36/182) protocol violators not included in analysis and 20.9% (38/182) not reached by phone for follow-up.	No
Lee et al. 2007 (United States) PMID: 17192450 ⁴⁹⁴	All patients over 18 years presenting to the emergency department with acute right lower quadrant abdominal pain (duration less than 7 hours) and suspected acute appendicitis. Exclusion criteria were pregnancy, evidence of diffuse peritonitis, a serum creatinine level greater than 1.6 mg/dL, and a history of contrast allergy.	1) The selective use of CT imaging, at the discretion of the treating physicians based on the clinical presentation. 2) Mandatory CT imaging. CT scans of the abdomen and pelvis were carried out with oral and iv contrast. Scans were interpreted by a board-certified radiologist.	January 2001 to May 31, 2004	1	Yes	Yes	Telephone call 48 hours after discharge from hospital or emergency department.	Unclear. All patients were included in analysis, however follow-up information was only available on 42% of non-operated (n=64?) patients overall	No
Lehtimaki et al. 2013 (Finland)	All patients over 18 years presenting to the surgical emergency department with	1) The selective use of CT imaging, at the discretion of the treating physicians based on the clinical	January 2009 to May 2010	1	Yes	Yes	Further examinations during 3	3.3% (10/300) did not meet inclusion	No

PMID: 23715771 ⁵⁰⁵	acute abdominal pain of unknown cause lasting for more than 2 hours and less than 7 days. Exclusion criteria were pregnancy, acute abdominal trauma, previous participation in the study, patient transfer as an inpatient from elsewhere with an established diagnosis for the cause of the abdominal pain, contraindication to iodinated contrast media, and withdrawal from active treatment, and requiring immediate surgery.	presentation. 2) Mandatory CT imaging within 24 hours of admission. All CT scans were carried out on a 64-row CT system. All CT scans in the mandatory arm were carried out with iv contrast and usually without oral contrast, but could be modified by radiologist preference. In the selective imaging arm, CT could be freely modified according to the clinical question. Scans were interpreted by a board-certified radiologist.					months of follow-up	criteria or withdrew consent and 12% (36/300) were lost to follow-up.	
Lopez et al. 2007 (United States) United States PMID: 18186378 ⁵²⁷	Female patients between 18 and 45 years presenting to the emergency room with a possible diagnosis of acute appendicitis and an Alvarado score of 2-8. Exclusion criteria were awaiting interval appendectomy, unable to receive IV contrast, and pregnancy, HIV positive status, or known IBD.	1) Clinical observation alone, consisting of admission to the surgical service and monitoring with serial physical examinations and laboratory studies until there is resolution of symptoms, another diagnosis is confirmed, or appendectomy is performed for high clinical suspicion. 2) Clinical observation and abdominal/pelvic CT. CT scans were performed on a helical scanner with oral and iv contrast. Scans interpreted by a senior radiology resident or a radiology attending.	November 1999 to February 2001 and March 2003 to December 2004	1	Yes	No	1 week phone call post discharge	2.2% (2/90) protocol violators not included in analysis and 21.1% (19/90) not reached by phone for follow-up.	No
Ng et al. 2002 (England) PMID: 12480851 (same study as Ng et al. 2007 PMID: 17329682, Ng et al. 2010 PMID: 20350244) ⁶⁰⁹	All patients over 18 years presenting to the emergency room from 9 am Friday to 5 pm Sunday with acute abdominal pain and admitted under the care of the surgical team. Exclusion criteria were requiring emergency surgery or urgent CT, and pregnancy, rectal bleeding, suspected gynaecological disorders or perianal abscesses.	1) Current standard practice, including plain radiography and, if indicated, ultrasonography, computed tomography, and fluoroscopic investigations. 2) Early CT (within 24 hours of admission). Other radiological investigations during the first 24 hours were also allowed. CT scans were performed on a helical scanner with oral, rectal, and contrast medium and pump injection. Scans	October 1999 to September 2000	1	Yes	Yes	Patients' notes reviewed 6 months after admission	1.7% (2/120) protocol violators not included in analysis	No

		reported by the on-call radiologist.							
Ng et al. 2007 (England) PMID: 17329682 (same study as Ng et al. 2002 PMID: 12480851, Ng et al. 2010 PMID: 20350244) ⁶⁰⁷	All patients over 18 years presenting to the emergency room from 9 am Friday to 5 pm Sunday with acute abdominal pain and admitted under the care of the surgical team. Exclusion criteria were requiring emergency surgery or urgent CT, and pregnancy, rectal bleeding, suspected gynaecological disorders or perianal abscesses.	1) Current standard practice, including plain radiography and, if indicated, ultrasonography, computed tomography, and fluoroscopic investigations. 2) Early CT (within 24 hours of admission). Other radiological investigations during the first 24 hours were also allowed. CT scans were performed on a helical scanner with oral, rectal, and contrast medium and pump injection. Scans reported by the on-call radiologist.	October 1999 to September 2000	1	Yes	Yes	Patients' notes reviewed 6 months after admission	1.7% (2/120) protocol violators not included in analysis	No
Ng et al. 2010 (England) PMID: 20350244 (same study as Ng et al. 2002 PMID: 12480851, Ng et al. 2007 PMID: 17329682) ⁶⁰⁸	All patients over 18 years presenting to the emergency room from 9 am Friday to 5 pm Sunday with acute abdominal pain and admitted under the care of the surgical team. Exclusion criteria were requiring emergency surgery or urgent CT, and pregnancy, rectal bleeding, suspected gynaecological disorders or perianal abscesses.	1) Current standard practice, including plain radiography and, if indicated, ultrasonography, computed tomography, and fluoroscopic investigations. 2) Early CT (within 24 hours of admission). Other radiological investigations during the first 24 hours were also allowed. CT scans were performed on a helical scanner with oral, rectal, and contrast medium and pump injection. Scans reported by the on-call radiologist.	October 1999 to September 2000	1	Yes	Yes	Patients' notes reviewed 6 months after admission	1.7% (2/120) protocol violators not included in analysis	No
Sala et al. 2009 PMID: 17901913 ⁷³⁴	All patients over 18 years presenting to the on-call general surgeons between 9 a.m. and 9 p.m. with a diagnosis of nonspecific acute abdominal pain, either following self-referral to the A&E or following referral by their GP. Exclusions were pregnancy, presenting complaint of rectal bleeding, suspected renal colic, suspected gynaecological disorders, or need for urgent CT or emergency surgery.	1) Current standard practice, which comprised plain radiography of the supine abdomen and erect chest. Patients were not denied access to CT if it was subsequently deemed necessary 2) Early CT (within 1 hour of presentation). CT scans from the diaphragm to the symphysis pubis were performed on a 16 detector scanner with iv contrast. Scans were reported by the CT on-call radiologist.	February 2004 to July 2004	1	Yes	Yes	Patient's medical records reviewed at 6 months.	3.4% (3/205) protocol violators not included in analysis, 3/205 patients randomized twice (only data from the first presentation were included), and 1/205 patients	No

								with medical records not available at 6 months)	
Walker et al. 2000 (United States) PMID: 11182396 ⁸⁶⁸	All patients over 18 years receiving general surgery consultation for appendicitis at the emergency department. Exclusion criteria were pregnancy, contraindication to rectal contrast material, and patients who had an appendiceal ultrasound performed prior to general surgical evaluation.	1) Standard management which varied from observation with serial abdominal examinations to right lower quadrant ultrasound, to immediate operation. CT scans with oral or IV contrast, or both, were allowed. 2) Limited CT scan with colorectal contrast. The randomized CT scan group patients received focused, helical, appendiceal CT. A staff radiologist read the CT scan. A single radiologist performed blinded, retrospective over-reads of all CT scans.	July 1998 to June 1999	1	No	N/A	Follow-up telephone call mentioned but timing not reported.	None	No
Comparison of different types of CT									
Study	Population selection criteria	Randomized interventions	Enrolment period	# centers	Power calculations?	Enrolment goal met?	Duration and method of follow-up	Loss to follow-up	Cluster trial, non-inferiority?
Hekimoglu et al. 2011 (Turkey) PMID: 22191292 ³²²	Patients at least 18 years old presenting to the emergency department with clinical signs and symptoms that suggested acute appendicitis. Exclusion criteria were possible contrast allergy, pregnancy, and traumatic cause of abdominal pain.	1) IV and oral contrast-enhanced CT 2) IV contrast-enhanced CT All CT scans were performed using scanners with 16-section multi detectors. Scans were read separately by two radiologists, each with over 5 years' experience in interpreting CT imaging of the abdomen.	March 2008 and October 2010	1	No	N/A	1 week phone call and medical record review post discharge	None	No
Hershko et al. 2007 (Israel) PMID: 17566826 ³²⁹	Consecutive patients with suspected acute appendicitis. Exclusion criteria were pregnancy and known contraindications to contrast	1) Nonenhanced CT 2) Rectal contrast-enhanced CT 3) IV and oral contrast-enhanced CT All CT scans were focused helical scans. Scans were read by six	June 2002 to January 2005	1	No	N/A	Clinical-followup mentioned but timing not	None	No

	material, including severe asthma or chronic renal failure.	radiology trainees who were at least two years into their training program.					reported		
Kepner et al. 2012 (United States) PMID: 22633722 ⁴²²	Patients at least 18 years old presenting to the emergency department with clinical signs and symptoms that suggested acute appendicitis. Exclusion criteria were allergy to IV or oral contrast, creatinine level of 1.5 or greater, current incarceration, pregnancy, and patients in whom appendicitis was not the primary concern of the treating emergency physician.	1) IV and oral contrast-enhanced CT 2) IV contrast-enhanced CT All CT scans were of the performed using 16-slice scanners. Scans were read contemporaneously by an attending radiologist, and decisions were made on the basis of this reading. Two board-certified study radiologists subsequently read the scans independently and these readings were used for analysis.	February 2007 and January 2010	1	No – post hoc only	N/A	1 week phone call after discharge.	7% (244 enrolled; 14 exclusions after randomization and 3 lost to follow-up)	No
Kim et al. 2012 (South Korea) PMID: 22533576 ⁴⁴⁴	Patients 15 to 44 years of age having an emergency department visit with suspicious signs and symptoms of acute appendicitis, who were requested to have IV contrast-enhanced CT examination because of this suspicion. Exclusion criteria were prior cross-sectional imaging tests to evaluate the presenting symptoms and signs, and contraindications to IV contrast-enhanced CT.	1) Low-dose CT, aiming at effective radiation doses of 2 mSv 2) Standard-dose CT, aiming at effective radiation doses of 8 mSv All CT scans were performed using scanners with 16, 64, or 256 detector rows and iv contrast. Reports were prepared by expert radiologists during the daytime and a range of on-call radiologists after hours.	September 2009 through January 2011	1	Yes	Yes	3 months phone interview post presentation	1.3% (12/891)	Non-inferiority
Mittal et al. 2004 (United States) PMID: 15136349 ⁵⁷⁵	Patients over 5 years of age with an uncertain clinical diagnosis of appendicitis. Exclusion criteria were pregnancy and a clinical contraindication to contrast media.	1) Standard triple-contrast abdominopelvic CT scan 2) Focused pelvic scan with rectal contrast only Helical scanning was performed with 5-mm collimation, a table speed of 5 mm/s (1.0 pitch), and a 5-mm image reconstruction interval. Board-certified radiologist interpreted all CT findings.	January 1 2000 through December 31, 2002	1	No	N/A	Standard follow-up for cases in which appendicitis was not found was observation for 23 hours. Follow-up to rule out readmission	None	No

							n for acute appendicitis mentioned but timing not reported.		
Comparison of US and CT									
Study	Population selection criteria	Randomized interventions	Enrolment period	# centers	Power calculations?	Enrolment goal met?	Duration and method of followup	Loss to followup	Cluster trial, crossover trial, non-inferiority?
Horton et al. 2000 (USA) PMID: 10930484 ³⁴⁰	Patients aged 18 to 65 presenting with possible appendicitis to emergency department, but have an atypical presentation after initial evaluation. Atypical patients defined as lacking one or more of the classic signs of acute appendicitis. 17 participants were excluded prior to randomization because the admitting surgeon felt the presentation was not atypical and admitted patients directly to operating room.	1) US only. Standard grey scale/real time scans performed by board-certified diagnostic physicians. 2) CT only. Limited noncontrast CT scans with 5-mm cuts from L3 through the inferior aspect of the cecum.	May 1997 through May 1999	1	NR	NR	NR	32.5% in US arm	No
Kaiser et al. 2002 (Sweden) PMID: 12034928 (same study as Kaiser et al. 2004 PMID: 15350578) ³⁹⁹	Patients 2 to 15 years of age clinically suspected of having acute appendicitis and were admitted to the emergency department. Exclusion criteria were abdominal pain considered to be due to obstruction without inflammation, history of asthma or possible previous reactions to contrast medium.	1) US Only. US performed by one of 12 paediatric radiologists or one of nine senior residents who completed rotations in general US and at least 2 months of paediatric radiology. 2) US plus abdominal CT. CT was interpreted by one of 12 paediatric radiologists or one of nine senior residents. US performed using a 7-MHZ linear-array transducer.	December 1999 to September 2000	1	NR	NR	6 months questionnaire after emergency department admission.	NR	No

		All CTs were helical and performed without contrast during scanning of the lower part of the abdomen, and with IV contrast during scans of the entire abdomen.							
Kaiser et al. 2004 (Sweden) PMID: 15350578 (same study as Kaiser et al. 2002 PMID: 12034928) ⁴⁰⁰	Patients 2 to 15 years of age clinically suspected of having acute appendicitis and were admitted to the emergency department. Exclusion criteria were abdominal pain considered to be due to obstruction without inflammation, history of asthma or possible previous reactions to contrast medium.	1) US Only. US performed by one of 12 paediatric radiologists or one of nine senior residents who completed rotations in general US and at least 2 months of paediatric radiology. 2) US plus abdominal CT. CT was interpreted by one of 12 paediatric radiologists or one of nine senior residents. US performed using a 7-MHZ linear-array transducer. All CTs were helical and performed without contrast during scanning of the lower part of the abdomen, and with IV contrast during scans of the entire abdomen.	December 1999 to September 2000	1	NR	NR	6 months questionnaire after emergency department admission.	NR	No
Comparison of US and routine management									
Douglas et al. 2000 (Australia) PMID: 11030676 ²⁰⁴	Patients referred to surgical service with a provisional diagnosis of acute appendicitis. Exclusion criteria included: age less than 5 years; evidence of generalized peritonitis; palpable mass in the right iliac fossa; evidence of acute confusional state or dementia; graded compression ultrasonography already performed.	1) Graded compression US informed by Alvarado Score: US for patients with Alvarado score of 4-8; and US for patients with scores 9-10 only if requested by admitted surgical team. 2) Clinical Assessment and Management: No US and not informed by Alvarado score. US was omitted for patients with extreme Alvarado Scores 1-3. For patients with Alvarado scores of 9 or	Between October 1997 and October 1998	1	Yes	NR	Patients were reviewed at one week and three months with a pro-forma assessment. When direct review was not	3% (8 / 306)	No

		<p>10, US was excluded unless requested by admitted surgical team.</p> <p>Graded compression ultrasonography results were designated positive, negative, or equivocal by the attending sonographer by using the following criteria: positive— appendix identified, tender and non-compressible or appendiceal phlegmon or abscess seen; negative— appendix not identified, no other relevant abnormality seen; equivocal—appendix not identified but abnormal amount of free fluid seen with thickened, dilated, or non-peristaltic bowel in the region of the caecum.</p>					possible, details were obtained from the patient's general practitioner or surgeon.		
<p>Lindelius et al. 2008 (Sweden) PMID: 18660395 (same study as Lindelius et al. 2009 PMID: 19625549, Lindelius et al. 2009 PMID: 19941671 and Lindelius et al. 2010 PMID: 21290005)⁵²¹</p>	<p>Patients aged 18 years or older admitted to the emergency ward for abdominal pain. Exclusion criteria included: pregnancy, previously diagnosed abdominal condition, acute conditions needing immediate care, inability to communicate with the investigator, drug or alcohol addiction and dementia.</p>	<p>1) Routine management + surgeon-performed US 2) Routine management</p> <p>US examination was performed with one of two handheld 2.5– 5 MHz or 4.3–6 MHz curved array transducers (Hawk 2102, transducers type 8801 and 8802, B-K Medical, Denmark) screening the entire abdomen. Interpreted by nine surgeons with at least 2 years' experience of surgery and 4wks US training.</p>	<p>Between February 2004 and June 2005</p>	1	Yes	Yes	<p>Participants contacted by telephone 4-6 wks. after their first visit</p>	<p>0.1% (1/800), 1 missing from analysis</p>	No
<p>Lindelius et al. 2009 (Sweden) PMID: 19625549 (same study as Lindelius et al. 2008 PMID: 18660395)</p>	<p>Patients aged 18 years or older admitted to the emergency ward for abdominal pain. Exclusion criteria included: pregnancy, previously diagnosed abdominal condition, acute conditions needing immediate care, inability to communicate with</p>	<p>1) Routine management + surgeon-performed US 2) Routine management</p> <p>US examination was performed with one of two handheld 2.5– 5 MHz or 4.3–6 MHz curved array transducers (Hawk 2102, transducers type 8801</p>	<p>Between February 2004 and June 2005</p>	1	Yes	Yes	<p>Participants contacted by telephone 4-6 wks. after their first visit</p>	<p>0.1% (1/800), 1 missing from analysis</p>	No

18660395) ⁵²⁰	the investigator, drug or alcohol addiction and dementia.	and 8802, B-K Medical, Denmark) screening the entire abdomen. Interpreted by nine surgeons with at least 2 years' experience of surgery and 4wks US training.							
Lindelius et al. 2009 (Sweden) PMID: 19941671 (same study as Lindelius et al. 2008 PMID: 18660395) ⁵¹⁹	Patients aged 18 years or older admitted to the emergency ward for abdominal pain. Exclusion criteria included: pregnancy, previously diagnosed abdominal condition, acute conditions needing immediate care, inability to communicate with the investigator, drug or alcohol addiction and dementia.	1) Routine management + surgeon-performed US 2) Routine management US examination was performed with one of two handheld 2.5– 5 MHz or 4.3–6 MHz curved array transducers (Hawk 2102, transducers type 8801 and 8802, B-K Medical, Denmark) screening the entire abdomen. Interpreted by nine surgeons with at least 2 years' experience of surgery and 4wks US training.	Between February 2004 and June 2005	1	Yes	Yes	Participants contacted by telephone 4-6 wks. after their first visit. Participants followed up using Stockholm regional registry during a two year period after the ED visit.	0.1% (1/800), 1 missing from analysis	No
Lindelius et al. 2010 (Sweden) PMID: 21290005 (same study as Lindelius et al. 2008 PMID: 18660395) ⁵¹⁸	Patients aged 18 years or older admitted to the emergency ward for abdominal pain. Exclusion criteria included: pregnancy, previously diagnosed abdominal condition, acute conditions needing immediate care, inability to communicate with the investigator, drug or alcohol addiction and dementia.	1) Routine management + surgeon-performed US 2) Routine management US examination was performed with one of two handheld 2.5– 5 MHz or 4.3–6 MHz curved array transducers (Hawk 2102, transducers type 8801 and 8802, B-K Medical, Denmark) screening the entire abdomen. Interpreted by nine surgeons with at least 2 years' experience of surgery and 4wks US training.	Between February 2004 and June 2005	1	Yes	Yes	NR	0.1% (1/800), 1 missing from analysis	No
Comparison of scores and routine management									
Study	Population selection criteria	Randomized interventions	Enrolment	#centers	Power	Enrol	Duration	Loss to	Cluster

			period		calculati ons?	ment goal met?	and method of follow-up	follow-up	trial, non- inferiority?
Farahnak et al. 2007 (Iran) PMID: 17870498 ²³⁸	All consecutive patients over 6 years initially admitted to the emergency service for abdominal pain. Exclusion criteria were: evidence of generalized peritonitis; suspicion of abdominal mass or abdominal involvement of degenerative or systemic disease; evidence of mental disturbances, acute confusional state, or dementia; or had already had any imaging including plain radiography, US or CT.	1) Standard clinical assessment and management 2) Management according to Alvarado score Management according to Alvarado score consisted of division into subgroups according to scores of 4 or less, 5-7, or 8-10. Patients with scores of 4 or less received discharge and no followup. Patients with scores of 8-10 received immediate operation after IV injection of antibiotics. Patients with scores of 5-7 received IV antibiotics and an outpatient prescription for antibiotics. They were asked to attend 1 day in the clinic.	September 1 2005 to December 15 2005	1	No	N/A	NR	None	No
Lintula et al. 2009 (Finland) PMID: 18841382 ⁵²³	Children aged 4-15 years presenting at the Emergency Department with suspected acute appendicitis. The diagnostic criteria for acute appendicitis were those set by the World Organization of Gastroenterology Research Committee. Exclusion criteria were a history of previous appendectomy, and abdominal trauma or hernia.	1) Standard clinical assessment and management 2) Management according to a diagnostic scoring system for children. The diagnostic scoring system was constructed and validated by the authors in a previous study. The score included nine variables and ranged from 0 to 32 points. A score of 15 or less corresponded to low probability of appendicitis (amenable to discharge), a score of 16-20 corresponded to intermediate probability of appendicitis (necessitating further observation), and a score of 21 or greater corresponded to high probability of appendicitis (justifying emergency appendectomy). Children with positive abdominal guarding or	January 2005 and January 2007	1	No, only post hoc	N/A	Telephone call at 4 weeks.	None	No

		rebound test were recommended to be observed/operated on, even if the sum of the appendicitis score was 15 or less. The diagnostic guidelines of the appendicitis score were not followed strictly. No imaging studies were used in the trial.							
Lintula et al. 2010 (Finland) PMID: 20379739 ⁵²⁴	Patients age 16 and above presenting at the Emergency Department with suspected acute appendicitis. Exclusion criteria were a history of previous appendectomies, abdominal trauma, hernia or chronic abdominal pathology, or other intra-abdominal pathology requiring emergency laparotomy.	1) Standard clinical assessment and management 2) Management according to a diagnostic scoring system for children, now applied in adults. The diagnostic scoring system was constructed and validated by the authors in a previous study. The score included nine variables and ranged from 0 to 32 points. A score of 15 or less corresponded to low probability of appendicitis (amenable to discharge), a score of 16-20 corresponded to intermediate probability of appendicitis (necessitating further observation), and a score of 21 or greater corresponded to high probability of appendicitis (justifying emergency appendectomy).	January 2005 and January 2007	1	Yes	Yes	Telephone call at 4 weeks	2.2% (4/181) (one in the score group and three in the no score group were excluded because they required imaging studies to exclude other intra-abdominal surgical pathologies)	No
Comparison of diagnostic laparoscopy and open exploration									
Study	Population selection criteria	Randomized interventions	Enrolment period	#centers	Power calculations?	Enrolment goal met?	Duration and method of follow-up	Loss to follow-up	Cluster trial, non-inferiority?
Bruwer et al. 2003 (South Africa) PMID: 14768141 ¹⁰⁹	Women aged 15-45 referred to one of the authors from the gastrointestinal surgical service. Inclusion criteria were that a diagnosis of acute appendicitis	1) Laparoscopic exploration 2) Open surgical exploration Open exploration was via a right iliac fossa incision in 10 patients and by means of lower midline	April 1997 to March 2000	1	No	N/A	Personal or telephone interview at 4 weeks postoperati	None	No

	could not be excluded on clinical and ancillary grounds, and an independent decision to undertake surgical exploration had been made. Exclusion criteria were: compromised immune status (known HIV positivity, malignancy, prior or current chemotherapy, immunosuppression); positive pregnancy test; major anaesthetic risk as a result of systemic disease (ASA II or worse); or evidence of systemic sepsis or complicated acute appendicitis (diffuse peritonitis, right iliac fossa mass).	laparotomy in 6 patients.					vely		
Comparison of diagnostic laparoscopy and routine management									
Study	Population selection criteria	Randomized interventions	Enrolment period	#centers	Power calculations?	Enrolment goal met?	Duration and method of follow-up	Loss to follow-up	Cluster trial, non-inferiority?
Decadt et al. 1999 (England) PMID: 10583282 ¹⁸³	Patients admitted to hospital with acute abdominal pain of less than 7 days duration and an uncertain diagnosis after examination and baseline investigations. Baseline investigations included full blood count, measurement of urea, electrolytes and serum amylase, urine culture, a pregnancy test in women of reproductive age, and a chest or abdominal radiograph if clinically indicated. Exclusion criteria were requirement for	1) Diagnostic laparoscopy within 18 hours of admission 2) Close active observation and conventional non-invasive investigation Laparoscopy was performed using an open Hasson technique for the first port placement in the umbilical area with one 5-mm port in the midline suprapubic area and a third port if necessary. When no abnormality was identified at laparoscopy, appendectomy was performed on the basis that symptoms caused by appendicitis	November 1995 and October 1998	1	No	N/A	NR	None	No

	acute surgical intervention on the basis of history, clinical examination and baseline investigations.	are not always obvious at laparoscopy.							
Gaitan et al. 2002 (Colombia) PMID: 11818109 ²⁶²	Women aged 18 to 45 with non-specific lower abdominal pain. Non-specific abdominal pain was defined as one of the following: pain was not proceeding in a classical course, or, after clinical history had been taken and physical examination, hemogram, urinalysis, pregnancy test, and pelvic and transvaginal ultrasonography performed, two examiners did not agree on a diagnosis by the end of a 6-hour observation. Exclusion criteria were: suspicion of pathology in upper hemiabdomen; background of peritonitis or intestinal surgery; two or more intra-abdominal surgeries; evidence of urinary infection, kidney lithiasis, cholelithiasis, infectious colitis or irritable colon; multiple organic dysfunction syndrome, septic shock or hypovolemic shock; chronic pelvic pain or pain with more than 3 months' evolution; possible intra-uterine pregnancy and unharmed sac; weight of more than 100 kg; and psychiatric disorder.	1) Diagnostic laparoscopy within 24 hours of admission 2) Clinical observation and conventional diagnosis Laparoscopy was direct observation of the pelvic cavity with a Wolf laparoscope fitted with a video camera and zoom, a light source, and the high-flow insufflator that allows surgical procedures to be performed. The conventional diagnosis method was based on clinical assessment and laboratory tests.	November 1 1997 to June 30, 2000	1	Yes	No (110/14 were enrolled)	Women followed to 7 days after discharge	11% (12/110) not followed at 7 days after discharge, however all participants included in tables reporting final diagnosis and time to diagnosis	No
Comparison of diagnostic laparoscopy and immediate appendectomy									

Study	Population selection criteria	Randomized interventions	Enrolment period	#centers	Power calculations?	Enrolment goal met?	Duration and method of follow-up	Loss to follow-up	Cluster trial, non-inferiority?
Jadallah et al 1994 (Sweden) PMID: 8186313 ³⁶⁷	Women of childbearing age presenting with acute lower abdominal pain suggestive of acute appendicitis. Exclusion criteria were cardiac and respiratory insufficiency, haemorrhagic diathesis, previous abdominal operations, morbid obesity, intestinal obstruction, generalized peritonitis or a pregnancy beyond the twelfth week.	1) Diagnostic laparoscopy followed by appendectomy if necessary 2) Immediate open appendectomy Laparoscopy was done under general anaesthesia after the bladder had been emptied. Pneumoperitoneum was induced with 2-4l carbon dioxide through a Verrey's needle introduced through a sub-umbilical stab incision which was later used for the laparoscopy. A manipulating probe was inserted through another small incision in the right iliac fossa under direct vision. All patients received IV antibiotic prophylaxis.	July 1988 to March 1990	1	No	N/A	Follow-up period of at least two weeks, method not stated.	None	No
Laine et al. 1997 (Finland) PMID: 9069134 ⁴⁷⁸	Women between the ages of 16 and 40 years with acute lower right quadrant abdominal pain and in whom the surgeon decided to operate for suspected acute appendicitis. No exclusion criteria listed.	1) Diagnostic laparoscopy followed by appendectomy if necessary 2) Immediate open appendectomy The laparoscopic operation was performed with the patient in the Trendelenburg position. A three-trocar method was used; a 10-mm periumbilical port for the optics, a 12-mm port in the left fossa, and a 10-mm port in the midclavicular line in the right upper quadrant of the abdomen for the instruments. If the appendix appeared to be normal and another cause for abdominal pain was found, the appendix was left in situ, but it was removed if no other evident cause for lower abdominal pain was found.	January 1994 to June 1995	1	No	N/A	NR	None	No
Larsson et al. 2001 (Sweden) PMID:	Women ages 15-47 with clinical signs of acute appendicitis. Exclusion criteria were diffuse	1) Diagnostic laparoscopy followed by appendectomy if necessary 2) Immediate open appendectomy	1991-1995	1	No	N/A	Mentioned that there was follow-	1.8% (110 randomized of which there	No

11285968 ⁴⁸⁷	peritonitis, suspicion of gynecologic disease or pregnancy, severe adipositas, known intra-abdominal adhesions, and severe cardiovascular disease.	If the appendix was considered inflamed, or if it could not be visualized, the surgeon performed an appendectomy. If the appendix was considered normal it was left in situ.					up was details not mentioned	was one protocol violation and one loss to follow-up. It is not reported which study arm was affected by these exclusions; they have tentatively been assigned to the control arm in these tables)	
Olsen et al. 1993 (Denmark) PMID: 8369940 ⁶¹⁹	Women aged 15-56 with clinical signs of acute appendicitis. Exclusion criteria include signs of diffuse peritonitis, a previous diagnosis of diffuse peritonitis, and more than two previous lower laparotomies.	1) Diagnostic laparoscopy followed by appendectomy if necessary 2) Immediate appendectomy, performed through a transverse incision in the right iliac fossa. Appendicitis was excluded if a normal appendix could be seen throughout its length. Appendectomy was performed when acute appendicitis was confirmed and when a diagnosis of appendicitis could not be excluded. If other abnormalities were found the appropriate treatment was given.	January 1 1988 to November 26 1991	1	No	N/A	Mention that 'late follow-up' was not performed. No other mention or description of follow-up.	None	No
Tzouvaras et al. 2007 (Greece) PMID: 17219281 ⁸⁴⁷	Men with suspected acute appendicitis.	1) Diagnostic laparoscopy followed by appendectomy 2) Open appendectomy Normal-looking appendixes were routinely removed unless another cause requiring surgical intervention was discovered. This was to obtain a definite histological diagnosis.	September 2002 to September 2005	1	No	N/C	All abnormal and normal appendixes were removed.	None	No
van Dalen et al. 2003 (New	Women aged 16-45 with a clinical diagnosis of acute	1) Diagnostic laparoscopy followed by appendectomy if necessary	July 1991 to July 1992	1	No	N/A	Participants with	None	No

Zealand) PMID: 12739123 ⁸⁵³	appendicitis. Exclusion criteria were any contraindications to laparoscopy.	2) Immediate appendectomy, performed through a transverse incision in the right iliac fossa. If an inflamed appendix was seen or evidence thereof, or if the appendix could not be seen, an open appendectomy was carried out. If other abnormalities were found the appropriate treatment was given. If the appendix was clearly seen and looked normal, no appendectomy was carried out.					appendixes appearing normal at laparoscopy and left in situ were reviewed at a median of 10 years.		
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Table C6. RCT test performance outcomes

Comparison of CT and routine management						
Study	Study arms	Number enrolled	Number followed to end	Sensitivity	Specificity	Test Performance Other
Hong et al. 2003 (United States) PMID: 14588157 ³³⁵	Clinical observation alone [total population]	85	58 (17 protocol violators not followed, 10 persons not reached for telephone follow-up although they were included in sensitivity and specificity calculations)	1.00 (42/42)	0.73 (19/26)	Accuracy 0.90
	Clinical observation and abdominal/pelvic CT [total population]	97	50 (19 protocol violators not followed, 28 persons not reached for telephone follow-up although they were included in test performance calculations)	0.91 (30/33)	0.93 (42/45)	Accuracy 0.92
	Clinical observation alone [women age 18-45]	NR	19	1.00 (11/11)	0.88 (7/8)	Accuracy 0.95
	Clinical observation and abdominal/pelvic CT [women age 18-45]	NR	29	1.0 (5/5)	0.92 (22/24)	Accuracy 0.93
Lee et al. 2007 (United States) PMID: 17192450 ⁴⁹⁴	Selective CT imaging	80	Unclear. 43 patients underwent laparotomy and follow-up information was only available on 42% of non-operated patients overall.	NR	NR	NR
	Mandatory CT imaging.	72	Unclear. Two patients underwent surgery before CT imaging could be performed, 43 patients underwent	NR	NR	NR

			laparotomy, and follow-up information was only available on 42% of non-operated patients overall.			
Lehtimaki et al. 2013 (Finland) PMID: 23715771 ⁵⁰⁵	Selective CT imaging	150	111 (7 did not meet inclusion criteria or withdrew consent and 32 were lost to follow-up.)	NR	NR	NR
	Mandatory CT imaging (within 24 hours of admission)	150	143 (3 did not meet inclusion criteria or withdrew consent and 4 were lost to follow-up.)	NR	NR	NR
Lopez et al. 2007 (United States) PMID: 18186378 ⁵²⁷	Clinical observation alone [women age 18-45]	48	39 (2 protocol violators not followed, 7 persons not reached for telephone follow-up although they were included in test performance calculations)	1.00 (22/22)	0.88 (21/24)	PPV 0.88 NPV 1.0 Accuracy 0.93
	Clinical observation and abdominal/pelvic CT [women age 18-45]	42	30 (12 persons not reached for telephone follow-up although they were included in test performance calculations)	0.89 (17/19)	0.96 (22/23)	PPV 0.944 NPV 0.917 Accuracy 0.93
Ng et al. 2002 (England) PMID: 12480851 (same study as Ng et al. 2007 PMID: 17329682, Ng et al. 2010 PMID: 20350244) ⁶⁰⁹	Current standard practice	63	63	NR	NR	Accuracy at 24 hours after initial diagnosis: 75% (47/63) Accuracy at 6 months follow-up: 49% (31/64)
	Early CT (within 24 hours of admission)	57	55 (2 protocol violators not followed)	NR	NR	Accuracy at 24 hours after initial diagnosis: 78% (43/55) Accuracy at 6 months follow-up: 51% (28/55)
Ng et al. 2007 (England) PMID: 17329682 (same study as Ng et al. 2002 PMID: 12480851, Ng et al. 2010 PMID:)	Current standard practice	63	63	NR	NR	NR

20350244) ⁶⁰⁷						
	Early CT (within 24 hours of admission)	62	62	98% (39/40)	50% (11/22)	Accuracy at 24 hours after initial diagnosis: 81% (50/62)
Ng et al. 2010 (England) PMID: 20350244 (same study as Ng et al. 2002 PMID: 12480851) ⁶⁰⁸	Current standard practice	63	63	NR	NR	NR
	Early CT (within 24 hours of admission)	57	55 (2 protocol violators not followed)	NR	NR	NR
Sala et al. 2009 (England) PMID: 17901913 ⁷³⁴	Current standard practice	NR	99	NR	NR	NR
	Early CT (within 1 hour of presentation)	NR	NR	NR	NR	NR
Walker et al. 2000 (United States) PMID: 11182396 ⁸⁶⁸	Standard management	63	63	1.0 (29/29)	0.79 (27/34)	Accuracy 0.89
	Limited CT scan with colorectal contrast.	65	65	0.94 (30/32) Note: 8 scans were equivocal; 3/8 had appendicitis and 5/8 did not have appendicitis, all were omitted from sensitivity calculations.	1.0 (25/25) Note: 8 scans were equivocal; 3/8 had appendicitis and 5/8 did not have appendicitis, all were omitted from specificity calculations.	Accuracy 0.96
	Standard management men [age 18 to 40]	13	13	NR	NR	Accuracy 0.85
	Limited CT scan with	14	14	NR	NR	Accuracy 0.96

	colorectal contrast men [age 18 to 40]					
Comparison of different types of CT						
Study	Study arms	Number enrolled	Number followed to end	Sensitivity	Specificity	Test Performance Outcomes Other
Hekimoglu et al. 2011 (Turkey) PMID: 22191292 ³²²	IV and oral contrast-enhanced CT	100	100	Radiologist 1: 0.97 (31/32) Radiologist 2: 0.94 (30/32)	Radiologist 1: 0.99 (67/68) Radiologist 2: 0.97 (66/68)	PPV Radiologist 1: 0.969 NPV Radiologist 1: 0.985 PPV Radiologist 2: 0.937 NPV Radiologist 2: 0.971
	IV contrast-enhanced CT	100	100	Radiologist 1: 0.84 (21/25) Radiologist 2: 0.72 (18/25)	Radiologist 1: 0.95 (71/75) Radiologist 2: 0.89 (67/75)	PPV Radiologist 1: 0.840 NPV Radiologist 1: 0.947 PPV Radiologist 2: 0.720 NPV Radiologist 2: 0.893
Hershko et al. 2007 (Israel) PMID: 17566826 ³²⁹	Nonenhanced CT	70	56 (Of 14 inconclusive scans,; 6 had appendicitis, 3 did not have appendicitis, and 5 are not discussed further)	0.90 (19/21) Note: 14 scans were inconclusive and are omitted from calculations.	0.86 (30/35) Note: 14 scans were inconclusive and are omitted from calculations.	PPV 0.79 NPV 0.94 Accuracy 0.70
	Rectal contrast-enhanced CT	78	78	0.95 (37/39)	0.92 (36/39)	PPV 0.94 NPV 0.93 Accuracy 0.94
	IV and oral contrast-enhanced CT	84	84	1.0 (43/43)	0.88 (36/41)	PPV 0.89 NPV 1.0 Accuracy 0.94
Kepner et al. 2012 (United States) PMID: 22633722 ⁴²²	IV and oral contrast-enhanced CT	113	113 (not known how many exclusions and lost to follow-up were in group)	1.0 (35/35)	0.96 (75/78)	PPV 0.895 NPV 1.0

	IV contrast-enhanced CT	114	114 (not known how many exclusions and lost to follow-up were in group)	1.0 (41/41)	0.99 (72/73)	PPV 0.976 NPV 1.0
Kim et al. 2012 (South Korea) PMID: 22533576 ⁴⁴⁴	Low-dose CT	444	438 (6 lost to follow-up; an additional 5 were excluded from analysis because data was missing; n=433 for test performance)	0.95 (156/165)	0.93 (250/268)	NR
	Standard-dose CT	447	441 (6 lost to follow-up; an additional person was excluded from analysis because data was missing; n=440 for test performance)	0.95 (171/180)	0.94 (244/260)	NR
Mittal et al. 2004 (United States) PMID: 15136349 ⁵⁷⁵	Standard triple-contrast abdominopelvic CT scan	52	52	0.98 (43/44)	0.50 (4/8)	PPV 0.90 NPV 0.93
	Focused pelvic scan with rectal contrast only	39	39	1.0 (36/36)	1.0 (3/3)	PPV 1.0 NPV 1.0
Comparison of US and CT						
Study	Study arms	Number enrolled	Number followed to end	Sensitivity	Specificity	Test Performance Other
Horton et al. 2000 (USA) PMID: 10930484 ³⁴⁰	US	40	28/40 (11 had nondiagnostic scans and 2 with negative scans were not followed up on after being sent home)	0.92 (23/25)	0.33 (1/3)	NR
	CT	49	49/49 (1 with a CT scan positive for appendicitis received intravenous antibiotics, improved, and was discharged home on a regimen of oral antibiotics; 1 with CT scan negative had a repeated scan which showed positive for appendicitis).	0.97 (36/37)	0.75 (9/12)	NR
Kaiser et al. 2002 (Sweden) PMID: 12034928 (same study as Kaiser et al. 2004 PMID: 15350578) ³⁹⁹	US only	283	283	0.86 (94/109)	0.95 (165/174)	PPV: 0.91 NPV: 0.92 Diagnostic Accuracy: 92%
	US plus abdominal CT	317	317	0.99 (133/135)	0.89 (162/182)	PPV: 0.87 NPV: 0.99 Diagnostic

						Accuracy: 93%
	All US	600	600	0.80 (196/244)	0.94 (336/356)	NR
	All abdominal CT	317	317	0.97 (131/135)	0.93 (170/182)	NR
Kaiser et al. 2004 (Sweden) PMID: 15350578 (same study as Kaiser et al. 2002 PMID: 12034928) ⁴⁰⁰	US only	283	283	0.86	0.95	PPV: 0.91 NPV: 0.92 Diagnostic Accuracy: 92% AUC for Sensitivity vs. Specificity (Initial surgical dx): 0.744 +/- 0.03 AUC for Sensitivity vs. Specificity (Radiologic surgical dx): 0.943 +/- 0.016 AUC for Sensitivity vs. Specificity (Final surgical dx): 0.972 +/- 0.009
	US plus abdominal CT	317	317	0.99	0.89	PPV: 0.87 NPV: 0.99 Diagnostic Accuracy: 93% AUC for Sensitivity vs. Specificity (Initial surgical dx): 0.744 +/- 0.029 AUC for Sensitivity vs. Specificity (Radiologic surgical dx): 0.982 +/- 0.007 AUC for Sensitivity vs. Specificity (Final surgical dx): 0.98 +/- 0.009
Comparison of US and routine management						
Study	Study arms	Number enrolled	Number followed to end	Sensitivity	Specificity	Test Performance Other
Douglas et al.	Graded compression	160	158 (including 2 lost to follow-up at 3 months)	94.7 (54/57*)	88.9 (16/18*)	Diagnostic

2000 (Australia) PMID: 11030676 ²⁰⁴	US informed by Alvarado Score		- please note: only 139 tested by US	Calculations based on histologically proved cases)	Calculations based on histologically proved cases)	Accuracy: 93.3% (70/75)
	Clinical Assessment and Management	142	158 (including 2 lost to follow-up at 3 months)	NA	NA	NR
Lindelius et al. 2008 (Sweden) PMID: 18660395 (same study as Lindelius et al. 2009 PMID: 19625549, Lindelius et al. 2009 PMID: 19941671 and Lindelius et al. 2010 PMID: 21290005) ⁵²¹	Routine management + US	400	382 (7 under age; 1 pregnant; 6 no primary diagnosis; 2 crossover; 1 withdrawal; 1 no final diagnosis)	NR	NR	Diagnostic Accuracy: Proportion of correct primary diagnoses: 64.7% (247/382) - Alternative ITT analysis (Assuming all excluded in US group had incorrect primary diagnosis): 61.8% (247/400) - Alternative ITT analysis (Assuming all excluded in US group had correct primary diagnosis): 66.3% (265/400)
	Routine management	400	380 (1 missing; 8 under age; 6 no primary diagnosis; 1 crossover; 2 withdrawal; 2 no final diagnosis)	NR	NR	Diagnostic Accuracy: Proportion of correct primary diagnoses: 56.8% (216/380) - Alternative ITT analysis (Assuming all excluded in No US group had incorrect primary diagnosis): 54.1% (216/399) - Alternative ITT analysis (Assuming all excluded in No US group had

						correct primary diagnosis): 58.9% (235/399)
Lindelius et al. 2009 (Sweden) PMID: 19625549 (same study as Lindelius et al. 2008 PMID: 18660395) ⁵²⁰	Routine management + US	400	392 (8 excluded for not meeting inclusion criteria)	NR	NR	NR
	Routine management	400	391 (1 missing; 8 excluded for not meeting inclusion criteria)	NR	NR	NR
Lindelius et al. 2009 (Sweden) PMID: 19941671 (same study as Lindelius et al. 2008 PMID: 18660395) ⁵¹⁹	Routine management + US	400	392 (8 excluded for not meeting inclusion criteria)	NR	NR	NR
	Routine management	400	391 (1 missing; 8 excluded for not meeting inclusion criteria)	NR	NR	NR
Lindelius et al. 2010 (Sweden) PMID: 21290005 (same study as Lindelius et al. 2008 PMID: 18660395) ⁵¹⁸	Routine management + US	400	392 (8 excluded for not meeting inclusion criteria)(only n=383 were included in BMI analyses)	NR	NR	Diagnostic Accuracy: - Diagnostic Accuracy of Intervention among participants with BMI < 25: 62% (135/223) - Diagnostic Accuracy of Intervention among participants with BMI >= 25: 67% (105/160) - Among participants with Age 18 < x < 30: 65% (56/87) - Among

						participants with Age 30-59: 68% (130/198) - Among participants with Age > = 60: 58% (61/107)
	Routine management	400	391 (1 missing; 8 excluded for not meeting inclusion criteria)(only n=370 were included in BMI analyses)	NR	NR	Diagnostic Accuracy: - Among participants with BMI < 25: 58% (119/213) - Diagnostic Accuracy of Intervention among participants with BMI >= 25: 54% (85/157) - Among participants with Age 18 < x < 30: 60% (52/90) - Among participants with Age 30-59: 58% (109/190) - Among participants with Age > = 60: 52% (55/111)
Comparison of scores and routine management						
Study	Study arms	Number enrolled	Number followed to end	Sensitivity	Specificity	Test Performance Other
Farahnak et al. 2007 (Iran) PMID: 17870498 ²³⁸	Standard clinical assessment and management	21	21	NR	NR	NR

	Management according to Alvarado score	21	21	NR	NR	NR
Lintula et al. 2009 (Finland) PMID: 18841382 ⁵²³	Standard clinical assessment and management	60	60	0.96 (26/27)	0.67 (23/33)	PPV 0.70 (26/37) NPV 0.96 (22/23) Accuracy 0.80 (48/60)
	Management based on a diagnostic scoring system for children.	66	66	1.0 (24/24)	0.88 (37/42)	PPV 0.83 (24/29) NPV 1.0 (37/37) Accuracy 0.92 (61/66)
Lintula et al. 2010 (Finland) PMID: 20379739 ⁵²⁴	Standard clinical assessment and management	84	81	0.89 (32/36)	0.80 (36/45)	PPV 0.78 (32/41) NPV 0.90 (36/40) Accuracy 0.84 (68/81) [Note: this diagnostic performance is for initial examination, data are also provided for final examination (at 3, 6, 9 or 12 hours after initial evaluation)]
	Management based on a diagnostic scoring system for children.	97	96	0.87 (45/52)	0.59 (26/44)	PPV 0.71 (45/63) NPV 0.79 (26/33) Accuracy 0.74 (71/96) [Note: this diagnostic performance is for initial examination, data are also provided for final examination (at 3, 6, 9 or 12 hours after initial evaluation)]
Comparison of diagnostic laparoscopy and						

open exploration						
Study	Study arms	Number enrolled	Number followed to end	Sensitivity	Specificity	Test Performance Other
Bruwer et al. 2003 (South Africa) PMID: 14768141 ¹⁰⁹	Laparoscopy	18	18	1.0 (9/9)	0.78 (2/9)	NR
	Open exploration	16	16	1.0 (6/6)	0.3 (3/10)	NR
Comparison of diagnostic laparoscopy and routine management						
Study	Study arms	Number enrolled	Number followed to end	Sensitivity	Specificity	Test Performance Other
Decadt et al. 1999 (England) PMID: 10583282 ¹⁸³	Laparoscopy within 18 hours of admission	59	59	NR	NR	Proportion visualized not reported.
	Close active observation and conventional non-invasive investigation	61	61	NR	NR	NR
Gaitan et al. 2002 (Colombia) PMID: 11818109 ²⁶²	Laparoscopy within 24 hours of admission	55	55	NR	NR	NR
	Clinical observation and conventional diagnosis	55	55	NR	NR	NR
Comparison of diagnostic laparoscopy and immediate appendectomy						
Study	Study arms	Number enrolled	Number followed to end	Sensitivity	Specificity	Test Performance Other
Jadallah et al 2994 (Sweden) PMID: 8186313 ³⁶⁷	Diagnostic laparoscopy followed by appendectomy if necessary	50	50	1.0 (26/26)	0.87 (20/24)	One appendix removed due to ectopic pregnancy and omitted from analyses by authors

						but is included as a TN here. Appendix could be visualized in 92% (46/50) of cases
	Immediate open appendectomy	50	50	NA	NA	NA
Laine et al. 1997 (Finland) PMID: 9069134 ⁴⁷⁸	Diagnostic laparoscopy followed by appendectomy if necessary	25	25	NR	NR	Proportion visualized not reported. Diagnosis was established in 96% (24/25) of cases.
	Immediate open appendectomy	25	25	NA	NA	NA
Larsson et al. 2001 (Sweden) PMID: 11285968 ⁴⁸⁷	Diagnostic laparoscopy followed by appendectomy if necessary	55	55	1.0 (40/40)	0.73 (11/15)	1 appendix could not be visualized, a 1.8% (1/55) rate Accuracy 0.72 (40/55)
	Immediate open appendectomy	55	53	NA	NA	NA
Olsen et al. 1993 (Denmark) PMID: 8369940 ⁶¹⁹	Diagnostic laparoscopy followed by appendectomy if necessary	30	30	NR	NR	5 appendixes could not be visualized, a 16.7% (5/30) rate
	Immediate appendectomy	30	30	NA	NA	NA
Tzovaras et al. 2007 (Greece) PMID: 17219281 ⁸⁴⁷	Diagnostic laparoscopy followed by appendectomy	38	38	NR	NR	NR
	Open appendectomy	40	40	NA	NA	NA
van Dalen et al. 2003 (New Zealand) PMID: 12739123 ⁸⁵³	Diagnostic laparoscopy followed by appendectomy if necessary	32	32	1.0 (24/24)	0.875 (7/8)	Accuracy 0.97 (31/32)
	Immediate appendectomy	31	31	NA	NA	NA

Table C7. RCT risk of bias

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Total proportion of missing outcome data is >10%	Difference in proportion of missing data between arms is >10%	Selective reporting of outcomes	Compliance with interventions, other
Comparison of CT and routine management								
Hong et al. 2003 (United States) PMID: 14588157 ³³⁵	UNCLEAR (no details about randomization procedures)	UNCLEAR (no description of allocation procedures)	UNCLEAR (blinding not described)	UNCLEAR (blinding not described)	HIGH (for test performance outcomes, participants omitted from analyses are 20% overall and an additional 22% (38/53) of participants requiring telephone follow-up could not be reached. All appendicitis-related outcomes are therefore subject to uncertainty due to omissions from analyses and also lack of follow-up)	HIGH (for test performance outcomes, participants omitted from analyses are 20% of each arm, however the percentage of participants requiring telephone follow-up who could not be reached was 82% in the CT arm and 53% in the clinical assessment arm)	LOW (expected outcomes reported in methods were included in results)	HIGH (more than 10% of each group discontinued the intervention and an ITT analysis was not attempted)
Lee et al. 2007 (United States) PMID: 17192450 ⁴⁹⁴	LOW (computerized random numbers program)	LOW (personnel not involved in any other aspects of the study generated intervention assignments)	UNCLEAR (participants and care providers were not blinded and this may possibly have affected the outcomes)	LOW (outcome assessors were blinded to group assignments)	HIGH (all appendicitis outcomes were assessed in >90% of operated participants, however follow-up information	UNCLEAR (all appendicitis outcomes were assessed in >90% of operated participants in each arm, however the	LOW (expected outcomes reported in methods were included in results)	LOW (no other problems observed)

					was only available on 42% of non-operated patients overall and although the authors stated these patients would have returned to their ED if they developed appendicitis all outcomes are subject to uncertainty due to lack of follow-up)	percentage of participants requiring telephone follow-up who could not be reached is not reported for each arm)		
Lehtimaki et al. 2013 (Finland) PMID: 23715771 ⁵⁰⁵	UNCLEAR (randomization was performed by the on-call surgeon using closed envelopes)	UNCLEAR (randomization was performed by the on-call surgeon using closed envelopes)	UNCLEAR (blinding not described)	UNCLEAR (blinding not described)	UNCLEAR (although the negative appendectomy, diagnostic procedures, and length of stay outcomes collected to time of discharge appear to have been assessed in >90% of participants, 12% of participants were reported to be missing data and/or lost to 3 month follow-up, which was designed to detect possible complications in patients	UNCLEAR (diagnosis, treatment and length of stay outcomes to discharge appear to have been assessed in >90% of participants in each group but the overall percentage of participants with missing data and/or lost to 3 month follow-up was 3% in CT arm and 22% in selective imaging arm – the reporting of follow-up vs. missing data is	LOW (expected outcomes reported in methods were included in results)	LOW (no other problems observed)

					diagnosed with nonspecific abdominal pain – however, the reporting of follow-up vs. missing data is unclear)	unclear)		
Lopez et al. 2007 (United States) PMID: 18186378 ⁵²⁷	LOW (randomization was done using a computer)	UNCLEAR (numbered envelopes, opened sequentially)	UNCLEAR (blinding not described)	UNCLEAR (blinding not described)	HIGH (for test performance outcomes, >90% of participants were included in analyses, however 44% (19/43) of participants requiring telephone follow-up could not be reached. All appendicitis-related outcomes are therefore subject to uncertainty due to lack of follow-up)	HIGH (for test performance outcomes, >90% of participants from each arm were included in analyses, however the percentage of participants requiring telephone follow-up who could not be reached was 54% in the CT arm and 33% in the clinical observation arm, and all appendicitis-related outcomes are therefore subject to differential uncertainty)	LOW (expected outcomes reported in methods were included in results)	LOW (no other problems observed)
Ng et al. 2002 (England) PMID: 12480851 (same study as Ng et al. 2007 PMID: 17329682, Ng et al. 2010 PMID: 20350244) ⁶⁰⁹	LOW (a predetermined sequence derived from a random number algorithm)	UNCLEAR (statement that participants were blinded to the randomization sequence is unclear)	UNCLEAR (blinding not described)	UNCLEAR (no statement about blinding for assessment of primary outcome of length of hospital stay or outcome of diagnostic	LOW (length of hospital stay and final diagnosis were assessed in >90% of participants overall)	LOW (length of hospital stay and final diagnosis were assessed in >90% of participants in each arm)	LOW (expected outcomes reported in methods were included in results)	LOW (no other problems observed)

				confidence, however assessment of changes in diagnoses and management were assessed blindly and scored by consensus)				
Ng et al. 2007 (England) PMID: 17329682 (same study as Ng et al. 2002 PMID: 12480851, Ng et al. 2010 PMID: 20350244) ⁶⁰⁷	LOW (a predetermined sequence derived from a random number algorithm)	UNCLEAR (statement that participants were blinded to the randomization sequence is unclear)	UNCLEAR (blinding not described)	UNCLEAR (no statement about blinding for assessment of primary outcome of length of hospital stay or outcome of diagnostic confidence, however assessment of changes in diagnoses and management were assessed blindly and scored by consensus)	HIGH (diagnostic accuracy, diagnostic confidence, sensitivity and specificity of the test were assessed in approx. 50% of participants overall)	HIGH (diagnostic accuracy, Diagnostic confidence, sensitivity and specificity of the test were assessed in < 90% of participants in each arm)	LOW (expected outcomes reported in methods were included in results)	LOW (no other problems observed)
Ng et al. 2010 (England) PMID: 20350244 (same study as Ng et al. 2002 PMID: 12480851, Ng et al. 2007 PMID: 17329682) ⁶⁰⁸	LOW (a predetermined sequence derived from a random number algorithm)	UNCLEAR (statement that participants were blinded to the randomization sequence is unclear)	UNCLEAR (blinding not described)	UNCLEAR (no statement about blinding for assessment of primary outcome of length of hospital stay or outcome of diagnostic confidence, however assessment of changes in diagnoses and management were assessed blindly	LOW (length of hospital stay and final diagnosis were assessed in >90% of participants overall)	LOW (length of hospital stay and final diagnosis were assessed in >90% of participants in each arm)	LOW (expected outcomes reported in methods were included in results)	LOW (no other problems observed)

				and scored by consensus)				
Sala et al. 2009 (England) PMID: 17901913 ⁷³⁴	UNCLEAR (no details about randomization procedures)	UNCLEAR (no description of allocation procedures)	UNCLEAR (blinding not described)	UNCLEAR (blinding not described)	UNCLEAR (no information about numbers of participants randomized, only about 99 participants randomized)	UNCLEAR (no information about numbers of participants randomized)	LOW (outcomes described in methods were included in results)	LOW (no other problems observed)
Walker et al. 2000 (United States) PMID: 11182396 ⁸⁶⁸	UNCLEAR (no details about randomization procedures)	UNCLEAR (no description of allocation procedures)	UNCLEAR (blinding not described)	UNCLEAR (blinding not described)	LOW (no participants lost to followup for any outcome other than sensitivity and specificity and sensitivity and specificity were reported for all participants with definite diagnostic results (120/128; 94%))	LOW (although CT participants with equivocal scans were omitted from calculations of sensitivity and specificity (12% (8/65) of arm) and 0% were omitted from calculations of sensitivity and specificity in the standard management group, the final appendicitis outcomes of participants with equivocal scans were reported and are not lost)	LOW (expected outcomes reported in methods were included in results)	LOW (no other problems observed)
Comparison of different types of CT								
Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Total proportion of missing outcome data is >10%	Difference in proportion of missing data between arms is >10%	Selective reporting of outcomes	Compliance with interventions, ITT analysis
Hekimoglu et al. 2011 (Turkey)	UNCLEAR (no details about	UNCLEAR (no details about	UNCLEAR (no mention of blinding of	UNCLEAR (no mention of blinding	LOW (no missing outcome data)	LOW (no missing outcome data)	LOW (all expected outcomes	LOW (no other sources of bias

PMID: 22191292 ³²²	randomization procedures)	randomization procedures)	participants but this would not be likely to affect outcomes. Radiologists were not mentioned to be blinded to group assignment, however they were not informed of results of imaging findings or of the final diagnosis. If radiologists were not blind to group assignment this may have affected their readings.	for assessors of the final diagnosis)			mentioned in methods were reported in results)	observed)
Hershko et al. 2007 (Israel) PMID: 17566826 ³²⁹	UNCLEAR (no details about randomization procedures)	UNCLEAR (no details about randomization procedures)	UNCLEAR (no mention of blinding of participants but this would not be likely to affect outcomes. Radiologists were not mentioned to be blinded to group assignment, and this may have affected their readings.)	UNCLEAR (no mention of blinding for assessors of the final diagnosis)	LOW (less than 10% missing overall)	LOW (no missing outcome data from contrast-enhanced arms and although the equivocal CT scans in the non-contrast enhanced arm were omitted from the calculations of sensitivity and specificity only 7% (5/70) of the non-contrast-enhanced arm were equivocal CT scans for which followup information is not given)	LOW (all expected outcomes mentioned in methods were reported in results)	LOW (no other sources of bias observed)
Kepner et al. 2012 (United States) PMID: 22633722 ⁴²²	UNCLEAR (no details about randomization	UNCLEAR (no details about randomization	UNCLEAR (no mention of blinding of participants but this	UNCLEAR (no mention of blinding for assessors of	LOW (less than 10% missing overall)	UNCLEAR (total exclusions for protocol	LOW (all expected outcomes mentioned in	LOW (no other sources of bias observed)

	procedures)	procedures)	would not be likely to affect outcomes. Radiologists were blinded to the clinical outcome of the patient visit but not mentioned to be blinded to group assignment, and this may have affected their readings.)	appendicitis, and both contemporaneous read and study reads were reviewed before telephone follow-up and there is no mention of blinding to group assignment)		violations and loss to follow-up could be balanced between groups but this is not clear and could theoretically be greater than 10% different between study arms)	methods were reported in results)	
Kim et al. 2012 (South Korea) PMID: 22533576 ⁴⁴⁴	LOW (computer-generated permuted block randomization)	LOW (sequentially numbered, opaque, sealed envelopes)	UNCLEAR (participants were blinded to assignment but care providers were not blinded and this may possibly have affected the outcomes)	LOW (although assessors who interpreted the reference standard were aware of preoperative CT results, all outcome assessors were blinded to group assignments)	LOW (primary outcome of negative appendectomy was assessed in all participants receiving appendectomy and all other outcomes were assessed in >90% of relevant participants)	LOW (less than 10% missing from any arm for any outcome)	LOW (all outcomes reported in protocol and methods were included in results)	UNCLEAR (authors report that radiologists participating in the study favoured low-dose CT and this may have biased the study setting towards low-dose CT)
Mittal et al. 2004 (United States) PMID: 15136349 ⁵⁷⁵	HIGH (assigned by odd vs. even medical record number, not true randomization)	HIGH (assigned by odd vs. even medical record number, not true randomization)	UNCLEAR (no mention of blinding of patients or providers)	UNCLEAR (no mention of blinding of assessors)	LOW (no reported loss to follow-up)	LOW (no reported loss to follow-up)	LOW (all expected outcomes mentioned in methods were reported in results)	LOW (no other sources of bias observed)
Comparison of US and CT								
Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Total proportion of missing outcome data is >10%	Difference in proportion of missing data between arms is >10%	Selective reporting of outcomes	Compliance with interventions, ITT analysis
Horton et al. 2000 (USA) PMID: 10930484 ³⁴⁰	UNCLEAR (randomization method not stated)	UNCLEAR (allocation concealment)	UNCLEAR (blinding of personnel to assignments not)	UNCLEAR (no statement about blinding for	HIGH (presence of appendicitis was followed up	HIGH (difference in follow up rates for presence of	HIGH (Negative appendectomy rate described in results)	LOW (no other problems observed)

		not reported)	reported)	assessment of primary or secondary outcomes)	on for only 67.5% of participants in US arm: CT arm had follow-up of 100%; Negative appendectomy rate also had follow-up of 91% among all participants who had surgery)	appendicitis in CT and US arms = 32.5%)	was not included in methods; sens spec not reported but can be calculated)	
Kaiser et al. 2002 (Sweden) PMID: 12034928 (same study as Kaiser et al. 2004 PMID: 15350578) ³⁹⁹	UNCLEAR (only stated that patients were "randomly assigned")	UNCLEAR (allocation concealment not reported)	UNCLEAR (blinding of personnel to assignments not reported)	UNCLEAR (no statement about blinding for assessment of primary outcome or negative appendectomy rate)	LOW (all outcomes were assessed in >90% of participants overall)	LOW (all outcomes were assessed in >90% of participants in each arm)	HIGH (Diagnostic confidence outcomes outlined in methods were not included in Results; negative appendectomy rate not reported in Methods, but appears in Results)	LOW (no other problems observed)
Kaiser et al. 2004 (Sweden) PMID: 15350578 (same study as Kaiser et al. 2002 PMID: 12034928) ⁴⁰⁰	UNCLEAR (only stated that patients were "randomly assigned")	UNCLEAR (allocation concealment not reported)	UNCLEAR (blinding of personnel to assignments not reported)	UNCLEAR (no statement about blinding for assessment of change in diagnosis decision)	HIGH (Analysis of Change in Diagnostic Decision was performed on only those patients in whom the initial and final examination was performed by a surgeon belonging to the same experience group; i.e. 209/600 = 34.8% of enrolled)	UNCLEAR (number of participants in either US only or CT plus US group who were analysed for Change in Diagnosis Decision, was not stated in the report)	LOW (all outcomes reported in methods were included in results)	LOW (no other problems observed)
Comparison of US and routine management								
Douglas et al. 2000 (Australia)	LOW (Randomization	UNCLEAR (allocation	UNCLEAR (no statement about	UNCLEAR (no statement about	LOW (the following	LOW (the following	HIGH (Sens, Spec, Diagnostic	NR

PMID: 11030676 ²⁰⁴	achieved by coin toss)	concealment not reported)	blinding for assessment of primary or secondary outcomes)	blinding for assessment of primary or secondary outcomes)	<p>outcomes were assessed in >90% of participants overall: Mean Time to Operation for therapeutic operations; Mean Duration of Stay; Rate of Non-therapeutic operations; Rate of delayed treatment in association with perforation; includes ITT analysis for 16 participants who in breach of trial protocol)</p> <p>HIGH (Diagnostic Accuracy, Sens, Spec was assessed for 46.8%of participants in intervention arm, who were operated on (75 / 160 in intervention arm). No readmissions for appendicitis were reported at one week or 3 months for participants in both arms of</p>	<p>outcomes were assessed in >90% of participants in each arm: Mean Time to Operation for therapeutic operations; Mean Duration of Stay; Rate of Non-therapeutic operations; Rate of delayed treatment in association with perforation)</p> <p>UNCLEAR (Diagnostic Accuracy, Sens, Spec was assessed only participants in the intervention arm, Not the control arm).</p>	Accuracy was assessed only for the intervention, not the control arm which used just clinical assessment and management).	
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					study, however, 4 participants (2 in each arm) were lost to follow-up at 3months.			
Lindelius et al. 2008 (Sweden) PMID: 18660395 (same study as Lindelius et al. 2009 PMID: 19625549, Lindelius et al. 2009 PMID: 19941671 and Lindelius et al. 2010 PMID: 21290005) ⁵²¹	UNCLEAR (randomization method not stated)	UNCLEAR (allocation concealment using sealed envelope but opacity of envelopes not described)	UNCLEAR (blinding of personnel to assignments not reported)	UNCLEAR (no statement about blinding for assessment of primary or secondary outcomes)	LOW (preliminary outcome, primary diagnosis, had complete follow-up for both groups; Final diagnosis is missing for 2.6% (382/392) of US Group and 2.8% (380/391))	LOW (all outcomes were assessed in >90% of participants in each arm)	Low (all outcomes reported in methods were included in results)	LOW (no other problems observed)
Lindelius et al. 2009 (Sweden) PMID: 19625549 (same study as Lindelius et al. 2008 PMID: 18660395) ⁵²⁰	UNCLEAR (randomization method not stated)	UNCLEAR (allocation concealment not reported)	HIGH (stated, that study is non-blinded randomized clinical trial)	HIGH (stated, that study is non-blinded randomized clinical trial)	LOW (Outcome data on Repeated Testing / Complementary Exams partially missing from 0.5% (2/390) of participants in both groups; Length of Hospital stay data missing from 2.6% of participants in No US group (10/390) and 3.8% of participants in US group)	LOW (all outcomes were assessed in >90% of participants in each arm)	Low (all outcomes reported in methods were included in results)	Possible Observer bias reported by Author since study surgeon reported "further examinations" without checking to see if the examinations were performed. If misclassification was made, it would be random and biased toward the Null.
Lindelius et al. 2009 (Sweden) PMID: 19941671 (same study as Lindelius et al. 2008 PMID: 18660395) ⁵¹⁹	UNCLEAR (randomization method not stated)	UNCLEAR (allocation concealment not reported)	UNCLEAR (no statement about blinding for assessment of primary or secondary outcomes)	UNCLEAR (no statement about blinding for assessment of primary or secondary	LOW (Outcomes taken at Baseline and 6-wk follow-up: Self-rated Patient satisfaction,	LOW (all outcomes were assessed in >90% of participants in each arm)	Low (all outcomes reported in methods were included in results)	NR

				outcomes)	Planned or Completed Complementary Exams, and Mortality were available for > 90% of participants in both groups. Outcomes taken at 2yr follow-up: Health Care consumption was also available for > 90% of participants in both groups)			
Lindelius et al. 2010 (Sweden) PMID: 21290005 (same study as Lindelius et al. 2008 PMID: 18660395) ⁵¹⁸	UNCLEAR (randomization method not stated)	UNCLEAR (allocation concealment not reported)	UNCLEAR (no statement about blinding for assessment of primary or secondary outcomes)	UNCLEAR (no statement about blinding for assessment of primary or secondary outcomes)	HIGH: partially missing data for > 10% of participants (74%) in group 1 for BMI subgroup analyses of Diagnostic Accuracy, US ordered, CT ordered and No Other Examination Ordered;	HIGH (>20% difference in missingness of data for BMI subgroup analyses between intervention and control arm for BMI subgroup analyses of Diagnostic Accuracy, US ordered, CT ordered and No Other Examination Ordered; (26% missing in intervention arm – 6% missing in control arm = 20%)	Low (all outcomes reported in methods were included in results)	NR

Comparison of scores and routine management								
Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Total proportion of missing outcome data is >10%	Difference in proportion of missing data between arms is >10%	Selective reporting of outcomes	Compliance with interventions, other
Farahnak et al. 2007 (Iran) PMID: 17870498 ²³⁸	LOW (randomized according to a computer-generated randomization list)	UNCLEAR (no description of allocation procedures)	UNCLEAR (blinding not described)	UNCLEAR (blinding not described)	LOW (no participants lost for any outcome)	LOW (no participants lost for any outcome)	LOW (expected outcomes proposed as primary and secondary endpoints were included in results)	LOW (no other problems observed)
Lintula et al. 2009 (Finland) PMID: 18841382 ⁵²³	LOW (randomization was performed with consecutively numbered sealed opaque envelopes containing a random number)	LOW (randomization was performed with consecutively numbered sealed opaque envelopes containing a random number)	UNCLEAR (blinding not described)	UNCLEAR (blinding not described)	LOW (no participants lost for any outcome)	LOW (no participants lost for any outcome)	LOW (expected outcomes proposed as primary and secondary endpoints were included in results)	LOW (no other problems observed)
Lintula et al. 2010 (Finland) PMID: 20379739 ⁵²⁴	UNCLEAR (no description of randomization procedures)	UNCLEAR (no description of allocation procedures)	UNCLEAR (blinding not described)	UNCLEAR (blinding not described)	LOW (all outcomes reported for >90% of participants)	LOW (all outcomes reported for >90% of participants in both arms)	LOW (expected outcomes proposed as primary and secondary endpoints were included in results)	LOW (no other problems observed)
Comparison of diagnostic laparoscopy and open diagnostic exploration								
Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Total proportion of missing outcome data is >10%	Difference in proportion of missing data between arms is >10%	Selective reporting of outcomes	Compliance with interventions, other
Bruwer et al. 2003	LOW (treatment	UNCLEAR	UNCLEAR (blinding	UNCLEAR (blinding	LOW (no	LOW (no	Low (all outcomes	LOW (no other

(South Africa) PMID: 14768141 ¹⁰⁹	assignment by opening sequentially numbered envelopes and the envelope sequence was prepared from a computer-generated randomization list)	(treatment assignment was by opening the next in a series of sequentially numbered envelopes, but envelopes not described as sealed)	not described)	not described)	participants lost for any outcome)	participants lost for any outcome)	reported in methods were included in results)	sources of bias observed)
Comparison of diagnostic laparoscopy and routine management								
Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Total proportion of missing outcome data is >10%	Difference in proportion of missing data between arms is >10%	Selective reporting of outcomes	Compliance with interventions, other
Decadt et al. 1999 (England) PMID: 10583282 ¹⁸³	UNCLEAR (patients were randomized by sealed envelopes)	UNCLEAR (patients were randomized by sealed envelopes)	UNCLEAR (blinding not described)	UNCLEAR (blinding not described)	LOW (no participants described as lost for any outcome but well-being) HIGH (well-being outcomes at follow-up were collected on <90% of participants)	LOW (no participants described as lost for any outcome but well-being, and difference in follow-up for well-being was <10% between intervention arms)	LOW (expected outcomes proposed as primary and secondary endpoints were included in results)	LOW (no other problems observed)
Gaitan et al. 2002 (Colombia) PMID: 11818109 ²⁶²	LOW (patients were assigned to one of the groups by means of a computer-generated, randomized table)	LOW (allocations were concealed in sealed, opaque, sequentially-numbered envelopes)	UNCLEAR (blinding not described)	UNCLEAR (blinding not described)	LOW (no participants described as lost for any outcomes extracted in this review)	LOW (no participants described as lost for any outcomes extracted in this review)	Low (all outcomes reported in methods were included in results)	LOW (no other sources of bias observed)
Comparison of								

diagnostic laparoscopy and immediate appendectomy								
Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Total proportion of missing outcome data is >10%	Difference in proportion of missing data between arms is >10%	Selective reporting of outcomes	Compliance with interventions, other
Jadallah et al 1994 (Sweden) PMID: 8186313 ³⁶⁷	UNCLEAR (patients were randomized by opening a sealed envelope in which management was specified)	UNCLEAR (patients were randomized by opening a sealed envelope in which management was specified)	UNCLEAR (blinding not described)	UNCLEAR (blinding not described)	LOW (all outcomes reported for >90% of participants)	LOW (all outcomes reported for >90% of participants in both arms)	LOW (expected outcomes proposed as primary and secondary endpoints were included in results)	LOW (no other problems observed)
Laine et al. 1997 (Finland) PMID: 9069134 ⁴⁷⁸	UNCLEAR (no description of randomization)	UNCLEAR (no description of randomization)	UNCLEAR (blinding not described)	UNCLEAR (blinding not described)	LOW (no participants lost for any outcome)	LOW (no participants lost for any outcome)	LOW (expected outcomes proposed in methods were included in results)	LOW (no other problems observed)
Larsson et al. 2001 (Sweden) PMID: 11285968 ⁴⁸⁷	UNCLEAR (randomization was performed by using sealed envelopes in blocks of 10 patients)	UNCLEAR (randomization was performed by using sealed envelopes in blocks of 10 patients, no further description of envelopes)	UNCLEAR (blinding not described)	UNCLEAR (blinding not described)	LOW (all outcomes reported for >90% of participants)	LOW (even if the 2/110 exclusions from analysis came from one study arm, the missing outcomes would be <10% in both study arms)	LOW (expected outcomes proposed in methods were included in results)	LOW (no other problems observed)
Olsen et al. 1993 (Denmark) PMID: 8369940 ⁶¹⁹	UNCLEAR (no description of randomization)	UNCLEAR (no description of randomization)	UNCLEAR (blinding not described)	UNCLEAR (blinding not described)	LOW (no participants lost for any outcome)	LOW (no participants lost for any outcome)	LOW (expected outcomes proposed in methods were included in results)	LOW (no other problems observed)
Tzovaras et al. 2007 (Greece) PMID: 17219281 ⁸⁴⁷	UNCLEAR (no description of randomization)	UNCLEAR (no description of randomization)	UNCLEAR (blinding not described)	UNCLEAR (blinding not described)	LOW (no participants lost for any outcome)	LOW (no participants lost for any outcome)	LOW (expected outcomes proposed in methods were included in results)	LOW (no other problems observed)

van Dalen et al. 2003 (New Zealand) PMID: 12739123 ⁸⁵³	UNCLEAR (patients were randomized by closed-envelope system, no description of sequence generation)	UNCLEAR (patients were randomized by closed-envelope system, no further description of envelopes)	UNCLEAR (blinding not described)	UNCLEAR (blinding not described)	LOW (no participants lost for any outcome)	LOW (no participants lost for any outcome)	LOW (expected outcomes proposed in methods were included in results)	LOW (no other problems observed)
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Table C8. RCT other outcomes

Comparison of CT and routine management				
Study	Study arms	Number enrolled	Number followed to end	Other outcomes
Hong et al. 2003 (United States) PMID: 14588157 ³³⁵	Clinical observation alone [total population]	85	58 (17 protocol violators not followed, 10 persons not reached for telephone follow-up)	Perforations = 6% (4/68) Mean time from presentation to surgery = 10.6 ± 8.4 hours Days hospital stay = 2.4 ± 3.2
	Clinical observation and abdominal/pelvic CT [total population]	97	50 (19 protocol violators not followed, 28 persons not reached for telephone follow-up)	Perforations = 9% (7/78) Mean time from presentation to surgery = 18.7 ± 18.8 hours Days hospital stay = 2.2 ± 2.2
	Differences between arms	NA	NA	P-value = 0.4 for perforations P-value <0.01 for mean time from presentation to surgery P-value = 0.55 for mean days hospital stay
	Clinical observation alone [women age 18-45]	NR	19	Mean time from presentation to surgery = 10.8 ± 6.4 hours Days hospital stay = 2.3 ± 2.3
	Clinical observation and abdominal/pelvic CT [women age 18-45]	NR	29	Mean time from presentation to surgery = 27.4 ± 34.1 hours Days hospital stay = 2.0 ± 2.1
	Differences between arms	NA	NA	P-value = 0.12 for mean time from presentation to surgery P-value = 0.68 for mean days hospital stay
Lee et al. 2007 (United States) PMID: 17192450 ⁴⁹⁴	Selective CT imaging	80	Unclear. 43 patients underwent laparotomy and follow-up information was only available on 42% of non-operated patients overall.	Perforations = 18.4% (7/38) Negative appendectomies = 13.9% (6/43) Mean hours from ED triage to surgery = 10.0 ± 7.0
	Mandatory CT imaging.	72	Unclear. Two patients underwent surgery before CT imaging could be performed, 43 patients underwent laparotomy, and follow-up information was	Perforations = 10.3% (4/39) Negative appendectomies = 2.6% (1/39) Mean hours from ED triage to surgery = 10.9 ± 6.9

			only available on 42% of non-operated patients overall.	
	Differences between arms	NA	NA	Perforations difference (95% CI) = 8.2% (-8.0, 24.4) Negative appendectomies difference (95% CI) = 11.3% (-3.5, 26.3) Mean hours to surgery difference (95% CI) = 0.9
Lehtimaki et al. 2013 (Finland) PMID: 23715771 ⁵⁰⁵	Selective CT imaging	150	111 (7 did not meet inclusion criteria or withdrew consent and 32 were lost to follow-up.)	Negative appendectomies = 0.9% (1/111) Mean days hospital stay 2.5 , range 0-21 "No deaths related to acute abdomen were reported in the study population during the follow-up period."
	Mandatory CT imaging (within 24 hours of admission)	150	143 (3 did not meet inclusion criteria or withdrew consent and 4 were lost to follow-up.)	Negative appendectomies = 0.7% (1/143) Mean days hospital stay 3.7 , range 0-32 "No deaths related to acute abdomen were reported in the study population during the follow-up period."
	Differences between arms	NA	NA	P-value = 0.010 for mean days hospital stay
Lopez et al. 2007 (United States) PMID: 18186378 ⁵²⁷	Clinical observation alone [women age 18-45]	48	39 (2 protocol violators not followed, 7 persons not reached for telephone follow-up)	Perforations = 0% Median days hospital stay = 1 (range 0 to 7)
	Clinical observation and abdominal/pelvic CT [women age 18-45]	42	30 (12 persons not reached for telephone follow-up)	Perforations = 0% Median days hospital stay = 1 (range 0 to 6)
	Differences between arms	NA	NA	P-value = 1.0 for perforations P-value = 0.22 for median days hospital stay
Ng et al. 2002 (England) PMID: 12480851 (same study as Ng et al. 2007 PMID: 17329682, Ng et al. 2010 PMID: 20350244) ⁶⁰⁹	Current standard practice	63	63	Days hospital stay mean (sd) = 9.2 (9.8) (untransformed); median = 5; geometric mean = 6.4 (range 1 to 60) Seven inpatients in the standard practice arm died during the study (11% (7 of 63)). Table of final diagnoses lists 3 perforated viscous
	Early computer tomography (within 24 hours)	57	55 (2 protocol violators not followed)	Days hospital stay mean (sd) = 6.6 (5.8) (untransformed); median = 5; geometric mean = 5.3 (range 1 to 31) No inpatients in the early computed tomography arm died (0% (0 of 55))
	Differences between arms	NA	NA	P- value = 0.17 for days hospital stay (geometric mean) Difference and 95% CI for geometric mean days hospital stay = 1.1 (-0.34 to 0.194) P-value = 0.20 for days hospital stay (median) P-value for deaths during study = 0.014
Ng et al. 2007 (England) PMID: 17329682 (same	Current standard practice	63	63	NA

study as Ng et al. 2002 PMID: 12480851, Ng et al. 2010 PMID: 20350244) ⁶⁰⁷				
	Early computer tomography (within 24 hours)	62	62	Difference in Pre- and Post-test Diagnostic Confidence using Score-method: 0.69 (SD: 1.73; 95% CI: 0.25 to 1.13, t= 3.12, p=0.003) Difference in Pre- and Post-test Diagnostic Confidence using conventional analysis which does not take into account the accuracy of the post-test diagnosis: 1.13 (SD: 1.24; 95% CI: 0.82 to 1.44, t= 7.20, p < 0.0001) Difference in Pre- and Post-test Diagnostic Confidence using conventional analysis which takes into account the accuracy of the post-test diagnosis / "Omary Correction": 1.32 (SD: 1.17; 95% CI: 1.03 to 1.62, t= 8.90, p < 0.0001)
	Differences between arms	NA	NA	NA
Ng et al. 2010 (England) PMID: 20350244 (same study as Ng et al. 2002 PMID: 12480851, Ng et al. 2007 PMID: 17329682) ⁶⁰⁸	Current standard practice	63	63	NR
	Early computer tomography (within 24 hours)	57	55 (2 protocol violators not followed)	NR
	Differences between arms	NA	NA	NR
Sala et al. 2009 (England) PMID: 17901913 ⁷³⁴	Current standard practice	101	99 (1 protocol violator not followed, 1 patient randomized twice) For analysis of correct diagnosis, n=98 as one had unknown diagnosis at discharge.	Median days hospital stay = 5.3 (IQR 2 to 9.5 days) 11% (11/99) died by 6 months
	Early computer tomography (within 1 hour)	104	99 (2 protocol violators not followed, 2 patients randomized twice, 1 patient lost to follow-up at 6 months) For analysis of correct diagnosis, n=96 as n=3 had unknown diagnosis at discharge.	Median days hospital stay = 4.2 (IQR 1.1 to 7.6 days) 6% (6/99) died by 6 months
	Differences between arms	NA	NA	Ratio of geometric means for length of stay = 1.31, 95% CI for ratio 0.86 to 2.01; t(194) = 1.29, P-value = 0.199 (t-test); z=1.52, P-value = 0.128 (Mann-Whitney U test) P-value = 0.31 for deaths; 95% CI for difference -13.4% to 3.1%

Walker et al. 2000 (United States) PMID: 11182396 ⁸⁶⁸	Standard management	63	63	Negative appendectomy rate 19% (7/36)
	Limited CT scan with colorectal contrast.	65	65	Negative appendectomy rate 5% (2/38) (also called negative exploration rate)
	Differences between arms	NA	NA	Perforation rate reported to be higher in standard management group, but numbers not given.
Comparison of different types of CT				
Study	Study arms	Number enrolled	Number followed to end	Other outcomes
Hekimoglu et al. 2011 (Turkey) PMID: 22191292 ³²²	IV and oral contrast-enhanced CT	100	100	NR
	IV contrast-enhanced CT	100	100	NR
	Differences between arms	NA	NA	NR
Hershko et al. 2007 (Israel) PMID: 17566826 ³²⁹	Nonenhanced CT	70	56 (14 inconclusive scans not discussed as positive or negative on reference standard)	Negative appendectomy rate = 25% (7/28)
	Rectal contrast-enhanced CT	78	78	Negative appendectomy rate = 7% (3/42)
	IV and oral contrast-enhanced CT	84	84	Negative appendectomy rate = 10% (5/48)
	Differences between arms	NA	NA	NR
Kepner et al. 2012 (United States) PMID: 22633722 ⁴²²	IV and oral contrast-enhanced CT	113	113 (not known how many exclusions and lost to follow-up were in group)	Mean time from presentation to ED disposition for all patients = 8:12 (IQR 6:40-9:44)
	IV contrast-enhanced CT	114	114 (not known how many exclusions and lost to follow-up were in group)	Mean time from presentation to ED disposition for all patients = 6:41 (IQR 5:03-8:49)
	Differences between arms	NA	NA	Difference for mean time from presentation to ED disposition for all patients = 1:31 (P-value <0.0001)
Kim et al. 2012 (South Korea) PMID: 22533576 ⁴⁴⁴	Low-dose CT	444	438 (6 lost to follow-up)	Perforations = 26.5% (44/166) Negative appendectomy rate = 3.5% (6/172) Median hours from CT to nonincidental appendectomy = 7.1 (IQR 4.3 to 11.7) Median days hospital stay associated with nonincidental appendectomy = 3.4 (IQR 2.7 to 4.1)
	Standard-dose CT	447	441 (6 lost to follow-up)	Perforations = 23.3% (42/180) Negative appendectomy rate = 3.2% (6/186) Median hours from CT to nonincidental appendectomy = 5.6 (IQR

				3.4 to 9.2) Median days hospital stay associated with nonincidental appendectomy = 3.2 (IQR 2.5 to 4.1)
	Differences between arms	NA	NA	P-value = 0.46 for perforation rate and Difference (95% CI) for perforation rate = 3.2% (-5.9 to 12.4) and RR (95% CI) = 1.14 (0.79 to 1.64) Difference (95% CI) for negative appendectomy rate = 0.3% (-3.8 to 4.6) and RR (95% CI) = 1.08 (0.37 to 3.13) P-value for median hours from CT to nonincidental appendectomy = 0.02 P-value for median days hospital stay associated with nonincidental appendectomy = 0.54
Mittal et al. 2004 (United States) PMID: 15136349 ⁵⁷⁵	Standard triple-contrast abdominopelvic CT scan	52	52	Negative appendectomy rate 8% (4/48) Perforations = 30% (13/44) One patient in the study died of sepsis due to perforated appendicitis in an older group. Mean hours from ED to OR = 8.3 (0.4)
	Focused pelvic scan with rectal contrast only	39	39	Negative appendectomy rate 7.7% (3/39) Perforations = 3% (1/36) One patient in the study died of sepsis due to perforated appendicitis in an older group Mean hours from ED to OR = 12.2 (0.3)
	Differences between arms	NA	NA	NR
Comparison of US and CT				
Study	Study arms	Number enrolled	Number followed to end	Other outcomes
Horton et al. 2000 (USA) PMID: 10930484 ³⁴⁰	US	40	27/40 (11 had nondiagnostic scans and 2 with negative scans were not followed up on after being sent home)	Negative appendectomy rate = 6.0% (4/70)
	CT	49	49/49 (1 with a CT scan positive for appendicitis received intravenous antibiotics, improved, and was discharged home on a regimen of oral antibiotics; 1 with CT scan negative had a repeated scan which showed positive for appendicitis).	Negative appendectomy rate = 6.0% (4/70)

	Differences between arms	NA	NA	NR
Kaiser et al. 2002 (Sweden) PMID: 12034928 (same study as Kaiser et al. 2004 PMID: 15350578) ³⁹⁹	US only	283	283	Negative appendectomies = 4 (based on Table 5)
	US plus abdominal CT	317	317	Perforations = 17.8% (24/135) Negative appendectomies = 5 (based on Table 5)
	Differences between arms	NA	NA	NR
	All US	600	600	Overall negative appendectomy rate = 3.7% (9/244)
	All abdominal CT	317	317	NR
	Differences between arms	NA	NA	NR
Kaiser et al. 2004 (Sweden) PMID: 15350578 (same study as Kaiser et al. 2002 PMID: 12034928) ⁴⁰⁰	US only	283	283	NR
	US plus abdominal CT	317	317	NR
	Differences between arms	NA	NA	NR
Comparison of US and routine management				
Study	Study arms	Number enrolled	Number followed to end	Other outcomes
Douglas et al. 2000 (Australia) PMID: 11030676 ²⁰⁴	Graded compression US informed by Alvarado Score	160	160	Readmission for complications: 1 (drainage of an abscess) Perforations: 14 or 8.8% Mean Time to Therapeutic Operation: 7.0 hrs (95% CI: 5.9 to 8.1) Mean duration of stay: 53.4 hrs (95% CI: 47 to 60) Age Subgroup Analysis: - Mean Time to Therapeutic Operation among participants with Age > 14 yrs: 7.1 hrs (95% CI: 5.8 to 9.4) - Mean Time to Therapeutic Operation among participants with Age < 14: 7.0 hrs (95% CI: 5.2 to 8.8) - Mean duration of stay among participants with Age > 14 yrs: 59.3 (95% CI: 49 to 69) - Mean duration of stay among participants with Age < 14 yrs: 45.0 (95% CI: 37 to 54)
	Clinical Assessment and Management	142	142	Readmission for complications: 1 (early small bowel obstruction) Perforations: 10 or 7.0% Mean Time to Operation: 10.2 (95% CI: 7.9 to 13) Mean duration of stay: 54.5 hrs (95% CI: 46 to 63)

				<p>Age Subgroup Analysis:</p> <ul style="list-style-type: none"> - Mean Time to Therapeutic Operation among participants with Age > 14 yrs: 9.7 hrs (95% CI: 7.2 to 12) - Mean Time to Therapeutic Operation among participants with Age < 14: 13.1 hrs (95% CI: 6.5 to 20) - Mean duration of stay among participants with Age > 14 yrs: 59.2 (95% CI: 49 to 69) - Mean duration of stay among participants with Age < 14 yrs: 40.5 (95% CI: 27 to 55)
	Differences between arms	NA	NA	<p>P-value for perforations = 0.58 P-value for time to therapeutic operation = 0.016 P-value for duration of stay = 0.99 P-value for mean time to therapeutic operations in adults (>14 years) = 0.068 P-value for mean time to therapeutic operations in children (<14 years) = 0.069 P-value for mean duration of stay in adults (>14 years) = 0.99 P-value for mean duration of stay in children (<14 years) = 0.58</p>
Lindelius et al. 2008 (Sweden) PMID: 18660395 (same study as Lindelius et al. 2009 PMID: 19625549, Lindelius et al. 2009 PMID: 19941671 and Lindelius et al. 2010 PMID: 21290005) ⁵²¹	Routine management + US	400	382 (7 under age; 1 pregnant; 6 no primary diagnosis; 2 crossover; 1 withdrawal; 1 no final diagnosis)	Proportion of patients in US group in which US led to or confirmed correct diagnosis: 24.1% (92/382)
	Routine management	400	380 (1 missing; 8 under age; 6 no primary diagnosis; 1 crossover; 2 withdrawal; 2 no final diagnosis)	Proportion of correct primary diagnoses: 56.8%
	Differences between arms	NA	NA	NR
Lindelius et al. 2009 (Sweden) PMID: 19625549 (same study as Lindelius et al. 2008 PMID: 18660395) ⁵²⁰	Routine management + US	400	390 (8 excluded for not meeting inclusion criteria; 2 did not receive intervention)	Mortality: 0.5% (2/390) – not due to US Mean Length of Hospital Stay: 4.3 +/- 5.7 days (p-value: 0.964)
	Routine management	400	390 (1 missing; 8 excluded for not meeting inclusion criteria; 1	Mortality: 0% Mean Length of Hospital Stay: 5.4 +/- 5.7 days

			did not receive intervention)	
	Differences between arms	NA	NA	P-value for mean length of hospital stay = 0.964
Lindelius et al. 2009 (Sweden) PMID: 19941671 (same study as Lindelius et al. 2008 PMID: 18660395) ⁵¹⁹	Routine management + US	400	392 (8 excluded for not meeting inclusion criteria)	Mean Total amount of hospital days at 2-yr follow-up: 6.0 +/- 26.3 (p-value: 0.733) Median (range) number of hospital days at 2-year follow up: 0.0 (0-462) Mortality at 6-wk follow-up: 0.8% (3/392)
	Routine management	400	391 (1 missing; 8 excluded for not meeting inclusion criteria)	Mean Total amount of hospital days at 2-yr follow-up: 8.7 +/- 35.6 Median (range) number of hospital days at 2-year follow up: 0.0 (0-470) Mortality at 6-wk follow-up: 0%
	Differences between arms	NA	NA	P-value for total amount of hospital days = 0.733
Lindelius et al. 2010 (Sweden) PMID: 21290005 (same study as Lindelius et al. 2008 PMID: 18660395) ⁵¹⁸	Routine management + US	400	392 (8 excluded for not meeting inclusion criteria)	NR
	Routine management	400	391 (1 missing; 8 excluded for not meeting inclusion criteria)	NR
	Differences between arms	NA	NA	NR
Comparison of scores and routine management				
Study	Study arms	Number enrolled	Number followed to end	Other outcomes
Farahnak et al. 2007 (Iran) PMID: 17870498 ²³⁸	Standard clinical assessment and management	21	21	Mean hours from randomization to surgery (n=10) 11.09 hrs (10.04) (median = 8.35, range = 2.40 to 37.10, IQR = 5.55) Duration of hospitalization (n=21) 66.27 hrs (61.89) (median = 60.40, range = 0.30 to 280.20, IQR = 40.70) Perforation with late treatment rate 0% (0/21) (treatment beginning at least 10 hours after randomization was considered late)
	Management according to Alvarado score	21	21	Mean hours from randomization to surgery (n=10) 6.39 hrs (9.93) (median=2.05, range = 0.4 to 32.4, IQR = 7.39) Duration of hospitalization (n=21) 42.61 hrs (62.48) (median = 37.00, range = 0.30 to 290.50, IQR = 58.40) Perforation with late treatment rate 4.8% (1/21) (treatment beginning at least 10 hours after randomization was considered late)
	Differences between arms	NA	NA	P-value for mean time to surgery = 0.03 P-value for duration of hospitalization = 0.034

				P-value for perforation with late treatment rate > 0.99
Lintula et al. 2009 (Finland) PMID: 18841382 ⁵²³	Standard clinical assessment and management	60	60	Negative appendectomy rate of 29% (11/38) Perforation rate 89% (24/27) and abscess rate 7.4% (2/27) Mean days stay in hospital = 2.9 (1.1) No deaths. One patient had a wound infection.
	Management based on a diagnostic scoring system for children.	66	66	Negative appendectomy rate of 17% (5/29) Perforation rate 88% (21/24) and abscess rate 8.3% (2/24) Mean days stay in hospital = 2.7 (1.8) No deaths. One patient had a wound infection.
	Differences between arms	NA	NA	P-value for negative appendectomy = 0.05 P-value for condition of appendix (normal, suppurative or gangrenous, perforated, abscessed) = ns P-value for hospital stay = ns
Lintula et al. 2010 (Finland) PMID: 20379739 ⁵²⁴	Standard clinical assessment and management	84	81	Negative appendectomy rate 16% (7/43) Mean (sd) days hospital stay 2.3 (2.6) Perforation rate = 7% (3/43); abscess rate = 0% (0/43)
	Management based on a diagnostic scoring system	97	96	Negative appendectomy rate 13% (8/60) Mean (sd) days hospital stay 2.2 (1.8) Perforation rate = 5% (3/60); abscess rate = 3% (2/60)
	Differences between arms			P-value for negative appendectomy = ns P-value for mean days hospital stay = ns
Comparison of diagnostic laparoscopy and open exploration				
Study	Study arms	Number enrolled	Number followed to end	Other outcomes
Bruwer et al. 2003 (South Africa) PMID: 14768141 ¹⁰⁹	Laparoscopy	18	18	Negative appendectomy rate of 18% (2/11) Mean days stay in hospital = 3.0 (SD=1.6)
	Open exploration	16	16	Per protocol, all appendixes removed regardless of findings on open exploration, of which 43.75% (7/16) were normal Mean days stay in hospital = 3.7 (SD=1.1)
	Differences between arms	NA	NA	P-value for hospital stay = ns
Comparison of diagnostic laparoscopy and routine management				
Study	Study arms	Number enrolled	Number followed to end	Other outcomes
Decadt et al. 1999 (England) PMID:	Laparoscopy within 18 hours of admission	59	59	Median hours from admission to laparoscopy = 10 (range 2-39) "Duration of hospital stay was 2 (range 1-13) days in each group

10583282 ¹⁸³				(P=0.87)” One patient died from a massive pulmonary embolus 5 days after laparotomy despite full thromboprophylaxis.
	Close active observation and conventional non-invasive investigation	61	61	Median hours from admission to operative intervention = 39 (range 15-119) hours for the n=17 patients who received operation “Duration of hospital stay was 2 (range 1-13) days in each group (P=0.87)” One patient died at home, 7 days after discharge from a presumed pulmonary embolism.
	Differences between arms	NA	NA	
Gaitan et al. 2002 (Colombia) PMID: 11818109 ²⁶²	Laparoscopy within 24 hours of admission	55	55	Days before diagnosis 1.41 (1.06)
	Clinical observation and conventional diagnosis	55	55	Days before diagnosis 2.32 (2.30)
	Differences between arms	NA	NA	P-value for time elapsed before diagnosis = 0.008
Comparison of diagnostic laparoscopy and immediate appendectomy				
Study	Study arms	Number enrolled	Number followed to end	Other outcomes
Jadallah et al 1994 (Sweden) PMID: 8186313 ³⁶⁷	Diagnostic laparoscopy followed by appendectomy if necessary	50	50	Negative appendectomy rate 13.3% (4/30) (does not include 1 ectopic pregnancy in which a normal appendix was removed but not for appendicitis; 19 patients received only laparoscopy) Median days hospital stay = 2 (range<1 to 7) based on n=49 Mean days hospital stay for all laparoscopy patients = 2.33 (calculated from Table IV)
	Immediate open appendectomy	50	50	Negative appendectomy rate 36.0% (18/50) Median days hospital stay = 3 (range 1 to 18) based on n=50 Mean days hospital stay = 3.1
	Differences between arms	NA	NA	P-value for hospital stay <0.001 when comparing laparoscopy alone (no appendectomy) to appendectomy without laparoscopy
Laine et al. 1997 (Finland) PMID: 9069134 ⁴⁷⁸	Diagnostic laparoscopy followed by appendectomy if necessary	25	25	Negative appendectomy rate of 5.9% based on 8 laparoscopy cases in which the appendix was left in situ, therefore there were a total of 25-8=17 appendectomies and 1/17= 5.9% [Called unnecessary appendectomies in publication] Mean days postoperative hospital stay = 2.7 (0.3)
	Immediate open appendectomy	25	25	Negative appendectomy rate of 44% (11/25) [Called unnecessary appendectomies in publication] Mean days postoperative hospital stay = 2.3 (0.1)

	Differences between arms	NA	NA	P-value n.s. for mean days postoperative hospital stay
Larsson et al. 2001 (Sweden) PMID: 11285968 ⁴⁸⁷	Diagnostic laparoscopy followed by appendectomy if necessary	55	55	Negative appendectomy rate 9% (4/44)
	Immediate open appendectomy	55	53	Negative appendectomy rate 34% (18/53)
	Differences between arms	NA	NA	Relative Risk of removing a healthy appendix was 6.6 (95% CI 2-21) for open compared to laparoscopic group
Olsen et al. 1993 (Denmark) PMID: 8369940 ⁶¹⁹	Diagnostic laparoscopy followed by appendectomy if necessary	30	30	Negative appendectomy rate 7% (2/30) [Called unnecessary appendectomies in publication] Mean days in hospital = 3.8 (range = 1-8)
	Immediate appendectomy	30	30	Negative appendectomy rate 37% (11/30) [Called unnecessary appendectomies in publication] Mean days in hospital = 3.2 (range = 1-7)
	Differences between arms	NA	NA	P-value for negative appendectomy = 0.01 P-value for days in hospital = 0.25
Tzovaras et al. 2007 (Greece) PMID: 17219281 ⁸⁴⁷	Diagnostic laparoscopy followed by appendectomy	38	38	No deaths Morbidity 10.5% (4/38) including 2 wound infections in patients in whom laparoscopy was converted to open procedure, 1 postoperative ileus in a patient in whom laparoscopy was converted to open procedure, and 1 readmission with collection. Gangrenous appendicitis 36.8% (14/38) Mean days postoperative stay = 2 (1-9)
	Open appendectomy	40	40	No deaths Morbidity 10% (4/40) including 3 wound infections and 1 urinary retention Gangrenous appendicitis 25% (10/40) Mean days postoperative stay = 2 (1-7)
	Differences between arms	NA	NA	The report states that there was not a statistically significant difference in any of the above outcomes.
van Dalen et al. 2003 (New Zealand) PMID: 12739123 ⁸⁵³	Diagnostic laparoscopy followed by appendectomy if necessary	32	32	Negative appendectomy rate 4% (1/25) Mean days in hospital = 4 (range 1-9)
	Immediate appendectomy	31	31	Negative appendectomy rate 26% (8/31) Mean days in hospital = 4.9 (range 2-11)
	Differences between arms	NA	NA	P value=.01 for mean days in hospital

Table C9. RCT harms

Comparison of US and CT				
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Study	Study arms	Number enrolled	Number followed to end	Harms
Kaiser et al. 2002 (Sweden) PMID: 12034928 ³⁹⁹	US only	283	283	NR
	US plus abdominal CT	317	317 (Two patients who were originally assigned to undergo US only underwent additional CT examinations and were excluded)	There were no severe adverse drug reactions to the intravenous administration of contrast medium. One patient had a minor reaction: a mild skin rash limited to the chest that resolved spontaneously within 10 minutes.
	All US	600	600	NR
	All abdominal CT	317	317	NR
Kaiser et al. 2004 (Sweden) PMID: 15350578 ⁴⁰⁰	US only	283	283	NR
	US plus abdominal CT	317	317 (Two patients who were originally assigned to undergo US only underwent additional CT examinations and were excluded)	NR
Horton et al. 2000 (USA) PMID: 10930484 ³⁴⁰	US	40	27/40 (11 had nondiagnostic scans and 2 with negative scans were not followed up on after being sent home)	NR
	CT	49	49/49 (1 with a CT scan positive for appendicitis received intravenous antibiotics, improved, and was discharged home on a regimen of oral antibiotics; 1 with CT scan negative had a repeated scan which showed positive for appendicitis).	
Comparison of US and Routine Management				
Study	Study arms	Number enrolled	Number followed to end	Harms
Lindelius et al. 2008 (Sweden) PMID: 18660395 ⁵²¹	Routine management + US	400	382 (7 under age; 1 pregnant; 6 no primary diagnosis; 2 crossover; 1 withdrawal; 1 no final diagnosis)	NR
	Routine management	400	380 (1 missing; 8 under age; 6 no primary diagnosis; 1 crossover; 2 withdrawal; 2 no final diagnosis)	NR
Lindelius et al. 2009 (Sweden) PMID: 19625549 ⁵²⁰	Routine management + US	400	390 (8 excluded for not meeting inclusion criteria; 2 did not receive intervention)	NR

	Routine management	400	390 (1 missing; 8 excluded for not meeting inclusion criteria; 1 did not receive intervention)	NR
Lindelius et al. 2009 (Sweden) PMID: 19941671 ⁵¹⁹	Routine management + US	400	392 (8 excluded for not meeting inclusion criteria)	NR
	Routine management	400	391 (1 missing; 8 excluded for not meeting inclusion criteria)	NR
Lindelius et al. 2010 (Sweden) PMID: 21290005 ⁵¹⁸	Routine management + US	400	392 (8 excluded for not meeting inclusion criteria)	NR
	Routine management	400	391 (1 missing; 8 excluded for not meeting inclusion criteria)	NR
Douglas Et Al. 2000 (Australia) PMID: 11030676 ²⁰⁴	Graded compression US informed by Alvarado Score	160	160	NR
	Clinical Assessment and Management	142	142	NR
Comparison of different types of CT				
Study	Study arms	Number enrolled	Number followed to end	Harms
Hekimoglu et al. 2011 (Turkey) PMID: 22191292 ³²²	IV and oral contrast-enhanced CT	100	100	NR
	IV contrast-enhanced CT	100	100	NR
Hershko et al. 2007 (Israel) PMID: 17566826 ³²⁹	Nonenhanced CT	70	56 (14 inconclusive scans not discussed as positive or negative on reference standard)	“CT-related complications, such as contrast material sensitivity reactions, aspiration, or renal failure, were not observed in any of the study groups.” “All techniques were found to be safe and no CT-related complications were observed.”
	Rectal contrast-enhanced CT	78	78	“CT-related complications, such as contrast material sensitivity reactions, aspiration, or renal failure, were not observed in any of the study groups.” “All techniques were found to be safe and no CT-related complications were observed.”
	IV and oral contrast-enhanced CT	84	84	“CT-related complications, such as contrast material sensitivity reactions, aspiration, or renal failure, were not observed in any of the study groups.”

				“All techniques were found to be safe and no CT-related complications were observed.”
Kepner et al. 2012 (United States) PMID: 22633722 ⁴²²	IV and oral contrast-enhanced CT	113	113 (not known how many exclusions and lost to follow-up were in group)	NR
	IV contrast-enhanced CT	114	114 (not known how many exclusions and lost to follow-up were in group)	NR
Kim et al. 2012 (South Korea) ⁴⁴⁴ PMID: 22533576	Low-dose CT	444	438 (6 lost to follow-up)	“The median radiation dose in terms of dose-length product was 116 mGy-cm in the low-dose group...”
	Standard-dose CT	447	441 (6 lost to follow-up)	“The median radiation dose in terms of dose-length product was ... 521 mGy-cm in the standard-dose group.”
Mittal et al. 2004 (United States) PMID: 15136349 ⁵⁷⁵	Standard triple-contrast abdominopelvic CT scan	52	52	“There were no complications as a result of the procedures in either group. No morbidities due to the CT scans were reported in either group.....”
	Focused pelvic scan with rectal contrast only	39	39	“There were no complications as a result of the procedures in either group. No morbidities due to the CT scans were reported in either group.....”
Comparison of CT and routine management				
Study	Study arms	Number enrolled	Number followed to end	Harms
Hong et al. 2003 (United States) PMID: 14588157 ³³⁵	Clinical observation alone [total population]	85	58 (17 protocol violators not followed, 10 persons not reached for telephone follow-up)	One patient had surgical wound complications after appendectomy
	Clinical observation and abdominal/pelvic CT [total population]	97	50 (19 protocol violators not followed, 28 persons not reached for telephone follow-up)	NR
	Clinical observation alone [women age 18-45]	NR	19	NR
	Clinical observation and abdominal/pelvic CT [women age 18-45]	NR	29	NR
Lee et al. 2007 (United States) PMID: 17192450 ⁴⁹⁴	Selective CT imaging	80	Unclear. 43 patients underwent laparotomy and follow-up information was only available on 42% of non-operated patients overall.	1 case of recurrent vomiting secondary to oral contrast ingestion. No deaths.
	Mandatory CT imaging.	72	Unclear. Two patients underwent surgery before CT imaging could be performed, 43	4 cases of recurrent vomiting secondary to oral contrast ingestion. No deaths.

			patients underwent laparotomy, and follow-up information was only available on 42% of non-operated patients overall.	
Lehtimaki et al. 2013 (Finland) PMID: 23715771 ⁵⁰⁵	Selective CT imaging	150	111 (7 did not meet inclusion criteria or withdrew consent and 32 were lost to follow-up.)	Two patients reported complications of operative treatment and one required reoperation.
	Mandatory CT imaging (within 24 hours of admission)	150	143 (3 did not meet inclusion criteria or withdrew consent and 4 were lost to follow-up.)	Nine patients reported complications of operative treatment and four required reoperation.
Lopez et al. 2007 (United States) PMID: 18186378 ⁵²⁷	Clinical observation alone [women age 18-45]	48	39 (2 protocol violators not followed, 7 persons not reached for telephone follow-up)	NR
	Clinical observation and abdominal/pelvic CT [women age 18-45]	42	30 (12 persons not reached for telephone follow-up)	“No complications were associated with the radiologic protocol”
Ng et al. 2002 (England) PMID: 12480851 ⁶⁰⁹	Current standard practice	63	63	NR
	Early computer tomography (within 24 hours)	57	55 (2 protocol violators not followed)	NR
Ng et al. 2010 (England) PMID: 20350244 (same study as above) ⁶⁰⁸	Current standard practice	63	63	NR
	Early computer tomography (within 24 hours)	57	55 (2 protocol violators not followed)	NR
Sala et al. 2009 (England) PMID: 17901913 ⁷³⁴	Current standard practice	101	99 (1 protocol violator not followed, 1 patient randomized twice) For analysis of correct diagnosis, n=98 as one had unknown diagnosis at discharge.	Estimated effective radiation dose = 0.82 mSv
	Early computer tomography (within 1 hour)	104	99 (2 protocol violators not followed, 2 patients randomized twice, 1 patient lost to follow-up at 6 months) For analysis of correct diagnosis, n=96 as n=3 had unknown diagnosis at discharge.	Estimated effective radiation dose = 9 mSv
Walker et al. 2000 (United States) PMID: 11182396 ⁸⁶⁸	Standard management	63	63	NR
	Limited CT scan with	65	65	“Rectal contrast for the CT scan was well tolerated by

	colorectal contrast.			the majority of patients. One patient refused more than 200 cc of rectal contrast and other received no contrast at all. In a third patient, rectal contrast did not provide adequate visualization of the appendix, requiring a second CT scan after the administration of oral contrast." [Would say that it was not well tolerated in at least two patients?]
Comparison of routine management and treatment guided by scores				
Study	Study arms	Number enrolled	Number followed to end	Harms
Farahnak et al. 2007 (Iran) PMID: 17870498 ²³⁸	Standard clinical assessment and management	21	21	NR
	Management according to Alvarado score	21	21	NR
Lintula et al. 2009 (Finland) PMID: 18841382 ⁵²³	Standard clinical assessment and management	60	60	NR
	Management based on a diagnostic scoring system for children.	66	66	NR
Lintula et al. 2010 (Finland) PMID: 20379739 ⁵²⁴	Standard clinical assessment and management	84	81	NR
	Management based on a diagnostic scoring system for children.	97	96	NR
Comparison of diagnostic laparoscopy and open exploration				
Study	Study arms	Number enrolled	Number followed to end	Harms
Bruwer et al. 2003 (South Africa) PMID: 14768141 ¹⁰⁹	Laparoscopy	18	18	1 patient with postoperative complications
	Open exploration	16	16	3 patients with postoperative complications
Comparison of diagnostic laparoscopy and routine				

management				
Study	Study arms	Number enrolled	Number followed to end	Harms
Decadt et al. 1999 (England) PMID: 10583282 ¹⁸³	Laparoscopy within 18 hours of admission	59	59	Complication rate 24% (14/59) including abdominal pain that persisted for at least 1 month after discharge (n=7), wound infection (n=5), wound dehiscence after laparotomy (n=1), and readmission with respiratory symptoms and shoulder tip pain (n=1). One patient died from a massive pulmonary embolus 5 days after laparotomy despite full thromboprophylaxis. [Don't think any of these can be connected directly to the laparoscopy but they're here for transparency since they're called complications. Delete and replace with NR?]
	Close active observation and conventional non-invasive investigation	61	61	Complication rate 31% (19/61) including abdominal pain persisting for at least 1 month (n=15), and wound infection (n=4). One patient died at home, 7 days after discharge from a presumed pulmonary embolism. [Don't think any of these can be connected directly to the routine management but they're here for transparency since they're called complications. Delete and replace with NR?]
Gaitan et al. 2002 (Colombia) PMID: 11818109 ²⁶²	Laparoscopy within 24 hours of admission	55	53	Complications caused by diagnostic intervention, delayed diagnosis, or pain control before admission were collected. Eleven percent (6/55) experienced complications.
	Clinical observation and conventional diagnosis	55	53	Complications caused by diagnostic intervention, delayed diagnosis, or pain control before admission were collected. Nine percent (5/55) experienced complications.
Comparison of diagnostic laparoscopy and immediate appendectomy				
Study	Study arms	Number enrolled	Number followed to end	Harms
Jadallah et al 2994 (Sweden) PMID: 8186313 ³⁶⁷	Diagnostic laparoscopy followed by appendectomy if necessary	50	50	NR
	Immediate open	50	50	NR

	appendectomy			
Laine et al. 1997 (Finland) PMID: 9069134 ⁴⁷⁸	Diagnostic laparoscopy followed by appendectomy if necessary	25	25	Laparoscopic operation was uncomplicated in all patients One postoperative ileus, which resolved with conservative treatment, 'but it was obviously not caused by the laparoscopic part of the operation'.
	Immediate open appendectomy	25	25	NR
Larsson et al. 2001 (Sweden) PMID: 11285968 ⁴⁸⁷	Diagnostic laparoscopy followed by appendectomy if necessary	55	55	NR
	Immediate open appendectomy	55	53	NR
Tzovaras et al. 2007 (Greece) PMID: 17219281 ⁸⁴⁷	Diagnostic laparoscopy followed by appendectomy	38	38	
	Open appendectomy	40	40	
Olsen et al. 1993 (Denmark) PMID: 8369940 ⁶¹⁹	Diagnostic laparoscopy followed by appendectomy if necessary	30	30	No complication related to laparoscopy occurred.
	Immediate appendectomy	30	30	NR
van Dalen et al. 2003 (New Zealand) PMID: 12739123 ⁸⁵³	Diagnostic laparoscopy followed by appendectomy if necessary	32	32	No postoperative complications were encountered.
	Immediate appendectomy	31	31	NR

Table C10. NRCS study design

Comparison of CT and routine management									
Study	Population selection criteria	Interventions	Enrolment period	#centers	Power calculations?	Enrolment goal met?	Duration and method of	Loss to follow-up	Study design

							follow-up		
McGory et al. 2005 (United States) PMID: 16468523 ⁵⁵ 9	Patients undergoing appendectomy in a hospital licensed by the state of California, excluding Veteran's Affairs Hospitals. All incidental appendectomy cases were excluded.	1) CT scan before appendectomy 2) No CT scan before appendectomy	1999-2000	The state of California	No	NA	UNCLEAR, all data obtained from administrative database (discharge data)	NA	Retrospective cohort study using administrative discharge database
Petrosyan et al. 2008 (Netherlands) PMID: 17998781 ⁶⁵ 6	Patients with the chief complaint of RL pain and suspected appendicitis who were evaluated by the Emergency Surgical Services (Non-Trauma).	1) CT scan as part of diagnostic workup 2) No CT scan as part of diagnostic workup CT scans were carried out with IV and oral contrast material. All CT scans were interpreted by attending radiologists.	December 2004 to December 2006	1	No	NA	UNCLEAR, no follow-up described; used medical records from the center	NA	Retrospective, institutional review
Raja et al. (United States) PMID: 20529988 ⁶⁸ 4	Patients age 16-92 (mean age: 38.6) (% Female: suspected of having appendicitis who presented to the emergency department.	1) CT scan as part of diagnostic workup 2) No CT scan as part of diagnostic workup Multiple CT scanners used, all were manufactured by Siemens, and scans were obtained at 120 kV. Axial section thickness evolved from 10 to 5mm. Oral contrast used from 1990 to 2008, except during 1999 to 2000 when rectal contrast was used.	From 1990 to 1994 for no CT and from 2003 to 2007 for CT	1	No	NA	UNCLEAR, no follow-up described; used medical records from the center	NA	Retrospective, institutional review; use of historical cohorts

Shaligram et al. 2012 (United States) PMID: 23022250 ⁷⁶ ₃	Males age 18-55 presenting at the University HealthSystem Consortium and identified in the consortium database with an ICD-9-CM diagnosis of acute appendicitis (540.9) or right lower quadrant pain (789.03). Exclusion criteria were an ICD-9-CM diagnosis of acute appendicitis with generalized peritonitis (540.0), acute appendicitis with peritoneal abscess (540.1), appendicitis unqualified (541), or other appendicitis (542).	1) CT scan as part of diagnostic workup 2) No CT scan as part of diagnostic workup No descriptions of type of CT scan	October 2007 to December 2011	The consortium is an alliance of more than 100 academic medical centers and nearly 250 affiliate hospitals	No	NA	UNCLEAR, No follow-up, used discharge data from administrative database	NA	Retrospective cohort study using administrative discharge database
Tsao et al. 2008 (United States) PMID: 18498874 ⁸⁴ ₀	Patients under the age of 18 years who underwent appendectomies for suspected appendicitis. Exclusion criteria were incidental or interval appendectomy.	1) CT scan as part of diagnostic workup 2) No CT scan as part of diagnostic workup All CT scans were read by a paediatric radiologist. No other details of CT scan given.	January 1, 2000 to January 1, 2006	One tertiary paediatric children's hospital	No	NA	UNCLEAR, No follow-up, used medical records of patients undergoing appendectomies.	NA	Retrospective cohort study using medical records
Wagner et al. 2008 (United States) PMID: 18656636 ⁸⁶ ₇	Patients undergoing appendectomy for suspicion of acute appendicitis.	1) CT scan as part of diagnostic workup 2) No CT scan as part of diagnostic workup	January 200 through March 2007	1	No	NA	UNCLEAR, No follow-up, used medical records of patients undergoing appendectomies.	NA	Retrospective cohort study using medical records
Comparison of US and CT									
Study	Population selection criteria	Interventions	Enrolment period	#centers	Power calculations?	Enrolment goal met?	Duration and method of	Loss to follow-up	Study design

							follow-up		
Raval et al. 2012 (United States) PMID: 22507689 ⁶⁹	Patients aged 1-18 years with an ICD-9 procedure code for a principal procedure of appendectomy and CT or US imaging reported during the same hospitalization as the appendectomy. Only patients undergoing appendectomy within a week of admission and surviving to discharge were included. Exclusion criterion was incidental appendectomy. All data from the Healthcare Cost and Utilization Project (HCUP) Kids' Inpatient Database (KID).	1) US 2) CT 3) US and CT US and CT not described in detail.	Encounters from 1997, 2000, 2003, 2006 and 2009	NR	No	NA	UNCLEAR, No follow-up, used data from administrative database	NA	Retrospective cohort study using administrative data
SCOAP Collaborative 2012 (United States) PMID: 22964731 ²⁰⁶	Patients aged 15 years or older who underwent appendectomy in a nonpediatric Surgical Care Outcomes and Assessment Program (SCOAP) hospital.	1) US 2) CT US and CT not described in detail and varied over time period. Imaging results were based on final radiologist interpretation and were reported as consistent with appendicitis, not consistent with appendicitis, or indeterminate. Indeterminate findings were considered discordant, regardless of pathologic findings.	January 1, 2006 to December 31, 2011	55 hospitals	No	NA	UNCLEAR, No follow-up, used data abstracted from clinical record	NA	Retrospective cohort study using abstracted clinical data
van Randen et al. 2011	Consecutive patients 18 years or older presenting to an	1) US 2) CT	March 2005 to	6, 2 university	Yes, in published	Yes	Six months of follow-	Case record	Prospective trial in

(Netherlands) PMID: 21365197 ⁸⁵ 8	Emergency Department with acute abdominal pain for more than 2 hours and less than 5 days. Exclusion criteria were pregnancy, blunt or penetrating trauma, distinctive flank pain, suspicion of renal colic, and haemorrhagic shock caused by gastrointestinal bleeding or acute abdominal aneurysm.	US was performed with convex transducer ranging from 4-5 Mhz to 8-5 and 5.2 Mhz or linear transducer ranging from 4-7 and 5-12 Mhz to 12-5 Mhz. CT was performed on MDCT system with IV contrast. US was always done and evaluated before CT was done and the radiologist evaluating CT was blinded to the US findings. US and CT were both read by radiologists.	November 2006	and 4 large teaching hospitals	protocol (PMID: 17683592)		up including course of disease, laboratory findings, operation reports, pathology reports, treatment outcome and costs. Sources of and methods of obtaining this information not clear.	forms were incomplete for 7.3% (80/1101) patients	which all participants receive both of two different treatments
Bachur et al. 2012 (USA) PMID: 22192815 ⁶⁸	Consecutive patients 19 years or younger who presented to the emergency department with suspected appendicitis and had an appendectomy performed during the course of their clinical encounter, excluding cases with other emergent surgical procedures (intra-abdominal manipulation of intestine, release of torsion of ovary)	1) CT 2) US 3) Both CT and US 4) Either CT or US	2005 to 2009, inclusive	Business alliance of 40, freestanding, paediatric hospitals (the Children's Hospital Corporation of America)	No	NA	UNCLEAR, No follow-up, used data from administrative database	NA	Retrospective cohort study using administrative data
Comparison of US and routine management									
Study	Population selection criteria	Interventions	Enrolment period	#centers	Power calculations?	Enrolment goal met?	Duration and method of follow-up	Loss to follow-up	Study design

Even-Bendahan et al. 2003 (Israel) PMID: 12635978 ²³⁴	Children (mean: 11) admitted to the Department of Pediatric Surgery, with complaints of abdominal pain and a differential diagnosis of acute appendicitis.	1) No diagnostic imaging 2) US for some equivocal cases followed by CT as needed 3) US for all equivocal cases followed by CT as necessary US was introduced in period 2 and became standardized protocol for equivocal cases in period 3. All US and CT scans were evaluated by an experienced senior radiologist	From 1991 to 1994 for no diagnostic imaging, from 1995 to 1999 for US in some equivocal cases, and from 1999 to 2000 for US in all equivocal cases	1	No	NA	UNCLEAR, no follow-up described, used; used clinical files from medical center	NA	Retrospective cohort study; use of historical cohorts
Comparison of imaging and no imaging									
Study	Population selection criteria	Interventions	Enrolment period	#centers	Power calculations?	Enrolment goal met?	Duration and method of follow-up	Loss to follow-up	Study design
SCOAP Collaborative 2012 (United State) PMID: 22964731 ²⁰⁶	Patients aged 15 years or older who underwent appendectomy in a nonpediatric Surgical Care Outcomes and Assessment Program (SCOAP) hospital.	1) Preoperative imaging (CT, US, or MRI) 2) No preoperative imaging Imaging not described in detail and varied over time period. Imaging results were based on final radiologist interpretation and were reported as	January 1, 2006 to December 31, 2011	55 hospitals	No	NA	UNCLEAR, No follow-up, used data abstracted from clinical record	NA	Retrospective cohort study using abstracted clinical data

		consistent with appendicitis, not consistent with appendicitis, or indeterminate. Indeterminate findings were considered discordant, regardless of pathologic findings.							
Comparison of diagnostic score and no diagnostic score									
Study	Population selection criteria	Interventions	Enrolment period	#centers		Enrolment goal met?	Duration and method of follow-up	Loss to follow-up	Study design
Ohmann et al. 1999 (Germany) PMID: 10487595 ⁶¹ 7	All patients with acute abdominal pain within 1 week before hospital admission and undergoing surgical department diagnostic workup. Exclusion criteria were age less than 6 years, post-operative acute abdominal pain, trauma, or hernia, and patients with no definite final diagnosis	1) Diagnostic score as part of diagnostic workup 2) No diagnostic score as part of diagnostic workup The score was developed using regression and database data (reference to German publication from 1995) and ranges from 0-16. A score of <6 indicates appendicitis is unlikely and patients were excluded, a score of 6-11.5	October 1, 1994 to April 30, 1995 for management without diagnostic score and February 1, 1995 to August 15, 1995 for management with diagnostic score	8 departments of surgery in Germany and Austria	No	NA	Outpatients were followed up by telephone interview after 30 days.	UNCLEAR (Final diagnoses were given for all participants but 3.9% (58/1484) participants are missing from the test performance calculations and	Before and after study testing intervention in second period

		indicates appendicitis is possible and patients were monitored, and a score of ≥ 12 indicates appendicitis very frequent and patients received appendectomy.						there is brief mention that statistical comparisons exclude missing data)	
Comparison of diagnostic laparoscopy and immediate appendectomy									
Study	Population selection criteria	Interventions	Enrolment period	#centers		Enrolment goal met?	Duration and method of follow-up	Loss to follow-up	Study design
Akbar 2010 (Wales) PMID: 20056066 ¹⁷	Patients undergoing surgery for suspected appendicitis. Patients who underwent incidental appendectomy were excluded.	1) Laparoscopy 2) Open appendectomy	January 2000 to December 2007	1	No	N/A	UNCLEAR, No follow-up described, collected computerized medical records prospectively.	NA	Prospective cohort study
Barrat et al. 1999 (France) PMID: 9950123 ⁷⁸	Adults who underwent surgery for suspected appendicitis.	1) Diagnostic laparoscopy followed by appendectomy if necessary 2) Immediate open appendectomy	January 1987 to January 1997 (diagnostic laparoscopy from 1992 to 1997 and immediate	1	No	N/A	Laparoscopy patients who did not have appendixes removed were followed up for a mean	None described	Prospective cohort study with historical comparison group

			appendectomy from 1987 to 1994)				duration of 3 years.		
Ekeh et al. 2007 (United States) PMID: 17320525 ²¹ 4	All patients who underwent appendectomies. Patients who underwent incidental appendectomies, interval appendectomies, or appendectomies for 'chronic pain' were excluded.	1) Laparoscopic appendectomy 2) Open appendectomy	January 2000 to December 2005	1	No	NA	UNCLEAR, No follow-up, used medical records of patients undergoing appendectomies.	NA	Retrospective cohort study using medical records
Wagner et al. 2008 (United States) PMID: 18656636 ⁸⁶ 7	Patients undergoing appendectomy for suspicion of acute appendicitis.	1) Laparoscopy 2) Open appendectomy	January 2000 through March 2007	1	No	NA	UNCLEAR, No follow-up, used medical records of patients undergoing appendectomies.	NA	Retrospective cohort study using medical records

Table C11. NRCS test performance outcomes

Comparison of CT and routine management						
Study	Study arms	Number enrolled	Number followed to end	Sensitivity	Specificity	Test Performance Outcomes Other
McGory et al. 2005 (United States) PMID: 16468523 ⁵⁵⁹	CT scan before appendectomy	4,731	4,731	NR	NR	NR
	No CT scan before appendectomy	70,721	70,721	NR	NR	NR
	Differences between arms	NA	NA	NA	NA	NR
Petrosyan et al. 2008 (Netherlands) PMID: 17998781 ⁶⁵⁶	CT scan as part of diagnostic workup	905	905	NR	NR	NR
	No CT scan as part of diagnostic workup	725	725	NR	NR	NR
	Differences between arms	NA	NA	NA	NA	NR
Raja et al. (United States) PMID: 20529988 ⁶⁸⁴	CT scan as part of diagnostic workup	637 (Includes only those undergoing appendectomies, of which 97.5% had preoperative CT)	637	NR	NR	NR
	No CT scan as part of diagnostic workup	971 (Includes only those undergoing appendectomies, of which 1% had preoperative CT)	971	NR	NR	NR
	Differences between arms	NA	NA	NA	NA	NR
Shaligram et al. 2012 (United States) PMID: 23022250 ⁷⁶³	CT scan as part of diagnostic workup	11,340	11,340	NR	NR	NR
	No CT scan as part of diagnostic workup	1,888	1,888	NR	NR	NR
	Differences between arms	NA	NA	NA	NA	NA
Tsao et al. 2008	CT scan as part of	697	697	0.96 (593/620)	0.41 (15/37)	PPV 0.964 (593/615)

(United States) PMID: 18498874 ⁸⁴⁰	diagnostic workup			excluding equivocal CT 0.92 (593/646) including equivocal CT		NPV 0.357 (15/42) PPV for perforated appendicitis 0.919 (159/173) 5.7% (40/697) CT scans were equivocal
	No CT scan as part of diagnostic workup	381	381	NA (all diagnosed positive and proceeded to surgery)	NA (all diagnosed positive and proceeded to surgery)	PPV 0.908 (346/381)
	Differences between arms	NA	NA	NA	NA	P value = .045 for PPV
Wagner et al. 2008 (United States) PMID: 18656636 ⁸⁶⁷	CT scan as part of diagnostic workup	1070	1070	NR	NR	NR
	No CT scan as part of diagnostic workup	129	129	NR	NR	NR
	Differences between arms	NA	NA	NA	NA	NA
Comparison of US and CT						
Study	Study arms	Number enrolled	Number followed to end	Sensitivity	Specificity	Test Performance Outcomes Other
Raval et al. 2012 (United States) PMID: 22507689 ⁶⁹⁹	CT only	6519	6519	NR	NR	NR
	US only	2076	2076	NR	NR	NR
	CT and US	782	782	NR	NR	NR
	Differences between arms	NA	NA	NR	NR	NR
SCOAP Collaborative 2012 (United State) PMID: 22964731 ²⁰⁶	US	NR	NR	0.478	NR	PPV 0.943
	CT	NR	NR	0.932	NR	PPV 0.976
	Differences between arms	NA	NA	NR	NR	NR
Van Randen et al. 2011 (Netherlands) PMID:	US	1101	1021	0.76	0.95	PPV 0.86 NPV 0.91

21365197 ⁸⁵⁸						
	CT	1101	1021	0.94	0.95	PPV 0.89 NPV 0.98
	Differences between arms	NA	NA	P<.01	P=1.0	P value =.35 for PPV P value <.01 for NPV
Bachur et al. 2012 (USA) PMID: 22192815 ⁶⁸	CT	8881	8881	NR	NR	NR
	US	6439	6439	NR	NR	NR
	Both CT and US	825	825	NR	NR	NR
	Either CT or US	14496	14496	NR	NR	NR
	Differences between arms	NA	NA	NR	NR	NR
Comparison of US and no US						
Study	Study arms	Number enrolled	Number followed to end	Sensitivity	Specificity	Test Performance Outcomes Other
Even-Bendahan et al. 2003 (Israel) PMID: 12635978 ²³⁴	No diagnostic imaging	1136	1136	NR	NR	NR
	US for some equivocal cases followed by CT as needed	1069	355 received US or US then CT imaging	0.734 (58/79) for US only NR for US followed by CT	0.953 (263/276) for US only NR for US followed by CT	FP rate = 4.7% (13/276) for US only FN rate = (21/79) for US only FP rate = 26.6% (6/46) for US followed by CT
	US for all equivocal cases followed by CT as necessary	121	66 received US or US then CT imaging	0.90 (18/20) for US only NR for US followed by CT	0.87 (40/46) for US only 0.957 (44/46) for US followed by CT	FP rate = 10% (2/20) for US only FN rate = NR for US only FP rate = 13% (6/46) for US followed by CT
	Differences between arms	NA	NA	NR	NR	NR
Comparison of imaging and no imaging						
Study	Study arms	Number enrolled	Number followed to end	Sensitivity	Specificity	Test Performance Outcomes Other
SCOAP	Preoperative imaging (CT,	91.3% of n=19,327 or	91.3% of n=19,327 or	NR	NR	NR

Collaborative 2012 (United State) PMID: 22964731 ²⁰⁶	US, or MRI)	approximately 17,646	approximately 17,646			
	No preoperative imaging	8.7% of n=19,327 or approximately 1,681	8.7% of n=19,327 or approximately 1,681	NR	NR	NR
	Differences between arms	NA	NA	NR	NR	NR
Comparison of diagnostic score and routine management						
Study	Study arms	Number enrolled	Number followed to end	Sensitivity	Specificity	Test Performance Outcomes Other
Ohmann et al. 1999 (Germany) PMID: 10487595 ⁶¹⁷	Diagnostic score as part of diagnostic workup	614	597	0.955 (107/112)	0.781 (379/485)	PPV 0.502 (107/213) NPV 0.987 (379/384) Accuracy 0.814 (486/597)
	No diagnostic score as part of diagnostic workup	870	829	0.915 (174/190)	0.864 (552/639)	PPV 0.667 (174/261) NPV 0.972 (552/568) Accuracy 0.876 (726/829)
	Difference between arms	NA	NA	P=0.24	P<.001	P value <.001 for PPV P value =.18 for NPV P value <.005 for Accuracy
Comparison of diagnostic laparoscopy and immediate appendectomy						
Study	Study arms	Number enrolled	Number followed to end	Sensitivity	Specificity	Test Performance Outcomes Other
Akbar 2010 (Wales) PMID: 20056066 ¹⁷	Laparoscopy	343	343	NR	NR	NR
	Open appendectomy	1357	1357	NA	NA	NA
	Differences between arms	NA	NA	NA	NA	NA
Barrat et al. 1999 (France) PMID: 9950123 ⁷⁸	Diagnostic laparoscopy followed by appendectomy if necessary	355	355	1.0 (266/266) 1.0 (180/180) in women	0.73 (65/89) 0.78 (59/76) in women	NR

	Open appendectomy	930	930	NA	NA	NA
	Difference between arms	NA	NA	NA	NA	NA
Ekeh et al. 2007 (United States) PMID: 17320525 ²¹⁴	Laparoscopic appendectomy	596	596	0.98 (450/457)	0.45 (62/139)	NA
	Open appendectomy	716	716	NA	NA	NA
		NA	NA	NA	NA	NA
Wagner et al. 2008 (United States) PMID: 18656636 ⁸⁶⁷	Laparoscopy	927	927	NR	NR	NR
	Open appendectomy	273	273	NA	NA	NA
	Differences between arms	NA	NA	NA	NA	NA

Table C12. NRCS risk of bias

	Confounding Bias	Selection Bias		Reporting Bias	Other Sources of Bias
Comparison of CT and routine management					
Study	Regression or adjustment by age and sex?	Total proportion of missing outcome data is >10%	Difference in proportion of missing data between arms is >10%	Selective reporting of outcomes	Secular trends, other
McGory et al. 2005 (United States) PMID: 16468523 ⁵⁵⁹	INTERMEDIATE (study conducted analyses in which only sex was stratified (age was grouped in multiple years))	UNCLEAR (administrative discharge database)	UNCLEAR (administrative discharge database)	LOW (expected outcomes proposed in methods were included in results)	LOW (no other major potential sources of bias noted)
Petrosyan et al. 2008 (Netherlands) PMID: 17998781 ⁶⁵⁶	HIGH (no adjustment or stratification by age or sex)	UNCLEAR (administrative discharge database)	UNCLEAR (administrative discharge database)	LOW (expected outcomes proposed in methods were included in results)	LOW (no other major potential sources of bias noted)
Raja et al. (United States) PMID: 20529988 ⁶⁸⁴	INTERMEDIATE (study conducted analyses in which only sex was stratified)	LOW (missing data appears to be <5% overall)	LOW (missing data appears to be <5% overall)	LOW (expected outcomes proposed in methods were included in results)	HIGH (secular trends likely as CT period is 2000-8 and non-CT period is 1990-8. No discussion of differences between periods other than that the sex proportion in the two periods is similar)
Shaligram et al. 2012 (United States) PMID: 23022250 ⁷⁶³	INTERMEDIATE (study includes only men ages 18-55)	UNCLEAR (administrative discharge database)	UNCLEAR (administrative discharge database)	LOW (expected outcomes proposed in methods were included in results)	LOW (no other major potential sources of bias noted)
Tsao et al. 2008 (United States) PMID: 18498874 ⁸⁴⁰	HIGH (no adjustment or stratification by age or sex)	UNCLEAR (medical records)	UNCLEAR (medical records)	UNCLEAR (outcomes not prespecified in methods)	LOW (no other major potential sources of bias noted)
Wagner et al. 2008 (United	INTERMEDIATE (outcomes stratified by sex)	UNCLEAR (medical records)	UNCLEAR (medical records)	LOW (expected outcomes proposed in	LOW (no other major potential sources of bias

States) PMID: 18656636 ⁸⁶⁷				methods were included in results)	noted)
Comparison of US and CT					
Study	Regression or adjustment by age and sex?	Total proportion of missing outcome data is >10%	Difference in proportion of missing data between arms is >10%	Selective reporting of outcomes	Secular trends, other
Raval et al. 2012 (United States) PMID: 22507689 ⁶⁹⁹	HIGH (outcomes not stratified or adjusted for age or sex)	UNCLEAR (administrative database)	UNCLEAR (administrative database)	LOW (expected outcomes in methods were included in results)	LOW (no other major potential sources of bias noted)
SCOAP Collaborative 2012 (United State) PMID: 22964731 ²⁰⁶	LOW (study conducted analyses adjusting for age (continuous variable) and sex)	UNCLEAR (data abstracted from clinical records)	UNCLEAR (data abstracted from clinical records)	LOW (expected outcomes proposed in methods were included in results)	LOW (no other major potential sources of bias noted)
Van Randen et al. 2011 (Netherlands) PMID: 21365197 ⁸⁵⁸	HIGH (study reports on percentage missed appendicitis diagnoses stratified by sex and age<45, but none of the test accuracy statistics extracted for this review were examined by sex or age)	LOW (missing data is <5% overall)	LOW (missing data is <5% overall)	UNCLEAR (not all of the outcomes in the protocol are reported in the publication, however there are no outcomes in the report that are not prespecified in the protocol, and it may be that additional publications will include other outcomes)	LOW (no other major potential sources of bias noted)
Bachur et al. 2012 (USA) PMID: 22192815 ⁶⁸	LOW (study conducted analyses adjusting for age (continuous variable) and sex)	UNCLEAR (administrative database)	UNCLEAR (administrative database)	LOW (expected outcomes in methods were included in results)	HIGH (the database does not allow analysis of cases that were evaluated for appendicitis but did not undergo an appendectomy. Therefore, the value of imaging in ruling out

					appendicitis could not be studied. In addition, because these hospitals serve as referral centers, imaging obtained before transfer to a center cannot be studied.
Comparison of US and no US					
Study	Regression or adjustment by age and sex?	Total proportion of missing outcome data is >10%	Difference in proportion of missing data between arms is >10%	Selective reporting of outcomes	Secular trends, other
Even-Bendahan et al. 2003 (Israel) PMID: 12635978 ²³⁴	HIGH (no adjustment or stratification by age or sex)	UNCLEAR (medical records)	UNCLEAR (medical records)	LOW (expected outcomes proposed in methods were included in results)	HIGH (secular trends likely; enrolment periods for the three management strategies do not overlap).
Comparison of imaging and no imaging					
Study	Regression or adjustment by age and sex?	Total proportion of missing outcome data is >10%	Difference in proportion of missing data between arms is >10%	Selective reporting of outcomes	Secular trends, other
SCOAP Collaborative 2012 (United State) PMID: 22964731 ²⁰⁶	LOW (study conducted analyses adjusting for age (continuous variable) and sex)	UNCLEAR (data abstracted from clinical records)	UNCLEAR (data abstracted from clinical records)	LOW (expected outcomes proposed in methods were included in results)	LOW (no other major potential sources of bias noted)
Comparison of diagnostic score and no diagnostic score					
Study	Regression or adjustment by age and sex?	Total proportion of missing outcome data is >10%	Difference in proportion of missing data between arms is >10%	Selective reporting of outcomes	Secular trends, other

Ohmann et al. 1999 (Germany) PMID: 10487595 ⁶¹⁷	HIGH (no adjustment or stratification by age or sex)	LOW (missing data is <5% overall)	LOW (missing data is <5% overall)	LOW (expected outcomes proposed in methods were included in results)	UNCLEAR (secular trends are possible, however the enrolment periods for the two management strategies overlap slightly)
Comparison of diagnostic laparoscopy and immediate appendectomy					
Study	Regression or adjustment by age and sex?	Total proportion of missing outcome data is >10%	Difference in proportion of missing data between arms is >10%	Selective reporting of outcomes	Secular trends, other
Akbar 2010 (Wales) PMID: 20056066 ¹⁷	HIGH (no adjustment or stratification by age or sex)	UNCLEAR (medical records)	UNCLEAR (medical records)	UNCLEAR (outcomes not clearly described in methods)	LOW (no other major potential sources of bias noted)
Barrat et al. 1999 (France) PMID: 9950123 ⁷⁸	INTERMEDIATE (test performance and negative appendectomy rate provided separately for men and women)	UNCLEAR (appears to be no missing data from laparoscopy group and open appendectomy data is collected from appears to be based on administrative or clinical records)	UNCLEAR (appears to be no missing data from laparoscopy group and open appendectomy data is collected from appears to be based on administrative or clinical records)	LOW (expected outcomes proposed in methods were included in results)	UNCLEAR (secular trends are possible, however the periods for laparoscopy and open appendectomy overlap)
Ekeh et al. 2007 (United States) PMID: 17320525 ²¹⁴	INTERMEDIATE (stratification by sex for one of two outcomes of interest)	UNCLEAR (medical records)	UNCLEAR (medical records)	LOW (expected outcomes proposed in methods were included in results)	LOW (no other major potential sources of bias noted)
Wagner et al. 2008 (United States) PMID: 18656636 ⁸⁶⁷	HIGH (mention that result was consistent among male and female patients but no stratified outcome data presented)	UNCLEAR (medical records)	UNCLEAR (medical records)	LOW (expected outcomes proposed in methods were included in results)	LOW (no other major potential sources of bias noted)

Table C13. NRCS other outcomes

Comparison of CT and routine				
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management				
Study	Study arms	Number enrolled	Number followed to end	Other outcomes
McGory et al. 2005 (United States) PMID: 16468523 ⁵⁵⁹	CT scan before appendectomy	4,731	4,731	Negative appendectomy rate: 8.0% Negative appendectomy rate in women of reproductive age: 13.0% Appendicitis with abscess: 18.6% Length of stay 5.46 +/- 5.21 days (median 4 (range 0-83))
	No CT scan before appendectomy	70,721	70,721	Negative appendectomy rate: 9.4% Negative appendectomy rate in women of reproductive age: 15.2% Appendicitis with abscess: 9.3% Length of stay 3.28 +/- 4.04 days (median 2 (range 0-289))
	Differences between arms	NA	NA	P-value for negative appendectomy rate = 0.36 P-value for negative appendectomy rate in women of reproductive age: 0.056 P-value for appendicitis with abscess <0.001 P-value for length of stay <0.001
Petrosyan et al. 2008 (Netherlands) PMID: 17998781 ⁶⁵⁶	CT scan as part of diagnostic workup	905	905	Negative appendectomy rate: 6% (31/546) Negative appendectomy rate among those with Alvarado score 5-7: 3.3% (12/357)
	No CT scan as part of diagnostic workup	725	725	Negative appendectomy rate: 6% (23/383) Negative appendectomy rate among those with Alvarado score 5-7: 6.2% (20/321)
	Differences between arms	NA	NA	Mean difference and 95% confidence interval for % NAR among those with Alvarado score 5-7: 2.9 (-0.3 to 6)
Raja et al. (United States) PMID: 20529988 ⁶⁸⁴	CT scan as part of diagnostic workup	637 (Includes only those undergoing appendectomies, of which 97.5% had preoperative CT in 2007)	637	Negative appendectomy rate: 1.7% in 2007 Negative appendectomy rate among females: 1.6% in 2007 Negative appendectomy rate among men: 1.8% in 2007 Preoperative US imaging: 5.8% (37 / 637) from 2003-2007 Preoperative MR imaging: 0.3% (2 / 637) from 2003-2007
	No CT scan as part of diagnostic workup	971 (Includes only those undergoing appendectomies, of which 1% had preoperative CT in 1990)	971	Negative appendectomy rate: 23% in 1990 Negative appendectomy rate among females: 29.8% in 1990 Negative appendectomy rate among men: 15.5% in 1990 No information on preoperative US or MR imaging during the no CT scan period.
	Differences	NA	NA	P-value < .0001 for difference in NAR between 1990 and 2007

	between arms			P-value < .0001 for difference in NAR among females between 1990 and 2007 P-value < .0001 for difference in NAR among males between 1990 and 2007
Shaligram et al. 2012 (United States) PMID: 23022250 ⁷⁶³	CT scan as part of diagnostic workup	11,340	11,340	Mean days in hospital (SD) = 1.66 (1.63) ICU admission = 1.38% Readmission at 30 days = 1.8% Morbidity 0.86% for CT group
	No CT scan as part of diagnostic workup	1,888	1,888	Mean days in hospital (SD) = 1.37 (0.60) ICU admission = 1.8% Readmission at 30 days = 5.13% Morbidity 2.2% for non-CT group
	Differences between arms	NA	NA	P value <.0001 for difference in mean days in hospital P value =.1936 for ICU admission P value <.0001 for difference in readmission rates P value <.0001 for difference in morbidity
Tsao et al. 2008 (United States) PMID: 18498874 ⁸⁴⁰	CT scan as part of diagnostic workup	697	697	Perforated appendix rate = 24.6% (159/646)
	No CT scan as part of diagnostic workup	381	381	Perforated appendix rate = 33.8% (117/346)
	Differences between arms	NA	NA	NR
Wagner et al. 2008 (United States) PMID: 18656636 ⁸⁶⁷	CT scan as part of diagnostic workup	1070	1070	Negative appendectomy rate= 7.2% Negative appendectomy rate in women = 7.5% (44/581)
	No CT scan as part of diagnostic workup	129	129	Negative appendectomy rate= 14.0% Negative appendectomy rate in women = 20.4% (10/49)
	Differences between arms	NA	NA	P-value for negative appendectomy rate = 0.007 P-value for negative appendectomy rate in women <0.005
Comparison of US and CT				
Study	Study arms	Number enrolled	Number followed to end	Other outcomes
Raval et al. 2012	US	6,519	6,519	Negative appendectomy rate: 6.5%

(United States) PMID: 22507689 ⁶⁹⁹				Perforation rate: 29.8% Hours from admission to surgery: 7.4 (not stated mean or median)
	CT	2,076	2,076	Negative appendectomy rate: 3.6% Perforation rate: 31.8% Hours from admission to surgery: 9.6 (not stated mean or median)
	US and CT	782	782	Negative appendectomy rate: 6.6% Perforation rate: 36.3% Hours from admission to surgery: 15.4 (not stated mean or median)
	Differences between arms	NA	NA	P value <0.001 for negative appendectomy rate for CT vs. US and for CT vs. US and CT P value =0.004 for perforation rate for US and CT vs. US and for US vs. CT P value <0.01 for hours between admission and surgery for US and CT vs. US and US and CT vs. CT
SCOAP Collaborative 2012 (United State) PMID: 22964731 (same as SCOAP study reporting imaging vs. no imaging) ²⁰⁶	US	NR	NR	Negative appendectomy rate: 10.4% Negative appendectomy rate ages 15-30 years: 12% Negative appendectomy rate ages 31-65 years: 8.6% Insufficient number of ages >65 years underwent US
	CT	NR	NR	Negative appendectomy rate: 4.1% Negative appendectomy rate ages 15-30 years: 4.6% Negative appendectomy rate ages 31-65 years: 3.8% Negative appendectomy rate ages >65 years: 3.6%
	Differences between arms	NA	NA	P value <0.001 for negative appendectomy rate P value <0.001 for negative appendectomy rate ages 15-30 years P value <0.001 for negative appendectomy rate ages 31-65 years
Van Randen et al. 2011 (Netherlands) PMID: 21365197 ⁸⁵⁸	US	1,101	1,021	NR
	CT	1,101	1,021	NR
	Differences between arms	NA	NA	NR
Bachur et al. 2012 (USA) PMID: 22508920 ⁶⁷	CT	8881	8881	Assoc. of diagnostic imaging with NARs among boys: Age < 5 yrs: OR [95%CI] = 0.18[0.12, 0.28], p <.001 Age 5-10 yrs: OR [95%CI] = 0.68[0.42, 1.11], p= .123 Age > 10 yrs: OR [95%CI] = 1.10[0.79, 1.57], p= .556 Assoc. of diagnostic imaging with NARs among girls: Age < 5 yrs: OR [95%CI] = 0.11[0.07, 0.18], p < .001

				Age 5-10 yrs: OR [95%CI] = 0.78[0.51, 1.18], p= .236 Age > 10 yrs: OR [95%CI] = 1.07[0.83, 1.38], p = .598
	US	6439	6439	Assoc. of diagnostic imaging with NARs among boys: Age < 5 yrs: OR [95%CI] = 2.07[1.21, 3.54], p = .008 Age 5-10 yrs: OR [95%CI] = 0.87[0.52, 1.47], p= .610 Age > 10 yrs: OR [95%CI] = 0.56[0.27, 1.17], p= .122 Assoc. of diagnostic imaging with NARs among girls: Age < 5 yrs: OR [95%CI] = 1.54 [0.88, 2.68], p = .130 Age 5-10 yrs: OR [95%CI] = 0.87 [0.49, 1.55], p = .636 Age > 10 yrs: OR [95%CI] = 1.03 [0.64, 1.67], p = .897
	Both CT and US	825	825	NR
	Either CT or US	14496	14496	Assoc. of diagnostic imaging with NARs among boys: Age < 5 yrs: OR [95%CI] = 0.56[0.27, 1.17], p=.125 Age 5-10 yrs: OR [95%CI] = 1.55[0.60, 3.98], p=.363 Age > 10 yrs: OR [95%CI] = 0.98[0.34, 2.85], p=.971 Assoc. of diagnostic imaging with NARs among girls: Age < 5 yrs: OR [95%CI] = 0.24[0.08, 0.72], p =.011 Age 5-10 yrs: OR [95%CI] = 1.83[0.83, 4.02], p= .135 Age > 10 yrs: OR [95%CI] = 1.97[1.42, 2.74], p < .001
	Differences between arms	NA	NA	NR
Comparison of US and routine management				
Study	Study arms	Number enrolled	Number followed to end	Other outcomes
Even-Bendahan et al. 2003 (Israel) PMID: 12635978 ²³⁴	No diagnostic imaging	1,136	1,136	Negative appendectomy rate: 13.2%
	US for some equivocal cases followed by CT as needed	1,069	355 received US or US then CT imaging	Negative appendectomy rate: 6.5%
	US for all equivocal cases followed by CT as necessary	121	66 received US or US then CT imaging	NR

	Differences between arms	NA	NA	NR
Comparison of imaging and no imaging				
Study	Study arms	Number enrolled	Number followed to end	Other outcomes
SCOAP Collaborative 2012 (United State) PMID: 22964731 (same as SCOAP study reporting US vs. CT) ²⁰⁶	Preoperative imaging (CT, US, or MRI)	91.3% of n=19,327 or approximately 17,646	91.3% of n=19,327 or approximately 17,646	Negative appendectomy rate: 4.5% Perforation rate: 15.8% Negative appendectomy rate in women ages 15-50 years: 6.9% Perforation rate in women ages 15-50 years: 9.9%
	No preoperative imaging	8.7% of n=19,327 or approximately 1,681	8.7% of n=19,327 or approximately 1,681	Negative appendectomy rate: 15.4% Perforation rate: 15.6% Negative appendectomy rate in women ages 15-50 years: 24.7% Perforation rate in women ages 15-50 years: 9.7%
	Differences between arms	NA	NA	P value < 0.001 for negative appendectomy rate OR 3.90 (95% CI: 3.34-4.55) for negative appendectomy rate OR 3.7 (95% CI: 3.01-4.42) for negative appendectomy rate adjusted for age, sex, WBC count and clustering by site P value = 0.16 for perforation rate P value < 0.001 for negative appendectomy rate among women ages 15-50 years OR 4.48 (95% CI: 3.49-5.64) for negative appendectomy rate among women ages 15-50 years OR 3.46 (95% CI: 2.43-4.94) for negative appendectomy rate among women ages 15-50 years adjusted for age, WBC count and clustering by site P value = 0.48 for perforation rate among women ages 15-50 years
Comparison of diagnostic score and routine management				
Study	Study arms	Number enrolled	Number followed to end	Other outcomes
Ohmann et al. 1999 (Germany) PMID:	Diagnostic score as part of	614	597 (UNCLEAR)	Perforated appendix rate =14.9% (17/114) Negative appendectomy rate = 10.2% (13/127)

10487595 ⁶¹⁷	diagnostic workup			Negative laparotomy rate = 3.4% (8/233) Delayed appendectomy (≥ 2 days) rate = 1.8% (2/114) Delayed discharge(>10 days) rate = 11.4% (13/114)
	No diagnostic score as part of diagnostic workup	870	829 (UNCLEAR)	Perforated appendix rate = 19.4% (38/196) Negative appendectomy rate = 8.4% (18/214) Negative laparotomy rate = 3.9% (14/358) Delayed appendectomy (≥ 2 days) rate = 7.7% (15/196) Delayed discharge(>10 days) rate = 21.6% (43/199)
	Difference between arms	NA	NA	P value for perforated appendix rate = .32 P value for negative appendectomy rate = .57 P value for negative laparotomy rate = .83 P value for delayed appendectomy rate = .03 P value for delayed discharge rate = .02
Comparison of diagnostic laparoscopy and immediate appendectomy				
Study	Study arms	Number enrolled	Number followed to end	Other outcomes
Akbar 2010 (Wales) PMID: 20056066 ¹⁷	Laparoscopy	343	343	Negative appendectomy rate = 24.5% (63/256)
	Open appendectomy	1357	1357	Negative appendectomy rate = 13% (178/1357)
	Differences between arms	NA	NA	NR
Barrat et al. 1999 (France) PMID: 9950123 ⁷⁸	Diagnostic laparoscopy followed by appendectomy if necessary	355	355	Negative appendectomy rate = 8.2% (24/290) Negative appendectomy rate in women = 8.6% (17/197)
	Open appendectomy	930	930	Negative appendectomy rate = 25.4% (236/930) Negative appendectomy rate in women = 28.7% (190/660)
	Difference between arms	NA	NA	P-value for negative appendectomy rate = 0.015
Ekeh et al. 2007 (United States) PMID: 17320525 ²¹⁴	Laparoscopic appendectomy	596	596	Negative appendectomy rate = 23.3% Negative appendectomy rate in women = 28.3% Time from ED to surgery = 10.8 hours (+/- 9 hours)
	Open	716	716	Negative appendectomy rate = 14.0%

	appendectomy			Negative appendectomy rate in women = 24.7% Time from ED to surgery = 9.75 hours (+/- 8.5 hours)
	Difference between arms	NA	NA	P-value for negative appendectomy rate <.0001 P-value for negative appendectomy rate in women = 0.3521 P-value for time from ED to surgery = 0.0333
Wagner et al. 2008 (United States) PMID: 18656636 ⁸⁶⁷	Laparoscopy	927	927	Negative appendectomy rate= 7.3%
	Open appendectomy	273	273	Negative appendectomy rate= 8.4%
	Differences between arms	NA	NA	P-value for negative appendectomy rate = 0.53

Table C14. NRCS harms

Comparison of US and no US				
Study	Study arms	Number enrolled	Number followed to end	Harms
Even-Bendahan et al. 2003 (Israel) PMID: 12635978 ²³⁴	No diagnostic imaging	1136	1136	NR
	US for some equivocal cases followed by CT as needed	1069	355 received US or US then CT imaging	NR
	US for all equivocal cases followed by CT as necessary	121	66 received US or US then CT imaging	NR
	Differences between arms	NA	NA	NR
Comparison of CT and no CT				
Study	Study arms	Number enrolled	Number followed to end	Harms
Raja et al. (United States) PMID: 20529988 ⁶⁸⁴	CT scan as part of diagnostic workup	637 (Includes only those undergoing appendectomies, of which 97.5% had preoperative CT in 2007)	637	NR
	No CT scan as part of diagnostic workup	971 (Includes only those undergoing appendectomies, of which 1% had preoperative CT in	971	NR

		1990)		
	Differences between arms	NA	NA	NR
Shaligram et al. 2012 (United States) PMID: 23022250 ⁷⁶³	CT scan as part of diagnostic workup	11,340	11,340	NR
	No CT scan as part of diagnostic workup	1,888	1,888	NR
	Differences between arms	NA	NA	NR
Tsao et al. 2008 (United States) PMID: 18498874 ⁸⁴⁰	CT scan as part of diagnostic workup	697	697	NR
	No CT scan as part of diagnostic workup	381	381	NR
	Differences between arms	NA	NA	NR
Comparison of US and CT				
Study	Study arms	Number enrolled	Number followed to end	Harms
Van Randen et al. 2011 (Netherlands) PMID: 21365197 ⁸⁵⁸	US	1101	1021	NR
	CT	1101	1021	Imaging dose ranged from 120 Kv, 80-140 mAs to 120 KV, 200-250 mAs [Table 1]
	Differences between arms	NA	NA	NR
Comparison of diagnostic score and no diagnostic score				
Study	Study arms	Number enrolled	Number followed to end	Harms
Ohmann et al. 1999 (Germany) PMID: 10487595 ⁶¹⁷	Diagnostic score as part of diagnostic workup	614	597 (UNCLEAR)	Peritonitis rate 1.8% (2/112) Wound infection rate 8.9% (10/112) Other complication rate 2.7% (3/112) [No indication these complications are is related to the test, think they should not be included and this should be NR] AGREED
	No diagnostic score as part of diagnostic workup	870	829 (UNCLEAR)	Peritonitis rate 1% (2/197) Wound infection rate 6.6% (13/197) Other complication rate 1.5% (3/197) [No indication these complications are is

				related to the test, think they should not be included and this should be NR]
	Difference between arms	NA	NA	P value for peritonitis rate = .62 P value for wound infection rate = .50 P value for other complication rate = .67 [NR?]

Appendix D. Sensitivity Analyses for Studies of Imaging Tests

Table D1. Sensitivity analysis assuming indeterminate results are false positives

Test	Population	N studies [affected/ unaffected]	Sensitivity	Specificity	LR+	LR-
CT	Adults	27 [3396/6517]	0.96 (0.93 to 0.98)	0.87 (0.79 to 0.93)	7.54 (4.60 to 13.27)	0.05 (0.02 to 0.09)
	Children	12 [1517/1634]	0.94 (0.90 to 0.97)	0.76 (0.51 to 0.91)	3.96 (1.91 to 9.98)	0.08 (0.04 to 0.15)
	Elderly	1 [17/27]	1.00	1.00	.	0.00
	Women of reproductive age	3 [180/277]	0.98 (0.84 to 1.00)	0.92 (0.25 to 0.94)	12.00 (1.12 to 15.46)	0.02 (0.00 to 0.64)
	Pregnant women	3 [22/80]	1.00 (0.92 to 1.00)	0.98 (0.89 to 1.00)	34.50 (9.00 to 60.00)	0.00 (0.00 to 0.08)
	Mixed	31 [4230/6788]	0.95 (0.93 to 0.97)	0.86 (0.79 to 0.91)	6.91 (4.52 to 10.90)	0.06 (0.04 to 0.09)
MRI	Adults	4 [249/256]	0.94 (0.85 to 1.00)	0.82 (0.60 to 0.97)	5.25 (2.50 to 33.00)	0.07 (0.00 to 0.16)
	Children	3 [133/261]	0.93 (0.89 to 1.00)	0.98 (0.89 to 0.99)	47.60 (9.20 to 72.89)	0.07 (0.00 to 0.11)
	Pregnant women	8 [71/558]	0.95 (0.86 to 1.00)	0.91 (0.70 to 0.98)	10.22 (3.09 to 46.50)	0.05 (0.01 to 0.17)
	Mixed	3 [167/136]	0.92 (0.86 to 0.98)	0.77 (0.48 to 1.00)	3.06 (1.78 to 4.35)	0.14 (0.02 to 0.16)
TC99M NUCLEAR	adults	1 [10/24]	0.90	0.96	21.60	0.10
	Children	2 [21/60]	0.80 (0.70 to 0.91)	0.78 (0.70 to 0.86)	4.51 (2.30 to 6.73)	0.27 (0.11 to 0.43)
	Women of reproductive age	2 [16/45]	0.66 (0.43 to 0.89)	0.87 (0.74 to 1.00)	1.63 (1.63 to 1.63)	0.44 (0.11 to 0.78)
	Mixed	5 [144/282]	0.92 (0.72 to 0.99)	0.92 (0.63 to 0.99)	11.54 (2.18 to 119.60)	0.09 (0.01 to 0.38)
US	adults	10 [633/1188]	0.73 (0.56 to 0.86)	0.31 (0.09 to 0.64)	1.05 (0.72 to 2.07)	0.89 (0.33 to 3.43)
	Children	31 [2364/6559]	0.84 (0.75 to 0.91)	0.70 (0.52 to 0.83)	2.80 (1.73 to 5.11)	0.23 (0.13 to 0.39)
	Women of reproductive age	1 [27/84]	0.93	0.95	19.44	0.08
	Pregnant women	11 [156/421]	0.48 (0.32 to 0.65)	0.12 (0.02 to 0.42)	0.55 (0.34 to 0.97)	4.43 (1.04 to 26.01)
	Mixed	41 [3889/5445]	0.86 (0.80 to 0.91)	0.61 (0.41 to 0.78)	2.19 (1.41 to 3.93)	0.23 (0.14 to 0.42)

Table D2. Sensitivity analysis assuming indeterminate results are false negatives

Test	Population	N studies [affected/ unaffected]	Sensitivity	Specificity	LR+	LR-
CT	Adults	27 [3636/6277]	0.94 (0.89 to 0.97)	0.89 (0.81 to 0.94)	8.81 (4.94 to 16.94)	0.07 (0.04 to 0.12)
	Children	12 [1600/1551]	0.90 (0.86 to 0.95)	0.80 (0.53 to 0.93)	4.44 (1.96 to 12.42)	0.12 (0.07 to 0.18)
	Elderly	1 [17/27]	1.00	1.00	.	0.00
	Women of reproductive age	3 [180/277]	0.98 (0.84 to 1.00)	0.92 (0.25 to 0.94)	12.00 (1.12 to 15.46)	0.02 (0.00 to 0.64)
	Pregnant women	3 [22/80]	1.00 (0.92 to 1.00)	0.98 (0.89 to 1.00)	34.50 (9.00 to 60.00)	0.00 (0.00 to 0.08)
	Mixed	31 [4322/6696]	0.94 (0.91 to 0.96)	0.88 (0.82 to 0.92)	7.77 (5.15 to 12.08)	0.07 (0.04 to 0.11)
MRI	Adults	4 [249/256]	0.94 (0.85 to 1.00)	0.82 (0.60 to 0.97)	5.25 (2.50 to 33.00)	0.07 (0.00 to 0.16)
	Children	3 [133/261]	0.93 (0.89 to 1.00)	0.98 (0.89 to 0.99)	47.60 (9.20 to 72.89)	0.07 (0.00 to 0.11)
	Pregnant women	8 [71/558]	0.95 (0.86 to 1.00)	0.91 (0.70 to 0.98)	10.22 (3.09 to 46.50)	0.05 (0.01 to 0.17)
	Mixed	3 [167/136]	0.92 (0.86 to 0.98)	0.77 (0.48 to 1.00)	3.06 (1.78 to 4.35)	0.14 (0.02 to 0.16)
TC99M NUCLEAR	adults	1 [10/24]	0.90	0.96	21.60	0.10
	Children	2 [21/60]	0.80 (0.70 to 0.91)	0.78 (0.70 to 0.86)	4.51 (2.30 to 6.73)	0.27 (0.11 to 0.43)
	Women of reproductive age	2 [16/45]	0.66 (0.43 to 0.89)	0.87 (0.74 to 1.00)	1.63 (1.63 to 1.63)	0.44 (0.11 to 0.78)
	Mixed	5 [144/282]	0.92 (0.72 to 0.99)	0.92 (0.63 to 0.99)	11.54 (2.18 to 119.60)	0.09 (0.01 to 0.38)
US	adults	10 [662/1159]	0.71 (0.53 to 0.85)	0.34 (0.09 to 0.69)	1.07 (0.70 to 2.27)	0.87 (0.34 to 3.31)
	Children	31 [2856/6067]	0.74 (0.61 to 0.85)	0.82 (0.66 to 0.91)	4.03 (2.12 to 8.63)	0.32 (0.19 to 0.50)
	Women of reproductive age	1 [27/84]	0.93	0.95	19.44	0.08
	Pregnant women	11 [184/393]	0.44 (0.27 to 0.65)	0.17 (0.03 to 0.55)	0.55 (0.31 to 1.12)	3.18 (0.88 to 17.76)
	Mixed	41 [4524/4810]	0.79 (0.71 to 0.85)	0.75 (0.55 to 0.88)	3.12 (1.74 to 6.43)	0.28 (0.19 to 0.43)

Appendix E. Classifiers and Computer-Aided Diagnosis

Studies that met the review inclusion criteria and reported information on the test performance of classifiers and methods for computer-aided diagnosis are listed in Table E1.

Table E1. Studies on test performance of classifiers and methods for computer-aided diagnosis

Author	Year	Journal	Title
I. D. Adams	1986	Br Med J (Clin Res Ed)	Computer aided diagnosis of acute abdominal pain: a multicentre study
T. I. Anatol and Y. Holder	1995	West Indian Med J	A scoring system for use in the diagnosis of acute abdominal pain in childhood
T. I. Anatol and Y. Holder	1995	J R Coll Surg Edinb	A multivariate analysis of childhood abdominal pain in Trinidad
R. H. Birkhahn	2006	Am J Surg	Classifying patients suspected of appendicitis with regard to likelihood
M. Blazadonakis	1996	Artif Intell Med	Deep assessment of machine learning techniques using patient treatment in acute abdominal pain in children
I. D. Burton	1987	Aust N Z J Surg	Acute appendicitis in childhood: a feasibility study of computer-assisted diagnosis
P. C. Clifford	1986	Ann R Coll Surg Engl	The acute abdomen: management with microcomputer aid
N. J. Crichton	1987	Stat Med	Some points on the use of 'independent Bayes' to diagnose acute abdominal pain
F. T. De Dombal	1973	Proc R Soc Lond B Biol Sci	Surgical diagnosis assisted by a computer
F. T. de Dombal	1979	Scand J Gastroenterol Suppl	Acute abdominal pain--an O.M.G.E. survey
F. T. de Dombal	1991	BMJ	Can computer aided teaching packages improve clinical care in patients with acute abdominal pain?
F. T. de Dombal and J. C. Horrocks	1978	Methods Inf Med	Use of receiver operating characteristic (ROC) curves to evaluate computer confidence threshold and clinical performance in the diagnosis appendicitis
F. T. De Dombal	1974	Br Med J	Human and computer-aided diagnosis of abdominal pain: further report with emphasis on performance of clinicians
F. T. de Dombal	1972	Br Med J	Computer-aided diagnosis of acute abdominal pain
F. T. deDombal	1975	J R Coll Physicians Lond	Computer-aided diagnosis and decision-making in the acute abdomen
J. A. Dickson	1985	Lancet	Computer-assisted diagnosis of acute abdominal pain in childhood
J. A. Dickson	1988	Scand J Gastroenterol Suppl	Acute abdominal pain in children
F. H. Edwards and R. S. Davies	1984	Surg Gynecol Obstet	Use of a Bayesian algorithm in the computer-assisted diagnosis of appendicitis
N. H. Edwards	1986	Comput Methods Programs Biomed	The accuracy of a Bayesian computer program for diagnosis and teaching in acute abdominal pain of childhood
M. Eskelinen	1994	Int J Biomed Comput	Acute appendicitis in patients over the age of 65 years; comparison of clinical and computer based decision making
M. Eskelinen	1994	Scand J Gastroenterol	Sex-specific diagnostic scores for acute appendicitis
K. J. Farion	2008	Int J Med Inform	Prospective evaluation of the MET-AP system providing triage plans for acute pediatric abdominal pain
G. Fenyo	1987	Scand J Gastroenterol Suppl	Computer-aided diagnosis of 233 acute abdominal cases at Nacka Hospital Sweden
J. M. Gronroos	1994	Clin Chem	Phospholipase A2, C-reactive protein, and white blood cell count in the diagnosis of acute appendicitis
A. A. Gunn	1976	J R Coll Surg Edinb	The diagnosis of acute abdominal pain with computer analysis
A. A. Gunn	1991	Baillieres Clin Gastroenterol	The acute abdomen: the role of computer-assisted diagnosis
J. C. Horrocks	1976	Can J Surg	Computer-aided diagnosis of gastroenterologic diseases in Sherbrooke: preliminary report

J. C. Horrocks	1972	Br Med J	Computer-aided diagnosis: description of an adaptable system, and operational experience with 2,034 cases
J. K. Ikonen	1983	Ann Chir Gynaecol	Presentation and diagnosis of acute abdominal pain in Finland: a computer aided study
O. J. Kirkeby and C. Riso	1987	Scand J Gastroenterol Suppl	Use of a computer system for diagnosing acute abdominal pain in a small hospital
M. W. Kurzynski	1987	Comput Biol Med	Diagnosis of acute abdominal pain using a three-stage classifier
P. C. Lawrence	1987	Ann R Coll Surg Engl	Acute abdominal pain: computer aided diagnosis by non-medically qualified staff
D. J. Leaper	1972	Br Med J	Computer-assisted diagnosis of abdominal pain using "estimates" provided by clinicians
Y. H. Lee	2013	Artif Intell Med	A preclustering-based ensemble learning technique for acute appendicitis diagnoses
K. C. Lin	2007	Acta Paediatr Taiwan	Discriminant analysis of serum inflammatory biomarkers which differentiate pediatric appendicitis from other acute abdominal diseases
W. A. McAdam	1990	Ann R Coll Surg Engl	Twelve years' experience of computer-aided diagnosis in a district general hospital
W. Michalowski	2001	Paediatr Child Health	Triage of the child with abdominal pain: A clinical algorithm for emergency patient management
C. Ohmann	1996	Artif Intell Med	Evaluation of automatic knowledge acquisition techniques in the diagnosis of acute abdominal pain. Acute Abdominal Pain Study Group
E. Pesonen	1997	Stud Health Technol Inform	Is neural network better than statistical methods in diagnosis of acute appendicitis?
E. Pesonen	1996	Int J Biomed Comput	Comparison of different neural network algorithms in the diagnosis of acute appendicitis
B. Puppe	1995	Methods Inf Med	Evaluating four diagnostic methods with acute abdominal pain cases
S. L. Reynolds and D. M. Jaffe	1992	Pediatr Emerg Care	Diagnosing abdominal pain in a pediatric emergency department
S. Sakai	2007	J Med Syst	Comparison of the levels of accuracy of an artificial neural network model and a logistic regression model for the diagnosis of acute appendicitis
D. R. Shah	1999	MD Comput	The utilization of a neural network system in the diagnosis of appendicitis
C. S. Son	2012	BMC Med Inform Decis Mak	A hybrid decision support model to discover informative knowledge in diagnosing acute appendicitis
G. C. Sutton	1989	Lancet	How accurate is computer-aided diagnosis?
J. Wellwood	1992	Ann R Coll Surg Engl	How does computer-aided diagnosis improve the management of acute abdominal pain?
J. M. Wellwood and D. J. Spiegelhalter	1989	Br J Hosp Med	Computers and the diagnosis of acute abdominal pain
P. D. Wilson	1975	Br Med J	Simplified computer-aided diagnosis of acute abdominal pain
O. Yoldas	2012	Am J Emerg Med	Artificial neural networks in the diagnosis of acute appendicitis
M. Zorman	2001	Stud Health Technol Inform	Comparison of three databases with a decision tree approach in the medical field of acute appendicitis

Appendix F. Risk of Bias Assessment for Studies of Test Performance

Table F1. Risk of bias assessment for studies of test performance

Variable	Definitions
Extractor 1	Extractor initials
study_author	First author in the publication
study_year	Year of publication
study_pmid	PMID of the publication If single publication reports multiple studies (eg. Retrospective and prospective cohorts with complete information), complete separate risk of bias row for each, labeled pmid_a, pmid_b ...
Was a consecutive or random sample of patients enrolled?	Do the authors state that (1) patients were enrolled consecutively? OR (2) Discuss a random sampling scheme for selecting patients for inclusion?
Was a case-control design avoided?	Did the study enroll preferentially affected and unaffected individuals? In most cases this should be “YES”, because of our selection criteria. Occasionally we should expect some “UNCLEAR”
Did the study avoid inappropriate exclusions?	Where more than 10% of enrolled patients excluded for any reason other than unavailability of index test results? YES: <=10% of enrolled patients were excluded for reasons other than the unavailability of index test results YES: >10% of enrolled patients were excluded for reasons other than the unavailability of index test results UNCLEAR: we cannot distinguish between the above two categories (includes cases where data on the % excluded are not reported, or cases where the reasons for exclusion are not reported and the total proportion of excluded patients is >10%. If the total % excluded is <10% - even if reasons are not reported – the study gets a “YES”).
Were the index test results interpreted without knowledge of the results of the reference standard?	Where index test assessors blinded to the reference standard results? YES: blinding is explicitly mentioned, or the authors clearly describe a process by which index test results were “called” before reference standard results were available NO: explicitly states or can confidently infer that no blinding of index test assessors was in place UNCLEAR: not reported or not enough information to be certain
If a threshold was used, was it prespecified?	Was the criterion for positive index test results defined a priori? E.g. is it stated that it was determined in the study protocol? Is it stated that it was determined based on the literature? YES: a priori determined (protocol, literature-based, prior studies) NO: clearly determined using data from the same study (e.g., determined via ROC analysis) UNCLEAR: not reported or not enough information to be certain
Is the reference standard likely to correctly classify the target condition?	Was the reference standard pathology OR followup of 14 days or more for 90% of the analyzed population? YES: >=90% or more of analyzed patients had pathology OR 14-day (or longer) followup

	<p>NO: <90% of patients had pathology OR 14-day (or longer) followup UNCLEAR: not reported or not enough information to be certain</p>
<p>Were the reference standard results interpreted without knowledge of the results of the index test?</p>	<p>Where reference standard test assessors blinded to the index test results?</p> <p>YES: blinding is explicitly mentioned, or the authors clearly describe a process by which reference standard test results were “called” with no knowledge of index test results NO: explicitly states or can confidently infer that no blinding of reference standard test assessors was in place UNCLEAR: not reported or not enough information to be certain</p>
<p>Was there an appropriate interval between index tests and reference standard?</p>	<p>If pathology was used on all patients: enter NOT APPLICABLE</p> <p>If followup was used as the reference standard at least for sum patients, was is >14 days?</p> <p>YES: followup was available for 14-days or more on >=90% of patients NO: followup was less than 14-days for >10% of patients UNCLEAR: not reported or not enough information to be certain</p> <p>Note: this variable will be correlated strongly with the “appropriateness of ref. standard” question.</p>
<p>Did all patients receive a reference standard?</p>	<p>Was <u>any acceptable</u> reference standard test used for >=90% of patients?</p> <p>YES: >= 90% of patients used an acceptable reference standard (pathology OR followup of any duration) NO: <90% of patients used an acceptable reference standard UNCLEAR: not reported or not enough information to be certain</p>
<p>Did all patients receive the same reference standard?</p>	<p>Was <u>the same reference</u> standard test used for >=90% of patients?</p> <p>YES: >= 90% had pathology as the reference standard YES: >= 90% had followup of any duration as the reference standard NO: <90% of patients used the same reference standard (all other cases where the proportion is reported and is <90% for each of the reference standards used) UNCLEAR: not reported or not enough information to be certain</p>
<p>Were all patients included in the analysis?</p>	<p>Was the percentage of patients included in the analysis >=90% of the patients enrolled in the study?</p> <p>YES: >= 90% of patients enrolled were analyzed (i.e., in 2x2 table) NO: <90% of patients enrolled were analyzed (i.e., in 2x2 table) UNCLEAR: not reported or not enough information to be certain</p>