Effective Health Care Program

Comparative Effectiveness Review
Number 50

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

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

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
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Contract No. HHSA 290 2007 10021 I

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AHRQ Publication No. 12-EHC015-EF
March 2012

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

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

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 evidences, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see 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 are essential to the Effective Health Care Program. Please visit the Web site www.effectivehealthcare.ahrq.gov to see draft research questions and reports or to join an email 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 email to epc@ahrq.hhs.gov.

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Acknowledgements

We are grateful to members of the Technical Expert Panel who provided direction for the scope and content of the review. We also thank all the individuals at AHRQ, the Scientific Resource Center, and the peer reviewers for their comments and suggestions.

We also thank the following University of Alberta Evidence-based Practice Center staff for their assistance: Amy Beaith (designed and conducted literature searches), Ben Vandermeer (statistical consultation), Heather McPhee (screening and inclusion/exclusion), and Teodora Radisic (literature retrieval).

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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 or joint swelling, compared with clinical diagnoses of pediatric systemic lupus erythematosus (pSLE) and juvenile idiopathic arthritis (JIA). To explore differences in test performance for accuracy modifiers including age, sex, race or 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. We conducted comprehensive searches in nine electronic databases. We also hand searched 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. We calculated sensitivity (Sn) and specificity (Sp).

Results. The search identified 11,695 citations; 28 were included in the review. Only one cohort study examined the test performance of RF to diagnose JIA among children with undiagnosed MSK pain. It demonstrated an Sn of 5 percent and an Sp of 98 percent. Fifteen case-control studies did not specifically address the test performance of RF among children with MSK pain. The strength of evidence is low for both Sn and Sp. The 12 case-control studies that examined other test-disease combinations did not specifically address the prevalence of positive tests for ANA or CCP among children presenting with undiagnosed MSK pain. The strength of evidence is insufficient to determine the test performance of ANA or CCP to diagnose JIA or pSLE in children with undiagnosed MSK pain. No studies addressed children with joint swelling. There was no evidence addressing the prespecified accuracy modifiers or clinically important outcomes.

Conclusions. Most of the evidence from the 28 studies included in the review was not applicable to the population of interest as most studies examined children with known disease rather than with undiagnosed MSK pain. No studies provided a complete investigation on accuracy modifiers. No studies examined clinically important outcomes such as the impact of the test results on referrals, ordering of additional tests, patient management, and patient and parent anxiety levels. Because the Sn and Sp of these tests have yet to be verified, current evidence does not support their use as diagnostic tests for children with undiagnosed MSK pain. They have a potential application as an adjunct to a clinical assessment that suggests the presence of an inflammatory arthritis or connective tissue disease.

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Executive Summary

Background

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

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

A complete history and physical examination is generally considered to be the best way to make a diagnosis of inflammatory arthritis.[3,5] Physicians may request serological tests such as antinuclear antibody (ANA), rheumatoid factor (RF), and cyclic-citrullinated peptide (CCP) when children and adolescents are suspected of having inflammatory arthritis, despite the fact that the diagnostic performance, usefulness, and proper interpretation of these tests are uncertain in pediatric populations.

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

Key Questions

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

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

KQ 1. Prevalence and Incidence

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

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

KQ 2. Natural History

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

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

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

KQ 3. Diagnostic Performance

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

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

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

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

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

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

KQ 4. Accuracy Modifiers

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

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

KQ 5. Clinical Impacts of Test Results

In children and adolescents aged 18 years or less with undiagnosed MSK pain and/or joint swelling, do ANA, RF, and CCP test results affect referral decisions, additional tests ordered, clinical management, and patient and parent anxiety due to the clinical uncertainty and additional tests?

Methods

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

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

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

We examined the diagnostic test characteristics, including Sn, Sp, PPV, and NPV, for each study and presented forest plots to summarize the results for each test–disease pairing. Accuracy modifiers including age, sex, race or ethnicity, recent infection, and comorbidity were analyzed if studies provided sufficient data to calculate Sn and Sp. We examined any qualitative or

quantitative information on clinically important outcomes including referral, additional tests ordered, change in clinical management, and patient or parent anxiety due to the test results.

Two reviewers independently assessed the strength of evidence for KQs 3 to 5 using the Agency for Healthcare Research and Quality (AHRQ) system for grading evidence (AHRQ Guidance for the Evaluation of Medical Tests [draft]).[8] We assessed the strength of evidence for Sn and Sp. Assessments were based on the quantity and quality of individual studies, the directness of evidence, and the consistency and precision of the results. For each outcome, the strength of evidence was graded as high, moderate, low, or insufficient.

Results

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

The prevalence of MSK pain ranged between 2 and 52 percent[9-11] and increased steadily with age throughout childhood and adolescence.[12,13] No studies reported the prevalence of joint swelling in children.

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

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

KQ 2. The Etiology and Resolution of Pediatric MSK Pain

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

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

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

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

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

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

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

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

One case-control study[35] with 46 children (14pSLE, 32 controls) examined the prevalence of a positive IgM-RF test for pSLE. The control group comprised healthy children and children with other rheumatic conditions or ulcerative colitis. The Sn was 29 percent, and Sp was 88 percent (Table A).

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

One retrospective cohort study[36] examined the records of pediatric patients who had an RF test and were seen at a children's hospital. Among the 437 patient records, 105 had a diagnosis of JIA. The remaining 332 patients had a mix of MSK complaints (n = 201) or symptoms suggestive of an underlying autoimmune disease (n = 131). The Sn was 5 percent, and Sp was 98 percent (Table A).

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

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

No studies provided information to address this question.

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

Seven case-control studies[24,25,30,48-51] including 1,643 participants (729 JIA, 914 controls) examined the prevalence of a positive CCP test in children with JIA and controls including healthy children, children with nonrheumatic conditions, and children with other autoimmune diseases. Sn ranged from 2 to 42 percent, and Sp ranged from 93 to 100 percent (Table A).

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

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

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

No studies provided information to address this question.

Summary

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

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

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

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

Implications

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

Limitations

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

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

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

Conclusion

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

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

Future Research

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

- In order to better understand the natural history of undiagnosed MSK pain in children and the probability of a diagnosis of JIA or pSLE in this population, prospective cohort studies of children and adolescents with MSK pain are needed. Given the low prevalence of JIA or pSLE, a sufficiently large number of participants is required.
- For the research to be generalizable, researchers need to use consistent test methodology and cutoffs as well as consistent and well-accepted clinical criteria for the diagnoses of JIA and pSLE.

- Potential accuracy modifiers of test performance need to be examined, including age, sex, race, history of recent infections, presence of clinical characteristics other than MSK pain (e.g., morning stiffness, joint swelling, uveitis, malar rash, cytopenias).
- The clinical impact of these tests (e.g., referral decisions, additional tests ordered, clinical management, quality of life, psychological distress of child and/or parents) should be assessed in cohort studies.
- Efforts are needed to improve the overall quality of reporting of primary studies of diagnostic test accuracy. The STARD checklist includes 25 items that address the level of detail that should be specified within such studies including descriptions of participants, tests methods, statistical methods, and results.[56] This could be considered as a guide for authors reporting studies that evaluate diagnostic tests.

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

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

*Median not presented if ≤ 4 studies.

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

Introduction

Musculoskeletal Symptoms

Musculoskeletal (MSK) pain is pain that affects muscles, bones, ligaments, tendons, and nerves.[57] Childhood MSK pain is common, with estimated prevalence ranging from 2 to 50 percent.[1,10,12] Young children especially may have difficulty characterizing their symptoms, which makes 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 the presence of a serious condition such as arthritis or lupus, which could lead to permanent damage, may prompt consultation with a physician.[58]

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.[3,5] In contrast, rheumatic causes, such as an inflammatory arthritis, are much less prevalent and 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 universally present in children with JIA (16 percent of children with JIA do not report pain[59]) and pSLE.

A complete history and physical examination is generally considered to be the best way to make a diagnosis of inflammatory arthritis.[3,5] However, the complaint of MSK pain is often nonspecific and when combined with a lack of confidence in the MSK physical examination, can make it difficult to arrive at an accurate diagnosis.[3,4] Hence, physicians may request additional laboratory tests. Serological tests such as antinuclear antibody (ANA), rheumatoid factor (RF), and cyclic-citrullinated peptide (CCP) may be ordered by physicians when children and adolescents are suspected of having a rheumatic cause for their MSK pain, despite the fact that the diagnostic performance and usefulness of these tests and the proper interpretation of the results for pediatric populations are largely uncertain.

This comparative effectiveness review provides a synthesis of the evidence on the test performance of ANA, RF, and CCP tests in children and adolescents with undiagnosed MSK pain and on the impact of test results on clinical decisionmaking and clinically important outcomes. The report is intended for a broad audience including: primary care physicians who may consider ordering ANA, RF, or CCP tests in a child with MSK pain; health payers who provide coverage for these tests; and parents or caregivers who would like to know whether these tests can determine if their child does or does not have a particular disease.

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.[60] It is estimated that the incidence of pSLE is 0.3 to 0.9 per 100,000 children per year[61] and the prevalence is 3.3 to 8.8 per 100,000.[62] The onset of pSLE is rare before 5 years of age and

uncommon before adolescence, after which the rates of occurrence stabilize.[60] The diagnosis of pSLE is generally based on the classification criteria of the American College of Rheumatology (ACR)[55,63] which include specific signs, symptoms, and laboratory tests, including a positive ANA (see Appendix A). Left untreated, SLE is often progressive and can be fatal.[64] As awareness of the occurrence of pSLE has increased, early diagnosis has become more common[60] and rapid introduction of effective immunosuppressive treatment has lead to improved outcomes.[64]

JIA is the most common chronic inflammatory disease of children affecting approximately 1 in 1,000 children.[65,66] Classification criteria developed by the International League of Associations for Rheumatology (ILAR)[67]are used worldwide to provide consistency across clinical research studies. The ILAR criteria have supplanted earlier criteria of the ACR[68] for the classification of juvenile rheumatoid arthritis (JRA) and the European League Against Rheumatism (EULAR)[69] for the classification of juvenile chronic arthritis (JCA). To maintain consistency, the acronym JIA will be used to represent JIA, JRA, and JCA throughout this report.

It is important to note that in all three of the published criteria patients are classified based on characteristic symptoms and signs, including the presence of objective arthritis for a minimum of 6 to 12 weeks. In spite of significant overlap, the classification criteria vary in terms of how the presence of RF is addressed. In the ILAR criteria, the presence of a positive RF on two occasions *excludes* five of the seven subtypes of JIA. In the EULAR criteria, a positive RF changes the classification from JCA to JRA. In the ACR criteria, RF is not considered at all in the classification. Therefore, depending on the criteria being used, the reported prevalence of RF will be different.

In adults with suspected rheumatoid arthritis, tests for RF[70] and, more recently, CCP antibodies are frequently requested as part of the diagnostic work-up.[70,71] 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 JIA.

Without effective treatment, JIA can progress and cause damage to cartilage, bone, and soft tissues, and may lead to severe disability, functional loss, and, in rare cases, organ failure and death.[66,71] 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.[66]

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 fragment crystallizable (Fc) portion of the immunoglobulin (Ig) G, and CCPs, respectively. An ANA test is often used to screen for autoimmune conditions,[74] especially when a diagnosis of SLE is suspected.

The gold standard for ANA testing is the indirect immunofluorescence (IIF) ANA test, which involves incubation of serial dilutions of the patient's sera with substrate cells, usually human

epithelial tumor line (HEp-2).[72] If antibody to nuclear elements is present, binding to the substrate will be detected by fluorescein-conjugated anti-human Ig, which attaches to the antibody and is visually inspected using a fluorescence microscope. The assessment of fluorescence is based on the interpretation of this inspection and, as a result, may be somewhat subjective and vary from one laboratory to another. Each laboratory determines the cutoff used for a positive test, and as a result, titers from one laboratory cannot be compared with another. Research has shown that using a high titer ANA does not increase the positive predictive value for connective tissue disease.[73]

The detection of antibodies may also be assessed using enzyme immunoassay (EIA). In EIA, an antigen is affixed to a surface, and then the patient serum sample is applied over the surface so ANA, if present, can bind to the antigen. EIA methods and expected results vary among manufacturers because there is no agreed standard for the antigen preparations that should be included or for the concentration(s) of the relevant antigen preparations.[74] Results of studies that compare IIF and EIA for ANA have been inconsistent, with some showing poor correlation,[26] and others demonstrating consistency.[74]

RFs are Ig that react specifically with the Fc fragment of the IgG molecule. 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 disease testing, including arthritis.[75] The presence of RFs is typically determined by agglutination assays, nephelometry, or EIA. The agglutination assay method mainly employs latex beads as a substrate to which human or rabbit IgG is bound. Nephelometry is a photometric test in which complexes formed between the IgG and RF are detected by light scattering, which is dependent upon the concentration of those immune complexes. Latex agglutination and nephelometry only measure 19S IgM-RF, whereas EIAs have been designed to measure the various RF isotypes.[75]

The CCP test detects the presence of autoantibodies to citrullinated peptides in serum.[76] Abnormal citrullination of various peptides is present in a variety of human diseases, including rheumatoid arthritis, psoriasis, and multiple sclerosis. However, the formation of antibodies to citrullinated peptides seems to be specific for adult patients with rheumatoid arthritis.[71] Anti-CCP2 (a second-generation assay) is currently the most widely used anti-CCP assay.[71]Anti-CCP antibodies and anti-citrullinated filaggrin antibodies are locally produced in inflamed joints, and citrullinated fibrin is found in the synovia of patients with rheumatoid arthritis.[77] In adults, a CCP test is usually ordered along with a RF test when evaluating a patient with inflammatory arthritis and when rheumatoid arthritis is considered on the differential diagnosis. The utility of the CCP test in pediatric rheumatic conditions is not clear.

Objectives of This Evidence Report

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

In addition to providing this background information, the objectives of this report were to assess the test performance of ANA, RF, and CCP tests in children and adolescents with

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

Key Questions

KQ 1. Prevalence and Incidence

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

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

KQ 2. Natural History

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

KQ 3. Diagnostic Performance

KQ 3.1. In children and adolescents aged 18 years or less with undiagnosed MSK pain and/or joint swelling, what is the test performance (sensitivity, 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?

KQ 4. Accuracy Modifiers

KQ 4.1. In children and adolescents aged 18 years or less with undiagnosed MSK pain and/or joint swelling, do age, sex, race/ethnicity, comorbidities, and recent infections modify the diagnostic performance (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?

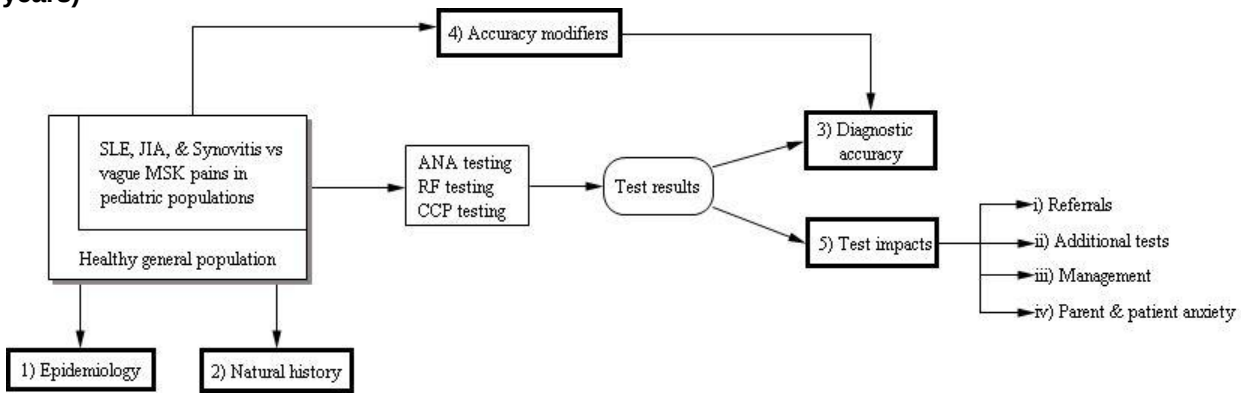
KQ 5. Clinical Impacts of Test Results

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?

Analytic Framework

The analytic framework (Figure 1) depicts the five KQs within the context of the pediatric population (≤18 years) with MSK complaints. 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 anxiety. The epidemiology and natural history of the targeted rheumatic conditions are described independently of the test results.

Figure 1. Analytic framework for antibody testing for MSK complaints 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 comparative effectiveness review. A core research team was assembled by the University of Alberta Evidence-based Practice Center. In consultation with the Agency for Healthcare Research and Quality (AHRQ), a panel of key informants was created to provide input in the development of the Key Questions (KQs) and scope of the evidence report. The public was invited to comment on these KQs over a period of 1 month. After reviewing the public comments, the KQs 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.

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).

KQs 1 and 2, the answers to which serve as background information, were addressed using a narrative approach by locating and summarizing information on the related disease prevalence, incidence, and natural history 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 rigorous systematic review process including a comprehensive search of the following electronic databases: MEDLINE®, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, 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. We applied a diagnostic search filter and a child filter, when applicable. We conducted the original searches from 1960 to January 2010, and updated them in December 2010 and September 2011.

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 "anticycliccitrullinated peptide" OR "anti-CCP").

In addition to the searches of electronic databases, we searched the following conference proceedings and scientific meetings: American College of Rheumatology, Joint meeting of the British Society for Rheumatology, Canadian Rheumatology Association, European League Against Rheumatism, International League of Associations for Rheumatology, and American

Academy of Pediatrics from 2005 to 2010. Additionally, we searched the bibliographies of the included studies and reviews for relevant studies. We set up search alerts for PubMed and Web of Science 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 database.

Study Selection

A two-stage selection was carried out. For the initial broad screening stage, each article was screened by two independent reviewers who assessed the relevance of the study based on its title and abstract using prespecified broad screening criteria. We excluded articles if they were judged clearly as (1) not primary studies reporting on prevalence of conditions, diagnostic test accuracy, or clinical impact, (2) not ANA, RF, or CCP tests, or (3) did not include a pediatric population. 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 (Sn) and specificity (Sp) or (2) clinically important outcomes. Discrepancies between the reviewers were resolved through discussion or third party adjudication, if needed. The corresponding author of the article was contacted when additional information was needed for making the inclusion/exclusion decisions.

Table 1. Inclusion and exclusion criteria

Article Type	- Studies reporting original research - Any language - No restriction on publication year, except studies of ANA published before 1980 (excluded because detection methods using animal substrates are no longer considered valid)
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 (i.e., ANA, RF, CCP)
Study Design	- Studies of any design that included at least 2 participants
Index Tests	- ANA, RF, CCP - The assay method of ANA using animal substrate was excluded (pre-1980 methodology) - The test of hidden RF was excluded (proposed as an alternate to RF in JIA in 1970s but does not relate to conventional RF tests)
Reference Standard	- Diagnosis of pSLE or JIA based on clinical criteria
Outcomes	- For KQ 3 and 4: Studies providing sufficient data to calculate Sn and Sp - For KQ 5: Studies providing numerical data or a narrative description regarding referral decisions, additional tests ordered, clinical management, and patient and parent anxiety due to the clinical uncertainty or additional tests

ANA = antinuclear antibody; CCP = cyclic-citrullinated peptide; JIA = juvenile idiopathic arthritis; KQ = Key Question; MSK = musculoskeletal; RF = rheumatoid factor; pSLE = pediatric systemic lupus erythematosus; Sn = sensitivity; Sp = specificity

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. We extracted data for the following categories: study characteristics, participant characteristics, index test, reference standard, and outcomes.

Quality Assessment

We assessed the methodological quality of each study using the QUADAS checklist.[7] The tool assesses important common biases in diagnostic studies including spectrum, incorporation, and verification biases (Appendix C). Spectrum bias occurs when included patients do not represent the intended spectrum of severity for the target condition (i.e., JIA or pSLE).[78] Incorporation bias occurs when the index test (i.e., ANA, RF, or CCP) is incorporated in the reference standard (e.g., ILAR or ACR criteria).[78] Partial verification bias occurs when a nonrandom set of patients does not undergo the reference standard.[78] Differential verification bias occurs when a set of patients is verified with a second reference standard, especially when this selection depends on the index test result.[78] Disease progression bias occurs when the patient's condition changes between administering the index test and the reference standard. Information bias occurs when the results of the index test are interpreted knowing the results of the reference standard, and vice versa.[78]

Two reviewers performed quality assessment independently. Decision rules regarding application of QUADAS were developed a priori. Discrepancies were resolved through discussion or third party adjudication, as needed.

Data Analysis and Synthesis

We summarized the general characteristics of studies using descriptive statistics. For the diagnostic performance, we constructed 2x2 tables and calculated Sn, Sp, and positive and negative predictive values. For visual interpretation we presented the results in forest plots. 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. 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 strength of evidence was graded for KQs 3 to 5 using the AHRQ system for grading the strength of evidence (AHRQ Guidance for the Evaluation of Medical Tests (draft)).[8] We assessed four domains including risk of bias, consistency, directness, and precision, and developed 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; "directness" was scored as direct or indirect based on the relevance of the evidence to the corresponding KQ; "precision" was scored as precise or imprecise based on the width of 95 percent confidence intervals. 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).[8]

Peer Review and Public Commentary

Six experts in pediatric medicine, pediatric rheumatology, rheumatology, pathology, and diagnostic testing reviewed the draft report and provided feedback. Reviewer comments were considered by the University of Alberta Evidence-based Practice Center in preparation of the final report. All peer reviewer comments and the 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 their 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 MSK pain within a 3 month period.[6,79] More girls reported pain (65 percent) than boys (55 percent).[79] Up to 30 percent of children and adolescents reported having experienced chronic pain (including MSK pain) which lasted for more than 6 months.[2,80-83] No studies reported the prevalence of joint swelling in children.

The prevalence of MSK pain ranges from 2 percent in 12-year-olds to 52 percent in 18-year-olds.[9-11] The prevalence of MSK pain increases steadily with age throughout childhood and adolescence.[12,13] Haraldstad, et al.,[79] examined 1,238 Norwegian schoolchildren aged 8 to 18 years and found that the prevalence of back pain increased with age for both sexes.[79] 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-year-olds.[80] While some studies reported that low back, neck, shoulder, leg, and chronic pain were more prevalent in girls than boys,[79,80,84] two studies found no such difference,[85,86] and one found male predominance.[13]

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[14-22] All of these studies examined children and adolescents 18 years old or less except Baig and Shere,[18] which included 1- to 19-year olds and Youngchiyud, et al.,[21] 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[87] indicated that most children with a positive RF test did not have JIA,[36,88] and most children with JIA did not have a positive RF.[89] Kasapcopur, et al.,[23] investigated 118 healthy Turkish children, using a cutoff of >25 IU/ml, and found a rate of 3 percent RF positivity.[23] The prevalence of CCP positivity in healthy children was 0 and 0.6 percent as reported in two studies.[24,25]

Key Question 2.1. Noninflammatory Causes of Pediatric Musculoskeletal Pain

De Inocencio[12] conducted a retrospective chart review on 317 children between 3 and 15 years of age in a primary care setting in Madrid.[12] 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 cause of 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). 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

De Inocencio[12] reported that 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 arthritis (0.8 percent). This was consistent with an earlier study by McGhee, et al.,[59] who conducted a retrospective chart review of 226 children with MSK pain who were referred for an initial rheumatology consultation. Among a group of 111 patients whose only presenting complaint was MSK pain, one child (1 percent) had a rheumatic disease (ankylosing spondylitis), and none had pSLE or JIA. The majority (81 percent) had mechanical MSK or overuse syndromes as explanations of their pain. In addition, the same study observed that among the 76 children diagnosed with JIA, only 12 (16 percent) included pain as part of their main complaints. Earlier observations by Sherry, et al.,[90] stated that 14 percent of patients with a confirmed diagnosis of JIA reported no pain. Although the numbers differ, both studies confirm that the absence of MSK pain does not rule out a diagnosis of JIA.

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.[91] Mikkelsson, et al.,[92] examined 1,628 school-aged children with weekly pain at baseline and found that 52 percent reported MSK pain at 1-year followup.

Results: Part Two

Literature Search

The search strategies identified 11,994 citations from electronic databases and hand searching (Figure 2). Initial broad screening identified 496 potentially relevant citations. Of these, we included one retrospective cohort study and 27 case-control studies; all 28 studies addressed KQ 3 (diagnostic performance). No study provided subgroup data to address KQ 4 (diagnostic modifiers). No study addressed KQ 5 (test impacts). See Appendix D for a list of excluded studies.

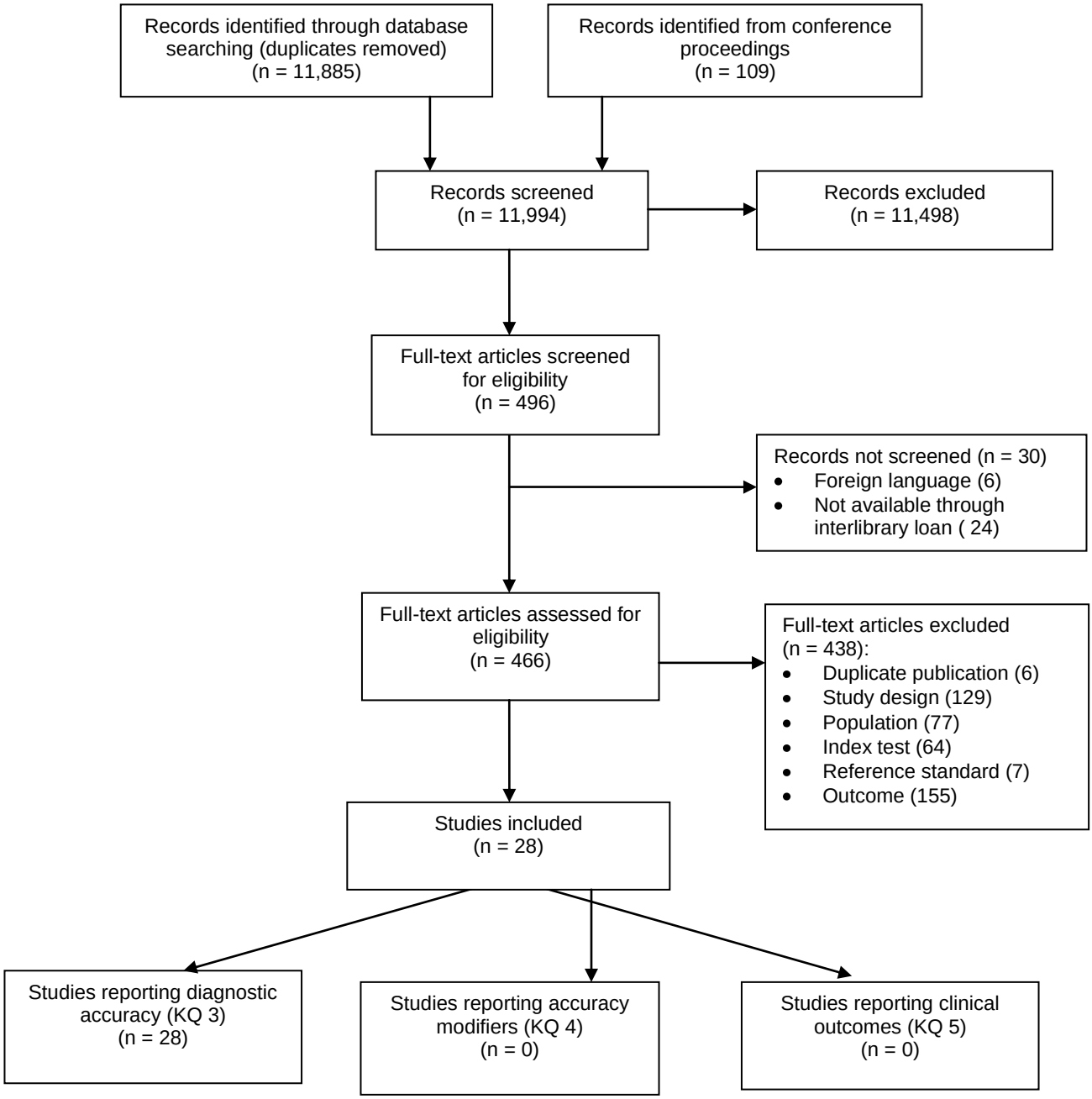
Characteristics of Included Studies

The 28 included studies were published between 1966 and 2009 (Appendix F). The mean age (where reported) of children ranged from 6.4 to 15 years of age. The studies were all published as full manuscripts in peer-reviewed journals. Thirteen studies[24,30,31,33,37-39,41,43,44,46,48,49] were conducted in Europe, nine [26,28,29,32,35,36,45,47,50] in North America, two[40,42] in South America, three[27,34,51] in Asia, and one[25] in Africa. Nine studies[26,28,32,37,39,45,46,48,50] received funding from government, four[24,30,34,51] from academic institutions, and four[27,31,41,47] from noncommercial institutions. The remaining 11 studies[25,29,33,35,36,38,40,42-44,49] did not report the source of funding.

One study[36] used a retrospective cohort design and included the spectrum of children with diagnosed and undiagnosed MSK pain. The remaining 27 studies used a case-control type design. The ANA test was examined in nine studies (two[26,27] for pSLE and eight[26,28-34] for JIA). The RF test was examined in 17 studies (one[35] for pSLE and 16[28,30,33,35-47] for JIA). The CCP test was examined in seven studies[24,25,30,48-51] for JIA. There were no studies that examined the CCP test for pSLE.

All of the studies included patients with MSK pain; none specifically addressed children with joint swelling.

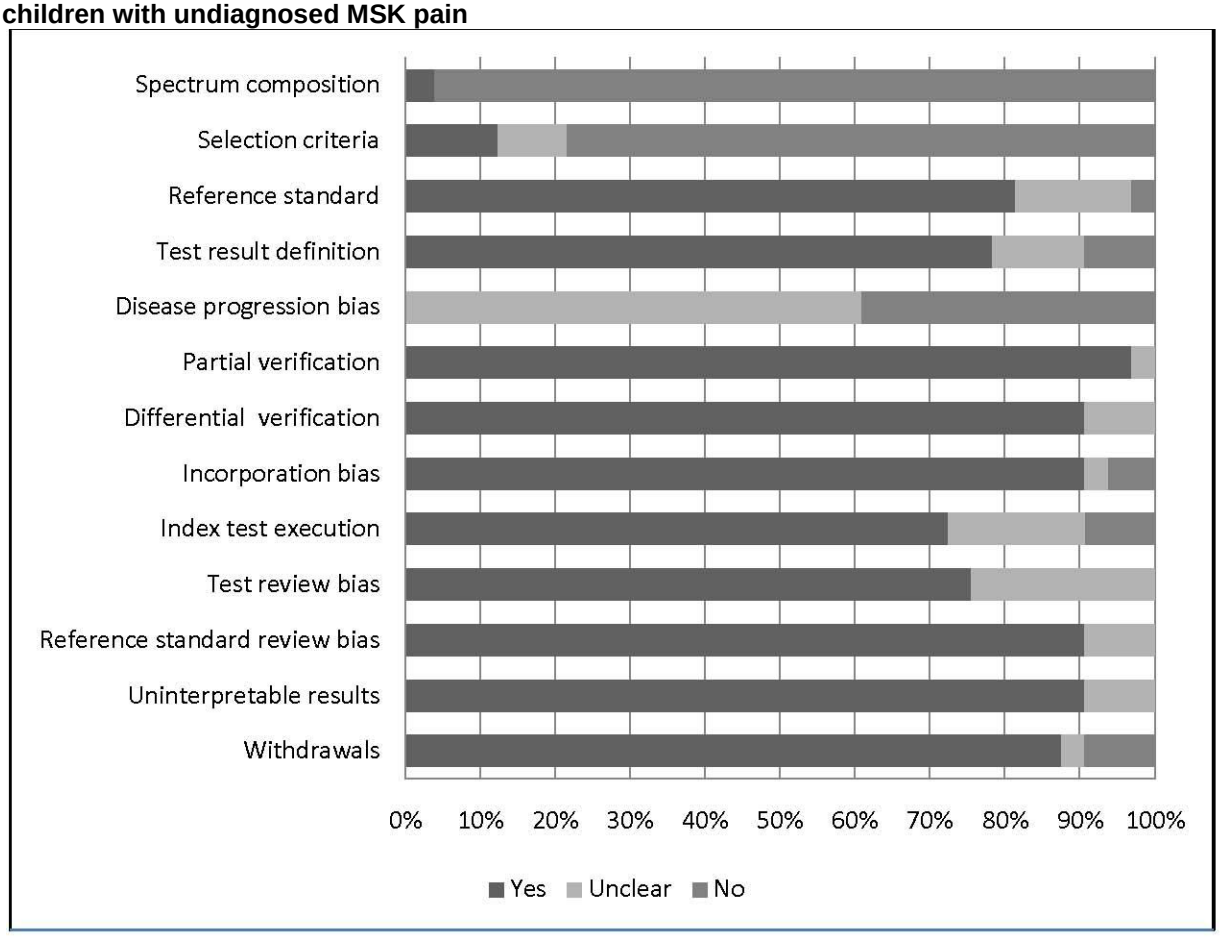
Figure 2. Results of literature search, retrieval, and selection



Methodological Quality of Included Studies

The methodological quality of the 28 included studies is summarized in Figure 3; summary tables are presented in Appendix E. Overall, there is substantial concern regarding spectrum bias. Most studies (97 percent) were rated "no" regarding the representativeness of the study population due to the case-control study design. The selection criteria of the population were not described adequately in most studies (83 percent). For studies examining ANA for pSLE, incorporation bias is a concern because ANA is considered one of the classification criteria for SLE.[55]

Figure 3. Methodological quality of studies evaluating ANA, RF, and CCP tests for pSLE and JIA in children with undiagnosed MSK pain



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

Key Question 3.1. Antinuclear Antibody Test for Pediatric Systemic Lupus Erythematosus

Study Characteristics

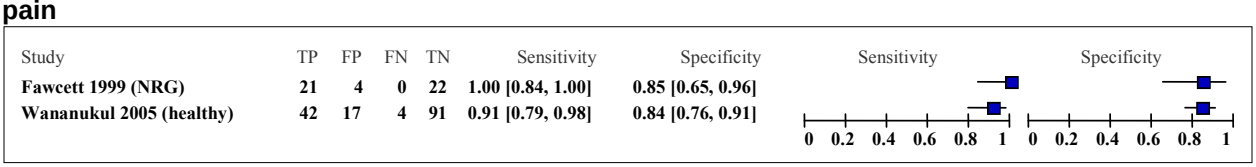
Two case-control studies[26,27] including 201 children (67 pSLE, 134 controls) examined the prevalence of a positive ANA test in children with pSLE and control groups including healthy children and children scheduled for elective orthopedic surgery (Table 2). No information was provided in either study about the presence or absence of MSK pain or joint swelling in either the patient or the control groups.

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

Quantitative Results

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). Among control groups, the proportions of children who tested positive on the ANA test were 16 percent (healthy children) and 15 percent among patients scheduled for elective orthopedic surgeries.

Figure 4. Sensitivity and specificity of an ANA test for pSLE in children with undiagnosed MSK pain



ANA = antinuclear antibody test; FN = false negative; FP = false positive; MSK = musculoskeletal; NRG = nonrheumatic diseases; pSLE = pediatric systemic lupus erythematosus; TN = true negative; TP = true positive

Table 2. Description of studies evaluating an ANA test for pSLE in children with undiagnosed MSK pain

Author Year Location	Design	Funding	Source of Study Population	Control	Classification Criteria	Assay Method	Positive Threshold
Fawcett[26] 1999	Case-control	Government	NR	Underwent elective orthopedic surgical procedures	ACR	IIF	Discernible fluorescence pattern at titer 1:40
Wananukul[27] 2005	Case-control	Non-commercial institution	NR	Scheduled for elective surgery (adenotonsillectomy, herniorrhaphy or plastic surgery)	ACR	IIF	Titer ≥ 1:40

ANA = antinuclear antibody test; ACR = American College of Rheumatologists; IIF = indirect immunofluorescence method; MSK = musculoskeletal; pSLE = pediatric systemic lupus erythematosus; NR = not reported

Key Question 3.2. Antinuclear Antibody Test for Juvenile Idiopathic Arthritis

Study Characteristics

Eight case-control studies[26,28-34] including 1,382 children (1,067 JIA, 315 controls) examined the prevalence of a positive ANA test in children with JIA and control groups (Table 3). In four studies all participants were under 18 years of age; two studies[28,34] included a small number of young adults. Two studies[26,31] did not report age.

For the control groups, three studies[32-34] included healthy children, five[26,28-31] included children with nonrheumatic conditions, and one[32] included children with other rheumatic diseases. Three studies[29,31,34] recruited JIA patients from general hospitals or clinics, and the source was unreported by the remaining studies. For the classification of JIA, four studies[26,28,32,34] used the ACR criteria, two[30,31] used the ILAR criteria, one[33] used the EULAR criteria, and the classification criteria were unreported in one study.[29] Only one study (Nordal, et al.,[31]) looked at children with MSK pain who either had a diagnosis of JIA or acute lymphoblastic leukemia; none of the other studies commented on the presence or absence of MSK pain or joint swelling in either the patient or control groups. The frequency of uveitis or iridocyclitis was reported by three studies: 18 percent of JIA patients in Nordal, et al.,[31] 6 percent of JIA patients in Osborn, et al.,[32] and 3 percent in Wakhlu, et al.[34]

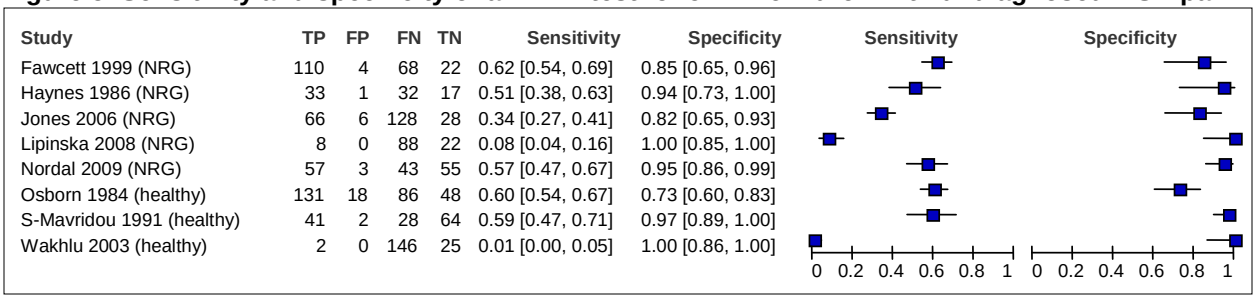
IIF was used in all studies except Jones, et al.,[29] who did not report the method used. In studies that reported the positive cutoff titers, the titers ranged from >1:20 to >1:320. Fawcett[26] and Nordal, et al.,[31] examined multiple assay methods of ANA for JIA (Appendix F).

Quantitative Results

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 5). Analyses by subtypes of JIA are presented in Appendix G.

Among the healthy controls, the proportion of children (three groups[32-34]) who tested positive for ANA ranged from 0 to 27 percent (median = 3). Among controls with nonrheumatic conditions,[26,28-31] the proportion of children with positive tests ranged from 0 to 18 percent (median = 6). There were two studies that reported very low Sn. Both had zero percent prevalence of a positive ANA among controls. In one,[30] this could be explained by their use of a high cutoff titer of >1:320. In the other study[34] the reason for the disparity is unclear.

Figure 5. Sensitivity and specificity of an ANA test for JIA in children with undiagnosed MSK pain



ANA = antinuclear antibody test; FN = false negative; FP = false positive; JIA = juvenile idiopathic arthritis; MSK = musculoskeletal; NRG = nonrheumatic disease group; TN = true negative; TP = true positive

Table 3. Description of studies evaluating an ANA test for JIA in children with undiagnosed MSK pain

Author Year Location	Design	Funding	Source of Study Population	Control	Classification Criteria	Assay Method	Positive Threshold
Fawcett[26] 1999 U.S.	Case-control	Government	NR	NRG: Undergoing elective orthopedic surgical procedures	ACR	IIF	Positive if a clearly discernible fluorescence pattern appears at 1:40 serum dilation
Haynes[28] 1986 U.S.	Case-control	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[29] 2006 North America	Case-control	NR	Randomly selected patients from multiple medical centers	NRG: Patients with acute lymphoblastic leukemia	NR	NR	Titer > 1:80
Lipinska[30] 2008 Poland	Case-control	Academic institution	NR	NRG: Children with functional CV system dysfunction	ILAR	IIF	Titer > 1:320
Nordal[31] 2009 Norway	Case-control	Non-commercial institution	NR	NRG: Children undergoing elective outpatient procedures; no diagnosis of inflammatory diseases	ILAR	IIF	Titer > 1:80
Osborn[32] 1984 U.S.	Case-control	Government	Pediatric clinic	Healthy and ORG	ACR	IIF	Titer > 1:40
Siamopoulou-Mavridou[33] 1991 Greece	Case-control	NR	NR	Healthy	EULAR	IIF	Titer > 1:40
Wakhlu[34] 2003 India	Case-control	Academic institution	Immunology clinic	Healthy	ACR	IIF	Titer: > 1:40

ANA = antinuclear antibody test; ACR = American College of Rheumatology; CV = cardiovascular; EULAR = The European League Against Rheumatism; IIF = indirect immunofluorescence method; ILAR = International League of Associations for Rheumatology; JIA = juvenile idiopathic arthritis; MSK = musculoskeletal; NR = not reported; NRG = nonrheumatic disease group; ORG = other rheumatic diseases group

Key Question 3.3. Rheumatoid Factor Test for Pediatric Systemic Lupus Erythematosus

Study Characteristics

One case-control study by Hanson, et al.,[35] examined the prevalence of a positive IgM-RF test in 14 children with pSLE and 32 controls. The study was published in 1966. The assay method for the RF test was latex fixation. As the study was conducted prior to the development of the ACR criteria for the classification of SLE, patients were diagnosed based on criteria developed by Cook, et al.,[93] and Urbach.[94] The control groups comprised a mix of healthy children and children with other rheumatic conditions and ulcerative colitis. The study did not comment on the presence or absence of MSK pain or joint swelling in either the patients or controls.

Quantitative Results

The Sn was 29 percent and Sp was 88 percent.[35] The proportion of children who tested positive for RF was 13 percent.

Key Question 3.4. Rheumatoid Factor Test for Juvenile Idiopathic Arthritis

Study Characteristics

One retrospective cohort study by Eichenfield, et al.,[36] examined the records of pediatric patients who had a RF test and were seen in the walk in clinic, inpatient service, emergency department, or Pediatric Rheumatology Center at The Children's Hospital of Philadelphia (Table 4). Among the 437 patient records that were evaluated, 105 had a diagnosis of JIA according to ACR criteria. The remaining 332 patients (combined into one control group) had a mix of MSK complaints (n = 201) or symptoms suggestive of an underlying autoimmune disease (n = 131).

Fifteen case-control studies examined the prevalence of a positive RF in children with JIA and controls (Table 4). The diagnosis was based on the ACR criteria in nine studies,[28,36,39-42,45-47] the EULAR criteria in four,[33,37,38,44] and the ILAR criteria in one.[33] Two[35,43] did not state which classification criteria were used. In one study, 62 percent of patients had chronic bilateral iridocyclitis.[46] For the control groups, nine studies[33,37-41,44,46,47] used healthy children, three[28,30,45] used children with nonrheumatic conditions, one[42] used children with other rheumatic conditions, and two studies[35,43] used a mixed group that included healthy children and children with nonrheumatic and other rheumatic conditions. None of the case-control studies commented on the presence or absence of MSK pain or joint swelling in the patient or control groups. Studies reporting data on non-IgM RF tests are presented in Appendix F.

Quantitative Results

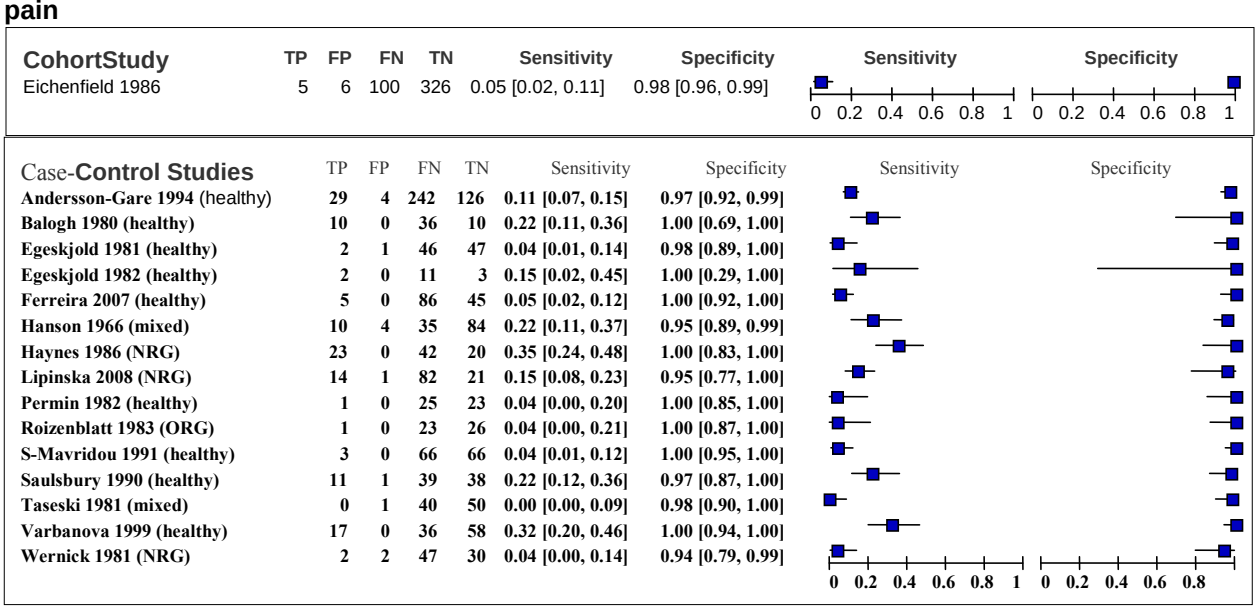
Results from the cohort study by Eichenfield, et al.,[36] show an Sn of 5 percent and a Sp of 98 percent (Figure 6). This is consistent with the RF results from the same center's total JIA population (6.9 percent) as reported in their paper. The authors also analyzed the post-test probability of JIA based on the reported Sn and Sp. The analyses take into account the pretest probability or prevalence of JIA, which in this cohort was 24 percent. The results showed that

probability of JIA increased to 45 percent with a positive test. They also showed that in a "typical" primary care practice, the probability of JIA went from 0.3 percent to 0.7 percent with a positive test.

Fifteen case-control studies, including 1,647 children (986 JIA, 661 controls) examined the prevalence of a positive IgM-RF test (Figure 6). Sn ranged from 0 to 35 percent (median = 11 percent), Sp ranged from 94 to 100 percent (median = 100 percent), PPV ranged from 0 to 100 percent (median = 100 percent), and NPV ranged from 20 to 71 percent (median = 48 percent).

The proportion of healthy children who tested positive ranged from 0 to 3 percent (median = 0). For the controls with nonrheumatic conditions, the proportion ranged from 0 to 6 percent (median = 5). For the controls (two groups) that included a mix of healthy children and children with other conditions, the proportion that tested positive ranged from 2 to 5 percent. There does not appear to be a relationship between the cutoff titer used (if reported) and Sn. Analyses by subtypes of JIA are presented in Appendix G.

Figure 6. Sensitivity and specificity of an RF (IgM) test for JIA in children with undiagnosed MSK pain



FN = false negative; FP = false positive; IgM = immunoglobulin M; JIA = juvenile idiopathic arthritis; MSK = musculoskeletal; NRG = nonrheumatic disease group; ORG = other rheumatic diseases group; RF = rheumatoid factor; TN = true negative; TP = true positive.

Table 4. Description of studies evaluating an RF (IgM) test for JIA in children with undiagnosed MSK pain

Author Year Location	Funding	Source of Study Population	Non-disease Group	Classification Criteria	Assay Method	Positive Threshold
Cohort Study						
Eichenfield[36] 1986 U.S.	NR	Consecutive patients from pediatric hospital	NA (due to cohort design)	ACR	Latex fixation test	Titer > 1:80
Case-Control Studies						
Andersson-Gare[37] 1994 Sweden	Government	Epidemiological survey in south-western Sweden	Healthy	EULAR	EIA	Mean of control group + 2 sd
Balogh[38] 1980 Hungary	NR	Hospital consecutive patients	Healthy: Age- and sex-matched	EULAR/WHO workshop	Latex fixation test	NR
Egeskjold[39] 1981 Denmark	Government	NR	Healthy: Age- and sex-matched	ACR	IIF	Titer > 1:9
Egeskjold[46] 1982 Denmark	Government	NR	Healthy	ACR	IIF	Maximum of peak 2 displacement beyond normal range
Ferreira[40] 2007 Brazil	NR	Randomly selected patients from multiple centers of pediatric rheumatology	Healthy	ACR	Latex fixation test	Latex: 20 IU/ml
Hanson[35] 1966 U.S.	NR	NR	Healthy, NRG, ORG	Unclear	Latex fixation test	Titer > 1:160
Haynes[28] 1986 U.S.	Government and non-commercial institution	NR	NRG: Age-matched children with nonrheumatic diseases	ACR	EIA	Mean of control + 2 sd
Lipinska[30] 2008 Poland	Academic institution	NR	NRG: Age- and sex-matched children with functional cardiovascular system dysfunction	ILAR	EIA	24 RU/ml
Permin[41] 1982 Denmark	Non-commercial institution	NR	Healthy	ACR	IIF	Titer > 1:10
Roizenblatt[42] 1983 Brazil	NR	Pediatric clinic	ORG: Age- and sex-matched hypermobile children	ACR	EIA	Mean of control group + 2 sd

Table 4. Description of studies evaluating an RF (IgM) test for JIA in children with undiagnosed MSK pain (continued)

Author Year Location	Funding	Source of Study Population	Non-disease Group	Classification Criteria	Assay Method	Positive Threshold
Saulsbury[47] 1990 U.S.	Non-commercial institution	NR	Healthy	ACR	EIA	Titer > 1:20
Siamopoulou-Mavridou[33] 1991 Greece	NR	NR	Healthy: Age- and sex-matched children without rheumatic disease	EULAR	Latex fixation test	Mean optical density of healthy control + 3 sd
Taseski[43] 1981 Yugoslavia	NR	NR	Healthy and ORG (collagen diseases)	NR	Latex slide test	Agglutination visually detectable
Varbanova[44] 1999 Bulgaria	NR	NR	Healthy	EULAR	EIA	Mean IU of healthy control + 2 sd
Wernick[45] 1981 U.S.	Government	NR	NRG (scoliosis and neurologic diseases)	ACR	Solid phase radioimmunoassay	Mean of normal control + 2 sd

ACR = American College of Rheumatology; EULAR = The European League Against Rheumatism; EIA = enzyme immunoassay; IgM = immunoglobulin M; IIF = indirect immunofluorescence; ILAR = International League of Associations for Rheumatology; IU = international unit; JIA = juvenile idiopathic arthritis; ml = milliliter; MSK = musculoskeletal; NA = not applicable; NR = not reported; NRG = nonrheumatic disease group; ORG = other rheumatic diseases group; RF = rheumatoid factor; RU = relative unit; sd= standard deviation; WHO = World Health Organization

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

No studies provided information to address this question.

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

Study Characteristics

Seven case-control studies[24,25,30,48-51] including 1,643 participants (729 JIA, 914 control) examined the prevalence of a positive CCP test in children with JIA and controls (Table 5). None of the studies reported on the presence or absence of MSK pain or joint swelling in either the patient or control groups.

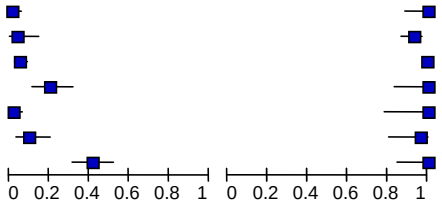
The control group in four studies[24,25,48,50] consisted of healthy children; two studies used a nonrheumatic patient control group (cardiovascular dysfunction,[30] allergies and idiopathic thrombocytopenia[51]). One study[49] used a mixed group of healthy children and children with other autoimmune diseases as their comparator. Four studies[24,25,30,51] used the ILAR criteria for classification of JIA; one study[50] used ACR criteria. All seven studies used the EIA method; however, different cutoff points were used. It is not clear from the reported methods which anti-CCP assays were used in the studies.

Quantitative Results

The Sn ranged from 2 to 42 percent and Sp ranged from 93 to 100 percent (Figure 7). The PPV ranged from 20 to 100 percent and NPV ranged from 11 to 71 percent. The proportion of healthy controls (four groups) that tested positive for CCP ranged from 0 to 0.6 percent (median = 0). The proportion of controls with nonrheumatic conditions (two groups) that tested positive ranged from 0 to 4 percent (median = 2). Among the mixed controls (one group), 7 percent tested positive. Subgroup analyses by subtypes of JIA are presented in Appendix G.

Figure 7. Sensitivity and specificity of a CCP test for JIA in children with undiagnosed MSK pain

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]



CCP = Cyclic-citrullinated peptide; FN = false negative; FP = false positive; JIA = juvenile idiopathic arthritis; MSK = musculoskeletal; NRG = nonrheumatic disease group; TN = true negative; TP = true positive

Table 5. Description of studies evaluating a CCP test for juvenile idiopathic arthritis in children with undiagnosed MSK pain

Author Year Location	Design	Funding	Source of Study Population	Control	Classification Criteria	Assay Method	Positive Threshold
Avcin 2002[48] Italy and Slovenia	Case-control	Government	NR	Healthy	NR	EIA	70 units
Brunner 2006[49] Germany	Case-control	NR	NR	Healthy, other autoimmunopathies, NRG (undergoing cardiac therapy)	NR	EIA	2.5 RU
Ferucci 2005[50] U.S.	Case-control	Government	Cohort from Cincinnati and NIAMSD registry	Healthy	ACR	EIA	5 units/ml
Habib 2008[25] Egypt	Case-control	NR	NR	Healthy	ILAR	EIA	20 units/ml
Lipinska 2008[30] Poland	Case-control	Academic institution	NR	NRG (functional cardiovascular system dysfunction)	ILAR	EIA	5 RU
Kasapcopur 2004[24] Turkey	Case-control	Academic institution	Consecutive patients admitted to hospital outpatient department	Healthy	ILAR	EIA	5 RU
Kwok 2005[51] Hong Kong	Case-control	Academic institution	NR	NRG (allergy, idiopathic thrombocytopenia, and hepatitis C)	ILAR	EIA	20 units

ACR = American College of Rheumatology; CCP = cyclic-citrullinated peptide; EIA = enzyme immunoassay; ILAR = International League of Associations for Rheumatology; ml = milliliter; MSK = musculoskeletal; NR = not reported; RU = relative unit

Key Question 4.1. Accuracy Modifiers of Antinuclear Antibody, Rheumatoid Factor, Cyclic-Citrullinated Peptide Test for Pediatric Systemic Lupus Erythematosus

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

Key Question 4.2. Accuracy Modifiers of Antinuclear Antibody, Rheumatoid Factor, Cyclic-Citrullinated Peptide Test for Juvenile Idiopathic Arthritis

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

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 (Table 6). All case-control studies were assessed as "high risk of bias" primarily due to spectrum bias and lack of adequate reporting of selection criteria. Therefore, strength of evidence derived from case-control studies was initially assessed as "low". This assessment was downgraded to "insufficient" when other limitations were noted in any of the other domains. All studies were considered to provide "indirect" evidence due to the use of surrogate outcomes (i.e., test performance) instead of health outcomes.

Table 6. Strength of evidence for ANA, RF, and CCP tests for pSLE and JIA in children with undiagnosed MSK pain

Key Question	N Studies, (N disease; N control)	Outcome	Risk of Bias	Consistency	Direct-ness	Precision	Overall Strength of Evidence
ANA – pSLE	2 c-c	Sn	High	Consistent	Indirect	Precise	Insufficient
	(67; 134)	Sp		Consistent	Indirect	Precise	Insufficient
ANA – JIA	8 c-c	Sn	High	Inconsistent	Indirect	Imprecise	Insufficient
	(1,067; 315)	Sp		Consistent	Indirect	Precise	Insufficient
IgM-RF – pSLE	1 c-c	Sn	High	Unknown	Indirect	Imprecise	Insufficient
	(14; 32)	Sp		(single study)	Indirect	Imprecise	Insufficient
IgM-RF – JIA	1 cohort	Sn	Medium	Unknown	Indirect	Imprecise	Low
	(437)	Sp	Medium	(single study)	Indirect	Imprecise	Low
	15 c-c	Sn	High	Inconsistent	Indirect	Imprecise	Insufficient
	(986; 661)	Sp	High	Consistent	Indirect	Precise	Insufficient
CCP – pSLE	No studies	NA	NA	NA	NA	NA	Insufficient
CCP – JIA	7 c-c	Sn	High	Inconsistent	Indirect	Imprecise	Insufficient
	(729; 914)	Sp		Consistent	Indirect	Precise	Insufficient
Accuracy modifiers	No studies	NA	NA	NA	NA	NA	Insufficient
Clinical impact of tests	No studies	NA	NA	NA	NA	NA	Insufficient

ANA = antinuclear antibody; c-c = case-control; CCP = cyclic-citrullinated peptide; IgM = immunoglobulin M; JIA = juvenile idiopathic arthritis; N = number; MSK = musculoskeletal; NA = not applicable; RF = rheumatoid factor; pSLE = pediatric systemic lupus erythematosus; Sn = sensitivity; Sp = specificity

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. The study populations were relatively heterogeneous in terms of the ethnicity, and a wide range of conditions were included. The age of the participants was similarly broad, as was the age of disease onset (generally between age 1 and 15 years when it was reported). The settings in which the tests were conducted also varied. Disease activity and severity were rarely described, but when reported more than half of the study participants had active disease. The diagnostic performance of the tests did not appear to differ significantly across the spectrum of patients and institutional sources, which would normally imply that the results are generalizable to a broader population.

Only one[36] of the 28 studies examined the performance of these tests in children with undiagnosed MSK pain—the primary population of interest for this review. In the study by Eichenfield, et al.,[36] even with a highly selected population of children who had undergone an RF test, only 4.8 percent of children with JIA had a positive RF, and 6 of 332 (1.8 percent) of the

remaining children—including 115 with only MSK pain—were RF positive. The authors conducted further analyses which demonstrated that in the primary care setting, the pretest probability of 0.3 percent only increased to 0.7 percent with a positive test.

None of the remaining studies reported on the presence or absence of MSK pain in either the patients or controls, and in all of these studies, the patients had known diagnoses of either JIA or pSLE. For this reason, the applicability of the tests to children with undiagnosed MSK pain is unclear. In the clinical setting of MSK pain, physicians are primarily interested in the degree to which the test results might change the probability that a patient with a positive or negative test may or may not have the disease (the positive predictive value [PPV] and negative predictive value [NPV], respectively). The PPV and NPV of these tests will change dramatically depending on the baseline prevalence (or pretest probability) of disease. Therefore, case-control studies that compare children with disease to a healthy population in a 1:1 ratio (a 50 percent disease prevalence) may overestimate test performance and utility. In contrast, in children with undiagnosed MSK pain seen in a primary care setting where prevalence of JIA or pSLE is less than one percent[12] the same test will identify more false positives than true positives. We developed a series of hypothetical scenarios to demonstrate this (Table 7).

Table 7. Hypothetical scenarios for PPV at different baseline disease prevalence

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

Studies that have investigated the prevalence of musculoskeletal (MSK) pain in children report a wide range of prevalence from 2 to 52 percent. Noninflammatory causes of MSK pain account for the majority of diagnoses (97 percent). No studies reported the prevalence of joint swelling in children.

Prevalence of Test Positivity in Healthy Children and Adolescents

From the studies included in our review, among the healthy control groups, the median antinuclear antibody (ANA) positivity is three percent, median RF positivity is zero percent, and CCP positivity is less than one percent.

Test Performance of ANA, RF, and CCP in Children and Adolescents With Undiagnosed MSK Pain

Only one retrospective cohort study examined the test performance of rheumatoid factor (RF) to diagnose juvenile idiopathic arthritis (JIA) among children with MSK pain. It demonstrated a sensitivity (Sn) of 5 percent and a specificity (Sp) of 98 percent. Fifteen case-control studies did not specifically address the test performance of RF among children with MSK pain. The strength of evidence is low for both Sn and Sp (Table 8). Further evidence is likely to change our confidence in the estimates of performance, and is likely to change the estimates.

The 12 case-control studies looking at other test-disease combinations did not specifically address the prevalence of positive tests for ANA or cyclic-citrullinated peptide (CCP) among children presenting with MSK pain. The strength of evidence is insufficient to determine the test performance of ANA or CCP to diagnose JIA or pediatric systemic lupus erythematosus (pSLE) in children with undiagnosed MSK pain (Table 9).

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

Implications

There is insufficient evidence to determine the test performance of ANA or CCP in children with undiagnosed MSK pain. The strength of evidence is low for the utility of RF in the diagnosis of JIA in children with undiagnosed MSK pain. A result of high Sp and low Sn was observed for almost all the test-disease combinations. The generally low Sn suggests that it is inappropriate to use these tests in isolation (i.e., without clinical assessment) to make a diagnosis of JIA and pSLE. In spite of the high Sp, the low prevalence of JIA and pSLE in the target

population (i.e., children with undiagnosed MSK pain) makes the tests of limited diagnostic value. The presence of other clinical characteristics (e.g., morning stiffness, joint swelling, malar rash, cytopenia) may increase the pretest probability of the disease in question. While both the Sn and Sp for ANA for pSLE were high, this test in isolation has limited diagnostic value for children with undiagnosed MSK given the very low prevalence of pSLE, and up to 18 percent prevalence of false positive ANA in the general population.

Limitations

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

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

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

Conclusion

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

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

Future Research

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

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

Table 8.Summary of evidence of the diagnostic characteristics of ANA, RF, and CCP tests for pSLE and JIA in children with undiagnosed MSK pain

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

*Median not presented if ≤ 4 studies.

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

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Acronyms

ACR	American College of Rheumatology
AHRQ	Agency for Healthcare Research and Quality
ANA	Antinuclear antibody
ARA	American Rheumatism Association
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
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
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 diseases group
PPV	Positive predictive value
pSLE	Pediatric systemic lupus erythematosus
RF	Rheumatoid factor
SD	Standard deviation
Sn	Sensitivity
Sp	Specificity
SSC	Standard sensitized test
TN	True negative
TP	True positive
WHO	World Health Organization

Appendix A. American College of Rheumatology Criteria for Classification of Systemic Lupus Erythematosus

1997 Update of the 1982 American College of Rheumatology revised criteria for classification of systemic lupus erythematosus

1. Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or pericarditis	1. Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion ***OR*** 2. Pericarditis--documented by electrocardigram or rub or evidence of pericardial effusion
7. Renal disorder	1. Persistent proteinuria > 0.5 grams per day or > than 3+ if quantitation not performed ***OR*** 2. Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	1. Seizures--in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance ***OR*** 2. Psychosis--in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic disorder	1. Hemolytic anemia--with reticulocytosis ***OR*** 2. Leukopenia--< 4,000/mm^3 on ≥ 2 occasions ***OR*** 3. Lyphopenia--< 1,500/ mm^3 on ≥ 2 occasions ***OR*** 4. Thrombocytopenia--<100,000/ mm^3 in the absence of offending drugs
10. Immunologic disorder	1. Anti-DNA: antibody to native DNA in abnormal titer ***OR*** 2. Anti-Sm: presence of antibody to Sm nuclear antigen ***OR*** 3. Positive finding of antiphospholipid antibodies on: 1. an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2. a positive test result for lupus anticoagulant using a standard method, or 3. a false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Positive antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

The classification is based on 11 criteria. For the purpose of identifying patients in clinical studies, a person is defined as having SLE if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.
From: Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997;40:1725. Reprinted with permission from John Wiley and Sons.

Appendix B. Literature Search Strings

Title: ANA RF Anti CCP Testing Search Strategies
Database: MEDLINE , 1950 - present
Search name: ANA RF Anti CCP Testing -MEDLINE -
Notes: limits: human, 1960-2009
Date searched: Jan 21, 2010
Results: 5,389

1. citrulline/	35. or/14-15,19-27,31-34
2. exp Peptides, Cyclic/	36. Arthritis/
3. 1 and 2	37. ($arthritis or ($articular adj arthritis)).ti,ab.
4. ((anti adj ccp) or (citrullinated adj peptide*)).mp.	38. or/36-37
5. ((citrulline adj antibod*) or (anti-citrulline adj antibod*)).ti,ab.	39. exp child/ or (adolesc* or early or juvenile).ti,ab.
6. exp Antibodies, Antinuclear/	40. (JIA or JRA).ti,ab.
7. ((antinuclear adj antibod*) or (antinuclear adj factor*)).ti,ab.	41. or/39-40
8. (ana adj titer).ti,ab.	42. 38 and 41
9. (ANA adj2 test*).ti,ab.	43. exp Arthritis, Juvenile Rheumatoid/
10. (FANA adj2 test*).ti,ab.	44. ((juvenile or early) adj (rheumatoid or idiopathic) adj arthritis).ti,ab.
11. exp Rheumatoid Factor/	45. or/42-44
12. (rheumatoid adj factor*).ti,ab.	46. or/14-15,19,21-27,31-34,45
13. or/3-12	47. incidence/
14. exp Lupus Erythematosus, Systemic/	48. prevalence/
15. (JSLE or SLE or "lupus erythematosus").ti,ab.	49. exp disease progression/
16. exp Pain/di, et	50. Natural History/
17. Growth/ph	51. natural history.ti,ab.
18. (grow* and (pain or pains)).ti,ab.	52. or/47-51
19. 16 and (17 or 18)	53. exp Mass Screening/
20. musculoskeletal diseases/ or arm/ or leg/ or extremities/	54. exp "referral and consultation"/
21. 16 and 20	55. (screen* or refer*).ti,ab.
22. Fibromyalgia/	56. or/53-55
23. fibromyalgia.ti,ab.	57. exp "Reproducibility of Results"/
24. exp arthralgia/	58. exp "Sensitivity and Specificity"/
25. arthralgia.ti,ab.	59. Predictive Value of Tests/
26. ((joint* adj pain*) or (limb* adj pain*)).ti,ab.	60. (di or bl or cl or im).fs.
27. limp*.ti,ab.	61. exp Diagnostic Errors/
28. benign.ti,ab.	62. early diagnosis/
29. exp Joint Instability/	63. exp delayed diagnosis/
30. (joint adj (instability or hypermobility)).ti,ab.	64. Diagnosis, Differential/
31. 28 and (29 or 30)	65. or/57-64
32. Patellofemoral Pain Syndrome/	66. (cost or costs or economic*).ti,ab.
33. (patellofemoral adj pain adj syndrome).ti,ab.	67. exp "Costs and Cost Analysis"/
34. exp Synovitis/ or synovitis.mp.	68. cost-benefit analysis/
71. exp demography/	69. ec.fs.
72. age factors/ or "age of onset"/	70. or/66-68
73. sex factors/	95. (Pubert* or Pubescen* or Prepubescen*).mp.
74. infection/ or infection*.ti,ab.	96. exp Pediatrics/
75. anxiety/ or (anxious* or anxiety).ti,ab.	97. (Pediatric* or Paediatric* or Peadiatric*).mp.
76. comorbidity/	98. exp Schools/
77. or/71-76	99. (Nursery school* or Kindergar* or Primary school* or Secondary school* or Elementary school* or High school* or Highschool*).mp.
78. exp Rheumatic Diseases/di, co, et, im, pa, pp	100. or/85-99
79. exp Connective Tissue Diseases/di, co, et, im, pa, pp	101. adolescent/ and adult/
80. exp arthritis/di, co, et, im, pa, pp	102. 100 not 101
81. arthritis, rheumatoid/di, co, et, im, pa, pp	103. (52 or 56) and 35 and 102
82. arthritis, juvenile rheumatoid/di, co, et, im, pa, pp	104. 13 and 102 and 65 and (84 or 46)
83. exp Lupus Erythematosus, Systemic/di, co, et, im,	105. 13 and 46 and 102

pa, pp 84. or/78-83 85. exp infant/ 86. (Infant* or infancy or Newborn* or Baby* or Babies or Neonat* or Preterm* or Prematur* or Postmatur*).mp. 87. exp Child/ 88. (Child* or Schoolchild* or School age* or Preschool* or Kid or kids or Toddler*).mp. 89. exp Adolescent/ 90. Adoles*.mp. 91. (Teen* or Boy* or Girl*).mp. 92. exp Minors/ 93. minors*.mp. 94. exp Puberty/	106. 13 and (56 or 65) and 46 and 102 107. 13 and 77 and 102 108. (13 or 84) and 70 109. 13 and (35 or 45) and 102 110. 77 and 65 and 13 and 102 111. (52 or 56) and (45 or 84) and 102 112. 13 and (56 or 65) and 70 113. 13 and 70 114. or/103-113 115. humans/ NOT (humans/ and animals/) 116. 114 AND 115

Topic: ANA RF Anti CCP Testing Search Strategies
Database: EMBASE, 1980 - present
Search name: ANA RF Anti CCP Testing - EMBASE-amy

Notes: limits of: human, 1980-2009
Date searched: Jan 21, 2010
Results: 4,849

1. cyclic citrullinated peptide/ 2. ((anti adj ccp) or (citrullinated adj peptide*)).mp. 3. ((citrulline adj antibod*) or (anti-citrulline adj antibod*)).ti,ab. 4. exp Antinuclear Antibody/ 5. ((antinuclear adj antibod*) or (antinuclear adj factor*)).ti,ab. 6. (ana adj titer).ti,ab. 7. (ANA adj2 test*).ti,ab. 8. (FANA adj2 test*).ti,ab. 9. exp Rheumatoid Factor/ 10. rheumatoid factor*.ti,ab. 11. or/1-10 12. exp Systemic Lupus Erythematosus/ 13. (JSLE or SLE or "lupus erythematosus").ti,ab. 14. (grow* and (pain or pains)).ti,ab. 15. musculoskeletal diseases/ or arm/ or leg/ or extremities/ 16. pain/di, et 17. 15 and 16 18. exp arthralgia/ 19. arthralgia.ti,ab. 20. ((joint* adj pain*) or (limb* adj pain*)).ti,ab. 21. limp*.ti,ab. 22. Fibromyalgia/ 23. fibromyalgia.ti,ab. 24. benign.ti,ab. 25. exp Joint Instability/ or Joint hypermobility/ 26. (joint adj (instability or hypermobility)).ti,ab. 27. 24 and (25 or 26) 28. Patellofemoral Pain Syndrome/ 29. patellofemoral joint/ and pain/ 30. (patellofemoral adj pain adj syndrome).ti,ab. 31. knee pain/ or ankle pain/ 32. exp Synovitis/ or synovitis.mp. 33. "complex regional pain syndrome"/	37. or/35-36 38. exp child/ or (adolesc* or early or juvenile).ti,ab. 39. (JIA or JRA).ti,ab. 40. or/38-39 41. 37 and 40 42. exp Juvenile Rheumatoid Arthritis/ 43. ((juvenile or early) adj (rheumatoid or idiopathic) adj arthritis).ti,ab. 44. or/41-43 45. incidence/ or prevalence/ or seasonal variation/ 46. exp disease course/ 47. natural history.ti,ab. 48. or/45-47 49. exp mass screening/ or screening/ 50. exp "referral and consultation"/ 51. (screen* or refer*).ti,ab. 52. or/49-51 53. Differential Diagnosis/ 54. exp Reproducibility/ 55. exp "sensitivity and specificity"/ 56. Predictive Value of Tests/ 57. serodiagnosis/ 58. (di or bl or cl or im).fs. 59. exp Diagnostic Error/ 60. "diagnostic techniques and procedures"/ 61. diagnostic procedure/ 62. early diagnosis/ 63. Diagnostic Accuracy/ 64. physical examination/ 65. blood examination/ 66. "Pain Assessment"/ 67. or/53-66 68. (cost or costs or economic*).ti,ab. 69. exp economic aspect/ 70. cost-benefit analysis/ 71. ec.fs.

34. or/12-23,27-33 35. Arthritis/ 36. ($arthritis or ($articular adj arthritis)).ti,ab. 75. gender/ or sex difference/ 76. infection/ or infection*.ti,ab. 77. anxiety/ or (anxious* or anxiety).ti,ab. 78. comorbidity/ 79. or/73-78 80. exp newborn/ 81. (Infant* or infancy or Newborn* or Baby* or Babies or Neonat* or Preterm* or Prematur* or Postmatur*).mp. 82. exp Child/ 83. (Child* or Schoolchild* or School age* or Preschool* or Kid or kids or Toddler*).mp. 84. exp Adolescent/ 85. Adoles*.mp. 86. (Teen* or Boy* or Girl*).mp. 87. (minors* or juvenil*).mp. 88. exp Adolescence/ 89. (Pubert* or Pubescen* or Prepubescen*).mp. 90. exp Pediatrics/	72. or/68-70 73. exp demography/ or geographic distribution/ 74. age/ 91. (Pediatric* or Paediatric* or Peadiatric*).mp. 92. exp school/ or high school/ or kindergarten/ or middle school/ or nursery school/ or primary school/ 93. (Nursery school* or Kindergar* or Primary school* or Secondary school* or Elementary school* or High school* or Highschool*).mp. 94. or/80-93 95. (48 or 52) and 67 and 34 and 94 96. 11 and 94 and 67 and (34 or 44) 97. 11 and 94 and (34 or 44) 98. 11 and (67 or 52) and (34 or 44) and 94 99. 11 and 79 and 94 100. 11 and 79 and 67 101. 11 and 72 and (44 or 94) 102. 11 and 72 and (34 or 44) and 94 and 67 103. 11 and 94 and 67 104. or/95-103 105. adolescent/ and adult/ 106. 104 not 105 107. humans/ and animals/ 108. 106 not 107

Topic: ANA RF Anti CCP Testing Search Strategies
Database: CINAHL, 1960-present
Notes: limits of: human, 1980-2009
Date searched: Jan 21, 2010
Topic: ANA RF Anti CCP Testing Search Strategies

Database: Cochrane Library – CDSR and CENTRAL
Notes: limits: human, 1960-2009
Date searched: Feb 2010
Results: 216

#1(citrulline OR anti-ccp) or (rheumatoid factor) or (citrullinated peptide) or (antinuclear AND (antibod* OR factor*)) or (ANA OR FANA) and test* in Cochrane Reviews and Clinical Trials
#2 (lupus) or (JSLE OR SLE) or (limb or grow*) AND pain or (fibromyalgia) or (arthralgia) in Cochrane Reviews and Clinical Trials
#3 (joint AND (instability OR hypermobility)) or (patellofemoral pain syndrome) or (synovitis) or (JRA OR JIA) or (juvenile OR early) AND (rheumatoid OR idiopathic) AND arthritis in Cochrane Reviews and Clinical Trials
#4 (#2 OR #3)
#5 (incidence OR prevalence) or (disease AND (progression OR history)) or (natural history) in Cochrane Reviews and Clinical Trials
#6 (mass screening) or (screen*) or (refer*) or (consultation) or (referral and consultation) in Cochrane Reviews and Clinical Trials
#7 (sensitivity OR specificity) or (diagnostic error*) or (early diagnosis) or (delayed diagnosis) or (differential diagnosis) in Cochrane Reviews and Clinical Trials
#8 (demography) or (age of onset) OR (age factors) or (sex factors) or (infection) or (anxiety OR anxious*) in Cochrane Reviews and Clinical Trials
#9 (child*) or (adolescen*) or (infant* OR infancy OR newborn* OR baby OR babies) or (pediatric* OR paediatric*) in Cochrane Reviews and Clinical Trials
#10 (#1 AND #4 AND #7 AND #9) 42 edit delete #11 (#1 AND #4 AND #9)
#12 (**#1** AND **#8** AND **#9**) 185 edit delete #13 (#1 AND #4 AND #6 AND #9)
#14 (**#4** AND **#6** AND **#9**) 642 edit delete #15 ((**#5** OR **#6**) AND **#4** AND **#9**)
#16 (#10 OR #11 OR #12 OR #13 OR #14 OR #15)
#17 (#16), from 1960 to 2009
#18 (#10 OR #11 OR #12 OR #13)

#19 (#10 OR #11 OR #12 OR #13), from 1960 to 2009

Topic: ANA RF Anti CCP Testing Search Strategies
Database: Web of Science (ISI): Science Expanded, Social Sciences Expanded
Notes: limits: english only, human, 1980
Date searched: 9Feb10
Results: 856 (line #17)a

#17= #14 OR #13 OR #12 OR #10 OR #8
Refined by: Languages=(ENGLISH)
Databases=SCI-EXPANDED, SSCI Timespan=1960-2009
# 16= #14 OR #13 OR #12 OR #10 OR #8
Databases=SCI-EXPANDED, SSCI Timespan=1960-2009

# 15= #14 OR #12 OR #10 OR #8
Databases=SCI-EXPANDED, SSCI Timespan=1960-2009

# 14= #7 AND #6 AND #5 AND #1
Databases=SCI-EXPANDED, SSCI Timespan=1960-2009

# 13= #7 AND #6 AND #1
Databases=SCI-EXPANDED, SSCI Timespan=1960-2009

# 12= #11 AND #7 AND #5 AND #2
Databases=SCI-EXPANDED, SSCI Timespan=1960-2009

# 11= #4 OR #3
Databases=SCI-EXPANDED, SSCI Timespan=1960-2009

# 10= #9 AND #7 AND #2 AND #1
Databases=SCI-EXPANDED, SSCI Timespan=1960-2009

# 9= #5 OR #4
Databases=SCI-EXPANDED, SSCI Timespan=1960-2009

# 8= #7 AND #5 AND #2 AND #1
Databases=SCI-EXPANDED, SSCI Timespan=1960-2009

# 7= Topic=(infant*) OR Topic=(child*) OR Topic=(adolescen*) OR Topic=(pediatric* OR paediatric*)
Databases=SCI-EXPANDED, SSCI Timespan=1960-2009

# 6= Topic=(demography) OR Topic=((age factor*) OR (age of onset)) OR Topic=(sex factor* OR gender) OR Topic=(infection*) OR Topic=(anxiety*) OR Topic=(comorbid*)
Databases=SCI-EXPANDED, SSCI Timespan=1960-2009

# 5= Topic=(early diagnos*) OR Topic=(differential diagnos*) OR Topic=(delayed diagnos*) OR Topic=(diagnostic error*)
Databases=SCI-EXPANDED, SSCI Timespan=1960-2009

# 4= Topic=(screen*) OR Topic=(referral OR refer*) OR Topic=(consultation OR consult*)
Databases=SCI-EXPANDED, SSCI Timespan=1960-2009
# 3= Topic=(incidence) OR Topic=(prevalence) OR Topic=(disease progression) OR Topic=(disease history) OR Topic=(natural history)
Databases=SCI-EXPANDED, SSCI Timespan=1960-2009

# 2= Topic=(JSLE OR SLE OR lupus OR JIA OR JRA) OR Topic=((limb pain) OR (grow* pain)) OR Topic=(fibromyalgia OR arthralgia) OR Topic=(joint AND (instability OR hypermobility)) OR Topic=((patellofemoral pain syndrome) OR synovitis) OR Topic=((juvenile OR early) AND (rheumatoid OR idiopathic) and arthritis)
Databases=SCI-EXPANDED, SSCI Timespan=1960-2009

1= Topic=(antinuclear AND (antibod* OR factor* OR test*)) OR Topic=(anti-ccp OR (citrullinated peptide)) OR Topic=((ANA OR FANA) AND (test*)) OR Topic=(rheumatoid factor*)

Databases=SCI-EXPANDED, SSCI Timespan=1960-2009

Topic: ANA RF Anti CCP Testing Search Strategies
Database: Academic Science Complete (EBSCO)
Notes: Limits: human, 1960
Date searched: 9Feb10
Results: 226

S20= S17 or S18 Limiters - Published Date from: 19600101-20091231
S19= S17 or S18
S18= S14 NOT S16
S17= S14 and S15
S16= Animal
S15= Human
S14= S8 or S9 or S10 or S11 or S12 or S13
S13= S2 and S5 and S7
S12= S2 and S4 and S7
S11= S1 and S2 and S4 and S7
S10= S1 and S2 and S7
S9= S1 and S3 and S6 and S8
S8= S1 and S2 and S3 and S7
S7= Children or Pediatric or Paediatric or Infant or Adolescent or Adolescence
S6= Demography or Gender or Anxiety or Infection
S5= Incidence or Prevalence or Natural history
S4= Screening or Referral or Consultation
S3= Diagnostic errors or Diagnosis
S2= Lupus or Rheumatoid arthritis or Fibromyalgia or Synovitis
S1= citrulline or anti-ccp or Rheumatoid factor

Database	Dates searched	Date search ran	Number of results
MEDLINE (OVID)	1960-2009	14Jan10	5,389
EMBASE (OVID)	1980-2009	14Jan10	4,849
CINAHL (EBSCO)	1960-2009	14Jan10	374
CDSR & CENTRAL (Cochrane)	1960-2009	9Feb10	216
Web of Science (ISI)	1960-2009	9Feb10	856
Academic Search Complete (EBSCO)	1960-2009	9Feb10	226
TOTAL RESULTS			**11,910**

Search alerts:

1) PubMed
2) Web of Science
3) Scopus – Forward searching only

Appendix C. Forms

ANA, RF, and CCP Testing in Pediatric Populations INCLUSION/EXCLUSION FORM

Reviewer's initial: Ref ID:

Criteria	Decision
1. **REPORT OF PRIMARY RESEARCH**	
2. **POPULATION** (at least two of the followings)	
a. Children and adolescents aged 18 years or younger	
AND (any of the followings)	
b1. Diagnosed with SLE or JIA/JRA/Still's disease	☐
b2. With undiagnosed limb pains	☐
b3. Given index test results	☐
3. **INDEX TEST** (any of the followings)	
a. Antinuclear antibody (ANA)*	☐
b. Rheumatoid factor (RF)†	☐
c. Cyclic-citrullinated peptide (CCP)	☐
EXCLUDE IF	
*Using non-human substrate for ANA or published before 1980	☐
†Testing for hidden RF	☐
4. **REFERENCE STANDARD**	
a. Clinical diagnosis of SLE or JIA/JRA/Still's disease	
5. **REPORT OF NUMERICAL DATA** (any of the following)	
a. Data sufficient to compute a 2x2 table	☐
b. Data on subsequent impacts due to test results	☐

Comments:

REVIEWER'S DECISION‡:

FINAL DECISION:

Foreign language (if applicable):

‡Reason for exclusion (if applicable):

Article excluded, but may inform the followings:

- ☐ Background
- ☐ KQ1a
- ☐ KQ1b
- ☐ KQ2

QUADAS CODING GUIDE

1. Spctrum composition This item examines the degree of similarity between the study's recruited sample and our population of interest (children with MSK symptoms) for the ANA review.	
Yes	The spectrum of patients included in the study was representative of those in whom the test will be used in practice. For cohort design, the recruited population should reflect a general children population (<18 years) with undiagnosed MSK pain.*
No†	If the characteristics of participants were too specific. For example, in cohort design, the undiagnosed MSK pain children all have "stunted" growth. In the case arm for case-control design, all the JIA patients have uveitis. For case-control design, one study arm being the known disease (SJE/JIA) and the other arm being the healthy children with or without MSK pain.
Unclear	Not reported or insufficient evidence by the study.

* Cohort and case-control study designs are illustrated in the following file: 'Ab testing_study designs.jpg' located in directory ' Z:\common\Arthritis Testing for children (AHRQ)\05_Data Extraction_Forms'.

† Note that if the participants' characteristics are drastically different from our desired population, it should be excluded altogether. If it is the case, describe in the comment section.

2. Selection criteria This item refers to whether the study provides clear inclusion/exclusion criteria for participant selection.	
Yes	Detailed information on the source and inclusion/exclusion criteria was reported
No	Information on the source and inclusion/exclusion criteria was poorly or not reported.
Unclear	Information was partly reported but not sufficient to score a "Yes".

3. Reference standard This item refers to whether the reference standard used can truly classify the disease status in participants.	
Yes	The study used widely accepted clinical standard, including but not limited to the ACR, ILAR, and Vancouver standards, for SLE or JIA.
No	The reported standard was unlikely to correctly classify the disease status.
Unclear	Not reported or insufficient evidence by the study.

4. Test result definition This item examines whether or not the serological cutoff of positive index test is clearly stated.	
Yes	Serological cutoff was clearly stated (ie: titer, IU/mL, etc).

No	Serological cutoff was not stated.
Unclear	Not reported or insufficient evidence by the study.

5. Disease progression bias

Over a long period of time, disease status might change due to spontaneous recovery or disease progression. This item specifies a reasonable time frame in which the underlying disease status is expected not to change drastically.

Yes	The time between the index test and reference standard was 6 months or less.
No	The time between the index test and reference standard was longer than 6 months.
Unclear	Not reported or insufficient evidence by the study.

6. Partial verification bias

This item refers to whether the selection of participants to receive confirmation using the reference standard might be biased.

Yes	All participants, or a random selection of participants, who received the index test went on to receive verification by a reference standard. For cohort design, generally all participants will go through the same reference standard, whereas in case-control design, each study arm could be examined based on different reference standards (for example, the known JIA might use ILAR by rheumatologist, whereas, the healthy controls are based on general physician assessment).
No	≥ 20% of the participants received the index test did not receive verification by the reference standard.
Unclear	Not reported or insufficient evidence by the study.

7. Differential verification bias

This item examines whether or not all participants are receiving the same reference standard to verify the disease status.

Yes	Same reference standard was used in all participants. Case-control design by default are likely to fall into this category since the patients were generally classified using the same reference standard.
No	Different reference standards were used in ≥ 20% of participants.
Unclear	Not reported or insufficient evidence by the study.

8. Incorporation bias

This item examines whether the index test forms part of the reference standard. If it is the case, overestimated agreement is likely to result.

If no explicit statement indicating ANA is <u>not</u> part of the ACR standard, a “no” should be scored. On the contrary, if RF/CCP is compared against the JIA’s ILAR standard, assume a score of “yes” unless an explicit statement indicates that RF/CCP was, indeed, part of the reference standard.

Yes	Using RF/CCP for SLE/JIA, assumes a “yes” unless an explicit statement indicated otherwise. Using ANA for SLE, assume a “no” unless an explicit statement indicated otherwise.
No	Using RF/CCP for SLE/JIA, assumes a “yes” unless an explicit statement indicated otherwise. Using ANA for SLE, assume a “no” unless an explicit statement indicated otherwise.
Unclear	Not reported or insufficient evidence by the study.

9. Index test execution Sufficient detail on carrying out the index test is important in tracking down the reasons for abnormal diagnostic results and in replicating the test in a different setting.	
Yes	The index test was sufficiently described including information on both the assay method and substrate used.
No	Either or both the assay method and substrate used was not described.
Unclear	Not reported or insufficient evidence by the study.

10. Test review bias This item examines whether the index test results are analyzed without the knowledge of the reference standard.	
Yes	Index test results were interpreted without the knowledge of reference standard. If the index test was done and analyzed prior the execution of reference standard, it will automatically score a “yes”.
No	Index test results were certainly or likely to be interpreted with the knowledge of reference standard.
Unclear	Not reported or insufficient evidence by the study.

11. Reference standard review bias This item examines whether the reference standard results are analyzed without the knowledge of the index test.	
Yes	Reference standard results were interpreted without the knowledge of index test.
No	Reference standard results were interpreted with knowledge of index test. ANA for SLE will automatically score a “no” unless an explicit statement indicated otherwise.
Unclear	Not reported or insufficient evidence by the study.

12. Uninterpretable results This item examines the reporting of the uninterpretable results from either index test or reference standard.	
Yes	The study has no uninterpretable/indeterminate/intermediate results (ie: suspected, instead of definite, diagnosis of SLE/JIA). Or, if existed, these results were adequately

	reported.
No	It was clear that the uninterpretable/indeterminate/intermediate results occur but was not reported.
Unclear	No insufficient evidence by the study.

13. Withdrawals This item examines the reporting of withdrawals.	
Yes	It was clear what happened to all patients who entered the study, for example if a flow diagram of study participants was reported explaining any withdrawals or exclusions, or the numbers recruited match those in the analysis. The drop out was not greater than 12% from the original sample size, and was appropriately accounted for.
No	It appears that >12% patients recruited did not complete the study
Unclear	Not reported or insufficient evidence by the study.

Guidleines for completing the QUADAS checklist

1) Spectrum composition
- Condition 1: In cohort design, the initial recruited sample consists solely of children with undiagnosed MSK pain. YES
- Condition 2: In case-control design, case arm as known disease (JIA/SLE) and control arm as healthy children. NO
- Condition 3: In case-control design, case arm as known disease (JIA/SLE) and control arm as other disease condition (ORG/NRG). NO
- Condition 4: In case-control design, case arm as known disease (JIA/SLE) along with specific characteristics (ie: JIA with uveitis or polyarticular JIA) and control arm as healthy children. NO
- Condition 5: In case-control design, case arm as known disease (JIA/SLE) along with specific characteristics (ie: JIA with uveitis or polyarticular JIA) and control arm as other disease condition (ORG/NRG). NO

2) Inclusion/exclusion criteria
- Condition 1: 3-5 of the following 5 selection criteria were used: Age, source of participants, method of diagnosis (for case-control design), condition of JIA/SLE (for case-control design), or any relevant demographic/clinical characteristic. YES
- Condition 2: 0-2 of the following 5 selection criteria were used: Age, source of participants, method of diagnosis (for case-control design), condition of JIA/SLE (for case-control design), or any relevant demographic/clinical characteristic. NO

3) Reference standard
- Condition 1: The diagnosis of JIA/SLE was based on a widely accepted diagnostic criteria including the ACR (American College of Rheumatology), ILAR (International League of Associations for Rheumatology), and Vancouver criteria. YES
- Condition 2: The diagnosis of JIA/SLE was based on other diagnostic criteria different from the ones listed under condition 1.UNSURE
- Condition 3: Patients were described as diagnosed with JIA/SLE by a healthcare professional. YES
- Condition 4: Patients were only described as diagnosed with JIA/SLE without further details. UNSURE

4) Test result definition
- Condition 1: Serological cutoff was explicitly stated (ie: in titer, IU/mL, or AU), thus what constitutes a positive/negative test was clear. YES
- Condition 2: Serological cutoff was not explicitly stated, thus what constitutes a positive/negative test was unclear. UNSURE
- Condition 3: Serological cutoff was not used, only mean measures were provided. NO

5) Disease progression bias
- Condition 1: The interval between the index test and reference standard was 6 months or less. YES
- Condition 2: The interval between the index test and reference standard was more than 6 months. NO
- Condition 3: In case control design, the mean disease duration of JIA/SLE was greater than 6 months and no reason to suggest that the index test was conducted within 6 months of the diagnosis. NO

6) Partial verification bias
- Condition 1: The whole or a random sample of participants with an index test was selected to receive the clinical diagnosis. YES
- Condition 2: Only a non-random sample of participants was selected, based on their index test results, to receive the diagnosis. NO
- Condition 3: In most case-control studies, in which, the diagnosis was generally done before the index test. YES

7) Differential verification bias
- Condition 1: Only one set of diagnostic criteria was used for JIA/SLE. YES
- Condition 2: More than 1 sets of diagnostic criteria were used for JIA/SLE. NO

8) Incorporation bias
- Condition 1: RF/CCP as index test against JIA/SLE diagnosis. YES
- Condition 2: ANA as index test against JIA diagnosis. YES
- Condition 3: ANA as index test against SLE diagnosis. NO
- Condition 4: ANA as index test against SLE diagnosis using the ACR criteria. NO
- Condition 5: ANA as index test against SLE diagnosis using other criteria. NO
- Condition 6: ANA as index test against SLE diagnosis, but explicitly stated that ANA was excluded from the diagnostic criteria. YES

9) Index test execution
- Condition 1: Both the assay method and substrate used were described. YES
- Condition 2: Either the assay method or substrate used was described. UNSURE
- Condition 3: Neither the assay method nor the substrate used was described. NO

10) Test review bias
- Condition 1: The index test was done before the diagnosis of JIA/SLE. YES
- Condition 2: The diagnosis of JIA/SLE was done before index test and explicitly stated that the interpretation of the index test results was blinded to the diagnosis. YES
- Condition 3: The diagnosis of JIA/SLE was done before index test but not explicitly stated that the interpretation of the index test results was blinded to the diagnosis. YES
- Condition 4: The index test results were likely to be interpreted with the knowledge of JIA/SLE diagnosis. UNSURE
- Condition 5: The index test results were interpreted and skewed with the knowledge of JIA/SLE diagnosis. NO

11) Reference standard review bias
- Condition 1: The diagnosis of JIA/SLE was done before the index test. YES
- Condition 2: The index test was done before the diagnosis of JIA/SLE and explicitly stated that the interpretation of diagnosis was blinded to index test results. YES
- Condition 3: The index test was done before the diagnosis of JIA/SLE but not explicitly stated that the interpretation diagnosis was blinded to index test results. UNSURE
- Condition 4: The diagnoses of JIA/SLE were likely to be interpreted with the knowledge of index test. NO

12) Uninterpretable results
- Condition1: No uninterpretable results (ie: serological cutoff is used and patients were classified as positive or negative). YES
- Condition 2: The uninterpretable results were adequately described. YES
- Condition 3: The uninterpretable results were likely to exist but not reported by authors. NO
- Condition 4: Could not determine whether all the study results were reported. UNSURE

13) Withdrawal
- Condition 1: No withdrawal. YES
- Condition 2: Withdrawal was small (≤10%) and with description on reasons of dropouts. YES
- Condition 3: Withdrawal was small (≤10%) and without description on reasons of dropouts. UNSURE
-
-
- Condition 4: Withdrawal was large (>10%) and with description on reasons of dropouts. UNSURE
- Condition 5: Withdrawals was large (>10%) and without description on reasons for dropouts. NO

Appendix D. List of Excluded Studies

EXCLUDED STUDIES (N = 438)

The following studies failed to meet at least one of the pre-specified inclusion criteria.

Study design (N = 129)

The following studies were excluded because they were not reports of primary research.

1. Miller E, Uleryk E, Doria AS. Evidence-based outcomes of studies addressing diagnostic accuracy of MRI of juvenile idiopathic arthritis. AJR 2009;American(5):1209-18.
2. Kallel-Sellami M, Baili-Klila L, Zerzeri Y, et al. Pediatric systemic lupus erythematosus with C1q deficiency. Annals of the New York Academy of Sciences 2007;1108:193-6.
3. Melegari A, Mascia MT, Sandri G, et al. Immunodeficiency and autoimmune phenomena in female hyper-IgM syndrome. Annals of the New York Academy of Sciences 2007;1109:106-8.
4. Mseddi M, Dammak A, Marrekchi S, et al. Subacute cutaneous lupus erythematosus in childhood: a case report [French]. Archives de Pediatrie 2007;14(2):164-6.
5. Gough-Palmer A, McHugh K. Investigating hip pain in a well child. BMJ: British Medical Journal 2007;334(7605):1216-7.
6. Banerjee P, Crain B. 2-year-old girl with right leg weakness. Brain Pathology 2008;18(4):608-10.
7. Abbassian A. The limping child: a clinical approach to diagnosis. British Journal of Hospital Medicine 2007;68(5):246-50.
8. Trueman CA. Joint disease: the future arthritis burden. Caring 2009;28(2):8-13.
9. Gilbert NF, Deavers MT, Madewell JE, et al. A 16-year-old girl with pain and swelling in the medial clavicle. CLIN ORTHOP RELATED RES 2008;466(12):3158-62.
10. Brown RJ. Introduction to the special issue on medically unexplained symptoms: background and future directions. Clinical Psychology Review 2007;27(7):769-80.
11. Wyndham M. The limping child. Community Practitioner 2007;80(9):42.
12. Syed RH, Gilliam BE, Moore TL. Rheumatoid factors and anticyclic citrullinated peptide antibodies in pediatric rheumatology. Current Rheumatology Reports 2008;10(2):156-63.
13. Yokota S, Mori M, Imagawa T, et al. Proposal for juvenile idiopathic arthritis guidance on diagnosis and treatment for primary care pediatricians and nonpediatric rheumatologists. Modern Rheumatology 2007;17(5):353-63.
14. Iwata N, Mori M, Miyamae T, et al. Sjogren's syndrome associated with childhood-onset systemic lupus erythematosus [Japanese]. Nihon Rinsho Meneki Gakkai Kaishi 2008;31(3):166-71.
15. van Holsbeeck MT. A role for US screening in juvenile idiopathic arthritis. Pediatric Radiology 2007;37(7):623-4.
16. Gottlieb BS, Ilowite NT. Systemic lupus erythematosus in children and adolescents. Pediatrics in Review 2006;27(9):323-30.
17. Al-Mendalawi MD. Juvenile systemic lupus erythematosus in Bahrain. A tertiary referral center experience. Saudi Medical Journal 2009;30(9):1240-1.
18. Quartier P, Prieur AM. Systemic lupus erythematosus [French]. Archives de Pediatrie 2003;10(4):367-73.
19. Gandon-Laloum S. Growth and limb pains [French]. Archives de Pediatrie 2006;13(6):550-2.
20. Bizzaro N, Wiik A. Appropriateness in anti-nuclear antibody testing: from clinical request to strategic laboratory practice. Clinical & Experimental Rheumatology 2004;22(3):349-55.
21. Jarvis JN. The unique clinical presentation of children with chronic arthritis: putting the pediatrics in pediatric rheumatology. Current Problems in Pediatric & Adolescent Health Care 2006;36(3):80-2.
22. Kaur S, Thami GP. Antinuclear antibody-negative systemic lupus erythematosus: revisited. INDIAN J PEDIATR 2003;70(2):185-6.
23. Leung AK, Lemay JF. The limping child. Journal of Pediatric Health Care 2004;18(5):219-23.
24. Gunther KP, Thielemann F, Bottesi M. Anterior knee pain in children and adolescents. Diagnosis and conservative treatment [German]. Orthopade 2003;32(2):110-8.

25. Shea KG, Pfeiffer R, Curtin M. Idiopathic anterior knee pain in adolescents. Orthopedic Clinics of North America 7 A.D.;34(3):377-83.
26. Siegel DM. Antinuclear Antibody (ANA) Testing. Pediatrics in Review 2003;24(9):320-1.
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Population (N = 77)

The following studies were excluded because the study population was not consisted primarily of individuals ≤ 18 years with a diagnosis of JIA, SLE, or with undiagnosed MSK pain .

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Outcome data (N = 155)

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Duplicates (N = 6)

The following studies were excluded because they were duplicates.

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Appendix E. Methodological Quality of Included Studies

Table E1. Methodological quality of studies evaluating an ANA test for pSLE in children with undiagnosed MSK pain

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	No	No	Yes	Yes	U	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Wananukul[30] 2005	No	Yes	Yes	Yes	U	Yes	Yes	No	Yes	Yes	Yes	Yes	No

U = unclear

Table E2. Methodological quality of studies evaluating an ANA test for JIA in children with undiagnosed MSK pain

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	No	No	Yes	Yes	U	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Haynes[31] 1986	No	No	Yes	Yes	U	Yes	Yes	Yes	Yes	U	Yes	Yes	Yes
Jones[32] 2006	No	No	U	Yes	U	Yes	U	Yes	No	U	Yes	Yes	No
Lipinska[33] 2008	No	No	Yes	Yes	U	Yes	Yes	Yes	U	Yes	Yes	Yes	Yes
Nordal[34] 2009	No	Yes	Yes	Yes	U	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Osborn[35] 1984	No	No	Yes	Yes	U	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Siamopoulou-Mavridou[36] 1991	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wakhlu[37] 2003	No	No	Yes	Yes	U	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

U = unclear

Table E3. Methodological quality of studies evaluating a RF test for pSLE in children with undiagnosed MSK pain

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

Table E4. Methodological quality of studies evaluating a RF (IgM) test for JIA in children with undiagnosed MSK pain

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	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Balogh[40] 1980	No	No	Yes	No	No	Yes	Yes	Yes	Yes	U	Yes	U	Yes
Egeskjold[41] 1981	No	No	Yes	Yes	U	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Egeskjold[49] 1982	No	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	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	U	Yes
Hanson[38] 1966	No	No	Yes	U	U	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Haynes[31] 1986	No	No	Yes	Yes	U	Yes	Yes	Yes	Yes	U	Yes	Yes	Yes
Lipinska[33] 2008	No	No	Yes	Yes	U	Yes	Yes	Yes	U	Yes	Yes	Yes	Yes
Permin[43] 1982	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Roizenblatt[44] 1993	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Saulsbury[50] 1990	No	No	Yes	Yes	U	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Siamopoulou-Mavridou[36] 1991	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Taseski[45] 1981	No	No	No	No	U	U	U	Yes	U	Yes	Yes	Yes	Yes
Varbanova[46] 1999	No	No	Yes	Yes	U	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wernick[47] 1981	No	No	Yes	Yes	U	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

U = unclear

Table E5. Methodological quality of studies evaluating a CCP test for JIA in children with undiagnosed MSK pain

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]	No	No	U	Yes	U	Yes	U	Yes	Yes	Yes	Yes	Yes	Yes
Brunner 2006 [52]	No	No	U	Yes	U	Yes	Yes	Yes	U	Yes	Yes	Yes	Yes
Ferucci 2005 [53]	No	Yes	Yes	Yes	No	Yes	Yes	Yes	U	Yes	Yes	Yes	Yes
Habib 2008 [54]	No	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	U	Yes
Kasapcopur 2004 [55]	No	U	Yes	Yes	No	Yes	Yes	Yes	No	U	Yes	Yes	Yes
Kwok 2005 [56]	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	U	Yes	Yes	Yes
Lipinska 2008 [33]	No	No	Yes	Yes	U	Yes	Yes	Yes	U	Yes	Yes	Yes	Yes

U = unclear

Appendix F. Evidence Tables

Study	Participants Characteristics	Index Test Characteristics
Andersson-Gare, B., 1994 (39) **Country (# centers):** Sweden (NR) **Funding:** Government **Study design:** Case control (Prospective) **Recruitment:** Epidemiological survey	**Inclusion criteria:** NR **Exclusion criteria:** NR **JIA patients** **$N_{analyzed}/N_{enrolled}$:** 271/271 **Mean/median age (range):** NR **Female:** NR **Median time since diagnosis (range):** 5.6yr (0.1-18.6yr) **Subtype:** Systemic (4.4%); Polyarticular (27.7%); Oligoarticular (36.9%); Monoarticular (24.7%); Juvenile ankylosing spondylitis (3.0%); Arthritis in connection with inflammatory bowel disease (0.4%); Juvenile psoriatic arthropathy (2.9%) **Reference standard for JIA diagnosis:** EULAR	**IgM-RF test** **Assay method:** Enzyme immunoassay **Source of antigen:** NR **Manufacturer (kit type):** Pharmacia Diagnostics, Uppsala, Sweden (RF IgM EIA) **Positive cutoff:** Mean of control group + 2 sd (= 7.34 AU/ml) **IgA-RF test** **Assay method:** Enzyme immunoassay **Source of antigen:** NR **Manufacturer (kit type):** Pharmacia Diagnostics, Uppsala, Sweden (RF IgA EIA) **Positive cutoff:** Mean of control group + 2 sd (= 3.58 AU/ml)

Results (Overall)

		Reference	
		+	-
Index test	+	29	4
	-	242	126

Disease group = JIA
Comparator = Healthy controls
Index = IgM-RF
Sensitivity = 10.7%
Specificity = 96.9%

Overall

		Reference	
		+	-
Index test	+	26	5
	-	245	124

Disease group = JIA
Comparator = Healthy controls
Index = IgA-RF
Sensitivity = 9.6%
Specificity = 96.1%

By subtype

		Reference	
		+	-
Index test	+	6	4
	-	111	126

Disease group = JIA (mono- and oligoarticular)
Comparator = Healthy controls
Index = IgM-RF
Sensitivity = 5.1%
Specificity = 96.9%

By subtype

		Reference	
		+	-
Index test	+	21	4
	-	102	126

Disease group = JIA (polyarticular)
Comparator = Healthy controls
Index = IgM-RF
Sensitivity = 17.1%
Specificity = 96.9%

By subtype

		Reference	
		+	-
Index test	+	1	4
	-	6	126

Disease group = JIA (systemic)
Comparator = Healthy controls
Index = IgM-RF
Sensitivity = 14.3%
Specificity = 96.9%

By subtype

		Reference	
		+	-
Index test	+	10	5
	-	107	124

Disease group = JIA (monoarticular and oligoarticular)
Comparator = Healthy controls
Index = IgA-RF
Sensitivity = 8.5%
Specificity = 96.1%

By subtype

		Reference	
		+	-
Index test	+	13	5
	-	110	124

Disease group = JIA (polyarticular)
Comparator = Healthy controls
Index = IgA-RF
Sensitivity = 10.6%
Specificity = 96.1%

By subtype

		Reference	
		+	-
Index test	+	0	5
	-	7	124

Disease group = JIA (systemic)
Comparator = Healthy controls
Index = IgA-RF
Sensitivity = 0%
Specificity = 96.1%

Study	Participants Characteristics	Index Test Characteristics
Avcin, T., 2002 (51) **Country (# centers):** Italy and Slovenia (4) **Funding:** Government **Study design:** Case control (Prospective) **Recruitment:** NR	**Inclusion criteria:** NR **Exclusion criteria:** NR **JIA patients** **$N_{analyzed}/N_{enrolled}$:** 109/109 **Mean age (range):** 8.7yr (0.6-20.3yr) **Female:** 72.5% **Mean time since diagnosis (range):** 3.6yr (0.3-15.6yr) **Subtype:** Polyarticular (47.7%); Oligoarticular (46.8%); Systemic (5.5%) **Reference standard for JIA diagnosis:** NR **SLE patients** **$N_{analyzed}/N_{enrolled}$:** 25/25 **Mean age (range):** NR **Female:** NR **Mean/median time since diagnosis (range):** NR **Reference standard for SLE diagnosis:** NR	**CCP test** **Assay method:** ELISA **Source of antigen:** NR **Manufacturer (kit type):** Euro-Diagnostica, Arnhem, The Netherlands (ImmunoScan RA anti-CCP test kit) **Positive cutoff:** 70 anti-CCP unit (AU)

Results (Overall)

		Reference	
		+	-
Index test	+	2	0
	-	107	30

Disease group = JIA
Comparator = Healthy controls
Index = CCP
Sensitivity = 1.8%
Specificity = 100.%

Overall

		Reference	
		+	-
Index test	+	0	0
	-	25	30

Disease group = SLE
Comparator = Healthy controls
Index = CCP
Sensitivity = 0.0%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	1	0
	-	50	30

Disease group = JIA (oligoarticular)
Comparator = Healthy controls
Index = CCP
Sensitivity = 2.0%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	1	0
	-	51	30

Disease group = JIA (polyarticular)
Comparator = Healthy controls
Index = CCP
Sensitivity = 1.9%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	0	0
	-	6	30

Disease group = JIA (systemic)
Comparator = Healthy controls
Index = CCP
Sensitivity = 0%
Specificity = 100.%

Study	Participants Characteristics	Index Test Characteristics
Balogh, Z., 1980 (40) **Country (# centers):** Hungary (1) **Funding:** NR **Study design:** Case control (Prospective) **Recruitment:** Consecutive patients	**Inclusion criteria:** Healthy controls: Age- and sex-matched with JIA patients **Exclusion criteria:** JIA group: Juvenile ankylosing spondylitis, psoriatic arthritis, and arthritis associated with inflammatory bowel disease patients **JIA patients** **$N_{analyzed}/N_{enrolled}$:** 46/46 **Mean age (range):** 9.6yr (2.7-15.8yr) **Female:** 47.8% **Mean/median time since diagnosis (range):** NR **Subtype:** Oligoarticular (56.5%); Systemic (19.6%); Polyarticular (17.4%); Seropositive “adult-type” JCA (6.5%) **Reference standard for JIA diagnosis:** EULAR/WHO workshop, Oslo, 1978	**ANA test** **Assay method:** Immunofluorescence technique (Holborow and Johnson 1969) **Source of antigen:** Fluorescein-labeled anti-IgG (H+L) specific serum **Manufacturer (kit type):** Hyland (NR) **Positive cutoff:** Titer 1:10 **IgM-RF test** **Assay method:** Latex fixation test **Source of antigen:** NR **Manufacturer (kit type):** NR **Positive cutoff:** NR **RF test (unspecified isotype)** **Assay method:** Waaler-Rose test **Source of antigen:** NR **Manufacturer (kit type):** NR **Positive cutoff:** NR

Results (Overall)

		Reference	
		+	-
Index test	+	6	0
	-	40	10

Disease group = JIA
Comparator = Healthy controls
Index = ANA
Sensitivity = 13.0%
Specificity = 100.%

Overall

		Reference	
		+	-
Index test	+	10	0
	-	36	10

Disease group = JIA
Comparator = Healthy controls
Index = IgM-RF (Latex)
Sensitivity = 21.7%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	7	0
	-	39	10

Disease group = JIA
Comparator = Healthy controls
Index = RF (Waaler-Rose)
Sensitivity = 15.2%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	2	0
	-	24	10

Disease group = JIA (oligoarticular)
Comparator = Healthy controls
Index = ANA
Sensitivity = 7.7%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	2	0
	-	6	10

Disease group = JIA (polyarticular)
Comparator = Healthy controls
Index = ANA
Sensitivity = 25.0%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	0	0
	-	9	10

Disease group = JIA (systemic)
Comparator = Healthy controls
Index = ANA
Sensitivity = 0%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	6	0
	-	20	10

Disease group = JIA (oligoarticular)
Comparator = Healthy controls
Index = IgM-RF (Latex)
Sensitivity = 23.1%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	0	0
	-	8	10

Disease group = JIA (polyarticular)
Comparator = Healthy controls
Index = IgM-RF (Latex)
Sensitivity = 0%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	1	0
	-	8	10

Disease group = JIA (systemic)
Comparator = Healthy controls
Index = IgM-RF (Latex)
Sensitivity = 11.1%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	3	0
	-	23	10

Disease group = JIA (oligoarticular)
Comparator = Healthy controls
Index = RF (Waaler-Rose)
Sensitivity = 11.5%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	0	0
	-	8	10

Disease group = JIA (polyarticular)
Comparator = Healthy controls
Index = RF (Waaler-Rose)
Sensitivity = 0%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	1	0
	-	8	10

Disease group = JIA (systemic)
Comparator = Healthy controls
Index = RF (Waaler-Rose)
Sensitivity = 11.1%
Specificity = 100.%

Study	Participants Characteristics	Index Test Characteristics
Brunner, J., 2006 (52) **Country (# centers):** Germany (1) **Funding:** NR **Study design:** Case control (Prospective) **Recruitment:** NR	**Inclusion criteria:** ORG: With other autoimmunopathies such as Crohn's disease, reactive arthritis, diabetes mellitus type 1, uveitis, and myositis NRG: Undergoing interventional cardiac therapy. With non-autoimmunopathies such as infectious diseases, endocrinopathies, arthralgias, cystic fibrosis, galactosemia, hemophilia, ADD, epilepsy, Raynaud's phenomenon, osteochondroma, and fibromyalgia Healthy controls: Newborns with no known diseases **Exclusion criteria:** JIA: Written consent not obtained, bilateral anophthalmia, and insufficient blood volumes **JIA patients** **$N_{analyzed}/N_{enrolled}$:** 45/45 **Mean age (range):** 11.0yr (1.9-17.3yr) **Female:** 66.7% **Mean time since diagnosis (range):** 2.1yr (NR) **Subtype:** Polyarticular (15.6%); Systemic (6.7%); Oligoarticular (55.6%); Enthesitis-related arthritis (13.3%); Psoriatric (4.4%) **Reference standard for JIA diagnosis:** NR **SLE patients** **$N_{analyzed}/N_{enrolled}$:** 4/4 **Mean age (range):** NR **Female:** NR **Mean time since diagnosis (range):** NR **Subtype:** NR **Reference standard for SLE diagnosis:** NR	**CCP test** **Assay method:** ELISA **Source of antigen:** NR **Manufacturer (kit type):** Euroimmun lot 21122m, Germany (NR) **Positive cutoff:** 2.5 relative units (RU)

Results (Overall)

		Reference	
		+	-
Index test	+	2	0
	-	43	42

Disease group = JIA
Comparator = Healthy controls
Index = CCP
Sensitivity = 4.4%
Specificity = 100%

Overall

		Reference	
		+	-
Index test	+	2	5
	-	43	29

Disease group = JIA
Comparator = NRG
Index = CCP
Sensitivity = 4.4%
Specificity = 85.3%

Overall

		Reference	
		+	-
Index test	+	2	3
	-	43	34

Disease group = JIA
Comparator = ORG
Index = CCP
Sensitivity = 4.4%
Specificity = 91.9%

Overall

		Reference	
		+	-
Index test	+	1	0
	-	3	42

Disease group = SLE
Comparator = Healthy controls
Index = CCP
Sensitivity = 25.0%
Specificity = 100%

Overall

		Reference	
		+	-
Index test	+	1	5
	-	3	29

Disease group = SLE
Comparator = NRG
Index = CCP
Sensitivity = 25.0%
Specificity = 85.3%

Overall

		Reference	
		+	-
Index test	+	1	3
	-	3	34

Disease group = SLE
Comparator = ORG
Index = CCP
Sensitivity = 25.0%
Specificity = 91.9%

Study	Participants Characteristics	Index Test Characteristics
Egeskjold, E.M., 1981 (41) **Country (# centers):** Denmark (NR) **Funding:** Government **Study design:** Case control (Prospective) **Recruitment:** NR	**Inclusion criteria:** Healthy controls: Age- and sex-matched children without arthritis or chronic disease **Exclusion criteria:** NR **JIA patients** **$N_{analyzed}/N_{enrolled}$:** 48/48 **Mean/median age (range):** NR (1.0-16.0yr) **Female:** 68.8% **Mean/median time since diagnosis (range):** NR **Subtype:** Oligoarticular (52.1%); Polyarticular (29.2%); Systemic (18.8%) **Reference standard for JIA diagnosis:** ARA	**ANA test** **Assay method:** Immunofluorescence technique **Source of antigen:** NR **Manufacturer (kit type):** NR **Positive cutoff:** Titer 1:18 **RF test (IgM, IgG, IgA)** **Assay method:** IIF **Source of antigen:** Sheep red cell **Manufacturer (kit type):** DAKO (NR) **Positive cutoff:** Titer 1:9
Results (Overall) Disease group = JIA Comparator = Healthy controls Index = ANA **Sensitivity** = 66.7% **Specificity** = 95.8%	**Overall** Disease group = JIA Comparator = Healthy controls Index = IgG-RF **Sensitivity** = 87.5% **Specificity** = 97.9%	**Overall** Disease group = JIA Comparator = Healthy controls Index = IgM-RF **Sensitivity** = 4.2% **Specificity** = 97.9%

		Reference	
		+	-
Index test	+	32	2
	-	16	46

		Reference	
		+	-
Index test	+	42	1
	-	6	47

		Reference	
		+	-
Index test	+	2	1
	-	46	47

Overall

		Reference	
		+	-
Index test	+	1	0
	-	47	48

Disease group = JIA
Comparator = Healthy controls
Index = IgA-RF
Sensitivity = 2.1%
Specificity = 100%

By subtype

		Reference	
		+	-
Index test	+	9	1
	-	0	47

Disease group = JIA (systemic)
Comparator = Healthy controls
Index = IgG-RF
Sensitivity = 100%
Specificity = 97.9%

By subtype

		Reference	
		+	-
Index test	+	12	1
	-	4	47

Disease group = JIA (oligoarticular)
Comparator = Healthy controls
Index = IgG-RF
Sensitivity = 75.0%
Specificity = 97.9%

By subtype

		Reference	
		+	-
Index test	+	12	1
	-	2	47

Disease group = JIA (polyarticular)
Comparator = Healthy controls
Index = IgG-RF
Sensitivity = 85.7%
Specificity = 97.9%

Study	Participants Characteristics	Index Test Characteristics
Egeskjold, E.M., 1982 (49) **Country (# centers):** Denmark (NR) **Funding:** Government **Study design:** Case control (NR) **Recruitment:** NR	**Inclusion criteria:** NR **Exclusion criteria:** NR **JIA patients $N_{analyzed}/N_{enrolled}$:** 13/13 **Mean/median age (range):** 7.1yr/ 7.0yr (2.0-15.0yr) **Female:** 69.2% **Mean time since diagnosis (range):** 3.5yr (0.6-6.4yr) **Subtype:** Oligoarticular (53.8%); Polyarticular (38.5%); Systemic (7.7%); Comorbid with chronical bilateral iridocyclitis (61.5%) **Reference standard for JIA diagnosis:** ARA	**ANA (IgM, IgG, IgA)** **Assay method:** IIF **Source of antigen:** Rat liver cryostat sections and leucocytes) **Manufacturer (kit type):** NR **Positive cutoff:** Maximum of peak 2 displacement beyond normal range **RF test (IgM, IgG, IgA)** **Assay method:** IIF **Source of antigen:** Sheep erythrocyte sensitized with rabbit IgG **Manufacturer (kit type):** NR **Positive cutoff:** Maximum of peak 2 displacement beyond normal range
Results (Overall) Reference: + / - Index test +: 8 / 0 Index test -: 5 / 3 Disease group = JIA Comparator = Healthy controls Index = IgM-ANA **Sensitivity** = 61.5% **Specificity** = 100.% **Overall** Reference: + / - Index test +: 2 / 0 Index test -: 11 / 3 Disease group = JIA Comparator = Healthy controls Index = IgM-RF **Sensitivity** = 15.4% **Specificity** = 100.%	**Overall** Reference: + / - Index test +: 11 / 0 Index test -: 2 / 3 Disease group = JIA Comparator = Healthy controls Index = IgG-ANA **Sensitivity** = 84.676.9% **Specificity** = 100.% **Overall** Reference: + / - Index test +: 10 / 0 Index test -: 3 / 3 Disease group = JIA Comparator = Healthy controls Index = IgG-RF **Sensitivity** = 76.9% **Specificity** = 100.%	**Overall** Reference: + / - Index test +: 0 / 0 Index test -: 13 / 3 Disease group = JIA Comparator = Healthy controls Index = IgA-ANA **Sensitivity** = 0.0% **Specificity** = 100.% **Overall** Reference: + / - Index test +: 0 / 0 Index test -: 13 / 3 Disease group = JIA Comparator = Healthy controls Index = IgA-RF **Sensitivity** = 0.0% **Specificity** = 100.%

Study	Participants Characteristics	Index Test Characteristics
Eichenfield, A.H., 1986 (48) **Country (# centers):** U.S. (1) **Funding:** NR **Study design:** Cohort (Retrospective) **Recruitment:** Consecutive patients	**Inclusion criteria:** Cohort: Children's complaints were referable to the musculoskeletal system or as being of an "autoimmune" nature. RF test results must be available and measured between Jan 1981 and Dec 1982 **Exclusion criteria:** NR **Historical patient cohort** **$N_{analyzed}/N_{enrolled}$:** 437/437 **Mean/median age (range):** NR **Female:** NR **Mean/median time since diagnosis (range):** NR **Subtype:** NR **Reference standard for JIA diagnosis:** ARA	**IgM-RF test** **Assay method:** Latex fixation test **Source of antigen:** NR **Manufacturer (kit type):** Hyland Laboratories (RA-test) **Positive cutoff:** Titer 1:80

Results (Overall)

		Reference	
		+	-
Index test	+	5	6
	-	100	326

Disease group = JIA
Comparator = Non-JIA children with MSK complaints
Index = IgM-RF (Latex)
Sensitivity = 5.0%
Specificity = 98.2%

Study	Participants Characteristics	Index Test Characteristics
Fawcett, P.T., 1999 (29) **Country (# centers):** U.S. **Funding:** Government **Study design:** Case control (Prospective) **Recruitment:** NR	**Inclusion criteria:** ORG: Underwent elective orthopedic surgical procedures **Exclusion criteria:** NR **JIA patients** **$N_{analyzed}/N_{enrolled}$:** 178/178 **Mean/median age (range):** NR **Female:** NR **Mean/median time since diagnosis (range):** NR **Subtype:** Oligoarticular (49.4%); Polyarticular (38.2%); Systemic (12.4%) **Reference standard for JIA diagnosis:** ACR **SLE patients** **$N_{analyzed}/N_{enrolled}$:** 21/21 **Mean/median age (range):** NR **Female:** NR **Mean/median time since diagnosis (range):** NR **Reference standard for SLE diagnosis:** ACR	**ANA test** **Assay method:** IIF and ELISA (Immuno Concepts, Helix, Zeus) **Source of antigen:** IIF: HEp-2 cell line . Immuno Concepts : Sm, RNP, SSA, SSB, Scl-70, Jo-1. Helix : Sm, SmRNP, SSA, SSB, Scl-70, Jo-1, ds-DNA, histones, and centromere antigens. Zeus: Sm, RNP, SSA, SSB, Scl-70, Jo-1, and ds-DNA **Manufacturer (kit type):** IIF: Antibodies Incorporated, Davis, CA. ELISA: Immuno Concepts, Sacramento/CA, Helix, Sacramento/CA, Zeus, Raritan/NJ; IIF: IFA kit; IIF: Zeiss Axioplan microscope equipped for epifluorescence with excitation filters **Positive cutoff:** IIF: Positive if a clearly discernible fluorescence pattern appears at 1:40 serum dilution.

Results (Overall)

		Reference	
		+	-
Index test	+	110	4
	-	68	22

Disease group = JIA
Comparator = ORG
Index = ANA (IIF)
Sensitivity = 61.8%
Specificity = 84.6%

Overall

		Reference	
		+	-
Index test	+	119	7
	-	59	19

Disease group = JIA
Comparator = ORG
Index = ANA (ELISA – Zeus)
Sensitivity = 67.1%
Specificity = 73.1%

Overall

		Reference	
		+	-
Index test	+	20	5
	-	1	21

Disease group = SLE
Comparator = ORG
Index = ANA (ELISA – Helix)
Sensitivity = 95.2%
Specificity = 80.8%

By subtype

		Reference	
		+	-
Index test	+	5	0
	-	83	26

Disease group = JIA (oligoarticular)

Overall

		Reference	
		+	-
Index test	+	16	0
	-	162	26

Disease group = JIA
Comparator = ORG
Index = ANA (ELISA – Immuno Concepts)
Sensitivity = 9.0%
Specificity = 100.%

Overall

		Reference	
		+	-
Index test	+	21	4
	-	0	22

Disease group = SLE
Comparator = ORG
Index = ANA (IIF)
Sensitivity = 100%
Specificity = 84.6%

Overall

		Reference	
		+	-
Index test	+	20	7
	-	1	19

Disease group = SLE
Comparator = ORG
Index = ANA (ELISA – Zeus)
Sensitivity = 95.2%
Specificity = 73%

By subtype

		Reference	
		+	-
Index test	+	33	5
	-	55	21

Disease group = JIA (oligoarticular)

Overall

		Reference	
		+	-
Index test	+	73	5
	-	105	21

Disease group = JIA
Comparator = ORG
Index = ANA (ELISA – Helix)
Sensitivity = 41.0%
Specificity = 80.8%

Overall

		Reference	
		+	-
Index test	+	16	0
	-	5	26

Disease group = SLE
Comparator = ORG
Index = ANA (ELISA – Immuno Concepts)
Sensitivity = 76.2%
Specificity = 100%

By subtype

		Reference	
		+	-
Index test	+	68	4
	-	20	22

Disease group = JIA (oligoarticular)
Comparator = ORG
Index = ANA (IIF)
Sensitivity = 77.3%
Specificity = 84.6%

By subtype

		Reference	
		+	-
Index test	+	56	7
	-	32	19

Disease group = JIA (oligoarticular)

Comparator = ORG
Index = ANA (ELISA – Immuno Concepts)
Sensitivity = 5.7%
Specificity = 100%

By subtype

		Reference	
		+	-
Index test	+	14	7
	-	8	19

Comparator = ORG
Index = ANA (ELISA – Helix)
Sensitivity = 37.5%
Specificity = 80.8%

By subtype

		Reference	
		+	-
Index test	+	10	0
	-	58	26

Comparator = ORG
Index = ANA (ELISA – Zeus)
Sensitivity = 63.6%
Specificity = 73.1%

By subtype

		Reference	
		+	-
Index test	+	33	5
	-	35	21

Disease group = JIA (systemic)
Comparator = ORG
Index = ANA (ELISA – Zeus)
Sensitivity = 63.6%
Specificity = 73.1%

By subtype

		Reference	
		+	-
Index test	+	49	7
	-	19	19

Disease group = JIA (polyarticular)
Comparator = ORG
Index = ANA (ELISA – Immuno Concepts)
Sensitivity = 14.7%
Specificity = 100%

By subtype

		Reference	
		+	-
Index test	+	4	4
	-	18	22

Disease group = JIA (polyarticular)
Comparator = ORG
Index = ANA (ELISA – Helix)
Sensitivity = 48.5%
Specificity = 80.8%

By subtype

		Reference	
		+	-
Index test	+	1	0
	-	21	26

Disease group = JIA (polyarticular)
Comparator = ORG
Index = ANA (ELISA - Zeus)
Sensitivity = 72.1%
Specificity = 73.1%

By subtype

		Reference	
		+	-
Index test	+	7	5
	-	15	21

Disease group = JIA (systemic)
Comparator = ORG
Index = ANA (IIF)
Sensitivity = 18.2%
Specificity = 84.6%

By subtype

		Reference	
		+	-
Index test	+	14	7
	-	8	19

Disease group = JIA (systemic)
Comparator = ORG
Index = ANA (ELISA – Immuno Concepts)
Sensitivity = 4.5%
Specificity = 100%

Disease group = JIA (systemic)
Comparator = ORG
Index = ANA (ELISA – Helix)
Sensitivity = 31.8%
Specificity = 80.8%

Disease group = JIA (systemic)
Comparator = ORG
Index = ANA (ELISA – Zeus)
Sensitivity = 63.6%
Specificity = 73.1%

Study	Participants Characteristics	Index Test Characteristics
Ferreira, R.A., 2007 (42) **Country (# centers):** Brazil (3) **Funding:** NR **Study design:** Case control (Prospective) **Recruitment:** Random selection	**Inclusion criteria:** NR **Exclusion criteria:** NR **JIA patients** **$N_{analyzed}/N_{enrolled}$:** 91/91 **Mean age (range):** 10.5yr (2.1-22.7yr) **Female:** 64.8% **Mean time since diagnosis (range):** 5.2yr (0.2-17.3yr) **Subtype:** Polyarticular (27.5%); Oligoarticular (30.8%); Systemic (41.8%) **Reference standard for JIA diagnosis:** ACR	**IgM-RF test** **Assay method:** Latex fixation test **Source of antigen:** NR **Manufacturer (kit type):** RapiTex, Hoechst, Marburg, Germany (RF) **Positive cutoff:** 20 IU/ml **IgM-RF test** **Assay method:** ELISA **Source of antigen:** NR **Manufacturer (kit type):** Flow Laboratories, U.S. (Titertek Multiskan Plus) **Positive cutoff:** EI (absorbance of serum samples/cut off)> 1.0 **IgA-RF test** **Assay method:** ELISA **Source of antigen:** Mouse IgG **Manufacturer (kit type):** Flow Laboratories, U.S. (Titertek Multiskan Plus) **Positive cutoff:** EI> 1.0

Results (Overall)

		Reference	
		+	-
Index test	+	5	0
	-	86	45

Disease group = JIA
Comparator = Healthy controls
Index = IgM-RF (Latex)
Sensitivity = 5.5%

Overall

		Reference	
		+	-
Index test	+	30	3
	-	61	42

Disease group = JIA
Comparator = Healthy controls
Index = IgM-RF (ELISA)
Sensitivity = 33.0%

Overall

		Reference	
		+	-
Index test	+	40	7
	-	51	38

Disease group = JIA
Comparator = Healthy controls
Index = IgA-RF (ELISA)
Sensitivity = 44.0%

Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	0	0
	-	28	45

Disease group = JIA (oligoarticular)
Comparator = Healthy controls
Index = IgM-RF (Latex)
Sensitivity = 0%
Specificity = 100%

By subtype

		Reference	
		+	-
Index test	+	5	0
	-	20	45

Disease group = JIA (polyarticular)
Comparator = Healthy controls
Index = IgM-RF (Latex)
Sensitivity = 20.0%
Specificity = 100%

By subtype

		Reference	
		+	-
Index test	+	0	0
	-	38	45

Disease group = JIA (systemic)
Comparator = Healthy controls
Index = IgM-RF (Latex)
Sensitivity = 0%
Specificity = 100%

Specificity = 93.3%

By subtype

		Reference	
		+	-
Index test	+	9	3
	-	19	42

Disease group = JIA (oligoarticular)
Comparator = Healthy controls
Index = IgM-RF (ELISA)
Sensitivity = 32.1%
Specificity = 93.3%

By subtype

		Reference	
		+	-
Index test	+	13	3
	-	12	42

Disease group = (polyarticular)
Comparator = Healthy controls
Index = IgM-RF (ELISA)
Sensitivity = 52.0%
Specificity = 93.3%

By subtype

		Reference	
		+	-
Index test	+	8	3
	-	30	42

Disease group = JIA (systemic)
Comparator = Healthy controls
Index = IgM-RF (ELISA)
Sensitivity = 21.1%
Specificity = 93.3%

Specificity = 84.4%

By subtype

		Reference	
		+	-
Index test	+	13	7
	-	15	38

Disease group = JIA (oligoarticular)
Comparator = Healthy controls
Index = IgA-RF (ELISA)
Sensitivity = 46.4%
Specificity = 84.4%

By subtype

		Reference	
		+	-
Index test	+	10	7
	-	15	38

Disease group = (polyarticular)
Comparator = Healthy controls
Index = IgA-RF (ELISA)
Sensitivity = 40.0%
Specificity = 84.4%

By subtype

		Reference	
		+	-
Index test	+	17	7
	-	21	38

Disease group = JIA (systemic)
Comparator = Healthy controls
Index = IgA-RF (ELISA)
Sensitivity = 44.7%
Specificity = 84.4%

Study	Participants Characteristics	Index Test Characteristics
Ferucci, E.D., 2005 (53) **Country (# centers):** U.S., throughout North America (NR) **Funding:** Government **Study design:** Case control (Prospective) **Recruitment:** Simplex patients were recruited among a local cohort in Cincinnatti; multiplex patients were recruited from the National Institute of Arthritis and Muscoloskeletal and Skin Diseases-supported JRA Affected Sibpair Registry. Siblings were selected randomly.	**Inclusion criteria:** Healthy controls: Children with increased risk of type I diabetes from the Diabetes and Autoimmunity Study in the Young (DAISY) **Exclusion criteria:** NR **JIA patients** **$N_{analyzed}/N_{enrolled}$:** 230/230 **Mean/median age (range):** 14.7yr (NR) **Female:** 73.9% **Mean/median time since diagnosis (range):** 9.7yr (NR) **Subtype:** Polyarticular (33.5%); Oligoarticular (60.4%); Systemic (6.1%) **Reference standard for JIA diagnosis:** ACR	**RF test (unspecified isotype)** **Assay method:** Nephelometry **Source of antigen:** NR **Manufacturer (kit type):** Dade-Behring, Newark, DE (NR) **Positive cutoff:** 15 IU/ml **CCP test** **Assay method:** ELISA **Source of antigen:** NR **Manufacturer (kit type):** Diastat; Axis-Shield Diagnostics, Dundee, Scotland, UK (NR) **Positive cutoff:** 5 units/ml

Results (Overall)

		Reference	
		+	-
Index test	+	25	23
	-	205	665

Disease group = JIA
Comparator = Healthy controls
Index = RF (unspecified isotype)
Sensitivity = 10.9%
Specificity = 96.7%

Overall

		Reference	
		+	-
Index test	+	13	4
	-	217	684

Disease group = JIA
Comparator = Healthy controls
Index = CCP
Sensitivity = 5.7%
Specificity = 99.4%

By subtype

		Reference	
		+	-
Index test	+	9	23
	-	130	665

Disease group = JIA (oligoarticular)
Comparator = Healthy controls
Index = RF (unspecified isotype)
Sensitivity = 6.5%
Specificity = 96.7%

By subtype

		Reference	
		+	-
Index test	+	3	4
	-	136	684

Disease group = JIA (oligoarticular)
Comparator = Healthy controls
Index = CCP
Sensitivity = 2.2%
Specificity = 99.4%

By subtype

		Reference	
		+	-
Index test	+	14	23
	-	63	665

Disease group = JIA (polyarticular)
Comparator = Healthy controls
Index = RF (unspecified isotype)
Sensitivity = 18.2%
Specificity = 96.7%

By subtype

		Reference	
		+	-
Index test	+	10	4
	-	67	684

Disease group = JIA (polyarticular)
Comparator = Healthy controls
Index = CCP
Sensitivity = 13.0%
Specificity = 99.4%

By subtype

		Reference	
		+	-
Index test	+	2	23
	-	12	665

Disease group = JIA (systemic)
Comparator = Healthy controls
Index = RF (unspecified isotype)
Sensitivity = 14.3%
Specificity = 96.7%

By subtype

		Reference	
		+	-
Index test	+	0	4
	-	14	684

Disease group = JIA (systemic)
Comparator = Healthy controls
Index = CCP
Sensitivity = 0%
Specificity = 99.4%

Study	Participants Characteristics	Index Test Characteristics
Habib, H.M., 2008 (54) **Country (# centers):** Eqypt (1) **Funding:** NR **Study design:** Case control (Prospective) **Recruitment:** NR	**Inclusion criteria:** NR **Exclusion criteria:** NR **JIA patients** **$N_{analyzed}/N_{enrolled}$:** 68/68 **Mean age (range):** 10.6yr (3.0-16.0yr) **Female:** 44.1% **Mean time since diagnosis (range):** 3.7yr (1.0-8.0yr) **Subtype:** Polyarticular (55.9%); Oligoarticular (29.4%); Systemic (14.7%) **Reference standard for JIA diagnosis:** ILAR **SLE patients** **$N_{analyzed}/N_{enrolled}$:** 14/14 **Mean age (range):** 12.1yr (NR) **Female:** 92.9% **Mean time since diagnosis (range):** 3.7yr (NR) **Reference standard for SLE diagnosis:** NR	**CCP test** **Assay method:** ELISA **Source of antigen:** Synthetic circular peptide containing citrulline **Manufacturer (kit type):** INOVA, San Diego, U.S. (Quanta LiteTM) **Positive cutoff:** 20 units/ml

Results (Overall)

		Reference	
		+	-
Index test	+	14	0
	-	54	20

Disease group = JIA
Comparator = Healthy controls
Index = CCP
Sensitivity = 20.6%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	14	0
	-	24	20

Disease group = JIA (polyarticular)
Comparator = Healthy controls
Index = CCP
Sensitivity = 36.8%
Specificity = 100.%

Overall

		Reference	
		+	-
Index test	+	0	0
	-	14	20

Disease group = SLE
Comparator = Healthy controls
Index = CCP
Sensitivity = 0.0%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	0	0
	-	10	20

Disease group = JIA (systemic)
Comparator = Healthy controls
Index = CCP
Sensitivity = 0%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	0	0
	-	20	20

Disease group = JIA (oligoarticular)
Comparator = Healthy controls
Index = CCP
Sensitivity = 0%
Specificity = 100.%

Study	Participants Characteristics	Index Test Characteristics
Hanson, V., 1966 (38) **Country (# centers):** U.S. (1) **Funding:** NR **Study design:** Case control (NR) **Recruitment:** NR	**Inclusion criteria:** NR **Exclusion criteria:** NR **JIA patients** **$N_{analyzed}/N_{enrolled}$:** 45/58 **Mean/median age (range):** NR **Female:** NR **Mean/median time since diagnosis (range):** NR **Subtype:** NR **Reference standard for JIA diagnosis:** ARA **SLE patients** **$N_{analyzed}/N_{enrolled}$:** 14/14 **Mean/median age (range):** NR **Female:** 80% **Mean/median time since diagnosis (range):** NR **Subtype:** NR **Reference standard for SLE diagnosis:** Conformed to Cook et al, and Urbach, and also met the criteria by Bywaters (Weir et al.)	**IgM-RF test** **Assay method:** Latex titration test **Source of antigen:** NR **Manufacturer (kit type):** NR **Positive cutoff:** Titer 1:160
Results (Overall) Disease group = JIA Comparator = Healthy controls Index = IgM-RF (Latex) **Sensitivity** = 22.2% **Specificity** = 100.%	**Overall** Disease group = JIA Comparator = ORG (other collagen diseases) Index = IgM-RF (Latex) **Sensitivity** = 22.2% **Specificity** = 90.9%	**Overall** Disease group = JIA Comparator = NRG (ulcerative collitis) Index = IgM-RF (Latex) **Sensitivity** = 22.2% **Specificity** = 95.7%

		Reference	
		+	-
Index test	+	10	0
	-	35	32

		Reference	
		+	-
Index test	+	10	3
	-	35	30

		Reference	
		+	-
Index test	+	10	1
	-	35	22

Overall

		Reference	
		+	-
Index test	+	4	0
	-	10	32

Disease group = SLE
Comparator = Healthy controls
Index = IgM-RF (Latex)
Sensitivity = 28.6%
Specificity = 100.%

Overall

		Reference	
		+	-
Index test	+	4	3
	-	10	30

Disease group = SLE
Comparator = ORG (other collagen diseases)
Index = IgM-RF (Latex)
Sensitivity = 28.6%
Specificity = 90.9%

Overall

		Reference	
		+	-
Index test	+	4	1
	-	10	22

Disease group = SLE
Comparator = NRG (ulcerative collitis)
Index = IgM-RF (Latex)
Sensitivity = 28.6%
Specificity = 95.7%

Study	Participants Characteristics	Index Test Characteristics
Haynes, D.C., 1986 (31) **Country (# centers):** U.S. (1) **Funding:** Government and non-commercial institution (NIH and House of St. Giles the Cripple) **Study design:** Case control (Prospective) **Recruitment:** NR	**Inclusion criteria:** NRG: Children with unspecified nonrheumatic disease. Age-matched with JIA patients **Exclusion criteria:** NR **JIA patients** **$N_{analyzed}/N_{enrolled}$:** 65/65 **Mean/median age (range):** NR (3.0-19.0yr) **Female:** NR **Mean/median time since diagnosis (range):** NR **Subtype:** Oligoarticular (35.3%); polyarticular (36.9%); systemic (27.7%) **Reference standard for JIA diagnosis:** ARA	**ANA test** **Assay method:** IIF **Source of antigen:** HEp-2 cell line **Manufacturer (kit type):** Breit Laboratories, Inc, Sacramento, CA (NR) **Positive cutoff:** A reading of 1+ or greater in fluorescence at 1:20 dilution **IgM-RF test** **Assay method:** ELISA **Source of antigen:** Human IgG **Manufacturer (kit type):** Sigma Chemical Co. (NR); Tago, Inc. (NR); and Pharmacia Fine Chemicals (NR) **Positive cutoff:** Mean of control group + 2 sd **IgG-RF test** **Assay method:** ELISA **Source of antigen:** Rabbit IgG **Manufacturer (kit type):** Sigma Chemical Co. (NR); Cappel Labs., Cochranville, PA (NR) **Positive cutoff:** Mean of control group + 2 sd
Results (Overall) Reference: + / - Index test: + (33, 1); - (32, 17) Disease group = JIA Comparator = NRG (Unspecified) Index = ANA **Sensitivity** = 50.8% **Specificity** = 94.4%	**Overall** Reference: + / - Index test: + (23, 0); - (42, 20) Disease group = JIA Comparator = NRG (Unspecified) Index = IgM-RF **Sensitivity** = 33.8% **Specificity** = 100.%	**Overall** Reference: + / - Index test: + (4, 0); - (61, 20) Disease group = JIA Comparator = NRG (Unspecified) Index = IgG-RF **Sensitivity** = 6.2% **Specificity** = 94.4%

By subtype

		Reference	
		+	-
Index test	+	18	1
	-	6	17

Disease group = JIA (oligoarticular)
Comparator = NRG (Unspecified)
Index = ANA
Sensitivity = 75.0%
Specificity = 94.4%

By subtype

		Reference	
		+	-
Index test	+	12	1
	-	11	17

Disease group = JIA (polyarticular)
Comparator = NRG (Unspecified)
Index = ANA
Sensitivity = 52.2%
Specificity = 94.4%

By subtype

		Reference	
		+	-
Index test	+	3	1
	-	15	17

Disease group = JIA (systemic)
Comparator = NRG (Unspecified)
Index = ANA
Sensitivity = 16.7%
Specificity = 94.4%

By subtype

		Reference	
		+	-
Index test	+	5	0
	-	19	20

Disease group = JIA (oligoarticular)
Comparator = NRG (Unspecified)
Index = IgM-RF
Sensitivity = 20.8%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	10	0
	-	13	20

Disease group = JIA (polyarticular)
Comparator = NRG (Unspecified)
Index = IgM-RF
Sensitivity = 43.5%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	8	0
	-	10	20

Disease group = JIA (systemic)
Comparator = NRG (Unspecified)
Index = IgM-RF
Sensitivity = 44.4%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	1	0
	-	23	20

Disease group = JIA (oligoarticular)
Comparator = NRG (Unspecified)
Index = IgG-RF
Sensitivity = 4.2%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	2	0
	-	21	20

Disease group = JIA (polyarticular)
Comparator = NRG (Unspecified)
Index = IgG-RF
Sensitivity = 8.7%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	1	0
	-	17	20

Disease group = JIA (systemic)
Comparator = NRG (Unspecified)
Index = IgG-RF
Sensitivity = 5.6%
Specificity = 100.%

Study	Participants Characteristics	Index Test Characteristics
Jones, O.Y., 2006 (32) **Country (# centers):** More than one countries from North America (7) **Funding:** NR **Study design:** Case control (Retrospective) **Recruitment:** Random selection	**Inclusion criteria:** NRG: Records available in the Pediatric Rheumatology Disease Registry (1992-1995) **Exclusion criteria:** NR **JIA patients** **$N_{analyzed}/N_{enrolled}$:** 194/206 **Mean age (range):** 6.4yr (2.4-17.1yr) **Female:** 75.2% **Mean/median time since diagnosis (range):** NR **Subtype:** Oligoarticular (41.8%); Polyarticular (38.4%); Systemic (19.9%) **Reference standard for JIA diagnosis:** NR	**ANA test** **Assay method:** NR **Source of antigen:** NR **Manufacturer (kit type):** NR **Positive cutoff:** Titer 1:80

Results (Overall)

		Reference	
		+	-
Index test	+	66	6
	-	128	28

Disease group = JIA
Comparator = NRG (Acute lymphocytic leukemia)
Index = ANA
Sensitivity = 34.0%
Specificity = 82.4%

Study	Participants Characteristics	Index Test Characteristics
Kasapcopur, O., 2004 (55) **Country (# centers):** Turkey (1) **Funding:** Academic institution **Study design:** Case control (Prospective) **Recruitment:** Consecutive patients	**Inclusion criteria:** NR **Exclusion criteria:** NR **JIA patients** **$N_{analyzed}/N_{enrolled}$:** 122/122 **Mean age (range):** 8.8yr (1.2-19.3yr) **Female:** 59.0% **Mean time since diagnosis (range):** 4.3yr (NR) **Subtype:** Polyarticular (39.3%); Oligoarticular (29.5%); Systemic (23.0%); Enthsitis-related arthritis (5.7%); Juvenile psoriatic arthritis (2.5%) **Reference standard for JIA diagnosis:** ILAR **SLE patients** **$N_{analyzed}/N_{enrolled}$:** 19/19 **Mean age (range):** 13.6yr (5.3-18.0yr) **Female:** 89.5% **Mean time since diagnosis (range):** 4.5yr (NR) **Reference standard for SLE diagnosis:** NR	**CCP test** **Assay method:** ELISA **Source of antigen:** NR **Manufacturer (kit type):** Euroimmun, Germany (NR) **Positive cutoff:** 5 relative units

Results (Overall)

		Reference	
		+	-
Index test	+	3	0
	-	119	15

Disease group = JIA
Comparator = Healthy controls
Index = CCP
Sensitivity = 2.5%
Specificity = 100.%

Overall

		Reference	
		+	-
Index test	+	0	0
	-	19	15

Disease group = SLE
Comparator = Healthy controls
Index = CCP
Sensitivity = 0.0%
Specificity = 100.%

Study	Participants Characteristics	Index Test Characteristics
Kwok, J.S.Y., 2005 (56) **Country (# centers):** Hong Kong (1) **Funding:** Academic institution **Study design:** Case control (Retrospective) **Recruitment:** NR	**Inclusion criteria:** NR **Exclusion criteria:** NR **JIA patients** **$N_{analyzed}/N_{enrolled}$:** 59/59 **Mean age (range):** 15.0yr (2.4-24.0yr) **Female:** 40.7% **Mean time since diagnosis (range):** 4.3yr (0.4-16.0yr) **Subtype:** Oligoarticular (25.4%); Polyarticular (32.2%); Systemic (6.8%); Enthesitis-related (20.3%); Other arthritides (15.3%) **Reference standard for JIA diagnosis:** ILAR **SLE patients** **$N_{analyzed}/N_{enrolled}$:** 21/21 **Mean age (range):** NR **Female:** NR **Mean time since diagnosis (range):** NR **Reference standard for SLE diagnosis:** NR	**CCP test** **Assay method:** ELISA **Source of antigen:** NR **Manufacturer (kit type):** Inova Diagnostics Inc, San Diego, CA; QuantaLite CCP IgG ELISA kit; NR **Positive cutoff:** 20 AU

Results (Overall)

		Reference	
		+	-
Index test	+	6	1
	-	53	25

Disease group = JIA
Comparator = NRG (allergy, idiopathic thrombocytopenia, and hepatitis C)
Index = CCP
Sensitivity = 10.2%
Specificity = 97.9%

Overall

		Reference	
		+	-
Index test	+	0	1
	-	21	25

Disease group = SLE
Comparator = NRG (allergy, idiopathic thrombocytopenia, and hepatitis C)
Index = CCP
Sensitivity = 0.0%
Specificity = 96.2%

By subtype

		Reference	
		+	-
Index test	+	1	1
	-	14	25

Disease group = JIA (oligoarticular)
Comparator = NRG (allergy, idiopathic thrombocytopenia, and hepatitis C)
Index = CCP
Sensitivity = 6.7%
Specificity = 97.9%

By subtype

		Reference	
		+	-
Index test	+	4	1
	-	15	25

Disease group = JIA (polyarticular)
Comparator = NRG (allergy, idiopathic thrombocytopenia, and hepatitis C)
Index = CCP
Sensitivity = 21.1%
Specificity = 97.9%

By subtype

		Reference	
		+	-
Index test	+	1	1
	-	3	25

Disease group = JIA (systemic)
Comparator = NRG (allergy, idiopathic thrombocytopenia, and hepatitis C)
Index = CCP
Sensitivity = 25.0%
Specificity = 97.9%

Study	Participants Characteristics	Index Test Characteristics
Lipinska, J., 2008 (33) **Country (# centers):** Poland (NR) **Funding:** Academic institution **Study design:** Case control (Prospective) **Recruitment:** NR	**Inclusion criteria:** NRG: With functional cardio-vascular system dysfunction. Age- and sex-matched with JIA patients **Exclusion criteria:** NR **JIA patients** **$N_{analyzed}/N_{enrolled}$:** 96/96 **Mean/median age (range):** 12.8yr (3.0-18.0yr) **Female:** 61.5% **Mean/median time since diagnosis (range):** NR **Subtype:** Oligoarticular (37.5%); Polyarticular (51.0%); Systemic (11.5%) **Reference standard for JIA diagnosis:** ILAR	**ANA test** **Assay method:** IIF **Source of antigen:** NR **Manufacturer (kit type):** Euroimmun Polska Sp. z o.o. (NR) **Positive cutoff:** Titer 1:320 **IgM-RF test** **Assay method:** ELISA **Source of antigen:** NR **Manufacturer (kit type):** Biomedica Poland Sp. Z.o.o. (05-500 Piaseczno ELISA kit) **Positive cutoff:** 24 RU/ml **CCP test** **Assay method:** ELISA **Source of antigen:** NR **Manufacturer (kit type):** Euroimmun Polska Sp. z o.o. (52-219 Wroclaw) **Positive cutoff:** 5 RU/ml
Results (Overall) Disease group = JIA Comparator = NRG Index = ANA **Sensitivity** = 8.3% **Specificity** = 100.%	**Overall** Disease group = JIA Comparator = NRG Index = IgM-RF **Sensitivity** = 14.6% **Specificity** = 95.5%	**Overall** Disease group = JIA Comparator = NRG Index = CCP **Sensitivity** = 41.7% **Specificity** = 100.%

		Reference	
		+	-
Index test	+	8	0
	-	88	22

		Reference	
		+	-
Index test	+	14	1
	-	82	21

		Reference	
		+	-
Index test	+	40	0
	-	56	22

By subtype

		Reference	
		+	-
Index test	+	2	1
	-	34	21

Disease group = JIA (oligoarticular)
Comparator = NRG
Index = IgM-RF
Sensitivity = 5.6%
Specificity = 95.5%

By subtype

		Reference	
		+	-
Index test	+	11	1
	-	38	21

Disease group = JIA (polyarticular)
Comparator = NRG
Index = IgM-RF
Sensitivity = 22.4%
Specificity = 95.5%

By subtype

		Reference	
		+	-
Index test	+	1	1
	-	10	21

Disease group = JIA (systemic)
Comparator = NRG
Index = IgM-RF
Sensitivity = 9.1%
Specificity = 95.5%

By subtype

		Reference	
		+	-
Index test	+	13	0
	-	23	22

Disease group = JIA (oligoarticular)
Comparator = NRG
Index = CCP
Sensitivity = 36.1%
Specificity = 100%

By subtype

		Reference	
		+	-
Index test	+	21	0
	-	28	22

Disease group = JIA (polyarticular)
Comparator = NRG
Index = CCP
Sensitivity = 42.9%
Specificity = 100%

By subtype

		Reference	
		+	-
Index test	+	6	0
	-	5	22

Disease group = JIA (systemic)
Comparator = NRG
Index = CCP
Sensitivity = 54.5%
Specificity = 100%

Study	Participants Characteristics	Index Test Characteristics
Nordal, E.B., 2009 (34) **Country (# centers):** Norway (5) **Funding:** Non-commercial institution **Study design:** Case control (Prospective) **Recruitment:** Consecutive patients	**Inclusion criteria:** JIA patients: Newly diagnosed cases NRG: Children undergoing elective outpatient procedures with no diagnosis of inflammatory diseases **Exclusion criteria:** NR **JIA patients** **$N_{analyzed}/N_{enrolled}$:** 100/174 **Mean/median age (range):** NR **Female:** 71.0% **Mean/median time since diagnosis (range):** NR (max: 1.0yr) **Subtype:** Oligoarticular (50.0%) **Reference standard for JIA diagnosis:** ILAR	**ANA test** **Assay method:** IIF **Source of antigen:** HEp-2 cell line **Manufacturer (kit type):** Immunoconcepts, Sacramento, CA (NR) **Positive cutoff:** Titer 1:80 **ANA test** **Assay method:** ELISA **Source of antigen:** Recombinant or purified native nuclear antigens **Manufacturer (kit type):** Pharmacia Diagnostics, Freiburg, Germany (Varelisa Recombi ANA screening test). **Positive cutoff:** Titer 1:101

Results (Overall)

		Reference	
		+	-
Index test	+	57	3
	-	43	55

Disease group = JIA
Comparator = NRG (no inflammatory diseases; undergoing elective surgery)
Index = ANA (IIF)
Sensitivity = 57.0%
Specificity = 94.8%

By comorbidity

		Reference	
		+	-
Index test	+	44	N/A
	-	40	N/A

Disease group = JIA (without uveitis)
Comparator = NRG (no inflammatory diseases; undergoing elective surgery)
Index = ANA (IIF)
Sensitivity = 52.4%
Specificity = N/A

Overall

		Reference	
		+	-
Index test	+	4	0
	-	96	58

Disease group = JIA
Comparator = NRG (no inflammatory diseases; undergoing elective surgery)
Index = ANA (ELISA)
Sensitivity = 4.0%
Specificity = 100.%

By comorbidity

		Reference	
		+	-
Index test	+	13	N/A
	-	3	N/A

Disease group = JIA (with uveitis)
Comparator = NRG (no inflammatory diseases; undergoing elective surgery)
Index = ANA (IIF)
Sensitivity = 81.3%
Specificity = N/A

Study	Participants Characteristics	Index Test Characteristics
Osborn, T.G., 1984 (35) **Country (# centers):** U.S. (1) **Funding:** Government **Study design:** Case control (Prospective) **Recruitment:** NR	**Inclusion criteria:** NR **Exclusion criteria:** NR **JIA patients** **$N_{analyzed}/N_{enrolled}$:** 217/217 **Mean/median age (range):** NR (0.2-16.0yr) **Female:** 66.4% **Mean/median time since diagnosis (range):** NR **Subtype:** Oligoarticular (46.5%); Systemic (12.9%); Polyarticular (40.6%) **Reference standard for JIA diagnosis:** ARA	**ANA test** **Assay method:** IIF **Source of antigen:** HEp-2 cell line **Manufacturer (kit type):** NR **Positive cutoff:** Titer 1:40

Results (Overall)

		Reference	
		+	-
Index test	+	131	3
	-	86	32

Disease group = JIA
Comparator = Healthy controls
Index = ANA
Sensitivity = 60.4%
Specificity = 91.4%

Overall

		Reference	
		+	-
Index test	+	131	15
	-	86	16

Disease group = JIA
Comparator = ORG (other connective tissue diseases)
Index = ANA
Sensitivity = 60.4%
Specificity = 51.6%

By subtype

		Reference	
		+	-
Index test	+	63	3
	-	38	32

Disease group = JIA (oligoarticular)
Comparator = Healthy controls
Index = ANA
Sensitivity = 62.4%
Specificity = 91.4%

By subtype

		Reference	
		+	-
Index test	+	59	3
	-	29	32

Disease group = JIA (polyarticular)
Comparator = Healthy controls
Index = ANA
Sensitivity = 67.0%
Specificity = 91.4%

By subtype

		Reference	
		+	-
Index test	+	9	3
	-	19	32

Disease group = JIA (systemic)
Comparator = Healthy controls
Index = ANA
Sensitivity = 32.1%
Specificity = 91.4%

By subtype

		Reference	
		+	-
Index test	+	63	15
	-	38	16

Disease group = JIA (oligoarticular)
Comparator = ORG (other connective tissue diseases)
Index = ANA
Sensitivity = 62.4%
Specificity = 51.6%

By subtype

		Reference	
		+	-
Index test	+	59	15
	-	29	16

Disease group = JIA (polyarticular)
Comparator = ORG (other connective tissue diseases)
Index = ANA
Sensitivity = 67.0%
Specificity = 51.6%

By subtype

		Reference	
		+	-
Index test	+	9	15
	-	19	16

Disease group = JIA (systemic)
Comparator = ORG (other connective tissue diseases)
Index = ANA
Sensitivity = 32.1%
Specificity = 51.6%

Study	Participants Characteristics	Index Test Characteristics
Permin, H., 1982 (43) **Country (# centers):** Denmark (NR) **Funding:** Non-commercial institution **Study design:** Case control (Prospective) **Recruitment:** Random selection	**Inclusion criteria:** NR **Exclusion criteria:** NR **JIA patients** **$N_{analyzed}/N_{enrolled}$:** 26/26 **Mean age (range):** 9.0yr (2.0-16.0yr) **Female:** 73.1% **Mean time since diagnosis (range):** 3.yr (0.5-15.0yr) **Subtype:** Polyarticular (42.3%); Oligoarticular (42.3%); Systemic (15.4%) **Reference standard for JIA diagnosis:** ARA	**IgM-RF test** **Assay method:** IIF **Source of antigen:** Formalin-fixed sheep red cell IgG **Manufacturer (kit type):** NR **Positive cutoff:** Titer 1:10 **IgG-RF test** **Assay method:** IIF **Source of antigen:** Formalin-fixed sheep red cell IgG **Manufacturer (kit type):** NR **Positive cutoff:** Titer 1:10 **IgA-RF test** **Assay method:** IIF **Source of antigen:** Formalin-fixed sheep red cell IgG **Manufacturer (kit type):** NR **Positive cutoff:** Titer 1:10 **IgE-RF test** **Assay method:** IIF **Source of antigen:** Formalin-fixed sheep red cell IgG **Manufacturer (kit type):** NR **Positive cutoff:** Titer 1:16

Results (Overall)

		Reference	
		+	-
Index test	+	1	0
	-	25	23

Disease group = JIA
Comparator = Healthy controls
Index = IgM-RF
Sensitivity = 3.9%
Specificity = 100.%

Overall

		Reference	
		+	-
Index test	+	22	0
	-	4	23

Disease group = JIA
Comparator = Healthy controls
Index = IgG-RF
Sensitivity = 84.6%
Specificity = 100.%

Overall

		Reference	
		+	-
Index test	+	0	0
	-	26	23

Disease group = JIA
Comparator = Healthy controls
Index = IgA-RF
Sensitivity = 0%
Specificity = 100.%

Overall

		Reference	
		+	-
Index test	+	0	0
	-	26	23

Disease group = JIA
Comparator = Healthy controls
Index = IgE-RF
Sensitivity = 0%
Specificity = 100.%

Study	Participants Characteristics	Index Test Characteristics
Roizenblatt, S., 1993 (44) **Country (# centers):** Brazil (1) **Funding:** NR **Study design:** Case control (Prospective) **Recruitment:** NR	**Inclusion criteria:** ORG: Hypermobile children. Matched age and sex. **Exclusion criteria:** NR **JIA patients** **$N_{analyzed}/N_{enrolled}$:** 24/24 **Mean age (range):** 9.0yr (2.3-15.0yr) **Female:** 54.2% **Mean/median time since diagnosis (range):** NR (Min: 0.5yr) **Subtype:** Polyarticular (37.5%); Oligoarticular (50.0%); Systemic (12.5%) **Reference standard for JIA diagnosis:** ACR	**IgM-RF test** **Assay method:** ELISA **Source of antigen:** Sheep erytrocyte **Manufacturer (kit type):** Dako Ab (NR) **Positive cutoff:** Mean of control group + 2 sd **IgG-RF test** **Assay method:** ELISA **Source of antigen:** NR **Manufacturer (kit type):** NR **Positive cutoff:** Mean of control group + 2 sd
Results (Overall) Disease group = JIA Comparator = ORG Index = IgM-RF **Sensitivity** = 4.2% **Specificity** = 100.%	**Overall** Disease group = JIA Comparator = ORG Index = IgG-RF **Sensitivity** = 79.2% **Specificity** = 100.%	**By subtype** Disease group = JIA (oligoarticular) Comparator = ORG Index = IgM-RF **Sensitivity** = 8.3% **Specificity** = 100%

		Reference	
		+	-
Index test	+	1	0
	-	23	26

		Reference	
		+	-
Index test	+	19	0
	-	5	26

		Reference	
		+	-
Index test	+	1	0
	-	11	26

By subtype

		Reference	
		+	-
Index test	+	0	0
	-	9	26

Disease group = JIA (polyarticular)
Comparator = ORG
Index = IgM-RF
Sensitivity = 0%
Specificity = 100%

By subtype

		Reference	
		+	-
Index test	+	0	0
	-	3	26

Disease group = JIA (systemic)
Comparator = ORG
Index = IgM-RF
Sensitivity = 0%
Specificity = 100%

By subtype

		Reference	
		+	-
Index test	+	10	0
	-	2	26

Disease group = JIA (oligoarticular)
Comparator = ORG
Index = IgG-RF
Sensitivity = 83.3%
Specificity = 100%

By subtype

		Reference	
		+	-
Index test	+	7	0
	-	2	26

Disease group = JIA (polyarticular)
Comparator = ORG
Index = IgG-RF
Sensitivity = 77.8%
Specificity = 100%

By subtype

		Reference	
		+	-
Index test	+	2	0
	-	1	26

Disease group = JIA (systemic)
Comparator = ORG
Index = IgG-RF
Sensitivity = 66.7%
Specificity = 100%

Study	Participants Characteristics	Index Test Characteristics
Saulsbury F.T., 1990 (50) **Country (# centers):** U.S. (NR) **Funding:** Non-commercial institution **Study design:** Case control (NR) **Recruitment:** NR	**Inclusion criteria:** NR **Exclusion criteria:** NR **JIA patients** **$N_{analyzed}/N_{enrolled}$:** 50/50 **Mean/median age (range):** NR (1.0-18.0yr) **Female:** 78.0% **Mean/median time since diagnosis (range):** NR **Subtype:** Oligoarticular (56.0%); polyarticular (28.0%); systemic (16.0%) **Reference standard for JIA diagnosis:** Based on reference No. 7	**IgM-RF test** **Assay method:** ELISA **Source of antigen:** Latex beads coated with human IgG **Manufacturer (kit type):** Dynatech Laboratories, Alexandria, VA (NR) **Positive cutoff:** Titer 1:20 **IgG-RF test** **Assay method:** ELISA **Source of antigen:** Rabbit IgG **Manufacturer (kit type):** Gamma Biologicals, Inc. Houston, TX (NR) **Positive cutoff:** Titer 1:20 **IgA-RF test** **Assay method:** ELISA **Source of antigen:** Latex beads coated with human IgG **Manufacturer (kit type):** Dynatech Laboratories, Alexandria, VA (NR) **Positive cutoff:** Titer 1:20
Results (Overall) Disease group = JIA Comparator = Healthy controls Index = IgM-RF **Sensitivity** = 22.0% **Specificity** = 97.4%	**Overall** Disease group = JIA Comparator = Healthy controls Index = IgG-RF **Sensitivity** = 58.0% **Specificity** = 94.9%	**Overall** Disease group = JIA Comparator = Healthy controls Index = IgA-RF **Sensitivity** = 32.0% **Specificity** = 97.4%

		Reference	
		+	-
Index test	+	11	1
	-	39	38

		Reference	
		+	-
Index test	+	2	0
	-	48	39

		Reference	
		+	-
Index test	+	11	1
	-	39	38

By subtype

		Reference	
		+	-
Index test	+	5	1
	-	23	38

Disease group = JIA (oligoarticular)
Comparator = Healthy controls
Index = IgM-RF
Sensitivity = 17.9%
Specificity = 97.4%

By subtype

		Reference	
		+	-
Index test	+	0	0
	-	28	39

Disease group = JIA (oligoarticular)
Comparator = Healthy controls
Index = IgG-RF
Sensitivity = 0%
Specificity = 100%

By subtype

		Reference	
		+	-
Index test	+	8	1
	-	20	38

Disease group = JIA (oligoarticular)
Comparator = Healthy controls
Index = IgA-RF
Sensitivity = 28.9%
Specificity = 97.4%

By subtype

		Reference	
		+	-
Index test	+	5	1
	-	9	38

Disease group = JIA (polyarticular)
Comparator = Healthy controls
Index = IgM-RF
Sensitivity = 35.7%
Specificity = 97.4%

By subtype

		Reference	
		+	-
Index test	+	1	0
	-	13	39

Disease group = JIA (polyarticular)
Comparator = Healthy controls
Index = IgG-RF
Sensitivity = 7.1%
Specificity = 100%

By subtype

		Reference	
		+	-
Index test	+	2	1
	-	12	38

Disease group = JIA (polyarticular)
Comparator = Healthy controls
Index = IgA-RF
Sensitivity = 14.3%
Specificity = 97.4%

By subtype

		Reference	
		+	-
Index test	+	1	1
	-	7	38

Disease group = JIA (systemic)
Comparator = Healthy controls
Index = IgM-RF
Sensitivity = 12.5%
Specificity = 97.4%

By subtype

		Reference	
		+	-
Index test	+	1	0
	-	7	39

Disease group = JIA (systemic)
Comparator = Healthy controls
Index = IgG-RF
Sensitivity = 12.5%
Specificity = 100%

By subtype

		Reference	
		+	-
Index test	+	1	1
	-	7	38

Disease group = JIA (systemic)
Comparator = Healthy controls
Index = IgA-RF
Sensitivity = 12.5%
Specificity = 97.4%

Study	Participants Characteristics	Index Test Characteristics
Siamopoulou-Mavridou, A., 1991 (36) **Country (# centers):** Greece (NR) **Funding:** NR **Study design:** Case control (Prospective) **Recruitment:** Consecutive patients	**Inclusion criteria:** Healthy controls: Age- and sex-matched children without rheumatic disease **Exclusion criteria:** NR **JIA patients** **$N_{analyzed}/N_{enrolled}$:** 69/69 **Mean age (range):** 8.6yr (1.0-15.0yr) **Female:** 59.4% **Mean/median time since diagnosis (range):** 5.7yr (1.0-9.0yr) **Subtype:** Oligoarticular (43.5%); Polyarticular (29.0%); Systemic (27.5%) **Reference standard for JIA diagnosis:** EULAR	**ANA test** **Assay method:** IIF **Source of antigen:** HEp-2 cell line **Manufacturer (kit type):** NR **Positive cutoff:** Titer 1:40 **IgM-RF test** **Assay method:** Latex fixation test **Source of antigen:** NR **Manufacturer (kit type):** Behringwerke AG (NR) **Positive cutoff:** Mean optical density (OD) of healthy controls + 3 sd

Results (Overall)

		Reference	
		+	-
Index test	+	41	2
	-	28	64

Disease group = JIA
Comparator = Healthy controls
Index = ANA
Sensitivity = 59.4%
Specificity = 97.0%

Overall

		Reference	
		+	-
Index test	+	3	0
	-	66	66

Disease group = JIA
Comparator = Healthy controls
Index = IgM-RF
Sensitivity = 4.4%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	21	2
	-	9	64

Disease group = JIA (oligoarticular)
Comparator = Healthy controls
Index = ANA
Sensitivity = 70.0%
Specificity = 97.0%

By subtype

		Reference	
		+	-
Index test	+	13	2
	-	7	64

Disease group = JIA (polyarticular)
Comparator = Healthy controls
Index = ANA
Sensitivity = 65.0%
Specificity = 97.0%

By subtype

		Reference	
		+	-
Index test	+	7	2
	-	12	64

Disease group = JIA (systemic)
Comparator = Healthy controls
Index = ANA
Sensitivity = 36.8%
Specificity = 97.0%

By subtype

		Reference	
		+	-
Index test	+	0	0
	-	30	66

Disease group = JIA (oligoarticular)
Comparator = Healthy controls
Index = IgM-RF
Sensitivity = 0%
Specificity = 100%

By subtype

		Reference	
		+	-
Index test	+	3	0
	-	17	66

Disease group = JIA (polyarticular)
Comparator = Healthy controls
Index = IgM-RF
Sensitivity = 15.0%
Specificity = 100%

By subtype

		Reference	
		+	-
Index test	+	0	0
	-	19	66

Disease group = JIA (systemic)
Comparator = Healthy controls
Index = IgM-RF
Sensitivity = 0%
Specificity = 100%

Study	Participants Characteristics	Index Test Characteristics
Taseski, B., 1981 (45) **Country (# centers):** Yugoslavia (1) **Funding:** NR **Study design:** Case control (Prospective) **Recruitment:** NR	**Inclusion criteria:** NR **Exclusion criteria:** NR **JIA patients** **$N_{analyzed}/N_{enrolled}$:** 40/40 **Mean/median age (range):** NR (Max: 17.0yr) **Female:** NR **Mean/median time since diagnosis (range):** NR **Subtype:** Monoarthicular (25.0%); Systemic (15.0%); Polyarticular (60.0%) **Reference standard for JIA diagnosis:** NR **Reference standard for SLE diagnosis:** NR	**RF test (unspecified isotype)** **Assay method:** Photometrical latex test (PLT) **Source of antigen:** NR **Manufacturer (kit type):** NR **Positive cutoff:** Photometrically measured even at the lowest serum dilution **RF test (unspecified isotype)** **Assay method:** Standard sensitized sheep-cell test (SSC) **Source of antigen:** Sheep cell **Manufacturer (kit type):** NR **Positive cutoff:** Titer 1:64 **IgM-RF test** **Assay method:** Latex slide test (LST) **Source of antigen:** NR **Manufacturer (kit type):** NR **Positive cutoff:** Agglutination visually detected

Results (Overall)

		Reference	
		+	-
Index test	+	20	4
	-	20	20

Disease group = JIA
Comparator = Healthy controls
Index = RF (PLT)
Sensitivity = 50.0%

Overall

		Reference	
		+	-
Index test	+	0	0
	-	40	24

Disease group = JIA
Comparator = Healthy controls
Index = IgM-RF (LST)
Sensitivity = 0%

Overall

		Reference	
		+	-
Index test	+	1	0
	-	39	24

Disease group = JIA
Comparator = Healthy controls
Index = RF (SSC)
Sensitivity = 2.5%

Specificity = 83.3%

Overall

		Reference	
		+	-
Index test	+	9	4
	-	18	20

Disease group = JIA
Comparator = ORG (collagen diseases)
Index = RF (PLT)
Sensitivity = 33.3%
Specificity = 83.3%

Overall

		Reference	
		+	-
Index test	+	2	4
	-	0	20

Disease group = SLE
Comparator = Healthy controls
Index = RF (PLT)
Sensitivity = 100 %
Specificity = 100.%

Specificity = 100.%

Overall

		Reference	
		+	-
Index test	+	1	0
	-	26	24

Disease group = JIA
Comparator = ORG (collagen diseases)
Index = IgM-RF (LST)
Sensitivity = 3.7%
Specificity = 100.%

Specificity = 100.%

Overall

		Reference	
		+	-
Index test	+	3	0
	-	24	24

Disease group = JIA
Comparator = ORG (collagen diseases)
Index = RF (SSC)
Sensitivity = 11.1%
Specificity = 100.%

Study	Participants Characteristics	Index Test Characteristics
Varbanova, B.B., 1999 (46) **Country (# centers):** Bulgaria (NR) **Funding:** NR **Study design:** Case control (Prospective) **Recruitment:** NR	**Inclusion criteria:** NR **Exclusion criteria:** NR **JIA patients** **$N_{analyzed}/N_{enrolled}$:** 53/53 **Mean/median age (range):** NR (1.5-18.0yr) **Female:** NR **Mean/median time since diagnosis (range):** NR (Min: 1yr) **Subtype:** Oligoarticular (62.3%); Seronegative Polyarticular (37.7%) **Reference standard for JIA diagnosis:** EULAR **SLE patients** **$N_{analyzed}/N_{enrolled}$:** 22/22 **Mean/median age (range):** NR **Female:** NR **Mean/median time since diagnosis (range):** NR **Reference standard for SLE diagnosis:** NR	**IgM-RF test** **Assay method:** ELISA **Source of antigen:** Human gamma globulin **Manufacturer (kit type):** CLB-Amsterdam (NR) **Positive cutoff:** 6.25 IU **IgG-RF test** **Assay method:** ELISA **Source of antigen:** Rabbit IgG **Manufacturer (kit type):** NR **Positive cutoff:** Mean international unit (IU) of healthy controls + 2 sd **IgA-RF test** **Assay method:** ELISA **Source of antigen:** Rabbit IgG **Manufacturer (kit type):** NR **Positive cutoff:** Mean IU of healthy controls + 2 sd
Results (Overall) Disease group = JIA Comparator = Healthy controls Index = IgM-RF **Sensitivity** = 32.1% **Specificity** = 100.%	**Overall** Disease group = JIA Comparator = Healthy controls Index = IgG-RF **Sensitivity** = 13.2% **Specificity** = 100.%	**Overall** Disease group = JIA Comparator = Healthy controls Index = IgA-RF **Sensitivity** = 28.3% **Specificity** = 100.%

		Reference	
		+	-
Index test	+	17	0
	-	36	58

		Reference	
		+	-
Index test	+	7	0
	-	46	58

		Reference	
		+	-
Index test	+	15	0
	-	38	58

Overall

		Reference	
		+	-
Index test	+	2	0
	-	20	58

Disease group = SLE
Comparator = Healthy controls
Index = IgM-RF
Sensitivity = 9.1%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	6	0
	-	27	58

Disease group = JIA (oligoarticular)
Comparator = Healthy controls
Index = IgM-RF
Sensitivity = 18.2%
Specificity = 100%

By subtype

		Reference	
		+	-
Index test	+	3	0
	-	17	58

Disease group = JIA (polyarticular)
Comparator = Healthy controls
Index = IgG-RF
Sensitivity = 15.0%
Specificity = 100%

Overall

		Reference	
		+	-
Index test	+	3	0
	-	19	58

Disease group = SLE
Comparator = Healthy controls
Index = IgG-RF
Sensitivity = 13.6%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	11	0
	-	9	58

Disease group = JIA (polyarticular)
Comparator = Healthy controls
Index = IgM-RF
Sensitivity = 55.0%
Specificity = 100%

By subtype

		Reference	
		+	-
Index test	+	7	0
	-	26	58

Disease group = JIA (oligoarticular)
Comparator = Healthy controls
Index = IgA-RF
Sensitivity = 21.2%
Specificity = 100%

Overall

		Reference	
		+	-
Index test	+	2	0
	-	20	58

Disease group = SLE
Comparator = Healthy controls
Index = IgA-RF
Sensitivity = 9.1%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	4	0
	-	29	58

Disease group = JIA (oligoarticular)
Comparator = Healthy controls
Index = IgG-RF
Sensitivity = 12.1%
Specificity = 100%

By subtype

		Reference	
		+	-
Index test	+	8	0
	-	12	58

Disease group = JIA (polyarticular)
Comparator = Healthy controls
Index = IgA-RF
Sensitivity = 40.0%
Specificity = 100%

Study	Participants Characteristics	Index Test Characteristics
Wakhlu, A., 2003 (37) **Country (# centers):** India (1) **Funding:** Academic institution **Study design:** Case control (Prospective) **Recruitment:** NR	**Inclusion criteria:** NR **Exclusion criteria:** NR **JIA patients** **$N_{analyzed}/N_{enrolled}$:** 148/148 **Median age (range):** 14.0yr (2.0-26.0yr) **Female:** 43.2% **Mean/median time since diagnosis (range):** NR **Subtype:** Oligoarticular (36.5%); Polyarticular (43.2%); Systemic (20.3%) **Reference standard for JIA diagnosis:** ARA	**ANA test** **Assay method:** IIF **Source of antigen:** HEp-2 cell line **Manufacturer (kit type):** NR **Positive cutoff:** Titer 1:40

Overall

		Reference	
		+	-
Index test	+	2	0
	-	146	25

Disease group = JIA
Comparator = Healthy controls
Index = ANA
Sensitivity = 1.4%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	0	0
	-	30	25

Disease group = JIA (systemic)
Comparator = Healthy controls
Index = ANA
Sensitivity = 0%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	0	0
	-	54	25

Disease group = JIA (oligoarticular)
Comparator = Healthy controls
Index = ANA
Sensitivity = 0%
Specificity = 100.%

By subtype

		Reference	
		+	-
Index test	+	2	0
	-	62	25

Disease group = JIA (polyarticular)
Comparator = Healthy controls
Index = ANA
Sensitivity = 3.1%
Specificity = 100.%

Study	Participants Characteristics	Index Test Characteristics
Wananukul, S., 2005 (30) **Country (# centers):** Thailand (1) **Funding:** Non-commercial institution **Study design:** Case control (Prospective) **Recruitment:** NR	**Inclusion criteria:** NRG: Scheduled for elective surgery (adenotonsillectomy, herniorrhaphy or plastic surgery) **Exclusion criteria:** All participants: Exclude overt autoimmune disease, or conditions associated with abnormal ANA titers (infection, hepatitis and malignancy) or underwent treatment with certain drugs (procainamide, hydralazine, chlorpromazine, etc) All participants: Exclude children aged less than 6 months old **SLE patients** **$N_{analyzed}/N_{enrolled}$:** 46/52 **Mean/median age (range):** NR (5.0-15.0yr) **Female:** NR **Mean/median time since diagnosis (range):** NR **Subtype:** NR **Reference standard for SLE diagnosis:** 1997 revised criteria for the classification of SLE	**ANA test** **Assay method:** IIF **Source of antigen:** HEp-2 cell line **Manufacturer (kit type):** Diasarin, Stillwater, MN (ANAFAST kits) **Positive cutoff:** Titer ≥ 1:40

Results (Overall)

		Reference	
		+	-
Index test	+	42	15
	-	4	84

Disease group = SLE
Comparator = Healthy controls (elective surgery)
Index = ANA
Sensitivity = 91.3%
Specificity = 84.8%

Overall

		Reference	
		+	-
Index test	+	42	17
	-	4	91

Disease group = SLE
Comparator = Healthy controls
Index = ANA
Sensitivity = 91.3%
Specificity = 84.3%

Study	Participants Characteristics	Index Test Characteristics
Wernick, R., 1981 (47) **Country (# centers):** U.S. (NR) **Funding:** Government **Study design:** Case control (Prospective) **Recruitment:** NR	**Inclusion criteria:** NR **Exclusion criteria:** NR **JIA patients** **$N_{analyzed}/N_{enrolled}$:** 49/49 **Mean/median age (range):** NR **Female:** NR **Mean/median time since diagnosis (range):** NR **Subtype:** Polyarticular (22.4%); Oligoarticular (59.2%); Systemic (18.4%) **Reference standard for JIA diagnosis:** ARA **SLE patients** **$N_{analyzed}/N_{enrolled}$:** 7/7 **Mean/median age (range):** NR **Female:** NR **Mean/median time since diagnosis (range):** NR **Reference standard for SLE diagnosis:** ARA	**IgM-RF test** **Assay method:** Solid phase radioimmunoassay **Source of antigen:** Rabbit and human IgG **Manufacturer (kit type):** Signma Chemical Co., St. Louis, MO (Cohn Fraction II) **Positive cutoff:** Mean of normal controls + 2 SD **IgG-RF test** **Assay method:** Solid phase radioimmunoassay **Source of antigen:** Rabbit and human IgG **Manufacturer (kit type):** Signma Chemical Co., St. Louis, MO (Cohn Fraction II) **Positive cutoff:** Mean of normal controls + 2 SD
Results (Overall) Disease group = JIA Comparator = NRG (Scoliosis and neurologic diseases) Index = IgM-RF **Sensitivity** = 4.1% **Specificity** = 93.8%	**Overall** Disease group = JIA Comparator = NRG (Scoliosis and neurologic diseases) Index = IgG-RF **Sensitivity** = 8.2% **Specificity** = 90.6%	**Overall** Disease group = SLE Comparator = NRG (scoliosis and neurologic diseases) Index = IgM-RF **Sensitivity** = 0% **Specificity** = 97.0%

		Reference	
		+	-
Index test	+	2	2
	-	47	30

		Reference	
		+	-
Index test	+	4	1
	-	45	32

		Reference	
		+	-
Index test	+	0	1
	-	7	32

Overall

		Reference	
		+	-
Index test	+	1	2
	-	6	30

Disease group = SLE
Comparator = NRG (Scoliosis and neurologic diseases)
Index = IgG-RF
Sensitivity = 14.3%
Specificity = 93.8%

By subtype

		Reference	
		+	-
Index test	+	0	2
	-	9	30

Disease group = JIA (systemic)
Comparator = NRG (Scoliosis and neurologic diseases)
Index = IgM-RF
Sensitivity = 0%
Specificity = 93.8%

By subtype

		Reference	
		+	-
Index test	+	1	1
	-	8	32

Disease group = JIA (systemic)
Comparator = NRG (Scoliosis and neurologic diseases)
Index = IgG-RF
Sensitivity = 11.1%
Specificity = 90.6%

By subtype

		Reference	
		+	-
Index test	+	1	2
	-	28	30

Disease group = JIA (oligoarticular)
Comparator = NRG (Scoliosis and neurologic diseases)
Index = IgM-RF
Sensitivity = 3.4%
Specificity = 93.8%

By subtype

		Reference	
		+	-
Index test	+	2	1
	-	27	32

Disease group = JIA (oligoarticular)
Comparator = NRG (Scoliosis and neurologic diseases)
Index = IgG-RF
Sensitivity = 6.9%
Specificity = 97.0%

By subtype

		Reference	
		+	-
Index test	+	1	2
	-	10	30

Disease group = JIA (polyarticular)
Comparator = NRG (Scoliosis and neurologic diseases)
Index = IgM-RF
Sensitivity = 9.1%
Specificity = 93.8%

By subtype

		Reference	
		+	-
Index test	+	1	1
	-	10	32

Disease group = JIA (polyarticular)
Comparator = NRG (Scoliosis and neurologic diseases)
Index = IgG-RF
Sensitivity = 9.1%
Specificity = 97.0%

Appendix G. Subgroup Analyses by Onset Type of Juvenile Idiopathic Arthritis

Subgroup analysis of studies examining antinuclear antibody test for juvenile idiopathic arthritis (JIA; Figures G1 – G3). None of the studies provided subgroup data based on RF positivity for patients with polyarticular JIA.

Figure G1. Forest plot of sensitivity and specificity of antinuclear antibody test for oligoarticular juvenile idiopathic arthritis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Fawcett 1999 (ORG)	68	4	20	22	0.77 [0.67, 0.86]	0.85 [0.65, 0.96]
Haynes 1986 (NRG)	18	1	6	17	0.75 [0.53, 0.90]	0.94 [0.73, 1.00]
Osborn 1984 (healthy)	63	18	38	48	0.62 [0.52, 0.72]	0.73 [0.60, 0.83]
S-Mavridou 1991 (healthy)	21	2	9	64	0.70 [0.51, 0.85]	0.97 [0.89, 1.00]
Wakhlu 2003 (healthy)	0	0	54	25	0.00 [0.00, 0.07]	1.00 [0.86, 1.00]

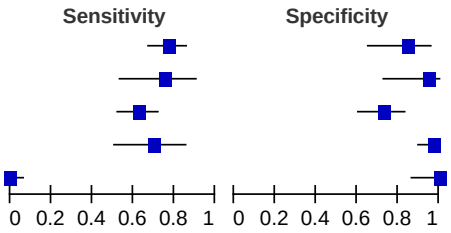


Figure G2. Forest plot of sensitivity and specificity of antinuclear antibody test for polyarticular juvenile idiopathic arthritis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Fawcett 1999 (ORG)	38	4	30	22	0.56 [0.43, 0.68]	0.85 [0.65, 0.96]
Haynes 1986 (NRG)	12	1	11	17	0.52 [0.31, 0.73]	0.94 [0.73, 1.00]
Osborn 1984 (healthy)	59	18	29	48	0.67 [0.56, 0.77]	0.73 [0.60, 0.83]
S-Mavridou 1991 (healthy)	13	2	7	64	0.65 [0.41, 0.85]	0.97 [0.89, 1.00]
Wakhlu 2003 (healthy)	2	0	62	25	0.03 [0.00, 0.11]	1.00 [0.86, 1.00]

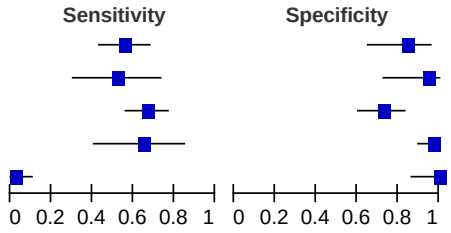
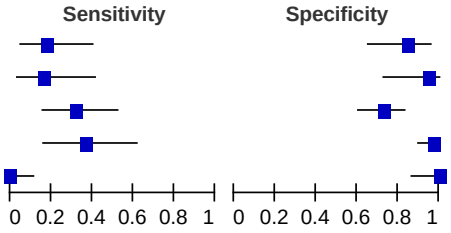


Figure G3. Forest plot of sensitivity and specificity of antinuclear antibody test for systemic juvenile idiopathic arthritis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Fawcett 1999 (ORG)	4	4	18	22	0.18 [0.05, 0.40]	0.85 [0.65, 0.96]
Haynes 1986 (NRG)	3	1	15	17	0.17 [0.04, 0.41]	0.94 [0.73, 1.00]
Osborn 1984 (healthy)	9	18	19	48	0.32 [0.16, 0.52]	0.73 [0.60, 0.83]
S-Mavridou 1991 (healthy)	7	2	12	64	0.37 [0.16, 0.62]	0.97 [0.89, 1.00]
Wakhlu 2003 (healthy)	0	0	30	25	0.00 [0.00, 0.12]	1.00 [0.86, 1.00]



Subgroup analysis of studies examining IgM-RF test for JIA (Figures G4–G6). None of the studies provided subgroup data based on RF positivity for patients with polyarticular JIA.

Figure G4. Forest plot of the sensitivity and specificity of IgM-rheumatoid factor test for oligoarticular juvenile idiopathic arthritis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Andersson-Gare 1994 (healthy)	6	4	111	126	0.05 [0.02, 0.11]	0.97 [0.92, 0.99]
Ferreira 2007 (healthy)	9	3	19	42	0.32 [0.16, 0.52]	0.93 [0.82, 0.99]
Haynes 1986 (NRG)	5	0	19	20	0.21 [0.07, 0.42]	1.00 [0.83, 1.00]
Lipinska 2008 (NRG)	2	1	34	21	0.06 [0.01, 0.19]	0.95 [0.77, 1.00]
Roizenblatt 1983 (ORG)	1	0	11	26	0.08 [0.00, 0.38]	1.00 [0.87, 1.00]
Saulsbury 1990 (healthy)	5	1	23	38	0.18 [0.06, 0.37]	0.97 [0.87, 1.00]
Varbanova 1999 (healthy)	6	0	27	58	0.18 [0.07, 0.35]	1.00 [0.94, 1.00]
Wernick 1981 (NRG)	1	2	28	30	0.03 [0.00, 0.18]	0.94 [0.79, 0.99]

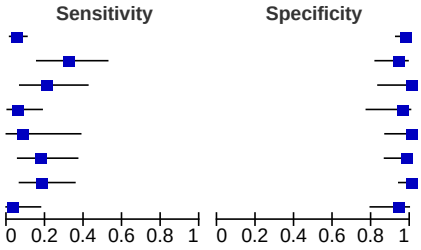


Figure G5. Forest plot of the sensitivity and specificity of IgM-rheumatoid factor test for polyarticular juvenile idiopathic arthritis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Andersson-Gare 1994 (healthy)	21	4	102	126	0.17 [0.11, 0.25]	0.97 [0.92, 0.99]
Ferreira 2007 (healthy)	13	3	12	42	0.52 [0.31, 0.72]	0.93 [0.82, 0.99]
Haynes 1986 (NRG)	10	0	13	20	0.43 [0.23, 0.66]	1.00 [0.83, 1.00]
Lipinska 2008 (NRG)	11	1	38	21	0.22 [0.12, 0.37]	0.95 [0.77, 1.00]
Roizenblatt 1983 (ORG)	0	0	9	26	0.00 [0.00, 0.34]	1.00 [0.87, 1.00]
Saulsbury 1990 (healthy)	5	1	9	38	0.36 [0.13, 0.65]	0.97 [0.87, 1.00]
Varbanova 1999 (healthy)	11	0	9	58	0.55 [0.32, 0.77]	1.00 [0.94, 1.00]
Wernick 1981 (NRG)	1	2	10	30	0.09 [0.00, 0.41]	0.94 [0.79, 0.99]

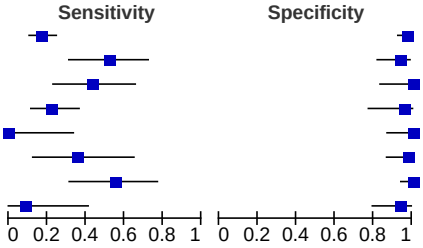
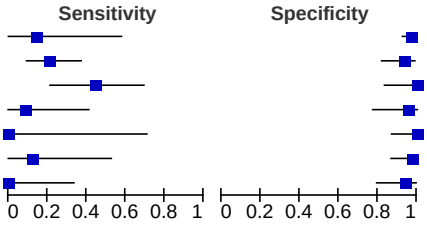


Figure G6. Forest plot of the sensitivity and specificity of IgM-rheumatoid factor test for systemic juvenile idiopathic arthritis

Study	TP	FP	FN	TN	Sensitivity	Specificity
Andersson-Gare 1994 (healthy)	1	4	6	126	0.14 [0.00, 0.58]	0.97 [0.92, 0.99]
Ferreira 2007 (healthy)	8	3	30	42	0.21 [0.10, 0.37]	0.93 [0.82, 0.99]
Haynes 1986 (NRG)	8	0	10	20	0.44 [0.22, 0.69]	1.00 [0.83, 1.00]
Lipinska 2008 (NRG)	1	1	10	21	0.09 [0.00, 0.41]	0.95 [0.77, 1.00]
Roizenblatt 1983 (ORG)	0	0	3	26	0.00 [0.00, 0.71]	1.00 [0.87, 1.00]
Saulsbury 1990 (healthy)	1	1	7	38	0.13 [0.00, 0.53]	0.97 [0.87, 1.00]
Wernick 1981 (NRG)	0	2	9	30	0.00 [0.00, 0.34]	0.94 [0.79, 0.99]



Subgroup analysis of studies examining CCP test for JIA (Figures G7–G9). None of the studies provided subgroup data based on RF positivity for patients with polyarticular JIA.

Figure G7. Forest plot of sensitivity and specificity of cyclic-citrullinated peptide test for oligoarticular juvenile idiopathic arthritis

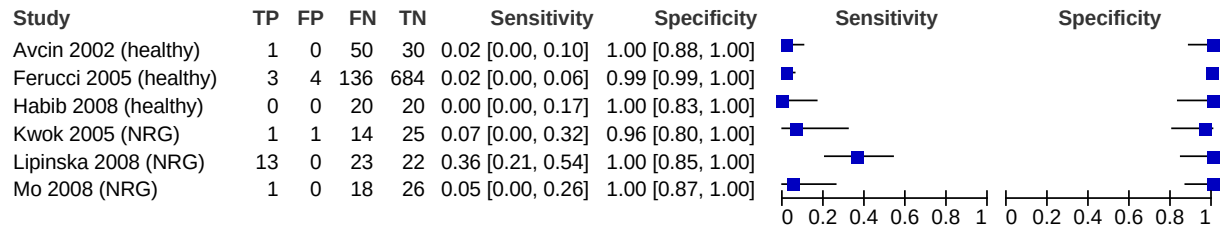


Figure G8. Forest plot of sensitivity and specificity of cyclic-citrullinated peptide test for polyarticular juvenile idiopathic arthritis

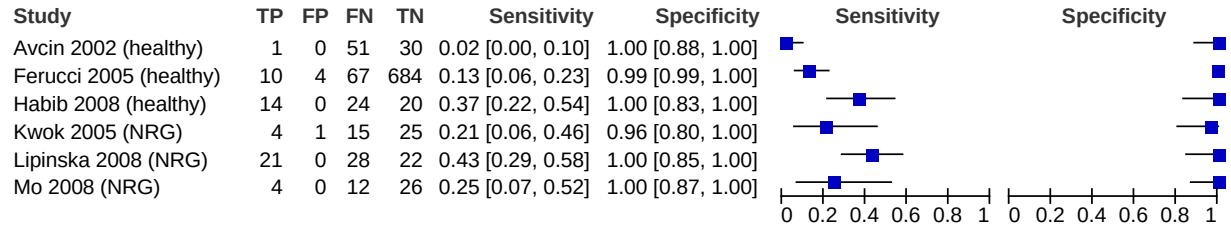


Figure G9. Forest plot of sensitivity and specificity of cyclic-citrullinated peptide test for systemic juvenile idiopathic arthritis