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Bristow, Claire C
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Little, Susan J
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Meta-analysis of the Cepheid Xpert® CT/NG assay for extragenital detection of *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) infections

Claire C. Bristow^{A,D}, Sheldon R. Morris^A, Susan J. Little^A, Sanjay R. Mehta^A
and Jeffrey D. Klausner^{B,C}

^ADivision of Infectious Diseases and Global Public Health, Department of Medicine, University of California San Diego, La Jolla, CA 92093, USA.

^BDivision of Infectious Diseases, Department of Medicine, University of California Los Angeles, Los Angeles, CA 90095, USA.

^CDepartment of Epidemiology, Fielding School of Public Health, University of California Los Angeles, Los Angeles, CA 90095, USA.

^DCorresponding author. Email: cbristow@ucsd.edu

Abstract. **Background:** Most studies evaluating extragenital testing performance for *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) detection by the Xpert® CT/NG show high per cent agreement with comparison assays; however, the precision around positive per cent agreement is low and thus the values that have been reported are not highly informative. Therefore, a systematic review was conducted and data from five studies were combined to better assess positive per cent agreement. **Methods:** The literature indexed on PubMed.gov was searched. Included studies were those that were an evaluation of the Xpert CT/NG assay with rectal and/or pharyngeal specimen types compared with another nucleic acid amplification test (NAAT), the Aptima transcription mediated amplification assay. A full Bayesian method was used for bivariate fixed-effect meta-analysis of positive and negative per cent agreement and pooled estimates (and 95% confidence intervals (CI)) were presented for each. **Results:** The pooled positive and negative per cent agreement for detection of CT in rectal specimens was 89.72% (95% CI: 84.97%, 93.64%) and 99.23% (95% CI: 98.74%, 99.60%), and in pharyngeal specimens, they were 89.96% (95% CI: 66.38%, 99.72%) and 99.62% (95% CI: 98.95%, 99.95%) respectively. For NG detection in rectal specimens, the pooled positive and negative per cent agreement was 92.75% (95% CI: 87.91%, 96.46%) and 99.75% (95% CI: 99.46%, 99.93%), and in pharyngeal specimens, they were 92.51% (95% CI: 85.84%, 97.18%) and 98.56% (95% CI: 97.69%, 99.23%) respectively. **Conclusions:** It was found that the Xpert CT/NG assay performed similarly to the Aptima transcription mediated amplification assay for the detection of CT and NG in extragenital specimens. The Xpert assay has the benefit of providing faster results at the point-of-care, thus reducing the turnaround time for results, potentially enabling same-day treatment.

Additional keywords: diagnosis, nucleic acid amplification test, pharyngeal, rectal.

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Introduction

Sexually transmissible infections (STIs) of *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) continue to place an immense health burden on men and women worldwide. Both CT and NG infections are common STIs accounting for 209 million cases globally each year.¹ In the USA alone, over 2 million chlamydial and gonococcal infections were reported to the USA Centers for Disease Control and Prevention (CDC) in 2016, making those the most common notifiable diseases in the USA.²

Routine screening, timely treatment and partner treatment are mainstays of STI control programs. However, both

urogenital and extragenital CT and NG infections are frequently asymptomatic³ and therefore go undetected and untreated if screening tests are not performed. In the absence of appropriate screening, extragenital sites may be important reservoirs for CT and NG in a population, and can serve to perpetuate the spread of these infections. Among men who have sex with men, 65–77% of extragenital NG infections and 75–85% of extragenital CT infections are detected in the absence of urethral infection, warranting routine screening at extragenital sites in addition to urethral screening.^{4–6} Among women, 14–44% of CT and NG infections may be missed without extragenital screening.^{7–10}

Studies have shown that nucleic acid amplification tests (NAATs) perform better than other tests available (e.g. culture) for CT and NG detection.^{11–14} The CDC currently recommends NAATs for the detection of CT and NG from all anatomic sites.¹⁵ The Xpert® CT/NG assay (Cepheid, Sunnyvale, CA, USA) is a NAAT with sample-to-result instrumentation (on the GeneXpert® system) that can be used in laboratories or at the point-of-care. Similar to other STI NAAT assays, the Xpert CT/NG is Food and Drug Administration (FDA) cleared for use with urogenital specimens,^{16–18} and has recently been approved for use with extragenital specimens.¹⁹

The Xpert CT/NG assay results are obtained in less than 90 min and are displayed on a computer system connected to the test instrument via a data cable. The assay contains internal quality control mechanisms including: a sample processing control; a sample adequacy control; and a probe check control, all of which are included in the Xpert CT/NG assay cartridge. The sample processing control spikes DNA from the non-pathogen, *Bacillus globigii*, which is then co-extracted and co-amplified with the sample nucleic acid. Detection of this control DNA verifies that binding and elution of target DNA have occurred. The sample adequacy control reagents detect the presence of the single-copy human gene encoding hydroxymethylbilane synthase to monitor whether the sample contains human DNA. Thus, a negative sample adequacy control indicates that inadequate numbers of human cells were present in the sample due to an inadequately collected specimen, sample degradation or insufficient mixing. The probe check control verifies reagent rehydration, polymerase chain reaction tube filling in the cartridge, probe integrity and dye stability.

Most studies evaluating extragenital testing performance for CT and NG detection by the Xpert CT/NG show high per cent agreement with comparison assays; however, because of the limited sample sizes of CT- and NG-positive cases, the precision around the positive per cent agreement is low.^{20–24} Therefore, we aimed to combine data from all published studies of the performance of extragenital testing with Xpert CT/NG to better assess positive per cent agreement.

Methods

We searched the literature indexed on PubMed.gov (<https://www.ncbi.nlm.nih.gov/pubmed/>) related to Xpert CT/NG extragenital testing evaluations. We used the following search terms: (Xpert OR GeneXpert OR Cepheid) AND (extragenital OR rectal OR pharyngeal OR throat) AND (chlamydia OR gonorrh*) (last search: 1 January 2018). There were no language restrictions; however, only English articles returned in our search. References within articles were reviewed to identify additional relevant studies. Titles, abstracts and full texts were reviewed for all articles, and a study was included if it met the inclusion criteria of being an evaluation of the Xpert CT/NG assay with rectal and/or pharyngeal specimen types compared with another NAAT platform. C. C. Bristow identified and selected articles. A review protocol was not written.

Data were extracted from all included studies, including author, publication year, sample size, sex of participants, specimen types, reference tests and numbers of positive and negative results on each assay into a data extraction spreadsheet. We used SAS v9.4 (Cary, NC, USA) to perform all analyses. We calculated per cent agreement, positive per cent agreement and negative per cent agreement for each study and for combined results. We calculated 95% confidence intervals using the exact binomial method for each study individually. We used a full Bayesian method for bivariate fixed-effect and random-effects meta-analysis of positive per cent agreement and negative per cent agreement with a SAS software procedure (PROC MCMC)²⁵ and present pooled estimates of each. We considered a test of the deviance information criterion (DIC) to assess the best model fit of the fixed-effect and random-effects model. The fixed-effect model was considered to be significantly better (substantial), if its DIC was less than 10 greater than the DIC of the random-effects model; that is, if $(DIC_{FIXED} - DIC_{RANDOM}) < 10$.²⁶ In addition, we report the between-study heterogeneity of positive per cent agreement and negative per cent agreement by univariate Cochran Q-tests, using the free meta-analytic program, Meta-DiSc, version 1.4.²⁷ We also used the Meta-DiSc program to calculate univariate I^2 -values for quantifying the between-study heterogeneity. However, the Cochran Q-test and I^2 -values were not used to determine best model fit.

Results

Our search yielded a total of eight publications,^{4,20–24,28,29} five^{20–24} of which met our inclusion criteria. We excluded three studies because they were not evaluation studies. Table 1 shows the included studies published between 2012 and 2017, with data from the USA and the UK. In total, the studies included results from 1743 rectal specimens and 986 pharyngeal specimens. All studies used the Aptima transcription mediated amplification assay (Combo 2, Hologic, San Diego, CA, USA) as the comparison test for the Xpert CT/NG.

Figure 1a–d shows the calculated positive per cent agreement and negative per cent agreement for each study along with the pooled positive per cent agreement and the pooled negative per cent agreement. The positive per cent agreement in the studies ranged from 85.7% to 95.5% for the detection of CT in rectal specimens and 88.4% to 100% for the detection of NG in rectal specimens. The negative per cent agreement ranged from 98.3% to 100% for CT in rectal specimens and 99.4% to 100% for NG in rectal specimens.

For the detection of CT in pharyngeal specimens, the positive per cent agreement ranged from 50% to 100% and the negative per cent agreement ranged from 99.5% to 100%. For the detection of NG in pharyngeal specimens, the positive per cent agreement ranged from 77.8% to 97.3% and the negative per cent agreement ranged from 97.5% to 100%.

We found that there was little heterogeneity (determined using DIC of each random-effects and fixed-effect model) between studies and therefore we report pooled estimates of positive and negative per cent agreement from a fixed-effect model. DIC values, Q-test results and I^2 values are in the

Table 1. Studies included in meta-analysis of Cepheid Xpert CT/NG assay extragenital testing
CT, *Chlamydia trachomatis*; NG, *Neisseria gonorrhoeae*; NA, not applicable

Author	Year Published	Xpert rectal specimen type	Xpert pharyngeal specimen type	Swab type/collection kit for Xpert test	Comparison test	Sex of and number of participants' specimens
Goldenberg <i>et al.</i> ²⁴	2012	Not stated	NA	Aptima unisex swab ^A	Aptima Combo 2 ^B	409 rectal (sex not stated)
Geiger <i>et al.</i> ²³	2016	Self-collected	Self-collected	Xpert CT/NG Swab Collection Kit	Aptima Combo 2	144 pharyngeal, 141 rectal from men who have sex with men
Dize <i>et al.</i> ²²	2018	Home self-collected	NA	Dry swab	Aptima Combo 2	225 ^C rectal from females, 223 rectal from males
Consentino <i>et al.</i> ²¹	2017	Clinician collected	Clinician collected	Xpert CT/NG Swab Collection Kit	Aptima Combo 2	224 ^C from males and 175 from females rectal and pharyngeal
Bristow <i>et al.</i> ²⁰	2017	Self-collected	Clinician collected	Xpert CT/NG Swab Collection Kit	Aptima Combo 2	393 ^C rectal and 448 pharyngeal specimens from males

^AThe authors used remnant Aptima swabs for Xpert testing with the addition of a sample dilution step.

^BAptima Combo 2-positive samples were confirmed with the Aptima CT or Aptima GC assay, which target alternate primers to those of the Aptima Combo 2.

^CSome specimen results excluded from analysis due to errors or invalid results.

footnotes of Figure 1a–d. The pooled positive per cent agreement and pooled negative per cent agreement for detection of CT in rectal specimens was 89.72% (95% CI: 84.97%, 93.64%) and 99.23% (95% CI: 98.74%, 99.60%) respectively. For NG detection in rectal specimens, the pooled positive per cent agreement and pooled negative per cent agreement was 92.75% (95% CI: 87.91%, 96.46%) and 99.75% (95% CI: 99.46%, 99.93%) respectively.

The pooled positive per cent agreement and the pooled negative per cent agreement for detection of CT in pharyngeal specimens was 89.96% (95% CI: 66.38%, 99.72%) and 99.62% (95% CI: 98.95%, 99.95%) respectively. For the detection of NG in pharyngeal specimens, the pooled positive per cent agreement and pooled negative per cent agreement was 92.51% (95% CI: 85.84%, 97.18%) and 98.56% (95% CI: 97.69%, 99.23%) respectively.

Discussion

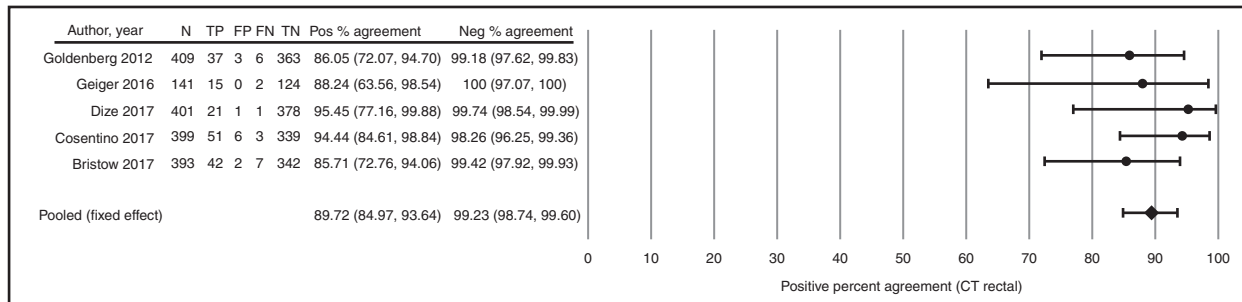
CT and NG screening must be conducted using specimens from the anatomic site of exposure if clinicians want to identify those sites as infected. In addition, given most extragenital infections in men and some in women occur in the absence of a urogenital CT or NG infection, there is a need for reliable and accurate screening tests for extragenital specimens. Currently, clinical trials funded by the NIH (clinicaltrials.gov; NCT02870101) have recently been completed to provide data and analyses to support FDA applications for multiple NAAT diagnostic platforms for the detection of pharyngeal and rectal CT and NG.¹⁹

In this meta-analysis, we combined evidence from five studies evaluating the Xpert CT/NG with extragenital specimen types using Aptima transcription mediated amplification assay, Combo 2, as the comparator. One study used residual Aptima specimens and required a dilution of the samples to overcome the incompatibility of the Aptima buffer with the Xpert system; however, this study found a good correlation between the two test systems.²⁴ That reference NAAT assay, the Aptima Combo 2, has demonstrated very

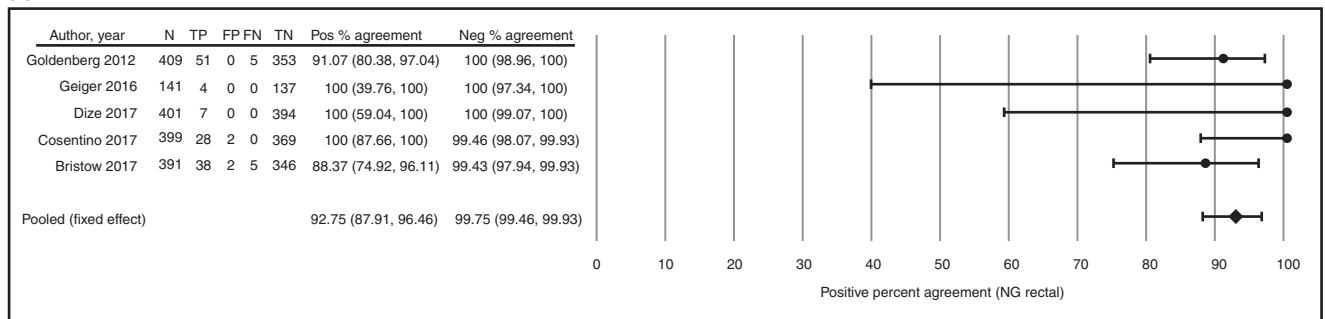
good sensitivity and specificity ranges for detection of NG and CT in extragenital specimens across several studies of 71–100% and 87.9–100% respectively.³⁰ In all studies we included, there was a lack of precision around estimates of positive per cent agreement because of the small or moderate sample size of positive specimens. Therefore, by combining evidence from all five studies, we were able to achieve narrower confidence intervals around positive per cent agreement. We chose to use a fixed-effect model to generate the pooled estimates of positive per cent agreement after identifying very little heterogeneity between studies. Our findings suggest that the Xpert CT/NG test was similar to another laboratory-based NAAT for the detection of CT and NG in extragenital specimens. We calculated per cent agreement for positive and negative results separately and found that negative per cent agreement was nearly 100% for both organisms at both extragenital sites included in the study. We found that positive per cent agreement was over 89% for both organisms at both extragenital sites. Further studies may be needed to assess what sensitivity value is acceptable in clinical practice in various settings. Under ideal conditions, patient infection status would be determined using an algorithm that includes multiple test assays to ensure that the reference for a test evaluation was as close to the true infection status of each participant as possible. That would control for potential disease status misclassification by the reference test(s). As a limitation, the positive per cent agreement values in this study should be interpreted with caution, as most studies did not include a tiebreaker or confirmatory testing, therefore, the determination of infection status of the anatomic site of each participant does not use an optimal anatomic site infection status determination. However, the clinical trial mentioned above uses multiple assays to determine anatomic site infection status.

Our findings demonstrate that Xpert CT/NG assay results were similar to a laboratory-based NAAT assay, Aptima transcription mediated amplification assay, Combo 2, for the detection of CT and NG in extragenital specimens. That Combo 2 NAAT has been laboratory verified for use with extragenital specimens at multiple reference laboratories and thus was used

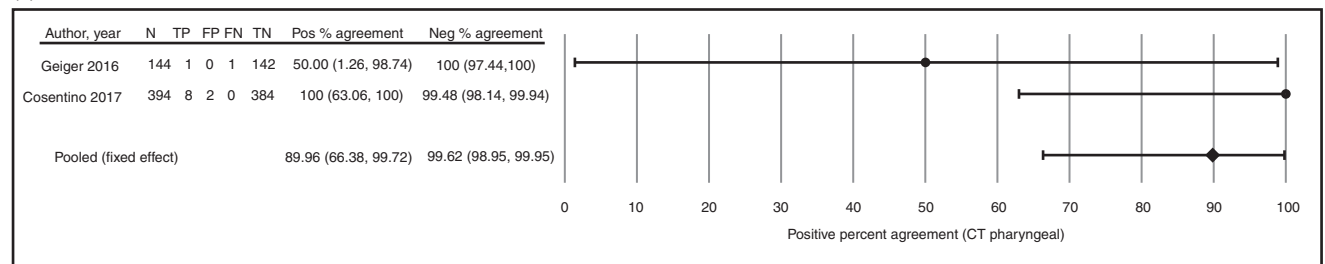
(a)



(b)



(c)



(d)

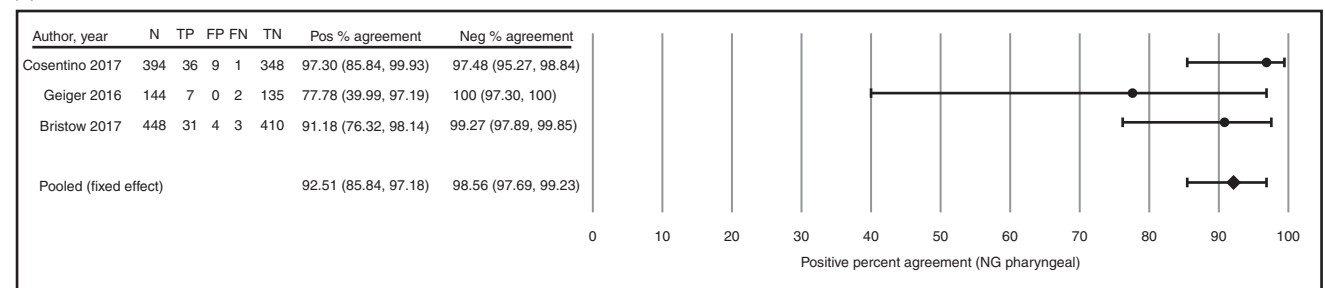


Fig. 1. (a) Xpert CT/NG *Chlamydia trachomatis* (CT) per cent agreement with comparison tests using rectal specimens. $DIC_{fixed}-DIC_{random} = 40.601-41.299$. Positive per cent agreement Q-test 3.89, d.f. = 4, $P = 0.421$; negative per cent agreement Q-test 5.26, d.f. = 4, $P = 0.262$. Positive per cent agreement $I^2 = 0\%$; negative per cent agreement $I^2 = 24.0\%$. (b) Xpert CT/NG *Neisseria gonorrhoeae* (NG) per cent agreement with comparison tests using rectal specimens. $DIC_{fixed}-DIC_{random} = 29.577-28.382$. Positive per cent agreement Q-test 2.97, d.f. = 4, $P = 0.563$; negative per cent agreement Q-test 2.06, d.f. = 4, $P = 0.724$. Positive per cent agreement $I^2 = 0\%$; negative per cent agreement $I^2 = 0\%$. (c) Xpert CT/NG *Chlamydia trachomatis* per cent agreement with comparison tests using pharyngeal specimens. $DIC_{fixed}-DIC_{random} = 13.083-11.502$. Positive per cent agreement Q-test 2.04, d.f. = 1, $P = 0.154$; negative per cent agreement Q-test 0.07, d.f. = 1, $P = 0.798$. Positive per cent agreement $I^2 = 50.9\%$; negative per cent agreement $I^2 = 0\%$. (d) Xpert CT/NG *Neisseria gonorrhoeae* per cent agreement with comparison tests using pharyngeal specimens. $DIC_{fixed}-DIC_{random} = 29.216-25.657$. Positive per cent agreement Q-test 3.6, d.f. = 2, $P = 0.165$; negative per cent agreement Q-test 4.69, d.f. = 2, $P = 0.096$. Positive per cent agreement $I^2 = 44.4\%$; negative per cent agreement $I^2 = 57.3\%$.

as the reference test in the studies we identified. The Xpert CT/NG assay has the benefit of providing faster results and can be done at the point-of-care,¹⁷ thus reducing the turnaround time for results,^{31–33} potentially enabling same-day treatment.

Conflicts of interest

All authors have received donated Cepheid test kits for research studies in the past 12 months. J. D. Klausner has received donated test kits and grant support for research from Hologic, research grant support and a \$2500 speaker's fee from Cepheid in the past 12 months. S. J. Little has received grants paid to her institution from Gilead Sciences.

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