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Diagnostic Accuracy of Point-of-Care Tests for Detecting Albuminuria

A Systematic Review and Meta-analysis

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Background: Experts recommend screening for albuminuria in patients at risk for kidney disease.

Purpose: To systematically review evidence about the diagnostic accuracy of point-of-care (POC) tests for detecting albuminuria in individuals for whom guidelines recommend such detection.

Data Sources: Cochrane Library, EMBASE, Medion database, MEDLINE, and Science Citation Index from 1963 through 5 December 2013; hand searches of other relevant journals; and reference lists.

Study Selection: Cross-sectional studies, published in any language, that compared the accuracy of machine-read POC tests of urinary albumin–creatinine ratio with that of laboratory measurement.

Data Extraction: Two independent reviewers extracted study data and assessed study quality using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) tool.

Data Synthesis: Sixteen studies ($n = 3356$ patients) that evaluated semiquantitative or quantitative POC tests and used random urine samples collected in primary or secondary ambulatory care settings met inclusion criteria. Pooling results from a bivariate random-effects model gave sensitivity and specificity estimates of 76% (95% CI, 63% to 86%) and 93% (CI, 84% to 97%), respectively, for the semiquantitative test. Sensitivity and specificity estimates for the quantitative test were 96% (CI, 78% to 99%) and 98% (CI, 93% to 99%), respectively. The negative likelihood ratios for the semiquantitative and quantitative tests were 0.26 (CI, 0.16 to 0.40) and 0.04 (CI, 0.01 to 0.25), respectively.

Limitation: Accuracy estimates were based on data from single-sample urine measurement, but guidelines require that diagnosis of albuminuria be based on at least 2 of 3 samples collected in a 6-month period.

Conclusion: A negative semiquantitative POC test result does not rule out albuminuria, whereas quantitative POC testing meets required performance standards and can be used to rule out albuminuria.

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Albuminuria, a cardinal sign of kidney disease, is routinely measured as the urinary albumin–creatinine ratio (uACR). A continuous relationship exists among uACR, kidney failure, and cardiovascular and all-cause mortality (1–7). Experts recommend screening for albuminuria by measuring uACR in patients with such conditions as diabetes mellitus, hypertension, and chronic kidney disease (8–14). Evidence suggests that such testing is not universally applied and that use of point-of-care (POC) testing could improve uptake (15, 16).

Point-of-care testing for albuminuria has several advantages over laboratory testing: There are no time-consuming sample logistics (such as specimen transport), results are obtained more quickly, and findings can be discussed with the patient during the clinic visit with no further action required in the case of a negative result. Moreover, POC testing can change processes of care by enabling faster decision making and reducing the need for further consultations. One potential disadvantage of POC testing is the increased direct cost of the test; however, this cost does not take into account the potential savings for the patient achieved by reducing length or number of clinic visits. A study in Australia found that POC testing for uACR was less costly than laboratory testing (17).

Tests must be rigorously assessed to determine whether they have sufficient diagnostic performance for use in clinical practice (18–23). A recent evidence-based recommendation by a joint committee of the American Diabetes Association (ADA) and the American Association for Clinical Chemistry (AACC) suggested that qualitative or semiquantitative screening tests should have clinical sensitivity exceeding 95% if they are to be used to detect albuminuria (13). We systematically reviewed diagnostic accuracy studies of POC tests for uACR to determine whether any have sufficient accuracy to be considered for use in screening patients at risk for renal disease.

METHODS

We followed standard methods for conducting and reporting systematic reviews (19, 24).

Data Sources and Searches

We performed an electronic search of the Cochrane Library (up to issue 11 of 2013), EMBASE (1974 to 5 December 2013), the Medion database (to 5 December 2013), MEDLINE (1946 to 5 December 2013), and the Science Citation Index (1945 to 5 December 2013) using the following Medical Subject Headings terms: "albuminuria," "microalbuminuria," "albumin:creatinine ratio," and "point of care test." No language restrictions were applied, and we adapted the search terms depending on the restrictions of individual resources. There was a long list of synonyms for "point of care test," which we combined with synonyms for albuminuria or uACR by using "AND." We also included the names of individual POC tests in the searches. Finally, one of the authors hand-searched the

journal *Point of Care* (http://journals.lww.com/poctjournal). Details of the MEDLINE search are given in **Appendix Table 1** (available at www.annals.org).

Study Selection

Studies were eligible for inclusion if they were cross-sectional studies that assessed a POC test for uACR; reported sensitivity and specificity or data that could be used to calculate those values; used laboratory uACR, including an immunochemical albumin method, as a reference standard; involved a patient population for whom guidelines recommend routine measurement of uACR for the early detection of albuminuria, such as patients with diabetes, hypertension, or established kidney disease, in primary or ambulatory secondary care settings; included at least 50 patients; measured uACR in urine samples; and were published in 1963 or later, given that the first immunochemical albumin method was described that year (25). Studies were excluded if the POC test being assessed was read visually without the use of a reflectometer.

Screening of Titles and Abstracts

Initially, titles and abstracts of all identified articles were read by 2 independent investigators, who each made an assessment of which to retain on the basis of the inclusion and exclusion criteria. Each investigator was blinded to the other's selections. Discrepancies among studies marked for inclusion were arbitrated by 2 other investigators. Full-text versions of the articles retained after screening were obtained, and a further round of selection was performed. We contacted corresponding authors if we believed they may have had key information that was not available in the published article.

Data Extraction and Quality Assessment

Estimates of sensitivity; specificity; and true-positive, false-positive, true-negative, and false-negative results were extracted from the source papers by 2 independent reviewers. When these were not provided, values were calculated. Positive and negative likelihood ratios, diagnostic odds ratios, and 95% CIs were also calculated. In addition, disease state of the study sample, the type of study, age range, mean age, type of operator of the index test (for example, clinical [such as nurse or medical practitioner] or laboratory staff), index test, reference test, threshold used for both tests, and study location were recorded.

Two independent investigators used the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) tool (26) to assess each study. The risk of bias was assessed in 4 domains: patient selection, execution of the index test and reference standard, and flow of patients (in particular, whether there was an appropriate interval between the index test and the reference standard). A third investigator arbitrated differences in the assessments to produce a consensus for risk of bias and applicability concerns in each domain.

Data Synthesis and Analysis

All statistical analysis was done using the metandi and midas commands in Stata, version 12 (StataCorp, College Station, Texas) (27, 28). A bivariate random-effects method was used to estimate average sensitivity and specificity. We use hierarchical summary receiver-operating characteristic curves to display the variation in diagnostic accuracy among studies. We computed a summary estimate with a corresponding confidence bound of the average sensitivity and specificity across studies for each test system (semiquantitative or quantitative) and category of operator. Heterogeneity among studies is reported using the I^2 statistic and was investigated by using subgroup analysis and multiple univariable meta-regression to investigate the effect of participant age, disease status, recruitment setting, test location, and operator type. We explored publication bias by using a regression of the log of the diagnostic odds ratio against the inverse of the square root of the effective sample size, weighted by effective sample size (29).

Role of the Funding Source

This review received no direct funding.

RESULTS

The searches generated 535 articles for screening after removal of duplicates (**Appendix Figure 1**, available at www.annals.org). Forty-seven full-text articles were assessed for eligibility; of these, 14 met inclusion criteria (30–43) (**Appendix Table 2**, available at www.annals.org) and 33 were excluded (**Appendix Table 3**, available at www.annals.org). Because 2 articles (32, 35) were subdivided into 2 separate studies, 16 data sets were analyzed (**Appendix Table 2**). The study by Guy and colleagues (32) provided separate assessments of the semiquantitative and quantitative uACR tests (Clinitek and DCA, Siemens HealthCare Diagnostics, Tarrytown, New York). They used 24-hour albumin loss as the reference standard in their published article, but we obtained data from the corresponding author that were based on the use of laboratory uACR as a reference method. The study by Pickersgill and associates (35) was divided into assessments of a semiquantitative assay with clinical and technical operators.

Most studies involved patients with diabetes mellitus (30, 33–38, 41, 43), with 1 including young patients (aged 13 to 24 years) with type 1 diabetes (34). Two studies included patients with kidney disease, diabetes mellitus, or both (39, 40), whereas 1 involved patients with advanced chronic kidney disease being treated in a renal outpatient clinic (32). The second-largest study recruited patients in primary care who had chronic kidney disease or were at increased risk for the condition according to U.K. national guidelines; most patients had diabetes mellitus, hypertension, or both (42). One study used urine samples that had been sent to a laboratory specifically for proteinuria testing

Table. **Summary of Diagnostic Accuracy Estimates***

Parameter	Meta-analysis				Estimates From Single Studies†	
	Clinitek‡			DCA‡ (All Operators)	DCA‡ (Clinical Operator)	Aution§ (Laboratory Operator)
	All Operators	Laboratory Operator	Clinical Operator			
Sensitivity, %	76 (63–86)	83 (70–91)	67 (45–83)	96 (78–99)	91 (82–96)	95 (92–98)
Specificity, %	93 (84–97)	91 (80–96)	96 (78–99)	98 (93–99)	98 (93–100)	81 (72–88)
LR+	11.0 (4.9–24.4)	9.1 (4.2–19.6)	15.1 (2.8–82.0)	44.7 (13.6–147.4)	52.9 (13.4–209.2)	5.0 (3.4–7.3)
LR−	0.26 (0.16–0.40)	0.19 (0.11–0.32)	0.34 (0.19–0.62)	0.04 (0.01–0.25)	0.09 (0.04–0.18)	0.06 (0.03–0.10)

LR− = negative likelihood ratio; LR+ = positive likelihood ratio.
* Numbers in parentheses are 95% CIs.
† There were not enough studies to perform meta-analysis of those assessing the Aution (1 study) or those assessing the DCA on the basis of operator type (there were too few studies with a laboratory operator [≥4 studies are required for the analysis] and only 1 study with a clinical operator). CIs were calculated using published data.
‡ Siemens HealthCare Diagnostics, Tarrytown, New York.
§ Aution was manufactured by Arkray, Kyoto, Japan.

but did not state the patients' diagnoses (31). In all of the studies, a random ("spot") urine sample was collected.

Index Tests

Three POC tests were studied: 2 semiquantitative tests (Clinitek and Aution [Arkray, Kyoto, Japan]) and 1 quantitative test (DCA). The Clinitek test involves dye-binding and catalytic methods for albumin and creatinine, respectively, embedded on "Microalbumin 9" reagent strips that are dipped into urine and automatically read by a Clinitek reflectometer (44). The test is semiquantitative, with uACR reported as less than 30, 30 to 300, or greater than 300 mg/g (<3.4, 3.4 to 33.9, or >33.9 mg/mmol). The Aution uACR test consists of a reagent strip with a dye-binding albumin method and a "chelate competition technique" for creatinine (31). The Aution "screen" strips are read by a bench-top reflectometer that semiquantitatively measures uACR and classifies samples in the same way as the Clinitek. Only 1 study provided performance data for the Aution test (**Appendix Table 4**, available at www.annals.org). The DCA test is fully quantitative and involves loading an aliquot of urine into a DCA "Microalbumin/Creatinine" cartridge, which is then inserted into the DCA analyzer (39). Albumin is measured by an immunoturbidimetric assay, and creatinine is measured by a spectrophotometric assay.

Quality Assessment

In the initial QUADAS-2 assessments, 99 of 112 domains across the 16 studies were scored identically. None of the studies was considered to have a high risk of bias in any of the domains (**Appendix Table 5** and **Appendix Figure 2**, available at www.annals.org). Three studies were assessed as having unclear risk of bias (34, 36, 38), 2 as having risk in 1 domain each (34, 38), and 1 as having possible bias in 2 domains (36). Patient selection may have caused bias in 1 study that assessed the Clinitek in patients with type 1 diabetes (34) because those with poor glucose control were excluded from testing. In the study that assessed the Aution test, there seemed to be an intention to test but the final selection of specimens for analysis was based on "optimization for evaluation of the analytical performance of the test strips," which is reflected in the high prevalence of albuminuria in the study. Two factors potentially caused bias in a study that assessed the Clinitek in a sample of patients from a diabetic outpatient clinic (36). First, the reference standard differed depending on the recruitment center; second, the interval between receipt of the index test and the reference standard was unclear. There was also an unclear interval between index and reference tests in a study assessing the quantitative test, which was considered to be a potential bias (38).

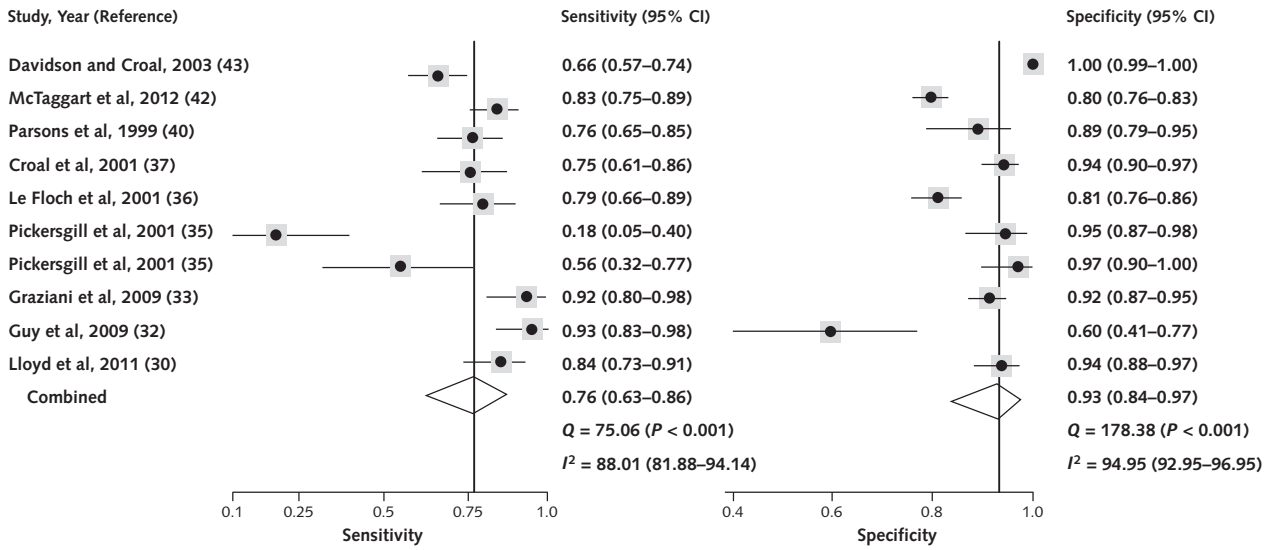
Diagnostic Accuracy Estimates

The prevalence of a uACR above the cutoff values used in the 16 studies ranged from 7.3% to 70.1% (mean, 35.0%). We found variation in the patient cohorts studied: Some studies included patients at risk for renal disease (30, 31, 33–38, 41–43), whereas others included patients with diagnosed renal disease (32, 39, 40). The data from the diagnostic accuracy meta-analysis for the semiquantitative and quantitative tests are summarized in the **Table**. The semiquantitative test was the most-studied (9 of 16 studies) POC test. We found considerable variation in the sensitivity and specificity estimates reported by individual studies assessing the semiquantitative test; the former ranged from 18.0% to 92.9%, and the latter ranged from 60% to 100% (**Appendix Table 4**).

For the semiquantitative test, sensitivity was 76% (95% CI, 63% to 86%), specificity was 93% (CI, 84% to 97%), the positive likelihood ratio was 11.0 (CI, 4.9 to 24.4), and the negative likelihood ratio was 0.26 (CI, 0.16 to 0.40) (**Table**; **Figure 1**; and **Appendix Figure 3**, available at www.annals.org). The pooled estimate for sensitivity was 67% (CI, 45% to 83%) among studies that used clinical operators and 83% (CI, 70% to 91%) among those that used laboratory operators (**Table** and **Figures 2** and **3**).

Pooling data for all included studies of the quantitative test gave a summary point with a sensitivity of 96% (CI, 78% to 99%) and a specificity of 98% (CI, 93% to 99%)

Figure 1. **Forest plots for the semiquantitative test.**



(**Table**; **Figure 4**; and **Appendix Figure 4**, available at www.annals.org). Only 1 study assessing the quantitative test had a confirmed clinical operator of the POC testing system (36), so we could not perform meta-analyses or produce receiver-operating characteristic curves for clinical and laboratory operators. The quantitative test showed positive and negative likelihood ratios of 44.7 (CI, 13.6 to 147.4) and 0.04 (CI, 0.01 to 0.25), respectively. One study assessing the quantitative test had a sensitivity of only 50% (34), although the specificity was 100%; the patient cohort in this study was small ($n = 55$ after exclusions). One limitation of the quantitative studies was the variability in cutoff values; such thresholds as 2.65 mg/mmol (39), 2.5 mg/mmol for women and 3.5 mg/mmol for men (41), and 3.4 mg/mmol (32, 34, 38) were used.

Likelihood ratios for the semiquantitative and quantitative tests were pooled and are graphically presented in scattergrams in **Appendix Figures 5** and **6** (available at www.annals.org). Likelihood ratios can be more clinically meaningful than sensitivity and specificity, so a graphical representation can aid clinical decision making by allowing a rapid visual assessment of the usefulness of a diagnostic test (45). The data suggest that the performance of the semiquantitative test does not meet the criteria for exclusion or confirmation, whereas the quantitative test might be suitable for exclusion and confirmation.

The heterogeneity among studies was large, with I^2 statistics for sensitivity and specificity of 88% and 95%, respectively, for the semiquantitative studies and 75% and 66%, respectively, for the quantitative studies. We performed metaregression on the semiquantitative device data to test the effect of disease (diabetes, renal, or other), setting (secondary care, laboratory, or other), test location (laboratory or point of care), and operator (technical or

Figure 2. **Forest plots for the semiquantitative test with a clinical operator.**

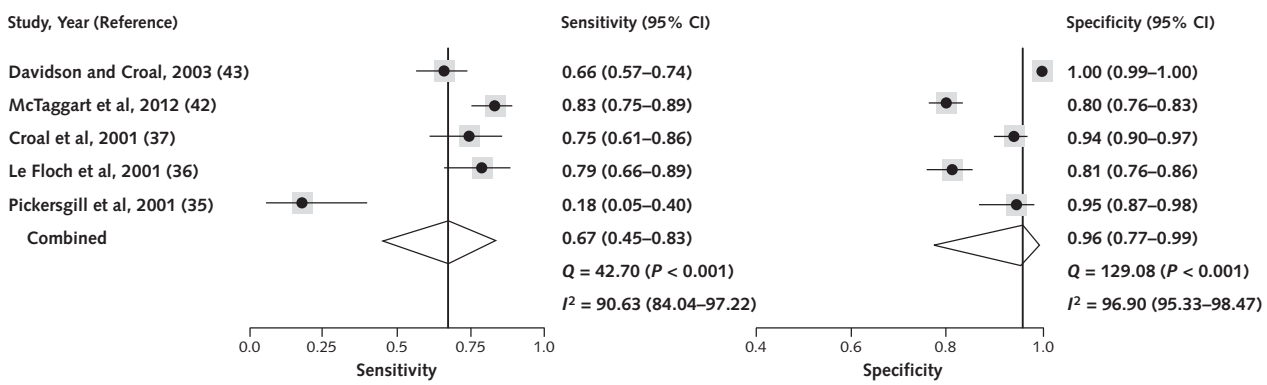
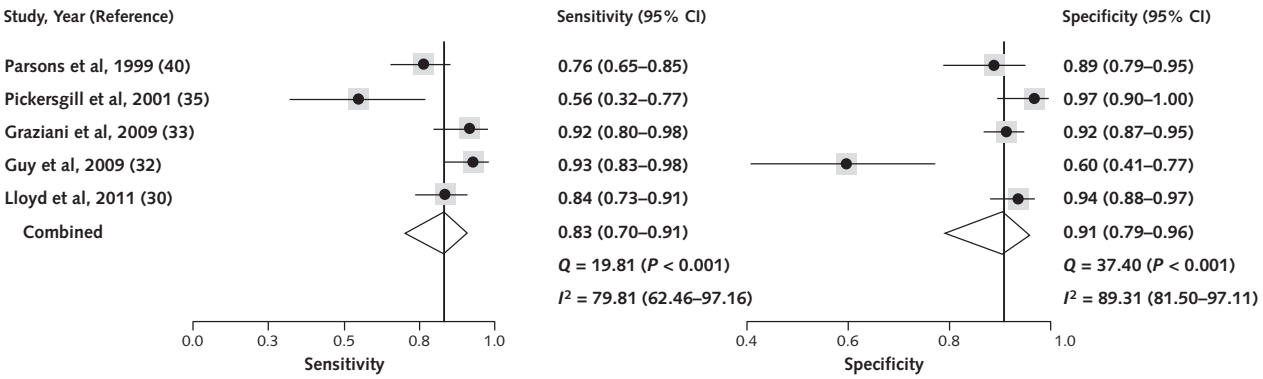


Figure 3. **Forest plots for the semiquantitative test with a laboratory operator.**



clinical) on these estimates. None were found to affect the mean sensitivity. We also performed metaregression on the quantitative test data to investigate the effect of setting and location. The former had no effect, but the latter had a statistically significant effect on the sensitivity and specificity ($P = 0.030$ in the joint model analysis). One study of children had a statistically significantly different sensitivity from that of the studies involving adults (34). There were only 5 studies on the quantitative system, which made further interpretation of these findings difficult. We found no statistically significant publication bias ($P = 0.68$).

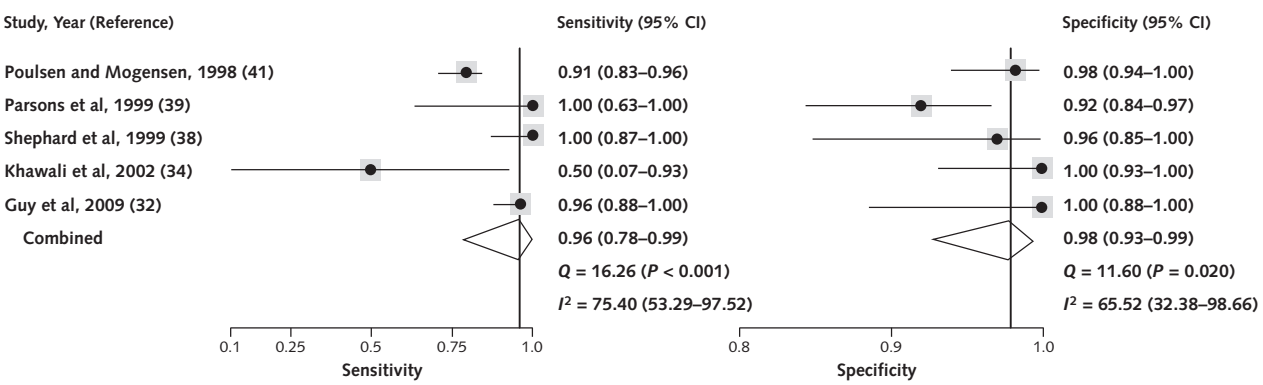
DISCUSSION

Point-of-care testing has potential benefits, including more rapid reporting of results that enables more timely treatment decisions compared with central laboratory testing (18). Confirming that a patient has albuminuria requires the demonstration of increased uACR in at least 2 of 3 urine samples collected within a 6-month period (11, 12, 14). Establishing the diagnosis therefore requires several clinic visits. However, if a positive result is obtained, the need for further tests can be explained to the patient immediately. Conversely, if a negative result is obtained from a sufficiently sensitive test, albuminuria can be ruled out until the next (typically annual) screening visit.

When semiquantitative or qualitative POC screening tests for albuminuria are being considered, sensitivity, rather than specificity, is paramount (13). Although a high specificity is also desirable, some false-positive results are acceptable given that the presence of albuminuria in a spot test requires confirmation. A sensitive POC test allows for immediate reassurance for patients with negative results at the point of care as well as potential cost savings in specimen transport and laboratory testing, although it could lead to an overall increase in albuminuria testing.

Our meta-analyses showed that the semiquantitative assay fell short of the ADA/AACC criteria of greater than 95% sensitivity (13), particularly when a clinical operator administered the POC testing. The sensitivity seemed to improve when a laboratory professional performed the test. This phenomenon has been observed in the evaluation of other POC testing systems, including tests for urinary albumin (46).

Figure 4. **Forest plots for the quantitative test.**



The quantitative uACR test meets the ADA/AACC sensitivity target (13), although sensitivity was only 91% in the study in which testing was administered by a clinical operator. In addition, 1 study found an anomalous sensitivity of 50% for the test (34), which may be explained by the small sample size and applicability concerns about the use of the index test. The study only tested patients with good glycemic control, and only 4 patients tested positive by the reference standard. The quantitative assay offers technical performance similar to that of laboratory assays (39), even when used in a clinical setting (47).

When considering the quality of studies, we selected those that involved an applicable patient group (that is, patients who had or were at risk for kidney disease [such as those with diabetes mellitus or hypertension]) (8–12, 14) and those with an intention to test (48). We also considered time between measurements (delay between sample collection and both index and reference testing) to be important because albumin concentration decreases because of degradation by proteases if it is stored at room temperature or at 4 °C for more than 7 days (49). In contrast, blinding of index test operators to reference test results and vice versa was considered less important because there is no subjectivity in interpreting uACR results if the threshold for albuminuria has been predefined.

One important limitation of these data is that no international reference method for urinary albumin measurement exists (50, 51). We selected studies that compared POC tests with the available local laboratory method. However, large biases are known to exist among laboratory methods (52). Thus, our approach may have placed the POC testing devices at an unfair disadvantage. Second, we used metaregression to explore whether statistical heterogeneity was explained by study-level characteristics. The Cochrane Handbook (53) recommends at least 10 studies for metaregression to be considered, and the Agency for Healthcare Research and Quality (54) recommends at least 4 studies. Because of the small number of studies included in our review (9 for semiquantitative tests and 5 for quantitative tests), the results from the metaregression should be interpreted with caution.

Analytic goals for biomarker tests are related to their biological variation, requiring less precision if the variation is large (13, 55). Urinary albumin concentration has high intraindividual biological variation, and an analytic goal of a coefficient of variation of 18% has been proposed in the case of a spot urinary albumin test (56). To reduce biological variation due to urine dilution or concentration, the uACR, which has a lower analytic goal of 15% (13), is in wide clinical use (57). Although qualitative or semiquantitative systems may meet these analytic goals, the high intraindividual variation means that no test can offer the desired sensitivity of detection. For this reason, as mentioned earlier, it is necessary to analyze more than 1 sample to confirm albuminuria, with 2 positive results out of 3 samples analyzed over 6 months required for the diagnosis (11, 12, 14, 58). A limitation of this review, therefore, is that the diagnostic accuracy of the POC testing systems has been assessed, with a laboratory test as comparator, on the basis of studies using a single measurement. Consequently, this analysis may not fully reflect the diagnostic performance of the test, although it may reflect current clinical practice. We are unaware of any studies that have assessed the diagnostic performance of POC testing systems for albuminuria based on a confirmatory testing approach. Further research is needed to answer this question.

The technical performance of POC tests needs to be equivalent to that obtained in the central laboratory, which is representative of the technical performance used in studies that have formed the basis of current clinical guidelines. We conclude that the semiquantitative test for the measurement of uACR does not have the required diagnostic accuracy for use in screening patients at risk for renal disease. In contrast, the technical performance of the quantitative assay is equivalent to that of laboratory tests, and its diagnostic accuracy meets the required standards for a POC test used in screening for albuminuria.

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visual results and quantitative methods. J Clin Lab Anal. 1998;12:280-4. [PMID: 9773958]
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Ad Libitum

The Last Watcher

I hope the birds never forget
What their renaissance meant to the old woman
Nestled on the sloping porch
Beneath a beige afghan
After the stroke.

Brian Christman, MD
Nashville, Tennessee

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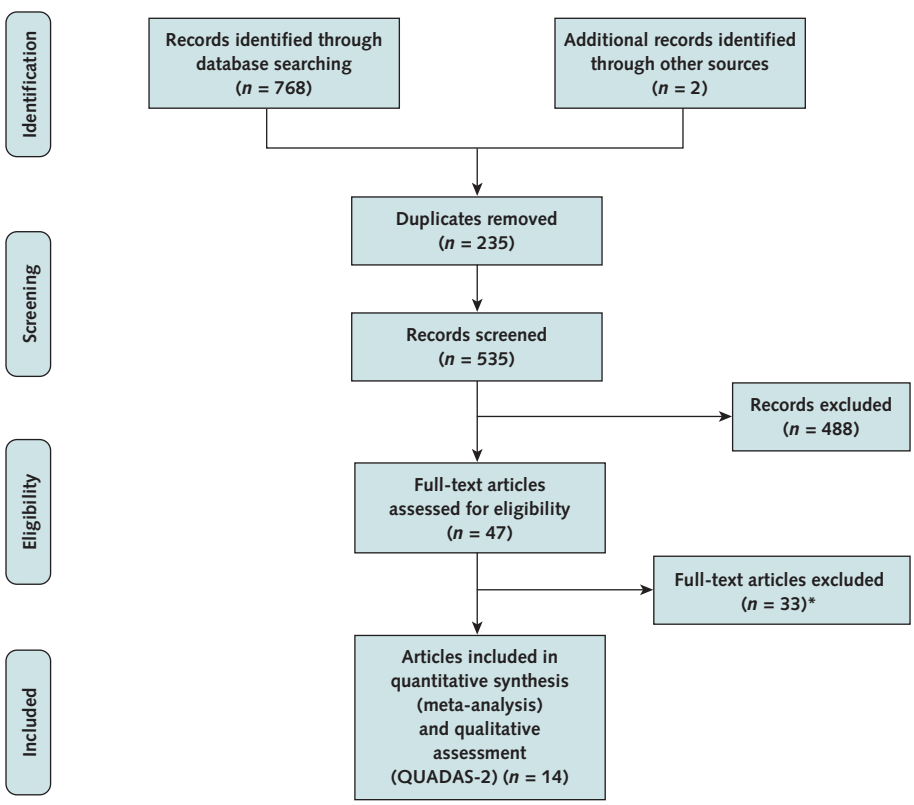
Administrative, technical, or logistic support: M.P. McTaggart, N.W. Roberts.
Collection and assembly of data: M.P. McTaggart, R.G. Newall, E.J. Lamb, N.W. Roberts, C.P. Price.

Appendix Table 1. Details of MEDLINE Search

1. Albuminuria/(12 301)
2. (albuminuria or microalbuminuria).ti,ab. (12 910)
3. 1 or 2 (17 789)
4. (urin* adj5 albumin* adj5 creatinine).ti,ab. (2371)
5. acr.ti,ab. (5866)
6. uacr.ti,ab. (329)
7. 4 or 5 or 6 (7862)
8. 3 or 7 (23 739)
9. ((immediate$ or rapid$ or same time or same visit or near patient or instant$ or portable or bedside or bed-side) adj3 (test$ or turnaround or analys$ or analyz$ or measure$ or assay$ or monitor*)).tw. (56 641)
10. (poc or poct or "point of care").tw. (8212)
11. Point-of-Care Systems/(7233)
12. afinion or dca vantage or dca 2000 or prospec nephelometer or clinitek microalbumin or clinitek 50 or hemocue or aution eleven).ti,ab. (419)
13. 9 or 10 or 11 or 12 (67 736)
14. 8 and 13 (140)
15. ((immediate$ or rapid$ or same time or same visit or near patient or instant$ or portable or bedside or bed-side) adj5 urin* adj5 albumin adj5 creatinine).ti,ab. (3)
16. 14 or 15 (142)
17. ((immediate$ or rapid$ or same time or same visit or near patient or instant$ or portable or bedside or bed-side) adj5 albumin adj5 creatinine).ti,ab. (6)
18. (("point of care" or poc or poct) adj5 albumin adj5 creatinine).ti,ab. (5)
19. 16 or 17 or 18 (145)

Appendix Figure 1. Summary of evidence search and selection.



After the literature search, titles and abstracts were screened by 2 independent investigators with arbitration by 2 other investigators. Full-text versions of retained articles were obtained, and a further round of selection was performed. Data were extracted from the remaining articles. QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies 2.

* **Appendix Table 3** provides reasons for exclusion.

Appendix Table 2. **Details of Patient Cohorts, Index Tests, and Operators for Included Studies***

Study, Year (Reference)	Patient Group	Index Test†	Index Test Operator
Lloyd et al, 2011 (30)	DM	Clinitek	Laboratory professional
Kouri et al, 2009 (31)	Routine testing	Aution	Laboratory professional
Guy et al, 2009 (32)‡	Renal outpatients	Clinitek and DCA	Laboratory professional
Graziani et al, 2009 (33)	DM	Clinitek	Laboratory professional
Khawali et al, 2002 (34)	DM	DCA	Not stated
Pickersgill et al, 2001 (35)§	DM	Clinitek	Clinical and laboratory professional
Le Floch et al, 2001 (36)	DM	Clinitek	Clinical professional
Croal et al, 2001 (37)	DM	Clinitek	Clinical professional
Shephard et al, 1999 (38)	DM	DCA	Laboratory professional
Parsons et al, 1999 (39)	DM and/or renal impairment	DCA	Laboratory professional
Parsons et al, 1999 (40)	DM and/or renal impairment	Clinitek	Laboratory professional
Poulsen and Mogensen, 1998 (41)	DM	DCA	Clinical professional
McTaggart et al, 2012 (42)	Tested in primary care	Clinitek	Clinical professional
Davidson and Croal, 2003 (43)	DM	Clinitek	Clinical professional

DM = diabetes mellitus.
* All studies were cross-sectional.
† Clinitek and DCA were manufactured by Siemens HealthCare Diagnostics (Tarrytown, New York); Aution was manufactured by Arkray (Kyoto, Japan).
‡ Data were subdivided into 2 sets: one assessing the Clinitek and another assessing the DCA. The published manuscript used laboratory 24-h albumin loss rather than laboratory urinary albumin–creatinine ratio as the reference test; however, data comparing the index tests with laboratory urinary albumin–creatinine ratio were obtained from the corresponding author.
§ Data were subdivided into 2 sets: one in which a clinical operator administered the index test and another in which a laboratory professional administered the index test.

Appendix Table 3. Studies Excluded After Review of Full-Text Articles

Study Citation	Article Type	Reason for Exclusion
Omoruyi FO, Mustafa GM, Okorodudu AO, Petersen JR. Evaluation of the performance of urine albumin, creatinine and albumin-creatinine ratio assay on two POCT analyzers relative to a central laboratory method. Clin Chim Acta. 2012;413:625-9. [PMID: 22212624]	Research paper	No diagnostic accuracy data
Morris RK, Riley RD, Doug M, Deeks JJ, Kilby MD. Diagnostic accuracy of spot urinary protein and albumin to creatinine ratios for detection of significant proteinuria or adverse pregnancy outcome in patients with suspected pre-eclampsia: systematic review and meta-analysis. BMJ. 2012;345:e4342. [PMID: 22777026]	Abstract	No point-of-care uACR test assessed
Gialamas A, St John A, Laurence CO, Bubner TK; PoCT Management Committee. Point-of-care testing for patients with diabetes, hyperlipidaemia or coagulation disorders in the general practice setting: a systematic review. Fam Pract. 2010;27:17-24. [PMID: 19969524]	Systematic review	No diagnostic accuracy data
Szymanowicz A, Blanc-Bernard E, Roche C, Neyron MJ, Perrin M, Nourdine K. Évaluation du Micral Test en vue du dépistage de la microalbuminurie en biologie délocalisée. Immunoanalyse et biologie spécialisée. 2008;23:109-15.	Research paper	No point-of-care uACR test assessed
Sarafidis PA, Riehle J, Bogojevic Z, Basta E, Chugh A, Bakris GL. A comparative evaluation of various methods for microalbuminuria screening. Am J Nephrol. 2008;28:324-9. [PMID: 18046079]	Research paper	Reference method not laboratory uACR
Magee LA. Albumin:creatinine ratio using an automated analyser was accurate for diagnosing proteinuria in pregnancy. Evid Based Med. 2008;13:119. [PMID: 18667678]	Commentary	No point-of-care uACR test assessed and reference method not laboratory uACR
Côté AM, Brown MA, Lam E, von Dadelszen P, Firoz T, Liston RM, et al. Diagnostic accuracy of urinary spot protein:creatinine ratio for proteinuria in hypertensive pregnant women: systematic review. BMJ. 2008;336:1003-6. [PMID: 18403498]	Systematic review	No point-of-care uACR test assessed and reference method not laboratory uACR
Lambers Heerspink HJ, Witte EC, Bakker SJ, de Jong PE, de Zeeuw D, Gansevoort RT. Screening and monitoring for albuminuria: the performance of the HemoCue point-of-care system. Kidney Int. 2008;74:377-83. [PMID: 18480748]	Research paper	No point-of-care uACR test assessed and reference method not laboratory uACR
Shemesh T, Rowley KG, Shephard M, Piers LS, O'Dea K. Agreement between laboratory results and on-site pathology testing using Bayer DCA2000+ and Cholestech LDX point-of-care methods in remote Australian Aboriginal communities. Clin Chim Acta. 2006;367:69-76. [PMID: 16388790]	Research paper	No diagnostic accuracy data
Florvall G, Basu S, Helmersson J, Larsson A. Hemocue urine albumin point-of-care test shows strong agreement with the results obtained with a large nephelometer. Diabetes Care. 2006;29:422-3. [PMID: 16443900]	Research paper	No point-of-care uACR test assessed and no diagnostic accuracy data
Waugh JJ, Bell SC, Kilby MD, Blackwell CN, Seed P, Shennan AH, et al. Optimal bedside urinalysis for the detection of proteinuria in hypertensive pregnancy: a study of diagnostic accuracy. BJOG. 2005;112:412-7. [PMID: 15777437]	Research paper	Reference method not laboratory uACR
Burtonwood C, Piggott C, Halloran S. Point of care devices for detection and semi-quantitation of microalbuminuria. Evaluation report 04098. London: MHRA; 2004.	MHRA review	<50 participants
Waugh J, Kilby M, Lambert P, Bell SC, Blackwell CN, Shennan A, et al. Validation of the DCA 2000 microalbumin:creatinine ratio urinanalyzer for its use in pregnancy and preeclampsia. Hypertens Pregnancy. 2003;22:77-92. [PMID: 12648445]	Research paper	No diagnostic accuracy data
Osta V, Natoli V, Diéguez S. [Evaluation of two rapid tests for the determination of microalbuminuria and the urinary albumin/creatinine ratio]. An Pediatr (Barc). 2003;59:131-7. [PMID: 12882741]	Research paper	Reference method for diagnostic accuracy calculations not laboratory uACR
Meinhardt U, Ammann RA, Flück C, Diem P, Mullis PE. Microalbuminuria in diabetes mellitus: efficacy of a new screening method in comparison with timed overnight urine collection. J Diabetes Complications. 2003;17:254-7. [PMID: 12954153]	Research paper	Reference method not laboratory uACR
Pugia MJ, Wallace JF, Lott JA, Sommer R, Luke KE, Shihabi ZK, et al. Albuminuria and proteinuria in hospitalized patients as measured by quantitative and dipstick methods. J Clin Lab Anal. 2001;15:295-300. [PMID: 11574957]	Research paper	No diagnostic accuracy data
Collins AC, Vincent J, Newall RG, Mitchell KM, Viberti GC. An aid to the early detection and management of diabetic nephropathy: assessment of a new point of care microalbuminuria system in the diabetic clinic. Diabet Med. 2001;18:928-32. [PMID: 11703439]	Research paper	Reference method for diagnostic accuracy calculations not laboratory uACR
Ng WY, Lui KF, Thai AC. Evaluation of a rapid screening test for microalbuminuria with a spot measurement of urine albumin-creatinine ratio. Ann Acad Med Singapore. 2000;29:62-5. [PMID: 10748967]	Research paper	Reference method not laboratory uACR
Lum G. How effective are screening tests for microalbuminuria in random urine specimens? Ann Clin Lab Sci. 2000;30:406-11. [PMID: 11045765]	Research paper	No point-of-care uACR test assessed
Pugia MJ, Lott JA, Luke KE, Shihabi ZK, Wians FH Jr, Phillips L. Comparison of instrument-read dipsticks for albumin and creatinine in urine with visual results and quantitative methods. J Clin Lab Anal. 1998;12:280-4. [PMID: 9773958]	Research paper	No diagnostic accuracy data
Hanslik A, Buergstein B, Haering HU, Schmuelling RM, Wahl HG. Evaluation of the point-of-care testing DCA 2000 analyzer for HbA1c measurements in capillary blood and albumin/creatinine in urine. Clin Chem. 1998; 44(suppl):A67.	Abstract	No diagnostic accuracy data
Moore RR Jr, Hirata-Dulas CA, Kasiske BL. Use of urine specific gravity to improve screening for albuminuria. Kidney Int. 1997;52:240-3. [PMID: 9211369]	Research paper	No point-of-care uACR test assessed, reference method not laboratory uACR, and no diagnostic accuracy data

Continued on following page

Appendix Table 3—Continued

Study Citation	Article Type	Reason for Exclusion
Marshall SM. Screening for microalbuminuria: which measurement? Diabet Med. 1991;8:706-11. [PMID: 1838060]	Review	No point-of-care uACR test assessed, reference method not laboratory uACR, and no diagnostic accuracy data
Manegold C, Werle E, Iwand A, Hasslacher C. Evaluation of a new rapid test — Micral-Test® — for the detection of microalbuminuria. Lab Med. 1991;15:384-7.	Research paper	No point-of-care uACR test assessed and reference method not laboratory uACR
Manegold C, Hasslacher P, Wahl P. Micral-test-a new semiquantitative test for detection of microalbuminuria. Kidney Int. 1991;36:1309.	Abstract	No point-of-care uACR test assessed and reference method not laboratory uACR
Irish GR, Madden TM, Snyder TD, Snyder AM. Rapid assays for microalbuminuria on 2 clinical-chemistry analyzers. Clin Chem. 1989;35:1196.	Abstract	No point-of-care uACR test assessed
Bostedt A, Stehle B, Hasslacher C. Screening for microalbuminuria in diabetics — a comparative study relating to new rapid tests. Munch Med Wochenschr. 1989;131:734-6.	Research paper	No point-of-care uACR test assessed
Dezier JF, Calen P. Rapid detection of microalbuminuria by inhibition of latex-particle agglutination compared with an immunonephelometric assay. Diabetes Metab. 1988;14:157.	Abstract	No point-of-care uACR test assessed
Giampietro O, Miccoli R, Clerico A, Di Palma L, Bertolotto A, Anichini R, et al. Rapid detection of microalbuminuria in diabetic patients by an agglutination inhibition test: comparison with radioimmunoassay. J Nucl Med Allied Sci. 1986;30:215-9. [PMID: 3585509]	Research paper	No point-of-care uACR test assessed
Colombo JP. [Rapid urine test]. Ther Umsch. 1971;28:653-7. [PMID: 5126000]	Review	No point-of-care uACR test assessed
Guy M, Borzomato JK, Newall RG, Price CP, Kalra PA. Albumin:creatinine ratios measured by the Bayer DCA 2000+ analyzer accurately predict 24 hour urine albumin excretion in renal patients. Clin Chem. 2007;53(suppl):A215.	Abstract	No diagnostic accuracy data and reference method not laboratory uACR
Luke PE, Pugia MJ. Evaluation of an albumin and creatinine reagent strip using the Bayer Clinitek 50 urine chemistry analyzer system. Clin Chem. 1997;43:60.	Abstract	No diagnostic accuracy data
Nagrebetsky A, Jin J, Stevens R, James T, Adler A, Park P, et al. Diagnostic accuracy of urine dipstick testing in screening for microalbuminuria in type 2 diabetes: a cohort study in primary care. Fam Pract. 2013;30:142-52. [PMID: 22990027]	Research paper	Point-of-care uACR test result read visually

MHRA = Medicines and Healthcare Products Regulatory Agency; uACR = urinary albumin–creatinine ratio.

Appendix Table 4. Diagnostic Accuracy Estimates of uACR Point-of-Care Tests From Included Studies

Study, Year (Reference)	Test Assessed*	Operator	Patients, *n*	Prevalence of Albuminuria, %†	uACR Threshold, *mg/mmol*	Sensitivity, %	Specificity, %	LR+	LR−
Lloyd et al, 2011 (30)	Clinitek	Laboratory	204	36.3	≥3.4	83.8	93.8	13.6	0.17
Kouri et al, 2009 (31)	Aution	Laboratory	368	70.1	≥3.4	95.3	80.9	5.0	0.06
Guy et al, 2009 (32)	Clinitek	Laboratory	86	65.1	≥3.4	92.9	60.0	2.3	0.12
Guy et al, 2009 (32)	DCA	Laboratory	86	65.1	≥3.4	96.4	100.0	+‡	0.04
Graziani et al, 2009 (33)	Clinitek	Laboratory	259	18.1	≥3.4	91.5	91.5	10.8	0.09
Khawali et al, 2002 (34)	DCA	Clinical	55	7.3	≥3.4	50.0	100.0	+‡	0.5
Pickersgill et al, 2001 (35)	Clinitek	Laboratory	87	23.2	≥3.4	56.0	97.0	18.7	0.45
Pickersgill et al, 2001 (35)	Clinitek	Clinical	95	23.2	≥3.4	18.0	95.0	3.3	0.87
Le Floch et al, 2001 (36)	Clinitek	Clinical	302	17.0	≥3.4	79.0	81.0	4.2	0.26
Croal et al, 2001 (37)	Clinitek	Clinical	252	20.6	≥3.4	75.0	94.0	4.2	0.27
Shephard et al, 1999 (38)	DCA	Laboratory	60	43.3	≥3.4	100.0	96.0	25.0	0.0
Parsons et al, 1999 (39)	DCA	Laboratory	96	8.3	≥2.7	100.0	92.0	12.5	0.0
Parsons et al, 1999 (40)	Clinitek	Laboratory	144	55.6	≥3.4	76.3	89.1	7.0	0.27
Poulsen and Mogensen, 1998 (41)	DCA	Clinical	195	40.5	≥2.5/≥3.5§	91.1	98.3	52.9	0.09
McTaggart et al, 2012 (42)	Clinitek	Clinical	619	20.2	≥3.4	83.2	80.0	4.2	0.21
Davidson and Croal, 2003 (43)	Clinitek	Clinical	621	19.8	≥3.4	65.9	100.0	+‡	0.34

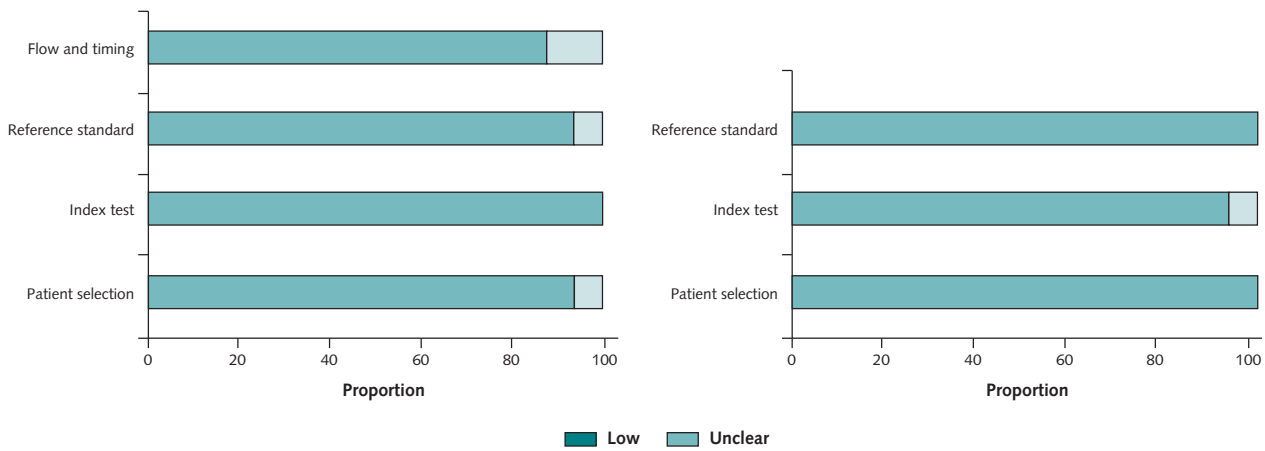
LR− = negative likelihood ratio; LR+ = positive likelihood ratio; uACR = urinary albumin–creatinine ratio.
* Clinitek and DCA were manufactured by Siemens HealthCare Diagnostics (Tarrytown, New York); Aution was manufactured by Arkray (Kyoto, Japan).
† Defined as percentage of samples with uACR above the cutoff used, as measured by the reference method.
‡ Could not be calculated because specificity was 100%.
§ For men/women.

Appendix Table 5. Summary of QUADAS-2 Assessment of Included Studies

Study, Year (Reference)	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Lloyd et al, 2011 (30)	Low	Low	Low	Low	Low	Low	Low
Kouri et al, 2009 (31)	Low	Low	Low	Low	Low	Unclear	Low
Guy et al, 2009 (32)	Low	Low	Low	Low	Low	Low	Low
Guy et al, 2009 (32)	Low	Low	Low	Low	Low	Low	Low
Graziani et al, 2009 (33)	Low	Low	Low	Low	Low	Low	Low
Khawali et al, 2002 (34)	Unclear	Low	Low	Low	Low	Low	Low
Pickersgill et al, 2001 (35)	Low	Low	Low	Low	Low	Low	Low
Pickersgill et al, 2001 (35)	Low	Low	Low	Low	Low	Low	Low
Le Floch et al, 2001 (36)	Low	Low	Unclear	Unclear	Low	Low	Low
Croal et al, 2001 (37)	Low	Low	Low	Low	Low	Low	Low
Shephard et al, 1999 (38)	Low	Low	Low	Unclear	Low	Low	Low
Parsons et al, 1999 (39)	Low	Low	Low	Low	Low	Low	Low
Parsons et al, 1999 (40)	Low	Low	Low	Low	Low	Low	Low
Poulsen and Mogensen, 1998 (41)	Low	Low	Low	Low	Low	Low	Low
McTaggart et al, 2012 (42)	Low	Low	Low	Low	Low	Low	Low
Davidson and Croal, 2003 (43)	Low	Low	Low	Low	Low	Low	Low

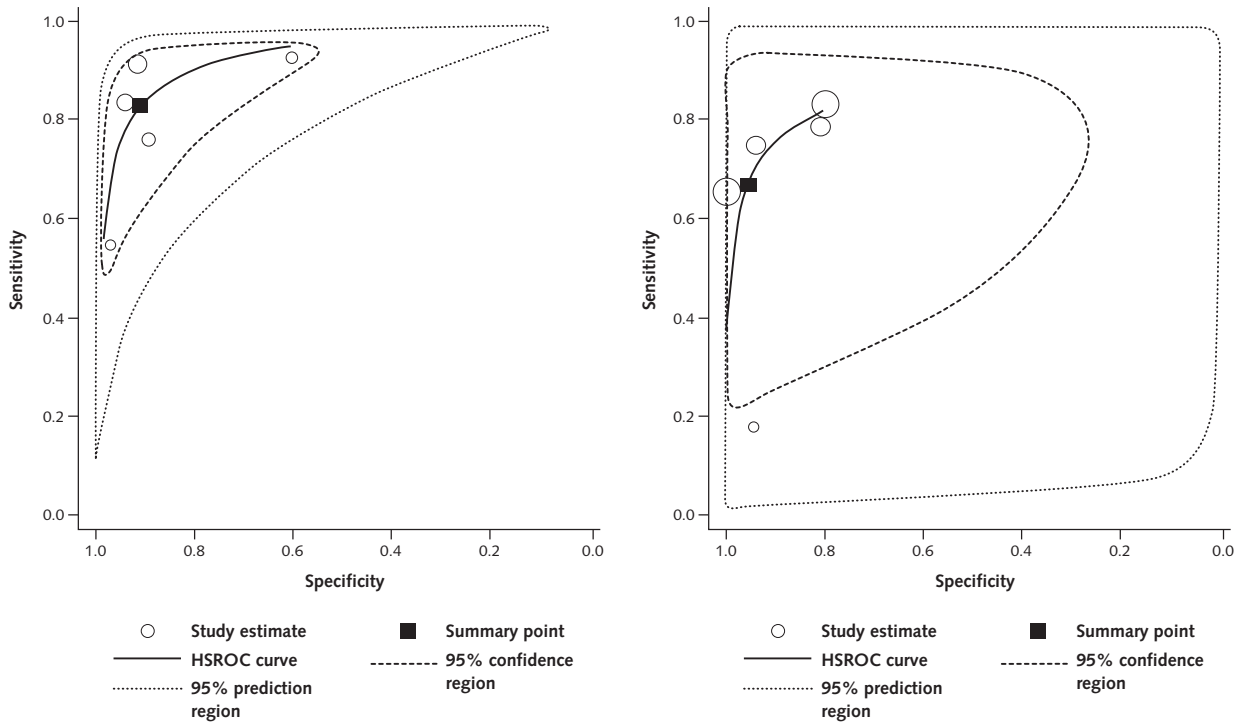
QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies 2.

Appendix Figure 2. Bar charts for QUADAS-2 analysis.



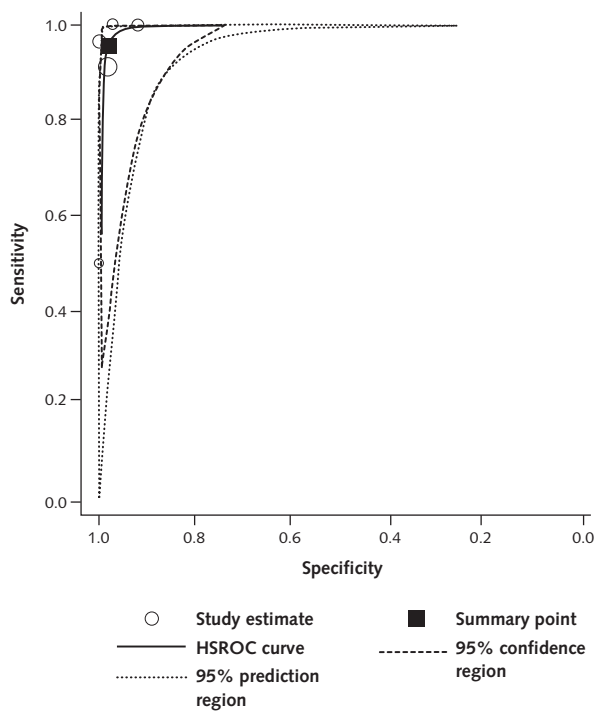
Risk of bias (*left*) and applicability concerns (*right*) were assessed by 2 independent investigators using a QUADAS-2 questionnaire across the domains shown, with arbitration on disagreements by a third investigator. QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies 2.

Appendix Figure 3. **HSROC curve plots for semiquantitative test.**



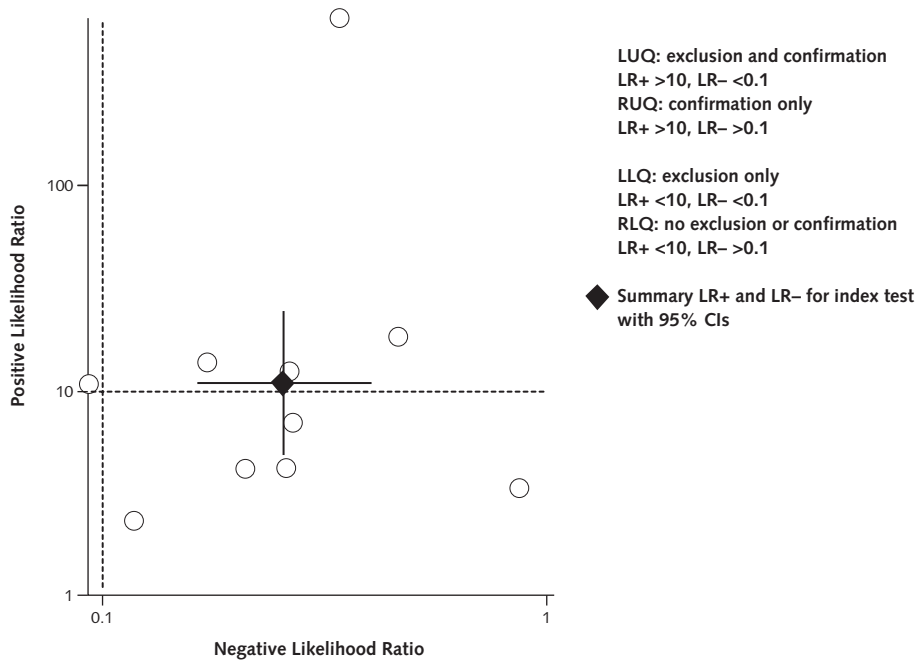
Plots for laboratory operators (*left*) and clinical operators (*right*) are shown. HSROC = hierarchical summary receiver-operating characteristic.

Appendix Figure 4. **HSROC curve plot for quantitative assay studies.**



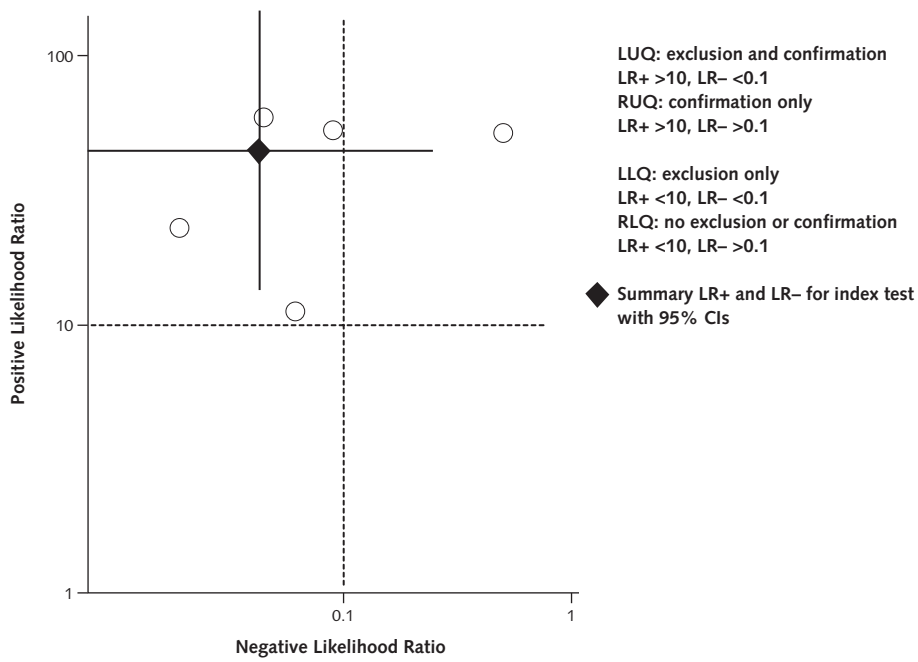
HSROC = hierarchical summary receiver-operating characteristic.

Appendix Figure 5. **Likelihood ratio scattergram for semiquantitative test.**



LLQ = left lower quadrant; LR− = negative likelihood ratio; LR+ = positive likelihood ratio; LUQ = left upper quadrant; RLQ = right lower quadrant; RUQ = right upper quadrant.

Appendix Figure 6. **Likelihood ratio scattergram for quantitative test.**



LLQ = left lower quadrant; LR− = negative likelihood ratio; LR+ = positive likelihood ratio; LUQ = left upper quadrant; RLQ = right lower quadrant; RUQ = right upper quadrant.