

# Systematic Review: Noninvasive Testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*

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**Background:** Testing of urine samples is noninvasive and could overcome several barriers to screening for chlamydial and gonococcal infections, but most test samples are obtained directly from the cervix or urethra.

**Purpose:** To systematically review studies that assessed the sensitivity and specificity of nucleic acid amplification tests for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in urine specimens and to compare test characteristics according to type of assay, site of sample collection, presence of symptoms, disease prevalence, and characteristics of the reference standard.

**Data Sources:** Relevant studies in all languages were identified by searching the MEDLINE database (January 1991 to December 2004) and by hand-searching the references of identified articles and relevant journals.

**Study Selection:** Studies were selected that evaluated 1 of 3 commercially available nucleic acid amplification tests, included data from tests of both a urine sample and a traditional sample (obtained from the cervix or urethra), and used an appropriate reference standard.

**Data Extraction:** From 29 eligible studies, 2 investigators independently abstracted data on sample characteristics, reference standard, sensitivity, and specificity.

**Data Synthesis:** Articles were assessed qualitatively and quantitatively. Summary estimates for men and women were calculated separately for chlamydial and gonococcal infections and were stratified by assay and presence of symptoms. The pooled study

specificities of each of the 3 assays exceeded 97% when urine samples were tested, for both chlamydial infection and gonorrhea and in both men and women. The pooled study sensitivities for the polymerase chain reaction, transcription-mediated amplification, and strand displacement amplification assays, respectively, were 83.3%, 92.5%, and 79.9% for chlamydial infections in women; 84.0%, 87.7%, and 93.1% for chlamydial infections in men; and 55.6%, 91.3%, and 84.9% for gonococcal infections in women. The pooled specificity of polymerase chain reaction to gonococcal infections in men was 90.4%. In subgroup analyses, the sensitivity did not vary according to the prevalence of infection or the presence of symptoms but did vary according to the reference standard used.

**Limitations:** Few published studies present data on the transcription-mediated amplification or strand displacement amplification assays, and few studies report data from asymptomatic patients or low-prevalence groups.

**Conclusions:** Results of nucleic acid amplification tests for *C. trachomatis* on urine samples are nearly identical to those obtained on samples collected directly from the cervix or urethra. Although all 3 assays can also be used to test for *N. gonorrhoeae*, the sensitivity of the polymerase chain reaction assay in women is too low to recommend its routine use to test for gonorrhea in urine specimens.

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**C***hlamydia trachomatis* and *Neisseria gonorrhoeae* infections are among the most common bacterial sexually transmitted infections worldwide (1). In the United States, experts estimate an annual incidence of 2.8 million new chlamydial infections and 720 000 new gonococcal infections, the majority of which are asymptomatic (2). Nearly every major U.S. public health organization now recommends routine screening of sexually active young women for chlamydial infection (3–5). Screening young women for chlamydia has been shown to be a cost-effective method of preventing pelvic inflammatory disease, which is a major cause of infertility and chronic pelvic pain (6). Although the proportion of women who are screened appears to be increasing, 60% or fewer women at risk undergo screening (7, 8).

In many settings, the prevalence of chlamydial infection in asymptomatic young men is around 3% to 5% (9–11). The screening of young men may be needed as part of a strategy to prevent chlamydial infection in young women, but little evidence is available to support recommendations for or against screening of men. Nonetheless,

in both men and women, chlamydial and gonococcal infections are associated with a 3-fold to 6-fold increase in the risk for transmission or acquisition of HIV (12).

Traditional methods of screening for chlamydial infection require a speculum examination in women and insertion of 1 or more swabs into the urethra in men. Not only are these screening methods embarrassing and uncomfortable, but they also require a clinic visit and use of an examination room, sterile equipment, gowns, and trained clinicians.

See also:

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Editors' Notes . . . . . 915

## Web-Only

Appendix Tables

Conversion of figures and tables into slides

CME Quiz

Noninvasive screening options, such as urine testing or self-collected vaginal swabs, could eliminate some of the barriers to screening for chlamydial infection. Noninvasive methods are clearly preferred by patients (13, 14) and could substantially increase the acceptability and convenience of screening in a variety of settings. Urine-based screening has been used to identify infections in young women in primary care settings who are not receiving pelvic examinations (15) and can increase the proportion of sexually active young persons who receive chlamydial screening in clinical practices (16). Therefore, replacing invasive screening procedures with noninvasive screening procedures might improve adherence with screening guidelines.

Several newly developed nucleic acid amplification tests that use noninvasive samples have been evaluated. Previous reviews of various types of tests for chlamydia concluded that nucleic acid amplification tests have superior sensitivity (17–19) but did not specifically address the question of whether tests on noninvasively obtained samples are as accurate as those obtained with cervical or urethral samples.

No widely accepted guidelines exist for screening for gonorrhea. However, each of the commercially available nucleic acid amplification tests can evaluate for *C. trachomatis* and *N. gonorrhoeae* in the same specimen. This combination testing option makes it convenient for many clinicians to test for chlamydial infection and gonorrhea simultaneously. The literature on these assays can be confusing because the study samples and reference standards used differ greatly.

We conducted a systematic review of the literature on the sensitivity and specificity of urine-based nucleic acid amplification tests for *C. trachomatis* and *N. gonorrhoeae*. We specifically sought to compare the results obtained with urine samples to those obtained with cervical and urethral samples and to further analyze the results according to type of assay, sample characteristics, and reference standard used.

## METHODS

We based our review strategy on several articles that outline procedures for conducting systematic reviews and meta-analyses, including the QUORUM guidelines for reporting of meta-analyses (20) and general guidelines for systematic reviews of diagnostic tests (21–24).

### Literature Search

We searched the MEDLINE database for articles published from 1 January 1991 to 31 December 2004. We specifically sought articles that contained the Medical Subject Headings Chlamydia trachomatis, *chlamydial infections* (*not pneumoniae*), or *Neisseria gonorrhoeae* and also included the terms *nucleic acid amplification techniques* or *polymerase chain reaction* or the text words *strand displacement*, *transcription-mediated*, or *polymerase*. Additional arti-

### Context

Can nucleic acid amplification tests on urine samples replace cervical and urethral samples to screen for chlamydia and gonorrhea?

### Contribution

Pooled data from 29 studies showed that 3 commercially available nucleic acid amplification tests had high specificity (>95%) for detecting chlamydia and gonorrhea. Sensitivity was reasonably high (approximately 80% to 93%), except for polymerase chain reaction (PCR) for gonococcal infections in women (approximately 56%).

### Limitations

Few studies tested transcription-mediated amplification and strand displacement amplification assays.

### Implications

Nucleic acid amplification tests are easily obtainable noninvasive tests on urine samples that detect chlamydia and gonorrhea reasonably well. However, negative results on PCR assays on urine samples are not useful to rule out gonococcal infections in women.

—The Editors

cles were identified through references of relevant articles and a hand search through January 2005 of the 3 journals in which articles on these topics most commonly appeared (*Journal of Clinical Microbiology*, *Sexually Transmitted Diseases*, and *Sexually Transmitted Infections*).

### Study Selection

We selected studies that evaluated 1 of 3 commercially available nucleic acid amplification tests, presented data separately by sex, included data obtained from the same assay on both a urine sample and a traditional sample (obtained from the cervix or urethra), and used an appropriate reference standard. We excluded studies that used a nucleic acid amplification test that is not commercially available, including studies that evaluated the ligase chain reaction assay (which was removed from the commercial market in 2002). We also excluded some studies in which data were obtained from urine samples only because one of our main objectives was to determine whether such results were similar to those obtained from cervical or urethral samples.

The choice of an appropriate reference standard is complicated because the nucleic acid amplification tests under evaluation are generally more sensitive than the other diagnostic methods that could be used for reference standards. The choice is also complicated by the fact that both *C. trachomatis* and *N. gonorrhoeae* can simultaneously infect multiple anatomic sites. In some women, chlamydia can be detected only in the cervix. In others, it can be detected only in the urethra or urine. The diagnostic test must therefore be able to detect the maximum number of infected persons who require treatment.

In evaluating reference standards, we included studies in which 2 conditions were met. First, samples must have been collected from at least 2 anatomic sites, including the cervix in women or the urethra in men. In addition, the reference standard required confirmation by culture (which most experts consider to be 100% specific) or by at least 1 additional nucleic acid amplification test that differed from the test under evaluation (to ensure acceptable sensitivity of the reference standard). Examples of reference standards that did not meet our site and test criteria included urine tests that were compared only with other urine tests, nucleic acid amplification tests that were compared only with culture or other less-sensitive assays, and nucleic acid amplification tests that were confirmed by the same test under evaluation but at a different anatomic site.

### Data Extraction and Validity Assessment

Two of the authors independently read each eligible article and extracted detailed information on the study sample, test characteristics, reference standard, and results. If a study included results from both symptomatic and asymptomatic patients, we included both sets of results. If a study presented data obtained by using more than 1 reference standard, we selected the results that were most consistent with the reference standard criteria outlined earlier.

Several guidelines suggest criteria to evaluate validity and report results of diagnostic test studies, although there is no consensus on which criteria are most important for study validity (21–24). We abstracted information that was consistently noted in these reports, including whether the study sample was clearly defined and not already known to have the condition, whether the reference standard tests were conducted without knowledge of the test under evaluation, whether all participants received the same diagnostic evaluation, and whether the reference standard was clearly defined.

For each study, we calculated 95% CIs for sensitivity and specificity by using the binomial distribution. We calculated positive likelihood ratios by using the following formula: sensitivity/(1–corresponding specificity). We calculated negative likelihood ratios by using the following formula: (1–sensitivity)/specificity. To calculate likelihood ratios, we converted sensitivities or specificities of 1.0 to 0.9999.

### Data Synthesis

Studies were assessed qualitatively and quantitatively. The qualitative assessment identified potential sources of heterogeneity, which included different types of assays, sex of study participants, and presence or absence of symptoms in the sample. We therefore aimed to stratify studies into groups with clinically similar tests, participants, and infections (25).

Our initial intent was to synthesize study results by constructing a summary receiver-operating characteristic curve (26, 27). This method is a particularly robust way of synthesizing diagnostic test information across studies be-

cause it is relatively insensitive to the particular test threshold that was evaluated in an individual study. However, the studies included in our systematic review reported specificities that were remarkably uniform, suggesting little variation among the test thresholds that were evaluated. Under this circumstance, a summary receiving-operating characteristic curve is difficult to interpret and offers no methodologic advantage over threshold-dependent measures (sensitivity and specificity).

We calculated summary estimates for sensitivity and specificity and their corresponding 95% CIs by using Intercooled Stata, version 7.0 (Stata Corp., College Station, Texas). We made separate calculations for chlamydial infections and gonococcal infections and stratified them by sex. Summary estimates were calculated separately for each type of assay (polymerase chain reaction [PCR], transcription-mediated amplification, and strand displacement amplification). Each of these analyses was conducted separately for noninvasive testing methods (on urine samples) and for traditional testing methods (on samples obtained from the cervix or urethra).

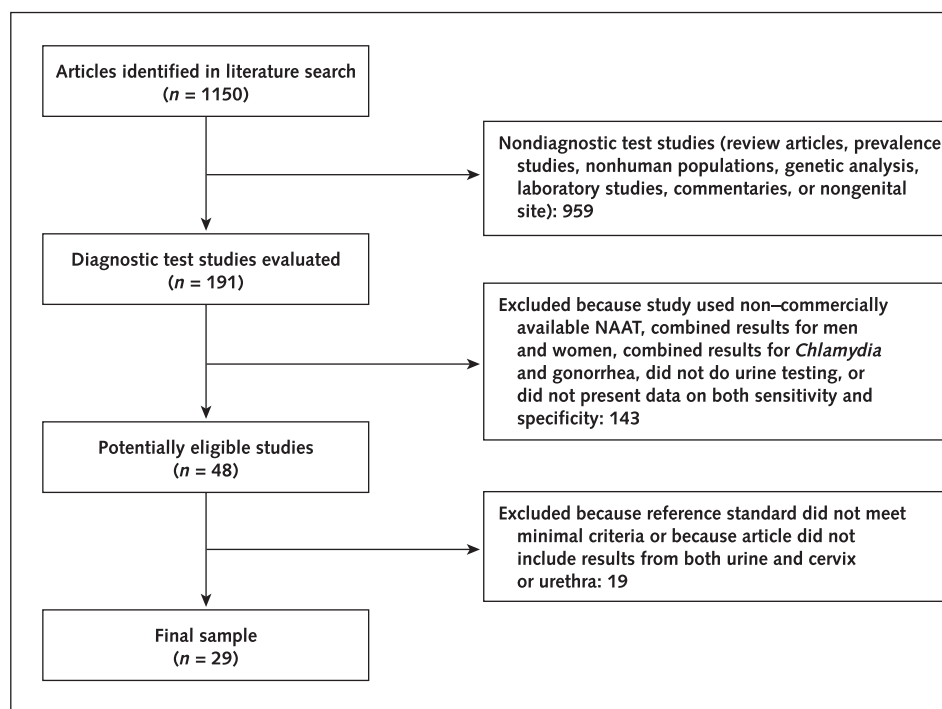
Preliminary analyses suggested statistical heterogeneity among some of the groups of studies that we analyzed. This finding was somewhat expected because our analyses involved many studies with large samples, a circumstance that increases the likelihood of statistically significant but clinically insignificant heterogeneity (25). Because of this heterogeneity, we used the random-effects method of DerSimonian and Laird to calculate summary estimates (28). Random-effects methods are more conservative than fixed-effects methods and yield larger CIs because they explicitly consider the possibility that each study may be measuring a separate “true effect.” These methods provide pooled estimates that are weighted for sample size.

Because more studies evaluated the PCR assay for chlamydia, we conducted additional sensitivity analyses for this assay to determine whether sensitivity or specificity varied according to the prevalence of disease in the sample ( $\leq 5\%$  or  $> 5\%$ ). We also explored the potential impact of differences in the definition of the reference standard by comparing reference standards that varied by the total number of tests done in each participant ( $\leq 3$  or  $\geq 4$ ) and by the type of testing done in women (testing only of urine and cervical samples or additional testing of urethral or vaginal samples). All but 1 study of the PCR assay reported that additional tests were conducted in some but not all participants. Therefore, we could not examine the impact of this discrepant analysis on the reference standard.

### Role of the Funding Source

The funding agency played no role in design of the study; the collection, analysis, or interpretation of the data; the writing of the report; or decisions about whether to submit the report for publication.

Figure 1. Search strategy for reports evaluated for inclusion.



NAAT = nucleic acid amplification test.

## RESULTS

The search strategy identified 29 eligible articles (Figure 1). Of these articles, 20 assessed chlamydial infections in women (29–48), 15 assessed chlamydial infections in men (34–39, 41, 44, 45, 47, 49–53), 6 assessed gonococcal infections in women (34, 39, 46, 47, 54, 55), and 4 assessed gonococcal infections in men (34, 39, 53, 56). Appendix Tables 1, 2, and 3 show characteristics of the studies.

The samples varied widely and included participants in North America, Europe, Africa, and Australia. The majority of studies included persons seeking evaluation at sexually transmitted disease clinics, whereas the remainder included persons who presented at gynecology clinics or other primary care settings. Most studies included a mixture of symptomatic and asymptomatic persons, although a few studies reported results separately for symptomatic and asymptomatic persons. The overall prevalence of disease varied from 3.3% to 21.5% for chlamydial infections and from 1.2% to 24% for gonococcal infections.

All studies that we included met our basic criteria for reference standards, but the specific reference standard used varied widely. Differences included the specific test used for comparison (some studies used 1 or more alternative nucleic acid amplification tests in all patients), the number of anatomic sites tested (in some women, additional test samples were collected from the urethra or vagina), the total number of tests conducted in all participants (3 to 8), and the use of discrepant analysis.

The specificity of the assays was uniformly high for

both chlamydial infection and gonorrhea, whereas the sensitivity varied from study to study. Figures 2 through 4 show the sensitivity and 95% CIs for each study, grouped by noninvasively or invasively obtained test samples from the same study and tested with the same assay. Detailed results of each individual study, including the sensitivity and specificity, positive and negative likelihood ratios, and the raw data used to calculate these operating characteristics, are included in Appendix Tables 4, 5, and 6.

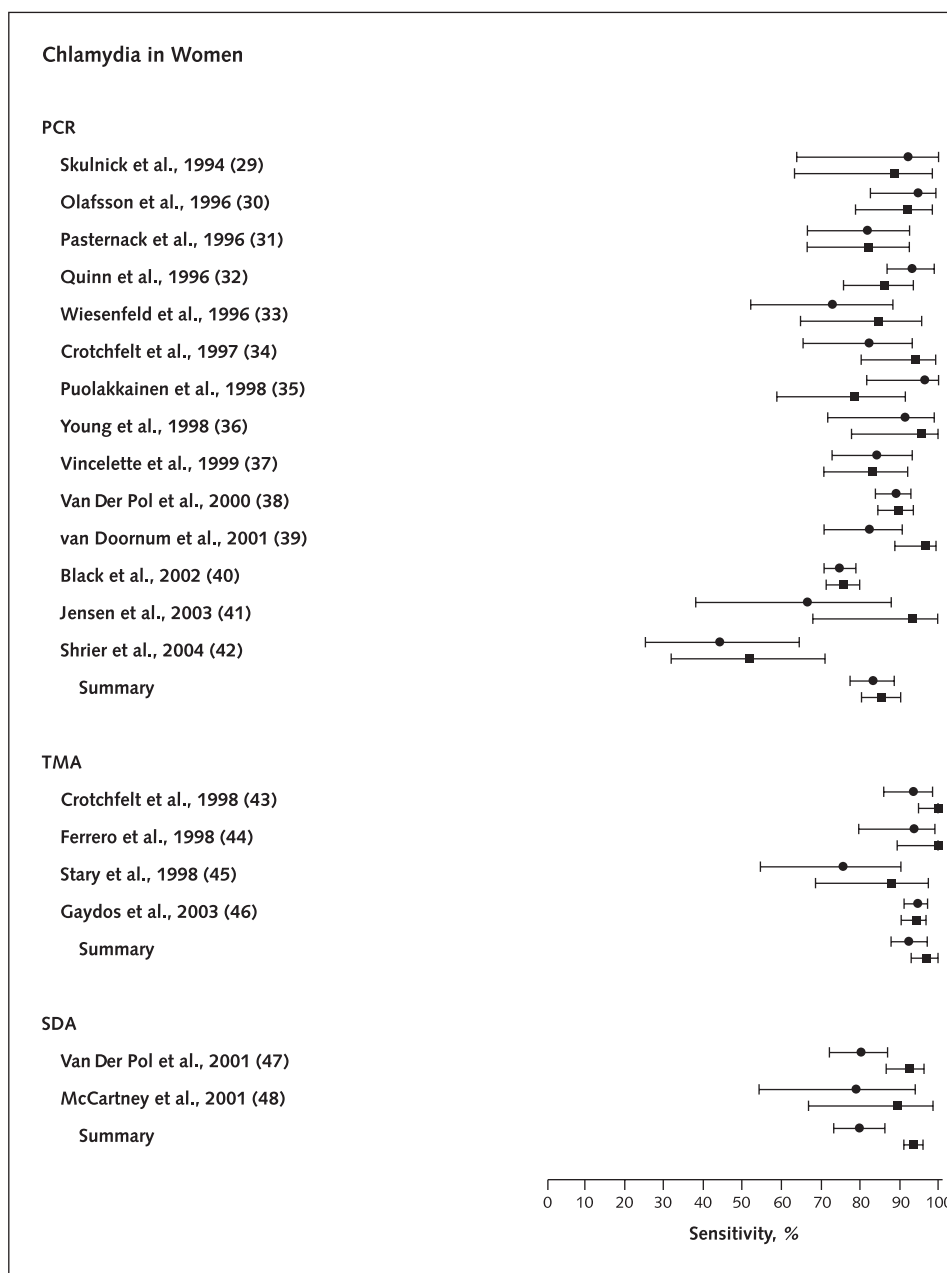
## Tests for *Chlamydia trachomatis*

### Women

For the 14 studies of PCR, the pooled sensitivity and specificity were 83.3% (95% CI, 77.7% to 88.9%) and 99.5% (CI, 99.3% to 99.8%) for urine samples and 85.5% (CI, 80.3% to 90.6%) and 99.6% (CI, 99.4% to 99.8%) for cervical samples (Figure 2). For the 4 studies of the transcription-mediated amplification assay, the pooled sensitivity and specificity were 92.5% (CI, 88.0% to 97.0%) and 98.6% (CI, 97.7% to 99.6%) for urine samples and 96.7% (CI, 93.0% to 100%) and 99.1% (CI, 98.2% to 100%) for cervical samples. For the 2 studies of the strand displacement amplification assay, the pooled sensitivity and specificity were 79.9% (CI, 73.3% to 86.4%) and 99.1% (CI, 97.7% to 100%) for urine samples and 93.6% (CI, 91.2% to 96.1%) and 97.9% (CI, 97.3% to 98.5%) for cervical samples.

Three studies, each of which involved the PCR assay, reported data separately for symptomatic women and

Figure 2. Sensitivity of nucleic acid amplification tests for *Chlamydia trachomatis* in women.



Circles represent results of urine tests, and squares represent results from the cervix. The bars represent 95% CIs. PCR = polymerase chain reaction; SDA = strand displacement amplification; TMA = transcription-mediated amplification.

asymptomatic women. In each of these studies, the results were nearly identical in the 2 groups (**Appendix Table 4**). Additional sensitivity analyses of the PCR assay showed that the pooled sensitivity in the 2 studies with a disease prevalence of less than 5% was 85.8% (CI, 77.5% to 94.0%) and that the pooled sensitivity in the 12 studies with a disease prevalence of 5% or greater was 82.7% (CI, 76.3% to 89.0%). Less comprehensive reference standards generally led to higher overall sensitivities. The 10 studies in which test samples were collected from only 2 sites (urine and cervix) had a pooled sensitivity of 86.7% (CI, 81.0% to 92.4%), whereas the 4 studies that also collected

samples from the urethra or vagina had a pooled sensitivity of 68.8% (CI, 48.7% to 88.9%). Similarly, the 8 studies in which only 3 specimens were collected from each participant had a pooled sensitivity of 87.1% (CI, 80.5% to 93.6%), whereas the 6 studies in which 4 to 8 specimens were collected from each participant had a pooled sensitivity of 75.3% (CI, 62.6% to 88.0%).

**Men**

For the 12 studies of the PCR assay, the pooled sensitivity and specificity were 84.0% (CI, 78.5% to 89.4%)

and 99.3% (CI, 98.9% to 99.7%) for urine samples and 87.5% (CI, 82.4% to 92.5%) and 99.2% (CI, 98.8% to 99.6%) for urethral samples. For the 2 studies of the transcription-mediated amplification assay, the pooled sensitivity and specificity were 87.7% (CI, 80.1% to 95.2%) and 99.4% (CI, 98.7% to 100%) for urine samples and 95.9% (CI, 91.3% to 100%) and 99.4% (CI, 98.7% to 100%) for urethral samples. For the 1 study of strand displacement amplification, the sensitivity and specificity were 93.1% (CI, 87.7% to 96.7%) and 93.8% (CI, 90.7% to 95.1%) for urine samples and 92.4% (CI, 86.8% to 96.2%) and 96.3% (CI, 94.3% to 97.8%) for urethral samples.

No study of the PCR assay to detect chlamydia in men was done in a sample in which the disease prevalence was less than 5%. Two studies presented results separately for symptomatic men and asymptomatic men, and the results were nearly identical (Appendix Table 5). The 6 studies in which only 3 test specimens were collected from each par-

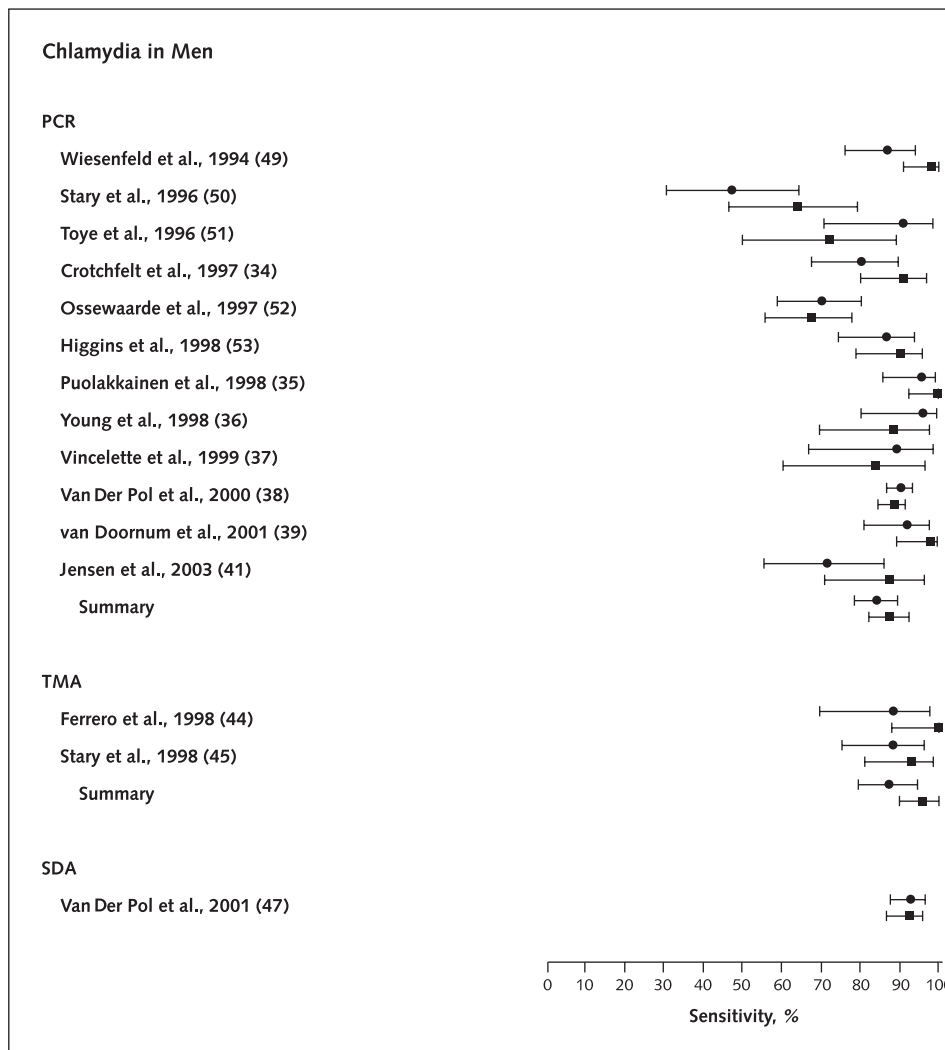
ticipant had a pooled sensitivity of 89.1% (CI, 86.8% to 92.0%), whereas the 5 studies in which 4 or more specimens were collected had a pooled sensitivity of 80.0% (CI, 67.4% to 92.6%).

**Tests for *Neisseria gonorrhoeae***

**Women**

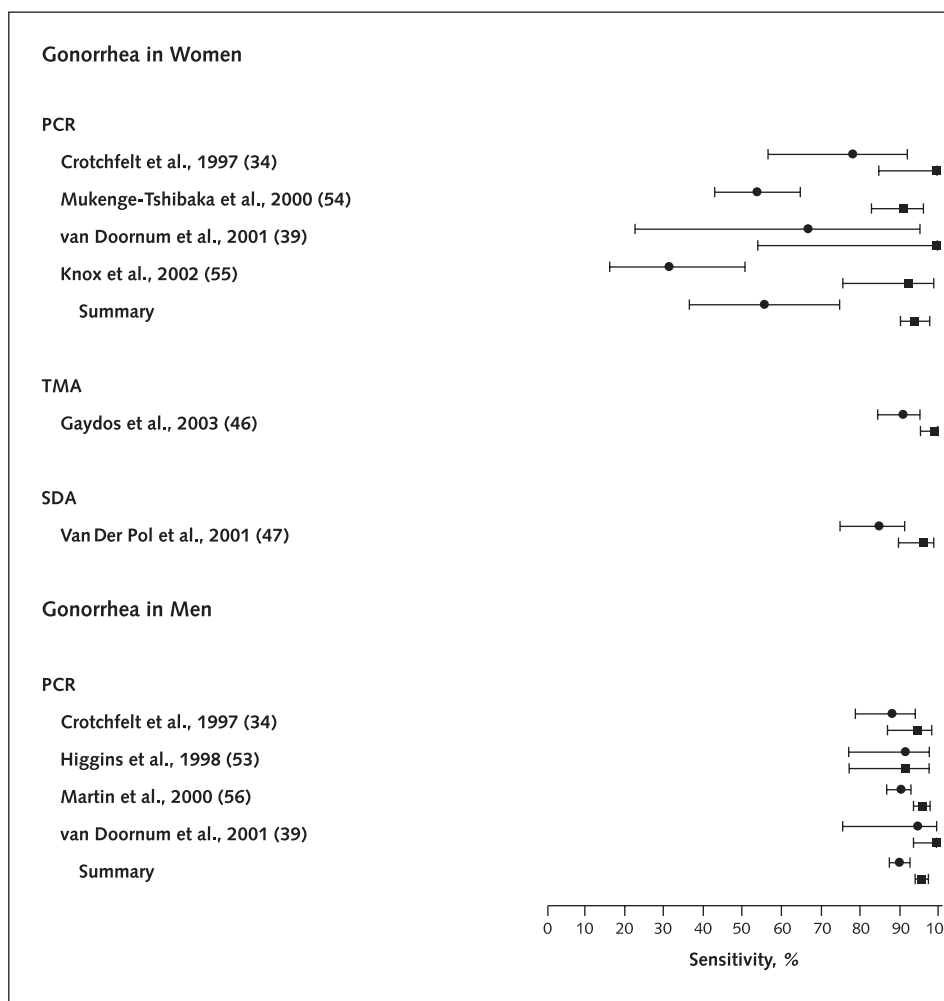
For the 4 studies of the PCR assay, the pooled sensitivity and specificity were 55.6% (CI, 36.3% to 74.9%) and 98.7% (CI, 97.5% to 99.9%) for urine samples and 94.2% (CI, 90.5% to 98.0%) and 99.2% (CI, 98.4% to 100%) for cervical samples. For the study of the transcription-mediated amplification assay, the sensitivity and specificity were 91.3% (CI, 85.0% to 95.6%) and 99.3% (CI, 98.6% to 99.6%) for urine samples and 99.2% (CI, 95.7% to 100%) and 98.7% (CI, 98.0% to 99.3%) for cervical samples. For the study of strand displacement amplification, the sensitivity and specificity were 84.9% (CI, 75.6%

Figure 3. Sensitivity of nucleic acid amplification tests for *Chlamydia trachomatis* in men.



Circles represent results of urine tests, and squares represent results from the urethra. The bars represent 95% CIs. PCR = polymerase chain reaction; SDA = strand displacement amplification; TMA = transcription-mediated amplification.

Figure 4. Sensitivity of nucleic acid amplification tests for *Neisseria gonorrhoeae* in women and men.



Circles represent results of urine tests, and squares represent results from the cervix (in women) or urethra (in men). The bars represent 95% CIs. PCR = polymerase chain reaction; SDA = strand displacement amplification; TMA = transcription-mediated amplification.

to 91.7%) and 99.4% (CI, 98.9% to 99.8%) for urine samples and 96.5% (CI, 90.1% to 99.3%) and 99.5% (CI, 99.0% to 99.8%) for cervical samples. No study of tests for gonorrhea presented data separately for asymptomatic and symptomatic women.

**Men**

Only 4 studies met our eligibility criteria for *N. gonorrhoeae* testing in men, all of which used the PCR assay. The pooled sensitivity and specificity were 90.4% (CI, 87.9% to 92.9%) and 99.7% (CI, 99.4% to 100%) for urine samples and 96.1% (CI, 94.4% to 97.7) and 99.0% (CI, 98.2% to 99.8%) for urethral samples. In the study that reported data separately by symptoms, the sensitivity was somewhat lower in asymptomatic men than in symptomatic men (Appendix Table 6).

**DISCUSSION**

For each of the 3 commercially available nucleic acid amplification tests for *C. trachomatis*, the sensitivity and

specificity of tests on noninvasively obtained samples (urine specimens) were nearly identical to those of tests on invasively obtained samples. This finding was true for men and women and did not vary by the presence or absence of clinical symptoms. When used to detect chlamydia in all types of samples, nucleic acid amplification tests have been reported to be more sensitive than non-nucleic acid amplification tests (17, 18), which continue to be used in the majority of public health laboratories in the United States (57). Indeed, no commercially available non-nucleic acid amplification test has been found to have sufficient sensitivity to recommend its use on urine samples (17, 18).

In women, the sensitivity and specificity of the PCR assay to detect *N. gonorrhoeae* were significantly lower when urine samples rather than cervical samples were used. This difference did not appear to be present for the transcription-mediated amplification and strand displacement amplification assays, although we examined only 1 study of each of these assays to detect gonorrhea in women. Overall

results of gonorrhea testing in men were similar for urine and urethral samples. However, the only study that presented data separately in asymptomatic and symptomatic men reported lower sensitivity in the asymptomatic group. Additional data on all 3 assays are needed to make more definitive conclusions about urine testing for gonorrhea in asymptomatic men and women.

Although our review focused on results from urine samples, self-collected vaginal swabs are another noninvasive method of sample collection that can be considered in women. Two studies in our review also presented results from self-collected vaginal swabs (33, 40). Both of these studies used the PCR assay for *C. trachomatis*, and the sensitivities for vaginal swab samples were nearly identical to those for cervical samples. Recent studies of other types of assays have also shown that results obtained with vaginal specimens are nearly identical (if not superior) to the results obtained with cervical specimens (58, 59). In fact, the transcription-mediated amplification assay was recently approved by the U.S. Food and Drug Administration for chlamydial and gonococcal testing of vaginal samples.

What are the advantages of testing based on noninvasively obtained samples? Noninvasive specimen collection is preferred by patients (13, 14); requires less specialized personnel and equipment; and can be performed in settings in which people do not traditionally receive genitourinary examinations, such as high schools (13), youth detention centers (60), and primary care clinics (15). A recent clinical trial demonstrated that the proportion of sexually active teenage girls who received recommended screening for chlamydial infection increased from about 8% to more than 40% when screening involved the collection of a urine specimen rather than the collection of a cervical sample (16). Noninvasively obtained samples can be sent through the mail, which may further increase opportunities for screening (61–63).

## Limitations of Diagnostic Test Results Reported in the Literature

### Imperfect Reference Standards

No consensus exists on an appropriate reference standard for nucleic acid amplification tests for chlamydial infection or gonorrhea, nor is there a well-defined clinical state that allows differentiation between sick and healthy persons. In addition, the nucleic acid amplification tests under evaluation are generally more sensitive than the earlier tests used for the reference standard. Erroneous conclusions will be made if the experimental test determines the presence or absence of disease better than the reference standard (64). Even when the test under evaluation is compared with 1 or more additional nucleic acid amplification tests, variation in the sensitivity and specificity of the comparator tests could greatly affect the performance estimates of the other test.

An excellent experimental test could appear to have poor specificity if the test correctly identifies disease as

present but the reference standard misclassifies the disease as absent. This issue has been particularly important for evaluation of nucleic acid amplification tests when the experimental test was compared only with a relatively insensitive reference standard, such as culture. Along the same lines, the sensitivity of an excellent experimental test could appear to be poor if the result is negative but the reference test incorrectly classifies a disease as present.

Conversely, a poor experimental test could appear to have excellent specificity or sensitivity if it and the reference test have similar misclassification errors. Such errors occur when the experimental test is not independent of the reference test, which is more likely if the 2 tests use similar methods; measure the same physiologic or anatomic changes; or are affected by the stage of illness, disease severity, or other covariates (64).

Because culture alone was an insensitive reference standard, many investigators initially attempted to avoid misclassification by using additional testing to confirm a positive result on an experimental test when the reference standard was negative (that is, discrepant analysis). Most experts argue that discrepant analysis always biases the results toward an improved sensitivity of the test under evaluation, although the degree of bias may be relatively negligible (65–68).

Other differences in reference standards could account for variation among studies in the operating characteristics of a diagnostic test. Some studies that we included evaluated participants more extensively by examining specimens collected from additional anatomic sites in women (for example, from the vagina or urethra), by using additional nucleic acid amplification tests to evaluate all study participants, or by conducting a greater number of diagnostic tests for each participant. Such studies tended to identify more infections (whether correctly or incorrectly), which generally resulted in a lower calculated sensitivity for the experimental test (42, 69). Martin and colleagues (70) recently used data from 1412 women participating in a diagnostic test study to examine the impact of using different combinations of reference standards on the calculated operating characteristics of a test. On the basis of their findings, they recommend that future evaluations of diagnostic tests use a reference standard that consists of 2 nucleic acid amplification tests that are different from the test under evaluation; include 3 samples for each participant, including urine and cervical samples from women and urine and urethral samples from men; and classify a participant as infected if any 2 of the 3 samples yield positive results (70).

### Differences in Disease Prevalence

We included studies of diagnostic tests across a wide range of disease prevalences. Some studies suggest that disease prevalence can affect the observed performance of diagnostic test assays, in that sensitivity is underestimated when the disease prevalence is low and specificity is underestimated when the prevalence is high (64). However, our

sensitivity analyses generally did not find significant differences in test characteristics according to disease prevalence or presence of symptoms. This finding has important implications, because the noninvasive nature of these tests make them ideal for use in screening.

Screening in low-prevalence settings could result in a greater proportion of positive test results that are falsely positive, depending on the exact specificity of the assay. The range of specificities was uniformly very high, from 98% to 100%, although the true specificity of each of the nucleic acid amplification tests has been hard to determine because of limitations in reference standards. If the actual specificity is closer to 98%, screening in a low-prevalence group (for example, 4%) could result in up to one third of positive results being falsely positive (19, 71). Because a false-positive result for chlamydia or gonorrhea can have profound psychosocial implications, the Centers for Disease Control and Prevention recommends consideration of a confirmatory test to help reduce the risk for false-positive results (19). Although this recommendation makes clinical sense if the specificity is less than 98%, the recommendation is not based on clinical or experimental data. If the specificity of the assay actually exceeds 99.9%, as suggested by some recent data (72), confirmatory testing is probably not needed.

#### Other Issues That Could Affect Test Performance

Inhibitors of enzyme amplification can prevent assays from providing a positive result, leading to a decrease in sensitivity. Inhibitors have been reported in 5% to 20% of samples for PCR and strand displacement amplification assays, and the rates of inhibition appear to vary among laboratories. Inhibitors appear to be more common in urine samples than in samples from more traditional collection sites (47, 73), which may explain the lower sensitivity in some of the studies involving PCR or strand displacement amplification. Inhibitors can be eliminated through freezing of samples (which was done in some studies) or dilution and retesting. The current versions of commercial PCR and strand displacement assays include amplification controls that can be used to detect inhibitors, whereas the target capture method used in the transcription-mediated amplification assay appears to be less affected by inhibitors than are the other 2 assays.

Unpublished data, including those presented at scientific meetings or collected by the test manufacturers, may also be relevant. For example, much of the data used by the U.S. Food and Drug Administration to approve the testing of urine samples by using the transcription-mediated amplification assay and the strand displacement amplification assay are not published in peer-reviewed journals. We considered inclusion of these data but could not consistently judge the study quality, identify the reference standards, or distinguish these results from published results. Publication bias would be of most concern if the unpublished data

differ substantially from the published data. We found no evidence that poor diagnostic test performance resulted in a decreased likelihood of publication, and the unpublished data of which we are aware are very consistent with the data published in the peer-reviewed literature. The current literature is also limited by the fact that few published studies present data on the transcription-mediated amplification or strand displacement amplification assay, and few studies report data from asymptomatic persons or low-prevalence groups.

#### Limitations of Nucleic Acid Amplification Tests

Limitations of nucleic acid amplification tests include their cost, lack of ability to monitor for antibiotic resistance, and occasional problems with reproducibility. The cost of nucleic acid amplification tests is generally greater than that of non-nucleic acid amplification tests for chlamydial and gonococcal infection, although this slightly higher cost may be offset by the decreased clinical resources required for noninvasive tests and the potential health benefits of identifying additional infections. Cost-effectiveness analyses have generally found that use of nucleic acid amplification tests to screen women for chlamydia can save health care costs over time (74, 75). The use of urine samples to screen for chlamydial infections may enhance the acceptability of screening in men, who traditionally have been reluctant to volunteer for urethral swabs when they are asymptomatic. Although no objective evidence supports chlamydial screening in men, modeling experts have shown that this screening can be cost-effective in groups in which the prevalence of chlamydial infection exceeds 5%. However, the cost-effectiveness in low-prevalence settings is less clear (76), and the importance of screening asymptomatic men for gonorrhea is even less certain.

Nucleic acid amplification tests cannot be used to monitor for antibiotic resistance. Culture methods will continue to be useful for this purpose. Site-to-site variation in performance of tests was demonstrated for each of the assays that were evaluated in multicenter trials. Problems with reproducibility led to the eventual withdrawal of the ligase chain reaction assay from the market, and several investigators now suggest that laboratories should routinely conduct reproducibility checks (77).

Finally, exclusive use of noninvasive testing could miss other types of sexually transmitted diseases, such as trichomonal infections, and the results should not be used to rule out treatment of persons identified by epidemiologic criteria (for example, when a sexual partner of someone in whom gonorrhea is diagnosed presents for assessment and treatment).

In conclusion, the commercially available nucleic acid amplification tests have excellent sensitivity and specificity for detection of *C. trachomatis* in urine samples. In both men and women, results in urine samples are nearly identical to those in cervical or urethral samples. Overall, the use of noninvasive testing is ideally suited for screening

asymptomatic persons who may shy away from the more traditional approaches to screening. Urine testing with nucleic acid amplification tests may obviate the need for urethral swab testing in the majority of men and the need for gynecologic examinations in women who only need to be screened for treatable sexually transmitted diseases.

Although most guidelines recommend routine screening for chlamydial infections and not gonococcal infections, each of the available nucleic acid amplification tests can be used to screen for both infections in the same specimen. The decision about whether to screen for chlamydial infection only or for both infections will depend somewhat on the prevalence of gonorrhea in the population served and on the costs involved in the additional testing for gonorrhea. In women, the available data do not support the use of the PCR assay to screen for gonorrhea in urine specimens, although the use of this assay in cervical specimens yields good results. More data are needed to clarify whether any of these assays are effective in screening for gonorrhea in asymptomatic men.

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Appendix Table 1. Studies of Noninvasively Obtained Test Samples for *Chlamydia trachomatis* Infection in Women\*

Study, Year (Reference)	Participants, Setting <i>n</i>	Age, <i>y</i>	Symptoms, %	Prevalence, %	Reference Standard	Additional Nucleic Acid Amplification Tests Done on All Participants?	Tests Done on All Participants, <i>n</i>	Discrepant Analysis Used?	Additional Anatomic Sites Tested?	
<b>Polymerase chain reaction</b>										
Skulnick et al., 1994 (29)	972	Hospital-based clinic, United States	31 (mean)	3.6	3.3	Culture (cervix), or PCR (cervix or urine) confirmed by MOMP PCR	No	3	Yes	No
Olafsson et al., 1996 (30)	203	STD clinic, Reykjavik	21 (mean)	NR	19	Culture (cervix), or PCR (cervix and urine) confirmed by MOMP PCR	No	3	Yes	No
Pasternack et al., 1996 (31)	666	Outpatient clinics, Finland	NR	NR	5.9	Culture (cervix), or PCR (urine or cervix) confirmed by DNA probe assay (cervix) or MOMP PCR (urine or cervix)	No	4	Yes	No
Quinn et al., 1996 (32)	576	STD clinic, Baltimore	24 (median)	71	11.4	Culture (cervix), or PCR (cervix or urine) confirmed by DFA testing (cervix) or MOMP PCR (cervix)	No	3	Yes	No
Wiesenfeld et al., 1996 (33)	200	STD clinic, Pittsburgh	NR	NR	13	Culture (cervix or urethra), or PCR (cervix, urethra, self-collected vaginal sample, clinician-obtained vaginal sample, urine) confirmed by MOMP PCR	No	7	Yes	Yes
Crotchfelt et al., 1997 (34)	192	STD clinic, Baltimore	NR	NR	17.7	Culture (cervix), or PCR (cervix or urine) confirmed by DFA (cervix) or MOMP PCR (cervix or urine)	No	3	Yes	No
Puolakkainen et al., 1998 (35)	450	STD and adolescent clinics, Helsinki	NR	NR	6.2	Culture (cervix), PCR and LCR of urine sample, or PCR and LCR of cervical sample	Yes	5	Yes	No
Young et al., 1998 (36)	232	STD clinic, Edinburgh	NR	NR	9.0	Culture (urethra or cervix), or PCR (urine or urethra/cervix) confirmed by MOMP PCR	No	3	Yes	Yes
Vincelette et al., 1999 (37)	1253	Family planning, STD, and general practice clinics, Montreal and Netherlands	NR	NR	4.3	Culture (cervix), or PCR (urine or cervix) confirmed by MOMP PCR (urine or cervix)	No	3	Yes	No
Van Der Pol et al., 2000 (38)	2236	STD and family planning clinics, United States	NR	51	9.1	Culture (cervix), or PCR (urine or cervix) confirmed by DFA testing (cervix) or MOMP PCR (urine or cervix)	No	3	Yes	No

Continued on following page

Appendix Table 1—Continued

Study, Year (Reference)	Participants, Setting <i>n</i>	Age, <i>y</i>	Symptoms, %	Prevalence, %	Reference Standard	Additional Nucleic Acid Amplification Tests Done on All Participants?	Tests Done on All Participants, <i>n</i>	Discrepant Analysis Used?	Additional Anatomic Sites Tested?	
van Doornum et al., 2001 (39)	503 STD clinic, Amsterdam	<30 (all)	NR	12.5	3 of 4 positive tests (cervical PCR and LCR, urine PCR and LCR), both urine tests positive (PCR and LCR), or both cervical tests positive (PCR and LCR)	Yes	4	Yes	No	
Black et al., 2002 (40)	3551 STD and family planning clinics, multiple U.S. sites	24 (median)	NR	13.4	Positive LCR (cervix or urine)	Yes	2	No	No	
Jensen et al., 2003 (41)	167 STD clinic, Copenhagen	25 (median)	56	9.0	Culture (cervix or urethra), or EIA (urine) confirmed by DFA, or PCR (cervix, urethra, or urine) confirmed by MOMP PCR	No	6	Yes	Yes	
Shrier et al., 2004 (42)	126 Adolescent clinic and outpatient clinics, Boston	19 (mean)	0	21.4	Culture, or LCR and PCR at same site (urine, vagina, cervix, urethra), or LCR or PCR positive 2 separate specimens, or LCR or PCR confirmed by nested PCR	Yes	9	Yes	Yes	
<b>Transcription-mediated amplification</b>										
Crotchfelt et al., 1998 (43)	479 STD and adolescent clinics, Baltimore	NR	NR	14.8	Culture (cervix), or TMA (urine or cervix) confirmed by DFA or TMA at alternate site (16-strand recombinant RNA)	No	3	Yes	No	
Ferrero et al., 1998 (44)	607 Family planning clinics, California	NR	NR	5.4	Culture (cervix), or TMA (urine or cervix) confirmed by DFA (urine or cervix) or TMA with alternate target (urine or cervix)	No	3	Yes	No	
Stary et al., 1998 (45)	308 STD clinic, Vienna	NR	46.4	8.1	Culture (cervix or vulva), or LCR and TMA both positive at same site (cervix, vulva, or urine), or either LCR or TMA positive (any site) confirmed by DFA or TMA at alternate site	Yes	6	Yes	Yes	
Gaydos et al., 2003 (46)	1391 STD, family planning, and OB/GYN clinics, multiple U.S. sites	25 (median); 18–35 (range)	59	15.0	2 or more positive results on PCR (cervix or urine) or LCR (cervix or urine)	Yes	4	No	No	

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Appendix Table 1—Continued

Study, Year (Reference)	Participants, Setting <i>n</i>	Age, <i>y</i>	Symptoms, %	Prevalence, %	Reference Standard	Additional Nucleic Acid Amplification Tests Done on All Participants?	Tests Done on All Participants, <i>n</i>	Discrepant Analysis Used?	Additional Anatomic Sites Tested?	
<b>Strand displacement amplification</b>										
Van Der Pol et al., 2001 (47)	1419	STD, family planning, and OB/GYN clinics, United States	NR	43	9.2	Culture (cervix), or LCR (cervix or urine) confirmed by DFA, or LCR (cervix) confirmed by LCR (urine)	Yes	3	Yes	No
McCartney et al., 2001 (48)	205	STD clinics, Glasgow	NR	NR	9.1	Positive results on 2 of 3 assays: LCR, SDA, in-house PCR (cervix or urine)	Yes	2	No	No

\* DFA = direct fluorescent antibody; EIA = enzyme immunoassay; LCR = ligase chain reaction; MOMP = major outer membrane protein; NR = not reported; OB/GYN = obstetrics/gynecology; PCR = polymerase chain reaction; STD = sexually transmitted disease; TMA = transcription-mediated amplification.

Appendix Table 2. Studies of Noninvasively Obtained Test Samples for *Chlamydia trachomatis* Infection in Men\*

Study, Year (Reference)	Participants, n	Setting	Age, y	Symptoms, %	Prevalence, %	Reference Standard	Additional Nucleic Acid Amplification Test Done on All Participants?	Tests Done on All Participants, n	Discrepant Analysis Used?
<b>Polymerase chain reaction</b>									
Wiesenfeld et al., 1994 (49)	362	STD clinic, Pittsburgh	NR	34.2	16.6	EIA (urine or urethra) and PCR (urine or urethra), or either test confirmed by PCR MOMP (urine or urethra)	No	4	Yes
Stary et al., 1996 (50)	316	Outpatient clinic, Austria	NR	66	11.3	Positive result on $\geq 2$ unique assays: DNA probe (urethra); PCR (urethra or urine); EIA (urine); and, if discrepancies were present, PCR MOMP (urethra and urine)	No	4	Yes
Toye et al., 1996 (51)	279	Sexual health clinic, Ottawa	27 (median)	0	5.8	Culture (urethra), or PCR (urethra or urine) confirmed by PCR MOMP (urine or urethra)	No	3	Yes
Crotchfelt et al., 1997 (34)	344	STD clinic, Baltimore	NR	NR	16.3	Culture (urethra), or PCR (urethra or urine) confirmed by DFA testing (urethra) or MOMP PCR (urethra or urine)	No	3	Yes
Ossewaarde et al., 1997 (52)	614	STD clinics, Amsterdam and Vienna	NR	NR	12.1	Any 2 independent assays: EIA (urethra), DNA probe (urethra), PCR (urine and urethra), or EIA (urine [Vienna only]), and OMP-1 PCR (urine and urethra) if discrepancies were present	No	3 or 4	Yes
Higgins et al., 1998 (53)	378	STD clinic, United Kingdom	NR	NR	15.4	In-house dot-blot assay (urethra) confirmed by DFA testing (urethra), or PCR (urine or urethra) confirmed by MOMP PCR (urine or urethra)	No	3	Yes
Puolakkainen et al., 1998 (35)	565	STD and adolescent clinics, Helsinki	NR	NR	8.7	Culture (urethra), PCR and LCR (urine), or PCR and LCR (urethra)	Yes	5	No
Young et al., 1998 (36)	244	STD clinic, Edinburgh	NR	NR	10.7	Culture (urethra), or PCR (urethra or urine) confirmed by MOMP PCR	No	3	Yes
Vincelette et al., 1999 (37)	251	Outpatient clinics, Meaux, France	NR	NR	7.6	Culture (urethra), or PCR (urine or urethra) confirmed by MOMP PCR (urine or urethra)	No	3	Yes
Van Der Pol et al., 2000 (38)	1940	STD and family planning clinics, United States	NR	63.4	18	Culture (urethra), PCR (urine or urethra) confirmed by DFA testing (urethra), or MOMP PCR (urine or urethra)	No	3	Yes

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Appendix Table 2—Continued

Study, Year (Reference)	Participants, n	Setting	Age, y	Symptoms, %	Prevalence, %	Reference Standard	Additional Nucleic Acid Amplification Test Done on All Participants?	Tests Done on All Participants, n	Discrepant Analysis Used?
van Doornum et al., 2001 (39)	498	STD clinic, Amsterdam	<30 (all)	NR	10	3 of 4 positive test results (urethral PCR and LCR, urine PCR and LCR), both urine tests positive (PCR and LCR), or both urethral tests positive (PCR and LCR)	Yes	4	Yes
Jensen et al., 2003 (41)	243	STD clinic, Copenhagen	28 (median)	79	13.2	Culture (urethra), EIA (urine) confirmed by DFA testing, or PCR (urine or urethra) confirmed by MOMP PCR	No	4	Yes
<b>Transcription-mediated amplification</b>									
Ferrero et al., 1998 (44)	193	STD clinics, California	NR	NR	15.3	Culture (urethra), TMA (urine or urethra) confirmed by DFA testing (urethra or urine), or TMA with alternate target (urine or urethra)	No	3	Yes
Sary et al., 1998 (45)	240	STD clinic, Vienna	NR	77.5	18.3	Culture (urethra), LCR and TMA (urine or urethra), LCR or TMA confirmed by DFA, or alternate TMA with alternate target	Yes	5	Yes
<b>Strand displacement amplification</b>									
Van Der Pol et al., 2001 (47)	675	STD, family planning, emergency department, and adolescent clinics, United States	NR	72.3	21.5	Culture (urethra), LCR (urine confirmed by DFA testing (urethra in discrepant cases only), or PCR (urethra in discrepant cases only)	Yes	2	Yes

\* DFA = direct fluorescent antibody; EIA = enzyme immunoassay; LCR: ligase chain reaction; MOMP = major outer membrane protein; NR = not reported; OMP-1 = outer membrane protein-1; PCR = polymerase chain reaction; STD = sexually transmitted disease; TMA = transcription-mediated amplification.

Appendix Table 3. Studies of Noninvasively Obtained Test Samples for *Neisseria gonorrhoeae* Infection\*

Study, Year (Reference)	Participants, n	Setting	Age, y	Symptoms, %	Prevalence, %	Reference Standard	Additional Nucleic Acid Amplification Test Done on All Participants?	Tests Done on All Participants, n	Discrepant Analysis Used?	Additional Anatomic Sites Tested?
<b>Women</b>										
<b>Polymerase chain reaction</b>										
Crotchfelt et al., 1997 (34)	192	STD clinic, Baltimore	NR	NR	12	Culture (cervix), or PCR (cervix or urine) confirmed by PCR on 16-strand recombinant RNA (cervix or urine)	No	3	Yes	No
Mukenge-Tshibaka et al., 2000 (54)	342	Sex workers, Africa	NR	NR	24	Culture (cervix); or PCR (urine or cervix but not sample under evaluation) confirmed by PCR on 16-strand recombinant RNA	No	3	Yes	No
van Doornum et al., 2001 (39)	503	STD clinic, Amsterdam	<30 (all)	NR	1.2	3 of 4 positive test results (cervical PCR and LCR, urine PCR and LCR), both urine tests positive (PCR and LCR), or both cervical tests positive (PCR and LCR), or single assay positive confirmed by PCR on 16-strand recombinant RNA or gonorrhea culture (cervix or urethra)	Yes	4	Yes	No
Knox et al., 2002 (55)	271	Remote health clinics, Australia	NR	NR	11.8	Culture (cervix), or PCR (cervix, vagina, or urine) confirmed by PCR on 16-strand recombinant RNA	No	4	Yes	Yes
<b>Transcription-mediated amplification</b>										
Gaydos et al., 2003 (46)	1484	STD, family planning, and OB/GYN clinics, multiple U.S. sites	25 (median)	59.5	8.6	Culture (cervix), or LCR (cervix and urine)	Yes	3	No	No

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Appendix Table 3—Continued

Study, Year (Reference)	Participants, n	Setting	Age, y	Symptoms, %	Prevalence, %	Reference Standard	Additional Nucleic Acid Amplification Test Done on All Participants?	Tests Done on All Participants, n	Discrepant Analysis Used?	Additional Anatomic Sites Tested?
Strand displacement amplification										
Van Der Pol et al., 2001 (47)	1411	STD, OB/GYN, family planning, and adolescent health clinics and emergency departments, United States	NR	43.4	6.5	Culture (cervix), or LCR (cervix) confirmed by LCR (urine)	Yes	3	No	No
<b>Men</b>										
<b>Polymerase chain reaction</b>										
Crotchfelt et al., 1997 (34)	344	STD clinic, Baltimore	NR	NR	22.4	Culture (urethra), or PCR (urethra or urine) confirmed by PCR on 16-strand recombinant RNA (urethra or urine)	No	3	Yes	No
Higgins et al., 1998 (53)	378	STD clinic, United Kingdom	NR	NR	9.5	Culture (urethra), or PCR (urethra or urine) confirmed by PCR on 16-strand recombinant RNA (urethra or urine)	No	3	Yes	No
Martin et al., 2000 (56)	1987	STD and family planning clinics, United States	NR	64	20.0	Culture (urethra), or PCR (urine or urethra) confirmed by PCR on 16-strand recombinant RNA (urine or urethra)	No	3	Yes	No
van Doornum et al., 2001 (39)	498	STD clinic, Amsterdam	<30 (all)		4.2	3 of 4 positive test results (urethral PCR and LCR, urine PCR and LCR), both urine tests positive (PCR and LCR), both urethral tests positive (PCR and LCR), or single assay positive confirmed by PCR on 16-strand recombinant RNA or gonorrhea culture (urethra)	Yes	4	Yes	No

\* LCR = ligase chain reaction; NR = not reported; OB/GYN = obstetrics/gynecology; PCR = polymerase chain reaction; STD = sexually transmitted disease.

Appendix Table 4. Characteristics of Tests for *Chlamydia trachomatis* Infection on Noninvasively Obtained Samples in Women

Study, Year (Reference)	Type of Specimen	Result, n				Sensitivity (95% CI), %	Specificity (95% CI), %	Positive Likelihood Ratio	Negative Likelihood Ratio
		True Positive	True Negative	False Negative	True Negative				
<b>Polymerase chain reaction</b>									
Skulnick et al., 1994 (29)	Urine	12	2	1	379	91.7 (64.0–99.8)	99.5 (98.1–99.9)	183	0.08
	Cervix	16	3	2	951	88.9 (65.3–98.6)	99.7 (99.1–99.9)	296	0.11
Olafsson et al., 1996 (30)	Urine	37	0	2	164	95 (82.7–99.4)	100 (82.7–99.4)	950	0.05
	Cervix	36	2	3	162	92.3 (79.1–98.4)	98.7 (95.6–99.8)	71	0.08
Pasternack et al., 1996 (31)	Urine	32	2	7	625	82 (66.5–92.5)	99.7 (98.9–100)	273	0.18
	Cervix	32	1	7	626	82 (66.5–92.5)	99.8 (99.1–100)	410	0.18
Quinn et al., 1996 (32)	Urine	62	12	3	498	93.3 (87.1–99.0)	97.6 (95.9–98.8)	39	0.07
	Cervix	57	5	9	505	86 (75.7–93.6)	99 (97.7–99.7)	86	0.14
Wiesenfeld et al., 1996 (33)	Urine	19	0	7	174	73 (52.2–88.4)	100 (97.9–100)	730	0.27
	Cervix	22	2	4	172	85 (65.1–95.6)	99 (95.9–100)	85	0.15
Crotchfelt et al., 1997 (34)	Urine	28	1	6	157	82.4 (65.5–93.2)	99.4 (96.5–100)	137	0.18
	Cervix	32	0	2	158	94.1 (80.3–99.3)	100 (97.9–100)	941	0.06
Puolakkainen et al., 1998 (35)	Urine	27	1	1	421	96.4 (81.6–99.9)	99.8 (98.7–100)	482	0.04
	Cervix	22	5	6	417	78.6 (59.0–91.7)	98.8 (97.3–99.6)	66	0.22
Young et al., 1998 (36)	Urine	21	0	2	232	91.3 (72.0–98.9)	100 (98.4–100)	913	0.09
	Cervix	22	0	1	232	95.6 (78.0–99.9)	100 (98.4–100)	956	0.44
Vincelette et al., 1999 (37)	Urine	46	0	8	1199	84.4 (72.9–93.4)	100 (99.7–100)	844	0.16
	Cervix	45	0	9	1199	82.6 (70.7–92.1)	100 (99.7–100)	826	0.17
Van Der Pol et al., 1999 (38)	Urine	181	20	22	2013	89.1 (84.0–93.1)	99.0 (98.5–99.4)	89	0.11
	Cervix	182	12	21	2021	89.6 (84.6–93.5)	99.4 (99.0–99.7)	149	0.11
	Urine	98	16	10	1014	90.7 (83.6–95.5)	98.4 (97.5–99.1)	57	0.10
	Cervix	99	8	9	1022	91.7 (84.8–99.7)	99.2 (98.5–99.7)	115	0.08
	Urine	83	4	12	999	87.4 (79.0–93.3)	99.6 (99.0–99.9)	218	0.13
	Cervix	83	5	12	998	87.4 (79.0–93.3)	99.5 (98.8–99.8)	175	0.13
van Doornum et al., 2001 (39)	Urine	52	1	11	439	82.5 (70.9–90.9)	99.8 (98.7–100)	412	0.18
	Cervix	61	4	2	436	96.8 (89.0–99.6)	99.1 (97.7–97.8)	108	0.03
Black et al., 2002 (40)	Urine	356	18	119	3058	74.9 (71.0–78.8)	99.4 (99.1–99.7)	125	0.25
	Cervix	360	9	115	3067	75.8 (71.7–80.0)	99.7 (99.4–99.9)	259	0.24
Jensen et al., 2003 (41)	Urine	10	0	5	152	66.7 (38.4–88.2)	100 (97.6–100)	667	0.33
	Cervix	14	0	1	152	93.3 (68.0–99.8)	100 (97.6–100)	933	0.06
Shrier et al., 2004 (42)	Urine	12	0	15	99	44.4 (25.5–64.7)	100 (96.4–100)	444	0.56
	Cervix	14	0	13	99	51.8 (31.9–71.3)	99.1 (96.3–100)	58	0.49
<b>Transcription-mediated amplification</b>									
Crotchfelt et al., 1998 (43)	Urine	60	18	4	408	93.8 (86.2–98.4)	100 (99.1–100)	938	0.06
	Cervix	71	2	0	406	100 (94.9–100)	99.5 (98.2–100)	200	<0.01
Ferrero et al., 1998 (44)	Urine	31	3	2	571	93.5 (79.8–99.2)	99.5 (98.5–99.9)	187	0.07
	Cervix	33	0	0	574	100 (89.4–100)	100 (99.4–100)	9999	<0.01
Stary et al., 1998 (45)	Urine	19	2	6	281	76 (54.9–90.6)	99.3 (97.5–100)	109	0.24
	Cervix	22	1	3	282	88 (68.8–97.4)	99.6 (98.0–100)	220	0.12
Gaydos et al., 2003 (46)	Urine	197	13	11	1170	94.7 (90.7–97.3)	98.9 (98.1–99.4)	86	0.05
	Cervix	195	28	12	1154	94.2 (90.1–97.0)	97.6 (96.6–98.4)	39	0.06
	Urine	136	8	9	668	93.8 (88.5–97.1)	98.8 (97.7–99.5)	78	0.06
	Cervix	133	22	11	653	92.4 (86.7–96.1)	96.7 (95.1–97.9)	28	0.08
	Urine	60	5	2	502	96.8 (88.8–99.6)	99.0 (97.7–99.7)	97	0.03
	Cervix	61	6	1	501	98.4 (91.3–100)	98.8 (97.4–99.6)	82	0.02
<b>Strand displacement amplification</b>									
Van Der Pol et al., 2001 (47)	Urine	99	19	24	1194	80.5 (72.4–87.1)	98.4 (97.6–99.1)	50	0.2
	Cervix	116	24	9	1270	92.8 (86.6–96.6)	98.1 (97.2–98.8)	49	0.07
	Urine	47	8	14	505	77 (64.5–86.8)	98.4 (97.0–99.3)	48	0.23
	Cervix	55	8	7	529	88.7 (78.1–95.3)	98.5 (97.1–99.4)	59	0.12
	Urine	52	12	10	688	83.9 (72.3–92.0)	98.3 (97.0–99.1)	49	0.16
	Cervix	60	16	2	742	96.8 (88.8–99.6)	97.9 (96.6–98.8)	46	0.03
McCartney et al., 2001 (48)	Urine	17	0	5	183	77.3 (59.8–94.8)	100 (98.0–100)	7730	0.23
	Cervix	20	0	2	183	90.9 (78.9–100)	100 (98.0–100)	9090	0.09

Appendix Table 5. Characteristics of Tests for *Chlamydia trachomatis* Infection on Noninvasively Obtained Samples in Men

Study, Year (Reference)	Type of Specimen	Result, n				Sensitivity (95% CI), %	Specificity (95% CI), %	Positive Likelihood Ratio	Negative Likelihood Ratio
		True Positive	False Positive	False Negative	True Negative				
<b>Polymerase chain reaction</b>									
Wiesenfeld et al., 1994 (49)	Urine	52	6	8	296	87.1 (76.2–94.3)	98 (95.7–99.3)	44	0.13
	Urethra	59	3	1	299	98.4 (91.3–100)	99 (97.1–99.8)	98	0.02
Stary et al., 1996 (50)	Urine	17	1	19	280	47.2 (30.4–64.5)	99.6 (98.0–100)	118	0.53
	Urethra	23	20	13	260	64.1 (46.2–79.1)	92.9 (89.2–95.6)	9.0	0.39
Toye et al., 1996 (51)	Urine	20	0	2	357	90.9 (70.8–98.9)	100 (99.0–100)	909	0.09
	Urethra	16	1	6	356	72.2 (49.8–89.3)	99.8 (98.4–100)	361	0.28
Crotchfelt et al., 1997 (34)	Urine	45	4	11	284	80.4 (67.6–89.8)	98.6 (96.5–99.6)	57	0.2
	Urethra	51	2	5	286	91.1 (80.4–97.0)	99.3 (97.5–99.4)	130	0.09
Ossewaarde et al., 1997 (52)	Urine	52	13	22	527	70.3 (58.5–80.3)	97.6 (95.9–98.7)	29	0.30
	Urethra	50	8	24	532	67.6 (55.7–78.0)	98.5 (97.1–99.4)	45	0.33
Higgins et al., 1998 (53)	Urine	50	0	8	320	86.7 (74.6–93.8)	100 (98.9–100)	867	0.13
	Urethra	52	0	6	320	90.0 (78.8–96.1)	100 (98.9–100)	900	0.10
Puolakkainen et al., 1998 (35)	Urine	47	3	2	513	95.9 (86.0–99.5)	99.4 (98.3–99.9)	160	0.04
	Urethra	49	3	0	513	100 (92.7–100)	99.4 (98.3–99.9)	167	<0.01
Young et al., 1998 (36)	Urine	25	2	1	216	96 (80.4–99.9)	99.1 (96.7–99.9)	107	0.04
	Urethra	23	1	3	217	88.4 (69.8–97.6)	99.5 (97.5–100)	177	0.12
Vincelette et al., 1999 (37)	Urine	17	0	2	232	89.5 (66.9–98.7)	100 (98.4–100)	895	0.11
	Urethra	16	0	3	232	84.2 (60.4–96.6)	100 (98.4–100)	842	0.16
Van Der Pol et al., 2000 (38)	Urine	315	26	34	1565	90.6 (86.6–93.2)	98.5 (97.6–98.9)	60	0.10
	Urethra	309	21	40	1570	88.6 (84.7–91.7)	98.7 (98.0–99.2)	68	0.12
Symptomatic patients (38)	Urine	234	15	27	954	89.7 (85.3–93.1)	98.5 (97.5–99.1)	60	0.11
	Urethra	228	13	33	956	87.4 (82.7–91.1)	98.5 (97.7–99.3)	58	0.13
Asymptomatic patients (38)	Urine	82	10	7	611	92.1 (84.5–96.6)	98.4 (97.1–99.2)	58	0.08
	Urethra	82	8	7	613	92.1 (84.5–96.8)	98.7 (97.5–99.4)	71	0.08
van Doornum et al., 2001 (39)	Urine	46	0	4	448	92 (80.8–97.8)	100 (99.2–100)	920	0.08
	Urethra	49	4	1	444	98.0 (89.4–99.9)	99.1 (97.7–99.8)	109	0.02
Jensen et al., 2003 (41)	Urine	23	0	9	211	71.9 (53.2–86.2)	100 (98.3–100)	719	0.28
	Urethra	28	0	4	211	87.5 (71.0–96.5)	100 (98.3–100)	875	0.13
<b>Transcription-mediated amplification</b>									
Ferrero et al., 1998 (44)	Urine	25	0	4	164	88.5 (69.8–97.6)	100 (97.8–100)	885	0.12
	Urethra	29	0	0	164	100 (88.1–100)	100 (97.8–100)	9999	<0.01
Stary et al., 1998 (45)	Urine	39	2	5	194	88.6 (79.2–98.0)	99.0 (97.6–100)	87	0.11
	Urethra	41	2	3	194	93.2 (85.7–100)	99.0 (97.6–100)	91	0.07
<b>Strand displacement amplification</b>									
Van Der Pol et al., 2001 (47)	Urine	135	37	10	503	93.1 (87.7–96.6)	93.8 (90.7–95.1)	15	0.07
	Urethra	134	20	11	520	92.5 (86.8–96.1)	96.4 (94.3–97.7)	26	0.08
Asymptomatic patients (47)	Urine	117	27	7	337	94.4 (88.7–97.7)	92.6 (89.4–95.0)	13	0.06
	Urethra	117	15	8	352	93.6 (87.8–97.2)	95.9 (93.3–97.7)	23	0.07
Symptomatic patients (47)	Urine	18	6	3	160	85.7 (63.6–97.0)	96.4 (92.3–98.7)	24	0.15
	Urethra	18	4	3	161	85.7 (63.6–97.0)	97.6 (93.9–99.3)	36	0.15

Appendix Table 6. Characteristics of Tests for *Neisseria gonorrhoeae* Infection on Noninvasively Obtained Samples in Women and Men

Study, Year (Reference)	Type of Specimen	Result, n				Sensitivity (95% CI), %	Specificity (95% CI), %	Positive Likelihood Ratio	Negative Likelihood Ratio
		True Positive	False Positive	False Negative	True Negative				
<b>Women</b>									
<b>Polymerase chain reaction</b>									
Crotchfelt et al., 1997 (34)	Urine	18	7	5	162	78.3 (56.3–92.5)	95.9 (91.7–98.3)	19	0.23
	Cervix	23	1	0	168	100 (85.2–100)	99.4 (96.7–100)	17	0.91
Mukenge-Tshibaka et al., 2000 (54)	Urine	44	3	38	257	53.8 (42.9–64.7)	98.9 (42.3–64.7)	49	0.47
	Cervix	75	0	7	260	91.5 (83.2–96.5)	100 (98.6–100)	915	0.09
van Doornum et al., 2001 (39)	Urine	4	7	2	490	66.7 (22.3–95.7)	99.5 (97.1–99.4)	133	0.33
	Cervix	6	13		484	100 (54.0–100)	97.4 (95.6–98.7)	38	<0.01
Knox et al., 2002 (55)	Urine	10	0	22	239	31.2 (16.1–50.5)	100 (16.1–50.0)	312	0.69
	Cervix	30	0	2	239	92.6 (75.7–99.1)	100 (98.6–100)	926	0.07
<b>Transcription-mediated amplification</b>									
Gaydos et al., 2003 (46)	Urine	116	10	11	1347	91.3 (85.0–95.6)	99.3 (98.7–99.7)	130	0.09
	Cervix	126	17	1	1335	99.2 (95.7–100)	98.7 (97.9–99.2)	76	0.01
Symptomatic patients (46)	Urine	87	7	7	782	92.6 (85.3–97.0)	99.1 (98.2–99.6)	103	0.08
	Cervix	94	15	2	772	100 (96.2–100)	98.1 (96.9–98.9)	53	<0.01
Asymptomatic patients (46)	Urine	28	3	4	564	87.5 (71.0–96.5)	99.5 (98.5–99.1)	175	0.13
	Cervix	31	2	1	562	96.9 (83.8–99.9)	99.6 (98.7–100)	242	0.03
<b>Strand displacement amplification</b>									
Van Der Pol et al., 2001 (47)	Urine	73	7	13	1238	84.9 (75.5–91.7)	99.4 (98.8–99.8)	142	0.15
	Cervix	83	6	3	1239	96.6 (90.1–99.3)	99.5 (99–99.8)	193	0.03
Symptomatic patients (47)	Urine	41	2	8	526	83.7 (70.3–92.7)	99.6 (98.6–99.9)	209	0.16
	Cervix	49	4	2	545	96.1 (86.5–99.5)	99.3 (98.1–99.8)	137	0.04
Asymptomatic patients (47)	Urine	32	5	5	712	86.5 (71.2–95.4)	99.3 (98.4–99.8)	124	0.14
	Cervix	37	3	1	770	97.4 (86.2–99.9)	99.6 (99.8–99.9)	244	0.03
<b>Men</b>									
<b>Polymerase chain reaction</b>									
Crotchfelt et al., 1997 (34)	Urine	68	4	9	263	88.3 (79.0–94.5)	98.5 (79–94.5)	59	0.12
	Urethra	73	8	4	259	94.8 (87.2–98.6)	97 (94.2–98.7)	32	0.05
Higgins et al., 1998 (53)	Urine	33	0	3	342	91.9 (77.5–98.2)	100 (98.9–100)	919	0.08
	Urethra	33	0	3	342	91.9 (77.5–98.2)	100 (98.9–100)	919	0.08
Martin et al., 2000 (56)	Urine	361	2	37	1581	90.7 (87.4–93.4)	99.8 (99.5–100)	46	0.09
	Urethra	384	17	14	1566	96.5 (94.2–98.1)	98.9 (98.3–99.4)	88	0.04
Symptomatic patients (56)	Urine	350	1	22	894	94.1 (91.2–96.2)	99.9 (97.9–99.6)	941	0.06
	Urethra	365	11	7	884	98.1 (96.2–99.2)	98.8 (97.8–99.4)	82	0.02
Asymptomatic patients (56)	Urine	11	1	15	687	42.3 (23.4–63.1)	99.9 (99.2–100)	423	0.58
	Urethra	19	7	7	681	73.1 (52.2–88.4)	99.0 (97.9–99.6)	73	0.27
van Doornum et al., 2001 (39)	Urine	20	3	1	474	95.2 (76.2–99.9)	99.4 (98.2–99.9)	159	0.05
	Urethra	21	4	0	473	100 (93.9–100)	99.2 (97.9–99.8)	125	<0.01