QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies

Penny F. Whiting, PhD; Anne W.S. Rutjes, PhD; Marie E. Westwood, PhD; Susan Mallett, PhD; Jonathan J. Deeks, PhD; Johannes B. Reitsma, MD, PhD; Mariska M.G. Leeflang, PhD; Jonathan A.C. Sterne, PhD; Patrick M.M. Bossuyt, PhD; and the QUADAS-2 Group*

In 2003, the QUADAS tool for systematic reviews of diagnostic accuracy studies was developed. Experience, anecdotal reports, and feedback suggested areas for improvement; therefore, QUADAS-2 was developed. This tool comprises 4 domains: patient selection, index test, reference standard, and flow and timing. Each domain is assessed in terms of risk of bias, and the first 3 domains are also assessed in terms of concerns regarding applicability. Signalling questions are included to help judge risk of bias.

The QUADAS-2 tool is applied in 4 phases: summarize the review question, tailor the tool and produce review-specific guidance, construct a flow diagram for the primary study, and judge bias and applicability. This tool will allow for more transparent rating of bias and applicability of primary diagnostic accuracy studies.

Ann Intern Med. 2011;155:529-536. www.annals.org

For author affiliations, see end of text.

* For members of the QUADAS-2 Group, see the **Appendix** (available at www.annals.org).

Systematic reviews of diagnostic accuracy studies are often characterized by markedly heterogeneous results originating from differences in the design and conduct of included studies. Careful assessment of the quality of included studies is therefore essential. Since its publication in 2003, the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) tool has been widely used (1, 2). More than 200 review abstracts in the Database of Abstracts of Reviews of Effects mention this tool, and it has been cited more than 500 times. The QUADAS tool is recommended for use in systematic reviews of diagnostic accuracy by the Agency for Healthcare Research and Quality, Cochrane Collaboration (3), and the U.K. National Institute for Health and Clinical Excellence.

The original QUADAS tool includes 14 items assessing risk of bias, sources of variation (applicability), and reporting quality; each item is rated "yes," "no," or "unclear" (1). Our experience, reports from users, and feedback from the Cochrane Collaboration suggested the potential for improvements. Users reported problems rating certain items (particularly those on patient spectrum, uninterpretable or intermediate test results, and withdrawals), possible overlap among items (for example, partial verification bias and withdrawals), and situations in which QUADAS is difficult to use (for example, topics for which the reference standard involves follow-up). Here we describe QUADAS-2, an improved, redesigned tool that is based on both experience using the original tool and new evidence about sources of bias and variation in diagnostic accuracy studies.

Methods

Development of QUADAS-2 was based on the 4-stage approach proposed by Moher and colleagues (4): define the scope, review the evidence base, hold a face-to-face consensus meeting, and refine the tool through piloting.

Define the Scope

We established a steering group of 9 experts in the area of diagnostic research, most of whom participated in developing the original QUADAS tool. This group agreed on key features of the desired scope of QUADAS-2. The main decision was to separate "quality" into "risk of bias" and "concerns regarding applicability." We defined *quality* as "both the risk of bias and applicability of a study; 1) the degree to which estimates of diagnostic accuracy avoided risk of bias, and 2) the extent to which primary studies are applicable to the review's research question." *Bias* occurs if systematic flaws or limitations in the design or conduct of a study distort the results. Evidence from a primary study may have *limited applicability* to the review if, compared with the review question, the study was conducted in a patient group with different demographic or clinical features, the index test was applied or interpreted differently, or the definition of the target condition differed.

Other decisions included limiting QUADAS-2 to a small number of key domains with minimal overlap and aiming to extend QUADAS-2 to assess studies comparing multiple index tests and those involving reference standards based on follow-up, but not studies addressing prognostic questions. We also proposed changing the rating of "yes," "no," or "unclear" used in the original QUADAS tool to "low risk of bias" or "high risk of bias" used to assess risk of bias in Cochrane reviews of interventions (5). An explicit judgment on the risk of bias was thought to be

See also:

Web-Only
Appendix
Appendix Table
Supplement
Conversion of graphics into slides

more informative, and feedback on the original Cochrane risk-of-bias tool suggested that a rating of "yes," "no," or "unclear" was confusing (5).

Review the Evidence Base

We conducted 4 reviews to inform the development of QUADAS-2 (6). In the first review, we investigated how quality was assessed and incorporated in 54 diagnostic accuracy reviews published between 2007 and 2009. The second review used a Web-based questionnaire to gather structured feedback from 64 systematic reviewers who had used QUADAS. The third review was an update on sources of bias and variation in diagnostic accuracy studies that included 101 studies (7). The final review examined 8 studies that evaluated QUADAS. Full details will be published separately.

Evidence from these reviews informed decisions on topics to discuss at the face-to-face consensus meeting. We summarized reported problems with the original QUADAS tool and the evidence for each original item and possible new items relating to bias and applicability. We also produced a list of candidate items for assessment of studies comparing multiple index tests.

Hold a Face-to-Face Consensus Meeting

We held a 1-day meeting to develop a first draft of QUADAS-2 on 21 September 2010 in Birmingham, United Kingdom. The 24 attendees, known as the QUADAS-2 Group, were methodological experts and reviewers working on diagnostic accuracy reviews. We presented summaries of the evidence and split into smaller groups of 4 to 6 participants to discuss tool content (test protocol, verification procedure, interpretation, analysis, patient selection or study design, and comparative test items), applicability, and conceptual decisions. On the basis of the agreed outcomes of the meeting, steering group members produced the first draft of QUADAS-2.

Pilot and Refine

We used multiple rounds of piloting to refine successively amended versions of QUADAS-2. Online questionnaires were developed to gather structured feedback for each round; feedback in other forms, such as e-mail or verbal discussion, was also accepted. Participants in the piloting process included members of the QUADAS-2 Group; workshop participants at the October 2010 Cochrane Colloquium in Keystone, Colorado; systematic reviewers attending a National Institute for Health and Clinical Excellence technical meeting; and biomedical science students in Switzerland.

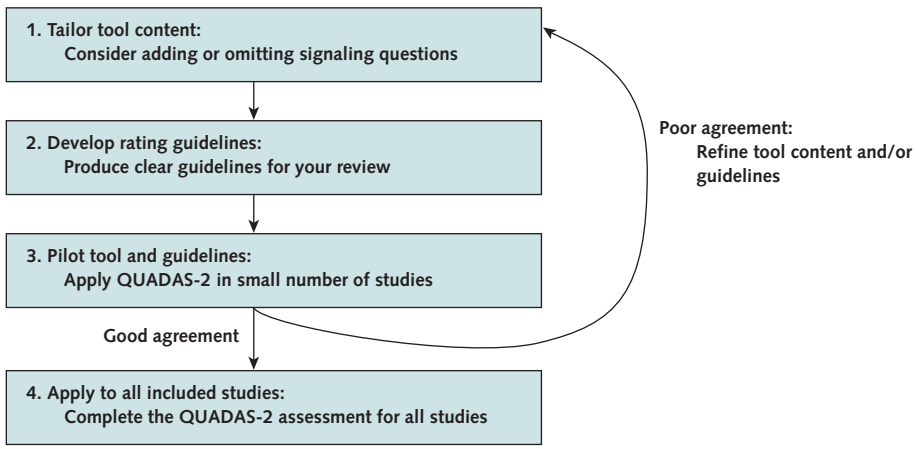
Pairs of reviewers piloted QUADAS-2 in 5 reviews on various topics. Interrater reliability varied considerably, with better agreement on applicability than on risk of bias (**Appendix Table**, available at www.annals.org). An additional pair of experienced review authors piloted the tool on a review with multiple index tests. Feedback from these reviewers showed poor interrater reliability and problems applying the domain on comparative accuracy studies.

On the basis of these problems and the limited evidence base on the risk of bias and sources of variation in such studies, we decided that we cannot currently include

Table 1. **Risk of Bias and Applicability Judgments in QUADAS-2**

Domain	Patient Selection	Index Test	Reference Standard	Flow and Timing
Description	Describe methods of patient selection Describe included patients (previous testing, presentation, intended use of index test, and setting)	Describe the index test and how it was conducted and interpreted	Describe the reference standard and how it was conducted and interpreted	Describe any patients who did not receive the index tests or reference standard or who were excluded from the 2 × 2 table (refer to flow diagram) Describe the interval and any interventions between index tests and the reference standard
Signaling questions (yes, no, or unclear)	Was a consecutive or random sample of patients enrolled? Was a case–control design avoided? Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard? If a threshold was used, was it prespecified?	Is the reference standard likely to correctly classify the target condition? Were the reference standard results interpreted without knowledge of the results of the index test?	Was there an appropriate interval between index tests and reference standard? Did all patients receive a reference standard? Did all patients receive the same reference standard? Were all patients included in the analysis?
Risk of bias (high, low, or unclear)	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns about applicability (high, low, or unclear)	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or its interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

Figure 1. **Process for tailoring QUADAS-2 to your systematic review.**



criteria for assessing studies that compare multiple index tests within QUADAS-2. Feedback at all other stages of the process was positive, with all participants preferring QUADAS-2 to the original tool.

Role of the Funding Source

This article was funded by the Medical Research Council, National Institute for Health Research, Cancer Research UK, and the Netherlands Organization for Scientific Research (916.10.034). The sponsors had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the manuscript for publication.

QUADAS-2

The full QUADAS-2 tool is available from the QUADAS Web site (www.quadas.org) (**Supplement**, available at www.annals.org). This tool is designed to assess the quality of primary diagnostic accuracy studies; it is not designed to replace the data extraction process of the review and should be applied in addition to extracting primary data (for example, study design and results) for use in the review. The QUADAS tool consists of 4 key domains that discuss patient selection, index test, reference standard, and flow of patients through the study and timing of the index tests and reference standard (*flow and timing*) (**Table 1**).

The tool is completed in 4 phases: report the review question, develop review-specific guidance, review the published flow diagram for the primary study or construct a flow diagram if none is reported, and judge bias and applicability. Each domain is assessed in terms of the risk of bias, and the first 3 domains are also assessed in terms of concerns about applicability. Signaling questions are included to help judge the risk of bias; these questions flag aspects of study design related to the potential for bias and aim to help reviewers judge risk of bias.

Phase 1: Review Question

Review authors first report their systematic review question in terms of patients, index tests, and reference standard and target condition. Because the accuracy of a test may depend on where it will be used in the diagnostic pathway, review authors are asked to describe patients in terms of setting, intended use of the index test, patient presentation, and previous testing (8, 9).

Phase 2: Review-Specific Tailoring

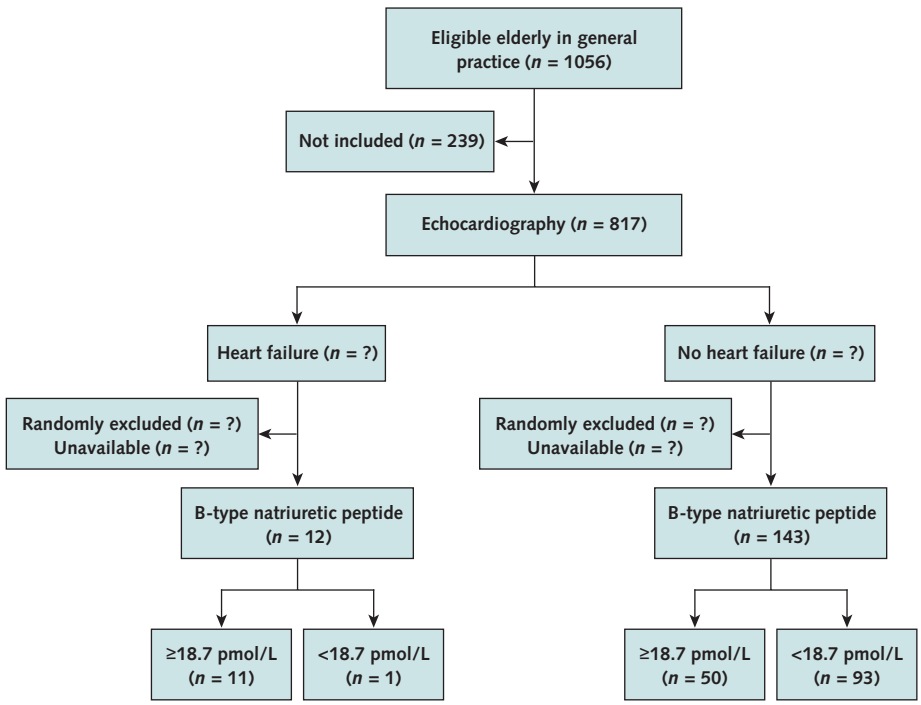
The QUADAS-2 tool must be tailored to each review by adding or omitting signaling questions and developing review-specific guidance on how to assess each signaling question and use this information to judge the risk of bias (**Figure 1**). The first step is to consider whether any signaling question does not apply to the review or whether the core signaling questions do not adequately cover any specific issues for the review. For example, for a review of an objective index test, it may be appropriate to omit the signaling question about blinding the test interpreter to the results of the reference standard.

Review authors should avoid complicating the tool by adding too many signaling questions. Once tool content has been agreed upon, rating guidance specific to the review should be developed. At least 2 persons should independently pilot the tool. If agreement is good, the tool can be used to rate all included studies; if agreement is poor, further refinement may be needed.

Phase 3: Flow Diagram

Next, review authors should review the published flow diagram for the primary study or draw one if none is reported or the published diagram is inadequate. The flow diagram will facilitate judgments of risk of bias and

Figure 2. **Sample of a study flow diagram.**



The diagram is based on a diagnostic cohort study on using B-type natriuretic peptide levels to diagnose heart failure. Based on data obtained from Smith H, Pickering RM, Struthers A, Simpson I, Mant D. Biochemical diagnosis of ventricular dysfunction in elderly patients in general practice: observational study. BMJ. 2000;320:906-8.

should provide information about the method of recruiting participants (for example, using a consecutive series of patients with specific symptoms suspected of having the target condition or of case patients and control participants), the order of test execution, and the number of patients undergoing the index test and the reference standard. A hand-drawn diagram is sufficient, as this step does not need to be reported as part of the QUADAS-2 assessment. **Figure 2** is a flow diagram of a primary study on using B-type natriuretic peptide levels to diagnose heart failure.

Phase 4: Judgments on Bias and Applicability

Risk of Bias

The first part of each domain concerns bias and comprises 3 sections: information used to support the judgment of risk of bias, signaling questions, and judgment of risk of bias. By recording the information used to reach the judgment (*support for judgment*), we aim to make the rating transparent and facilitate discussion among review authors independently completing assessments (5). The additional signaling questions are included to assist judgments. They are answered as "yes," "no," or "unclear" and are phrased such that "yes" indicates low risk of bias.

Risk of bias is judged as "low," "high," or "unclear." If the answers to all signaling questions for a domain are "yes," then risk of bias can be judged low. If any signaling question is answered "no," potential for bias exists. Review authors must then use the guidelines developed in phase 2 to judge risk of bias. The "unclear" category should be used only when insufficient data are reported to permit a judgment.

Applicability

Applicability sections are structured in a way similar to that of the bias sections but do not include signaling questions. Review authors record the information on which the judgment of applicability is made and then rate their concern that the study does not match the review question. Concerns about applicability are rated as "low," "high," or "unclear." Applicability judgments should refer to phase 1, where the review question was recorded. Again, the "unclear" category should be used only when insufficient data are reported.

The following sections briefly explain the signaling questions and risk of bias or concerns about applicability questions for each domain.

Domain 1: Patient Selection

Risk of Bias: Could the Selection of Patients Have Introduced Bias?

Signaling question 1: Was a consecutive or random sample of patients enrolled?

Signaling question 2: Was a case–control design avoided?

Signaling question 3: Did the study avoid inappropriate exclusions?

A study ideally should enroll a consecutive or random sample of eligible patients with suspected disease to prevent the potential for bias. Studies that make inappropriate exclusions (for example, not including "difficult-to-diagnose" patients) may result in overestimation of diagnostic accuracy. In a review on anti–cyclic citrullinated peptide antibodies for diagnosing rheumatoid arthritis (10), we found that some studies enrolled consecutive participants with confirmed diagnoses. In these studies, testing for anti–cyclic citrullinated peptide antibody showed greater sensitivity than in studies that included patients with suspected disease but an unconfirmed diagnosis (that is, difficult-to-diagnose patients). Studies enrolling participants with known disease and a control group without the condition may similarly exaggerate diagnostic accuracy (7, 11). Excluding patients with "red flags" for the target condition who may be easier to diagnose may lead to underestimation of diagnostic accuracy.

Applicability: Are There Concerns That the Included Patients and Setting Do Not Match the Review Question?

Concerns about applicability may exist if patients included in the study differ from those targeted by the review question in terms of severity of the target condition, demographic features, presence of differential diagnosis or comorbid conditions, setting of the study, and previous testing protocols. For example, larger tumors are more easily seen than smaller ones on imaging studies, and larger myocardial infarctions lead to higher levels of cardiac enzymes than small infarctions and are easier to detect, thereby increasing estimates of sensitivity (3).

Domain 2: Index Test

Risk of Bias: Could the Conduct or Interpretation of the Index Test Have Introduced Bias?

Signaling question 1: Were the index test results interpreted without knowledge of the results of the reference standard?

This item is similar to "blinding" in intervention studies. Knowledge of the reference standard may influence interpretation of index test results (7). The potential for bias is related to the subjectivity of interpreting index test and the order of testing. If the index test is always conducted and interpreted before the reference standard, this item can be rated "yes."

Signaling question 2: If a threshold was used, was it prespecified?

Selecting the test threshold to optimize sensitivity and/or specificity may lead to overestimation of test performance. Test performance is likely to be poorer in an independent sample of patients in whom the same threshold is used (12).

Applicability: Are There Concerns That the Index Test, Its Conduct, or Its Interpretation Differ From the Review Question?

Variations in test technology, execution, or interpretation may affect estimates of the diagnostic accuracy of a test. If index test methods vary from those specified in the review question, concerns about applicability may exist. For example, a higher ultrasonography transducer frequency has been shown to improve sensitivity for the evaluation of patients with abdominal trauma (13).

Domain 3: Reference Standard

Risk of Bias: Could the Reference Standard, Its Conduct, or Its Interpretation Have Introduced Bias?

Signaling question 1: Is the reference standard likely to correctly classify the target condition?

Estimates of test accuracy are based on the assumptions that the reference standard is 100% sensitive and that specific disagreements between the reference standard and index test result from incorrect classification by the index test (14, 15).

Signaling question 2: Were the reference standard results interpreted without knowledge of the results of the index test?

This item is similar to the signaling question related to interpretation of the index test. Potential for bias is related to the potential influence of previous knowledge on the interpretation of the reference standard (7).

Applicability: Are There Concerns That the Target Condition as Defined by the Reference Standard Does Not Match the Question?

The reference standard may be free of bias, but the target condition that it defines may differ from the target condition specified in the review question. For example, when defining urinary tract infection, the reference standard is generally based on specimen culture; however, the threshold above which a result is considered positive may vary (16).

Domain 4: Flow and Timing

Risk of Bias: Could the Patient Flow Have Introduced Bias?

Signaling question 1: Was there an appropriate interval between the index test and reference standard?

Results of the index test and reference standard are ideally collected on the same patients at the same time. If a delay occurs or if treatment begins between the index test and the reference standard, recovery or deterioration of the condition may cause misclassification. The interval leading to a high risk of bias varies among conditions. A delay of a few days may not be problematic for patients with chronic conditions, but it could be problematic for patients with acute infectious diseases.

Conversely, a reference standard that involves follow-up may require a minimum follow-up period to assess whether the target condition is present. For example, to evaluate magnetic resonance imaging for early diagnosis of multiple sclerosis, a minimum follow-up period of ap-

Table 2. **Suggested Tabular Presentation for QUADAS-2 Results**

Study	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
1	☺	☺	☺	☺	☹	☺	☺
2	☺	☺	☺	☺	☹	☺	☺
3	☹	☹	☺	☺	☹	☺	☺
4	☹	☹	☺	☺	☹	☺	☺
5	☹	?	☺	☺	☹	☺	☺
6	☹	?	☺	☺	☹	?	☺
7	☹	?	☺	☺	☹	☺	☺
8	☹	?	☺	☺	☹	?	☺
9	☹	?	☺	☺	☹	☺	☺
10	☹	?	☺	☹	☹	☺	☺
11	☺	?	☺	☹	☺	☺	☺

☺ = low risk; ☹ = high risk; ? = unclear risk.

proximately 10 years is required to be confident that all patients who will fulfill the diagnostic criteria for multiple sclerosis will have done so (17).

Signaling question 2: Did all patients receive the same reference standard?

Verification bias occurs when only a proportion of the study group receives confirmation of the diagnosis by the reference standard, or if some patients receive a different reference standard. If the results of the index test influence the decision on whether to perform the reference standard or which reference standard is used, estimated diagnostic accuracy may be biased (11, 18). For example, in a study evaluating the accuracy of D-dimer testing to diagnose pulmonary embolism, ventilation–perfusion scans (reference standard 1) were performed in participants with positive test results for this condition, and clinical follow-up was used to determine whether those with negative test results had pulmonary embolism (reference standard 2).

This method may result in misclassifying some false-negative results as true-negative because clinical follow-up may miss some patients who had pulmonary embolism but negative results on the index test. These patients would be classified as not having pulmonary embolism, and this misclassification would overestimate sensitivity and specificity.

Signaling question 3: Were all patients included in the analysis?

All participants recruited into the study should be included in the analysis (19). A potential for bias exists if the number of patients enrolled differs from the number of patients included in the 2×2 table of results, because patients lost to follow-up differ systematically from those who remain.

Incorporating QUADAS-2 Assessments in Diagnostic Accuracy Reviews

We emphasize that QUADAS-2 should not be used to generate a summary "quality score" because of the well-known problems associated with such scores (20, 21). If a study is judged as "low" on all domains relating to bias or applicability, then it is appropriate to have an overall judgment of "low risk of bias" or "low concern regarding applicability" for that study. If a study is judged "high" or "unclear" in 1 or more domains, then it may be judged "at risk of bias" or as having "concerns regarding applicability."

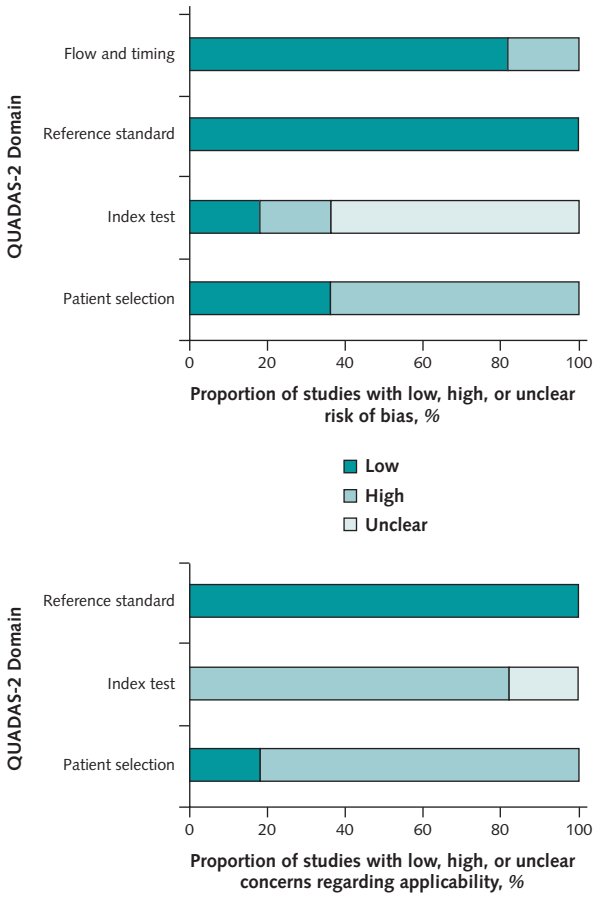
At minimum, reviews should summarize the results of the QUADAS-2 assessment for all included studies. This could include summarizing the number of studies that had a low, a high, or an unclear risk of bias or concerns about applicability for each domain. Reviewers may choose to highlight particular signaling questions on which studies consistently rate poorly or well. Tabular (**Table 2**) and graphic (**Figure 3**) displays help to summarize QUADAS-2 assessments.

Review authors may choose to restrict the primary analysis to include only studies at low risk of bias or with low concern about applicability for either all or specified domains. Restricting inclusion to the review on the basis of similar criteria may be appropriate, but it is often preferable to review all relevant evidence and then investigate possible reasons for heterogeneity (17, 22).

Subgroup or sensitivity analysis can be conducted by investigating how estimates of accuracy of the index test vary among studies rated high, low, or unclear on all or selected domains. Domains or signaling questions can be included as items in metaregression analyses to investigate the association of these questions with estimated accuracy.

The QUADAS Web site (www.quadas.org) contains the QUADAS-2 tool; information on training; a bank of additional signaling questions; more detailed guidance for each domain; examples of completed QUADAS-2 assessments; and downloadable resources, including an Access database for data extraction, an Excel spreadsheet to produce graphic displays of results, and templates for Word tables to summarize results.

Figure 3. **Suggested graphical display for QUADAS-2 results.**



Discussion

Careful assessment of the quality of included studies is essential for systematic reviews of diagnostic accuracy studies. We used a rigorous, evidence-based process to develop QUADAS-2 from the widely used QUADAS tool. The QUADAS-2 tool offers additional and improved features, including distinguishing between bias and applicability, identifying 4 key domains supported by signaling questions to aid judgment on risk of bias, rating risk of bias and concerns about applicability as "high" and "low," and handling studies in which the reference standard consists of follow-up.

We believe that QUADAS-2 is a considerable improvement over the original tool. It would be desirable to extend QUADAS-2 to permit assessment of studies comparing multiple index tests, but we concluded that the evidence base for such criteria is currently insufficient and plan future work on this topic. We hope that QUADAS-2 will help to develop a robust evidence base for diagnostic tests and procedures, and invite further comment and feedback via the QUADAS Web site.

From the University of Bristol, Bristol, United Kingdom; Kleijnen Systematic Reviews, York, United Kingdom; University of Oxford, Oxford, United Kingdom; University of Birmingham, Birmingham, United Kingdom; University Medical Center Utrecht, Utrecht the Netherlands; University of Amsterdam, Amsterdam, the Netherlands; and University of Bern, Bern, Switzerland.

Acknowledgment: The authors thank the following reviewers who participated in the piloting exercise: Gianni Virgilli, Vittoria Murro, Karen Steingardt, Laura Flores, Beth Shaw, Toni Tan, Kurinchi Gurusamy, Mario Cruciani, Lee Hooper, and Catherine Jameson. The authors also thank the Cochrane Collaboration's Diagnostic Test Accuracy Working Group, which facilitated part of the activity for this project.

Grant Support: This work was funded by the Medical Research Council as part of the Medical Research Council–National Institute for Health Research Methodology Research Programme and the National Institute for Health Research. Dr. Mallett is supported by Cancer Research UK. Dr Leeflang is supported by the Netherlands Organization for Scientific Research (project 916.10.034).

Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M11-1238.

Requests for Single Reprints: Penny F. Whiting, PhD, School of Social and Community Medicine, Canynge Hall, 39 Whatley Road, Bristol BS8 2PS, United Kingdom; e-mail, penny.whiting@bristol.ac.uk.

Current author addresses and author contributions are available at www.annals.org.

References

1. **Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J.** The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol. 2003;3:25. [PMID: 14606960]

2. **Willis BH, Quigley M.** Uptake of newer methodological developments and the deployment of meta-analysis in diagnostic test research: a systematic review. BMC Med Res Methodol. 2011;11:27. [PMID: 21401947]

3. **Reitsma JB, Rutjes AW, Whiting P, Vlassov VV, Leeflang MM, Deeks JJ.** Chapter 9: Assessing methodological quality. In: Deeks JJ, Bossuyt PM, Gatsonis C, eds. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0.0. The Cochrane Collaboration; 2009. Accessed at http://srdta.cochrane.org/handbook-dta-reviews on 5 September 2011.

4. **Moher D, Schulz KF, Simera I, Altman DG.** Guidance for developers of health research reporting guidelines. PLoS Med. 2010;7:e1000217. [PMID: 20169112]

5. **Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al.** The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. BMJ. [Forthcoming]

6. **Whiting P, Rutjesw AW, Westwood M, Mallett S, Leefland M, Reitsma JB, et al.** Updating QUADAS: evidence to inform the development of QUADAS-2. 2010. Accessed at www.bris.ac.uk/quadas/resources/quadas2reportv4.pdf on 5 September 2011.

7. **Whiting P, Rutjes AW, Reitsma JB, Glas AS, Bossuyt PM, Kleijnen J.** Sources of variation and bias in studies of diagnostic accuracy: a systematic review. Ann Intern Med. 2004;140:189-202. [PMID: 14757617]

8. **Bossuyt PM, Leeflang MM.** Chapter 6: Developing criteria for including studies. In: Deeks JJ, Bossuyt PM, Gatsonis C, eds. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0.0. The Cochrane Collaboration. 2009. Accessed at http://srdta.cochrane.org/handbook-dta-reviews on 5 September 2011.

9. **Leeflang MM, Deeks JJ, Gatsonis C, Bossuyt PM; Cochrane Diagnostic Test Accuracy Working Group.** Systematic reviews of diagnostic test accuracy.

Ann Intern Med. 2008;149:889-97. [PMID: 19075208]
10. **Whiting PF, Smidt N, Sterne JA, Harbord R, Burton A, Burke M, et al.** Systematic review: accuracy of anti-citrullinated peptide antibodies for diagnosing rheumatoid arthritis. Ann Intern Med. 2010;152:456-64. [PMID: 20368651]
11. **Lijmer JG, Mol BW, Heisterkamp S, Bonsel GJ, Prins MH, van der Meulen JH, et al.** Empirical evidence of design-related bias in studies of diagnostic tests. JAMA. 1999;282:1061-6. [PMID: 10493205]
12. **Leeflang MM, Moons KG, Reitsma JB, Zwinderman AH.** Bias in sensitivity and specificity caused by data-driven selection of optimal cutoff values: mechanisms, magnitude, and solutions. Clin Chem. 2008;54:729-37. [PMID: 18258670]
13. **Stengel D, Bauwens K, Rademacher G, Mutze S, Ekkernkamp A.** Association between compliance with methodological standards of diagnostic research and reported test accuracy: meta-analysis of focused assessment of US for trauma. Radiology. 2005;236:102-11. [PMID: 15983072]
14. **Biesheuvel C, Irwig L, Bossuyt P.** Observed differences in diagnostic test accuracy between patient subgroups: is it real or due to reference standard misclassification? Clin Chem. 2007;53:1725-9. [PMID: 17885138]
15. **van Rijkom HM, Verdonschot EH.** Factors involved in validity measurements of diagnostic tests for approximal caries—a meta-analysis. Caries Res. 1995;29:364-70. [PMID: 8521438]
16. **Whiting P, Westwood M, Bojke L, Palmer S, Richardson G, Cooper J, et al.** Clinical effectiveness and cost-effectiveness of tests for the diagnosis and investigation of urinary tract infection in children: a systematic review and economic model. Health Technol Assess. 2006;10:iii-iv, xi-xiii, 1-154. [PMID: 17014747]
17. **Whiting P, Harbord R, Main C, Deeks JJ, Filippini G, Egger M, et al.** Accuracy of magnetic resonance imaging for the diagnosis of multiple sclerosis: systematic review. BMJ. 2006;332:875-84. [PMID: 16565096]
18. **Rutjes A, Reitsma J, Di NM, Smidt N, Zwinderman A, Van RJ, et al.** Bias in estimates of diagnostic accuracy due to shortcomings in design and conduct: empirical evidence [Abstract]. Presented at XI Cochrane Colloquium: Evidence, Health Care and Culture, Barcelona, Spain, 26–31 October 2003. Abstract 45.
19. **Macaskill P, Gatsonis C, Deeks JJ, Harbord R, Takwoingi Y.** Chapter 10: Analysing and presenting results. In: Deeks JJ, Bossuyt PM, Gatsonis C, eds. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0.0. The Cochrane Collaboration. 2010. Accessed at http://srdta.cochrane.org/handbook-dta-reviews on 5 September 2011.
20. **J ni P, Witschi A, Bloch R, Egger M.** The hazards of scoring the quality of clinical trials for meta-analysis. JAMA. 1999;282:1054-60. [PMID: 10493204]
21. **Whiting P, Harbord R, Kleijnen J.** No role for quality scores in systematic reviews of diagnostic accuracy studies. BMC Med Res Methodol. 2005;5:19. [PMID: 15918898]
22. **Whiting PF, Weswood ME, Rutjes AW, Reitsma JB, Bossuyt PN, Kleijnen J.** Evaluation of QUADAS, a tool for the quality assessment of diagnostic accuracy studies. BMC Med Res Methodol. 2006;6:9. [PMID: 16519814]

Current Author Addresses: Drs. Whiting and Sterne: School of Social and Community Medicine, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol BS8 2PS, United Kingdom.
Dr. Rutjes: Division of Clinical Epidemiology and Biostatistics, Institute of Social and Preventive Medicine, University of Bern, Finkenhubelweg 11, 3012 Bern, Switzerland.
Dr. Westwood: Kleijnen Systematic Reviews, Unit 6, Escrick Business Park, Riccall Road, Escrick, York YO19 6FD, United Kingdom.
Dr. Mallett: Centre for Statistics in Medicine and Department of Primary Health Care, Wolfson College Annexe, Linton Road, Oxford OX2 6UD, United Kingdom.
Dr. Deeks: Unit of Public Health, Epidemiology & Biostatistics, University of Birmingham, Edgbaston B15 2TT, United Kingdom.
Dr. Reitsma: Julius Center for Health Sciences and Primary Care, UMC Utrecht, PO Box 85500, 3508GA Utrecht, the Netherlands.
Drs. Leeflang and Bossuyt: Department of Clinical Epidemiology, Biostatistics and Bioinformatics, AMC, University of Amsterdam, Postbus 22660, 1100 DD Amsterdam, the Netherlands.

Author Contributions: Conception and design: P.F. Whiting, A.W.S. Rutjes, J.B. Reitsma, M.M.G. Leeflang, J.A.C. Sterne, P.M.M. Bossuyt.
Analysis and interpretation of the data: P.F. Whiting, A.W.S. Rutjes, M.E. Westwood, J.J. Deeks, J.B. Reitsma, J.A.C. Sterne, P.M.M. Bossuyt.
Drafting of the article: P.F. Whiting, M.E. Westwood, S. Mallett, M.M.G. Leeflang, J.A.C. Sterne.
Critical revision for important intellectual content: A.W.S. Rutjes, M.E. Westwood, J.J. Deeks, J.B. Reitsma, M.M.G. Leeflang, J.A.C. Sterne, P.M.M. Bossuyt.
Final approval of the article: P.F. Whiting, A.W.S. Rutjes, M.E. Westwood, S. Mallett, J.J. Deeks, J.B. Reitsma, M.M.G. Leeflang, J.A.C. Sterne, P.M.M. Bossuyt.
Statistical expertise: J.J. Deeks, J.A.C. Sterne.
Obtaining of funding: P.F. Whiting, J.J. Deeks, J.A.C. Sterne.
Administrative, technical, or logistic support: J.A.C. Sterne.
Collection and assembly of data: P.F. Whiting, A.W.S. Rutjes, M.E. Westwood, J.B. Reitsma, M.M.G. Leeflang.

Appendix: The QUADAS-2 Group

University of Oxford: Doug Altman, Susan Mallett*; *Memorial Sloan-Kettering Cancer Center:* Colin Begg; *University of Bristol:* Rebecca Beynon, Jonathan A.C. Sterne*, Penny F. Whiting*; *University of Amsterdam:* Patrick M.M. Bossuyt*, Mariska M.G. Leeflang*, Jeroen Lijmer; *American College of Physicians:* John Cornell; *University of Birmingham:* Clare Davenport, Jonathan J. Deeks*, Khalid Khan; *Bond University:* Paul Glasziou; *University of Sydney:* Rita Horvath, Les Irwig, Petra Macaskill; *University of Exeter:* Chris Hyde; *Maastricht University:* Jos Kleijnen; *University Medical Center Utrecht:* Karel G.M. Moons, Johannes B. Reitsma*; *Basel Institute of Clinical Epidemiology and Biostatistics:* Heike Raatz; *University of Bern:* Anne W.S. Rutjes*; *National Institute for Health and Clinical Excellence:* Beth Shaw, Toni Tan; *Keele University:* Danielle van der Windt; *University of Florence:* Gianni Virgili; *Kleijnen Systematic Reviews:* Marie E. Westwood*.

* = steering group members.

Appendix Table. **Percentage of Overall Agreement and κ Statistics Showing Agreement Between Review Authors by Using QUADAS-2***

Review	Review Topic	Studies Included in the Review, *n*	Patient Selection		Index Test		Reference Standard		Flow and Timing		Total	
			Percentage	κ Statistic	Percentage	κ Statistic	Percentage	κ Statistic	Percentage	κ Statistic	Percentage	κ Statistic
Risk of bias												
Review 1	β-Glucan testing to diagnose invasive fungal infections in patients with neutropenia	8	87.5	0.76	62.5	0.40	50.0	0.16	25.0	0.09	56.3	0.33
Review 2	Laparoscopy to assess resectability in pancreatic and periampullary cancer	6	93.7	0.90	93.8	0.77	87.5	0.62	93.8	0.82	92.2	0.84
Review 3	Investigations to diagnose osteomyelitis in persons with foot problems associated with diabetes	13	30.8	0.01	84.6	0.66	46.2	0.05	30.8	–0.36	48.0	0.03
Review 4	Antigen detection testing to diagnose active tuberculosis	47	100.0	1.00	100.0	1.00	100.0	NA	100.0	1.00	100.0	1.00
Review 5	Optical coherence tomography to detect macular edema in patients with diabetic retinopathy	9	44.4	0.08	55.6	0.29	100.0	1.00	66.7	0.44	66.7	0.41
Applicability												
Review 1	β-Glucan testing to diagnose invasive fungal infections in patients with neutropenia	8	62.5	–0.20	37.5	0.00	100.0	1.00	–	–	66.7	0.11
Review 2	Laparoscopy to assess resectability in pancreatic and periampullary cancer	6	81.3	0.51	93.8	0.77	87.5	0.62	–	–	87.5	0.62
Review 3	Investigations to diagnose osteomyelitis in persons with foot problems associated with diabetes	13	100.0	NA	100.0	NA	100.0	NA	–	–	100.0	NA
Review 4	Antigen detection testing to diagnose active tuberculosis	47	100.0	1.00	100.0	NA	100.0	NA	–	–	100.0	1.00
Review 5	Optical coherence tomography to detect macular edema in patients with diabetic retinopathy	9	88.9	0.00	88.9	0.00	88.9	0.00	–	–	88.9	0.00

NA = not available.

* Ratings refer to agreements between pairs of reviewers rating each QUADAS-2 domain as high, low, or unclear on the basis of their initial assessment. Agreement for signaling questions was not assessed.