



Effective Health Care Program

Antinuclear Antibody, Rheumatoid Factor, and Cyclic-Citrullinated Peptide Tests for Evaluating Musculoskeletal Complaints in Children

Executive Summary

Background

Musculoskeletal (MSK) pain is common in children and adolescents, with an estimated prevalence ranging from 2 to 50 percent.¹ MSK pain can affect physical, psychological, and social function and often prompts consultation with a physician.² However, MSK pain is often nonspecific, which can make it difficult to arrive at an accurate diagnosis.^{3,4}

MSK pain may be due to rheumatic or nonrheumatic causes. Nonrheumatic causes are more common, generally benign, and most often attributable to trauma, overuse, and normal bone growth.⁵ Rheumatic causes, such as inflammatory arthritis, are infrequent, generally chronic, and require accurate, timely diagnosis and effective intervention to prevent progression and long-term damage.⁶ Common rheumatic causes of childhood MSK pain include pediatric systemic lupus erythematosus (pSLE) and juvenile idiopathic arthritis (JIA).

A complete history and physical examination is generally considered to be the best way to make a diagnosis of inflammatory arthritis.^{3,5} Physicians may request serological tests such as antinuclear antibody (ANA), rheumatoid factor (RF), and cyclic-citrullinated peptide (CCP) when children and adolescents

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

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are suspected of having inflammatory arthritis, despite the fact that the diagnostic performance, usefulness, and proper interpretation of these tests are uncertain in pediatric populations.



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This comparative effectiveness review summarizes the evidence on the test performance of ANA, RF, or CCP tests for pSLE and JIA in children with undiagnosed MSK pain. The report is intended for a broad audience including primary care physicians who may consider ordering these tests in a child with MSK pain, health payers who provide coverage for these tests, and parents or caregivers who want to know whether these tests can determine if their child does or does not have a particular disease.

Key Questions

In order to better understand how the ANA, RF, and CCP tests perform in the clinical setting of a child with undiagnosed MSK pain, it is important to know the prevalence of MSK complaints (including MSK pain and joint swelling) in children who do not have JIA and pSLE. It is also important to be aware of the rate of false positives for these tests (i.e., the proportion of otherwise healthy children who have a positive ANA, RF, or CCP test). Appropriate interpretation of test performance also requires an understanding of the disease progression and changes in signs and symptoms in children with MSK pain who may or may not also have JIA or pSLE.

In addition to providing this background information, the objectives of this report were to assess the test performance of ANA, RF, and CCP tests in children and adolescents with undiagnosed MSK pain and/or joint swelling compared with clinical diagnoses of pSLE and JIA; to explore the difference in test performance for accuracy modifiers including age, sex, race or ethnicity, comorbidities, and recent infections; and to evaluate the impact of test results on clinical decisionmaking and clinically important outcomes such as referrals, ordering of additional tests, clinical management, and anxiety experienced by children and parents. We addressed the following Key Questions (KQs):

KQ 1. Prevalence and Incidence

KQ 1.1. In children and adolescents aged 18 years or less, what is the incidence and prevalence of undiagnosed MSK complaints?

KQ 1.2. In healthy children and adolescents aged 18 years or less, what is the incidence of positive test results in ANA, RF, and CCP?

KQ 2. Natural History

KQ 2.1. What proportion of children and adolescents aged 18 years or less with undiagnosed MSK pain is due to noninflammatory causes?

KQ 2.2. What proportion of children and adolescents aged 18 years or less with undiagnosed MSK pain is due to inflammatory causes?

KQ 2.3. What proportion of children and adolescents aged 18 years or less experiences symptom resolution or recurrence?

KQ 3. Diagnostic Performance

KQ 3.1. In children and adolescents aged 18 years or less with undiagnosed MSK pain and/or joint swelling, what is the test performance (sensitivity [Sn], specificity [Sp], and positive and negative predictive values [PPV, NPV]) of ANA for pSLE compared with a clinical diagnosis?

KQ 3.2. In children and adolescents aged 18 years or less with undiagnosed MSK pain and/or joint swelling, what is the test performance (Sn, Sp, PPV, NPV) of ANA for JIA compared with a clinical diagnosis?

KQ 3.3. In children and adolescents aged 18 years or less with undiagnosed MSK pain and/or joint swelling, what is the test performance (Sn, Sp, PPV, NPV) of RF for pSLE compared with a clinical diagnosis?

KQ 3.4. In children and adolescents aged 18 years or less with undiagnosed MSK pain and/or joint swelling, what is the test performance (Sn, Sp, PPV, NPV) of RF for JIA compared with a clinical diagnosis?

KQ 3.5. In children and adolescents aged 18 years or less with undiagnosed MSK pain and/or joint swelling, what is the test performance (Sn, Sp, PPV, NPV) of CCP for pSLE compared with a clinical diagnosis?

KQ 3.6. In children and adolescents aged 18 years or less with undiagnosed MSK pain and/or joint swelling, what is the test performance (Sn, Sp, PPV, NPV) of CCP for JIA compared with a clinical diagnosis?

KQ 4. Accuracy Modifiers

KQ 4.1. In children and adolescents aged 18 years or less with undiagnosed MSK pain and/or joint swelling, do age, sex, race/ethnicity, comorbidities, and recent infections modify the diagnostic performance of ANA, RF, and CCP for pSLE compared with a clinical diagnosis?

KQ 4.2. In children and adolescents aged 18 years or less with undiagnosed MSK pain and/or joint swelling, do age, sex, race/ethnicity, comorbidities, and recent infections modify the diagnostic performance of ANA, RF, and CCP for JIA compared with a clinical diagnosis?

KQ 5. Clinical Impacts of Test Results

In children and adolescents aged 18 years or less with undiagnosed MSK pain and/or joint swelling, do ANA, RF, and CCP test results affect referral decisions, additional

tests ordered, clinical management, and patient and parent anxiety due to the clinical uncertainty and additional tests?

Methods

KQs 1 and 2, serving as background information, were addressed in a narrative approach by locating and summarizing the related prevalence, incidence, and natural history information from the main search (described below) and additional searches using MEDLINE® and Google Scholar. For KQs 3 to 5, we followed standard methods for conducting comparative effectiveness reviews; these methods were outlined in a prospectively developed protocol.

We searched electronic databases including MEDLINE®, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews (CDSR), Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL®), Science Citation Index Expanded® and Social Sciences Citation Index® (both via Web of Science®), Academic Search Complete, Proquest Dissertations & Theses, and OCLC PapersFirst. In addition, we searched conference proceedings from key scientific meetings, grey literature, and reference lists of included studies. We applied a diagnostic search filter and a child filter, when applicable. We conducted the original searches from 1960 to January 2010, and updated them in December 2010 and September 2011.

Two reviewers independently screened the search results (titles and abstracts) to determine if an article met broad inclusion criteria. The full text of potentially relevant articles was assessed independently by two reviewers using detailed standardized criteria. Two reviewers independently assessed the methodological quality of individual studies using the QUADAS tool.⁷ Data were extracted by one reviewer and verified by another using a standardized data extraction form. For each of these steps, disagreements were resolved through discussion or third-party adjudication, as needed.

We examined the diagnostic test characteristics, including Sn, Sp, PPV, and NPV, for each study and presented forest plots to summarize the results for each test–disease pairing. Accuracy modifiers including age, sex, race or ethnicity, recent infection, and comorbidity were analyzed if studies provided sufficient data to calculate Sn and Sp. We examined any qualitative or quantitative information on clinically important outcomes including referral, additional tests ordered, change in clinical management, and patient or parent anxiety due to the test results.

Two reviewers independently assessed the strength of evidence for KQs 3 to 5 using the Agency for Healthcare Research and Quality (AHRQ) system for grading

evidence (AHRQ Guidance for the Evaluation of Medical Tests [draft]).⁸ We assessed the strength of evidence for Sn and Sp. Assessments were based on the quantity and quality of individual studies, the directness of evidence, and the consistency and precision of the results. For each outcome, the strength of evidence was graded as high, moderate, low, or insufficient.

Results

KQ 1.1. The Prevalence of Undiagnosed MSK Complaints in Children and Adolescents

The prevalence of MSK pain ranged between 2 and 52 percent⁹⁻¹¹ and increased steadily with age throughout childhood and adolescence.^{12,13} No studies reported the prevalence of joint swelling in children.

KQ 1.2. The Prevalence of Test Positivity in Healthy Children and Adolescents

The prevalence of positive ANA in healthy children ranged from 0 to 18 percent.¹⁴⁻²² The prevalence of positive RF in healthy children was estimated at 3 percent.²³ The prevalence of CCP positivity in healthy children was reported in two studies and ranged from 0 to 0.6 percent.^{24,25}

KQ 2. The Etiology and Resolution of Pediatric MSK Pain

Noninflammatory etiologies accounted for the MSK pain in almost all (97 percent) children seen in a primary care setting.¹² Physical trauma was the most common noninflammatory cause and accounted for 44 percent of children with MSK pain. In contrast, only 3.3 percent of children had their MSK pain attributed to inflammatory causes including toxic synovitis (2.5 percent) and inflammatory arthritides (0.8 percent). The recurrence rates of pediatric MSK pain were generally high and varied considerably by site of the pain.

KQ 3. Test Performance of ANA, RF, and CCP

One cohort study and 27 case-control studies addressed KQ 3 (diagnostic performance). In studies using the case-control design, children with known disease (i.e., JIA or pSLE) were compared with children who were healthy (i.e., the control group). This does not represent the target population of children with undiagnosed MSK pain, and therefore, these studies are at high risk of spectrum bias. None of the case-control studies provided information about the presence of MSK pain in either the cases or controls. None of the studies specifically addressed children with joint swelling.

KQ 3.1. ANA Test for pSLE in Children With MSK Pain

Two case-control studies^{26,27} including 201 children (67 pSLE, 134 controls) examined the prevalence of a positive ANA test in children with pSLE and control groups including healthy children and children scheduled for elective orthopedic surgery. The Sn's were 91 and 100 percent, and Sp's were 84 and 85 percent (Table A).

KQ 3.2. ANA Test for JIA in Children With MSK Pain

Eight case-control studies^{26,28-34} including 1,382 children (1,067 JIA, 315 controls) examined the prevalence of a positive ANA test in children with JIA and controls including healthy children, children with nonrheumatic conditions, and children with other rheumatic diseases. The Sn ranged from 1 to 62 percent, and Sp ranged from 73 to 100 percent (Table A).

KQ 3.3. RF Test for pSLE in Children With MSK Pain

One case-control study³⁵ with 46 children (14 pSLE, 32 controls) examined the prevalence of a positive IgM-RF test for pSLE. The control group comprised healthy children and children with other rheumatic conditions or ulcerative colitis. The Sn was 29 percent, and Sp was 88 percent (Table A).

KQ 3.4. RF Test for JIA in Children With MSK Pain

One retrospective cohort study³⁶ examined the records of pediatric patients who had an RF test and were seen at a children's hospital. Among the 437 patient records, 105 had a diagnosis of JIA. The remaining 332 patients had a mix of MSK complaints (n = 201) or symptoms suggestive of an underlying autoimmune disease (n = 131). The Sn was 5 percent, and Sp was 98 percent (Table A).

Fifteen case-control studies^{28,30,33,35-47} including 1,647 children (986 JIA, 661 controls) examined the prevalence of a positive IgM-RF test in children with JIA and controls. The control groups included healthy children, children with nonrheumatic conditions, and children with other rheumatic conditions. The Sn ranged from 0 to 35 percent, and Sp ranged from 94 to 100 percent (Table A).

KQ 3.5. CCP Test for pSLE in Children With MSK Pain

No studies provided information to address this question.

KQ 3.6. CCP Test for JIA in Children With MSK Pain

Seven case-control studies^{24,25,30,48-51} including 1,643 participants (729 JIA, 914 controls) examined the prevalence of a positive CCP test in children with JIA and controls including healthy children, children with nonrheumatic conditions, and children with other

autoimmune diseases. Sn ranged from 2 to 42 percent, and Sp ranged from 93 to 100 percent (Table A).

KQ 4. Accuracy Modifiers of ANA, RF, and CCP Tests

No studies provided data on accuracy modifiers (age, sex, race or ethnicity, comorbidities, recent infections) for any of the tests.

KQ 5. Clinical Impacts of ANA, RF, and CCP Tests

No studies provided information to address this question.

Summary

Studies that have investigated the prevalence of MSK pain in children report a wide range of prevalence from 2 to 52 percent. Noninflammatory causes of MSK pain account for the majority of diagnoses (97 percent). Among the healthy children, the median ANA positivity is 3 percent, median RF positivity is 0 percent, and CCP positivity is less than 1 percent.

Only one retrospective cohort study examined the diagnostic test characteristics of RF to diagnose JIA among children with undiagnosed MSK pain compared with a clinical diagnosis. It demonstrated a Sn of 5 percent and a Sp of 98 percent. Fifteen case-control studies did not specifically address the test performance of RF among children with undiagnosed MSK pain. The strength of evidence is low for both Sn and Sp (Table A). Further evidence is likely to change our confidence in the estimates of performance and is likely to change the estimates.

The 12 case-control studies looking at other test-disease combinations did not specifically address the prevalence of positive tests for ANA or CCP among children presenting with undiagnosed MSK pain. The strength of evidence is insufficient to determine the test performance of ANA or CCP to diagnose JIA or pSLE in children with undiagnosed MSK pain. No studies specifically addressed children with joint swelling.

A general pattern of high Sp and low Sn was observed for almost all the test-disease combinations; however, the design of case-control studies may lead to bias.⁵²⁻⁵⁴ The selective inclusion of cases with established disease (i.e., JIA or pSLE) is likely to lead to an overestimation of Sn. The inclusion of healthy controls is expected to decrease the likelihood of false positive test results and lead to an overestimation of Sp.

Implications

There is insufficient evidence to determine the test performance of ANA or CCP in children with undiagnosed MSK pain. The strength of evidence is low for the utility

of RF in the diagnosis of JIA in children with undiagnosed MSK pain. A result of high Sp and low Sn was observed for almost all the test–disease combinations. The generally low Sn suggests that it is inappropriate to use these tests in isolation (i.e., without clinical assessment) to make a diagnosis of JIA and pSLE. In spite of the high Sp, the low prevalence of JIA and pSLE in the target population (i.e., children with undiagnosed MSK pain) makes the tests of limited diagnostic value. The presence of other clinical characteristics (e.g., morning stiffness, joint swelling, malar rash, cytopenia) may increase the pretest probability of the disease in question. While both the Sn and Sp for ANA for pSLE were high, this test in isolation has limited diagnostic value for children with undiagnosed MSK given the very low prevalence of pSLE, and up to 18 percent prevalence of a false positive ANA in the general population.

Limitations

The generally insufficient strength of evidence is primarily attributable to the high risk of spectrum bias of the case-control studies, a result of the distinct disease and control groups not being representative of the target population of children with undiagnosed MSK pain. For studies examining ANA for pSLE, incorporation bias is a concern because ANA is considered one of the classification criteria for SLE.⁵⁵

There is no evidence with which to assess the impact of potential accuracy modifiers, and there is no evidence with which to assess the clinical utility of the tests including the impact of the test results on referrals, ordering of additional tests, patient management, and patient and parent anxiety levels.

In addition to the issues identified above, there are general limitations for systematic reviews such as publication bias. We addressed this issue by conducting a comprehensive search of the published literature for potentially relevant studies. Search strategies included combinations of subject headings and free text words. Even though we applied a diagnostic search filter to the search strategies of the electronic databases, our searches identified over 11,000 records. Furthermore, these searches were supplemented by hand searching for grey literature (i.e., unpublished or difficult to find studies). There is also a possibility of study selection bias. However, we employed at least two independent reviewers to identify potentially relevant studies, and feel confident that the studies that were excluded from this report were done so for consistent and appropriate reasons.

Conclusion

Most of the evidence from the 28 studies included in this review was not applicable to the population of interest as studies examined children with known disease rather than with undiagnosed MSK pain. No studies specifically addressed children with joint swelling. No study provided a complete investigation on accuracy modifiers. No studies examined clinically important outcomes such as the impact of the test results on referrals, ordering of additional tests, patient management, and patient and parent anxiety levels.

Because the Sn and Sp of these tests have yet to be verified, current evidence does not support their use as diagnostic tests for children with undiagnosed MSK pain. They have a potential application as an adjunct to a clinical assessment that suggests the presence of an inflammatory arthritis or connective tissue disease.

Future Research

The following general recommendations for future research are based on the preceding discussion of the evidence.

- In order to better understand the natural history of undiagnosed MSK pain in children and the probability of a diagnosis of JIA or pSLE in this population, prospective cohort studies of children and adolescents with MSK pain are needed. Given the low prevalence of JIA or pSLE, a sufficiently large number of participants is required.
- For the research to be generalizable, researchers need to use consistent test methodology and cutoffs as well as consistent and well-accepted clinical criteria for the diagnoses of JIA and pSLE.
- Potential accuracy modifiers of test performance need to be examined, including age, sex, race, history of recent infections, presence of clinical characteristics other than MSK pain (e.g., morning stiffness, joint swelling, uveitis, malar rash, cytopenias).
- The clinical impact of these tests (e.g., referral decisions, additional tests ordered, clinical management, quality of life, psychological distress of child and/or parents) should be assessed in cohort studies.
- Efforts are needed to improve the overall quality of reporting of primary studies of diagnostic test accuracy. The STARD checklist includes 25 items that address the level of detail that should be specified within such studies including descriptions of participants, tests methods, statistical methods, and results.⁵⁶ This could be considered as a guide for authors reporting studies that evaluate diagnostic tests.

Table A. Summary of evidence of the diagnostic characteristics of ANA, RF, and CCP tests for pSLE and JIA in children with undiagnosed MSK pain

Key Questions	N Studies, Sample Size	Sensitivity Range (median)*	Specificity Range (median)	PPV Range (median)	NPV Range (median)	Strength of Evidence
KQ 3: Test performance						
3.1 ANA – pSLE	2 case-control, 201	91–100%	84–85%	71–84%	96–100%	Insufficient
3.2 ANA – JIA	8 case-control, 1,382	1–62% (54)	73–100% (95)	88–100% (96)	15–70% (30)	Insufficient
3.3 RF (IgM) – pSLE	1 case-control, 46	29%	88%	50%	74%	Insufficient
3.4 RF (IgM) – JIA	1 cohort study, 437 15 case-control, 1,647	5% 0–35% (11)	98% 94–100% (100)	45% 0–100% (100)	77% 20–71% (48)	Low Insufficient
3.5 CCP – pSLE	No studies					Insufficient
3.6 CCP – JIA	7 case-control, 1,643	2–42% (6)	93–100% (100)	20–100% (100)	11–71% (28)	Insufficient
KQ 4: Accuracy modifiers	No studies	NA	NA	NA	NA	Insufficient
KQ 5: Clinical impacts	No studies	NA	NA	NA	NA	Insufficient

*Median not presented if ≤ 4 studies.

ANA = antinuclear antibody; CCP = cyclic-citrullinated peptide; IgM = immunoglobulin M; JIA = juvenile idiopathic arthritis; KQ = Key Question; MSK = musculoskeletal; N = number; NA = not applicable; NPV = negative predictive value; PPV = positive predictive value; pSLE = pediatric systemic lupus erythematosus; RF = rheumatoid factor

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This executive summary is part of the following document: Wong KO, Bond K, Homik J, Ellsworth JE, Karkhaneh M, Ha C, Dryden DM. Antinuclear Antibody, Rheumatoid Factor, and Cyclic-Citrullinated Peptide Tests for Evaluating Musculoskeletal Complaints in Children. Comparative Effectiveness Review No. 50 (Prepared by the University of Alberta Evidence-based Practice Center under Contract No. HHS 290-2007-10021-I). AHRQ Publication No. 12-EHC015-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

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