Evidence-based Practice Center Systematic Review Protocol

Project Title: Antinuclear Antibody, Rheumatoid Factor, and Cyclic-Citrullinated Peptide Testing for the Evaluation of Musculoskeletal Complaints in Pediatric Populations

I. Background and Objectives for the Systematic Review

Childhood musculoskeletal (MSK) pain is common, with estimated prevalences in the general pediatric population ranging from 5 to 30 percent.[1] Despite their prevalence, most complaints of MSK pain in children and adolescents are benign in nature. MSK pain can be difficult for children to characterize and can cause children and parents great anxiety; the pain in otherwise healthy children can persist for several months or even years. In addition to concerns about physical pain, parents may worry about risks for future disability in their children, prompting visits to their pediatricians for evaluation, treatment, and reassurance.

Causes of MSK pain are divided into nonrheumatic and rheumatic categories. Nonrheumatic causes are generally benign and self-limited and are generally attributable to trauma (sprains and strains), overuse, normal skeletal growth variation, and growing pains. In contrast, rheumatic causes may be chronic and require early diagnosis and treatment to prevent progression and disability. Rheumatic causes of MSK pain include juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), spondyloarthropathies (including enthesitis, juvenile anklyosing spondylitis, and reactive arthritis), acute rheumatic fever, and Henoch-Schonlein purpura. However, MSK pain is neither a necessary nor sufficient indicator of rheumatic diseases (for instance, approximately 15 percent of children with JIA do not report pain[2]).

Diagnoses of both rheumatic and non-rheumatic diseases are made only after an appropriate patient history and physical examination. To support a clinical diagnosis, physicians who are presented with a child with MSK pain or limb or joint swelling may use serological tests such as antinuclear antibody (ANA), rheumatoid factor (RF), cyclic citrullinated peptide (CCP), erythrocyte sedimentation rate, and C-reactive protein. The ANA, RF, and CCP tests are commonly used in adults in the workup of SLE and inflammatory arthritis. In general, physicians have assumed a similar diagnostic utility in diagnosing childhood rheumatic conditions.

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The indirect immunofluorescence ANA (FANA) test involves incubation of serial dilutions of the patient's sera with substrate cells (commonly human epithelial tumor line or HEp-2). If antibody to nuclear elements is present, binding to the substrate is detected by fluorescein conjugated antihuman immunoglobulin, which attaches to the antibody and is visualized by using a fluorescence microscope. The test results are the highest dilution titer at which binding is still present and a description of the pattern of staining. The pattern is expressed as homogeneous, rim, or speckled.[3] An ANA test is commonly used to screen for autoimmune conditions[4] and the test is often used in both adults and children where a diagnosis of SLE is considered.

The rheumatoid factor (RF) test is the most commonly used serological test to determine the presence of RF antibodies. RFs are immunoglobulins (Ig) that are reactive specifically with the Fc fragment of the IgG molecule. RFs are found in all Ig isotypes (e.g., IgA, IgG, IgD, IgM, and IgE), but 19S IgM RF is the most frequently used isotype.[4] The presence of RFs is typically determined by agglutination assays, nephelometry, or enzyme-linked immunosorbent assay (ELISA) tests.[5] Agglutination tests detecting IgM RF are commonly used in laboratory diagnosis of RA. This test method employs latex, charcoal, or human erythrocytes as carrier molecules to which human or rabbit IgG is bound. Nephelometry is a quantitative test in which latex particles are coated with human IgG that captures RF. Complexes formed between the IgG and RF are detected by light scattering, which is dependent upon the concentration of immune complexes formed. The ELISA test is a solid phase assay that detects IgM and IgA RF when human IgG Fc is used as the substrate and detects IgM, IgG, and IgA RF if rabbit IgG is used as the substrate.[6] Latex agglutination and nephelometry only measure 19S IgM RF, whereas ELISAs have been designed to measure the various RF isotypes.[4] Though the biological function of RF is unclear, RF has been used in both adults and children as a marker for rheumatoid arthritis.

The CCP test detects the presence of autoantibodies to citrullinated peptides found in the patient's blood serum.[6] Abnormal citrullination of various peptides is present in a variety of human diseases, including RA, psoriasis, and multiple sclerosis; however, the formation of antibodies to citrullinated peptides seems to be specific for RA patients.[7] Anti-CCP2 (a second-generation assay) is currently the most widely used anti-citrullinated peptide assay.[7] Anti-CCP antibodies and anticitrullinated filaggrin antibodies are locally produced in inflamed joints, and citrullinated fibrin is found in the synovia of patients with rheumatoid arthritis.[8] In adults, a CCP test is usually ordered along with an RF test when a patient has previously undiagnosed

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inflammatory arthritis or has been diagnosed with undifferentiated arthritis. A CCP test may also be ordered as a follow-up to a negative RF test when clinical signs, such as symmetrical joint pain and inflammation, lead the physician to suspect RA.

A fear of missing a rheumatic disease and potentially delaying treatment or a lack of confidence or expertise in the MSK physical exam may motivate primary care physicians to request serologic tests.[9,10] However, in children who do have a rheumatic disease such as JIA, serologic tests, especially RF, may be negative, leading the physician and family to a false sense of security and resulting in a delay in diagnosis and referral. In addition, overuse of these serologic tests could escalate the economic and social burden of medical care, while requests for further testing and consultation may increase anxiety for the patient and family.

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA), formerly juvenile rheumatoid arthritis (JRA), is an autoimmune-inflammatory disease of unknown etiology that affects as many as 1 in 1,000 children worldwide.[11,12] The American College of Rheumatology (ACR),[13] the European League Against Rheumatism (EULAR),[14] and the International League of Associations for Rheumatology (ILAR)[15] have developed classification criteria that are frequently used to classify patients under 16 years of age with chronic arthritis.[16] The classification criteria for JIA developed jointly by the ILAR and ACR[17] includes seven subtypes: systemic arthritis, oligoarthritis, polyarthritis (RF Negative), polyarthritis (RF Positive), psoriatic Arthritis, enthesitis related arthritis, undifferentiated arthritis.[15] Diagnosis of JIA currently relies on clinical symptoms and signs[11,15,17] however, serological tests for RF antibodies,[18,19] and more recently, CCP antibodies are frequently requested as part of the diagnostic work up based on their utility in the diagnosis of Rheumatoid Arthritis in adults.[7,19] Although the pathophysiological link is not yet fully understood, the presence of RF may be the body's response to the chronic inflammation of JIA, and may therefore be found in other inflammatory and infectious diseases. Without effective treatment, JIA can progress and cause damage to cartilage, bone and soft tissues, and may lead to severe disability and functional loss, and, in rare instances, organ failure and death.[7,12] Although early diagnosis and treatment may reduce the progression of the disease and induce remission, only a small proportion of patients experience complete resolution of JIA prior to adulthood.[12]

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Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE), is an episodic (i.e., intermittent symptoms), multisystem, autoimmune disease characterized by widespread inflammation of blood vessels and connective tissues and by the presence of antinuclear antibodies.[20] Adult studies have estimated the incidence of SLE at 2.0 to 7.6 per 100,000 per year and the prevalence at 12 to 50 per 100,000 individuals. Data on children are few,[12] but pediatric data suggest an estimated incidence of SLE to be 0.36 per 100,000.[21] The onset of SLE is rare before 5 years of age and uncommon before adolescence, after which it becomes almost as frequent as in any subsequent decade.[20] The diagnosis of SLE in a child is based on clinical presentation and laboratory test results. The ANA test is the primary screening test for SLE: an abnormal FANA titre with a homogeneous or speckled pattern is considered a marker of SLE and is one of the ACR diagnostic criteria.[22] Left untreated, SLE is often progressive and has a significant fatality rate.[23] The prognosis for an individual child with SLE is relatively unpredictable, and generalizations about prognosis are especially unreliable during the first 24 months after diagnosis.[20] As awareness of the occurrence of SLE in children has increased, early diagnosis has become more common[20] and rapid introduction of aggressive immunosuppressive treatment may lead to an improved outcome.[23]

To support a diagnosis of either JIA or SLE, the ideal serologic test would have high sensitivity (to screen out non-disease individuals), specificity (to differentially diagnose those with the target disease), positive predictive value (probability of positive results correctly identifying those with the disease), and negative predictive value (probability of negative results correctly identifying those without the disease). For the general pediatrician using ANA, RF, and CCP tests, some of the most important questions are who should be tested and how positive and negative results should be interpreted.[3]

A preliminary literature scan indicated that the availability of evidence may vary depending on the tests and conditions of interest. Though there is good evidence regarding the performance characteristics and use of ANA, RF, and CCP tests in the adult population, there is considerable uncertainty with respect to these aspects of the tests in the pediatric population with undiagnosed MSK complaints. The scan identified two systematic reviews examining the use of ANA testing in JIA, one focused specifically on this topic and one examining serological markers in general for JIA. No systematic reviews examining ANA for pediatric SLE or RF and CCP testing for JIA were identified. As a result, a systematic review of ANA, RF, and CCP tests

for these conditions is required to reduce uncertainty regarding the quality and quantity of evidence regarding the test performance characteristics and the impact of the test results on physician decision making and patient important outcomes.

Objectives of This Review

The overall goal of this systematic review is to identify and appraise all relevant research evidence and to summarize what is known about the diagnostic performance and test result impacts of the ANA, RF, and CCP testing for systematic lupus erythematosus and juvenile idiopathic arthritis in children and adolescents (<18 years) presenting with MSK symptoms. More specifically, the diagnostic accuracies (such as sensitivity, specificity, and positive and negative predictive values) and the impact of test results on clinical practice and patient/parents' anxiety level of these immunologic tests will be examined. The key questions below (Section II) will be explored and answered through a systematic review. The systematic review is intended for a broad audience, including clinicians, policymakers and funding agencies, professional societies developing clinical practice guidelines, patients and their care providers, and researchers conducting studies on the utilization of antibody testing for rheumatic diseases in the pediatric population. The evidence generated from this review may enhance the clinical understanding of the properties and proper interpretations of the tests, assist in the development of clinical guidelines for pediatric populations, and highlight information gaps which can serve as a basic framework for future research.

II. The Key Questions

The Key Questions (KQs) were posted for public comment on the AHRQ Effective Health Care Program website. No comments were received from public posting. The KQs to be investigated in this systematic review are presented below.

KQ.1:

a. What is the incidence and prevalence of undiagnosed musculoskeletal (MSK) pain and/or joint swelling in children and adolescents aged less than 18 years?
b. What is the incidence of positive results in antinuclear antibody (ANA), rheumatoid factor (RF), and cyclic citrullinated peptide (CCP) test in healthy normal children and adolescents aged less than 18 years?

KQ.2: What is the natural history of undiagnosed MSK pain and/or joint swelling in children and adolescents aged less than 18 years?

a. The frequency of subsequent diagnosis of SLE or JIA
b. The frequency of subsequent diagnosis of non-inflammatory conditions
c. The frequency of subsequent resolution of symptoms

KQ.3: What are the diagnostic performance characteristics of the ANA, RF, and CCP testing against the clinical diagnoses for SLE and JIA in children and adolescents aged less than 18 years with undiagnosed MSK pain and/or joint swelling?

a. The sensitivity and specificity of ANA, RF, and CCP for SLE
b. The sensitivity and specificity of ANA, RF, and CCP for JIA
c. The positive and negative predictive values of ANA, RF, and CCP for SLE
d. The positive and negative predictive values of ANA, RF, and CCP for JIA

PICO components:

- Population(s): Children aged less than 18 years with undiagnosed limb pain and/or joint swelling
- Interventions: ANA, RF, or CCP test
- Comparator: Clinical diagnosis
- Outcomes: Sensitivity, specificity, and positive and negative predictive values

KQ.4: How do the demographic and clinical factors modify sensitivity, specificity, and positive and negative predictive values of in children and adolescents aged less than 18 years with undiagnosed MSK pain and/or joint swelling?

a. Sex
b. Age
c. Race/ethnicity
d. Co-morbidities
e. Recent infections

PICO components:

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- Population(s): Children aged less than 18 years with undiagnosed limb pain and/or joint swelling
- Interventions: ANA, RF, or CCP test
- Comparator: Clinical diagnosis
- Outcomes: Sensitivity, specificity, and positive and negative predictive values

KQ.5: What are the impacts of positive and negative test results for children aged less than 18 years with undiagnosed MSK pain and/or joint swelling on the following outcomes:

a. Referrals
b. Additional tests
c. Management
d. Parent and patient anxiety due to clinical uncertainty and additional tests

PICO components:

- Population(s): Health care providers (for referral, additional tests, and management) and parents and patients (for anxiety due to clinical uncertainty and additional tests).)
- Interventions: Clinical diagnosis with knowledge of ANA, RF, or CCP test results (positive or negative)
- Comparator: Clinical diagnosis without knowledge of ANA, RF, or CCP test results
- Outcomes: Referrals, additional tests, change in management, and levels of anxiety in parents and/or patients related to the knowledge of test results

III. Analytic Framework

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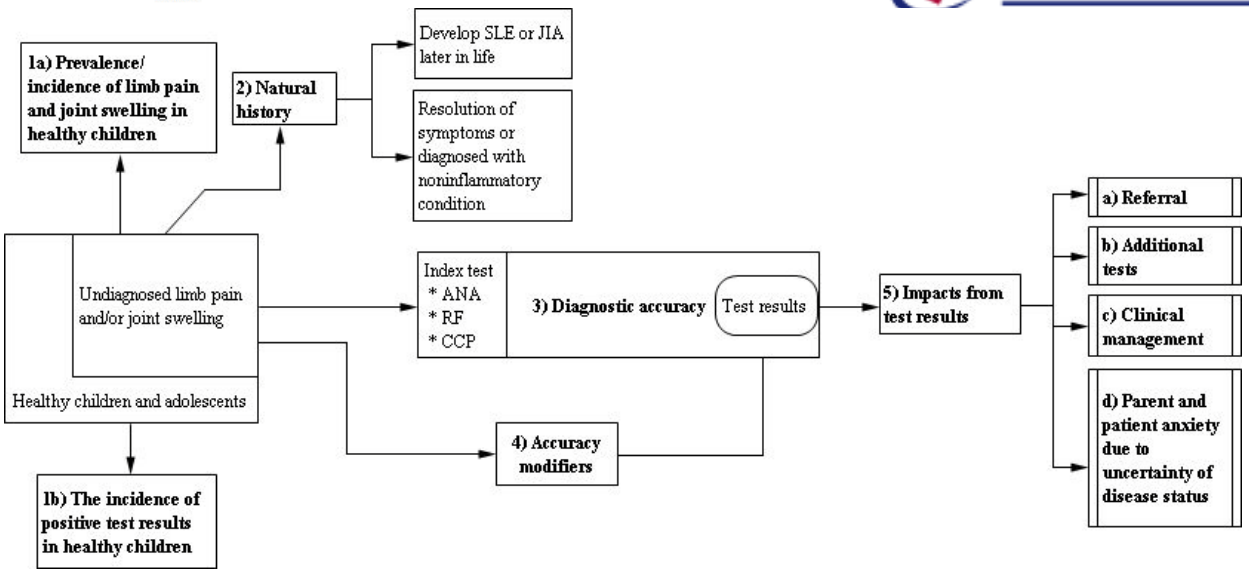

Figure 1: Flow diagram of analytic framework of ANA, RF, and CCP testing for SLE and JIA in children and adolescents aged less than 18 years

IV. Methods

The approach for this systematic review is described below. They follow the methods suggested in the Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews, Version 1.0 published by AHRQ (available at http://effectivehealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf), and the AHRQ Guidance for the Evaluation of Medical Tests (draft in development).

A. Literature Search Strategies

The research librarian, in collaboration with the investigative team, will develop and implement search strategies designed to identify evidence relevant to questions of efficacy, effectiveness and safety.

As noted in the background section, patients with JIA can have symptoms of MSK pain and joint swelling independently or concurrently. The search strategy is designed to capture studies including participants with the different manifestations of these symptoms. Key questions 1 and 2 will be addressed in a narrative approach by locating the most relevant and up-to-date prevalence, incidence, and natural history data for North American children (<18 years). For key questions 3, 4, and 5, a full systematic review process will be carried out and comprehensive searches will be conducted in the following electronic databases: Ovid MEDLINE®, Cochrane

Central Register of Controlled Trials, Cochrane Database of Systematic Reviews (CDSR), Embase, CINAHL®, Science Citation Index Expanded® and Social Sciences Citation Index®(both via Web of Science®), Academic Search Complete, Proquest Dissertations & Theses, and OCLC PapersFirst. A diagnostic search filter and a child filter will be applied when appropriate.

The main search strings are as follows: (arthritis OR "lupus erythematosus" OR pain OR fibromyalgia OR "benign joint hypermobility" OR "joint instability" OR "patellofemoral pain syndrome" OR "arthralgia" OR "limb pain" OR "synovitis" OR "JIA" OR "JRA" OR "JSLE" OR "joint swelling") AND (child* OR infant* OR kid* OR toddler* OR adoles* OR teen* OR pubescen* OR puberty* OR p?ediatric) AND (screening OR "natural history" OR "incidence" OR "prevalence" OR "referral" OR diagnosis OR "predictive value of tests" OR "reproducibility of results" OR "sex factors" OR "age factors" OR anxiety OR comorbidity) AND (" ANA test" OR "FANA test" OR "antinuclear antibod*" OR "rheumatoid factor*" OR "cyclic citrulline peptide" OR "anticyclic citrullinated peptide" OR "anti-CCP") (Appendix A).

In addition to the searches of electronic databases, we will also search the following proceedings from the following scientific meetings: American College of Rheumatology, Joint meeting of the British Society for Rheumatology, Canadian Rheumatology Association, European Congress of Rheumatology (EULAR), International League of Associations for Rheumatology (ILAR), and the American Academy of Pediatrics for 2005-2010. Additionally, the bibliographies of the included studies and reviews will be searched for relevant studies. Search alerts for PubMed and Web of Science will be set up to identify any new and potentially relevant studies during the course of the review.

Results from the literature searches will be entered into a Thomson Reuters Reference Manager 11.0.1® bibliographic management database.

B. Literature Selection

Liberal Screening

In the initial screening, each article will be screened by two independent reviewers who will judge the relevance of the study based on its title and abstract using prespecified screening criteria. Articles will be rated as "include", "exclude", or "unsure". The full text of studies rated as "include" or "unsure" by both reviewers will be retrieved. Disagreements between reviewers will

resolved through discussion between the two reviewers, a third party adjudication will be applied if consensus is not achieved.

Literature Selection: Detailed Evaluation

Each "include" and "unsure" article will then be examined by two independent reviewers using a standard inclusion/exclusion form. This form will be based on the more extensive and specific set of criteria to further determine the relevance of the studies. Each reviewer will once again rate the article as "include", "exclude", or "unsure". While there is no restriction on study design and language, included studies must have sufficient data to complete a 2x2 table for diagnostic accuracy or to provide information on test impact in the target population. Disagreements between the reviewers will be resolved through discussion or, if needed, by third party adjudication. Articles screened in after this inclusion/exclusion stage will constitute the evidence base of this systematic review.

Table 1. Inclusion and Exclusion Criteria

Category	Criteria
Source	• Studies reporting original research • Any language
Population	• The study provides separate data for a population consisting of children (<18 years) with diagnosed JIA or SLE, undiagnosed limb pain or index test results
Design	• Two or more participants • Diagnostic randomized controlled trial: Studies randomly assigned participants into receiving either the test or the reference standard. And the subsequent patient-related outcomes are compared • Cohort: Studies with pediatric population presented with MSK pain and/or joint swelling • Case control: Consist of both disease group and a reference group which can either be healthy children or disease comparator
Test	• Studies of ANA, RF, or CCP • The assay method of ANA using animal substrate is excluded • The test of hidden RF is excluded
Comparator	• Diagnosis based on clinical criteria, e.g., American Rheumatological Association, International League of Associations for Rheumatology
Outcomes of interest	• For KQs 3 and 4: Study must provide sufficient data to derive the true positive, true negative, false positive, and false negative

- For KQ 5: Study must provide at least a narrative description although adjunct with numerical data is more preferable.

C. Assessment of Methodological Quality

The methodological quality of each included study will be determined using the quality assessment tool described by the Cochrane Collaboration Diagnostic Test Accuracy Review Group.[24] This tool is a modified version of the Quality Assessment of Studies of Diagnostic Accuracy (QUADAS) tool [25] and consists of 11 items that assess important common biases in diagnostic studies including selection bias, spectrum bias, incorporation bias, verification bias, and review bias. Two reviewers will perform quality assessment independently for each included studies. Decision rules regarding application of the assessment tool will be developed a priori. Discrepancies will be resolved through discussion or third party adjudication as needed.

D. Data Collection

Data will be abstracted by a single reviewer using a standard data extraction form and verified by a second reviewer. Reviewers will resolve any discrepancy in data extraction by consensus or, if needed, third party adjudication. In general, extracted data will include details of study design, inclusion/exclusion criteria for the study population, population demographics (i.e., age, sex, ethnicity, comorbidities, and recent infections), diagnostic tools, and results obtained for the prespecified outcomes.

E. Data Analysis and Synthesis

Characteristics of the included studies will be summarized using descriptive statistics (i.e., proportions and percentages for categorical data; means with standard deviations [SD], or medians with interquartile ranges [IQR], for continuous data).

For the question related to the diagnostic test performance of ANA, RF, and CCP, two-by-two tables (or one-by-two if only reference standard positive or reference standard negative subjects are included) will be constructed for each comparison test or combination of tests within the individual studies. Sensitivity and specificity will be calculated for each study using standard formulas. If possible, results will be graphed in forest plots for visual analysis, and, if appropriate, pooled statistically. Individual study results will be pooled when two or more studies have assessed the same test for similar purposes, have similar study design (e.g., prospective or retrospective), and have usable data for common outcomes of interest.

Data on diagnostic performance will also be synthesized using the hierarchical summary receiver operating characteristic (HSROC) approach, which is a measure of test accuracy.[26] The ROC curve is a plot of true positive rate (sensitivity) versus the false positive rate (1 - specificity) for various possible cutpoints of a diagnostic test. The closer the curve follows the left hand and top borders of the ROC curve space, the more accurate the test is, while a test of lower accuracy will come closer to the 45 degree diagonal. Thus, the area under the curve is indicative of the accuracy of a diagnostic test, where area of 1.0 represents a perfect test; an area of 0.5 represents a worthless test.

Evidence tables and descriptive analyses will be presented for each rheumatic condition and then by antibody test. For each of the questions concerning the diagnostic characteristics of the specified tests, we will develop 2x2 tables and compute sensitivity, specificity, predictive values, and likelihood ratios. Where possible, subgroup analyses will be conducted based on age, sex, race/ethnicity, co-morbities, and recent infections.

F. Grading the Evidence

For this diagnostic test accuracy review, evidence will be graded for KQ.3, KQ.4 and KQ.5 using the AHRQ system for grading the strength of evidence (AHRQ Guidance for the Evaluation of Medical Tests [draft in development].

As this system has only been developed for reviews of treatment interventions, where appropriate the grading system will be modified following the GRADE system for rating the quality of evidence and strength of recommendations for diagnostic tests.[27] The strength of the study designs, quantity and quality of individual studies, and consistency and precision of the results will be evaluated. The directness of evidence will also be assessed. The strength of evidence for primary (diagnostic test performance) and secondary (test referrals, additional test, change in patient management, and parent and patient anxiety) outcomes will be graded as high, moderate, low, or insufficient.[28] Key characteristics for determining the applicability of the findings (such as patient populations, settings, and disease status) will also be summarized.

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VI. Definition of Terms

- Antinuclear antibody test (ANA): The measure of serum level of antinuclear antibody which is an antibody targets against the contents of the cell nucleus.
- Rheumatoid factor test (RF): The measure of serum level of rheumatoid factor antibody which is an antibody targeting against the Fc portion of IgG.
- Anti-cyclic citrullinated peptide test (CCP): During inflammation, citrulline is incorporated enzymatically into proteins. The CCP test measures of serum level of the autoantibody targeting these citrullinated peptides.
- Juvenile idiopathic arthritis (JIA): Juvenile idiopathic arthritis is a persistent or recurring inflammation of the joints similar to rheumatoid arthritis. JIA is usually classified as pauciarticular or oligoarticular arthritis (affecting four or fewer joints), polyarthritis (affecting five or more joints), or systemic (characterized by fever, pink rash, and possible multi-organ involvement).
- Systemic lupus erythematosus (SLE): A treatable, chronic, autoimmune, inflammatory disease that can affect any organ in the body and in a pattern that varies greatly from person to person. Lupus is characterized by inflammation in various organs which causes the symptoms of lupus to appear.
- Undiagnosed limb pain and/or swelling: Patients comprising this population are most easily defined through the description of a clinical encounter. A patient with undiagnosed limb pain and/or joint swelling is considered to be a patient who presents to a general practice or family physician with limb pain (this may include a limp) with or without joint swelling. After a thorough and complete patient history and physical examination the physician is able to rule out the more obvious rheumatic diseases and make a differential diagnosis. However, the nonspecificity of the complaint and the overlapping nature of the signs and symptoms of many rheumatic diseases and noninflammatory pain syndromes make it difficult to arrive at a definitive diagnosis.
- Prevalence: The proportion of existing cases of the condition (e.g., JIA or SLE) over a defined population at a specified time.
- Incidence: The proportion of new events (e.g., diagnosis or JIA or SLE) over a defined population during a specified time period.
- Sensitivity: The ability of a diagnostic test to correctly identify those who have the condition.

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- Specificity: The ability of a diagnostic test to correctly identify those who do not have the condition.
- Positive predictive value: The proportion of patients with the target condition and tested positive over all those tested positive.
- Negative predictive value: The proportion of individuals without the target condition and tested negative over all those tested negative.

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VII. Summary of Protocol Amendments

NOTE: The following protocol elements are standard procedures for all protocols.

VIII. Review of Key Questions

For Comparative Effectiveness reviews (systematic reviews) the key questions were posted for public comment and finalized after review of the comments. For other systematic reviews, key questions submitted by partners are reviewed and refined as needed by the EPC and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed.

IX. Technical Expert Panel (TEP)

A TEP panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. The TEP provides information to the EPC to identify literature search strategies, review the draft report and recommend approaches to specific issues as requested by the EPC. The TEP does not do analysis of any kind nor contribute to the writing of the report.

X. Peer Review

Approximately five experts in the field will be asked to peer review the draft report and provide comments. The peer reviewer may represent stakeholder groups such as professional or advocacy organizations with knowledge of the topic. On some specific reports such as reports requested by the Office of Medical Applications of Research and National Institutes of Health there may be other rules that apply regarding participation in the peer review process. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for systematic reviews and Technical briefs, be published three months after the

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publication of the Evidence report.

It is our policy not to release the names of the Peer reviewers or TEP panel members until the report is published so that they can maintain their objectivity during the review process.

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APPENDIX A. MEDLINE Search Strategy

Database: MEDLINE

Notes: limits: humans, publication date: 1960-2009

Date searched: Jan 21, 2010

Results: 5389 (S116)

1	citrulline/	61	Predictive Value of Tests/
2	exp Peptides, Cyclic/	62	(di or bl or cl or im).fs.
3	117 and 118	63	exp Diagnostic Errors/
4	((anti adj ccp) or (citrullinated adj peptide*)).mp.	64	early diagnosis/
5	((citrulline adj antibod*) or (anti-citrulline adj antibod*)).ti,ab.	65	exp delayed diagnosis/
6	exp Antibodies, Antinuclear/	66	Diagnosis, Differential/
7	((antinuclear adj antibod*) or (antinuclear adj factor*)).ti,ab.	67	or/175-182
8	(ana adj titer).ti,ab.	68	(cost or costs or economic*).ti,ab.
9	(ANA adj2 test*).ti,ab.	69	exp "Costs and Cost Analysis"/
10	(FANA adj2 test*).ti,ab.	70	cost-benefit analysis/
11	exp Rheumatoid Factor/	71	ec.fs.
12	(rheumatoid adj factor*).ti,ab.	72	or/184-186
13	or/119-128	73	exp demography/
14	exp Lupus Erythematosus, Systemic/	74	age factors/ or "age of onset"/
15	(JSLE or SLE or "lupus erythematosus").ti,ab.	75	sex factors/
16	exp Pain/di, et	76	infection/ or infection*.ti,ab.
17	Growth/ph	77	anxiety/ or (anxious* or anxiety).ti,ab.
18	(grow* and (pain or pains)).ti,ab.	78	comorbidity/
19	132 and (133 or 134)	79	or/189-194
20	musculoskeletal diseases/ or arm/ or leg/ or extremities/	80	exp Rheumatic Diseases/di, co, et, im, pa, pp
21	132 and 136	81	exp Connective Tissue Diseases/di, co, et, im, pa, pp
22	Fibromyalgia/	82	exp arthritis/di, co, et, im, pa, pp
23	fibromyalgia.ti,ab.	83	arthritis, rheumatoid/di, co, et, im, pa, pp
24	exp arthralgia/	84	arthritis, juvenile rheumatoid/di, co, et, im, pa, pp
25	arthralgia.ti,ab.	85	exp Lupus Erythematosus, Systemic/di, co, et, im, pa, pp
26	((joint* adj pain*) or (limb* adj pain*)).ti,ab.	86	or/196-201
27	limp*.ti,ab.	87	exp infant/
28	benign.ti,ab.	88	(Infant* or infancy or Newborn* or Baby* or Babies or Neonat* or Preterm* or Prematur* or Postmatur*).mp.

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29	exp Joint Instability/	89	exp Child/
30	(joint adj (instability or hypermobility)).ti,ab.	90	(Child* or Schoolchild* or School age* or Preschool* or Kid or kids or Toddler*).mp.
31	144 and (145 or 146)	91	exp Adolescent/
32	Patellofemoral Pain Syndrome/	92	Adoles*.mp.
33	(patellofemoral adj pain adj syndrome).ti,ab.	93	(Teen* or Boy* or Girl*).mp.
34	exp Synovitis/ or synovitis.mp.	94	exp Minors/
35	(joint* adj (swell* or inflamm*)).tw.	95	minors*.mp.
36	(swollen adj joint*).tw.	96	exp Puberty/
37	or/130-131,135-143,147-152	97	(Pubert* or Pubescen* or Prepubescen*).mp.
38	Arthritis/	98	exp Pediatrics/
39	($arthritis or ($articular adj arthritis)).ti,ab.	99	(Pediatric* or Paediatric* or Peadiatric*).mp.
40	or/154-155	100	exp Schools/
41	exp child/ or (adolesc* or early or juvenile).ti,ab.	101	(Nursery school* or Kindergar* or Primary school* or Secondary school* or Elementary school* or High school* or Highschool*).mp.
42	(JIA or JRA).ti,ab.	102	or/203-217
43	or/157-158	103	adolescent/ and adult/
44	156 and 159	104	218 not 219
45	exp Arthritis, Juvenile Rheumatoid/	105	(170 or 174) and 153 and 220
46	((juvenile or early) adj (rheumatoid or idiopathic) adj arthritis).ti,ab.	106	129 and 220 and 183 and (202 or 164)
47	or/160-162	107	129 and 164 and 220
48	or/130-131,135,137-143,147-152,163	108	129 and (174 or 183) and 164 and 220
49	incidence/	109	129 and 195 and 220
50	prevalence/	110	(129 or 202) and 188
51	exp disease progression/	111	129 and (153 or 163) and 220
52	Natural History/	112	195 and 183 and 129 and 220
53	natural history.ti,ab.	113	(170 or 174) and (163 or 202) and 220
54	or/165-169	114	129 and (174 or 183) and 188
55	exp Mass Screening/	115	129 and 188
56	exp "referral and consultation"/	116	or/221-231
57	(screen* or refer*).ti,ab.	117	humans/ and animals/
58	or/171-173	118	232 not 233
59	exp "Reproducibility of Results"/	119	234 not 116
60	exp "Sensitivity and Specificity"/	120	from 235 keep 1-2

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