510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT COMBINATION TEMPLATE

A. 510(k) Number:

k121710

B. Purpose for Submission:

To obtain substantial equivalence determination for the Xpert® CT/NG Assay

C. Measurand:

Genomic DNA of *Chlamydia trachomatis* (CT) and/or *Neisseria gonorrhoeae* (NG)

D. Type of Test:

Real Time Polymerase Chain Reaction (PCR)

E. Applicant:

Cepheid

F. Proprietary and Established Names:

Xpert® CT/NG Assay

G. Regulatory Information:

1. Regulation section:

   21 CFR 866.3120 Chlamydia serological reagents

   21 CFR 866.3390 Neisseria spp. direct serological test reagents

   21 CFR 862.2570 Instrumentation for clinical multiplex systems

2. Classification:

   Class II

3. Product code:

MKZ: DNA Probe, Nucleic Acid Amplification, Chlamydia
LSL: DNA-Reagents, Neisseria
OOI: Real Time Nucleic Acid Amplification System

4. Panel:

Microbiology 083

H. Intended Use:

1. Intended use(s):

Xpert® CT/NG Assay

The Xpert® CT/NG Assay, performed on the GeneXpert® Instrument Systems, is a qualitative *in vitro* real-time PCR test for the automated detection and differentiation of genomic DNA from *Chlamydia trachomatis* (CT) and/or *Neisseria gonorrhoeae* (NG) to aid in the diagnosis of chlamydial and gonorrheal urogenital disease. The assay may be used to test the following specimens from asymptomatic and symptomatic individuals: female and male urine, endocervical swab, and patient-collected vaginal swab (collected in a clinical setting).

Ancillary Specimen Collection Kits

Cepheid® Xpert® CT/NG Vaginal/Endocervical Specimen Collection Kit

The Cepheid® Xpert® CT/NG Vaginal/Endocervical Specimen Collection Kit is designed to collect, preserve and transport patient *Chlamydia trachomatis* and *Neisseria gonorrhoeae* DNA in endocervical and vaginal specimens from symptomatic and asymptomatic individuals prior to analysis with the Cepheid Xpert CT/NG Assay.

The Cepheid Xpert CT/NG Vaginal/Endocervical Specimen Collection Kit has only been cleared for use with the Cepheid Xpert CT/NG Assay.

Cepheid® Xpert® CT/NG Urine Specimen Collection Kit

Cepheid® Xpert® CT/NG Urine Specimen Collection Kit is designed to preserve and transport *Chlamydia trachomatis* and *Neisseria gonorrhoeae* DNA in first-catch male and female urine specimens from symptomatic and asymptomatic individuals prior to analysis with the Cepheid Xpert CT/NG Assay.

2. Indication(s) for use:

Same as the Intended Use

3. Special conditions for use statement(s):

Prescription Use Only

4. Special instrument requirements:

GeneXpert Instrument Systems

- GeneXpert Dx
- GeneXpert Infinity-48
- GeneXpert Infinity-80

I. Device Description:

The Xpert CT/NG Assay is a rapid, automated *in vitro* diagnostic test for qualitative detection and differentiation of DNA from *Chlamydia trachomatis* (CT) and/or *Neisseria gonorrhoeae* (NG). The assay is performed on the Cepheid GeneXpert Instrument Systems. The GeneXpert Instrument Systems automate and integrate sample purification, nucleic acid amplification, and detection of the target sequences in urogenital samples using real-time PCR for gene specific sequence amplification.

The GeneXpert Instrument Systems, comprised of the GeneXpert Dx System, the GeneXpert Infinity-48 System and the GeneXpert Infinity-80 System, have 1 to 80 randomly accessible modules, depending upon the instrument, that are each capable of performing sample preparation and real-time PCR tests individually for each patient. Each module contains a syringe drive for dispensing fluids (i.e., the syringe drive activates the plunger that works in concert with the rotary valve in the cartridge to move fluids between chambers), an ultrasonic horn for lysing cells or spores, and a proprietary I-CORE® thermocycler for performing real-time PCR and detection.

The system consists of an instrument, personal computer, and preloaded software for running the tests on collected samples and viewing the results. The system is designed to minimize cross-contamination during the testing process by the use of assay specific single-use disposable cartridges that hold the PCR reagents and host the PCR process.

The Xpert CT/NG Assay includes reagents for the 5' exonuclease real-time PCR detection and differentiation of CT and NG. Reagents for the detection of a Sample Processing Control (SPC), a Sample Adequacy Control (SAC), and a Probe Check Control (PCC) are also included in the cartridge. The SPC is present to control for adequate processing of the target bacteria and to monitor the presence of inhibitors in the PCR reaction. The SAC reagents detect the presence of a single copy human gene and monitor whether the specimen contains human DNA. The PCC verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability. The primers and probes in the Xpert CT/NG Assay detect chromosomal sequences in the bacteria.

The Xpert CT/NG Assay is designed for use with genital and urine specimens (first-catch male urine, female urine, endocervical specimens and vaginal swab specimens) collected in specific Urine and Endocervical /Vaginal Specimen Collection kits designed to preserve patient specimens to allow transport to the laboratory for analysis with Xpert CT/NG Assay and GeneXpert Instrument System. The specimen is briefly mixed and transferred to the sample chamber of the Xpert CT/NG cartridge using the supplied transfer pipette. The provided Binding Reagent is manually added into the designated chamber of the Xpert CT/NG cartridge. The cartridge is loaded onto the GeneXpert Instrument System platform, which performs hands-off, automated sample processing, and real-time PCR for detection of DNA. Test results are obtained in approximately 90 minutes and are displayed in tabular and graphic formats.

J. Substantial Equivalence Information:

1. Predicate device names:

GEN-PROBE APTIMA Combo 2® Assay

Becton Dickenson ProbeTec™ ET *Chlamydia trachomatis/Neisseria gonorrhoeae* Amplified DNA Assay

2. Predicate 510(k) numbers:

K043224
K012351

3. Comparison with predicate:

	Device	**Predicates**	
Item	**Cepheid Xpert CT/NG Assay**	**GEN-PROBE® APTIMA Combo 2® Assay**	**Becton Dickenson ProbeTec™ ET Chlamydia trachomatis /Neisseria gonorrhoeae**
Regulation	866.3120, 866.3390	866.3120, 866.3390	866.3120, 866.3390
Device Class	I, II	I, II	I, II
Technology / Detection	An automated multiplex real-time polymerase chain	An automated multiplex transcription-mediated amplification (TMA)	An automated multiplex strand displacement amplification (SDA)
Intended Use	An automated, multiplex real-time RT-PCR assay,	A target amplification nucleic acid probe test	Strand Displacement Amplification (SDA)

	performed on the GeneXpert Instrument Systems, intended for the *in vitro* qualitative and differentiation of genomic DNA from *Chlamydia trachomatis* (CT) and/or *Neisseria gonorrhoeae* (NG) to aid in the diagnosis of chlamydial gonorrheal urogenital disease. The assay may be used to test the following specimens from asymptomatic and symptomatic individuals: female and male urine, endocervical swab, and patient-collected vaginal swab (collected in a clinical setting).	that utilizes target capture for the *in vitro* qualitative detection and differentiation of ribosomal RNA (rRNA) from *Chlamydia trachomatis* (CT) and/or *Neisseria gonorrhoeae* (GC) in clinician-collected endocervical, vaginal, and male urethral swab specimens, patient-collected vaginal swab specimens*, and female and male urine specimens. The assay is also intended for use with testing of gynecological specimens collected in the PreservCyt Solution and processed with the Cytyc ThinPrep 2000 System. The assay may be used to test specimens from symptomatic and asymptomatic individuals to aid in the diagnosis of gonococcal and/or chlamydial urogenital disease. *Patient-collected vaginal swab specimens are an option for screening women when a pelvic exam is not otherwise indicated. The	technology for the direct, qualitative detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* DNA in endocervical swabs, male urethral swabs, and in female and male urine specimens as evidence of infection with C. *trachomatis, N. gonorrhoeae,* or of co-infection with both C. *trachomatis* and *N. gonorrhoeae.* Specimens may be from symptomatic or asymptomatic females and males. A separate Amplification Control is an option for inhibition testing (BDProbeTec™ ET *CT/GC/AC* Reagent Pack).
Indication for Use	Asymptomatic and symptomatic patients	Same	Same

Assay Targets	DNA from *Chlamydia trachomatis* (CT) and/or *Neisseria gonorrhoeae* (NG)	ribosomal RNA (rRNA) from *Chlamydia trachomatis* (CT) and/or *Neisseria gonorrhoeae* (GC)	DNA from *Chlamydia trachomatis* (CT) and *Neisseria gonorrhea* (NG)
Specimen Types	Urine (male and female), endocervical swab, and patient-collected vaginal swab	Clinician-collected endocervical, vaginal, and male urethral swab specimens, patient-collected vaginal swab specimens, and female and male urine specimens	Endocervical swabs, male urethral swabs, and urine specimens for females and males
CT Analyte Targets	CT genomic DNA	CT ribosomal RNA	CT cryptic plasmid DNA
NG Analyte Targets	NG genomic DNA	NG ribosomal RNA	NG genomic DNA
Collection Kit	Urine collection kit Swab collection kit	Urine collection kit Swab collection kit	Urine collection kit Swab collection kit
Nucleic Acid Extraction	Yes	Yes	Yes
Sample Extraction	Self-contained and automated after specimen sample elution and two single-dose reagent additions.	Manual	Manual
Assay Results	Qualitative	Qualitative	Qualitative
Instrument System	Cepheid GeneXpert Instrument Systems	Gen-Probe Leader HC+ Luminometer and Gen-Probe Target Capture System	ProbeTec ET™ System
Assay Controls	Internal sample processing control (SPC), sample adequacy control (SAC), and probe check control (PCC). External controls available.	The Positive Control, CT / Negative Control, GC and the Positive Control, GC / Negative Control, CT act as controls for the target capture, amplification, and detection steps of the assay.	Amplification Control (AC)

Time to test results	Approximately 90 minutes (1.5 hours) to results.	Approximately 4.5 hours to results.	Approximately 3.5 hours to results

Similarities and Differences between the Cepheid Collection Kits and the Predicate Collection Devices

	Device :	Predicate:	Predicate:
Item	**Cepheid Xpert CT/NG Vaginal/Endocervical Specimen Collection Kit**	**GEN-PROBE® APTIMA® Unisex Swab Specimen Collection kit for Endocervical and Male Urethral Swab Specimen**	**GEN-PROBE® APTIMA® Vaginal Swab Specimen Collection kit**
Description	Contains an individually packaged sterile large cleaning swab (for endocervical samples) and a package containing an individually packaged sterile collection swab (for vaginal and endocervical sampling) and a Xpert CT/NG Swab Transport Reagent tube. The collection swab is placed into the Transport Reagent Tube after swab sampling to stabilize the nucleic acid until sample preparation.	Contains an individually packaged sterile Endocervical cleaning swab and an individually-packaged sterile specimen collection swab that is placed into the Transport Tube after swab sampling and is used to stabilize the nucleic acid until sample preparation.	Contains an individually packaged sterile specimen collection swab that is placed into the Transport Tube after swab sampling and is used to stabilize the nucleic acid until sample preparation.

Item	Cepheid Xpert CT/NG Urine Specimen Collection Kit	GEN-PROBE® APTIMA® Urine Specimen Collection kit
Description	Contains one individually packaged sterile disposable transfer pipette and one Xpert CT/NG Urine Transport Reagent tube. Approximately 7 mL of a first-catch urine specimen is transferred to the Urine Transport Reagent tube to preserve and transport the specimen prior to analysis with the Cepheid Xpert CT/NG Assay.	Contains a disposable transfer pipette for adding approximately 2 mL of urine to a Specimen Transport Tube containing 2.0 mL of Transport Buffer.

K. Standard/Guidance Document Referenced:

1. *Establishing the Performance Characteristics of In Vitro Diagnostic Devices for Chlamydia trachomatis and/or Neisseria gonorrhea: Screening and Diagnostic Testing* - Draft Guidance for Industry and FDA Staff, May 11, 2011.

2. CLSI EP5-A2, *Evaluation of Precision Performance of Quantitative Measurement Methods*; Approved Guideline –Second Edition.
3. EN 13640, Stability Testing of *in vitro* Diagnostic Reagents, June 2002
4. ASTM D4169-05 and ASTM D4169-09, *Standard Practice for Performance Testing of Shipping Containers and Systems*.
5. CLSI MM3-A2, *Molecular Diagnostic Methods for Infectious Disease;* Approved Guideline –Second Edition
6. *Nucleic Acid Based In Vitro Diagnostic Devices for Detection of Microbial Pathogens* - Draft Guidance for Industry and FDA Staff, December 8, 2005.
7. Guidance for Industry and FDA Staff, Format for Traditional and Abbreviated 510(k), August 12, 2005.
8. *Guidance for Industry and FDA Staff - Class II Special Controls Guidance Document: Instrumentation for Clinical Multiplex Test Systems,* March 10, 2005.
9. *Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices* - Guidance for Industry and FDA Staff, May 11, 2005.
10. *Guidance for Off-the-Shelf Software Use in Medical Devices; Final,* September 9, 1999.

L. Test Principle:

Detection of the amplified DNA is by fluorogenic target-specific probe hybridization followed by 5'-nuclease cleavage of the probe to release the fluorophore. The primers and probes in the Xpert CT/NG Assay are designed to amplify and detect one unique chromosomal gene sequence for *Chlamydia trachomatis* and two unique chromosomal gene sequences for *Neisseria gonorrhoeae*.

The GeneXpert Instrument Systems perform hands-off, automated sample preparation by first mixing the sample with Lysis Reagent and then taking the mixture to re-suspend the Sample Processing Control in the form of a lyophilized bead within the cartridge. Lysis of bacterial cells with Lysis Reagent is followed by mixing with Binding Reagent which allows capture of the nucleic acids on the glass fiber column. The column is then washed to remove contaminants and finally, the purified nucleic acids are eluted with an elution reagent. The nucleic acid solution is mixed with dry real-time PCR reagents and transferred into the PCR tube for real-time PCR and detection of chromosomal DNA gene sequences for *Chlamydia trachomatis* and/or *Neisseria gonorrhoeae.* During real time-PCR cycling, optical signals from five (5) sequence specific fluorescent probes within the reaction are monitored in real time. The probes correspond to the one CT and two NG targets, SAC target and the SPC target.

Controls:

Internal Controls:

The Xpert CT/NG Assay includes three internal controls contained in each cartridge:

- The Probe Check Control (PCC) performs a check on the amplification portion of the assay. It controls for missing or incompletely hydrated beads of enzyme and target specific reagent. It also controls for the generated fluorescence which must meet internal acceptance criteria.

- The Sample Processing Control (SPC) contains DNA from *Bacillus globigii* and verifies the sample processing and target amplification.

- The Sample Adequacy Control (SAC) ensures that the sample contains human cells and that the cells are adequately lysed in order to extract nucleic acids.

Additionally, the GeneExpert Instrument performs a System Control Check for Temperature. This check ensures that the instrument is operating within validated heating and cooling specifications.

External Controls:

External Controls are not included with the kit and must be obtained by the user.

Interpretation of Results:

The results are interpolated by the GeneXpert System from measured fluorescent signals and embedded calculation algorithms. The diagnostic algorithm is based on the results for the optical curves associated with the CT and NG targets as well as the Sample Processing Control (SPC) and Sample Adequacy Control (SAC). A cycle threshold (Ct) is obtained for each curve. The values for Ct are used to determine the presence or absence of the targets being detected (CT, NG, SAC, and SPC). The optical curves for the CT and/or NG target are interpreted as positive if they satisfy fixed criteria for valid threshold fluorescence crossing. The optical curves for the CT and/or NG targets are interpreted as negative if they fail to satisfy fixed criteria for a valid threshold crossing. The following table shows the possible final test results:

Result Text	CT1	NG2	NG4	SPC	SA
CT DETECTED; NG DETECTED	+	+	+	+/-	+/
CT DETECTED; NG NOT DETECTED	+	+	-	+/-	+/
CT DETECTED; NG NOT DETECTED	+	-	+	+/-	+/
CT NOT DETECTED; NG DETECTED	-	+	+	+/-	+/
CT NOT DETECTED, NG NOT DETECTED	-	-	+	+/-	+/
CT NOT DETECTED, NG NOT DETECTED	-	-	-	+	+
INVALID	-	-	-	-	+/
INVALID	-	-	-	+/-	-

There are 3 possible outcomes that require a re-test of the specimen:

INVALID indicates that the SPC and/or the SAC failed. The sample was not properly processed, PCR was inhibited, or the sample was inadequate.

ERROR indicates that the PCC failed and the assay was aborted possibly because the reaction tube was filled improperly, a reagent probe integrity problem was detected, pressure limits were exceeded, or a valve positioning error was detected.

NO RESULT indicates that insufficient data were collected. For example, the operator stopped a test that was in progress.

A re-test is performed on the leftover sample from the CT/NG Transport Reagent tube using a new cartridge.

M. Performance Characteristics

1. Analytical performance:

a. Precision/Reproducibility:

Reproducibility Study:

Reproducibility of the Xpert CT/NG Assay was evaluated at three sites using specimens comprised of CT and NG organisms seeded into pooled, negative male urine (urine matrix) or pooled, negative female vaginal swab samples (swab matrix). The specimens were prepared at concentration levels representing low positive (1X LoD), moderate positive (2-3X LoD), and high positive (>20X LoD) for each organism. The panel members prepared with high concentrations (>20xLoD) of one organism and low concentrations (1xLoD) of the other organism allowed for the evaluation of potential competitive inhibition of one organism by the other one.

Negative panel members were also included, and were comprised of pooled, negative male urine and pooled, negative vaginal swab samples. A panel of 22 specimens (11 in urine matrix and 11 in swab matrix) was tested on five different days by two different operators four times per day at three sites (22 specimens x 2 operators x 5 days x 4 replicates per day x 3 sites). Three lots of Xpert CT/NG reagents were included in the study, with two lots being tested at each site. Xpert CT/NG Assays were performed according to the Xpert CT/NG Assay procedure. The rate of agreement with expected results of CT and NG for each panel member was calculated for each site. The results are presented separately for swab samples and urine samples.

Summary of Reproducibility Results for Swab Samples; Percent Agreement by Study Site

Sample		Site 1 (GeneXpert Dx)	Site 2 (Infinity-80)	Site 3 (Infinity-48)	% Total Agreement by Sample
CT >20X LoD; NG >20X LoD	**CT**	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)
	NG	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)
CT >20X LoD; NG 1X LoD	**CT**	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)
	NG	87.5% (35/40)	97.5% (39/40)	95.0% (38/40)	93.3% (112/120)
CT >20X LoD; NG neg	**CT**	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)
	NG	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)
CT 1X LoD; NG >20X LoD	**CT**	90.0% (36/40)	97.5% (39/40)	95.0% (38/40)	94.2% (113/120)
	NG	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)
CT 1X LoD; NG 1X LoD	**CT**	97.5% (39/40)	100% (40/40)	100% (40/40)	99.2% (119/120)
	NG	92.5% (37/40)	90.0% (36/40)	90.0% (36/40)	90.8% (109/120)
CT 1X LoD; NG neg	**CT**	97.5% (39/40)	90.0% (36/40)	90.0% (36/40)	92.5% (111/120)
	NG	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)
CT 2-3X LoD; NG neg	**CT**	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)
	NG	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)
CT neg; NG >20X LoD	**CT**	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)

Sample		Site 1 (GeneXpert Dx)	Site 2 (Infinity-80)	Site 3 (Infinity-48)	% Total Agreement by Sample
	NG	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)
CT neg; NG 1X LoD	**CT**	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)
	NG	100.0% (40/40)	97.5% (39/40)	97.5% (39/40)	98.3% (118/120)
CT neg; NG 2-3X LoD	**CT**	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)
	NG	97.5% (39/40)	100% (40/40)	100% (40/40)	99.2% (119/120)
CT neg; NG neg	**CT**	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)
	NG	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)

Summary of Reproducibility Results for Urine Samples; Percent Agreement by Study Site

Sample		Site 1 (GeneXpert Dx)	Site 2 (Infinity-80)	Site 3 (Infinity-48)	% Total Agreement by Sample
CT >20X LoD; NG >20X LoD	**CT**	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)
	NG	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)
CT >20X LoD; NG 1X LoD	**CT**	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)
	NG	92.5% (37/40)	97.5% (39/40)	97.5% (39/40)	95.8% (115/120)
CT >20X LoD; NG neg	**CT**	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)
	NG	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)
CT 1X LoD; NG >20X LoD	**CT**	92.5% (37/40)	95.0% (38/40)	90.0% (36/40)	92.5% (111/120)
	NG	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)
CT 1X LoD; NG 1X LoD	**CT**	95.0% (38/40)	80.0% (32/40)	87.5% (35/40)	87.5% (105/120)
	NG	95.0% (38/40)	85.0% (34/40)	87.5% (35/40)	89.2% (107/120)
CT 1X LoD; NG neg	**CT**	87.5% (35/40)	97.5% (39/40)	97.5% (39/40)	94.2% (113/120)
	NG	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)
CT 2-3X LoD; NG neg	**CT**	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)
	NG	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)
CT neg; NG >20X LoD	**CT**	97.5% (39/40)	100% (40/40)	100% (40/40)	99.2% (119/120)
	NG	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)
CT neg;	**CT**	100% (40/40)	100% (40/40)	97.5% (39/40)	99.2% (119/120)

Sample		Site 1 (GeneXpert Dx)	Site 2 (Infinity-80)	Site 3 (Infinity-48)	% Total Agreement by Sample
NG 1X LoD	**NG**	100% (40/40)	97.5% (39/40)	100% (40/40)	99.2% (119/120)
CT neg; NG 2-3X LoD	**CT**	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)
	NG	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)
CT neg; NG neg	**CT**	100% (40/40)	100% (40/40)	97.5% (39/40)	99.2% (119/120)
	NG	100% (40/40)	100% (40/40)	100% (40/40)	100% (120/120)

The reproducibility of the Xpert CT/NG Assay was also evaluated in terms of the fluorescence signal expressed in Ct values for each target detected. The mean, standard deviation (SD), and coefficient of variation (CV) measures between-sites, between-lots, between-days, and between-runs for each panel member, for each target detected, are presented below.

Summary of Reproducibility data for Swab and Urine Specimens – CT1 Target

Type	Target Conc.					Between-Site		Between- Lot		Between-Day		Between-Run[1]		Within-Run		Total	
	CT (LoD)	NG (LoD)	Agree/N	Agrmt (%)	Mean Ct	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
Swab	>20X	>20X	120/120	100	20.67	0.21	1.0	0.11	0.5	0.11	0.5	0.00	0.0	0.29	1.4	0.39	1.9
	>20X	1X	112/120	93.3	20.73	0.29	1.4	0.37	1.8	0.00	0.0	0.00	0.0	1.59	7.7	1.66	8.0
	>20X	NEG	120/120	100	20.59	0.00	0.0	0.21	1.0	0.06	0.3	0.08	0.4	0.26	1.3	0.35	1.7
	1X	>20X	113/120	94.2	37.20	0.10	0.3	0.21	0.6	0.00	0.0	0.00	0.0	1.15	3.1	1.18	3.2
	1X	1X	106/120	88.3	37.04	0.17	0.5	0.00	0.0	0.00	0.0	0.12	0.3	1.08	2.9	1.10	3.0
	1X	NEG	111/120	92.5	37.04	0.06	0.2	0.00	0.0	0.00	0.0	0.00	0.0	1.12	3.0	1.12	3.0
	2-3X	NEG	120/120	100	35.63	0.13	0.4	0.00	0.0	0.15	0.4	0.10	0.3	0.77	2.2	0.80	2.3
	NEG	>20X	120/120	100	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	NEG	1X	118/120	98.3	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	NEG	2-3X	119/120	99.2	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	NEG	NEG	120/120	100	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Urine	>20X	>20X	120/120	100	21.46	0.23	1.0	0.00	0.0	0.12	0.5	0.02	0.1	0.31	1.4	0.40	1.9
	>20X	1X	115/120	95.8	21.33	0.13	0.6	0.05	0.2	0.13	0.6	0.00	0.0	0.43	2.0	0.47	2.2
	>20X	NEG	120/120	100	21.36	0.19	0.9	0.00	0.0	0.12	0.6	0.02	0.1	0.47	2.2	0.52	2.4
	1X	>20X	111/120	92.5	37.24	0.36	1.0	0.00	0.0	0.00	0.0	0.00	0.0	1.33	3.6	1.38	3.7
	1X	1X	97/120	80.8	37.15	0.40	1.1	0.18	0.5	0.17	0.4	0.00	0.0	1.02	2.8	1.13	3.0
	1X	NEG	113/120	94.2	37.39	0.10	0.3	0.32	0.9	0.00	0.0	0.00	0.0	1.38	3.7	1.42	3.8
	2-3X	NEG	120/120	100	35.26	0.24	0.7	0.00	0.0	0.30	0.9	0.00	0.0	0.80	2.3	0.89	2.5
	NEG	>20X	119/120	99.2	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	NEG	1X	118/120	98.3	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	NEG	2-3X	120/120	100	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	NEG	NEG	119/120	99.2	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Agrmt=Agreement, Conc=concentration, CV=coefficient of variation, N/A=Not Applicable for negative samples, SD=standard deviation

Note: Variability from some factors may be numerically negative, which can occur if the variability due to those factors is very small. When this occurs, the variability as measured with SD and CV is set to 0.

[1]A run is defined as the four samples per panel member run by one operator at one site on one day

Summary of Reproducibility data for Swab and Urine Specimens – NG2 Target

Type	Target Conc.					Between-Site		Between- Lot		Between-Day		Between-Run[1]		Within-Run		Total	
	CT (LoD)	NG (LoD)	Agree/N	Agrmt (%)	Mean Ct	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
Swab	>20X	>20X	120/120	100	19.65	0.03	0.1	0.09	0.4	0.07	0.3	0.02	0.1	0.24	1.2	0.26	1.3
	>20X	1X	112/120	93.3	35.38	0.22	0.6	0.00	0.0	0.00	0.0	0.00	0.0	1.98	5.6	1.99	5.6
	>20X	NEG	120/120	100	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	1X	>20X	113/120	94.2	19.69	0.12	0.6	0.00	0.0	0.19	1.0	0.00	0.0	0.43	2.2	0.49	2.5
	1X	1X	106/120	88.3	35.61	0.00	0.0	0.53	1.5	0.00	0.0	0.80	2.2	1.37	3.9	1.67	4.7
	1X	NEG	111/120	92.5	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	2-3X	NEG	120/120	100	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	NEG	>20X	120/120	100	19.60	0.10	0.5	0.07	0.4	0.00	0.0	0.07	0.4	0.20	1.0	0.25	1.3
	NEG	1X	118/120	98.3	35.43	0.39	1.1	0.00	0.0	0.04	0.1	0.22	0.6	0.94	2.6	1.04	2.9
	NEG	2-3X	119/120	99.2	33.97	0.00	0.0	0.15	0.4	0.00	0.0	0.15	0.4	0.71	2.1	0.74	2.2
	NEG	NEG	120/120	100	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Urine	>20X	>20X	120/120	100	20.34	0.06	0.3	0.09	0.4	0.00	0.0	0.07	0.3	0.23	1.1	0.26	1.3
	>20X	1X	115/120	95.8	35.41	0.00	0.0	0.00	0.0	0.19	0.5	0.30	0.8	1.15	3.3	1.20	3.4
	>20X	NEG	120/120	100	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	1X	>20X	111/120	92.5	20.40	0.06	0.3	0.07	0.3	0.00	0.0	0.00	0.0	0.39	1.9	0.40	2.0
	1X	1X	97/120	80.8	35.57	0.20	0.6	0.00	0.0	0.13	0.4	0.10	0.3	1.28	3.6	1.31	3.7
	1X	NEG	113/120	94.2	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	2-3X	NEG	120/120	100	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	NEG	>20X	119/120	99.2	20.39	0.00	0.0	0.07	0.4	0.14	0.7	0.05	0.3	0.26	1.3	0.31	1.5
	NEG	1X	118/120	98.3	35.35	0.00	0.0	0.11	0.3	0.00	0.0	0.36	1.0	0.92	2.6	0.99	2.8
	NEG	2-3X	120/120	100	33.80	0.00	0.0	0.18	0.5	0.00	0.0	0.00	0.0	0.54	1.6	0.57	1.7
	NEG	NEG	119/120	99.2	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Agrmt=Agreement, Conc=concentration, CV=coefficient of variation, N/A=Not Applicable for negative samples, SD=standard deviation

Note: Variability from some factors may be numerically negative, which can occur if the variability due to those factors is very small. When this occurs, the variability as measured with SD and CV is set to 0.

[1]A run is defined as the four samples per panel member run by one operator at one site on one day

Summary of Reproducibility data for Swab and Urine Specimens – NG4 Target

Type	Target Conc.					Between-Site		Between- Lot		Between-Day		Between-Run[1]		Within-Run		Total	
	CT (LoD)	NG (LoD)	Agree/N	Agrmt (%)	Mean Ct	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
Swab	>20X	>20X	120/120	100	19.34	0.00	0.0	0.12	0.6	0.11	0.6	0.00	0.0	0.39	2.0	0.42	2.2
	>20X	1X	112/120	93.3	35.00	0.41	1.2	0.00	0.0	0.00	0.0	0.32	0.9	1.89	5.4	1.96	5.6
	>20X	NEG	120/120	100	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	1X	>20X	113/120	94.2	19.41	0.07	0.4	0.00	0.0	0.14	0.7	0.03	0.2	0.49	2.5	0.52	2.7
	1X	1X	106/120	88.3	35.47	0.32	0.9	0.00	0.0	0.00	0.0	0.70	2.0	0.90	2.5	1.19	3.3
	1X	NEG	111/120	92.5	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	2-3X	NEG	120/120	100	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	NEG	>20X	120/120	100	19.35	0.02	0.1	0.04	0.2	0.00	0.0	0.07	0.4	0.28	1.5	0.29	1.5
	NEG	1X	118/120	98.3	35.05	0.00	0.0	0.16	0.5	0.00	0.0	0.00	0.0	1.00	2.9	1.01	2.9
	NEG	2-3X	119/120	99.2	33.57	0.14	0.4	0.17	0.5	0.00	0.0	0.00	0.0	0.78	2.3	0.81	2.4
	NEG	NEG	120/120	100	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Urine	>20X	>20X	120/120	100	20.06	0.12	0.6	0.12	0.6	0.09	0.4	0.00	0.0	0.39	1.9	0.43	2.1
	>20X	1X	115/120	95.8	35.27	0.17	0.5	0.13	0.4	0.00	0.0	0.00	0.0	1.04	2.9	1.06	3.0
	>20X	NEG	120/120	100	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	1X	>20X	111/120	92.5	20.16	0.00	0.0	0.08	0.4	0.00	0.0	0.12	0.6	0.56	2.8	0.58	2.9
	1X	1X	97/120	80.8	35.25	0.00	0.0	0.00	0.0	0.41	1.2	0.00	0.0	1.17	3.3	1.24	3.5
	1X	NEG	113/120	94.2	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	2-3X	NEG	120/120	100	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	NEG	>20X	119/120	99.2	20.12	0.09	0.5	0.10	0.5	0.06	0.3	0.00	0.0	0.41	2.0	0.43	2.2
	NEG	1X	118/120	98.3	35.05	0.24	0.7	0.00	0.0	0.15	0.4	0.12	0.4	1.09	3.1	1.13	3.2
	NEG	2-3X	120/120	100	33.67	0.00	0.0	0.33	1.0	0.00	0.0	0.16	0.5	0.83	2.5	0.91	2.7
	NEG	NEG	119/120	99.2	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Agrmt=Agreement, Conc=concentration, CV=coefficient of variation, N/A=Not Applicable for negative samples, SD=standard deviation

Note: Variability from some factors may be numerically negative, which can occur if the variability due to those factors is very small. When this occurs, the variability as measured with SD and CV is set to 0.

[1]A run is defined as the four samples per panel member run by one operator at one site on one day

Instrument Precision Study:

An in-house precision study was conducted to compare the performance of the GeneXpert Dx and the Infinity-80 Instrument Systems using specimens comprised of CT and NG organisms seeded into negative urine simulated swab matrix. The specimens were prepared at concentration levels representing low positive (0.25-0.5X LoD), moderate positive (2-3X LoD), and high positive (>20X LoD) for each organism. Negative panel members were also included and were comprised of negative urine and negative diluent. A panel of 20 specimens (10 in urine matrix and 10 in swab matrix) was tested on 12 different days by two operators. The samples were tested in a different order throughout the study; the specimens were blinded with a Specimen ID, which was used to define the order in which the samples were tested. Each operator conducted four runs of each panel specimen per day on each of the two instrument systems (20 specimens x 4 times/ day x 12 days x 2 operators x 2 instrument systems). One lot of Xpert CT/NG Assay was used for the study. Xpert CT/NG assays were performed according to the Xpert CT/NG Assay procedure. External controls were run on each instrument by each operator on each day that samples were tested. The study challenged the Infinity-80 system by loading the test cartridges continuously by the two operators, which resulted in the worst-case scenario where the maximum number of cartridges was loaded and analyzed simultaneously. Xpert CT/NG assays were performed according to the Xpert CT/NG Assay procedure.

The rate of agreement with expected results of CT and NG for each panel member, in swab matrix, is presented below.

Summary of Instrument System Precision Results;
Percent Agreement Swab Matrix

Sample		**GeneXpert Dx**	**Infinity-80**	**% Total Agreement by Sample**
CT >20X LoD; NG >20X LoD	**CT**	100% (96/96)	100% (95/95)[a]	100% (191/191)
	NG	100% (96/96)	100% (95/95)[a]	100% (191/191)
CT >20X LoD; NG 0.25-0.5X LoD	**CT**	100% (96/96)	100% (96/96)	100% (192/192)
	NG	62.5% (60/96)	52.1% (50/96)	57.3% (110/192)
CT >20X LoD; NG neg	**CT**	100% (96/96)	100% (95/95)[b]	100% (191/191)
	NG	100% (96/96)	100% (95/95)[b]	100% (191/191)
CT 0.25-0.5X LoD; NG >20X LoD	**CT**	46.9% (45/96)	42.7% (41/96)	44.8% (86/192)
	NG	100%	100% (96/96)	100% (192/192)

Sample		GeneXpert Dx	Infinity-80	% Total Agreement by Sample
		(96/96)		
CT 0.25-0.5X LoD; NG 0.25-0.5X LoD	**CT**	55.2% (53/96)	60.4% (58/96)	57.8% (111/192)
	NG	50.0% (48/96)	66.7% (64/96)	58.3% (112/192)
CT 0.25-0.5X LoD; NG neg	**CT**	61.5% (59/96)	62.1% (59/95)[c]	61.8% (118/191)
	NG	100% (96/96)	100% (95/95)[c]	100% (191/191)
CT 2-3X LoD; NG 2-3X LoD	**CT**	100% (96/96)	100% (96/96)	100% (192/192)
	NG	100% (96/96)	100% (96/96)	100% (192/192)
CT neg; NG >20X LoD	**CT**	100% (96/96)	100% (96/96)	100% (192/192)
	NG	100% (96/96)	100% (96/96)	100% (192/192)
CT neg; NG 0.25-0.5X LoD	**CT**	100% (95/95)[b]	100% (96/96)	100% (191/191)
	NG	58.9% (56/95)[b]	62.5% (60/96)	60.7% (116/191)
CT neg; NG neg	**CT**	100% (96/96)	100% (96/96)	100% (192/192)
	NG	100% (96/96)	100% (96/96)	100% (192/192)

[a]One sample was indeterminate after initial and retest.
[b]One sample each of CT >20X LoD;NG neg sample and CT neg; NG 0.25-0.5X LoD resulted in ERROR on initial test and were not retested.
[c]One sample mistakenly not tested.

The rate of agreement with expected results of CT and NG for each panel member, in urine matrix, is presented below.

Summary of Instrument System Precision Results;
Percent Agreement Urine Matrix

Sample		GeneXpert Dx	Infinity-80	% Total Agreement by Sample
CT >20X LoD; NG >20X LoD	**CT**	100% (96/96)	100% (96/96)	100% (192/192)
	NG	100% (96/96)	100% (96/96)	100% (192/192)
CT >20X LoD; NG 0.25-0.5X LoD	**CT**	100% (96/96)	100% (96/96)	100% (192/192)
	NG	46.9% (45/96)	49.0% (47/96)	47.9% (92/192)
CT >20X LoD;	**CT**	100% (96/96)	100% (96/96)	100% (192/192)

Sample		GeneXpert Dx	Infinity-80	% Total Agreement by Sample
NG neg	**NG**	100% (96/96)	100% (96/96)	100% (192/192)
CT 0.25-0.5X LoD; NG >20X LoD	**CT**	50.0% (48/96)	52.1% (50/96)	51.0% (98/192)
	NG	100% (96/96)	100% (96/96)	100% (192/192)
CT 0.25-0.5X LoD; NG 0.25-0.5X LoD	**CT**	44.8% (43/96)	39.6% (38/96)	42.2% (81/192)
	NG	62.5% (60/96)	58.3% (56/96)	60.4% (116/192)
CT 0.25-0.5X LoD; NG neg	**CT**	46.9% (45/96)	46.9% (45/96)	46.9% (90/192)
	NG	100% (96/96)	100% (96/96)	100% (192/192)
CT 2-3X LoD; NG 2-3X LoD	**CT**	100% (96/96)	100% (96/96)	100% (192/192)
	NG	100% (96/96)	100% (96/96)	100% (192/192)
CT neg; NG >20X LoD	**CT**	100% (96/96)	100% (96/96)	100% (192/192)
	NG	100% (96/96)	100% (96/96)	100% (192/192)
CT neg; NG 0.25-0.5X LoD	**CT**	100% (96/96)	100% (96/96)	100% (192/192)
	NG	36.5% (35/96)	33.3% (32/96)	34.9% (67/192)
CT neg; NG neg	**CT**	100% (96/96)	100% (96/96)	100% (192/192)
	NG	100% (96/96)	100% (96/96)	100% (192/192)

The precision of the Xpert CT/NG Assay in this study was also evaluated in terms of the fluorescence signal expressed in Ct values for each target detected. The mean, standard deviation (SD), and coefficient of variation (CV) between-instruments, between-days, and between-runs for each panel member, for each target detected, are presented below.

Summary of In-house Precision Data for Swab and Urine Specimens – CT1 Target

Type	Target Conc.					Between-Instrument		Between-Day		Between-Run[1]		Within-Run		Total	
	CT (LoD)	NG (LoD)	Agree/N	Agrmt (%)	Mean Ct	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
Swab	>20X	>20X	191/191	100	23.52	0.05	0.2	0.02	0.1	0.00	0.0	0.25	1.1	0.26	1.1
	>20X	0.25-0.5X	110/192	57.3	23.52	0.00	0.0	0.00	0.0	0.08	0.3	0.18	0.7	0.19	0.8
	>20X	NEG	191/191	100	23.55	0.03	0.1	0.00	0.0	0.00	0.0	0.22	0.9	0.22	0.9
	0.25-0.5X	>20X	86/192	44.8	38.77	0.00	0.0	0.00	0.0	0.32	0.8	1.38	3.6	1.42	3.7
	0.25-0.5X	0.25-0.5X	59/192	30.7	38.46	0.00	0.0	0.30	0.8	0.00	0.0	1.35	3.5	1.39	3.6
	0.25-0.5X	NEG	118/191	61.8	38.05	0.08	0.2	0.00	0.0	0.00	0.0	1.26	3.3	1.26	3.3
	2-3X	2-3X	192/192	100	31.49	0.04	0.1	0.00	0.0	0.06	0.2	0.24	0.8	0.25	0.8
	NEG	>20X	192/192	100	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	NEG	0.25-0.5X	116/191	60.7	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	NEG	NEG	192/192	100	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Urine	>20X	>20X	192/192	100	24.35	0.05	0.2	0.20	0.8	0.10	0.4	0.30	1.2	0.38	1.6
	>20X	0.25-0.5X	92/192	47.9	24.25	0.00	0.0	0.06	0.3	0.00	0.0	0.62	2.6	0.62	2.6
	>20X	NEG	192/192	100	24.12	0.00	0.0	0.15	0.6	0.19	0.8	0.34	1.4	0.41	1.7
	0.25-	>20X	98/192	51.0	38.33	0.12	0.3	0.00	0.0	0.84	2.2	1.03	2.7	1.33	3.5

Type	Target Conc.					Between-Instrument		Between-Day		Between-Run[1]		Within-Run		Total	
	CT (LoD)	NG (LoD)	Agree/N	Agrmt (%)	Mean Ct	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
	0.5X														
	0.25-0.5X	0.25-0.5X	48/192	25.0	38.26	0.00	0.0	0.00	0.0	0.56	1.5	1.05	2.7	1.19	3.1
	0.25-0.5X	NEG	90/192	46.9	38.39	0.00	0.0	0.00	0.0	0.00	0.0	1.09	2.8	1.09	2.8
	2-3X	2-3X	192/192	100	31.85	0.00	0.0	0.11	0.4	0.18	0.6	0.32	1.0	0.39	1.2
	NEG	>20X	192/192	100	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	NEG	0.25-0.5X	67/192	34.9	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	NEG	NEG	192/192	100	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Agrmt=Agreement, Conc=concentration, CV=coefficient of variation, N/A=Not Applicable for negative samples, SD=standard deviation
Note: Variability from some factors may be numerically negative, which can occur if the variability due to those factors is very small. When this occurs, the variability as measured with SD and CV is set to 0.
[1]A run is defined as the four samples per panel member run by one operator at one site on one day

Summary of In-house Precision Data for Swab and Urine Specimens – NG2 Target

Type	Target Conc.					Between-Instrument		Between-Day		Between-Run[1]		Within-Run		Total	
	CT (LoD)	NG (LoD)	Agree/N	Agrmt (%)	Mean Ct	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
Swab	>20X	>20X	191/191	100	19.03	0.01	0.0	0.02	0.1	0.00	0.0	0.21	1.1	0.21	1.1
	>20X	0.25-0.5X	110/192	57.3	37.63	0.07	0.2	0.46	1.2	0.00	0.0	1.55	4.1	1.62	4.3
	>20X	NEG	191/191	100	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	0.25-0.5X	>20X	86/192	44.8	19.08	0.00	0.0	0.00	0.0	0.10	0.5	0.31	1.6	0.32	1.7
	0.25-0.5X	0.25-0.5X	59/192	30.7	36.78	0.00	0.0	0.24	0.6	0.00	0.0	1.47	4.0	1.49	4.0
	0.25-0.5X	NEG	118/191	61.8	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	2-3X	2-3X	192/192	100	31.35	0.00	0.0	0.00	0.0	0.00	0.0	0.33	1.1	0.33	1.1
	NEG	>20X	192/192	100	19.02	0.00	0.0	0.00	0.0	0.07	0.4	0.22	1.2	0.23	1.2
	NEG	0.25-0.5X	116/191	60.7	36.77	0.00	0.0	0.46	1.2	0.00	0.0	1.65	4.5	1.71	4.7
	NEG	NEG	192/192	100	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Urine	>20X	>20X	192/192	100	19.85	0.00	0.0	0.15	0.7	0.00	0.0	0.34	1.7	0.37	1.8
	>20X	0.25-0.5X	92/192	47.9	36.72	0.15	0.4	0.00	0	0.00	0.0	1.36	3.7	1.37	3.7
	>20X	NEG	192/192	100	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	0.25-0.5X	>20X	98/192	51.0	19.51	0.00	0.0	0.00	0.0	0.00	0.0	1.20	6.1	1.20	6.1
	0.25-0.5X	0.25-0.5X	48/192	25.0	36.38	0.26	0.7	0.00	0.0	1.98	5.5	1.13	3.1	2.30	6.3
	0.25-0.5X	NEG	90/192	46.9	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	2-3X	2-3X	192/192	100	31.53	0.00	0.0	0.09	0.3	0.16	0.5	0.42	1.3	0.46	1.4
	NEG	>20X	192/192	100	19.26	0.14	0.7	0.00	0.0	0.17	0.9	0.43	2.3	0.49	2.4
	NEG	0.25-0.5X	67/192	34.9	36.88	0.00	0.0	0.31	0.8	0.00	0	1.45	3.9	1.48	7.5
	NEG	NEG	192/192	100	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Agrmt=Agreement, Conc=concentration, CV=coefficient of variation, N/A=Not Applicable for negative samples, SD=standard deviation
Note: Variability from some factors may be numerically negative, which can occur if the variability due to those factors is very small. When this occurs, the variability as measured with SD and CV is set to 0.
[1]A run is defined as the four samples per panel member run by one operator at one site on one day

Summary of In-house Precision Data for Swab and Urine Specimens – NG4 Target

Type	Target Conc.					Between-Instrument		Between-Day		Between-Run[1]		Within-Run		Total	
	CT (LoD)	NG (LoD)	Agree/N	Agrmt (%)	Mean Ct	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
Swab	>20X	>20X	191/191	100	18.67	0.00	0.0	0.00	0.0	0.19	1.0	0.34	1.8	0.39	2.1
	>20X	0.25-0.5X	110/192	57.3	36.94	0.49	1.3	0.00	0.0	0.10	0.3	1.63	4.4	1.71	4.6
	>20X	NEG	191/191	100	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	0.25-0.5X	>20X	86/192	44.8	18.72	0.06	0.3	0.00	0.0	0.21	1.1	0.41	2.2	0.46	2.5
	0.25-0.5X	0.25-0.5X	59/192	30.7	36.57	0.00	0.0	0.50	1.4	0.00	0.0	1.55	4.3	1.63	4.5
	0.25-0.5X	NEG	118/191	61.8	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	2-3X	2-3X	192/192	100	31.06	0.00	0.0	0.05	0.2	0.00	0.0	0.42	1.4	0.43	1.4
	NEG	>20X	192/192	100	18.69	0.00	0.0	0.00	0.0	0.22	1.2	0.38	2.0	0.44	2.3
	NEG	0.25-0.5X	116/191	60.7	36.31	0.08	0.2	0.13	0.4	0.00	0.0	1.24	3.4	1.25	3.4
	NEG	NEG	192/192	100	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Urine	>20X	>20X	192/192	100	19.44	0.01	0.1	0.10	0.5	0	0	0.45	2.3	0.46	2.4
	>20X	0.25-0.5X	92/192	47.9	36.31	0	0	0.04	0.1	0.17	0.5	1.18	3.2	1.19	6.1
	>20X	NEG	192/192	100	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	0.25-0.5X	>20X	98/192	51.0	19.08	0	0	0	0	0	0	1.35	7.1	1.35	6.9
	0.25-0.5X	0.25-0.5X	48/192	25.0	36.16	0	0	0.24	0.7	0	0	1.98	5.5	2.00	10.3
	0.25-0.5X	NEG	90/192	46.9	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	2-3X	2-3X	192/192	100	31.09	0	0	0.16	0.5	0.11	0.4	0.49	1.6	0.53	2.7
	NEG	>20X	192/192	100	18.80	0.04	0.2	0	0	0.14	0.7	0.47	2.5	0.50	2.6
	NEG	0.25-0.5X	67/192	34.9	36.58	0.18	0.5	0	0	0.74	2.0	1.40	3.8	1.60	8.2
	NEG	NEG	192/192	100	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Agrmt=Agreement, Conc=concentration, CV=coefficient of variation, N/A=Not Applicable for negative samples, SD=standard deviation
Note: Variability from some factors may be numerically negative, which can occur if the variability due to those factors is very small. When this occurs, the variability as measured with SD and CV is set to 0.
[1]A run is defined as the four samples per panel member run by one operator at one site on one

b. Linearity/assay reportable range:

Not Applicable, The Xpert CT/NG Assay is a qualitative assay.

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

Specimen Stability

Specimen stability studies were conducted to evaluate the length of time the claimed specimen types can be stored prior to analysis with the Xpert CT/NG Assay. This study was conducted using cultured and tittered *C. trachomatis* and *N. gonorrhoeae* cells spiked into known negative urine and swab specimens and transferred to the appropriate transport reagent tubes. The samples were stored at different temperatures and tested at various time intervals to determine the conditions under which the specimens remain stable. Replicates of three (3) were tested at each time and temperature.

Urine Specimens

Preserved urine:

Aliquots of pooled negative urine were diluted into Xpert CT/NG Urine Transport Reagent at a ratio of 7:1 (v/v) consistent with Package Insert instructions. *C. trachomatis* LGVII (ATCC 434/VR-902B0) and *N. gonorrhoeae* (ATCC 19424) were spiked into the preserved pooled negative urines. Specimens were stored at 2°C, 15°C and 30°C and tested at several time points out to 45 days. Female urine and male urine were evaluated separately. The data supported stability of preserved female urine specimens up to 45 days when stored at refrigerator temperatures (approximately 4°C) and up to 3 days when left at room temperature. The preserved male urine was stable for 45 days when stored at temperatures from 2°C to 15°C and up to 30 days at temperatures not exceeding 30°C.

Unpreserved urine:

Spiked unpreserved urines were stored at 4°C and at room temperature and tested at several time points out to 14 days. The data supported stability of unpreserved female and male first catch urine specimens for 1 day at room temperature and for up to 8 days when stored in a refrigerator (4°C).

Swab Specimens

C. trachomatis LGVII (ATCC 434/VR-902B0) and *N. gonorrhoeae* (ATCC 49226) were spiked into preserved pooled negative endocervical swabs and pooled negative vaginal swabs. Specimens were stored at 2°C and 30°C and tested with Xpert CT/NG Assay at several time points out to 60 days. The study data indicate that endocervical and vaginal swab specimens transferred into the Xpert CT/NG Swab Transport Reagent tube (preserved endocervical/vaginal swab specimen) can be stored up to 60 days at temperatures from 2°C to 30°C prior to testing with the Xpert CT/NG Assay.

d. Detection limit:

Studies were performed to determine the analytical limit of detection (LoD) of the Xpert CT/NG Assay with purified CT elementary bodies seeded into negative natural human pooled vaginal swab and pooled male urine matrices and NG cells seeded into negative pooled simulated swab and pooled male urine matrices.

Limit of Detection for CT in Pooled Vaginal Swab Matrix

Elementary bodies from two CT serovars, ATCC vr885 serovar D and ATCC vr879 serovar H, were purified by centrifugation through a 30% sucrose cushion and titered by enumeration of elementary bodies using transmission electron microscopy. Each serovar was diluted into pooled negative vaginal swab matrix and tested with the Xpert CT/NG Assay. Replicates of 20 were evaluated at eight concentrations for CT

serovar D and at seven concentrations for CT serovar H and LoDs were estimated by probit analysis. The claimed LoDs were confirmed by analyzing at least 20 replicate samples with elementary bodies diluted to the estimated LoD concentrations. For this study, the claimed LoD is defined as the lowest concentration at which 95% of at least 20 replicates are positive.

The claimed LoD for purified CT serovar D elementary bodies (EB) in vaginal swab matrix is 84 EB/mL. The claimed LoD for purified CT serovar H elementary bodies in vaginal swab matrix is 161 EB/mL (Table 13). In this study, LoDs for the remaining purified CT serovars (in EB/mL) are A (600), B (6), Ba (1900), C (34), E (6), F (202), G (96), I (21), J (150), K (117), LGV I (31), LGV II (20) and LGV III (210) EB/mL.

LoD of Two CT Serovars in Pooled Vaginal Swab Matrix

Organism	LoD (EB/mL)
CT ATCC vr885 serovar D	84
CT ATCC vr879 serovar H	161

Limit of Detection for NG in Simulated Vaginal Swab Matrix

Two NG strains (ATCC 19424 and ATCC 49226) were tested. Replicates of 20 were evaluated at six concentrations. The LoD was estimated by probit analysis.

The LoD for NG, estimated by probit analysis, is 1.5 – 1.6 CFU/mL in a simulated swab matrix background (Table 14). An additional 30 NG strains were tested in a simulated matrix and the LoD was confirmed by testing replicates of three at or near the LoD.

LoD of Two NG Strains in Pooled Vaginal Swab Matrix

Organism	LoD (CFU/mL)
NG ATCC19424	1.5
NG ATCC49226	1.6

Limit of Detection for CT in Pooled Male Urine Matrix

Purified and titered elementary bodies from two CT serovars, ATCC vr885 serovar D and ATCC vr879 serovar H, were each tested in a sample matrix of negative pooled male urine. Replicates of 20 were evaluated at eight concentrations for CT serovar D and at seven concentrations for CT serovar H and LoDs were estimated by probit analysis. The claimed LoDs were confirmed by analyzing at least 20 replicate samples with elementary bodies diluted to the estimated LoD concentrations. For this study, the claimed LoD is defined as the lowest concentration at which 95% of at least 20 replicates are positive.

The claimed LoD for purified CT serovar D elementary bodies in male urine matrix is 75 EB/mL. The claimed LoD for purified CT serovar H elementary bodies in male

urine matrix is 134 EB/mL (Table 15). In this study, LoDs for the remaining purified CT serovars (in EB/mL) are A (900), B (11), Ba (3037), C (34), E (12), F (151), G (48), I (43), J (112), K (88), LGV I (31), LGV II (40) and LGV III (157).

LoD of Two CT Serovars in Pooled Male Urine Matrix

Organism	LoD (EB/mL)
CT ATCC vr885 serovar D	75
CT ATCC vr879 serovar H	134

Limit of Detection for NG in Pooled Male Urine Matrix

Two NG strains, ATCC 19424 and ATCC 49226, were tested in a sample matrix of negative pooled male urine. Replicates of 20 were evaluated at six concentrations. The LoD was estimated by probit analysis.

The LoD for NG, estimated by probit analysis, is 1.2 – 2.7 CFU/mL in a male urine matrix background (Table 16). LoD for 30 additional NG strains was confirmed by testing replicates of three at or near the LoD.

LoD of Two NG Strains in Pooled Male Urine Matrix

Organism	LoD (CFU/mL)
NG ATCC19424 (CFU/mL)	2.7
NG ATCC49226 (CFU/mL)	1.2

e. Inclusivity

Analytical reactivity of additional 13 serotypes and 30 additional NG strains was evaluated in the LoD studies above.

f. Interference

The analytical performance of the assay was evaluated in the presence of potentially interfering substances that may be found in vaginal/endocervical swab and urine specimens. Potentially interfering exogenous substances were diluted into vaginal/endocervical swab simulated matrix and urine matrix containing two different mixtures of CT and NG cells. The first mixture contained CT serovar D and NG strain ATCC 49226, each at the 5x LoD concentration. The second mixture contained CT serovar H and NG strain ATCC 19424, each at the 5x LoD concentration.

The following table lists the highest concentration of each potential interferent tested, at which no assay interference was observed for samples in vaginal/endocervical matrix.

Potentially Interfering Substances in Vaginal/Endocervical Matrix

Substance	Concentration
Blood	1.0% v/v
Mucin	0.8% w/v
Seminal Fluid	5.0% v/v
Hormones	7mg/mL Progesterone + 0.07mg/mL Beta Estradiol
LGV II (CT EB)	10^6 EB/mL
Vagisil Anti-Itch Cream	0.25% w/v
Clotrimazole Vaginal Cream	0.25% w/v
Preparation H Hemorroidal Cream	0.25% w/v
Miconazole 3	0.25% w/v
Monistat 1	0.25% w/v
Zovirax Cold Sore Cream	0.25% w/v
Vagisil Moisturizer	0.25% w/v
Vagi Gard Moisturizing Gel	0.25% w/v
KY Jelly Personal Lubricant	0.25% w/v
Yeast Gard Douche	0.25% w/v
Delfen Vaginal Contraceptive Foam	0.25% w/v
VH Essentials Povidone-Iodine Medicated Douche	0.25% v/v
Leukocytes	10^6 cells/mL

The following table lists the highest concentration of each potential interferent tested, at which no assay interference was observed for samples in urine matrix.

Potentially Interfering Substances in Urine Matrix

Substance	Concentration
Blood	0.3% v/v
Mucin	0.2% v/v
Seminal Fluid	5.0% v/v
Hormones	7mg/mL Progesterone + 0.07mg/mL Beta Estradiol
LGV II (CT EB)	10^6 EB/mL
Leukocytes	10^6 cells/mL
Norforms Deodorant Suppositories	0.25% w/v
BSA	10mg/ml
Glucose	10mg/mL
Bilirubin	0.2mg/mL
Aspirin	40mg/mL
Azithromycin	1.8mg/mL
Doxycycline	3.6 mg/mL
Organisms - UTI *Candida albicans*/	2.9 x 10^4 CFU/mL

Substance	Concentration
Staphylococcus aureus/*Escherichia coli*	
Acetaminophen	3.2 mg/mL
Vagisil Feminine Powder	0.25% w/v
Acidic Urine	pH 4.0
Alkaline Urine	pH 9.0

With vaginal/endocervical specimens, assay interference may be observed in the presence of:

- Blood at a concentration greater than 1% v/v;
- Mucin at a concentration greater than 0.8% w/v.

With urine specimens, assay interference may be observed in the presence of:

- Blood at a concentration greater than 0.3% v/v;
- Mucin at a concentration greater than 0.2% w/v;
- Bilirubin at a concentration greater than 0.2 mg/mL (20 mg/dL);
- Vagisil feminine powder at a concentration greater than 0.2% w/v.

g. Analytical specificity:

One hundred and one (101) different microorganisms at a concentration of at least 10^6 CFU/mL or 10^5 genome copies/mL were tested in replicates of three. All isolates were reported CT NOT DETECTED; NG NOT DETECTED; none of the organisms tested were detected by the Xpert CT/NG Assay. Positive and negative controls were included in the study.

Potential Cross-reacting Microorganisms in the Xpert CT/NG Assay

Acinetobacter calcoaceticus	Herpes simplex virus I[1]	*Neisseria sicca (3)*
Acinetobacter Iwoffi	Herpes simplex virus II[1]	*Neisseria subflava (2)*
Aerococcus viridans	Human papilloma virus[1]	*Paracoccus denitrificans*
Aeromonas hydrophila	*Kingella denitrificans*	*Peptostreptococcus anaerobius*
Alcaligenes faecalis	*Kingella kingae*	*Plesiomonas shigelloides*
Arcanobacterium pyogenes	*Klebsiella oxytoca*	*Propionibacterium acnes*
Bacteriodes fragilis	*Klebsiella pneumoniae*	*Proteus mirabilis*
Bifidobacterium adolescentis	*Lactobacillus acidophilus*	*Proteus vulgaris*
Branhamella catarrhalis	*Lactobacillus brevis*	*Providencia stuartii*
Brevibacterium linens	*Lactobacillus jensonii*	*Pseudomonas aeruginosa*
Candida albicans	*Lactobacillus lactis*	*Pseudomonas fluorescens*
Candida glabrata	*Legionella pneumophila*	*Pseudomonas putida*
Candida parapsilosis	*Leuconostoc paramensenteroides*	*Rahnella aquatilis*
Candida tropicalis	*Listeria monocytogenes*	*Saccharomyces cerevisiae*
Chlamydia pneumoniae	*Micrococcus luteus*	*Salmonella minnesota*

Chromobacterium violaceum	*Moraxella lacunata*	*Salmonella typhimurium*
Citrobacter freundii	*Moraxella osloensis*	*Serratia marcescens*
Clostridium perfringens	*Morganella morganii*	*Staphylococcus aureus*
Corynebacterium genitalium	*Mycobacterium smegmatis*	*Staphylococcus epidermidis*
Corynebacterium xerosis	*N. meningiditis*	*Staphylococcus saprophyticus*
Cryptococcus neoformans	*N. meningitidis Serogroup A*	*Streptococcus agalactiae*
Cytomegalovirus[1]	*N. meningitidis Serogroup B*	*Streptococcus bovis*
Eikenella corrodens	*N. meningitidis Serogroup C*	*Streptococcus mitis*
Entercoccus avium	*N. meningitidis Serogroup D*	*Streptococcus mutans*
Entercoccus faecalis	*N. meningitidis Serogroup W135*	*Streptococcus pneumoniae*
Entercoccus faecium	*N. meningitidis Serogroup Y*	*Streptococcus pyogenes*
Enterobacter aerogenes	*Neisseria cinerea*	*Streptococcus salivarius*
Enterobacter cloacae	*Neisseria dentrificans*	*Streptococcus sanguis*
Erysipelothrix rhusiopathiae	*Neisseria elongata (3)*	*Streptococcus griseinus*
Escherichia coli	*Neisseria flava*	*Vibrio parahaemolyticus*
Elizabethkingia meningoseptica[2]	*Neisseria flavescens (2)*	*Yersinia enterocolitica*
Fusobacterium nucleatum	*Neisseria lactamica (5)*	
Gardnerella vaginalis	*Neisseria mucosa (3)*	
Gemella haemolysans	*Neisseria perflava*	
Haemophilus influenzae	*Neisseria polysaccharea*	

(n) number of strains tested
[1] Tested at 1 x 10^5 genome copies/mL
[2] Previously known as *Flavobacterium meningosepticum*

h. Carryover/Cross-contamination

A study was conducted to demonstrate that single-use, self-contained GeneXpert cartridges prevent carry-over contamination in negative samples run following very high positive samples in the same GeneXpert module. The study consisted of a negative sample processed in the same GeneXpert module immediately following a sample with high CT spike (1.9 x 10^4 EB/mL) and a high NG spike (5.2 x 10^5 CFU/mL). Two sample types were used for this testing: a) known pooled negative urine samples; and b) known pooled negative swab samples. Each sample type was tested in each of four GeneXpert modules for a total of 44 runs for both swab and urine samples resulting in 20 positives and 24 negatives. All 40 positive samples were correctly reported as CT DETECTED; NG DETECTED. All 48 negative samples were correctly reported as CT NOT DETECTED; NG NOT DETECTED. There was no cross-contamination observed during this study.

i. Assay cut-off:

The valid cycle threshold (Ct) range for the *C. trachomatis* CT1 analyte, the *N. gonorrhoeae* analyte 1 (NG2), the *N. gonorrhoeae* analyte 2 (NG4), and the Sample Adequacy Control (SAC) is 12 to 45. The valid Ct range for the Sample Processing Control (SPC) is 25 to 45. For a valid "NG DETECTED" result, Cts for both *N.*

gonorrhoeae analytes (NG2 and NG4) must be reported in the valid detectable range. These cutoffs maximize sensitivity without specificity falling below 98%. The cutoff of 45 Cts for each target was validated in the clinical study.

2. Comparison studies

a. Comparison with predicate device:

The comparison studies were conducted in a clinical study with prospectively collected samples (see the Clinical studies section below).The performance of the Xpert CT/NG assay with patient specimens was evaluated by comparison to a Patient Infected Status (PIS) algorithm based on a combination of results from two sample types (matrices) each tested by two predicate devices. A patient was considered infected (I), for CT or for NG, if at least one positive result for the respective organism was obtained from each reference assay. Any other combination of results was categorized as not infected (NI). In this study, reference testing was performed using endocervical swab specimens and urine specimens from females, and urethral swabs and urine specimens from male patients. Result obtained by Xpert CT/NG assay for each claimed specimen type (female endocervical swabs and self-collected vaginal swabs, female urine specimens and male urine specimens) was evaluated against the Patient Infected Status (PIS). One exception was made for females with positive results on both reference urine specimens and negative results on both reference swab specimens; these patients were categorized as infected (I) for urine and not infected (NI) for the swab specimens.

The table below shows the results from symptomatic and asymptomatic females designated as infected or not infected with CT based on the PIS algorithm.

Patient Infected Status – Female CT

PIS[a]	NAAT1		NAAT2		Xpert			Symptom Status		Total
	SW[a]	UR[a]	SW	UR	PC-VS[a]	ES[a]	UR	Symp	Asymp	
NI[b]	-	-	-	-	-	-	-	1160	2269	3429
NI	-	-	-	-	IND	-	-	6	8	14
NI	-	-	-	-	-	IND[c]	-	6	16	22
NI	-	-	-	-	-	-	IND	5	6	11
NI	-	-	-	-	+	+	-	0	1	1
NI	-	-	-	-	+	-	-	6	4	10
NI	-	-	-	-	-	+	-	3	5	8
NI	-	-	-	-	-	-	+	1	0	1
NI	-	-	-	EQ[d]	-	-	-	6	20	26
NI	-	-	-	EQ	IND	IND	-	1	0	1
NI	-	-	EQ	-	-	-	-	3	4	7
NI	-	-	EQ	-	-	-	IND	1	0	1
NI	-	-	-	+	-	-	-	0	7	7
NI	-	-	+	-	-	-	-	3	0	3

PIS[a]	NAAT1		NAAT2		Xpert			Symptom Status		Total
	SW[a]	UR[a]	SW	UR	PC-VS[a]	ES[a]	UR	Symp	Asymp	
NI	-	-	+	-	-	+	-	0	1	1
NI[f]	-	+	-	+	+	-	+	7	1	8
NI[f]	-	+	-	+	+	-	-	0	1	1
NI[f]	-	+	-	+	-	-	+	0	1	1
NI	-	+	-	-	-	-	-	1	0	1
NI	-	+	-	-	+	-	+	1	0	1
NI	+	-	-	-	-	-	-	4	8	12
NI	+	-	-	-	+	-	-	2	1	3
NI	+	-	-	-	+	+	-	1	2	3
NI	+	-	-	-	-	+	-	0	1	1
NI	+	+	-	-	-	-	-	1	0	1
NI	+	+	-	-	-	-	+	0	1	1
NI	+	+	-	-	+	+	+	1	1	2
NI	+	+	-	-	+	-	+	1	0	1
NI	+	+	-	-	+	-	-	1	0	1
Total Non-Infected								1221	2358	3579
I[e]	+	+	+	+	+	+	+	65	104	169
I	+	+	+	+	IND	+	+	0	1	1
I	+	+	+	+	+	IND	+	0	1	1
I	+	+	+	+	+	+	IND	1	0	1
I	+	+	+	+	-	+	+	0	1	1
I	+	+	+	+	+	-	+	0	1	1
I[f]	-	+	-	+	+	-	+	7	1	8
I[f]	-	+	-	+	+	-	-	0	1	1
I[f]	-	+	-	+	-	-	+	0	1	1
I	-	+	+	+	+	+	+	0	2	2
I	+	-	+	+	+	+	+	1	0	1
I	+	-	+	+	+	-	+	0	1	1
I	+	-	+	+	+	+	+	1	0	1
I	+	+	-	+	+	-	+	3	2	5
I	+	+	-	+	+	+	+	4	2	6
I	+	+	+	-	+	+	+	3	4	7
I	+	+	+	-	+	+	-	1	1	2
I	+	+	+	-	+	-	+	0	1	1
I	+	-	+	-	+	+	+	1	0	1
I	+	-	EQ	+	+	+	+	0	1	1
Total Infected								87	125	212

[a]PIS = Patient Infected Status; SW = swab; UR = urine; PC-VS = patient-collected vaginal swab; ES = endocervical swab
[b]NI = Non-infected
[c]IND = Indeterminate – ERROR, INVALID or NO RESULT by Xpert CT/NG Assay; specimens with IND results by Xpert are not included in the performance tables for that specimen type.
[d]EQ = Equivocal result for this individual specimen type only; PIS status determined based on remaining specimens.
[e]I = Infected
[f]These samples are infected for urine and non-infected for swabs. In this table they appear twice.

The table below shows the results from symptomatic and asymptomatic females designated as infected or not infected with NG based on the PIS algorithm.

Patient Infected Status – Female NG

PIS[a]	NAAT1		NAAT2		Xpert			Symptom Status		Total
	SW[a]	UR[a]	SW	UR	PC-VS[a]	ES[a]	UR	Symp	Asymp	
NI[b]	-	-	-	-	-	-	-	1229	2390	3619
NI	-	-	-	-	IND[c]	-	-	6	9	15
NI	-	-	-	-	-	IND	-	6	17	23
NI	-	-	-	-	-	-	IND	6	6	12
NI	-	-	-	-	+	-	+	0	1	1
NI	-	-	-	-	+	-	-	1	0	1
NI	-	-	EQ[d]	-	-	-	-	2	5	7
NI	-	-	-	EQ	-	-	-	9	20	29
NI	-	-	-	+	-	-	-	1	3	4
NI	-	-	+	-	-	-	-	7	4	11
NI[f]	-	+	-	+	+	+	+	1	0	1
NI[f]	-	+	-	+	-	-	+	1	0	1
NI	-	-	+	+	-	-	-	1	0	1
NI	+	-	-	-	-	-	-	1	1	2
NI	-	-	EQ	-	-	-	IND	1	0	1
NI	-	-	-	EQ	-	IND	IND	1	0	1
Total Non-Infected								1273	2456	3729
I[e]	+	+	+	+	+	+	+	19	19	38
I	+	+	+	-	+	+	+	2	2	4
I	+	-	+	+	+	+	+	1	1	2
I[f]	-	+	-	+	+	+	+	1	0	1
I[f]	-	+	-	+	-	-	+	1	0	1
I	+	-	+	-	+	+	-	1	2	3
I	+	-	+	-	+	+	+	1	0	1
I	+	+	-	+	+	+	+	1	0	1
I	+	+	+	EQ	+	+	+	0	1	1
I	+	+	EQ	+	+	+	+	1	0	1
I	+	EQ	+	-	+	+	+	1	0	1
Total Infected								29	25	54

[a]PIS = Patient Infected Status; SW = swab; UR = urine; PC-VS = patient-collected vaginal swab; ES = endocervical swab
[b]NI = Non-infected
[c]IND = Indeterminate – ERROR, INVALID or NO RESULT by Xpert CT/NG Assay; specimens with IND results by Xpert are not included in the performance tables for that specimen type.
[d]EQ = Equivocal result for this individual specimen type only; PIS status determined based on remaining specimens.
[e]I = Infected
[f]These samples are infected for urine and non-infected for swabs. In this table they appear twice.

The table below shows the results from symptomatic and asymptomatic males designated as infected or not infected with CT based on the PIS algorithm.

Patient Infected Status – Male CT

PIS[a]	NAAT1		NAAT2		GX	Symptom Status		Total
	SW[a]	UR[a]	SW	UR	UR	Symp	Asymp	
NI[b]	-	-	-	-	-	568	2621	3189
NI	-	-	-	EQ[c]	-	0	19	19
NI	-	-	+	-	-	2	1	3
NI	+	-	-	-	-	6	1	7

NI	+	+	-	-	-	1	1	2
NI	-	-	-	+	-	2	7	9
NI	-	+	-	-	-	2	1	3
NI	-	-	EQ	-	-	0	1	1
NI	+	+	-	-	+	2	4	6
NI	-	-	-	-	+	0	1	1
NI	-	-	-	-	IND[d]	1	6	7
NI	-	-	-	EQ	IND	0	1	1
Total Non-Infected						584	2664	3248
I[e]	+	+	+	+	+	104	50	154
I	+	+	-	+	+	8	10	18
I	-	+	-	+	+	4	7	11
I	+	+	+	-	+	2	2	4
I	+	-	+	-	+	1	0	1
I	+	-	-	+	+	1	0	1
I	-	+	+	+	+	0	1	1
I	+	+	+	EQ	+	0	2	2
I	EQ	+	-	+	+	0	1	1
I	+	-	+	-	-	2	0	2
I	+	+	+	-	-	1	0	1
Total Infected						123	73	196

[a]PIS = Patient Infected Status; SW = Swab; UR = urine.
[b]NI = Non-infected
[c]EQ = Equivocal result for this individual specimen type only; PIS status determined based on remaining specimens.
[d]IND = Indeterminate – ERROR, INVALID or NO RESULT by Xpert CT/NG Assay; specimens with IND results by Xpert are not included in the performance tables for that specimen type.
[e]I = Infected

The table below shows the results from symptomatic and asymptomatic males designated as infected or not infected with NG based on the PIS algorithm.

Patient Infected Status – Male NG

PIS[a]	NAAT1		NAAT2		GX	Symptom Status		Total
	SW[a]	UR[a]	SW	UR	UR	Symp	Asymp	
NI[b]	-	-	-	-	-	597	2680	3277
NI	-	-	-	EQ[c]	-	0	21	21
NI	-	-	EQ	-	-	0	1	1
NI	EQ	EQ	-	-	-	1	0	1
NI	-	-	+	-	-	0	3	3
NI	-	-	-	+	-	0	3	3
NI	-	+	-	-	-	0	1	1
NI	+	-	-	-	-	2	5	7
NI	-	EQ	-	-	+	0	1	1
NI	EQ	-	+	-	+	0	1	1
NI	-	-	-	-	+	0	1	1
NI	-	-	-	-	IND[d]	1	6	7
NI	-	-	-	EQ	IND	0	1	1
Total Non-Infected						601	2724	3325
I[e]	+	+	+	+	+	105	11	116
I	+	+	+	-	+	0	1	1

PIS[a]	NAAT1		NAAT2		GX	Symptom Status		Total
	SW[a]	UR[a]	SW	UR	UR	Symp	Asymp	
I	+	-	+	-	-	0	1	1
I	+	-	-	+	-	1	0	1
Total Infected						106	13	119

[a]PIS = Patient Infected Status; SW = Swab; UR = urine.
[b]NI = Non-infected
[c]EQ = Equivocal result for this individual specimen type only; PIS status determined based on remaining specimens.
[d]IND = Indeterminate – ERROR, INVALID or NO RESULT by Xpert CT/NG Assay; specimens with IND results by Xpert are not included in the performance tables for that specimen type.
[e]I = Infected

b. Matrix comparison:

Each claimed specimen type was evaluated individually against the Patient Infected Status algorithm, as presented above.

3. Clinical studies:

a. Prospective Clinical Studies:

The performance of the Xpert CT/NG assay was evaluated in a multi-site investigational study comparing the Xpert CT/NG Assay on the GeneXpert instrument systems to a patient infected status algorithm (PIS) based on results from the BD ProbeTec™ ET *Chlamydia trachomatis* and *Neisseria gonorrhoeae* Amplified DNA Assays, and the Gen-Probe® APTIMA Combo 2® Assay. The study included prospectively collected male urine, male urethral swab, female urine, endocervical swab, and patient-collected vaginal swab (collected in a clinical setting) specimens. Specimens included in the study were collected at 36 geographically diverse sites (including four sites located in the United Kingdom) from consenting asymptomatic and symptomatic, sexually active males and females seen at locations including, but not limited to: OB/GYN, sexually transmitted disease (STD), teen, public health, and family planning clinics. All reference testing was conducted at one of two central testing laboratories. Collection-only sites also shipped specimens to laboratories for Xpert testing. Collection and testing sites conducted Xpert testing on site. There were 36 collection sites and 15 testing sites. Nine testing sites used the GeneXpert Dx system, five sites used the GeneXpert 16 system and one site used the Infinity 48 and the Infinity 80 systems. Site personnel performing the Xpert CT/NG Assay testing were trained prior to performing any study procedures. The training included the minimum requirements to be eligible for CLIA moderate complexity. Three external controls (commercially available), one positive for *Neisseria gonorrhoeae*, one positive for *Chlamydia trachomatis* and one negative (human cell line) control, were run each day of testing to monitor the performance of the Xpert CT/NG Assay. A total of 1525 controls were run during the study (502 negative, 525 CT positive, 498 NG negative).

The study subjects ranged from 17 to 61 years of age. Each female study participant provided three endocervical swabs, one self-collected vaginal swab (collected in a

clinical setting), and one urine specimen. Each male study participant provided one urine specimen and two urethral swabs.

Performance of the Xpert CT/NG Assay was calculated relative to the PIS for each of the three female sample types (endocervical swabs, patient-collected vaginal swabs and urine), and male urine.

Performance with *Chlamydia trachomatis*

Among the 3781 females, a total of 212 female subjects were infected with CT. Symptoms were reported in 41.0% (87/212) of infected and 34.1% (1221/3579) non-infected female subjects. Among the 3444 males, 196 male subjects were infected with CT. The calculated sensitivity, specificity, and predictive values (based on the prevalence of infection observed during the study) of the Xpert CT/NG Assay for CT, compared against the PIS algorithm, are presented by gender, sample type, and symptom status in the following table.

Xpert CT/NG Assay vs. Patient Infected Status for CT Detection

Specimen		Sx Status	n	TP	FP	TN	FN	Prev %	Sensitivity % (95 CI)	Specificity % (95 CI)	PPV % (95 CI)	NPV % (95 CI)
Female	PC-VS	Sym	1294	79	20	1195	0	6.1	100 (95.4-100)	98.4 (97.5-99.0)	79.8 (70.5-87.2)	100 (99.7-100)
		Asym	2472	121	11	2339	1	4.9	99.2 (95.5-100)	99.5 (99.2-99.8)	91.7 (85.6-95.8)	>99.9 (99.8-100)
		All	3766	200	31	3534	1	5.3	99.5 (97.3-100)	99.1 (98.8-99.4)	86.6 (81.5-90.7)	>99.9 (99.8-100)
	ES	Sym	1293	76	5	1209	3	6.1	96.2 (89.3-99.2)	99.6 (99.0-99.9)	93.8 (86.2-98.0)	99.8 (99.3-99.9)
		Asym	2464	117	11	2331	5	5.0	95.9 (90.7-98.7)	99.5 (99.2-99.8)	91.4 (85.1-95.6)	99.8 (99.5-99.9)
		All	3757	193	16	3540	8	5.4	96.0 (92.3-98.3)	99.6 (99.3-99.7)	92.3 (87.9-95.6)	99.8 (99.6-99.9)
	Urine	Sym	1292	84	4	1203	1	6.6	98.8 (93.6-100)	99.7 (99.2-99.9)	95.5 (88.8-98.7)	99.9 (99.5-100)
		Asym	2475	123	2	2347	3	5.1	97.6 (93.2-99.5)	99.9 (99.7-100)	98.4 (94.3-99.8)	99.9 (99.6-100)
		All	3767	207	6	3550	4	5.6	98.1 (95.2-99.5)	99.8 (99.6-99.9)	97.2 (94.0-99.0)	99.9 (99.7-100)
Male	Urine	Sym	706	120	2	581	3	17.4	97.6 (93.0-99.5)	99.7 (98.8-100)	98.4 (94.2-99.8)	99.5 (98.5-99.9)
		Asym	2730	73	5	2652	0	2.7	100.0 (95.1-100)	99.8 (99.6-99.9)	93.6 (85.7-97.9)	100 (99.9-100)
		All	3436	193	7	3233	3	5.7	98.5 (95.6-99.7)	99.8 (99.6-99.9)	96.5 (92.9-98.6)	99.9 (99.7-100)

TP=true positive**, FP**=false positive, **TN**=true negative, **FN**=false negative, ES=endocervical swab, PC-VS=patient-collected vaginal swab

Performance with *Neisseria gonorrhoeae*

Among the 3781 females, a total of 54 female subjects were infected with NG. Symptoms were reported in 53.7% (29/54) of infected and 34.1% (1273/3729) non-infected female subjects. Among the 3444 males, 119 male subjects were infected with NG. The calculated sensitivity, specificity, and predictive values (based on the prevalence of infection observed during the study) of the Xpert CT/NG Assay for NG, compared against the PIS algorithm, are presented by gender, sample type, and symptom status in the following table.

Xpert CT/NG Assay vs. Patient Infected Status for NG Detection

Specimen		Sx Status	n	TP	FP	TN	FN	Prev %	Sensitivity % (95 CI)	Specificity % (95 CI)	PPV % (95 CI)	NPV % (95 CI)
Female	PC-VS	Sym	1294	27	2	1265	0	2.1	100 (87.2-100)	99.8 (99.4-100)	93.1 (77.2-99.2)	100 (99.7-100)
		Asym	2472	25	1	2446	0	1.0	100 (86.3-100)	>99.9 (99.8-100)	96.2 (80.4-99.9)	100 (99.8-100)
		All	3766	52	3	3711	0	1.4	100 (93.2-100)	99.9 (99.8-100)	94.5 (84.9-98.9)	100 (99.9-100)
	ES	Sym	1293	27	1	1265	0	2.1	100 (87.2-100)	99.9 (99.6-100)	96.4 (81.7-99.9)	100 (99.7-100)
		Asym	2464	25	0	2439	0	1.0	100 (86.3-100)	100 (99.8-100)	100 (86.3-100)	100 (99.8-100)
		All	3757	52	1	3704	0	1.4	100 (93.2-100)	>99.9 (99.8-100)	98.1 (89.9-100)	100 (99.9-100)
	Urine	Sym	1292	28	0	1263	1	2.2	96.6 (82.2-99.9)	100 (99.7-100)	100 (87.7-100)	99.9 (99.6-100)
		Asym	2475	23	1	2449	2	1.0	92.0 (74.0-99.0)	>99.9 (99.8-100)	95.8 (78.9-99.9)	99.9 (99.7-100)
		All	3767	51	1	3712	3	1.4	94.4 (84.6-98.8)	>99.9 (99.9-100)	98.1 (89.7-100)	99.9 (99.8-100)
Male	Urine	Sym	706	105	0	600	1	15.0	99.1 (94.9-100)	100 (99.4-100)	100 (96.5-100)	99.8 (99.1-100)
		Asym	2730	12	3	2714	1	0.5	92.3 (64.0-99.8)	99.9 (99.7-100)	80.0 (51.9-95.7)	>99.9 (99.8-100)
		All	3436	117	3	3314	2	3.5	98.3 (94.1-99.8)	99.9 (99.7-100)	97.5 (92.9-99.5)	99.9 (99.8-100)

TP=true positive**, FP**=false positive, **TN**=true negative, **FN**=false negative, ES=endocervical swab, PC-VS=patient-collected vaginal swab

Rate of Invalid Results

Among the 14,790 tests performed, 416 had to be re-tested due to ERROR, INVALID or NO RESULT outcomes (2.81%, 95% CI 2.56-3.09). Of those, 355

specimens yielded valid results upon repeat assay (18 specimens were not retested). The rate of indeterminate results in the study overall was 2.81% (95% CI: 2.56-3.09). The rate of indeterminate results for each testing site is presented below.

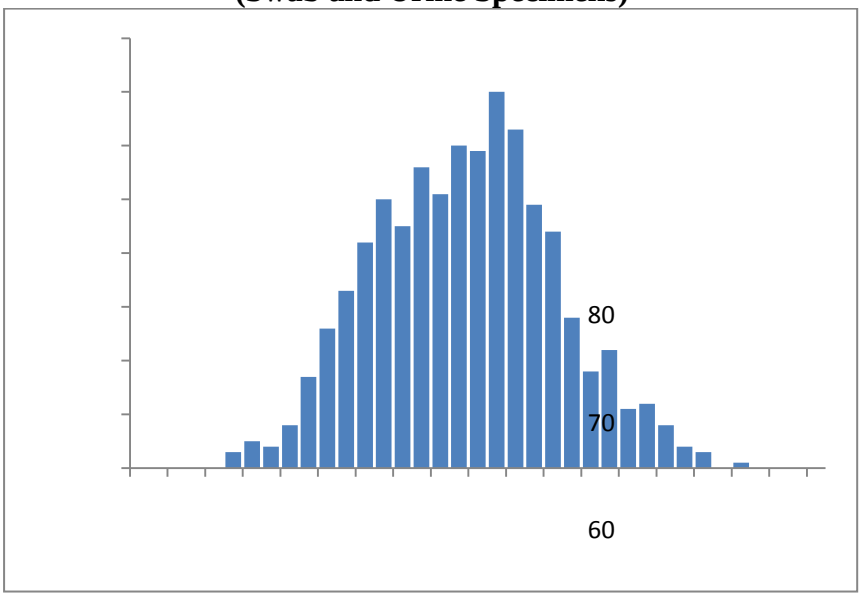
Testing Site	Error	Invalid	No Result	Total Indeterminate	Total Tested	% Rate of Repeats
14	8	0	0	8	286	2.80
21	12	2	0	14	516	2.33
27	16	1	1	18	501	3.19
77	19	1	0	20	590	3.22
78	11	0	1	12	246	4.47
85	7	2	4	13	666	1.05
89	10	1	1	12	158	6.33
93	6	2	0	8	154	3.90
95	7	0	1	8	376	1.86
96	0	0	0	0	74	0.00
98	6	3	2	11	325	1.85
100	17	0	0	17	1372	1.24
121	205	16	16	237	7525	2.72
144	0	0	1	1	8	0.00
150	27	8	2	37	1993	1.35
Total	351	36	29	416	14,790	2.37

The rate of indeterminate results ranged from 0.00 to 6.33% and was less than 5% at all the sites, except for site #89.

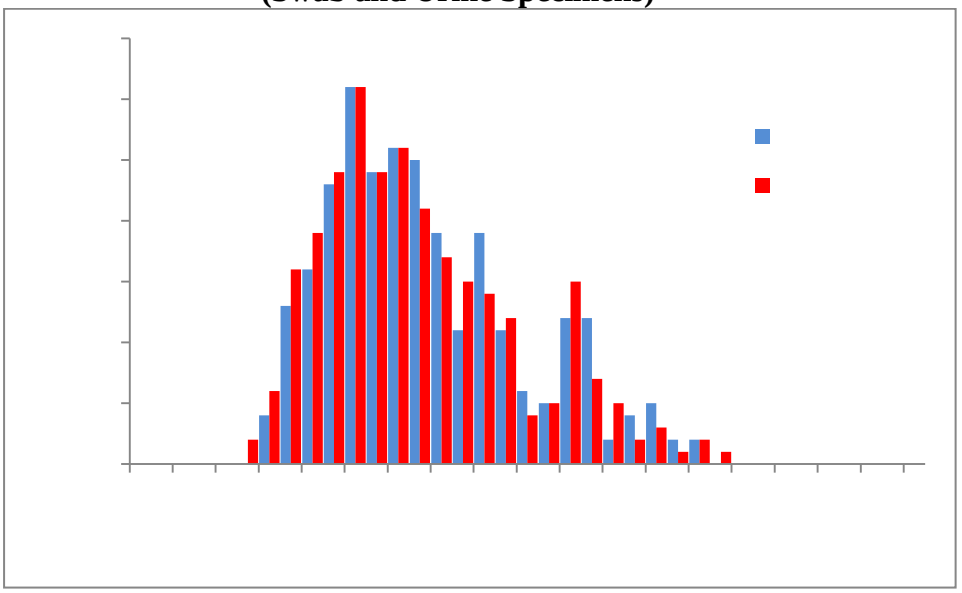
Cycle Threshold (Ct) Frequency Distribution

Patient-collected vaginal swabs, endocervical swabs and urine specimens were collected from 3781 females and urine specimens were collected from 3444 males at 36 collection sites in the US and the UK. A total of 212 females and 196 males were infected with CT and a total of 54 females and 119 males were infected with NG. The frequency distribution of Xpert CT/NG Assay positive results for CT and NG infected study subjects (infected by PIS) are shown below.

Ct Distribution of Patients Designated as Positive for CT Based on PIS Algorithm (Swab and Urine Specimens)



Ct Distribution of Patients Designated as Positive for NG Based on PIS Algorithm (Swab and Urine Specimens)



b. Other clinical supportive data

Not applicable.

4. Clinical cut-off**:**

Not applicable.

5. Expected values:

The prevalence of infection with CT and/or NG in patient populations depends on risk factors such as age, gender, the presence or absence of symptoms, the type of clinic, and the sensitivity of the test used to detect infections. During the clinical evaluation of the Xpert CT/NG Assay, the observed CT prevalence rates in females and males were 5.4% and 5.7%, respectively. The observed NG prevalence rates in females and males were 1.4% and 3.5%, respectively.

Positive and Negative Predictive Values

Hypothetical estimated positive and negative predictive values (PPV and NPV) for different prevalence rates using the Xpert CT/NG Assay are shown in tables below. These calculations are based on a hypothetical prevalence and the overall sensitivity and specificity (compared to the patient infected status) of the Xpert CT/NG Assay observed during the multi-center clinical study.

In patient-collected vaginal swab specimens, the overall sensitivity and specificity for CT were 99.5 and 99.1%, respectively. The overall sensitivity and specificity for NG were 100% and 99.9%, respectively. The following table shows PPV and NPV for patient-collected vaginal swab specimens using hypothetical prevalence rates.

Hypothetical PPV and NPV– Patient-collected Vaginal Swabs

Prevalence Rate (%)	CT				NG			
	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
1	99.5	99.1	53.6	100	100	99.9	92.6	100
2	99.5	99.1	70.0	100	100	99.9	96.2	100
5	99.5	99.1	85.8	100	100	99.9	98.5	100
10	99.5	99.1	92.7	99.9	100	99.9	99.3	100
15	99.5	99.1	95.3	99.9	100	99.9	99.5	100
20	99.5	99.1	96.6	99.9	100	99.9	99.7	100
25	99.5	99.1	97.4	99.8	100	99.9	99.8	100
30	99.5	99.1	98.0	99.8	100	99.9	99.8	100
50	99.5	99.1	99.1	99.5	100	99.9	99.9	100

In endocervical swab specimens, the overall sensitivity and specificity for CT were 96.0% and 99.6%, respectively. The overall sensitivity and specificity for NG were 100% and >99.9%, respectively. The following table shows PPV and NPV for endocervical swab specimens using hypothetical prevalence rates.

Hypothetical PPV and NPV– Endocervical Swabs

	CT				NG			
Prevalence Rate (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
1	96.0	99.6	68.3	100	100	>99.9	97.4	100
2	96.0	99.6	81.3	99.9	100	>99.9	98.7	100
5	96.0	99.6	91.8	99.8	100	>99.9	99.5	100
10	96.0	99.6	96.0	99.6	100	>99.9	99.8	100

15	96.0	99.6	97.4	99.3	100	>99.9	99.8	100
20	96.0	99.6	98.2	99.0	100	>99.9	99.9	100
25	96.0	99.6	98.6	98.7	100	>99.9	99.9	100
30	96.0	99.6	98.9	98.3	100	>99.9	99.9	100
50	96.0	99.6	99.5	96.2	100	>99.9	100	100

In female urine specimens, the overall sensitivity and specificity for CT were 98.1% and 99.8%, respectively. The overall sensitivity and specificity for NG were 94.4% and >99.9%, respectively. The following table shows PPV and NPV for female urine specimens using hypothetical prevalence rates.

Hypothetical PPV and NPV– Female Urine

	CT				NG			
Prevalence Rate (%)	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**
1	98.1	99.8	85.5	100	94.4	>99.9	97.3	99.9
2	98.1	99.8	92.2	100	94.4	>99.9	98.6	99.9
5	98.1	99.8	96.8	99.9	94.4	>99.9	99.5	99.7
10	98.1	99.8	98.5	99.8	94.4	>99.9	99.7	99.4
15	98.1	99.8	99.0	99.7	94.4	>99.9	99.8	99.0
20	98.1	99.8	99.3	99.5	94.4	>99.9	99.9	98.6
25	98.1	99.8	99.5	99.4	94.4	>99.9	99.9	98.2
30	98.1	99.8	99.6	99.2	94.4	>99.9	99.9	97.7
50	98.1	99.8	99.8	98.1	94.4	>99.9	100	94.7

In male urine specimens, the overall sensitivity and specificity for CT were 98.5% and 99.8%, respectively. The overall sensitivity and specificity for NG were 98.3% and 99.9%, respectively. The following table shows PPV and NPV for male urine specimens using hypothetical prevalence rates.

Hypothetical PPV and NPV– Male Urine

	CT				NG			
Prevalence Rate (%)	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**
1	98.5	99.8	82.2	100	98.3	99.9	91.7	100
2	98.5	99.8	90.3	100	98.3	99.9	95.7	100
5	98.5	99.8	96.0	99.9	98.3	99.9	98.3	99.9
10	98.5	99.8	98.1	99.8	98.3	99.9	99.2	99.8
15	98.5	99.8	98.8	99.7	98.3	99.9	99.5	99.7
20	98.5	99.8	99.1	99.6	98.3	99.9	99.6	99.6
25	98.5	99.8	99.3	99.5	98.3	99.9	99.7	99.4
30	98.5	99.8	99.5	99.3	98.3	99.9	99.8	99.3
50	98.5	99.8	99.8	98.5	98.3	99.9	99.9	98.3

N. Instrument Name:

GeneXpert Instrument Systems

- GeneXpert Dx System
- GeneXpert Infinity-48 System

- GeneXpert Infinity-80 System

O. System Descriptions:

1. Modes of Operation:

Automated

2. Software:

FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:

Yes ___x___ or No _____

3. Specimen Identification:

Specimen identification is performed with a barcode scanner or by manually entering the information into GeneXpert system software.

4. Specimen Sampling and Handling:

Specimen handling (once loaded test cartridge) is performed in either an Automation Mode or in a Manual Mode. In the Automation Mode, test cartridges are placed on a conveyor belt, picked up by a gantry, and introduced into an available module for processing.

5. Calibration:

Calibration is performed by Cepheid prior to installation. Cepheid recommends the GeneXpert Infinity-80 System be recalibrated after 1 year of use or at 2000 tests per instrument module, whichever comes first. The user does not calibrate or perform any serviceable functions on the instruments.

6. Quality Control:

The integrity of the system is verified and controlled by specific hardware/software checks during the cartridge load process, and during the test itself. During each test, the system uses internal controls included in each cartridge to monitor the sample processing, check for PCR inhibition and to ensure that the sample used is adequate. In addition to the internal controls, the GeneXpert instrument performs a probe check during the first stage of the test. A probe check verifies the presence and the integrity of the labeled probes. A probe-check status of Pass indicates that the probe check results meet the programmed acceptance criteria. The instrument also contains an internal temperature control which ensures that the GeneXpert is operating within validated heating and cooling specifications. The system is capable of generating Control Trend reports to check for reagent degradation over time.

P. Other Supportive Instrument Performance Characteristics Data not Covered in Sections above:

Not Applicable.

Q. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

R. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.