AHRQ Comparative Effectiveness Review Surveillance Program

CER #50:
Antinuclear Antibody, Rheumatoid Factor, and Cyclic-Citrullinated Peptide Tests for Evaluating Musculoskeletal Complaints in Children

Original release date:
March, 2012

Surveillance Report:
March, 2013

Key Findings:

- All conclusions from the original CER are up to date.

Summary Decision

This CER's priority for updating is **low.**

Authors:
Margaret Maglione, MPP
Susanne Hempel, PhD
Sydne Newberry, PhD
Jennifer Schneider Chafen, MS, MD
Aneesa Motala, BA
Roberta Shanman, MS
Paul Shekelle, MD, PhD

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

Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project:

Subject Matter Experts

Donna Dryden, Ph.D.
University of Alberta Evidence-based Practice Center
Alberta, Canada

David Keren, M.D.
University of Michigan
Ann Arbor, Michigan

Sarah Ringold, M.D.
Seattle Children's Hospital
Seattle, Washington

Contents

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

1. Introduction

Comparative Effectiveness Review (CER) #50, Antinuclear Antibody, Rheumatoid Factor, and Cyclic-Citrullinated Peptide Tests for Evaluating Musculoskeletal Complaints in Children, was released in March 2012.[1] It was therefore due for a surveillance assessment in September, 2012, but resource constraints at the Surveillance Center delayed this until January, 2013. At that time, we contacted experts involved in the original CER to get their opinions as to whether the conclusions had changed and need to be updated. We also conducted an update electronic literature search.

2. Methods

2.1 Literature Searches

We conducted an initial limited literature search covering January 1, 2009 to January 8, 2013, using the identical search strategy used for the original report. This search included five high-profile general medical interest journals (Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Lancet, and the New England Journal of Medicine) and five specialty journals (Arthritis and Rheumatism, Journal of Rheumatology, Pain, Pediatrics, and Rheumatology). The specialty journals were those most highly represented among the references for the original report. This search resulted in only 88 titles/abstracts to review so a full search was conducted which resulted in 632 titles/abstracts. Appendix A includes the search strategy.

2.2 Study selection

We used the same inclusion and exclusion criteria as the original CER. We screened the titles and abstracts and obtained full text copies of publications accordingly.

2.3 Expert Opinion

We shared the conclusions of the original report with 8 experts in the field (including the original project leader, all original technical expert panel (TEP) members and peer reviewers for their assessment of the need to update the report and their recommendations of any relevant new studies.; The original project leader and two subject matter experts responded. Appendix C shows the questionnaire matrix that was sent to the experts.

2.4 Check for qualitative and quantitative signals

After abstracting the study conditions and findings for each new included study into an evidence table, we assessed whether the new findings provided a signal according to the Ottawa Method and/or the RAND Method, suggesting the need for an update. The criteria are listed in the table below.[2, 3]

	Ottawa Method
	Ottawa Qualitative Criteria for Signals of Potentially Invalidating Changes in Evidence
A1	Opposing findings: A pivotal trial or systematic review (or guidelines) including at least one new trial that characterized the treatment in terms opposite to those used earlier.
A2	Substantial harm: A pivotal trial or systematic review (or guidelines) whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making.
A3	A superior new treatment: A pivotal trial or systematic review (or guidelines) whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.
	Criteria for Signals of Major Changes in Evidence
A4	Important changes in effectiveness short of "opposing findings"
A5	Clinically important expansion of treatment
A6	Clinically important caveat
A7	Opposing findings from discordant meta-analysis or nonpivotal trial
	Quantitative Criteria for Signals of Potentially Invalidating Changes in Evidence
B1	A change in statistical significance (from nonsignificant to significant)
B2	A change in relative effect size of at least 50 percent
	RAND Method Indications for the Need for an Update
1	Original conclusion is still valid and this portion of the original report does not need updating
2	Original conclusion is possibly out of date and this portion of the original report may need updating
3	Original conclusion is probably out of date and this portion of the original report may need updating
4	Original conclusion is out of date

2.5 Compilation of Findings and Conclusions

For this assessment we constructed a summary table that included the key questions, the original conclusions, and the findings of the new literature search, the expert assessments, and any FDA reports that pertained to each key question. To assess the conclusions in terms of the evidence that they might need updating, we used the 4-category scheme described in the table above for the RAND Method.

In making the decision to classify a CER conclusion into one category or another, we used the following factors when making our assessments:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still valid.

- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.
- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out of date.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

2.6 Determining Priority for Updating

We used the following two criteria in making our final conclusion for this CER:

- How much of the CER is possibly, probably, or certainly out of date?
- How out of date is that portion of the CER? For example, would the potential changes to the conclusions involve refinement of original estimates or do the potential changes mean some therapies are no longer favored or may not exist? Is the portion of the CER that is probably or certainly out of date an issue of safety (a drug withdrawn from the market, a black box warning) or the availability of a new drug within class (the latter being less of a signal to update than the former)?

3. Results

3.1 Search

The literature search identified 632 titles. After title and abstract review, we obtained the full text of 42 journal articles. The remaining titles were rejected because they clearly did not meet inclusion criteria for any of the review questions. We asked the experts to recommend new studies; they suggested two already identified by our search. We reference-mined articles that met inclusion criteria as well as systematic reviews identified by the literature searches to identify additional articles, but found none.

Thus, 42 articles went on to full text review. Of these, 38 articles were rejected because they did not meet the inclusion criteria of the original report. Most of these studies focused on adults, rather than children; the age groups involved were often unclear in the abstracts. The four remaining articles, were abstracted into an evidence table (Appendix B) for this assessment.[4-7]

3.2 Expert Opinion

The original project leader and two experts completed the matrix. With the exception of one conclusion, the respondents felt all conclusions were up to date or did not know. One expert provided data for Key Question 1.2 from a study we had also identified in our electronic search.[7] That study reported the prevalence of Rheumatoid Factor (RF) positivity in healthy children as 8% and prevalence of cyclic-citrullinated peptide (CCP) positivity as 2%. We felt this was not clinically different from earlier studies.

3.3 Identifying qualitative and quantitative signals

Table 1 shows the original key questions, the conclusions of the original report, the results of the literature and drug database searches, the experts' assessments, the recommendations of the Southern California Evidence-based Practice Center (SCEPC) regarding the need for update, and qualitative signals. Again, only four new studies met inclusion criteria, and these did not change any of the conclusions from the original CER. Thus, no update of the CER is warranted at this time.

Table 1: Summary Table

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Key Question 1. Prevalence and Incidence **Key Question 1.1. In children and adolescents aged 18 years or less, what is the incidence and prevalence of undiagnosed MSK complaints?**				
The prevalence of MSK pain ranged between 2 and 52 percent and increased steadily with age throughout childhood and adolescence. No studies reported the prevalence of joint swelling in children.	No new studies identified.	NA	All three experts felt the conclusion was up to date.	Up to date
Key Question 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. The prevalence of positive RF in healthy children was estimated at 3 percent. The prevalence of CCP positivity in healthy children was reported in two studies and ranged from 0 to 0.6 percent.	A new case control study including 50 healthy children[7] found 8% RF positive and 2% CCP positive. We felt this difference is not clinically important enough to warrant an update.	NA	Two experts felt the conclusion was up to date. The third expert reported the findings of the new study.[7]	Up to date
Key Question 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. 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.	No new studies identified.	NA	All three experts felt the conclusion was up to date.	Up to date
Key Question 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.				
Key Question 3.1 ANA Test for pSLE in Children With MSK Pain				

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
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).	reported Sn of 100% for ANA test. In a new case control [5] study of 20 cases and 20 controls, Sn was 100% for ANA using immunoflourense assay (IFA), 55% for ANA test using enzyme immunoassay (EIA). Sp was 65% for ANA-IFA, 100% for ANA-EIA.		was up to date. One did not know.	
Key Question 3.2. ANA Test for JIA in Children With MSK Pain				
Eight case-control studies 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).	No new studies identified.	NA	All three experts felt the conclusion was up to date.	Up to date
Key Question 3.3. RF Test for pSLE in Children With MSK Pain				
One case-control study with 46 children (14 pSLE, 32 controls) examined the prevalence of a positive IgM-RF test for pSLE. The control group comprised healthy children and children with other rheumatic conditions or ulcerative colitis. The Sn was 29 percent, and Sp was 88 percent.	No new studies identified.	NA	All three experts felt the conclusion was up to date.	Up to date
Key Question 3.4. RF Test for JIA in Children With MSK Pain				
One retrospective cohort study 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).	A new case control study[7] reported Sn of 12% for RF-IgM, Sp of 92%.	NA	Two experts felt the conclusion was up to date. One did not know.	Up to date

Conclusions From CER Executive Summary	RAND Literature Search	FDA / Health Canada / MHRA (UK)	Expert Opinion EPC Investigator Other Experts	Conclusion from SCEPC
Fifteen case-control studies 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).				
Key Question 3.5. CCP Test for pSLE in Children With MSK Pain				
No studies provided information to address this question.	No new studies identified.	NA	All three experts felt the conclusion was up to date.	Up to date
Key Question 3.6. CCP Test for JIA in Children With MSK Pain				
Seven case-control studies 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).	One new case-control study[7] reported Sn= 14% and Sp = 98% for ACPA-IgA,	NA	One expert felt the conclusion was up to date. One expert did not know. One expert suggested a 3rd generation CCP assay should be watched, although no studies on children have been published yet.	Up to date
Key Question 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.	One prospective cohort[6] reported anti-CCP antibody positive more often in polyarticular JIA than pauciarticular JIA or systemic onset JIA.	NA	All three experts did not know.	Up to date
Key Question 5: Clinical Impacts of ANA, RF, and CCP Tests				
No studies provided information to address this question.	No studies identified.	NA	Two experts felt the conclusion was up to date. One did not know.	Up to date

Legend: ANA: Antinuclear Antibodies; CCP: Cyclic-Citrullinated Peptide; JIA: Juvenile idiopathic arthritis; KQ: Key Question; MSK: Musculoskeletal; NA: Not available; pSLE: pediatric Systemic Lupus Erythematosus; RF: Rheumatoid Factor; SCEPC: Southern California Evidence-based Practice Center; SN: Seronegative; SP: Seropositive

References

1. Wong KO, Bond K, Homik J, et al. 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. Agency for Healthcare Research and Quality. Rockville, MD: Mar for Evaluating Musculoskeletal Complaints in Children March 2012. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22514802.

2. Shekelle PG, Newberry SJ, Maglione M, et al. Assessment of the Need to Update Comparative Effectiveness Reviews: Report of an Initial Rapid Program Assessment (2005-2009) (Prepared by the Southern California Evidence-based Practice Center). Rockville, MD: Agency for Healthcare Research and Quality; October 2009.

3. Shojania KG, Sampson M, Ansari MT, et al. How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med. 2007 Aug 21;147(4):224-33. PMID 17638714.

4. Breda L, Nozzi M, De Sanctis S, et a Laboratory tests in the diagnosis and fo up of pediatric rheumatic diseases: an update. Seminars in Arthritis & Rheumatism. 2010 Aug;40(1):53-72. P 19246077.

5. Dipti TR, Azam MS, Sattar MH, et a Detection of anti-nuclear antibody by immunofluorescence assay and enzyme immunoassay in childhood systemic lu erythematosus: experience from Bangla International Journal of Rheumatic Dis 2012 Feb;15(1):121-5. PMID 2232495

6. Gupta R, Thabah MM, Vaidya B, et a Anti-cyclic citrullinated peptide antibo in juvenile idiopathic arthritis. Indian Journal of Pediatrics. 2010 Jan;77(1):4 PMID 20135267.

7. Tebo AE, Jaskowski T, Davis KW, e Profiling anti-cyclic citrullinated peptid antibodies in patients with juvenile idiopathic arthritis. Pediatric Rheumato Online Journal. 2012;10(1):29. PMID 22931121.

Appendices

Appendix A: Search Methodology

Appendix B: Evidence Tables

Appendix C: Questionnaire Matrix

Appendix A. Search Methodology

DATABASE SEARCHED AND TIME PERIOD COVERED:
Medline on OVID – 1/1/2009-1/8/2013

LANGUAGE:
English

SEARCH STRATEGY:
1 citrulline/ AND exp Peptides, Cyclic/
2 limit 1 to (english language and yr="2009 - 2013")
3 ((anti adj ccp) or (citrullinated adj peptide*)).mp. or ((citrulline adj antibod*) or (anti-citrulline adj antibod*)).ti,ab. or exp Antibodies, Antinuclear/ or ((antinuclear adj antibod*) or (antinuclear adj factor*)).ti,ab. or (ana adj titer).ti,ab. or (ANA adj2 test*).ti,ab. or (FANA adj2 test*).ti,ab. or exp Rheumatoid Factor/ or (rheumatoid adj factor*).ti,ab.
4 limit 3 to (english language and yr="2009 - 2013")
5 2 or 4
6 exp Lupus Erythematosus, Systemic/ or (JSLE or SLE or "lupus erythematosus").ti,ab.
7 limit 6 to (english language and yr="2009 - 2013")
8 exp Pain/di, et and (Growth/ph or (grow* and (pain or pains)).ti,ab.)
9 limit 8 to (english language and yr="2009 - 2013")
10 musculoskeletal diseases/ or arm/ or leg/ or extremities/
11 limit 10 to (english language and yr="2009 - 2013")
12 exp Pain/di, et
13 limit 12 to (english language and yr="2009 - 2013") 20093
14 11 and 13
15 Fibromyalgia/ or fibromyalgia.ti,ab. or exp arthralgia/ or arthralgia.ti,ab. or ((joint* adj pain*) or (limb* adj pain*)).ti,ab. or limp*.ti,ab.
16 limit 15 to (english language and yr="2009 - 2013")
17 benign.ti,ab. and (exp Joint Instability/ or (joint adj (instability or hypermobility)).ti,ab.)
18 limit 17 to (english language and yr="2009 - 2013")
19 Patellofemoral Pain Syndrome/ or (patellofemoral adj pain adj syndrome).ti,ab. or exp Synovitis/ or synovitis.mp.
20 limit 19 to (english language and yr="2009 - 2013")
21 7 or 9 or 14 or 16 or 18 or 20
22 (Arthritis/ or ($arthritis or ($articular adj arthritis)).ti,ab.) and (exp child/ or (adolesc* or early or juvenile).ti,ab. or (JIA or JRA).ti,ab.)
23 limit 22 to (english language and yr="2009 - 2013")
24 exp Arthritis, Juvenile Rheumatoid/ or ((juvenile or early) adj (rheumatoid or idiopathic) adj arthritis).ti,ab.
25 limit 24 to (english language and yr="2009 - 2013")
26 exp Rheumatic Diseases/di, co, et, im, pa, pp or exp Connective Tissue Diseases/di, co, et, im, pa, pp or exp arthritis/di, co, et, im, pa, pp or arthritis, rheumatoid/di, co, et, im, pa, pp or arthritis, juvenile rheumatoid/di, co, et, im, pa, pp or exp Lupus Erythematosus, Systemic/di, co, et, im, pa, pp
27 limit 26 to (english language and yr="2009 - 2013")

28 21 or 23 or 25 or 27
29 5 and 28
30 exp child/ or (adolesc* or early or juvenile).ti,ab. or (Pubert* or Pubescen* or Prepubescen*).mp. or exp Pediatrics/ or (Pediatric* or Paediatric* or Peadiatric*).mp. or exp Schools/ or (Nursery school* or Kindergar* or Primary school* or Secondary school* or Elementary school* or High school* or Highschool*).mp. or exp infant/ or (Infant* or infancy or Newborn* or Baby* or Babies or Neonat* or Preterm* or Prematur* or Postmatur*).mp. or (Child* or Schoolchild* or School age* or Preschool* or Kid or kids or Toddler*).mp. or exp Adolescent/ or Adoles*.mp. or (Teen* or Boy* or Girl*).mp. or exp Minors/ or minors*.mp. or exp Puberty/
31 limit 30 to (english language and yr="2009 - 2013")
32 29 and 31 636
NUMBER OF RESULTS: 632

Appendix B. Evidence Table

Author, year	Study design	Population	Test	Assay Method	Sensitivity	Specificity	Modifiers
Breda, 2010[4]	Systematic review	NRw	ANA, RF, CCP	Various	100% for ANA for juvenile SLE	NR	NR
Dipti, 2012[5]	Case control	20 childhood SLE cases, 20 children with other rhueumatic dieases as control	ANA	Immunoflourescence (IFA) vs enzyme immunoassay (EIA)	100% for ANA-IFA, 55% for ANA-EIA	65% for ANA-IFA, 100% for ANA-EIA	NR
Gupta, 2010[6]	Prospective cohort	78 patients with JIA subtypes pauciarticular, polyarticular, or systematic onset	CCP	Enzyme-linked immunosorbent assay (ELISA)	NA	NA	Anti-CCP antibodies were positive in 5.9% of patients with pauciarticular JIA, 17.6% with systemic onset JIA, and 48.1% with polyarticular JIA. They were detected more frequency in patients with erosions and deformity.
Tebo, 2012[7]	Case control	Cases were 334 children with JIA, 30 of whom had RF+ and polyarticular JIA. Controls were 50 healthy children	CCP, RF	ELISA	14% for ACPA-IgG, 12% for RF-IgM	98% for ACPA-IgG, 92% for RF-IgM	NR

Legend: ANA: Antinuclear Antibodies; CCP: Cyclic-Citrullinated Peptide; JIA: Juvenile idiopathic arthritis; KQ: Key Question; MSK: Musculoskeletal; NA: Not available; pSLE: pediatric Systemic Lupus Erythematosus; RF: Rheumatoid Factor; SCEPC: Southern California Evidence-based Practice Center; SN: Seronegative; SP: Seropositive

Appendix C. Questionnaire Matrix

Surveillance and Identification of Triggers for Updating Systematic Reviews for the EHC Program

Title: **Antinuclear Antibody (ANA), Rheumatoid Factor (RF), and Cyclic-Citrullinated Peptide (CCP) Tests for Evaluating Musculoskeletal Complaints in Children**

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 1. Prevalence and Incidence **Key Question 1.1. In children and adolescents aged 18 years or less, what is the incidence and prevalence of undiagnosed MSK complaints?**			
The prevalence of MSK pain ranged between 2 and 52 percent and increased steadily with age throughout childhood and adolescence. No studies reported the prevalence of joint swelling in children.	☐	New Evidence:	☐
Key Question 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. The prevalence of positive RF in healthy children was estimated at 3 percent. The prevalence of CCP positivity in healthy children was reported in two studies and ranged from 0 to 0.6 percent.	☐	New Evidence:	☐
Key Question 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. Physical trauma was the most common	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
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.			
Key Question 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.	☐	New Evidence:	☐
Key Question 3.1 ANA Test for pSLE in Children With MSK Pain			
Two case-control studies 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	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
were 84 and 85 percent (Table A).			
Key Question 3.2. ANA Test for JIA in Children With MSK Pain			
Eight case-control studies 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).	☐	New Evidence:	☐
Key Question 3.3. RF Test for pSLE in Children With MSK Pain			
One case-control study with 46 children (14 pSLE, 32 controls) examined the prevalence of a positive IgM-RF test for pSLE. The control group comprised healthy children and children with other rheumatic conditions or ulcerative colitis. The Sn was 29 percent, and Sp was 88 percent (Table A).	☐	New Evidence:	☐
Key Question 3.4. RF Test for JIA in Children With MSK Pain			
One retrospective cohort study 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	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
percent (Table A). Fifteen case-control studies 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).			
Key Question 3.5. CCP Test for pSLE in Children With MSK Pain			
No studies provided information to address this question.	☐	New Evidence:	☐
Key Question 3.6. CCP Test for JIA in Children With MSK Pain			
Seven case-control studies 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).	☐	New Evidence:	☐
Key Question 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.	☐	New Evidence:	☐

Conclusions From CER Executive Summary	Is this conclusion almost certainly still supported by the evidence?	Has there been new evidence that may change this conclusion?	Do Not Know
Key Question 5: Clinical Impacts of ANA, RF, and CCP Tests			
No studies provided information to address this question.	☐	New Evidence:	☐
Are there new data that could inform the key questions that might not be addressed in the conclusions?			