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Draft Comparative Effectiveness Review

Number XX

Antinuclear Antibody, Rheumatoid Factor, and Cyclic-citrullinated Peptide Tests for the Evaluation of Musculoskeletal Complaints in Pediatric Populations

Prepared for:
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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (http://www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Structured Abstract

Objectives: To assess the test performance of antinuclear antibody (ANA), rheumatoid factor (RF), and cyclic-citrullinated peptide (CCP) tests in children and adolescents with undiagnosed musculoskeletal (MSK) pain and/or joint swelling, compared with clinical diagnoses of pediatric systemic lupus erythematosus (pSLE) and juvenile idiopathic arthritis (JIA). To explore the difference in test performance for accuracy modifiers including age, sex, race/ethnicity, comorbidities, and recent infections. 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.

Data Sources: A systematic and comprehensive literature search was conducted in nine electronic databases. Additional searches were conducted through hand searching reference lists and conference proceedings. There were no restrictions on language, year of publication, and study design.

Review Methods: Study selection, quality assessment, data extraction, and grading the evidence were conducted independently by two reviewers. A combination of qualitative and quantitative approaches was used to synthesize the data. Sensitivity (Sn), specificity (Sp), positive predictive value, and negative predictive value were calculated.

Results: The search identified 10,512 citations; 29 were included in the review. Only one retrospective cohort study provided direct evidence on test performance in children with MSK pain. The remaing 28 case control studies provided indirect evidence. Two studies on ANA for pSLE reported Sn and Sp ranging from 91 to 100 percent and 84 to 85 percent, respectively. Eight studies on ANA for JIA reported Sn and Sp ranging from 1 to 62 percent and 73 to 100 percent, respectively. Sixteen studies on RF for JIA reported Sn and Sp ranging from 4 to 50 percent and 67 to 100 percent, respectively. Eight studies on CCP for JIA reported Sn and Sp ranging from 2 to 42 percent and 85 to 100 percent, respectively. Generally for the three tests, Sn was poor and inconsistent, and Sp was consistently high.The strength of evidence ranged from insufficient to moderate. There was no evidence addressing the prespecified accuracy modifiers or clinically important outcomes.

Conclusions: There is generally a lack of consistent and sufficient evidence to determine the diagnostic performance, applicability, and clinical utility of these tests in children with MSK pain. Indirect evidence showed that in general ANA, RF, and CCP tests were specific but not sensitive, with the exception of ANA for pSLE. Based on the available evidence, these tests should not be considered diagnostic tools by themselves. The high Sp suggests their potential application as an adjunct to clinical assessment if the clinical assessment is suggestive of an inflammatory arthritis or connective tissue disease.

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Executive Summary

Background

Musculoskeletal (MSK) pain is common in children and adolescents, with estimated prevalence ranging from 5 to 30 percent.[1] MSK pain is a common reason for children accessing medical care and can affect physical, psychological, and social function.[2]

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.[3] Rheumatic causes are infrequent, generally chronic, and require accurate, timely diagnosis, and effective intervention to prevent progression and long-term damage.[4] Our systematic review examines the diagnostic accuracy of three tests antinuclear antibody (ANA), rheumatoid factor (RF), or cyclic-citrullinated peptide (CCP) for two common rheumatic conditions: pediatric systemic lupus erythematosus (pSLE) and juvenile idiopathic arthritis (JIA). Although the combination of physical examination and patient history is an effective diagnostic approach for pediatric rheumatic diseases, ANA, RF, or CCP tests are often used as a part of the diagnostic strategy. However, the evidence for the diagnostic performance and clinical usefulness of these tests has not been systematically reviewed.

Key Questions

The primary objective of this report was to synthesize the evidence for five Key Questions (KQs) related to the diagnostic performance and clinical impact of ANA, RF, and CCP tests for the diagnosis of pSLE and JIA in children and adolescents aged 18 years or less presenting with undiagnosed MSK symptoms. The evidence generated from this review may enhance the understanding of the test characteristics and proper interpretation, assist in the development of clinical guidelines for pediatric conditions, and identify gaps in the current body of knowledge. In this review, the five KQs were addressed using two different approaches. KQs 1 and 2 provided background information and thus were examined through a narrative (nonsystematic review) approach; KQs 3, 4, and 5 served as the main focus of this review by investigating the test diagnostic performance and clinically important impacts, and were addressed through a systematic review approach.

Key Question 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?

Key Question 2: Natural history

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

Key Question 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, specificity, and positive and negative predictive values) 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 (sensitivity, specificity, and positive and negative predictive values) 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 (sensitivity, specificity, and positive and negative predictive values) 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 (sensitivity, specificity, and positive and negative predictive values) 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 (sensitivity, specificity, and positive and negative predictive values) 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 (sensitivity, specificity, and positive and negative predictive values) of CCP for JIA compared with a clinical diagnosis?

Key Question 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 (sensitivity, specificity, and positive and negative predictive values) 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 (sensitivity, specificity, and positive and negative predictive values) of ANA, RF, and CCP for JIA compared with a clinical diagnosis?

Key Question 5: Clinical impacts of test results

KQ-5. 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

We searched electronic databases including 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. In addition, we searched conference proceedings from key scientific meetings, grey literature, and reference lists of included studies.

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 retrieved, and two reviewers independently assessed each study using a standardized inclusion/exclusion

form. Disagreements were resolved by discussion or third party adjudication, as needed. Two reviewers independently assessed the methodological quality of individual studies using the Quality Assessment of Studies of Diagnostic Accuracy (QUADAS) tool.[5] Data were extracted by one reviewer and verified by another using a standardized data extraction form. Disagreement was resolved through discussion or third party adjudication.

The diagnostic characteristics, including sensitivity (Sn), specificity (Sp), positive predictive value (PPV), and negative predictive (NPV), were examined for each study. Forest plots and hierarchical summary receiver operating characteristic (HSROC) curves were presented to summarize the performance for each test-disease pairing. Accuracy modifiers including age, sex, race/ethnicity, recent infection, and comorbidity were analyzed if studies provided sufficient data to calculate Sn and Sp. Any qualitative or quantitative information on clinically important outcomes including referral, additional tests ordered, change in clinical management, and patient/parent anxiety due to the test results were examined.

Two reviewers independently assessed the strength of evidence for KQs 3, 4, and 5 using the AHRQ system for grading the strength of evidence. Assessments were based on the quantity and quality of individual studies, the directness of evidence, and the consistency and precision of the results. For all studies, the outcomes were measures of test accuracy (i.e., Sn, Sp). For each outcome the strength of evidence was graded as high, moderate, low, or insufficient.

Results

Key Question 1.1. The prevalence of undiagnosed musculoskeletal pain in children and adolescents

The prevalence of MSK pain ranged between 2 and 52 percent[6-9] and increased steadily throughout childhood and adolescence.[10,11] The rate of increase in prevalence and type of MSK pain differed by sex.[11-17]

Key Question 1.2. The prevalence of test positivity in healthy children and adolescents

The prevalence of positive ANA in healthy children and adolescents ranged from 0 to 18 percent.[18-26] The prevalence of positive RF in healthy children was estimated at 3 percent.[27] We did not identify any studies that examined CCP positivity in healthy children and adolescents.

Key Question 2. The etiology and resolution of pediatric musculoskeletal pain

Noninflammatory etiologies accounted for the MSK pain in almost all (97 percent) children seen in a primary care setting.[28] Physical trauma was the most common noninflammatory cause and accounted for 44 percent of pediatric cases with MSK symptoms. In contrast, only 3.3 percent of pediatric cases of MSK pain were 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 body sites.

Key Question 3.1. Antinuclear antibody for pediatric systemic lupus erythematosus

There was no direct evidence addressing this KQ since no study examined children with undiagnosed MSK pain and/or joint swelling. Two case control studies[29,30] including 201 children (67 pSLE, 134 controls) examined the use of the ANA test for pSLE. The Sn was 91 and 100 percent, and Sp was 84 and 85 percent. The PPV was 71 and 84 percent, and the NPV was 96 and 100 percent. In general, spectrum composition, selection criteria, disease progression

bias, and incorporation bias were potential concerns in these studies. The overall strength of evidence was low for both Sn and Sp.

Key Question 3.2. Antinuclear antibody for juvenile idiopathic arthritis

There was no direct evidence addressing this KQ since no study examined children with undiagnosed MSK pain and/or joint swelling. Eight case control studies[29,31-37] with a total of 1,382 children (1,067 JIA, 315 controls) provided indirect evidence on the performance of the ANA test for JIA. The Sn ranged from 1 to 62 percent, and Sp ranged from 52 to 100 percent. PPV ranged from 90 to 100 percent, and NPV ranged from 15 to 70 percent. The HSROC curve indicated ANA was potentially useful in classifying children with JIA and those without JIA. In general, spectrum composition, selection criteria, and disease progression bias were potential concerns across these studies. The overall strength of evidence was rated low for Sn and moderate for Sp.

Key Question 3.3. Rheumatoid factor for pediatric systemic lupus erythematosus

One case control study[38] provided indirect evidence on this issue and included 46 children (14 pSLE, 32 controls) examined the use of the IgM-RF test for pSLE. The Sn was 29 percent, and Sp was 88 percent. The strength of evidence was rated as insufficient.

Key Question 3.4. Rheumatoid factor for juvenile idiopathic arthritis

Sixteen studies[31,33,36,38-50] with a total of 2,084 children (1,094 JIA, 993 controls) examined the performance of IgM-RF for JIA. Of these, one retrospective cohort study[48] provided direct evidence by examining a cohort of children with undiagnosed MSK symptoms. The remaining studies used a case control design. Overall, the Sn ranged from 4 to 50 percent, and Sp ranged from 67 to 100 percent, with the cohort study finding a Sn of 5 percent and a Sp of 98 percent. The PPV ranged from 45 to 100 percent, and NPV ranged from 19 to 89 percent. Despite the poor Sn, the HSROC curve indicated that the RF test was potentially useful for classifying children with JIA and those without JIA. In general, spectrum composition, selection criteria, and disease progression bias were potential concerns across these studies. The overall strength of evidence was rated as “low” for Sn and “moderate” for Sp.

Key Question 3.5. Cyclic-citrullinated peptide test for pediatric systemic lupus erythematosus

No studies addressed this question.

Key Question 3.6. Cyclic-citrullinated peptide test for juvenile idiopathic arthritis

There was no direct evidence addressing this KQ since no study examined children with undiagnosed MSK pain and/or joint swelling. Eight case control studies[33,51-57] with a total of 1,712 children (772 JIA, 940 controls) provided indirect evidence on the performance of the CCP test for JIA. Sn ranged from 2 to 42 percent. Sp ranged from 85 to 100 percent. The PPV ranged from 20 to 100 percent and NPV ranged from 11 to 76 percent. The HSROC curve did not indicate the usefulness of CCP for classifying children with and without JIA. In general, spectrum composition, selection criteria, and disease progression bias were potential concerns across these studies. The overall strength of evidence was rated as “low” for Sn and “moderate” for Sp.

Key Question 4. Accuracy modifiers of antinuclear antibody, rheumatoid factor, and cyclic-citrullinated peptide tests

There was limited evidence indicating sex and comorbidity with uveitis may result in different test performance of the ANA test for JIA.

Key Question 5. Clinical impacts of antinuclear antibody, rheumatoid factor, and cyclic-citrullinated peptide tests

No studies provided data to address this question.

Summary

While one study provided direct evidence by examining the target population of children with undiagnosed MSK pain, the remaining 28 studies only provided indirect evidence to assess the test characteristics of ANA, RF, and CCP. The studies generally indicated that the tests were very specific, but not sensitive (Table ES-1).

Antinuclear antibody test for children with undiagnosed MSK pain

No studies directly examined the question of the usefulness of ANA testing in a child with MSK pain. Although ANA had a high Sp for a diagnosis of pSLE or JIA, the results do not take into account the difference in prevalence between MSK pain and specific diagnoses of JIA and SLE in the pediatric population. The overall prevalence of MSK pain in childhood is 2 to 50 percent, compared with a prevalence of 0.1 percent for JIA and incidence of 0.28 per 100,000 children per year for pSLE. The studies included in this review showed a range of positive ANAs in healthy controls of between 0 and 27 percent (median = 3 percent based on three studies).

If children with MSK pain are assumed to have the same likelihood of a positive ANA as healthy children, then there will be many more children with MSK pain who have a positive ANA than have either JIA or SLE as a clinical diagnosis, making the positive predictive value (PPV) in this population insufficient. The evidence therefore does not support the routine testing of ANA in the population of children with MSK pain.

Rheumatoid factor test for children with undiagnosed MSK pain

The one retrospective cohort study that examined RF testing in children presenting with MSK complaints showed low Sn (5 percent) and high Sp (98 percent). As outlined for ANA testing (above), if the prevalence of JIA is low (i.e., 0.1 percent) even in a population of children with MSK complaints there will be more false positives than true positives. Furthermore, in a cohort of JIA patients, more will be RF negative than positive. This suggests that a positive test for RF has little predictive value. The evidence does not support the routine testing of RF in the population of children with MSK pain.

Cyclic-citrullinated peptide test for children with undiagnosed MSK pain

No studies directly assessed this question. This test has low Sn and high Sp, and even in a JIA cohort, the majority of children will have a negative test. A negative CCP test, like a negative RF test, may falsely reassure the patient, parent, or physician that the child does not have an inflammatory arthritis. With the low prevalence of inflammatory arthritis in a population of children with MSK pain, the predictive value of a positive CCP test will be low. The evidence does not support the routine testing of CCP in the population.

Based on the available evidence, these tests should not be considered as diagnostic by themselves. A recurring result of strong Sp and poor Sn was observed for almost all the test-disease combinations. The low Sn suggests the inappropriateness for broad screening of rheumatic diseases. The high Sp implies the tests may be useful to help confirm a suspected diagnosis. Where patient history and physical assessment by physicians strongly suggest the presence of an inflammatory arthritis or connective tissue disease, the pretest probability of the serologic tests would correspondingly increase potentially making them more useful in this group of patients. The serological tests should be considered as adjunctive tools to increase the diagnostic accuracy.

Conclusion

We conducted a systematic review to assess the diagnostic characteristiscs of ANA, RF, and CCP tests to diagnose pSLE and JIA in children with MSK pain. Virtually all the evidence was indirect as studies examined children with known disease status rather than a spectrum of children with undiagnosed MSK symptoms. The included studies generally indicated that the tests were specific but not sensitive, with the exception of ANA for pSLE. 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.

Based on the available evidence, these tests should not be considered as diagnostic by themselves. The low Sn suggests the inappropriateness of using them for broad screening in children and adolescents with MSK pain. However, the high Sp may imply their potential application in confirming a diagnosis as an adjunct to a clinical assessment that suggests the presence of an inflammatory arthritis or connective tissue disease. The serological tests may be useful as supplementary tools to increase diagnostic accuracy.

Future Research

The following general recommendations for future research are based on our assessment of the limitations of the current evidence base.

- Conduct prospective cohort studies or diagnostic randomized trials
- Include a spectrum of children and adolescents with MSK symptoms
- Include a sufficiently large number of participants in order to produce precise estimates
- Conduct multiple test measures to increase reliability
- Schedule a short duration between the index test and reference standard
- Examine potential accuracy modifier and include clinically important outcomes
- Studies examining ANA to diagnose pSLE should explicitly describe whether a positive ANA is part of the diagnostic criteria.

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.[58] This could be considered as a guide for authors reporting studies that evaluate diagnostic tests. Particularly, prospective studies should report duration between index test and reference standard, selection criteria for both disease and controls, and detailed

information regarding the index test including assay method, manufacturer, cutoff used, and any multiple measures employed.

Future studies should also consider investigating various accuracy modifiers. Accuracy modifiers allow the assessment of the robustness of the test estimates over a wide range of clinical and biological determinants. Tests might perform with greater or lesser accuracy based on specific patient characteristics, and it is important for physicians to have this knowledge in order to assess the applicability of the tests to children presenting to primary care physicians with MSK pain and/or joint swelling. Finally, future studies should include clinically important outcomes such as quality of life and psychological distress. Such outcomes are critical for decisionmaking for health care professionals and for patients and their parents.

Table ES-1. Summary of evidence of the diagnostic characteristics of antinuclear antibody, rheumatoid factor, and cyclic-citrullinated peptide tests for pediatric systemic lupus erythematosus and juvenile idiopathic arthritis

Key Questions	# 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 for pSLE	2, N = 201	91-100%	84-85%	71-84%	96-100%	Low for Sn Low for Sp
3.2 ANA for JIA	8, N = 1,382	1-62% (51%)	73-100% (95%)	88-100% (96%)	15-70% (30%)	Low for Sn Moderate for Sp
3.3 RF (IgM) for pSLE	1, N = 46	29%	88%	50%	74%	Insufficient
3.4 RF (IgM) for JIA	16, N = 2,084	4-50% (13%)	67-100% (99%)	45-100% (93%)	20-77% (47%)	Low for Sn Moderate for Sp
3.5 CCP for pSLE	No studies					Insufficient
3.6 CCP for JIA	8, N = 1,712	2-42% (8%)	85-100% (100%)	20-100% (100%)	11-76% (30%)	Low for Sn Moderate for Sp
KQ 4: Accuracy modifiers	No studies†	-	-	-	-	Insufficient
KQ 5: Clinical impacts	No studies	-	-	-	-	Insufficient

*Median is not presented if there are ≤4 studies.
†No study provided complete data on both subgroup-specific Sn and Sp.
ANA = antinuclear antibody; CCP = cyclic-citrullinated peptide; IgM = immunoglobulin M; JIA = juvenile idiopathic arthritis; PPV = positive predictive value; N = number; NPV = negative predictive value; RF = rheumatoid factor; SLE = systemic lupus erythematosus; Sn = sensitivity; Sp = specificity

Evidence Report

Introduction

Musculoskeletal Symptoms

Musculoskeletal (MSK) pain is pain that affects muscles, bones, ligaments, tendons, and nerves.[59] Childhood MSK pain is common, with estimated prevalence ranging from 5 to 30 percent.[1] However, most MSK complaints in children are due to benign causes.[3] Young children especially may have difficulty characterizing their symptoms, making accurate assessment based on the patient history difficult. In addition, the presence of MSK pain can cause anxiety among children and their parents. Concerns about serious diagnoses such as arthritis or lupus being missed and/or causing damage may prompt consultation with a physician.[60]

MSK pain can be divided into rheumatic and nonrheumatic causes. Nonrheumatic causes account for the majority of childhood MSK pain and are generally attributable to benign conditions including minor physical trauma (i.e., sprains and strains), overuse, and normal body growth.[3,61] In contrast, rheumatic causes are generally chronic and require early diagnosis and treatment to prevent progression and disability. Common rheumatic causes of childhood MSK pain include pediatric systemic lupus erythematosus (pSLE), juvenile idiopathic arthritis (JIA), spondyloarthropathies (including enthesitis, juvenile anklyosing spondylitis, and reactive arthritis), acute rheumatic fever, and Henoch-Schonlein purpura. However, MSK pain is not a prerequisite for a diagnosis of JIA, as approximately 15 percent of children with JIA do not report pain.[62]

A complete history and physical examination is generally considered to be the best tool for the diagnosis of inflammatory arthritis.[3,61] However, due to nonspecificity of symptoms in children presenting with MSK pain and lack of confidence in musculoskeletal examination, making an accurate diagnosis is sometimes difficult.[61,63] Hence, physicians may request additional laboratory tests. Serological tests such as antinuclear antibody (ANA), rheumatoid factor (RF), and cyclic-citrullinated peptide (CCP) may therefore be ordered by physicians when patients are suspected of having a rheumatic cause of childhood MSK pain. However, the diagnostic performance, usefulness, and proper interpretation in pediatric populations for these tests remain largely uncertain.

Pediatric Systemic Lupus Erythematosus and Juvenile Idiopathic Arthritis

Systemic lupus erythematosus (SLE) is an episodic, multisystem, autoimmune disease characterized by widespread inflammation of blood vessels and connective tissues.[64] It is estimated that the incidence of pediatric SLE (pSLE) is 0.28 per 100,000 children at risk per year.[65] The onset of pSLE is rare before 5 years of age and uncommon before adolescence, after which the rates of occurrence stabilize.[64] The diagnosis of pSLE is generally based on specific signs and symptoms and laboratory tests which fulfill the diagnostic criteria of the American College of Rheumatology (ACR).[66] These criteria include ANA. Left untreated, SLE is often progressive and poses a significant fatality risk.[67] As awareness of the occurrence of pSLE has increased, early diagnosis has become more common[64] and rapid introduction of effective immunosuppressive treatment has to improved outcomes.[67]

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory disease of children affecting as many as 1 in 1,000 children worldwide.[68,69] Classification criteria developed by the International League of Associations for Rheumatology (ILAR)[70] are used worldwide for

the diagnosis and have supplanted earlier classification criteria of the ACR[71] for the diagnosis of juvenile rheumatoid arthritis (JRA) and the European League Against Rheumatism (EULAR)[72] for the diagnosis of juvenile chronic polyarthritis (JCP). Therefore, in order to maintain consistency, the acronym JIA will be used to represent JIA, JRA, and JCP throughout this report. Diagnosis of JIA currently relies on the presence of characteristic signs and symptoms.[68,73] However, in adults with rheumatoid arthritis (RA), tests for RF,[74,75] and, more recently, CCP antibodies are frequently requested as part of the diagnostic work-up.[75,76] Although there is less evidence supporting the usefulness of these tests in children, they are often ordered as part of the diagnostic evaluation of a child suspected to have arthritis.

Without effective treatment, JIA can progress and cause damage to cartilage, bone, and soft tissues, and may lead to severe disability, functional loss, and rarely, organ failure and death.[69,76] Although early diagnosis and treatment may reduce the progression of the disease and induce remission, only a minority of patients experience complete resolution of JIA prior to adulthood.[69]

Antinuclear Antibody, Rheumatoid Factor, and Cyclic-citrullinated Peptide Tests

The immune system is a defense system that fends off foreign invaders including bacteria and viruses. However, the immune system may malfunction and mislabel one's own body cells as foreign particles, and this may elicit an attack response. When the immune system attacks one's own body cells, it produces autoantibodies that target specific antigens naturally found in the body. ANA, RF, and CCP are examples of the autoantibodies specifically targeting the nuclear particles, the Fc portion of the Ig G, and CCPs, respectively. Many theories have been postulated to explain the pathways of persistent overproduction of autoantibodies in rheumatic diseases.[77]

The indirect immunofluorescence ANA, or Fluorescent ANA (FANA), test involves incubation of serial dilutions of the patient's sera with substrate cells such as human epithelial tumor line (HEp-2). If antibody to nuclear elements is present, binding to the substrate is detected by fluorescein conjugated antihuman Ig, 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.[78] An ANA test is commonly used to screen for autoimmune conditions,[4] and the test is often used in both children and adults where a diagnosis of SLE is suspected.

The RF test is the most commonly used antibody test to determine the presence of RF antibodies. Rheumatoid factors are Ig that reacts specifically with the Fc fragment of the IgG molecules. RFs are found in all Ig isotypes (i.e., IgA, IgG, IgD, IgM, and IgE), but the 19S IgM-RF is the most frequently used isotype for rheumatic diseases testing.[79] The presence of RFs is typically determined by agglutination assays, nephelometry, or enzyme-linked immunosorbent assay (ELISA). Agglutination tests detecting the IgM-RF are commonly used in laboratory diagnosis of RA in adults. This assay 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. Latex agglutination and nephelometry only measure 19S IgM-RF, whereas ELISAs have been designed to measure the various RF isotypes.[79]

The CCP test detects the presence of autoantibodies to citrullinated peptides found in the patient's blood serum.[80] 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 adult RA patients.[76] Anti-CCP2 (a second-generation assay) is currently the most widely used anti-citrullinated peptide assay.[76] Anti-CCP antibodies and anticitrullinated filaggrin antibodies are locally produced in inflamed joints, and citrullinated fibrin is found in the synovia of patients with RA.[81] In adults, a CCP test is usually ordered along with a RF test when a patient has previously undiagnosed inflammatory arthritis or has been diagnosed with undifferentiated arthritis. A CCP test may also be ordered as a followup to a negative RF test when clinical signs, such as symmetrical joint pain and inflammation, lead the physician to suspect adult RA. The knowledge and use of CCP test for pediatric rheumatic conditions are very limited.

Objectives of this Evidence Report

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/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 KQs.

Key Questions

Key Question 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?

Key Question 2. Natural history

KQ 2.1. What proportion of children and adolescents aged 18 years or less with undiagnosed MSK pain is due to non-inflammatory etiologies?

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

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

Key Question 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, specificity, and positive and negative predictive values) 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 (sensitivity, specificity, and positive and negative predictive values) 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 (sensitivity, specificity, and positive and negative predictive values) 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 (sensitivity, specificity, and positive and negative predictive values) 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 (sensitivity, specificity, and positive and negative predictive values) 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 (sensitivity, specificity, and positive and negative predictive values) of CCP for JIA compared with a clinical diagnosis?

Key Question 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 (sensitivity, specificity, and positive and negative predictive values) 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 (sensitivity, specificity, and positive and negative predictive values) of ANA, RF, and CCP for JIA compared with a clinical diagnosis?

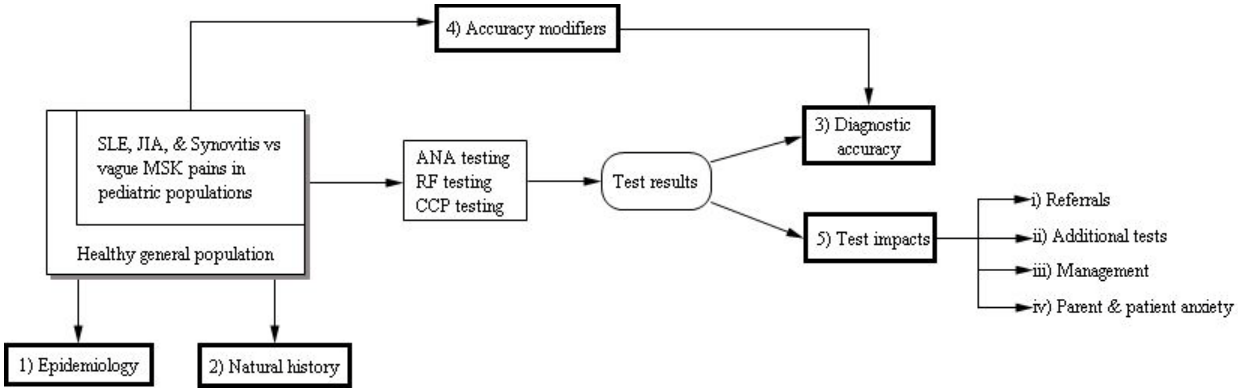
Key Question 5. Clinical impacts of test results

KQ 5. 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 test ordered, clinical management, and patient and parent anxiety due to the clinical uncertainty and additional tests?

Analytic Framework

The analytic framework (Figure 1) depicts the five key questions within the context of the pediatric population (≤ 18 years) with MSK pain. In general, the figure illustrates how diagnostic accuracy may be modified by demographic and clinical factors. It also indicates how test results may influence four important areas including referral to specialists, additional tests, decisions regarding clinical management, and parents' and patients' level of level. The epidemiology and natural history of the targeted rheumatic conditions will be described independently of the test results.

Figure 1. Analytic framework for antibody testing for musculoskeletal conditions in pediatric populations (≤ 18 years)



ANA = antinuclear antibody; CCP = cyclic-citrullinated peptide; JIA = juvenile idiopathic arthritis; MSK = musculoskeletal; SLE = systemic lupus erythematosus; RF = rheumatoid factor

Methods

Topic Development and Refinement

In this chapter we document a prospectively developed protocol that was used to conduct this evidence report. A core research team was assembled by the Evidence-based Practice Center (EPC). In consultation with AHRQ, a panel of key informants was created to provide input in the development of the key questions and scope of the evidence report. The public was invited to comment on these key questions over a period of 1 month. After reviewing the public comments, the key questions were finalized and submitted to AHRQ for approval. A technical expert panel was subsequently created to provide content and methodological expertise throughout the development of the comparative effectiveness review. The technical experts are identified in Appendix A.

Search Strategy

The research librarian, in collaboration with the investigative team, developed and implemented search strategies designed to identify evidence relevant to questions of diagnostic performance and clinical impact of the tests (Appendix B).

KQ 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. As the primary of focuses of this report, KQs 3, 4, and 5 were addressed by a full systematic review process via a comprehensive search of the following electronic databases: 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 were applied, when applicable.

Search terms were identified by reviewing search strategies of systematic reviews on similar topics and by examining how potentially relevant studies were indexed in various databases (Appendix B). A combination of subject headings and text words was adapted for each electronic resource: (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”).

In addition to the searches of electronic databases, we searched the following conference proceedings and scientific meetings: ACR, Joint meeting of the British Society for Rheumatology (BSR), Canadian Rheumatology Association, EULAR, ILAR, and the American Academy of Pediatrics (AAP) from 2005 to 2010. Additionally, the bibliographies of the included studies and reviews were searched for relevant studies. Search alerts for PubMed and

Web of Science were set up to identify any new and potentially relevant studies during the course of the review.

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

Study Selection

A two-stage screening was carried out. For the initial broad screening, each article was screened by two independent reviewers who assessed the relevance of the study based on its title and abstract using prespecified screening criteria. Articles were rated as "include", "exclude", or "unsure". The full-text of studies rated as "include" or "unsure" by both reviewers were retrieved. Discrepancies in decisions between reviewers were resolved through discussion or third party adjudication, if needed.

For the second level of screening the full-text of each article was further examined by two independent reviewers using a standard inclusion/exclusion form (Appendix C). This form was based on a specific and comprehensive set of criteria (Table 1). Each reviewer rated the article as "include", "exclude", or "unsure". There was no restriction on study design, language, or publication year. The minimal requirement for inclusion was that studies must have recruited a population comprised of children and adolescents aged 18 years or less, examined the appropriate tests and reference standards, and provided information on 1) sensitivity and specificity or 2) clinically-important outcomes. Discrepancies between the reviewers were resolved through discussion or third party adjudication, if needed. The first author of the article was contacted when additional information was needed for making the inclusion/exclusion decisions. Articles screened in after this inclusion/exclusion stage constituted the evidence base of this systematic review.

Table 1. Inclusion and Exclusion Criteria

Article type	- Studies reporting original research - Any language - No restriction on publication year
Participants	- Studies providing separate data for a population comprising children (≤18 years) with undiagnosed MSK pain or joint swelling, a diagnosis of pSLE or JIA, or index test results
Study design	- At least 2 participants - Diagnostic randomized controlled trial, cohort, case control, or any study design that provides sufficient data to calculate sensitivity and specificity
Index tests	- ANA, RF, CCP - The assay method of ANA using animal substrate was excluded - Studies of ANA published before 1980 - The test of hidden RF was excluded
Reference standard	- Diagnosis of pSLE or JIA based on clinical criteria
Outcomes	- For Key Questions 3 and 4: Studies providing sufficient data to calculate sensitivity and specificity - For Key Question 5: Studies providing at least a narrative description although supplemented with numerical data was more preferable

ANA = antinuclear antibody; CCP = cyclic-citrullinated peptide; JIA = Juvenile Idiopathic Arthritis; MSK = musculoskeletal; RF = rheumatoid factor; pSLE = pediatric systemic lupus erythematosus

Data Extraction

Data were extracted by a single reviewer using a standard data extraction form and verified by a second reviewer. Any disagreements were resolved through discussion or third party

adjudication, if needed. Extracted data could be categorized into the following specific areas including study characteristics, participant characteristics, index test, reference standard, and outcomes.

Quality Assessment

The methodological quality of each included study was determined using the quality assessment tool described by Diagnostic Test Accuracy Working Group of the Cochrane Collaboration.[82] This tool is a modified version of the Quality Assessment of Studies of Diagnostic Accuracy (QUADAS) tool[5] and consists of 11 items that assess important common biases in diagnostic studies including spectrum, selection, incorporation, verification, and review biases. Two reviewers performed quality assessment independently. Decision rules regarding application of the assessment tool were developed a priori. Discrepancies were resolved through discussion or third party adjudication, as needed.

Data Analysis and Synthesis

The general characteristics of studies were summarized using descriptive statistics. For the diagnostic performance, 2x2 tables were constructed. Sn, Sp, and positive and negative predictive values were calculated. Results were graphed in forest plots for visual interpretation. An a priori decision was made to not conduct meta-analysis due to the expected large degree of heterogeneity in participant characteristics and test positive thresholds across studies. The hierarchical summary receiver operating characteristic (HSROC) curve, serving as a summary measure including both Sn and Sp, was generated whenever appropriate: at least four studies for each curve and convergence of the bivariate models.[83,84] When data were available, subgroup analyses were conducted by accuracy modifiers, as well as by assay methods used and JIA onset-types.

Rating the Body of Evidence

The collected evidence was graded for KQ 3 to 5 using the AHRQ system for grading the strength of evidence (AHRQ Guidance for the Evaluation of Medical Tests (draft)).[85] We assessed four domains including i) risk of bias, ii) consistency, iii) directness, and iv) precision, as well as a summary of overall strength of evidence. The grading was done by two independent reviewers, and any discrepancy was resolved by discussion or third party adjudication as needed. The “risk of bias” domain was scored as low, medium, or high risk of bias corresponding to the results of QUADAS; the “consistency” domain was scored as consistent, inconsistent, or unknown based on the visual interpretation of the forest plots and HSROC curves; the “directness” was scored as direct or indirect based on the relevance of the presenting evidence to the corresponding KQ; the “precision” was scored as precise or imprecise based on the width of 95% confidence intervals and HSROC curves; and the overall summary rating was evaluated as high, moderate, low, or insufficient.

Applicability

Applicability refers to how generalizable the findings of this report are to a wider range of populations that vary by age, sex, clinical presentation, disease severity, and clinical setting. It was assessed according to the AHRQ Guidance for the Evaluation of Medical Tests (draft).[85]

Peer Review and Public Commentary

(To be completed after peer review) XX experts in pediatric medicine, pediatric rheumatology, rheumatology, pathology, and diagnostic testing (Appendix A) agreed to peer review the draft report and provide feedback. Reviewer comments were considered by the EPC in preparation of the final report. All peer reviewer comments and the EPC disposition of comments were submitted to AHRQ for assessment and approval.

Results: Part One

The aim of Key Questions (KQs) 1 and 2 was to provide background information for the interpretation of the results of KQs 3, 4, and 5. Studies were selected based on the availability of the evidence and its representativeness to the pediatric population of North America.

Key Question 1.1. Incidence and prevalence of undiagnosed musculoskeletal complaints in children

In studies of the epidemiology of musculoskeletal (MSK) pain in children, 60–85 percent of school-aged children reported at least one episode of pain within a 3 month period.[4,12] More girls reported pain (65 percent) than boys (55 percent).[12] Overall, the prevalence of pain has risen in the past 20 years for both sexes.[12,15,86] Up to 30 percent of children and adolescents reported having experienced chronic pain which lasted for more than 6 months.[2,15,87-89]

A wide range of MSK pain prevalence was found, ranging from 2 percent in 12 year olds to 52 percent in 18 year olds.[6-9] The prevalence of MSK pain increases steadily with age throughout childhood and adolescence.[10,11] Haraldstad et al.[12] examined 1,238 Norwegian school children aged 8 to 18 years and found that the prevalence of back pain significantly increased with age for both sexes, yet the prevalence of throat and chest pain significantly increased with age only for boys.[12] A 4-year prospective study reported that the incidence of new-onset low back pain doubled with age from 13 percent in 12-year olds to 24 percent in 15-years olds.[15] However, a review article suggested that the trends in sex were ambivalent.[13] Some studies reported that low back, neck, shoulder, leg, and chronic pain were more prevalent in girls than boys,[12,14,15] two studies found no such difference,[16,17] and one found male predominance.[11]

Key Question 1.2: The positivity of antinuclear antibody, rheumatoid factor, and cyclic-citrullinated peptide tests in healthy children

Nine studies examined the prevalence of a positive ANA in a total of 1,413 healthy children and found a range of 0 to 18 percent[18-26] All of these studies examined children and adolescents 18 years or less except Baig and Shere[22] which included 1 to 19 year olds and Youngchiyud et al.[25] which included 12 to 20 year olds. The definition of a positive cutoff of ANA titer ranged from 1:5 to 1:40.

Studies on the positivity of the RF and CCP tests in healthy children were scarce. A commentary[90] indicated that most children with a positive RF test did not have JIA,[48,91] and most children with JIA did not have a positive RF.[92] Kasapcopur et al.[27] investigated 118 healthy Turkish children, using a diagnostic cutoff of >25 IU/ml and found a rate of 3 percent RF positivity.[27] No studies specifically addressed the positivity of the CCP test in healthy children.

Key Question 2.1. Noninflammatory causes of pediatric musculoskeletal pain

De Inocencio[10] conducted a retrospective chart review on 317 children between 3 and 15 years of age in a primary care setting in Madrid.[10] Noninflammatory etiologies accounted for the overwhelming majority (96.7 percent) of the MSK pain for children seen in primary care. He found that physical trauma (43.6 percent) was the most common etiology for pediatric MSK pain, and bone and muscle contusions were the most common trauma subgroup. Other noninflammatory etiologies included overuse (24.0 percent), osteochondroses (10.3 percent), hypermobility (3.3 percent), non-specific pain (7.6 percent), growing pain (3.5 percent), and viral infection (4.5 percent). The age of the children was related to the etiologies of MSK pain. Non-specific pain, growing pains, and hypermobility were much more common in preschool children (3 to 5 years) than in both school-aged children (6 to 9 years) and adolescents (10 to 14 years).

Key Question 2.2. Inflammatory causes of pediatric musculoskeletal pain

In De Inocencio[10], the inflammatory etiologies accounted for a small fraction (3.3 percent) of primary care visits from children with MSK pain and included toxic synovitis (2.5 percent) and inflammatory arthritides (0.8 percent). This was consistent with an earlier study by McGhee et al.[74] who conducted a retrospective chart review of 226 children referred for an initial rheumatology consultation due to MSK pain.[74] From the group of 111 patients who presented with MSK pain as the sole complaint, only one child (1 percent) had a rheumatic disease (e.g., ankylosing spondylitis), and none had pSLE or JIA. The majority (81 percent) had mechanical MSK or overuse syndromes as explanation of their pain. Contrary to the conventional belief, of the 76 children diagnosed with JIA in the study, only 12 children (16 percent) included pain as part of their chief complaints, suggesting that pediatric MSK pain might not be a common presenting feature in pediatric rheumatic disease.

Key Question 2.3. The resolution or recurrence of pediatric musculoskeletal pain

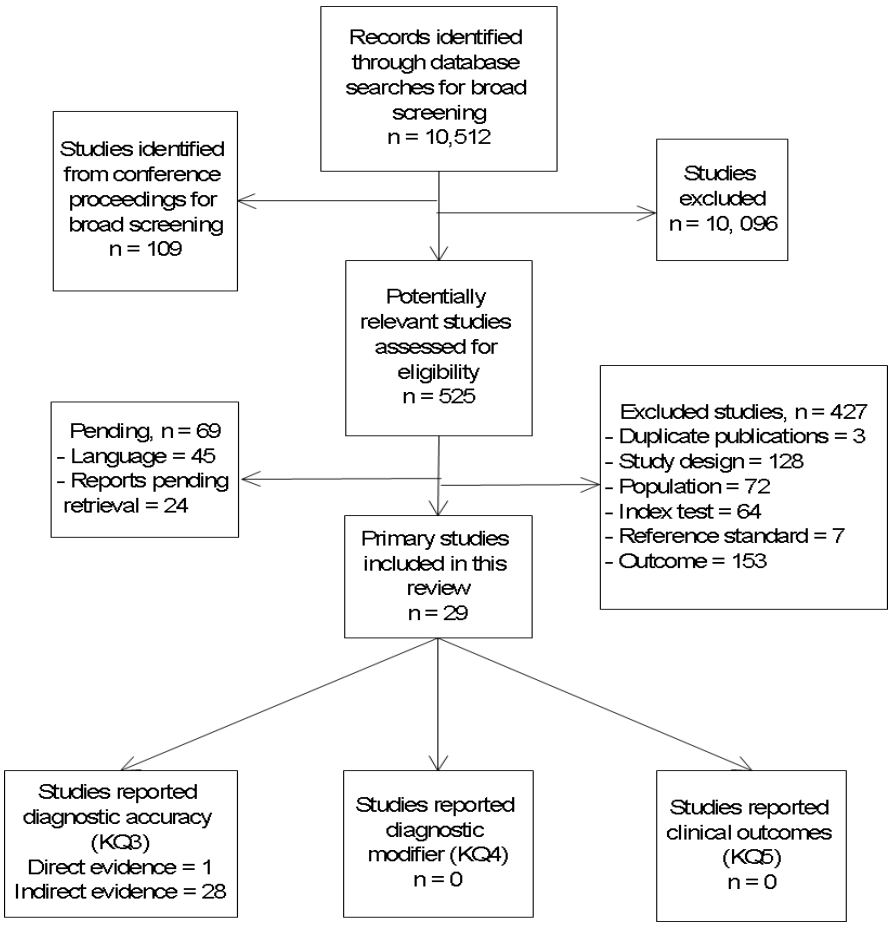
The recurrence of MSK pain was common in children. Thirty-five percent of 14 year olds who previously complained of low back pain reported recurrent episodes at age 18 and into early adulthood.[93] Mikkelsson et al.[94] examined 1,628 school-aged children with weekly pain at baseline and found that 52 percent reported MSK pain at 1-year followup. The recurrence of site-specific MSK pain of 403 children was similar between 1-year and 4-year followups.[9] The rate of recurrent neck pain (1-year: 48 percent; 4-year: 54 percent) was considerably higher than pain experienced in other body locations: lower limbs (1-year: 35 percent; 4-year: 31 percent), upper back (1-year: 35 percent; 4-year: 33 percent), buttock (1-year: 38 percent; 4-year: 48 percent), upper limb (1-year: 31 percent; 4-year: 24 percent), and chest (1-year: 15 percent; 4-year: 14 percent). From 244 children who initially experienced regional pain, approximately 41, 29, and 30 percent later reported having no pain, regional pain, and pain at multiple sites at 4-year followup, respectively. Age, sex, headache, abdominal pain, and combined pain were found to be significant predictors for the recurrence of nontraumatic MSK pain.

Results: Part Two

Literature Search

The search strategy for the diagnostic performance and utility of ANA, RF, and CCP tests identified 10,512 citations from electronic databases and 109 additional references from hand searching and conference proceedings (Figure 2). Initial broad screening identified 525 potentially relevant citations. A total of 424 reports were excluded. Main reasons for exclusion were wrong population, (n = 72) no outcomes of interest, (n = 153) wrong study design, (n = 128) and inappropriate index test, (n = 61) leaving 10 studies excluded for other reasons. Twenty-four studies are pending retrieval and 45 non-English language studies are pending full translation. See Appendix D for a list of excluded studies with reasons for exclusion. Twenty-nine studies were included in this review. All 29 studies addressed KQ 3 (diagnostic performance). Three studies provided some subgroup information by sex and comorbidity which partly addressed the KQ 4 (diagnostic modifiers). No study addressed KQ 5 (test impacts).

Figure 2. Results of literature search, retrieval, and selection



Characteristics of Included Studies

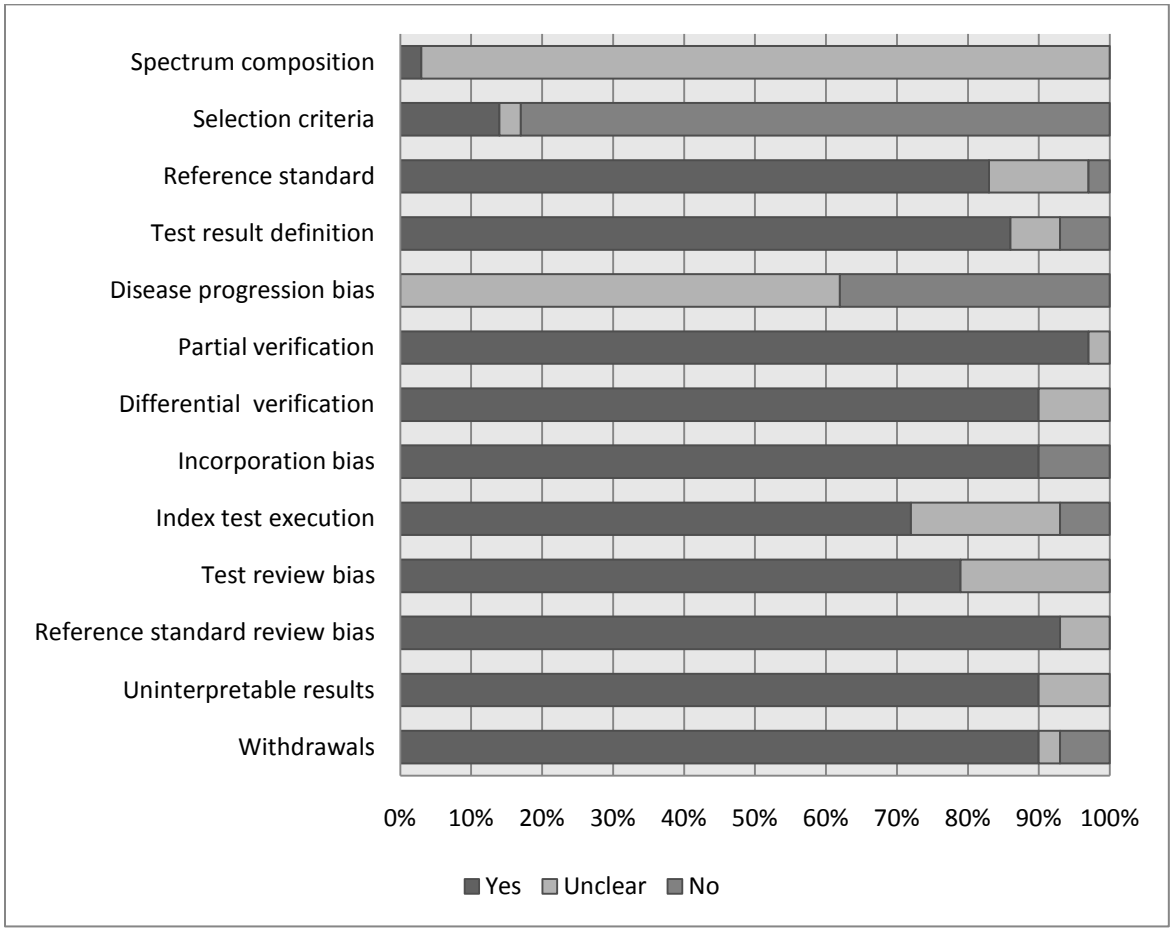
The 29 included studies were published between 1966 and 2009. Twenty-eight[29-55,57] were published as journal articles and one[56] as a conference proceeding. Fourteen studies[33,34,36,39-41,43,45,46,49,51,52,55,56] were conducted in Europe, nine [29,31,32,35,38,47,48,50,53] in North America, two[42,44] in South America, three[30,37,57] in Asia, and one[54] in Africa. Nine studies[29,31,35,39,41,47,49,51,53] received funding from government, four[33,37,55,57] from academic institutions, and four[30,34,43,50] from noncommercial institutions. The remaining 12 studies[32,36,38,40,42,44-46,48,52,54,56] did not report the source of funding.

One study[48] used a retrospective cohort design and included the spectrum of diagnosed and undiagnosed children with MSK symptoms. This is the only study that provided direct evidence to address KQ 3. The remaining 28 studies used a case control design (23 prospective,[29-31,33-37,39-47,51-56] two,[32,57] retrospective, and three[38,49,50] with unclear temporality). The ANA test was examined in seven studies (two[29,30] for pSLE and eight[29,31-37] for JIA). The RF test was examined in 17 studies (16[31,33,36,38-50,53] for JIA and one[38] for pSLE). The CCP test was examined in eight studies[33,51-57] for JIA. There were no studies that examined the CCP test for pSLE.

Methodological Quality of Included Studies

Overall, the methodological quality of the 29 included studies was considered moderate with particular concern regarding spectrum bias, selection bias, and disease progression bias (Figure 3). Most studies (97 percent) were "unclear" regarding the representativeness of the study population due primarily to the case control study design. The selection criteria of the population were not described adequately in most studies (83 percent). Disease progression bias was a potential concern in 38 percent of studies and was unclear for the remaining studies because of the lack of reporting of the period between the test and diagnosis. In general, most studies were considered to have adequately addressed all other items.

Figure 3. Methodological quality of studies evaluating antinuclear antibody, rheumatoid factor, and cyclic-citrullinated peptide tests for pediatric systemic lupus erythematosus and juvenile idiopathic arthritis



Key Question 3.1. Antinuclear antibody test for pediatric systemic lupus erythematosus

Study characteristics

There was no direct evidence addressing this KQ since no study examined children with undiagnosed MSK pain and/or joint swelling. As indirect evidence, two case control studies[29,30] including 201 children (67 pSLE, 134 controls) examined the use of the ANA test for pSLE (Table 2). The control groups consisted of healthy children[30] and patients with other rheumatic diseases (ORG) scheduled for elective orthopedic surgeries.[29] None of the studies reported the comorbidity status among the pSLE patients.

The assay method of the index test used in all three studies was indirect immunofluorescence method (IIF). Both studies used a positive cutoff of titer ≥1:40.

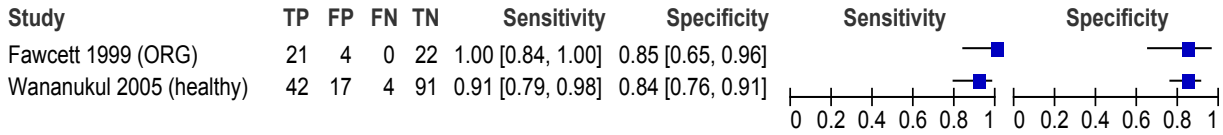
Methodological quality

Overall, the methodological quality of the studies was considered moderate (Table 3). Of major concern is the risk of spectrum bias. It is unclear whether the distinctive groups of pSLE and control children represent target population of this review—children with undiagnosed MSK pain and /or joint swelling. Other areas of concern are disease progression bias and incorporation bias.

Quantitative results

Overall, the sensitivities (Sn) were 91 and 100 percent, the specificities (Sp) were 84 and 85 percent, the positive predictive values (PPV) were 71 and 84 percent, and negative predictive values (NPV) were 96 and 100 percent (Figure 4). The HSROC curve was not generated because there were only three studies. Among control groups, the proportions of children who tested positive on the ANA test were 16 percent (healthy children) and 15 percent (ORG).

Figure 4. Forest plot of sensitivity and specificity of antinuclear antibody test for pediatric systemic lupus erythematosus



FN = false negative; FP = false positive; ORG = other rheumatic diseases; TN = true negative; TP = true positive

Table 2. Description of studies evaluating antinuclear antibody test for pediatric systemic lupus erythematosus

Author Year Location	Design Temporality	Funding	Source of study population	Control	Diagnostic criteria	Assay method	Positive threshold
Fawcett[29] 1999	Case control prospective	Government	NR	ORG: Underwent elective orthopedic surgical procedures	ACR	IIF and ELISA (Immuno Concepts, Helix, Zeus)	IIF: Discernible fluorescence pattern at titer 1:40
Wananukul[30] 2005	Case control prospective	Non-commercial institution	NR	NRG: Scheduled for elective surgery (adenotonsillectomy, herniorrhaphy or plastic surgery)	1997 revised criteria for the classification of SLE	IIF	Titer ≥ 1:40

ARC = American College of Rheumatologists; ELISA = enzyme-linked immunosorbent assay; IIF = indirect immunofluorescence method; NR = not reported; NRG = nonrheumatic disease group; ORG = other rheumatic disease group; SLE = systemic lupus erythematosus

Table 3. Methodological quality of antinuclear antibody test for pediatric systemic lupus erythematosus

Author Year	Spectrum composition	Selection criteria	Reference standard	Test result definition	Disease progression bias	Partial verification	Differential verification	Incorporation bias	Index test execution	Test review bias	Reference standard bias	Uninterpretable results	Withdrawals
Fawcett[29] 1999	U	No	Yes	Yes	U	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Wananukul[30] 2005	U	Yes	Yes	Yes	U	Yes	Yes	No	Yes	Yes	Yes	Yes	No

U = unclear

Key Question 3.2. Antinuclear antibody test for juvenile idiopathic arthritis

Study characteristics

There was no direct evidence addressing this KQ since no study examined children with undiagnosed MSK pain and/or joint swelling. As indirect evidence, eight case control studies[29,31-37] including 1,382 children (1,067 JIA, 315 controls) examined the use of the ANA test for JIA (Table 4). The age of the JIA patients in these studies was under 18 years. Two studies[31,37] included a small number of patients just over 18 years. Two studies[29,34] did not report age.

For the control groups, three studies[35-37] included healthy children, four[31-34] included children with nonrheumatic conditions (NRG), one[35] included children with other rheumatic diseases (ORG), and one[29] had a mix of children with nonrheumatic and other rheumatic diseases. Three studies[32,34,37] recruited JIA patients from general hospitals or clinics, and the source of participants was unreported by the remaining studies. For the classification of JIA, four studies[29,31,35,37] used the ACR criteria, two studies[33,34] used the ILAR criteria, one[36] used the EULAR criteria, and the classification criteria were unreported by the remaining study.[32] Comorbidity status was reported by three studies:[34,35,37] 18 percent of JIA patients in Nordal et al.[34] had uveitis, 6 percent of JIA patients in Osborn et al.[35] had iridocyclitis, and 3 percent of patients in Wakhlu et al.[37] had uveitis and late onset pauciarticular JIA.

IIF was used in all studies except Jones et al.[32] who did not report the method used. In studies that reported the positive cutoff titers, the titers ranged from >1:20 to >1:320. Fawcett et al.[29] and Nordal et al.[34] examined multiple assay methods of ANA for JIA (Appendix F).

Methodological quality

Overall, the methodological quality of the eight studies was considered moderate (Table 5). Of particular concern is the risk of spectrum bias in the case control studies. Most studies (88 percent) did not report their selection criteria. Disease progression bias was unclear in the majority of studies (88 percent).

Table 4. Description of studies evaluating antinuclear antibody test for juvenile idiopathic arthritis

Author Year Location	Design Temporality	Funding	Source of study population	Control	Diagnostic criteria	Assay method	Positive threshold
Fawcett[29] 1999 U.S.	Case control prospective	Government	NR	ORG: Underwent elective orthopedic surgical procedures	ACR	IIF and ELISA (Immune Concepts, Helix, Zeus)	IIF: Positive if a clearly discernible fluorescence pattern appears at 1:40 serum dilation
Haynes[31] 1986 U.S.	Case control prospective	Government and non-commercial institution	NR	NRG: Age-matched children with nonrheumatic diseases	ACR	IIF	Reading of ≥1+ in fluorescence at 1:20 dilution
Jones[32] 2006 North America	Case control retrospective	NR	Randomly selected patients from multiple medical centers	NRG: Records available in Pediatric Rheumatology Disease Registry (1992-1995)	NR	NR	Titer > 1:80
Lipinska[33] 2008 Poland	Case control prospective	Academic institution	NR	NRG: Age- and sex-matched children with functional cardiovascular system dysfunction.	ILAR	IIF	Titer > 1:320
Nordal[34] 2009 Norway	Case control prospective	Non-commercial institution	NR	NRG: Children undergoing elective outpatient procedures with no diagnosis of inflammatory diseases	ILAR	IIF and ELISA	IIF: Titer > 1:80 ELISA: Titer > 1:101
Osborn[35] 1984 U.S.	Case control prospective	Government	Pediatric clinic	Healthy and ORG: Other connective tissue diseases	ACR	IIF	Titer > 1:40
Siamopoulou-Mavridou[36] 1991 Greece	Case control prospective	NR	NR	Healthy: Age- and sex-matched children without rheumatic disease	EULAR	IIF	Titer > 1:40
Wakhlu[37] 2003 India	Case control prospective	Academic institution	Immunology clinic	Healthy	ACR	IIF	Titer: > 1:40

ACR = American College of Rheumatologists; ELISA = enzyme-linked immunosorbent assay; EULAR = The European League Against Rheumatism; IIF = indirect immunofluorescence method; ILAR = International League of Associations for Rheumatology; NR = not reported; NRG = nonrheumatic disease group; WHO = World Health Organization

Table 5. Methodological quality of studies evaluating antinuclear antibody test for juvenile idiopathic arthritis

Author Year	Spectrum composition	Selection criteria	Reference standard	Test result definition	Disease progression bias	Partial verification	Differential verification	Incorporation bias	Index test execution	Test review bias	Reference standard bias	Uninterpretable results	Withdrawals
Fawcett[29] 1999	U	No	Yes	Yes	U	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Haynes[31] 1986	U	No	Yes	Yes	U	Yes	Yes	Yes	Yes	U	Yes	Yes	Yes
Jones[32] 2006	U	No	U	Yes	U	Yes	U	Yes	No	U	Yes	Yes	No
Lipinska[33] 2008	U	No	Yes	Yes	U	Yes	Yes	Yes	U	Yes	Yes	Yes	Yes
Nordal[34] 2009	U	Yes	Yes	Yes	U	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Osborn[35] 1984	U	No	Yes	Yes	U	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Siamopoulou-Mavridou[36] 1991	U	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wakhlu[37] 2003	U	No	Yes	Yes	U	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

U = unclear

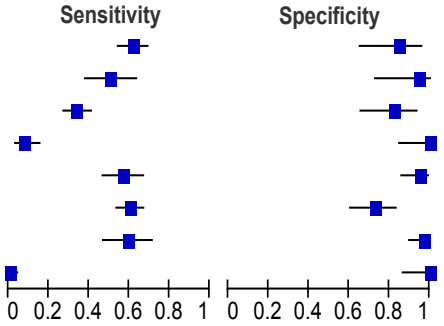
Quantitative results

Overall, the Sn ranged from 1 to 62 percent (median = 54 percent); the Sp ranged from 73 to 100 percent (median = 95 percent); PPV ranged from 88 to 100 percent (median = 96 percent); and NPV ranged from 15 to 70 percent (median = 30 percent) (Figure 55). The corresponding HSROC curve with 95% confidence ellipse is presented in **Error! Reference source not found.**. Without the overlapping between the 95% confidence ellipse and the diagonal null line, the test's correctness in classifying patients and controls was significantly better than random classification.

Among the healthy control groups, the proportion of children (three control groups) who tested positive for ANA ranged from 3 to 27 percent (median = 3). Among NRG controls (four groups), the proportion of children with positive tests ranged from 0 to 18 percent (median = 5.5). Among ORG controls (one study), the proportion was 15 percent. Subgroup analyses by subtypes of JIA explained some of the heterogeneity in Sn (Appendix F).

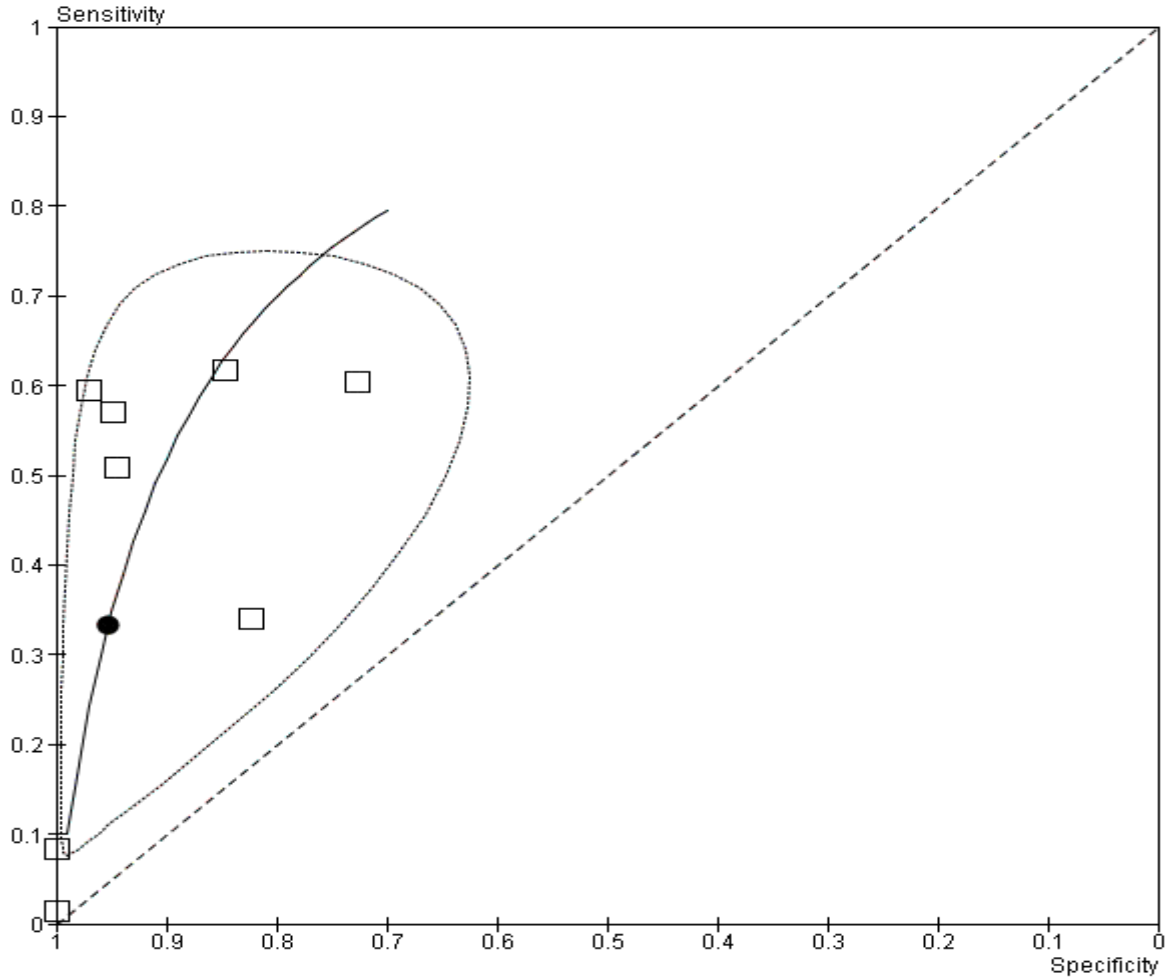
Figure 5. Forest plot of sensitivity and specificity of antinuclear antibody test for juvenile idiopathic arthritis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Fawcett 1999 (ORG)	110	4	68	22	0.62 [0.54, 0.69]	0.85 [0.65, 0.96]
Haynes 1986 (NRG)	33	1	32	17	0.51 [0.38, 0.63]	0.94 [0.73, 1.00]
Jones 2006 (NRG)	66	6	128	28	0.34 [0.27, 0.41]	0.82 [0.65, 0.93]
Lipinska 2008 (NRG)	8	0	88	22	0.08 [0.04, 0.16]	1.00 [0.85, 1.00]
Nordal 2009 (NRG)	57	3	43	55	0.57 [0.47, 0.67]	0.95 [0.86, 0.99]
Osborn 1984 (healthy)	131	18	86	48	0.60 [0.54, 0.67]	0.73 [0.60, 0.83]
S-Mavridou 1991 (healthy)	41	2	28	64	0.59 [0.47, 0.71]	0.97 [0.89, 1.00]
Wakhlu 2003 (healthy)	2	0	146	25	0.01 [0.00, 0.05]	1.00 [0.86, 1.00]



FN = false negative; FP = false positive; NRG = nonrheumatic disease group; ORG = other rheumatic diseases; TN = true negative; TP = true positive

Figure 6. Hierarchical summary receiver-operating characteristic curve of antinuclear antibody test for juvenile idiopathic arthritis



Key Question 3.3. Rheumatoid factor test for pediatric systemic lupus erythematosus

Study characteristics

There was no direct evidence addressing this KQ since no study examined children with undiagnosed MSK pain and/or joint swelling. As indirect evidence, one case control study[38] including 46 participants (14 pSLE, 32 controls), examined the use of the IgM-RF test for pSLE (Table 6). Patients were diagnosed based on criteria developed by Cook et al.[95] and Urbach,[96] The control groups comprised a mix of healthy children and children with other rheumatic (ORG) and nonrheumatic (NRG) conditions.

Methodological quality

The methodological quality of the study was moderate (**Error! Reference source not found.**). Of particular concern were the risk of spectrum, selection, and disease progression biases.

Quantitative results

The Sn was 29 percent and Sp was 88 percent. The proportion of children who tested positive for RF was 13 percent.

Table 6. Description of studies evaluating rheumatoid factor test for pediatric systemic lupus erythematosus

Author Year Location	Design Temporality	Funding	Source of study population	Control	Diagnostic criteria	Assay method (Isotype)	Positive threshold
Hanson[38] 1966 U.S.	Case control NR	NR	NR	Healthy, ORG (other collagen diseases), NRG (ulcerative colitis)	Cook[95] and Urbach[96]	Latex (IgM)	Titer ≥ 1:160

Ig = immunoglobulin; NR = not reported; NRG = nonrheumatic disease group; ORG = other rheumatic disease group

Table 7. Methodological quality of studies evaluating rheumatoid factor test for pediatric systemic lupus erythematosus

Author Year	Spectrum composition	Selection criteria	Reference standard	Test result definition	Disease progression bias	Partial verification	Differential verification	Incorporation bias	Index test execution	Test review bias	Reference standard bias	Uninterpretable results	Withdrawals
Hanson[38] 1966	U	No	Yes	U	U	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No

U = unclear

Key Question 3.4. Rheumatoid factor test for juvenile idiopathic arthritis

Study characteristics

The study by Eichenfield et al.[48] presented direct evidence to answer the KQ (Table 8). This was a retrospective cohort study that examined the historical records of pediatric patients seen in the walk in clinic, inpatient service, emergency room, or Pediatric Rheumatology Center at The Children's Hospital of Philadelphia. RF was measured in all patients. From the cohort of 450 patients, 105 had a diagnosis of JIA according to ACR criteria. The remaining 332 patients had a mix of musculoskeletal complaints (n = 198) and connective tissue disease complaints (n = 128). The analysis for Sn and Sp combined these two groups as the controls.

Fifteen studies provided indirect evidence for the KQ by examining the Sn and Sp of RF for the diagnosis of JIA in a case control design (Table 9). Two studies[42,44] recruited the JIA patients from pediatric clinic or centers, one study[39] used an epidemiologic survey, and patient source was not reported by 11 studies.[31,33,36,38,41,43,45-47,49,50] Twelve studies were prospective,[31,33,36,39-47] and the temporality was unreported by three studies.[38,49,50]

For the classification of JIA, eight studies[31,38,41-44,47,49] used the ACR criteria, four[36,39,40,46] used the EULAR criteria, one[33] used the ILAR criteria, one[50] used criteria based on Brewer et al.,[71] and one study[45] did not report the criteria used. The status of comorbidity was reported by two studies:[39,49] three percent of JIA patients in one[39] had psoriatic arthropathy; 62 percent of JIA patients in another study[49] had chronic bilateral iridocyclitis. For the control groups, ten studies[36,38-43,45,46,49,50] used healthy children, three[31,33,47] used children with nonrheumatic conditions (NRG), one study[44] used children with other rheumatic conditions (ORG), and one study[45] used both healthy and ORG.

As supplementary information, studies presented data on non-IgM RF tests were illustrated in Appendix E.

Methodological quality

Overall, the methodological quality of the 16 studies was considered moderate (Table 9). The spectrum composition of most studies (94 percent) was unclear due to the case control study design. The selection criteria of the population were mostly unreported (94 percent). Eight studies (44 percent) were at risk for progression bias as the index test and reference standard were separated by more than 6 months.

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Table 8. Description of studies evaluating IgM-rheumatoid factor test for juvenile idiopathic arthritis

Author Year Location	Design Temporality	Funding	Source of study population	Non-disease group	Diagnostic criteria	Assay method	Positive threshold
Andersson-Gare[39] 1994 Sweden	Case control prospective	Government	Epidemiological survey in south-western Sweden	Healthy	EULAR	Enzyme immunoassay	Mean of control group + 2 s.d.
Balogh[40] 1980 Hungary	Case control prospective	ND	Hospital consecutive patients	Healthy: Age- and sex-matched	EULAR/WHO workshop	Latex fixation test and Waaler-Rose test	ND
Egeskjold[41] 1981 Denmark	Case control prospective	Government	ND	Healthy: Age- and sex-matched	ACR	IIF	Titer > 1:9
Egeskjold[49] 1982 Denmark	Case control	Government	ND	Healthy	ACR	IIF	Maximum of peak 2 displacement beyond normal range
Eichenfield[48] 1986 US	Cohort retrospective	ND	Consecutive patients from pediatric hospital	NA (due to cohort design)	ACR	Latex fixation test	Titer > 1:80
Ferreira[42] 2007 Brazil	Case control prospective	ND	Randomly selected patients from multiple centers of pediatric rheumatology	Healthy	ACR	Latex and ELISA	Latex: 20 IU/ml ELISA: Absorbance of serum samples/cutoff > 1
Hanson[38] 1966 US	Case control	ND	ND	Healthy, NRG, ORG	Published by Cook[95] and Urbach[96]	Latex titration test	Titer > 1:160
Haynes[31] 1986 US	Case control prospective	Government and non-commercial institution	ND	NRG: Age-matched children with non-rheumatic diseases	ACR	ELISA	Mean of control + 2 s.d.
Lipinska[33] 2008 Poland	Case control prospective	Academic institution	ND	NRG: Age- and sex-matched children with functional cardiovascular system dysfunction.	ILAR	ELISA	24 RU/ml
Permin[43] 1982 Denmark	Case control prospective	Non-commercial	ND	Healthy	ACR	IIF	Titer > 1:10

		institution					
Roizenblatt[44] 1983 Brazil	Case control prospective	ND	Pediatric clinic	ORG: Age- and sex-matched hypermobile children	ACR	ELISA	Mean of control group + 2 s.d.
Saulsbury[50] 1990 US	Case control	Non-commercial institution	ND	Healthy	Brewer[97]	ELISA	Titer > 1:20
Siamopoulou-Mavridou[36] 1991 Greece	Case control prospective	ND	ND	Healthy: Age- and sex-matched children without rheumatic disease	EULAR	Latex fixation test	Mean optical density of healthy control + 3 s.d.
Taseski[45] 1981 Yugoslavia	Case control prospective	ND	ND	Healthy and ORG (collagen diseases)	ND	Photometrical latex test (PLT), standard sensitized sheep-cell test (SSC), and latex slide test (LST)	PLT: Photometrically detectable even at the lowest serum dilution. SSC: Titer > 1:64. LST: Agglutination visually detectable.
Varbanova[46] 1999 Bulgaria	Case control prospective	ND	ND	Healthy	EULAR	ELISA	Mean IU of healthy control + 2 s.d.
Wernick[47] 1981 US	Case control prospective	Government	ND	NRG (scoliosis and neurologic diseases)	ACR	Solid phase radioimmunoassay	Mean of normal control + 2 s.d.

ACR = American College of Rheumatology; EULAR =The European League Against Rheumatism; ELISA = Enzyme linked immunosorbent assay; Ig = immunoglobulin; IIF = indirect immunofluorescence; ILAR = International League of Associations for Rheumatology; IU = international unit; LST = latex slide test; ml = milliliter; NIAMSK = National Institute of Arthritis and Musculoskeletal and Skin Diseases; NR = not reported; NRG = nonrheumatic disease group; OD = optical density; ORG = other rheumatic disease group; PLT = photometrical latex test; RU = relative unit; sd= standard deviation; SSC = sensitized sheep-cell test; WHO = World Health Organization

Table 9. Methodological quality of studies evaluating IgM-rheumatoid factor test for juvenile idiopathic arthritis

Author Year	Spectrum composition	Selection criteria	Reference standard	Test result definition	Disease progression bias	Partial verification	Differential verification	Incorporation bias	Index test execution	Test review bias	Reference standard bias	Uninterpretable results	Withdrawals
Andersson-Gare[39] 1994	U	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Balogh[40] 1980	U	No	Yes	No	No	Yes	Yes	Yes	Yes	U	Yes	U	Yes
Egeskjold[41] 1981	U	No	Yes	Yes	U	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Egeskjold[49] 1982	U	No	Yes	U	No	Yes	Yes	Yes	Yes	U	U	Yes	Yes
Eichenfield[48] 1986	Yes	No	Yes	Yes	U	Yes	Yes	Yes	U	Yes	U	Yes	U
Ferreira[42] 2007	U	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	U	Yes
Hanson[38] 1966	U	No	Yes	U	U	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Haynes[31] 1986	U	No	Yes	Yes	U	Yes	Yes	Yes	Yes	U	Yes	Yes	Yes
Lipinska[33] 2008	U	No	Yes	Yes	U	Yes	Yes	Yes	U	Yes	Yes	Yes	Yes
Permin[43] 1982	U	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Roizenblatt[44] 1993	U	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Saulsbury[50] 1990	U	No	Yes	Yes	U	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Siamopoulou-Mavridou[36] 1991	U	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Taseski[45] 1981	U	No	No	No	U	U	U	Yes	U	Yes	Yes	Yes	Yes
Varbanova[46] 1999	U	No	Yes	Yes	U	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wernick[47] 1981	U	No	Yes	Yes	U	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

U = unclear

Quantitative results

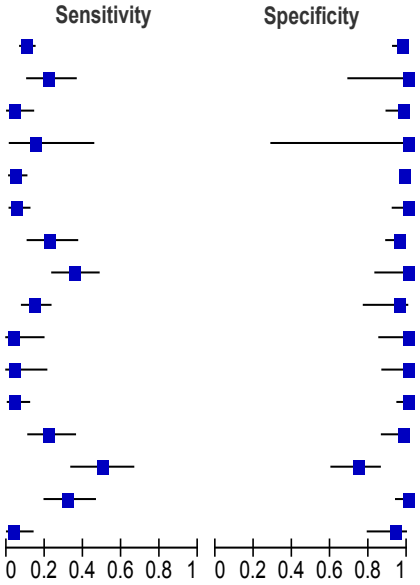
Results from the cohort study[48] show a Sn of 5 percent and a Sp of 98 percent. This is consistent with the RF results from the same center's total JIA population (6.9 percent) as referred to in their paper. This article also analyzes post-test probability of JIA given the Sn and Sp reported. The analyses take into account the pretest probability or prevalence of JIA, which in this cohort was 24 percent. The modeling showed that probability increased in this cohort to 45 percent with a positive test. In an unselected cohort, (e.g., a primary care practice) the probability went from 3 percent to 7 percent with a positive test.

In total 16 studies including 2,084 children (1,094 JIA, 993 controls) and examined the IgM-RF test for JIA (Figure 7). Sn ranged from 4 to 50 percent (median = 15 percent), Sp ranged from 67 to 100 percent (median = 98 percent), PPV ranged from 45 to 100 percent (median = 93 percent), and NPV ranged from 20 to 77 percent (median = 47 percent).

The HSROC curve incorporating all study results with 95 percent confidence ellipse is shown in Figure 8. The summary graphic emphasizes the low Sn and high Sp of this test, with all results clustered in the lower left hand quadrant. The proportion of healthy children who tested positive ranged from 0 to 17 percent (median = 0). For the NRG, the proportion ranged from 0 to 6 percent (median = 4.5). For the ORG, the proportion of children who tested positive ranged from 0 to 9 percent (median = 2.5). There does not appear to be a relationship between the cut off titer used (if reported) and Sn. Subgroup analyses by subtypes of JIA are presented in Appendix F and could not explain the heterogeneity of Sn.

Figure 7. Forest plot of sensitivity and specificity of IgM-rheumatoid factor test for juvenile idiopathic arthritis

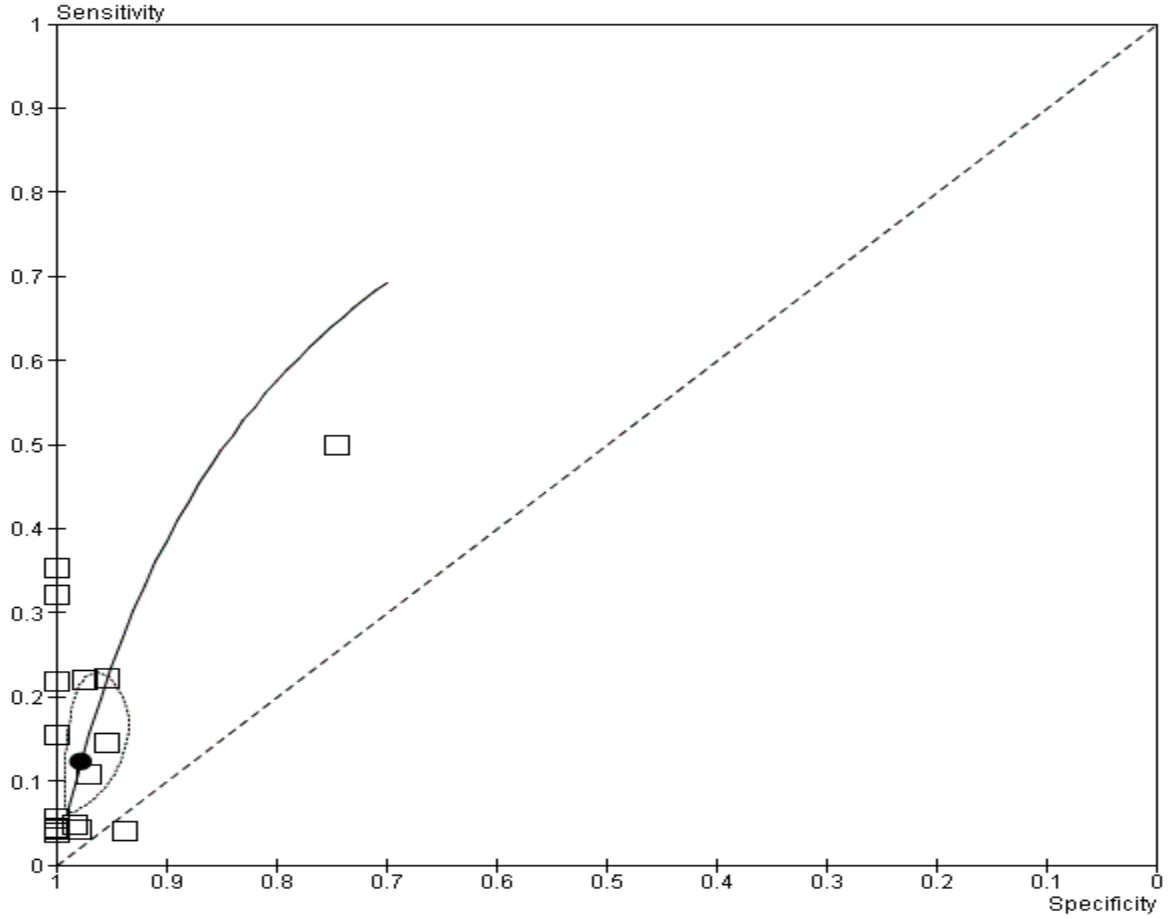
Study	TP	FP	FN	TN	Sensitivity	Specificity
Andersson-Gare 1994 (healthy)	29	4	242	126	0.11 [0.07, 0.15]	0.97 [0.92, 0.99]
Balogh 1980 (healthy)	10	0	36	10	0.22 [0.11, 0.36]	1.00 [0.69, 1.00]
Egeskjold 1981 (healthy)	2	1	46	47	0.04 [0.01, 0.14]	0.98 [0.89, 1.00]
Egeskjold 1982 (healthy)	2	0	11	3	0.15 [0.02, 0.45]	1.00 [0.29, 1.00]
Eichenfield 1986*	5	6	100	326	0.05 [0.02, 0.11]	0.98 [0.96, 0.99]
Ferreira 2007 (healthy)	5	0	86	45	0.05 [0.02, 0.12]	1.00 [0.92, 1.00]
Hanson 1966 (mixed)	10	4	35	84	0.22 [0.11, 0.37]	0.95 [0.89, 0.99]
Haynes 1986 (NRG)	23	0	42	20	0.35 [0.24, 0.48]	1.00 [0.83, 1.00]
Lipinska 2008 (NRG)	14	1	82	21	0.15 [0.08, 0.23]	0.95 [0.77, 1.00]
Permin 1982 (healthy)	1	0	25	23	0.04 [0.00, 0.20]	1.00 [0.85, 1.00]
Roizenblatt 1983 (ORG)	1	0	23	26	0.04 [0.00, 0.21]	1.00 [0.87, 1.00]
S-Mavridou 1991 (healthy)	3	0	66	66	0.04 [0.01, 0.12]	1.00 [0.95, 1.00]
Saulsbury 1990 (healthy)	11	1	39	38	0.22 [0.12, 0.36]	0.97 [0.87, 1.00]
Taseski 1981 (mixed)	20	13	20	38	0.50 [0.34, 0.66]	0.75 [0.60, 0.86]
Varbanova 1999 (healthy)	17	0	36	58	0.32 [0.20, 0.46]	1.00 [0.94, 1.00]
Wernick 1981 (NRG)	2	2	47	30	0.04 [0.00, 0.14]	0.94 [0.79, 0.99]



FN = false negative; FP = false positive; NRG = nonrheumatic disease group; ORG = other rheumatic diseases; TN = true negative; TP = true positive

*The only study that provided direct evidence by examining children with MSK complaints; this study used a cohort design while the rest were case control studies

Figure 8. Hierarchical summary receiver-operating characteristic curve of IgM-rheumatoid factor test for juvenile idiopathic arthritis



Key Question 3.5. Cyclic-citrullinated Peptide Test for Pediatric Systemic Lupus Erythematosus

There were no studies that addressed this question.

Key Question 3.6. Cyclic-citrullinated Peptide Test for Juvenile Idiopathic Arthritis

Study characteristics

There was no direct evidence addressing this KQ since no study examined children with undiagnosed MSK pain and/or joint swelling. As indirect evidence, eight case control studies[33,51-57] including 1,712 participants (772 JIA, 940 control) examined the use of the CCP test for JIA (Table 10). The age of the JIA patients ranged from 7 months to 18 years with three studies[51,55,57] including a small number of patients older than 18 years. Two studies[53,56] did not report any age information.

The control group in four studies[51-55] consisted of healthy children; four studies used a nonrheumatic patient control group (NRG; patients undergoing cardiac therapy without immunopathies,[52] cardiovascular dysfunction,[33] allergies and idiopathic thrombocytopenia,[57] and

not described in detail.[56]) One study[52] used children with other autoimmunopathies (ORG) as their comparator. The population for one study[53] was a cohort from Cincinnati and a National Institute of Arthritis and Musculoskeletal and Skin Diseases registry. The population for another study[55] comprised consecutive patients admitted to a hospital outpatient department. The remaining studies did not describe the source of their study populations. Four studies[33,54,55,57] used the ILAR criteria for classification of JIA; one study[53] used ACR criteria. The remaining studies did not describe their classification criteria. All eight studies used the ELISA method.

Methodological quality

Overall, the methodological quality of the studies was considered medium (Table 11). The spectrum composition of the case control studies was unclear due to the study design. The selection criteria of the population were mostly unreported or unclear (75 percent). Four studies (50 percent) were at risk for progression bias as the index test and reference standard were separated by more than 6 months.

Table 10. Description of studies evaluating cyclic-citrullinated peptide test for juvenile idiopathic arthritis

Author Year Location	Design Temporality	Funding	Source of study population	Control	Diagnostic criteria	Assay method	Positive threshold
Avcin 2002[51] Italy and Slovenia	Case control Prospective	Government	NR	Healthy	NR	ELISA	70 AU
Brunner 2006[52] Germany	Case control Prospective	NR	NR	Healthy, ORG (other autoimmunopathies), NRG (undergoing cardiac therapy and with non-autoimmunopathies)	NR	ELISA	2.5 RU
Ferucci 2005[53] U.S.	Case control Prospective	Government	Cohort from Cincinnati and NIAMSD registry	Healthy	ACR	ELISA	5 units/ml
Habib 2008[54] Egypt	Case control Prospective	NR	NR	Healthy	ILAR	ELISA	20 units/ml
Lipinska 2008[33] Poland	Case control Prospective	Academic institution	NR	NRG (functional cardiovascular system dysfunction)	ILAR	ELISA	5 RU
Kasapcopur 2004[55] Turkey	Case control Prospective	Academic institution	Consecutive patients admitted to hospital outpatient department	Healthy	ILAR	ELISA	5 RU
Kwok 2005[57] Hong Kong	Case control Retrospective	Academic institution	NR	NRG (allergy, idiopathic thrombocytopenia, and hepatitis C)	ILAR	ELISA	20 AU
Mo 2008[56] United Kingdom	Case control Prospective	NR	Pediatric rheumatology outpatients	NRG (non-JIA)	NR	ELISA	NR

ACR = American College of Rheumatology; AU=anti-CCP unit; ELISA = Enzyme linked immunosorbent assay; ILAR = International League of Associations for Rheumatology; ml = milliliter; NIAMSK = National Institute of Arthritis and Musculoskeletal and Skin Diseases; NR = not reported; RU=relative unit

Table 11. Methodological quality of studies evaluating cyclic-citrullinated peptide test for juvenile idiopathic arthritis

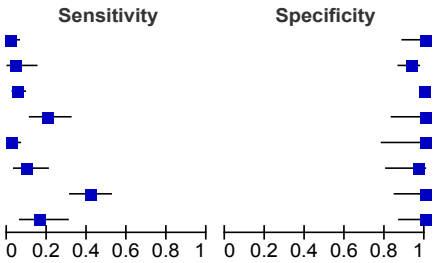
Author Year	Spectrum composition	Selection criteria	Reference standard	Test result definition	Disease progression bias	Partial verification	Differential verification	Incorporation bias	Index test execution	Test review bias	Reference standard bias	Uninterpretable results	Withdrawals
Avcin 2002 [51]	U	No	U	Yes	U	Yes	U	Yes	Yes	Yes	Yes	Yes	Yes
Brunner 2006 [52]	U	No	U	Yes	U	Yes	Yes	Yes	U	Yes	Yes	Yes	Yes
Ferucci 2005 [53]	U	Yes	Yes	Yes	No	Yes	Yes	Yes	U	Yes	Yes	Yes	Yes
Habib 2008 [54]	U	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	U	Yes
Kasapcopur 2004 [55]	U	U	Yes	Yes	No	Yes	Yes	Yes	No	U	Yes	Yes	Yes
Kwok 2005 [57]	U	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	U	Yes	Yes	Yes
Lipinska 2008 [33]	U	No	Yes	Yes	U	Yes	Yes	Yes	U	Yes	Yes	Yes	Yes
Mo 2008 [56]	U	No	U	U	U	Yes	Yes	Yes	U	Yes	Yes	Yes	Yes

U = unclear

Quantitative results

Overall, the Sn ranged from 2 to 42 percent and Sp ranged from 85 to 100 percent. The PPV ranged from 29 to 100 percent; and NPV ranged from 11 to 76 percent (Figure 9). The corresponding HSROC curve is presented in

Study	TP	FP	FN	TN	Sensitivity	Specificity
Avcin 2002 (healthy)	2	0	107	30	0.02 [0.00, 0.06]	1.00 [0.88, 1.00]
Brunner 2006 (mixed)	2	8	43	105	0.04 [0.01, 0.15]	0.93 [0.87, 0.97]
Ferucci 2005 (healthy)	13	4	217	684	0.06 [0.03, 0.09]	0.99 [0.99, 1.00]
Habib 2008 (healthy)	14	0	54	20	0.21 [0.12, 0.32]	1.00 [0.83, 1.00]
Kasapcopur 2004 (healthy)	3	0	119	15	0.02 [0.01, 0.07]	1.00 [0.78, 1.00]
Kwok 2005 (NRG)	6	1	53	25	0.10 [0.04, 0.21]	0.96 [0.80, 1.00]
Lipinska 2008 (NRG)	40	0	56	22	0.42 [0.32, 0.52]	1.00 [0.85, 1.00]
Mo 2008 (NRG)	7	0	36	26	0.16 [0.07, 0.31]	1.00 [0.87, 1.00]



FN = false negative; FP = false positive; NRG = nonrheumatic disease group; ORG = other rheumatic diseases; TN = true negative; TP = true positive

Figure 10. The summary graphics emphasize the low Sn and high Sp of this test, with all results clustered in the lower left hand quadrant. The proportion of healthy controls (five control groups) who tested positive for CCP ranged from 0 to 0.6 percent (median = 0). The proportion of NRG controls (four groups) who tested positive ranged from 0 to 15 percent (median = 2). Among the ORG controls (one group), 8 percent tested positive. Subgroup analyses by subtypes of JIA were presented in Appendix F and could not explain the heterogeneity of sensitivity.

Figure 9. Forest plot of sensitivity and specificity of cyclic-citrullinated peptide test for juvenile idiopathic arthritis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Avcin 2002 (healthy)	2	0	107	30	0.02 [0.00, 0.06]	1.00 [0.88, 1.00]
Brunner 2006 (mixed)	2	8	43	105	0.04 [0.01, 0.15]	0.93 [0.87, 0.97]
Ferucci 2005 (healthy)	13	4	217	684	0.06 [0.03, 0.09]	0.99 [0.99, 1.00]
Habib 2008 (healthy)	14	0	54	20	0.21 [0.12, 0.32]	1.00 [0.83, 1.00]
Kasapcopur 2004 (healthy)	3	0	119	15	0.02 [0.01, 0.07]	1.00 [0.78, 1.00]
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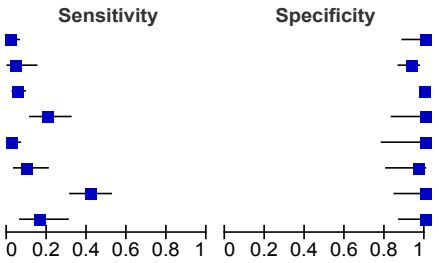
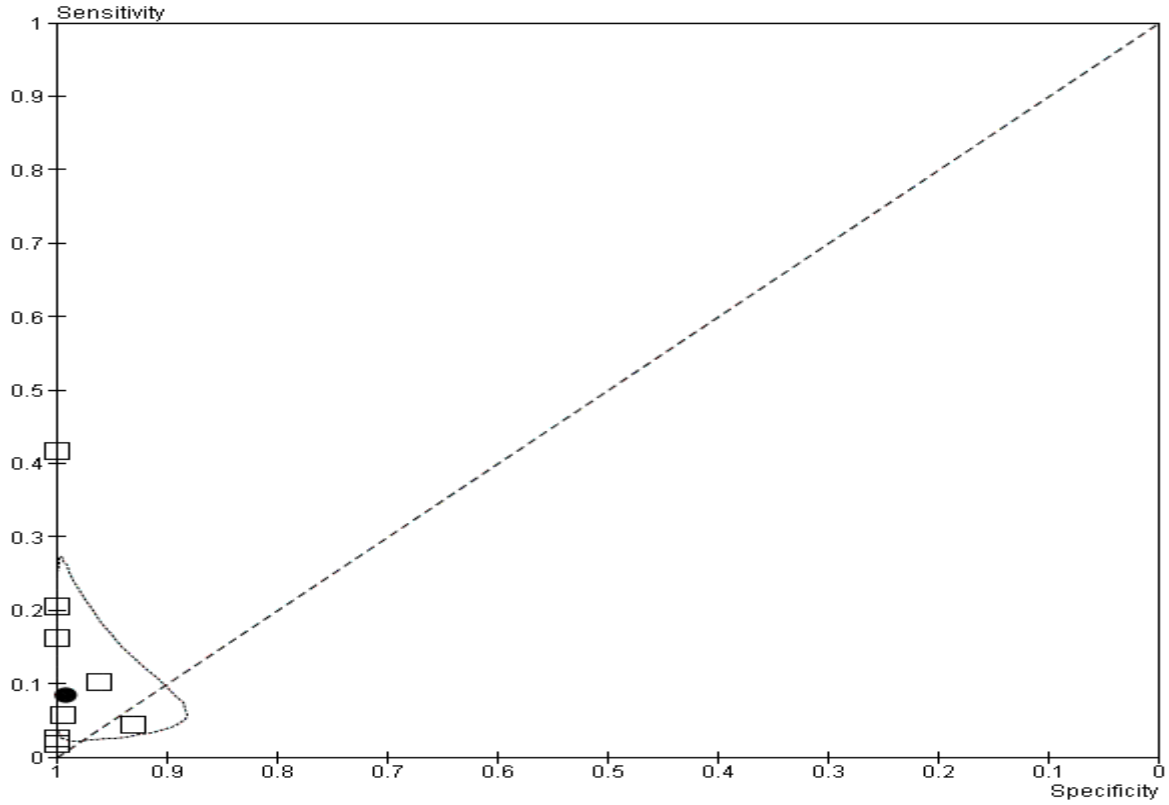
Lipinska 2008 (NRG)	40	0	56	22	0.42 [0.32, 0.52]	1.00 [0.85, 1.00]
Mo 2008 (NRG)	7	0	36	26	0.16 [0.07, 0.31]	1.00 [0.87, 1.00]



FN = false negative; FP = false positive; NRG = nonrheumatic disease group; ORG = other rheumatic diseases; TN = true negative; TP = true positive

Figure 10. Hierarchical summary receiver-operating characteristic curve of cyclic-citrullinated peptide test for juvenile idiopathic arthritis



Key Question 4.1. Accuracy modifiers of age, sex, race/ethnicity, comorbidities, and recent infections of antinuclear antibody, rheumatoid factor, cyclic-citrullinated peptide test for pediatric systemic lupus erythematosus

No study provided data for any of the five prespecified accuracy modifiers.

Key Question 4.2. Accuracy modifiers of age, sex, race/ethnicity, comorbidities, and recent infections of antinuclear antibody, rheumatoid factor, cyclic-citrullinated peptide test for juvenile idiopathic arthritis

No study provided complete information on accuracy modifiers of tests for JIA. Nordal et al.[34] addressed the test performance of ANA for JIA by subgroups based on the status of uveitis. The Sn of 81 percent for children with uveitis was considered higher than the Sn of 52 percent for children without uveitis. The authors did not provide the subgroup-specific Sp.

Key Question 5. Clinical impacts due to the results of antinuclear antibody, rheumatoid factor, and cyclic-citrullinated peptide tests

No studies provided information to address this question.

Rating the Body of Evidence

The body of evidence was assessed using the AHRQ system for grading the strength of evidence and is presented in Table 12. The risk of bias domain was based on the QUADAS results. Overall studies were assessed as "moderate" primarily due to spectrum composition bias, disease progression bias, and lack of adequate reporting of selection criteria. The consistency domain was based on the degree of agreement of the test estimates across the studies. Most studies were considered to provide "indirect" evidence due to underlying difference between the target population of children with undiagnosed MSK symptoms and the study populations with known disease status. The precision domain was based on the sample size and the size of the 95 percent confidence intervals of the Sn and Sp estimates.

Table 12. Strength of evidence of diagnostic accuracy and validity of antinuclear antibody, rheumatoid factor, and cyclic-citrullinated peptide tests for pediatric systemic lupus erythematosus and juvenile idiopathic arthritis

Key Question	N studies (N disease; N control)	Outcome	Strength of evidence domains				Overall strength of evidence
			Risk of bias	Consistency	Directness	Precision	
3.1 ANA for pSLE	2 (67; 134)	Sn	Moderate	Consistent	Indirect	Precise	Low
		Sp	Moderate	Consistent	Indirect	Precise	Low
3.2 ANA for JIA	8 (1,067; 315)	Sn	Moderate	Inconsistent	Indirect	Imprecise	Low
		Sp	Moderate	Consistent	Indirect	Precise	Moderate
3.3 IgM-RF for pSLE	1 (14; 32)	Sn	Moderate	Unknown	Indirect	Imprecise	Insufficient
		Sp	Moderate	(Single study)	Indirect	Imprecise	Insufficient
3.4 IgM-RF for JIA	16 (1,091; 993)	Sn	Moderate	Inconsistent	Indirect	Imprecise	Low
		Sp	Moderate	Consistent	Indirect	Precise	Moderate
3.5 CCP for pSLE	No studies	-		-	-	-	Insufficient
3.6 CCP for JIA	8 (772; 940)	Sn	Moderate	Inconsistent	Indirect	Imprecise	Low
		Sp	Moderate	Consistent	Indirect	Precise	Moderate
4 Accuracy modifier	No studies	-	-	-	-	-	Insufficient
5 Clinical impact of tests	No studies	-	-	-	-	-	Insufficient

ANA = antinuclear antibody; CCP = cyclic-citrullinated peptide; Ig = immunoglobulin; JIA = Juvenile Idiopathic Arthritis; N = number; NA = not applicable; RF = rheumatoid factor; SLE = systemic lupus erythematosus; Sn = sensitivity; Sp = specificity

Applicability

The study populations were relatively heterogeneous. Studies came from various geographic regions including North and South America, Europe, and Asia. Patients came from a variety of settings including medical centers, inpatient and outpatient clinics, pediatric hospitals, specialized pediatric rheumatology departments, and local communities. Control groups captured a wide range of conditions from healthy to various nonrheumatic and other rheumatic diseases. Overall, the age of participants covered a wide range from infancy to the end of adolescence. Age of disease onset was not reported by most studies, but when reported was generally between age 1 and 15 years. Disease activity and severity were rarely described, but when reported more than half of the study participants had active disease. A wide range of test positive cutoffs (in titers) were also considered in the included studies. The diagnostic performance of the tests did not differ significantly across the spectrum of patients, institutional sources, and cutoff thresholds, thus implying an acceptable generalizability of the results of ANA, RF, and CCP tests.

Of particular note with respect to applicability is the study design used in the majority of studies. All studies, but one, used a case control design in which the index tests were administered to patients with known disease status. However, their usefulness when administered to children with undiagnosed MSK symptoms is not clear. This is because, while test performance as measured by Sn and Sp does not vary across populations, the PPV changes dramatically depending on the baseline prevalence (or pretest probability of disease). Case control studies that compare children with disease to a healthy population in a 1:1 ratio (in effect a 50 percent disease prevalence) will appear to have good discriminatory power. In an unselected group of children with MSK pain where prevalence of JIA or pSLE is less than one percent, the same test will identify more false positives than true positives. We developed a series of hypothetical scenarios to demonstrate this (Table 13).

Table 13. Hypothetical scenarios for PPV at different baseline disease prevalence

	PPV	NPV
ANA for pSLE (Sn = 91%, Sp = 84%)		
Baseline prevalence 1%	5%	100%
Baseline prevalence 50%	85%	90%
ANA for JIA (Sn = 36%, Sp = 96%)		
Baseline prevalence 1%	8%	99%
Baseline prevalence 50%	90%	60%
RF for JIA (Sn = 12%, Sp = 98%)		
Baseline prevalence 1%	6%	99%
Baseline prevalence 50%	86%	53%
CCP for JIA (Sn = 9%, Sp = 99%)		
Baseline prevalence 1%	8%	99%
Baseline prevalence 50%	90%	52%

ANA = antinuclear antibody; CCP = cyclic-citrullinated peptide; JIA = juvenile idiopathic arthritis; NPV = negative predictive value; PPV = positive predictive value; pSLE = pediatric systemic lupus erythematosus; RF = rheumatoid factor; Sn = sensitivity; Sp = specificity

Summary and Discussion

Summary

Incidence and prevalence of musculoskeletal pain in children and adolescents

There is a paucity of data to address Key Question (KQ) 1 regarding the incidence and prevalence of musculoskeletal (MSK) pain in children. While the prevalence of MSK pain ranged between 2 and 52 percent, it is notable that as many as 50 percent of children reported that they experience MSK pain. The noninflammatory causes of MSK pain among children were much more common than inflammatory causes (97 percent versus 3 percent).

Prevalence of test positivity in health children and adolescents

Similarly, there was little evidence to address KQ 2 about test positivity in healthy children. From our review, we found that among the healthy control groups, ANA positivity ranged from 0 to 18 percent, and RF positivity was estimated at 3 percent. We did not identify any studies that examined CCP positivity among healthy children.

Antinuclear antibody test for pediatric systemic lupus erythematosus

Two case control studies provided indirect evidence addressing KQ 3.1 (ANA for pSLE). High sensitivity (Sn) (91 and 100 percent) and specificity (Sp) (84 and 85 percent) were observed; however, these test characteristics might be inflated due to incorporation bias since a positive ANA test was likely used as one of the criteria for diagnosing pSLE. The strength of the body of evidence for both Sn and Sp is low due to the small number of studies and potential biases. Further research is very likely to have an important impact on our confidence in the test estimates and may change the estimates.

Antinuclear antibody test for juvenile idiopathic arthritis

Eight studies provided indirect evidence addressing KQ 3.2 (ANA for JIA). Most studies used the indirect immunofluorescence (IIF) assay method. The positive cutoffs ranged from titer 1:10 to 1:320. Despite this range of cutoffs, studies appeared to only spread within the lower left quadrant in the HSROC curve, indicating a pattern of low Sn and high Sp. The test could classify JIA patients from control subjects significantly better than random chance, as indicated by the lack of overlap between the 95 percent confidence ellipse and the diagonal line in the hierarchical summary receiver operating curve (HSROC) curve. Overall, Sn ranged from 1 to 62 percent, while Sp was generally high, ranging from 73 to 100 percent. The variability of Sn was partly explained by the onset types of JIA, in which the Sn tended to be lower for systemic JIA compared with both the pauci/oligoarticular and polyarticular subgroups. The strength of evidence is low for Sn and moderate for Sp, suggesting that further research is very likely (for Sn) and likely (for Sp) to change our confidence in the test estimates and may change the estimates.

Antinuclear antibody test for children with undiagnosed MSK pain

No studies directly examined the question of the usefulness of ANA testing in a child with MSK pain. Although ANA had a high Sp for a diagnosis of pSLE or JIA in the studies examined, the results do not take into account the difference in prevalence between MSK pain and specific diagnoses of JIA and SLE in the pediatric population. The overall prevalence of MSK pain in childhood is 2 to 50 percent, compared with a prevalence of 0.1 percent for JIA and incidence of

0.00036 percent for pSLE. The studies included in this review showed a range of positive ANAs in healthy controls between 0 and 27 percent (median = 3 percent based on three studies).

If children with MSK pain are assumed to have the same likelihood of a positive ANA as healthy children, then there will be many more children with MSK pain who have a positive ANA than have either JIA or SLE as a clinical diagnosis, making the positive predictive value (PPV) in this population insufficient (see Table 14 in the previous section). The evidence therefore does not support the routine testing of ANA in the population of children with MSK pain.

Rheumatoid factor for pediatric systemic lupus erythematosus

One study published in 1966 provided indirect evidence addressing KQ 3.3 (RF for pSLE). The strength of evidence is insufficient. However, further research is unlikely to be published given the general perception among rheumatologists that RF is not an appropriate diagnostic test for pSLE.

Rheumatoid factor test for juvenile idiopathic arthritis

One study provided direct evidence and 15 studies provided indirect evidence addressing KQ 3.4 (RF for JIA). Half of the studies used solid-phase immunoassay as the assay method, while the other half generally used IIF and Latex methods. A variety of positive thresholds was used with the cutoff titers ranging from ≥1:9 to ≥1:160.

Studies tended to aggregate tightly in the lower left quadrant of the HSROC curve. The 95 percent confidence ellipse did not overlap but was in close proximity with the diagonal line, suggesting the test could distinguish JIA patients from control subjects significantly better than random chance. Sn was poor and ranged from 4 to 50 percent. Sp tended to be high with almost all studies reporting Sp above 90 percent. The wide range of Sn could not be explained by subgroup analysis by JIA onset types. The strength of evidence is low for Sn and moderate for Sp suggesting that further research is very likely (for Sn) and likely (for Sp) to change our confidence in the test estimates and may change the estimates.

Rheumatoid factor test for children with undiagnosed MSK pain

The one retrospective cohort study that examined RF testing in children presenting with MSK complaints showed low Sn (5 percent) and high Sp (98 percent). As outlined for ANA testing, if the prevalence of JIA is low,(0.1 percent even in a population of children with MSK complaints, there will be more false positives than true positives. Furthermore, in a cohort of JIA patients more will be RF negative than positive. This suggests that a positive test for RF has little predictive value when used in a setting where the prevalence of JIA is low. The authors further suggest that since RF tends to be positive in older girls with JIA, there is little reason to order RF in the assessment of a young child with MSK complaints even if JIA is likely.

Cyclic-citrullinated peptide test for pediatric systemic lupus erythematosus

No studies addressed this question (KQ 3.5).

Cyclic-citrullinated peptide test for juvenile idiopathic arthritis.

Eight studies provided indirect evidence addressing KQ 3.6 (CCP for JIA). All studies used the ELISA assay method. The definitions of test positive cutoffs varied across studies. Studies tended to aggregate tightly in the lower left corner in the HSROC curve, indicating high Sp and

low Sn. The test does not appear to adequately classify children with and without JIA. Sn was poor and ranged from 2 to 42 percent. Sp was considered high in most studies, ranging from 85 to 100 percent. The strength of the body of evidence is low for Sn and moderate for Sp suggesting that further research is very likely (for Sn) and likely (for Sp) to change our confidence in the test estimates and may change the estimates.

Cyclic-citrullinated peptide test for children with undiagnosed MSK pain.

No studies directly assessed this question. As previously mentioned the predictive value of a test varies with baseline prevalence of the disease and is generally higher when the prevalence or pretest probability is 50 percent or greater. This test has low Sn and high Sp, and even in a JIA cohort, the majority of children will have a negative test. This result may falsely reassure the patient, parent, or physician that the child does not have an inflammatory arthritis. In an unselected population where the prevalence of JIA is likely to be less than one percent, even fewer positive tests will be seen and the PPV is less than 10 percent. The situation is not that different in a population of children with MSK pain where the probability of inflammatory disease is approximately 3 percent.

Implications

While one study provided direct evidence by examining the target population of children with undiagnosed MSK pain, the remaining 28 included studies only provided indirect evidence to address the test characteristics of ANA, RF, and CCP. The studies generally indicated that the tests were very specific, but not sensitive, with the exception of ANA for pSLE (Table 14); however, the strength of evidence for Sn was low. There is limited evidence indicating sex and comorbidity with uveitis may result in different test performance of the ANA test for JIA. No conclusion can be drawn regarding 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.

Based on the available evidence, the tests should not be considered as diagnostic by themselves. A recurring result of strong Sp and poor Sn was observed for almost all the test-disease combinations The low Sn suggests the inappropriateness for broad screening of rheumatic diseases. The high Sp implies the tests may be useful to help confirm a suspected diagnosis. Where patient history and physical assessment by physicians strongly suggest the presence of an inflammatory arthritis or connective tissue disease, the pretest probability of the serologic tests would correspondingly increase potentially making them more useful in this group of patients. The serological tests should be considered as adjunctive tools to increase the diagnostic accuracy.

The ANA, RF, and CCP tests are generally considered poor for ruling out JIA due to the high false negative rates, which is also the case for RF and CCP tests in pSLE. However, two studies[29,30] examining ANA for pSLE showed high performance in both Sn and Sp.

Limitations

The generally low strength of evidence is attributable to the small number of studies, small number of participants, medium risk of bias, lack of consistency, and lack of precision in this literature. All the case control studies were rated as “unclear” for their spectrum composition since there was uncertainty on how representative the distinctive disease and control groups were of the target population (children with undiagnosed MSK pain). The selection criteria of patients

were rarely described in sufficient detail. Since most studies did not report the time between the clinical diagnosis and administration of tests or, if reported, whether the time was longer than 6 months, the studies were prone to progression bias. For studies examining ANA for pSLE, incorporation bias is a concern because ANA is considered one of the diagnostic criteria for SLE.[66]

There was also lack of consistency and precision of results. The inconsistency mainly occurred with Sn in which most of the test-disease combinations had a wide range of Sn from very poor to poor (between 0 and 60 percent). No variables (e.g., accuracy modifiers, cutoff thresholds) could entirely explain the variation of Sn performance; however, some subgroup analyses by test assay method and subtype of JIA explained some of the variation. Imprecision could partially be explained by the small sample size which resulted in very wide 95 percent confidence intervals.

There is a paucity of evidence examining potential accuracy modifiers.Three studies provided some test performance estimates by sex and uveitis. However, the reporting was incomplete as both subgroup-specific Sn and Sp estimates were not always presented precluding meaningful interpretation. There was no evidence that addressed clinically important outcomes.

In addition to the issues identified above, there are limitations for systematic reviews of diagnostic test accuracy. First, there is a possibility of publication bias. The impact of publication bias on the results of diagnostic test accuracy reviews is not well understood nor have the tools to investigate publication bias in these reviews been developed.[98] However, we conducted a comprehensive and systematic search of the published literature for potentially relevant studies. Search strategies included combinations of subject headings and free text words. These searches were supplemented by hand searching for grey literature (i.e., unpublished or difficult to find studies). Despite these efforts, we recognize that we may have missed some studies.

There is also a possibility of study selection bias. However, we employed at least two independent reviewers to identify potentially relevant studies, and therefore feel confident that the studies that were excluded from this report were done so for consistent and appropriate reasons.

Conclusion

We conducted a systematic review to assess the diagnostic characteristics of ANA, RF, and CCP tests to diagnose pSLE and JIA in children with MSK pain. Virtually all the evidence was indirect as studies examined children with known disease status rather than a spectrum of children with undiagnosed MSK symptoms. The included studies generally indicated that the tests were specific but not sensitive, with the exception of ANA for pSLE. 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.

Based on the available evidence, these tests should not be considered as diagnostic by themselves. The low Sn suggests the inappropriateness using them for broad screening in children and adolescents with MSK pain. However, the high Sp may imply their potential application in confirming a diagnosis as an adjunct to a clinical assessment that suggests the presence of an inflammatory arthritis or connective tissue disease. The serological tests may be useful as supplementary tools to increase diagnostic accuracy.

Future Research

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

- Conduct prospective cohort studies or diagnostic randomized trials
- Include a spectrum of children and adolescents with MSK symptoms
- Include a sufficiently large number of participants in order to produce precise estimates
- Conduct multiple test measures to increase reliability
- Schedule a short duration between the index test and reference standard
- Examine potential accuracy modifier and include clinically important outcomes
- Studies examining ANA to diagnose pSLE should explicitly describe whether a positive ANA is part of the diagnostic criteria.

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.[58] This could be considered as a guide for authors reporting studies that evaluate diagnostic tests. Particularly, prospective studies should report duration between index test and reference standard, selection criteria for both disease and controls, and detailed information on the index test including assay method, manufacturer, cutoff used, and any multiple measures employed.

Future studies should also consider investigating various accuracy modifiers. Accuracy modifiers allow the assessment of the robustness of the test estimates over a wide range of clinical and biological determinants. Tests might perform with greater or lesser accuracy based on specific patient characteristics, and it is important for physicians to have this knowledge in order to assess the applicability of the tests to children presenting to primary care physicians with MSK pain and/or joint swelling. Finally, future studies should include clinically important outcomes such as quality of life and psychological distress. Such outcomes are critical for decisionmaking for health care professionals and for patients and their parents.

Table 14. Summary of evidence of the diagnostic characteristics of antinuclear antibody, rheumatoid factor, and cyclic-citrullinated peptide tests for pediatric systemic lupus erythematosus and juvenile idiopathic arthritis

Key Questions	# 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 for pSLE	2, N = 201	91-100%	84-85%	71-84%	96-100%	Low for Sn Low for Sp
3.2 ANA for JIA	8, N = 1,382	1-62% (51%)	73-100% (95%)	88-100% (96%)	15-70% (30%)	Low for Sn Moderate for Sp
3.3 RF (IgM) for pSLE	1, N = 46	29%	88%	50%	74%	Insufficient
3.4 RF (IgM) for JIA	16, N = 2,084	4-50% (13%)	67-100% (99%)	45-100% (93%)	20-77% (47%)	Low for Sn Moderate for Sp
3.5 CCP for pSLE	No studies					Insufficient
3.6 CCP for JIA	8, N = 1,712	2-42% (8%)	85-100% (100%)	20-100% (100%)	11-76% (30%)	Low for Sn Moderate for Sp
KQ 4: Accuracy modifiers	No studies†	-	-	-	-	Insufficient
KQ 5: Clinical impacts	No studies	-	-	-	-	Insufficient

*Median is not presented if there are ≤4 studies.

†No study provided complete data on both subgroup-specific Sn and Sp.

ANA = antinuclear antibody; CCP = cyclic-citrullinated peptide; IgM = immunoglobulin M; JIA = juvenile idiopathic arthritis; PPV = positive predictive value; N = number; NPV = negative predictive value; RF = rheumatoid factor; SLE = systemic lupus erythematosus; Sn = sensitivity; Sp = specificity

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Abbreviations

AAP	American Academy of Pediatrics
ACR	American College of Rheumatology
AHRQ	Agency of Healthcare Research and Quality
ANA	Antinuclear antibody
ARA	American Rheumatism Association
AU	Arbitrary unit
BSR	British Society for Rheumatology
CCP	Cyclic-citrullinated peptide
CDSR	Cochrane Database of Systematic Reviews
CINAHL	Cumulative Index to Nursing and Allied Health Literature
ELISA	Enzyme linked immunosorbent assay
EPC	Evidence-based practice center
EULAR	European League Against Rheumatism
FANA	Fluorescent antinuclear antibody test
FN	False negative
FP	False positive
HEp	Human epithelial cell line
HSROC	Hierarchical summary receiver operating characteristic
Ig	Immunoglobulin
IIF	Indirect immunofluorescence
ILAR	International League of Associations for Rheumatology
IU	International unit
JIA	Juvenile idiopathic arthritis
JRA	Juvenile rheumatoid arthritis
KQ	Key question
LST	Latex slide test
ml	Milliliter
MSK	Musculoskeletal
NIAMSK	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NPV	Negative predictive value
NRG	Nonrheumatic disease group
OD	Optical density
ORG	Other-rheumatic disease group
PLT	Photometric latex test
PPV	Positive predictive value
pSLE	Pediatric systemic lupus erythematosus
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RU	Relative unit
SD	Standard deviation
Sn	Sensitivity
Sp	Specificity
SSC	Standard sensitized test
TEP	Technical expert panel

TN	True negative
TOO	Task order officer
TP	True positive
U	Unclear
U.S.	United States
WHO	World Health Organization