JAMA Pediatrics | Original Investigation

Diagnostic Performance of Magnetic Resonance Enterography for Detection of Active Inflammation in Children and Adolescents With Inflammatory Bowel Disease
A Systematic Review and Diagnostic Meta-analysis

Hee Mang Yoon, MD, PhD; Chong Hyun Suh, MD; Jeong Rye Kim, MD; Jin Seong Lee, MD, PhD; Ah Young Jung, MD; Kyung Mo Kim, MD, PhD; Young Ah Cho, MD, PhD

IMPORTANCE Magnetic resonance (MR) enterography has the advantage over other techniques of being noninvasive, lacking ionizing radiation, and demonstrating excellent soft-tissue contrast to evaluate pediatric patients with inflammatory bowel disease (IBD).

OBJECTIVE To evaluate the diagnostic performance of MR enterography for detection of active inflammation in children and adolescents with known or suspected IBD.

DATA SOURCES A search of MEDLINE and EMBASE up to January 2, 2017, was performed to identify studies. Search terms included *child*, *pediatric*, *adolescent*, *Crohn disease*, *inflammatory bowel disease*, and *magnetic resonance enterography*. The search was limited to English-language publications.

STUDY SELECTION Studies evaluating the diagnostic performance of MR enterography for detection of active inflammation in pediatric patients with known or suspected IBD were selected. Two reviewers independently assessed the eligibility of the selected articles.

DATA EXTRACTION AND SYNTHESIS The study was performed and reported in accordance with the PRISMA guidelines. Pooled summary estimates of sensitivity and specificity were calculated using hierarchical logistic regression modeling.

MAIN OUTCOMES AND MEASURES The diagnostic performance of MR enterography for detection of active inflammation in pediatric patients with known or suspected IBD was the primary outcome. Subgroup analyses and meta-regression were performed.

RESULTS Eighteen original articles involving a total of 687 patients were included. The summary sensitivity was 83% (95% CI, 75%-89%), the summary specificity was 93% (95% CI, 90%-95%), and the area under the hierarchical summary receiver operating characteristic curve was 0.95 (95% CI, 0.93-0.97). The Higgins I^2 statistics demonstrated substantial heterogeneity in terms of sensitivity (I^2 = 84.1%) and specificity (I^2 = 68.8%). Based on per-patient analysis, the summary sensitivity was 86% (95% CI, 78%-91%) and specificity was 91% (95% CI, 82%-96%). In meta-regression, among the various potential covariates, scanner manufacturer was associated with study heterogeneity.

CONCLUSIONS AND RELEVANCE Magnetic resonance enterography, which is a noninvasive, radiation-free modality, demonstrates high diagnostic performance in the diagnosis of active inflammation in pediatric patients with IBD, especially at the per-patient level.

JAMA Pediatr. doi:10.1001/jamapediatrics.2017.3400
Published online October 9, 2017.

Supplemental content

Author Affiliations: Department of Radiology and Research Institute of Radiology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea (Yoon, J. R. Kim, Lee, Jung, Cho); Department of Radiology, Namwon Medical Center, Namwon-si, Republic of Korea (Suh); Department of Pediatrics, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea (K. M. Kim).

Corresponding Author: Young Ah Cho, MD, PhD, Department of Radiology and Research Institute of Radiology, University of Ulsan College of Medicine, Asan Medical Center, 86 Asanbyeongwon-Gil, Songpa-Gu, Seoul 138-736, Republic of Korea (ped.yacho@gmail.com).

Inflammatory bowel disease (IBD) is relatively common in pediatric populations and its incidence in children has increased.[1] Although histopathologic evaluation via tissue biopsy through ileocolonoscopy is the primary tool for the diagnosis of IBD, assessments with small-bowel imaging are frequently performed in almost all patients. Modalities for bowel imaging include a small-bowel follow-through, abdominal ultrasonography (US), computed tomographic (CT) enterography, and capsule endoscopy. However, the small-bowel follow-through has low sensitivity for detection of the involved bowel segment, and significant exposure to ionizing radiation is the major drawback of this study.[2] Abdominal US is a noninvasive and radiation-free imaging modality; however, it does not allow for whole-bowel imaging and depends on the operator's experience. In addition, a recent study reported that abdominal US had moderate interrater agreement and low agreement with MR enterography, especially in mid- and proximal small-bowel imaging.[3] Computed tomographic enterography can objectively demonstrate mural as well as extraintestinal diseases; however, careful consideration should be given when performing CT enterography owing to radiation exposure. Capsule endoscopy can directly visualize the small bowel, but evaluation of extraintestinal disease is impossible and capsule retention, which necessitates surgical exploration, may occur in patients who have substantial luminal narrowing.

Magnetic resonance (MR) enterography has rapidly emerged as the diagnostic imaging modality of choice to identify disease involvement and assess disease activity.[4-21] Magnetic resonance enterography has the advantage of being noninvasive, lacking ionizing radiation, and demonstrating excellent soft-tissue contrast. Because children are more sensitive to ionizing radiation and they have to undergo multiple imaging studies during their lifetime to monitor disease activity, MR enterography is the best radiologic imaging modality in the field of pediatric IBD.[22]

As interest in MR enterography grows, there are multiple studies that evaluated the diagnostic performance of MR enterography in pediatric patients. However, to our knowledge, the diagnostic performance of MR enterography in that population has not been systematically evaluated. Moreover, factors affecting the diagnostic performance should be identified if heterogeneity exists. Therefore, the purpose of our study was to evaluate the diagnostic performance of MR enterography for detection of active inflammation using histopathology as the reference standard in children and adolescents with known or suspected IBD.

Key Points

Question What is the diagnostic performance of magnetic resonance enterography, which is a noninvasive and radiation-free technique, for detection of active inflammation in pediatric patients with known or suspected inflammatory bowel disease?

Findings In this systematic review and meta-analysis that included 18 original articles involving 687 patients, the summary sensitivity was 83% and the summary specificity was 93%. Based on per-patient analysis, the summary sensitivity was 86% and specificity was 91%.

Meaning Magnetic resonance enterography demonstrates high diagnostic performance in the diagnosis of active inflammation in pediatric patients with known or suspected inflammatory bowel disease, especially at the per-patient level.

Methods

This systematic review and meta-analysis was performed and is reported in accordance with the PRISMA guidelines.[23] This study was approved by Asan Medical Center.

Literature Search

A search of MEDLINE and EMBASE up to January 2, 2017, was performed to identify studies evaluating the diagnostic performance of MR enterography for detection of active inflammation in pediatric patients with known or suspected IBD. The search terms combined synonyms for children, Crohn disease or IBD, and MR enterography as follows: ([*child**] or [*pediatric**] or [*pediatric**] or [*adolescent**]) and ([*Crohn**] or [*inflammatory bowel disease*] or [*IBD*]) and ([*magnetic resonance enterography*] or [*MR enterography*] or [*MRE*] or [*MR-E*]). Bibliographies of identified studies were also screened to expand the extent of search. Our search was limited to English-language publications.

Inclusion Criteria

Studies or subsets of studies were included if they satisfied all of the following criteria: (1) involved pediatric patients who underwent MR enterography for known or suspected IBD, (2) included reference standards based on histopathologic test findings, and (3) contained results published in sufficient detail for reconstruction of 2 × 2 tables for determination of the diagnostic performance of MR enterography for detection of active inflammation.

Exclusion Criteria

Studies were excluded if any of following criteria were met: (1) case reports or case series involving fewer than 10 patients; (2) conference abstracts, letters, editorials, reviews, meta-analyses, consensus statements, and guidelines; (3) studies focusing on topics other than the use of MR enterography to diagnose active inflammation; (4) studies with partially overlapping patient populations; and (5) studies using clinical setting or other imaging modalities as a reference standard. Two of us (H.M.Y., with 4 years of experience in pediatric radiology, and C.H.S., with 4 years of experience performing systematic reviews and meta-analyses) independently assessed the eligibility of the articles selected from the literature.

Data Extraction and Quality Assessment

We extracted the following data on study design and results from the included studies using a standardized form: (1) study characteristics (authors, year of publication, affiliation, country of origin, duration of patient recruitment, and study design), (2) demographic and clinical characteristics (sample size, male to female ratio, patient age, and study population),

(3) technical characteristics of MR enterography (scanner manufacturer and model, magnetic field strength, bowel preparation, spasmolytic agents, and specific sequences used), (4) MR enterography interpretation (number of reviewers, experience, and blinding to clinicopathologic findings), (5) time intervals between MR enterography and the reference standard, and (6) diagnostic performance of MR enterography (type of analysis and bowel location).

The methodologic quality of the studies was evaluated using tailored questionnaires and criteria by Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2).[24] Data extraction and quality assessment were performed independently by 2 of us (H.M.Y. and C.H.S.).

Data Synthesis and Analysis

The diagnostic performance of MR enterography for detection of active inflammation in pediatric patients with known or suspected IBD was the primary outcome for our meta-analysis. Heterogeneity was determined using the inconsistency index (I^2) as follows: 0% to 40%, might not be important; 30% to 60%, moderate heterogeneity; 50% to 90%, substantial heterogeneity; and 75% to 100%, considerable heterogeneity.[25] The threshold effect was analyzed by visual assessment of the coupled forest plots of sensitivity and specificity. The Spearman correlation coefficient between the sensitivity and false-positive rates greater than 0.6 was assessed to indicate a considerable threshold effect.[26]

The pooled sensitivity and specificity and their 95% CIs were calculated using the bivariate random-effects model.[27-31] For graphic presentation of the study results, a hierarchical summary receiver operating characteristic (HSROC) curve with a 95% confidence region and prediction region was plotted. Publication bias was assessed using the Deeks funnel plot, and statistical significance was determined with the Deeks asymmetry test.[32]

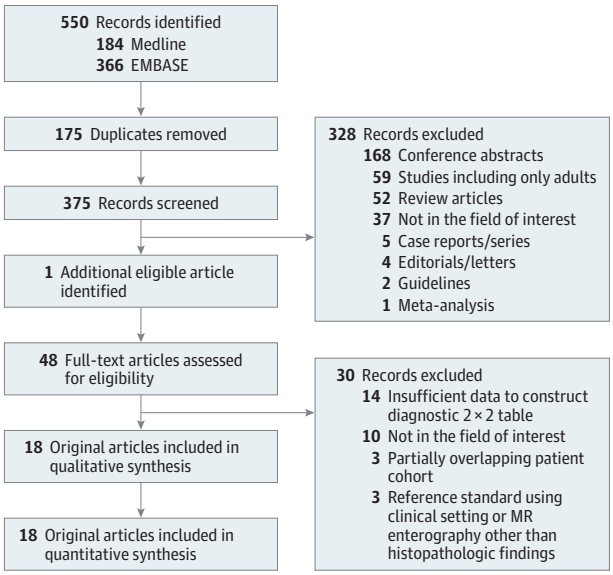
We performed subgroup analyses to assess various clinical settings: (1) per-patient analysis, (2) per-lesion analysis, and (3) assessment of overall bowel segments for all studies. We also performed meta-regression to explain the effects of heterogeneity. The following covariates were considered for the bivariate model: (1) study design (prospective vs retrospective), (2) population (Crohn disease vs IBD), (3) scanner manufacturer (GE vs Philips, GE vs Siemens, and Siemens vs Philips), (4) magnetic field strength of MR (3.0 vs 1.5 T), (5) use of spasmolytic agents, (6) use of diffusion-weighted imaging (DWI), (7) MR enterography reviewers blinded to pathologic test findings, (8) time intervals between MR enterography and the reference standard (≤1 month vs >1 month), and (9) bowel location (overall vs small bowel). *P* values <.05 were considered as having statistical significance. The metandi and midas modules in Stata, version 10.0 (StataCorp LP) and R, version 3.2.3 (R Foundation) with the mada module were used for statistical analyses.

Results

Literature Search

Our detailed study selection process is described in **Figure 1**. The systematic literature search initially identified 550 articles. After removing 175 duplicates, screening of the 375 titles and abstracts was performed and a total of 328 articles were excluded. Searches of the bibliographies of articles identified 1 additional eligible study.[8] Full-text reviews of 48 potentially eligible articles were performed and 30 articles were excluded for the following reasons: 14 articles with insufficient data to reconstruct 2 × 2 tables, 10 articles that were not in the field of interest, 3 articles that included partially overlapping patient cohorts with other studies,[33-35] and 3 articles that used clinical settings or imaging modalities other than histopathological findings as a reference standard.[36-38] Finally, 18 original articles including a total of 687 patients evaluating the diagnostic performance of MR enterography for detection of active inflammation in patients with known or suspected IBD were included in our study.[4-21]

Figure 1. Study Selection Process for This Systematic Review and Meta-analysis



Characteristics of the Included Studies

The detailed patient characteristics are reported in **Table 1**. Nine of the included studies were prospective,[6,9,11-13,17,18,20,21] and the remaining 9 studies were retrospective.[4,5,7,8,10,14-16,19] The size of the study population ranged from 15 to 91 patients and the patients had a mean age of 9.9-17.7 years. In 10 studies, the population comprised patients with known or suspected Crohn disease,[4-7,11,13,16-20] and in 8 studies, the study population comprised patients with known or suspected IBD.[8-10,12,14,15,17,21]

Further detailed characteristics of the studies are summarized in **Table 2**. Magnetic resonance enterography was performed using 1.5-T scanners in 12 studies,[5,7,9-11,13-15,17-20] 3.0-T scanners in 2 studies,[12,21] and either 1.5- or 3.0-T scanners in 2 studies.[4,8] In terms of scanner manufacturer, 7 studies used Siemens only,[5,7,10,11,13,18,20] 3 studies used GE,[8,14,15] 3 studies used Philips,[12,19,21] 2 studies used Siemens Corp or GE Healthcare.[4,9] The methods used for bowel preparation were a barium sulfate product (VoLumen; Bracco Diagnostics Inc)

Table 1. Characteristics of the Included Studies

Source	Affiliation	Duration of Patient Recruitment	Study Design	Patients, No.	Males:Females	Age, Mean (Range), y	Diagnosis
Shenoy-Bhangle et al,[4] 2016	Beth Israel Deaconess Medical Center, United States	January 2010-December 2012	Retrospective	27	10:17	14.5 (10.0-19.0)	Crohn disease
Pomerri et al,[5] 2017	University of Padova, Italy	January 2009-June 2014	Retrospective	32	18:14	14.0 (7.0-20.0)	Crohn disease
Oliva et al,[6] 2016	Sapienza University of Rome, Italy	September 2013-July 2014	Prospective	40	22:18	13.1 (8.0-18.0)	Crohn disease
Li et al,[7] 2016	University Hospital Wuerzburg, Germany	January 2013-September 2014	Retrospective	44	26:18	14.0 (9.0-18.0)	Crohn disease
Ehman et al,[8] 2016	UCSF Benioff Children's Hospital, United States	August 2011-March 2014	Retrospective	20	11:9	14.5 (6.0-21.0)	Known or suspected IBD
Dubron et al,[9] 2016	Hospital Jeanne de Flandre, France	April 2013-December 2014	Prospective	48	23:25	13.0 (12.0-15.0)	Known or suspected IBD
Barber et al,[10] 2016	Great Ormond Street Hospital for Children NHS Foundation Trust, England	March 2010-January 2014	Retrospective	15	8:7	9.9 (5.0-15.0)	IBD
Aloi et al,[11] 2015	Sapienza University of Rome, Italy	April 2012-April 2013	Prospective	34	23:11	12.2 (NA)	Crohn disease
Ziech et al,[12] 2014	Academic Medical Center, the Netherlands	August 2010-April 2011	Prospective	28	15:13	14.0 (10.0-17.0)	Suspected IBD
Maccioni et al,[13] 2014	Sapienza University of Rome, Italy	April 2010-June 2012	Prospective	50	26:24	13.5 (6.0-18.0)	Crohn disease
Kovanlikaya et al,[14] 2013	New York-Presbyterian/Weill Cornell Medical Center, United States	January 2008-June 2010	Retrospective	20	NA	15.0 (8.0-21.0)	Known or suspected IBD
Wallihan et al,[15] 2012	Cincinnati Children's Hospital Medical Center, United States	July 2009-July 2010	Retrospective	91	51:40	15.3 (8.0-22.0)	Known or suspected IBD
Silverstein et al,[16] 2012	Hasbro Children's Hospital/Rhode Island Hospital, United States	June 2007-April 2010	Retrospective	72	NA	14.0 (6.0-18.0)	Known or suspected Crohn disease
de Ridder et al,[17] 2012	Erasmus Medical Center, the Netherlands	February 2009-April 2010	Prospective	20	14:6	15.0 (11.3-18.0)	Crohn disease or suspected IBD
Gee et al,[18] 2011	Massachusetts General Hospital, Harvard Medical School, United States	NA	Prospective	21	10:11	17.7 (12.0-22.0)	Crohn disease
Dillman et al,[19] 2011	C.S. Mott Children's Hospital, United States	April 2009-December 2010	Retrospective	32	18:14	13.2 (6.0-17.0)	Crohn disease
Casciani et al,[20] 2011	Sapienza University of Rome, Italy	January 2009-December 2009	Prospective	60	36:24	14.0 (6.0-18.0)	Suspected Crohn disease
Horsthuis et al,[21] 2010	Academic Medical Center and University Medical Center Utrecht, the Netherlands	November 2004-November 2006	Prospective	33	15:18	13.5 (8.0-17.0)	Suspected IBD

Abbreviations: IBD, inflammatory bowel disease; NA, not available; NHS, National Health Service; UCSF, University of California, San Francisco.

in 7 studies[4,8,14-16,18,19]; a mannitol product, 4 studies[7,9,10,17]; polyethylene glycol (PEG), 4 studies[5,6,11,20]; sorbitol, 1 study[12]; a superparamagnetic contrast agent, 1 study[13]; and psyllium husk, 1 study.[21] In addition, 11 studies used spasmolytic agents.[5-7,11,12,14,15,17,19-21] In almost all studies, the MR enterography protocol included dynamic contrast-enhanced images. In 7 studies, MR enterography protocol included DWI.[4,7-10,12,19] One study included the protocol with DWI and T2 fusion images,[8] and 1 study included a CAIPIRINHA (controlled aliasing in parallel imaging results in higher acceleration) sequence.[7] Magnetic resonance enterography was interpreted by 1 to 3 radiologists, and the level of experience of the readers ranged from 2 to 20 years in the pediatric radiology field. In most studies, the readers were blinded to patients' clinicopathologic findings[4,5,7-11,13-18,20,21]; however, 3 studies were not explicit in terms of blinding.[6,12,19]

In the majority of the studies, time intervals between MR enterography and the reference standard were less than 1 month; however, the details were not reported in 4 studies.[7,14,18,20] For the diagnostic performance of MR enterography, per-patient analyses were performed in 11 studies,[6,7,9,11,12,14-17,20,21] per-lesion analyses in 5 studies,[4,8,13,18,19] and both analyses in 2 studies.[5,10] Pooled summary estimates of sensitivity and specificity were analyzed on a per-patient basis. If the diagnostic performance had been assessed only on a per-lesion basis, those results were included in the analysis. Thirteen studies reported the diagnostic performance based on overall bowel segments,[4,5,7-9,12-15,18-21] 3 studies based on the small bowel,[6,11,17] 1 study based on the colon,[10] and 1 study based on the terminal ileum.[16] The quality of the included studies using QUADAS-2 was moderate overall, and all of the studies satisfied 4 or more of the 7 items (eFigure 1 in the Supplement).

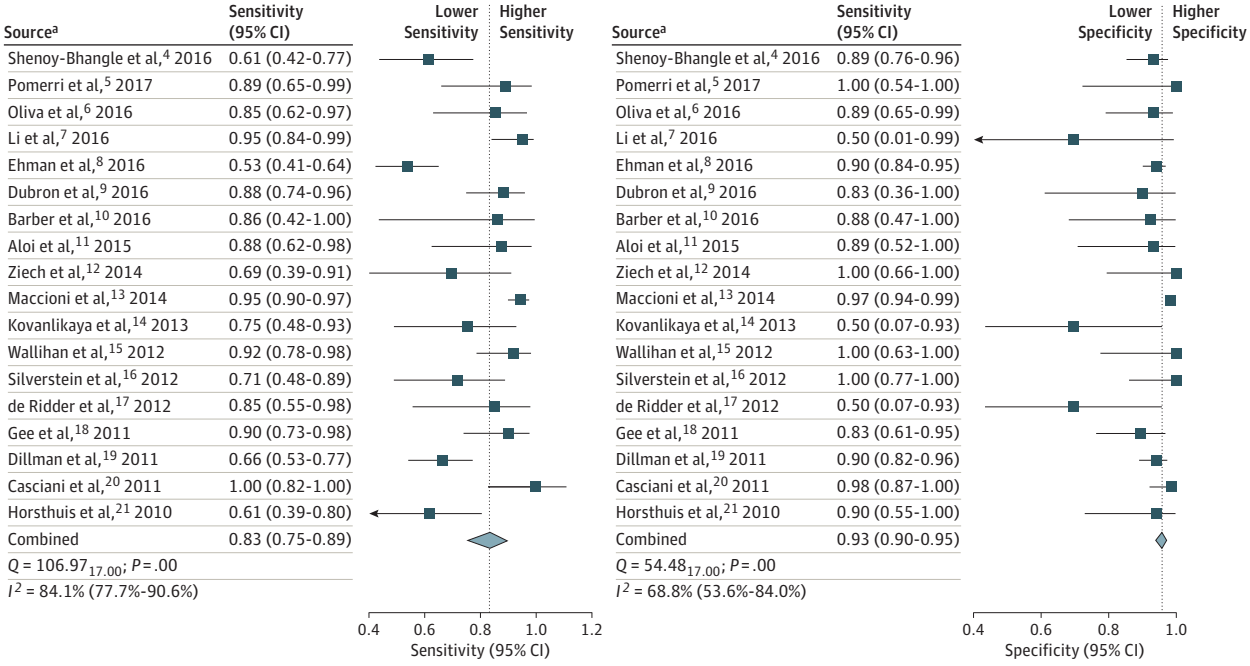
Table 2. MRE Characteristics of Included Studies

Source	MR Enterography				Readers		Reference Standard		Data Analysis	Bowel Location
	Vendor (Model)	Magnet Strength, T	Bowel Preparation	MR Sequences	No. (Years of Experience)	Blinding	Reference Standard	Interval[a]		
Shenoy-Bhangle et al,[4] 2016	GE Healthcare or Siemens Corp (HD Excite or Magnetom Trio)	1.5 or 3.0	Barium sulfate	Conventional MRE plus DWI	1 (9)	Yes	Endoscopy with biopsy	1-28 d	Per lesion	Overall
Pomerri et al,[5] 2017	Siemens Corp (Avanto)	1.5	PEG, spasmolytic agent	Conventional MRE	2 (NA)	Yes	Endoscopy with biopsy	4-7 d	Both	Overall
Oliva et al,[6] 2016	NA	NA	PEG, spasmolytic agent	NA	NA	NA	Endoscopy with biopsy	5 d	Per patient	Small bowel
Li et al,[7] 2016	Siemens Corp (Magnetom)	1.5	Mannitol, spasmolytic agent	Conventional MRE, DWI, and CAIPIRINHA	2 (10, resident)	Yes	Endoscopy with biopsy and MRE	NA	Per patient	Overall
Ehman et al,[8] 2016	GE Healthcare (HD750 or HDx)	1.5 or 3.0	Barium sulfate	DWI/T2 fusion only	2 (NA)	Yes	Endoscopy with biopsy	15.3 d	Per lesion	Overall
Dubron et al,[9] 2016	Siemens Corp or GE Healthcare (Magnetom or Signa)	1.5	Mannitol	Conventional MRE with DWI	2 (5, 2)	Yes	Endoscopy with biopsy or surgery	8 wk	Per patient	Overall
Barber et al,[10] 2016	Siemens Corp (Avanto)	1.5	Mannitol	Conventional MRE with DWI	2 (6, 4)	Yes	Endoscopy with biopsy	4 wk	Both	Colon
Aloi et al,[11] 2015	Siemens Corp (NA)	1.5	PEG, spasmolytic agent	Conventional MRE	1 (NA)	Yes	Endoscopy with biopsy and consensus	5 d	Per-patient	Small bowel
Ziech et al,[12] 2014	Philips (Intera)	3.0	Sorbitol, spasmolytic agent	Conventional MRE with DWI	2 (20, 12)	NA	Endoscopy with biopsy	5 wk	Per patient	Overall
Maccioni et al,[13] 2014	Siemens Corp (Magnetom Avanto)	1.5	Superparamagnetic contrast agent	Conventional MRE	2 (NA)	Yes	Endoscopy with biopsy, US, clinical examination, and surgery	10 d	Per lesion	Overall
Kovanlikaya et al,[14] 2013	GE Healthcare (Signa HDxt)	1.5	Barium sulfate, spasmolytic agent	Conventional MRE	2 (NA)	Yes	Endoscopy with biopsy	NA	Per patient	Overall
Wallihan et al,[15] 2012	GE Healthcare (Signa HDxt)	1.5	Barium sulfate, spasmolytic agent	Conventional MRE	2 (5, 2)	Yes	Endoscopy with biopsy or surgery	45 d	Per patient	Overall
Silverstein et al,[16] 2012	NA	NA	Barium sulfate	Conventional MRE	1 (NA)	Yes	Endoscopy with biopsy	90 d	Per patient	Terminal ileum
de Ridder et al,[17] 2012	NA	1.5	Mannitol, spasmolytic agent	Conventional MRE	1 (NA)	Yes	Single-balloon enteroscopy with biopsy	8 d	Per patient	Small bowel
Gee et al,[18] 2011	Siemens Corp (Magnetom)	1.5	Barium sulfate combine with superparamagnetic iron oxide solution	Conventional MRE	2 (NA)	Yes	Endoscopy with biopsy or surgery	NA	Per lesion	Overall
Dillman et al,[19] 2011	Philips (Achieva)	1.5	Barium sulfate, spasmolytic agent	Conventional MRE and DWI	3 (NA)	NA	Endoscopy with biopsy	8 wk	Per lesion	Overall
Casciani et al,[20] 2011	Siemens Corp (NA) NA	1.5	PEG, spasmolytic agent	Conventional MRE	2 (9, 7)	Yes	Endoscopy with biopsy	NA	Per patient	Overall
Horsthuis et al,[21] 2010	Philips (Achieva and Intera)	3.0	Psyllium husk, spasmolytic agent	Conventional MRE	3 (20, 20, 11)	Yes	Endoscopy with biopsy	2 wk	Per patient	Overall

Abbreviations: CAIPIRINHA, controlled aliasing in parallel imaging results in higher acceleration; DWI, diffusion-weighted imaging; MR, magnetic resonance; MRE, MR enterography; NA, not available; PEG, polyethylene glycol; US, ultrasonography.

[a] Interval between MR enterography and the reference standard.

Figure 2. Pooled Sensitivity and Specificity for the Diagnostic Performance of Magnetic Resonance Enterography for Detection of Active Inflammation



Pooled estimates showing heterogeneity in sensitivity and specificity.

Diagnostic Performance of MR Enterography

The sensitivity and specificity of the individual studies were 53% to 100% and 50% to 100%, respectively. The *Q* test demonstrated that heterogeneity was present ($P < .00$). The Higgins I^2 statistic demonstrated substantial heterogeneity in terms of sensitivity ($I^2 = 84.1\%$) and specificity ($I^2 = 68.8\%$). The coupled forest plot of sensitivity and specificity revealed the lack of a threshold effect (**Figure 2**). The Spearman correlation coefficient between the sensitivity and false-positive rate was 0.127 (95% CI, −0.361 to 0.560), also indicating the no-threshold effect.

For all 18 studies, the summary sensitivity was 83% (95% CI, 75%-89%) and the summary specificity was 93% (95% CI, 90%-95%) (Figure 2). There was a small difference between the 95% confidence region and the 95% prediction region, indicating a low possibility of heterogeneity between the studies in the HSROC curve (eFigure 2 in the Supplement). The area under the HSROC curve was 0.95 (95% CI, 0.93-0.97). In the Deeks funnel plot, the likelihood of publication bias was low ($P = .13$ for slope coefficient) (eFigure 3 in the Supplement).

Subgroup Analysis

We performed multiple subgroup analyses to assess various clinical settings. In per-patient analysis (n = 13), the summary sensitivity was 86% (95% CI, 78%-91%; $I^2 = 54.9\%$) and specificity was 91% (95% CI, 82%-96%; $I^2 = 56.9\%$). In per-lesion analysis (n = 7), the summary sensitivity was 72% (95% CI, 55%-84%; $I^2 = 91.9\%$) and the summary specificity was 93% (95% CI, 90%-95%; $I^2 = 62.9\%$). In terms of overall bowel segments (n = 13), a summary sensitivity was 83% (95% CI, 73%-90%; $I^2 = 88.8\%$) with a specificity of 93% (95% CI, 90%-95%; $I^2 = 73.4\%$).

Meta-Regression

To explain the effects of heterogeneity, meta-regression was performed (**Table 3**). Among the various potential covariates, study design, population, scanner manufacturer, magnetic field strength, use of spasmolytic agents, use of DWI, MR enterography reviewers blinded to pathologic findings, and time intervals between MR enterography and the reference standard were associated with study heterogeneity. However, among these variables, only scanner manufacturer (73% in studies using GE Healthcare vs 93% in studies using Siemens Corp) showed a clinically meaningful difference in sensitivity. Other variables did not show clinically meaningful differences, although there were statistically significant differences.

Discussion

Our meta-analysis confirms that the diagnostic performance of MR enterography in determination of active inflammation in pediatric patients with IBD was within the clinically acceptable range, depicting a summary sensitivity of 83% (95% CI, 75%-89%), summary specificity of 93% (95% CI, 90%-95%), and area under the HSROC curve of 0.95 (95% CI, 0.93-0.97). In per-patient analysis, the summary sensitivity was 86% (95% CI, 78%-91%) and specificity was 91% (95% CI, 82%-96%). In per-lesion

Table 3. Results of Meta-Regression of MR Enterography for Detection of Active Inflammation

Covariate	Subgroup	Meta-analytic Summary Estimates			
		Sensitivity, % (95% CI)	*P* Value	Specificity, % (95% CI)	*P* Value
Study design	Prospective	87 (80-94)	.40	93 (88-97)	<.01
	Retrospective	78 (67-88)		93 (89-97)	
Study population	Crohn disease	87 (79-94)	.47	94 (91-96)	<.01
	IBD	77 (65-89)		91 (87-96)	
Scanner manufacturer	GE Healthcare	74 (58-90)	.98	90 (80-99)	.13
	Philips	65 (47-84)		91 (86-97)	
	GE Healthcare	73 (55-90)	<.01	94 (88-100)	.27
	Siemens Corp	93 (88-98)		94 (90-99)	
	Siemens Corp	93 (90-96)	.45	94 (89-99)	.37
	Philips	65 (56-75)		92 (84-100)	
Magnet strength	3.0T	60 (44-77)	.30	91 (86-97)	<.01
	1.5T	88 (83-93)		93 (90-96)	
Spasmolytic agents	Yes	85 (77-93)	.25	92 (87-96)	<.01
	No	80 (69-92)		93 (90-96)	
DWI	Yes	83 (72-95)	.04	91 (81-100)	.27
	No	87 (81-94)		92 (87-98)	
Blinding	Yes	84 (78-91)	.97	93 (91-96)	<.01
	No	74 (53-95)		92 (86-98)	
Time interval	≤1 mo	79 (69-90)	.17	93 (90-96)	<.01
	>1 mo	80 (68-93)		94 (89-98)	
Bowel location	Overall bowel segments	83 (75-91)	.21	93 (91-96)	.13
	Small bowel	84 (70-97)		89 (80-98)	

Abbreviations: DWI, diffusion-weighted imaging; IBD, inflammatory bowel disease.

analysis, the summary sensitivity was only 72% (95% CI, 55%-84%) and specificity was 93% (95% CI, 90%-95%). There was substantial heterogeneity across the studies and scanner manufacturer was a statistically significant and clinically meaningful cause of heterogeneity in meta-regression analysis. Based on our results, MR enterography, which is a noninvasive and radiation-free modality, demonstrates high diagnostic performance in the diagnosis of active inflammation in pediatric patients with IBD, especially at the per-patient level.

Imaging studies for the diagnosis and monitoring of pediatric patients with IBD should be noninvasive and highly accurate. Being radiation-free is more important because the patients undergo multiple imaging studies in their lifetime. Its noninvasive technique and lack of radiation are undoubtedly benefits of MR enterography. In terms of the diagnostic accuracy of MR enterography, our study provides solid evidence for the high diagnostic performance of this modality. The summary sensitivity and specificity that we noted were 83% (95% CI, 75%-89%) and 93% (95% CI, 90%-95%), respectively. Previous studies regarding the diagnostic performance of MR enterography in adults with Crohn disease demonstrated a summary sensitivity of 80% to 88% and a summary specificity of 81% to 90%,[39-41] which were comparable to those of our study.

There was substantial heterogeneity in terms of the sensitivity (I^2 = 84.1%) and specificity (I^2 = 68.8%). In the subgroup per-patient analysis, study heterogeneity was reduced in both sensitivity (I^2 = 54.9%) and specificity (I^2 = 56.9%). Regarding the meta-regression analysis for investigating the causes of the heterogeneity, scanner manufacturer was a clinically meaningful factor affecting study heterogeneity in our study. However, 7 studies used Siemens Corp products only,[5,7,10,11,13,18,20] 3 studies used GE Healthcare products,[8,14,15] 3 studies used Philips,[12,19,21] and 2 studies used Siemens Corp or GE Healthcare equipment.[4,9] Owing to the paucity of the studies, caution is needed when interpreting this result.

Pulse sequences in pediatric MR enterography presently are recommended to include T2-weighted images, DWI, and dynamic precontrast and postcontrast T1-weighted images.[42] Recently, the use of DWI has been expanded to evaluations of the bowel inflammation in Crohn disease and the technique has become more popular in imaging of IBD.[43] Restricted diffusion (ie, high signal intensity on DWI with low apparent diffusion coefficients) within the bowel wall is known to reflect active inflammation.[42,44] In our meta-regression analysis, the use of DWI was associated with study heterogeneity in terms of sensitivity (with DWI, 83%; 95% CI, 72%-95% vs without DWI, 87%; 95% CI, 81%-94%). This minute difference in sensitivity between 2 groups might not be clinically significant. Moreover, only 1 study provided head-to-head comparison between conventional MR enterography with DWI and without DWI.[4] There were limited studies that compared conventional MR enterography and DWI in pediatric patients; thus, further studies with head-to-head comparison are needed.

In terms of the use of spasmolytic agents, a statistically significant difference was observed in specificity in meta-regression analysis, but this finding was clinically insignificant (92% in studies with vs 93% in studies without spasmolytic agents) Although several studies reported that MR enterogra-

phy might be performed without spasmolytic agents,[45,46] those agents are generally administered in clinical practice and recommended for use.[47] A recent study revealed that omitting spasmolytic agents might cause significant loss in the sensitivity of DWI in evaluating bowel inflammation in adults with Crohn disease.[48] In this regard, comparison between diagnostic benefits vs any adverse effects as well as cost-effectiveness for the use of spasmolytic agents is needed for further investigation in pediatric patients.

We performed multiple subgroup analyses. When we restricted subgroup analysis to the per-patient level using 13 studies, the range of diagnostic performance was within clinically acceptable levels with respect to sensitivity (86%; 95% CI, 78%-91%; I^2 = 54.9%) and specificity (91%; 95% CI, 82%-96%; I^2 = 56.9%). In contrast, per-lesion analysis using 7 studies showed lower summary sensitivity (72%; 95% CI, 55%-84%; I^2 = 91.9%) but similar summary specificity (93%; 95% CI, 90%-95%; I^2 = 62.9%), compared with per-patient analysis. Regarding the lower sensitivity in per-lesion analysis, endoscopy is unable to assess proximal small-bowel diseases, and the terminal ileum cannot always be intubated.[5] These drawbacks of endoscopic evaluation, which was a standard of our analysis, may result in lower sensitivity in per-lesion analysis. Moreover, lower detection rates may be attributable to bowel loops with inadequate fluid distention, particularly in the colorectum and jejunum.

Limitations

There were some limitations in our study. First, the heterogeneity was substantial. To overcome this heterogeneity, we performed meta-regression and multiple subgroup analyses. We found several factors associated with the heterogeneity; however, some factors remain unexplained. However, we applied solid and robust methodology for the systematic review and meta-analysis using the guidelines published by the Cochrane Collaboration.[49] Second, 9 of 18 studies were retrospective, resulting in a high risk of bias in patient selection.

Conclusions

Magnetic resonance enterography, which is a noninvasive and radiation-free modality, demonstrates high diagnostic performance in the diagnosis of active inflammation in pediatric patients with known or suspected IBD, especially at the per-patient level. We hope that our study might be evidence of justification for the application of MR enterography in this population.

ARTICLE INFORMATION

Accepted for Publication: July 8, 2017.

Published Online: October 9, 2017. doi:10.1001/jamapediatrics.2017.3400

Author Contributions: Drs Yoon and Suh contributed equally to the study, had full access to all of the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Yoon, Suh, J.R. Kim, Lee, Cho.
Acquisition, analysis, or interpretation of data: Yoon, Suh, Jung, K.M. Kim, Cho.
Drafting of the manuscript: Yoon, Suh, J.R. Kim, Lee, Cho.
Critical revision of the manuscript for important intellectual content: Suh, Lee, Jung, K.M. Kim, Cho.
Statistical analysis: Yoon, Suh, Lee.
Administrative, technical, or material support: Yoon, Suh, Lee, Jung.
Study supervision: Suh, Lee, K.M. Kim, Cho.

Conflict of Interest Disclosures: None reported.

REFERENCES

1. Malaty HM, Fan X, Opekun AR, Thibodeaux C, Ferry GD. Rising incidence of inflammatory bowel disease among children: a 12-year study. *J Pediatr Gastroenterol Nutr*. 2010;50(1):27-31.

2. IBD Working Group of the European Society for Paediatric Gastroenterology, Hepatology and NutritionIBD Working Group of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition. Inflammatory bowel disease in children and adolescents: recommendations for diagnosis—the Porto criteria. *J Pediatr Gastroenterol Nutr*. 2005;41(1):1-7.

3. Ahmad TM, Greer ML, Walters TD, Navarro OM. Bowel sonography and mr enterography in children. *AJR Am J Roentgenol*. 2016;206(1):173-181.

4. Shenoy-Bhangle AS, Nimkin K, Aranson T, Gee MS. Value of diffusion-weighted imaging when added to magnetic resonance enterographic evaluation of Crohn disease in children. *Pediatr Radiol*. 2016;46(1):34-42.

5. Pomerri F, Al Bunni F, Zuliani M, et al. Assessing pediatric ileocolonic Crohn's disease activity based on global MR enterography scores. *Eur Radiol*. 2017;27(3):1044-1051.

6. Oliva S, Cucchiara S, Civitelli F, et al. Colon capsule endoscopy compared with other modalities in the evaluation of pediatric Crohn's disease of the small bowel and colon. *Gastrointest Endosc*. 2016;83(5):975-983.

7. Li M, Dick A, Hassold N, et al. CAIPIRINHA-accelerated T1w 3D-FLASH for small-bowel MR imaging in pediatric patients with Crohn's disease: assessment of image quality and diagnostic performance. *World J Pediatr*. 2016;12(4):455-462.

8. Ehman EC, Phelps AS, Ohliger MA, Rhee SJ, MacKenzie JD, Courtier JL. Detection of bowel inflammation with fused DWI/T2 images versus contrast-enhanced images in pediatric MR enterography with histopathologic correlation. *Clin Imaging*. 2016;40(6):1135-1139.

9. Dubron C, Avni F, Boutry N, Turck D, Duhamel A, Amzallag-Bellenger E. Prospective evaluation of free-breathing diffusion-weighted imaging for the detection of inflammatory bowel disease with MR enterography in childhood population. *Br J Radiol*. 2016;89(1060):20150840.

10. Barber JL, Lozinsky AC, Kiparissi F, Shah N, Watson TA. Detecting inflammation in the unprepared pediatric colon: how reliable is magnetic resonance enterography? *Pediatr Radiol*. 2016;46(5):646-652.

11. Aloi M, Di Nardo G, Romano G, et al. Magnetic resonance enterography, small-intestine contrast US, and capsule endoscopy to evaluate the small bowel in pediatric Crohn's disease: a prospective, blinded, comparison study. *Gastrointest Endosc*. 2015;81(2):420-427.

12. Ziech ML, Hummel TZ, Smets AM, et al. Accuracy of abdominal ultrasound and MRI for detection of Crohn disease and ulcerative colitis in children. *Pediatr Radiol*. 2014;44(11):1370-1378.

13. Maccioni F, Al Ansari N, Mazzamurro F, et al. Detection of Crohn disease lesions of the small and large bowel in pediatric patients: diagnostic value of MR enterography versus reference examinations. *AJR Am J Roentgenol*. 2014;203(5):W533-42.

14. Kovanlikaya A, Watson E, Hayward J, et al. Magnetic resonance enterography and wireless capsule endoscopy in the evaluation of patients with inflammatory bowel disease. *Clin Imaging*. 2013;37(1):77-82.

15. Wallihan DB, Towbin AJ, Denson LA, Salisbury S, Podberesky DJ. Inflammatory bowel disease in children and adolescents: assessing the diagnostic performance and interreader agreement of magnetic resonance enterography compared to histopathology. *Acad Radiol*. 2012;19(7):819-826.

16. Silverstein J, Grand D, Kawatu D, Shah SA, Steinkeler J, LeLeiko N. Feasibility of using MR enterography for the assessment of terminal ileitis and inflammatory activity in children with Crohn disease. *J Pediatr Gastroenterol Nutr*. 2012;55(2):173-177.

17. de Ridder L, Mensink PB, Lequin MH, et al. Single-balloon enteroscopy, magnetic resonance enterography, and abdominal US useful for evaluation of small-bowel disease in children with (suspected) Crohn's disease. *Gastrointest Endosc*. 2012;75(1):87-94.

18. Gee MS, Nimkin K, Hsu M, et al. Prospective evaluation of MR enterography as the primary

imaging modality for pediatric Crohn disease assessment. *AJR Am J Roentgenol*. 2011;197(1):224-231.

19. Dillman JR, Ladino-Torres MF, Adler J, et al. Comparison of MR enterography and histopathology in the evaluation of pediatric Crohn disease. *Pediatr Radiol*. 2011;41(12):1552-1558.

20. Casciani E, Masselli G, Di Nardo G, et al. MR enterography versus capsule endoscopy in paediatric patients with suspected Crohn's disease. *Eur Radiol*. 2011;21(4):823-831.

21. Horsthuis K, de Ridder L, Smets AM, et al. Magnetic resonance enterography for suspected inflammatory bowel disease in a pediatric population. *J Pediatr Gastroenterol Nutr*. 2010;51(5):603-609.

22. Levine A, Koletzko S, Turner D, et al; European Society of Pediatric Gastroenterology, Hepatology, and Nutrition. ESPGHAN revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. *J Pediatr Gastroenterol Nutr*. 2014;58(6):795-806.

23. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med*. 2009;151(4):W65-94.

24. Whiting PF, Rutjes AW, Westwood ME, et al; QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155(8):529-536.

25. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0. The Cochrane Collaboration. http://handbook-5-1.cochrane.org. Updated March 2011. Accessed January 8, 2017.

26. Devillé WL, Buntinx F, Bouter LM, et al. Conducting systematic reviews of diagnostic studies: didactic guidelines. *BMC Med Res Methodol*. 2002;2:9.

27. Suh CH, Park SH. Successful publication of systematic review and meta-analysis of studies evaluating diagnostic test accuracy. *Korean J Radiol*. 2016;17(1):5-6.

28. Kim KW, Lee J, Choi SH, Huh J, Park SH. Systematic review and meta-analysis of studies evaluating diagnostic test accuracy: a practical review for clinical researchers—part I: general guidance and tips. *Korean J Radiol*. 2015;16(6):1175-1187.

29. Lee J, Kim KW, Choi SH, Huh J, Park SH. Systematic review and meta-analysis of studies evaluating diagnostic test accuracy: a practical review for clinical researchers—part II. statistical methods of meta-analysis. *Korean J Radiol*. 2015;16(6):1188-1196.

30. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol*. 2005;58(10):982-990.

31. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. *Stat Med*. 2001;20(19):2865-2884.

32. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. *J Clin Epidemiol*. 2005;58(9):882-893.

33. Maccioni F, Viola F, Carrozzo F, et al. Differences in the location and activity of intestinal Crohn's disease lesions between adult and paediatric patients detected with MRI. *Eur Radiol*. 2012;22(11):2465-2477.

34. Quencer KB, Nimkin K, Mino-Kenudson M, Gee MS. Detecting active inflammation and fibrosis in pediatric Crohn's disease: prospective evaluation of MR-E and CT-E. *Abdom Imaging*. 2013;38(4):705-713.

35. Courtier J, Cardenas A, Tan C, et al. Nonanesthesia MR enterography in very young children: feasibility, technique and performance. *J Pediatr Gastroenterol Nutr*. 2015;60(6):754-761.

36. AlSabban Z, Church P, Moineddin R, et al. Accuracy and interobserver agreement of diffusion-weighted imaging in pediatric inflammatory bowel disease. *Clin Imaging*. 2017;41:14-22.

37. Lai C, Zhou HC, Ma M, Zhang HX, Jia X. Comparison of magnetic resonance enterography, capsule endoscopy and gastrointestinal radiography of children with small bowel Crohn's disease. *Exp Ther Med*. 2013;6(1):115-120.

38. Spieler B, Hindman N, Levy J, et al. Contrast-enhanced MR enterography as a stand-alone tool to evaluate Crohn's disease in a paediatric population. *Clin Radiol*. 2013;68(10):1024-1030.

39. Qiu Y, Mao R, Chen BL, et al. Systematic review with meta-analysis: magnetic resonance enterography vs. computed tomography enterography for evaluating disease activity in small bowel Crohn's disease. *Aliment Pharmacol Ther*. 2014;40(2):134-146.

40. Church PC, Turner D, Feldman BM, et al; ImageKids Study Group. Systematic review with meta-analysis: magnetic resonance enterography signs for the detection of inflammation and intestinal damage in Crohn's disease. *Aliment Pharmacol Ther*. 2015;41(2):153-166.

41. Ahmed O, Rodrigues DM, Nguyen GC. Magnetic resonance imaging of the small bowel in Crohn's disease: a systematic review and meta-analysis. *Can J Gastroenterol Hepatol*. 2016;2016:7857352.

42. Mollard BJ, Smith EA, Dillman JR. Pediatric MR enterography: technique and approach to interpretation-how we do it. *Radiology*. 2015;274(1):29-43.

43. Park SH. DWI at MR enterography for evaluating bowel inflammation in Crohn disease. *AJR Am J Roentgenol*. 2016;207(1):40-48.

44. Ream JM, Dillman JR, Adler J, et al. MRI diffusion-weighted imaging (DWI) in pediatric small bowel Crohn disease: correlation with MRI findings of active bowel wall inflammation. *Pediatr Radiol*. 2013;43(9):1077-1085.

45. Grand DJ, Beland MD, Machan JT, Mayo-Smith WW. Detection of Crohn's disease: comparison of CT and MR enterography without anti-peristaltic agents performed on the same day. *Eur J Radiol*. 2012;81(8):1735-1741.

46. Grand DJ, Kampalath V, Harris A, et al. MR enterography correlates highly with colonoscopy and histology for both distal ileal and colonic Crohn's disease in 310 patients. *Eur J Radiol*. 2012;81(5):e763-e769.

47. Grand DJ, Guglielmo FF, Al-Hawary MM. MR enterography in Crohn's disease: current consensus on optimal imaging technique and future advances from the SAR Crohn's disease-focused panel. *Abdom Imaging*. 2015;40(5):953-964.

48. Park SH, Huh J, Park SH, Lee SS, Kim AY, Yang SK. Diffusion-weighted MR enterography for evaluating Crohn's disease: Effect of anti-peristaltic agent on the diagnosis of bowel inflammation. *Eur Radiol*. 2017;27(6):2554-2562.

49. Deeks JJ, Bossuyt PM, Gatsonis C, eds. 2013 Cochrane handbook for systematic reviews of diagnostic test accuracy, version 1.0.0. The Cochrane Collaboration. http://srdta.cochrane.org/handbook-dta-reviews. Published 2017. Accessed January 8, 2017.