cobas® 4800 CT/NG Test

FOR *IN VITRO* DIAGNOSTIC USE.

cobas® 4800 System Sample Preparation Kit	**c4800 SMPL PREP**	960 Tests 240 Tests	P/N: 05235804190 P/N: 05235782190
cobas® 4800 CT/NG Amplification/Detection Kit	**c4800 CT/NG AMP/DET**	960 Tests 240 Tests	P/N: 05235979190 P/N: 05235952190
cobas® 4800 CT/NG Controls Kit	**c4800 CT/NG CTLS**	10 Sets	P/N: 05235928190
cobas® 4800 System Control Diluent Kit	**c4800 CDIL**	10 Sets	P/N: 05235847190
cobas® 4800 System Wash Buffer Kit	**c4800 WB**	960 Tests 240 Tests	P/N: 05235871190 P/N: 05235863190
cobas® 4800 System Liquid Cytology Preparation Kit	**c4800 LIQ CYT**	960 Tests 240 Tests	P/N: 05235839190 P/N: 05235812190

NOTICE: The purchase of this product allows the purchaser to use it for amplification and detection of nucleic acid sequences by polymerase chain reaction (PCR) and related processes for human *in vitro* diagnostics. No general patent or other license of any kind other than this specific right of use from purchase is granted hereby.

INTENDED USE

The **cobas®** 4800 CT/NG Test is an *in vitro* nucleic acid amplification test for the qualitative detection of *Chlamydia trachomatis* (CT) and/or *Neisseria gonorrhoeae (NG)* in patient specimens. The Test utilizes amplification of target DNA by the Polymerase Chain Reaction (PCR) and nucleic acid hybridization for the detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* DNA in endocervical swab specimens, clinician-collected vaginal swab specimens, clinician-instructed self-collected vaginal swab specimens, and male and female urine in **cobas®** PCR Media (Roche Molecular Systems, Inc.), and cervical specimens in PreservCyt® Solution (Hologic, Inc.). This test is intended to be used as a diagnostic as well as a screening tool in both symptomatic and asymptomatic populations.

SUMMARY AND EXPLANATION OF THE TEST

Chlamydia are gram-negative, non-motile bacteria that exist as obligate intracellular parasites of eukaryotic cells. The genus Chlamydia consists of four reported species: *C. trachomatis, C. psittaci, C. pecorum* and *C. pneumoniae* (TWAR). *C. psittaci* is primarily an animal pathogen and the pathogenic role of *C. pecorum* is not clear[1]. *C. trachomatis* is composed of fifteen major serovars that can cause disease in humans.

Chlamydia trachomatis (CT) is the most frequently reported bacterial sexually transmitted disease (STD) in the United States[1,2] as well as the second most leading cause of sexually transmitted diseases worldwide, with approximately 89.1 million cases occurring annually[2]. The Centers for Disease Control (CDC) Sexually Transmitted Disease Surveillance 2008 Supplement reports 1,210,523 CT infections from the 50 states.[3] The U.S. National Health and Nutrition Examination reports that 2,291,000 U.S. civilians ages 14-39 are carriers of CT[4].

CT is the causative infectious agent for a variety of diseases in men: urethritis, proctitis, conjunctivitis, epididymitis and Reiter's Syndrome. Among women, the consequences of chlamydial infections are severe if left untreated. Since approximately half of these infections are asymptomatic, many cases go undetected and untreated, leading to additional problems, particularly with pregnant women. In addition, re-infections are frequent if the sex partners are not treated.[5] CT infection can cause urethritis, cervicitis, proctitis, conjunctivitis, endometritis, salpingitis (with subsequent infertility or ectopic pregnancy) and perihepatitis. Infants from infected mothers can develop conjunctivitis, pharyngitis and pneumonia.[6]

Neisseria gonorrhoeae (gonococci) is the causative agent of gonorrhoeae. *N. gonorrhoeae* are gram-negative diplococci, cytochrome oxidase positive, non-motile and non-spore forming. A total of 336,742 cases of NG infection have been reported to the CDC in 2008,[7] and it is estimated that more than 700,000 persons get new infections each year. After several years of stable infection rates, a 5.4% decrease to 111.5 cases per 100,000 persons in the U.S. since 2007 has been noted.[8]

Clinical manifestations of NG infections are numerous. In men, acute urethritis presents itself after a 1-10 day incubation period with urethral discharge and dysuria.[9] Only a small proportion of men remain asymptomatic without signs of urethritis.[10] Acute epididymitis is the most common complication, especially in young men. In women, the primary site of infection is the endocervix. There is a high prevalence of co-infections with CT, *Trichomonas vaginalis*, and bacterial vaginosis; many women remain asymptomatic and therefore do not seek medical care. The predominant symptoms are increased discharge, dysuria, and intermenstrual bleeding.[11] Pelvic inflammatory disease can occur in 10%-20% of women, combined with endometritis, salpingitis, tubo ovarian abscess, pelvic peritonitis, and perihepatitis.[12] Other gonococcal infected sites are the rectum, pharynx, conjunctiva, and to a lesser degree the disease presents itself as disseminated gonococcal infection.[13] Infants from infected mothers can develop conjunctivitis.[13]

Presumptive diagnosis of gonorrhoea is based on: (1) observation of gram-negative intracellular diplococci in gram-stained smears of urethral discharges from men and of endocervical secretions from women; (2) growth of *N. gonorrhoeae* from the urethra (men) or endocervix on selective culture media followed by demonstration of typical colonial morphology, positive oxidase activity, and typical gram-negative diploccal morphology; and/or (3) detection of *N. gonorrhoeae* with non-culture laboratory tests. A definitive diagnosis of gonorrhoeae requires (1) isolation of *Neisseria gonorrhoeae* from the sites of exposure by culture (48-72 hour cultures on selective medium), demonstration of typical colonial morphology, positive oxidase test, typical gram-negative morphology, and (2) confirmation of

N. gonorrhoeae culture isolates by specific identification methods (acid production from carbohydrates, rapid enzymes tests, serologic assays, tests for specific nucleic acid).[14-17] Culture is required for determination of antimicrobial susceptibility.

The intended targets for the **cobas**® 4800 CT/NG Test include all fifteen major *Chlamydia trachomatis* serovars, the Swedish *C. trachomatis* mutant (nvCT), and both wild-type and variant DR-9 sequences of *Neisseria gonorrhoeae.*

PRINCIPLES OF THE PROCEDURE

The **cobas**® 4800 CT/NG Test for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* is based on 2 major processes: (1) automated sample preparation to obtain nucleic acids, including CT and NG DNA; (2) simultaneous PCR amplification of target DNA sequences using both CT and NG specific complementary primer pairs and real-time detection of cleaved fluorescent-labeled CT and NG specific oligonucleotide detection probes. Internal Control, containing CT and NG DNA, is added to all samples during automated sample preparation and is amplified and detected simultaneously with each sample to monitor the entire process.

Sample preparation for the **cobas**® 4800 CT/NG Test is automated with the use of the **cobas x** 480 instrument. Specimens are lysed in the collection device or during sample preparation by the chaotropic agent in the **cobas**® PCR Media and Lysis Buffer, respectively. Released nucleic acids, along with added CT/NG Internal Control DNA, are purified through absorption to magnetic glass particles, washed and finally separated from these particles, making them ready for PCR amplification and detection.

The Master Mix reagent contains primer pairs and probes specific for CT cryptic plasmid DNA, the CT genomic *ompA* gene DNA, wild-type and variant NG target DNA within the DR-9 region and CT and NG Internal Control DNA.

PCR Amplification

Target Selection

In addition to chromosomal DNA, *C. trachomatis* contains an approximately 7,500 base pair cryptic plasmid that is common to all serovars of *C. trachomatis*.[18,19] The **cobas**® 4800 CT/NG Test uses the CT primers CP102 and CP103 to define a sequence of approximately 206 nucleotides within the cryptic plasmid DNA of *C. trachomatis*. In addition, the **cobas**® 4800 CT/NG Test uses the CT primers CTMP101 and CTMP102 to define a sequence of approximately 182 nucleotides within the chromosomal DNA of *C. trachomatis*.

The *N. gonorrhoeae* target site is a highly conserved direct repeat region called DR-9. The **cobas**® 4800 CT/NG Test uses the NG primers NG514 and NG519 to define a sequence of approximately 190 nucleotides from this region. In addition, the **cobas**® 4800 CT/NG Test uses another set of NG primers, NG552 and NG579, to define a second sequence of approximately 215 nucleotides identified as a conserved sequence variant from this region.

Target Amplification

Processed samples are added to the amplification mixture in a microwell plate, in which PCR amplification occurs. The reaction mixture is heated to separate the isolated double-stranded DNA and expose the primer target sequences. As the mixture cools, the primers anneal to the target DNA. Z05 DNA polymerase, in the presence of Mn^{2+} and excess dNTPs, extends the annealed primers along the target templates to produce double-stranded DNA. This completes the first cycle of PCR, yielding a double-stranded DNA copy of the target regions of the CT and/or NG DNA and the CT/NG Internal Control DNA. Repetition of this process results in the amplification of DNA between the primer target sequences, producing a double-stranded DNA molecule termed an amplicon. The **cobas z** 480 analyzer automatically repeats this process for a designated number of cycles, with each cycle intended to double the amount of amplicon DNA. The required number of cycles is preprogrammed into the **cobas**® 4800 Software. Amplification occurs only in the specific CT and/or NG targets between their respective primers; the entire CT cryptic plasmid or CT and/or NG genomes are not amplified.

Internal Control Amplification

The CT/NG Internal Control is a combination of two non-infectious recombinant plasmid DNAs, each with primer binding regions identical to those of either the *C. trachomatis* or the *N. gonorrhoeae* genomic target sequences. Both recombinant plasmid DNAs have an identical randomized internal target sequence, and a unique probe binding region that differentiates the CT/NG Internal Control from target amplicon. These features were selected to ensure independent amplification of both the CT/NG Internal Control and the *C. trachomatis* and *N. gonorrhoeae* target DNAs. The CT/NG Internal Control Reagent is included in the **cobas**® 4800 CT/NG Test and is introduced into each sample on the **cobas x** 480 instrument during sample processing.

Selective Amplification

Selective amplification of target nucleic acid from the specimen is achieved in the **cobas**® 4800 CT/NG Test by the use of AmpErase (uracil-N-glycosylase) enzyme and deoxyuridine triphosphate (dUTP). The AmpErase enzyme recognizes and catalyzes the destruction of DNA strands containing deoxyuridine[20], but not DNA containing deoxythymidine. Deoxyuridine is not present in naturally occurring DNA, but is always present in amplicon due to the use of deoxyuridine triphosphate in place of thymidine triphosphate as one of the dNTPs in the Master Mix reagent; therefore, only amplicon contain deoxyuridine. Deoxyuridine renders contaminating amplicon susceptible to destruction by AmpErase enzyme prior to amplification of the target DNA. AmpErase enzyme, which is included in the Master Mix reagent, catalyzes the cleavage of deoxyuridine-containing DNA at the deoxyuridine residues by opening the deoxyribose chain at the C1-position. When heated in the first thermal cycling step at the alkaline pH of Master Mix, the amplicon DNA chain breaks at the position of the deoxyuridine, thereby rendering the DNA non-amplifiable. AmpErase enzyme is inactive at temperatures above 55ºC, i.e., throughout the thermal cycling steps, and therefore does not destroy target amplicon. The **cobas**® 4800 CT/NG Test has been demonstrated to inactivate at least 10^3 copies of deoxyuridine-containing CT/NG amplicon per PCR.

Detection of PCR Products in the cobas® 4800 CT/NG Test

The **cobas**® 4800 CT/NG Test utilizes real-time[21,22] PCR technology. The use of fluorescent probes provides for real-time detection of PCR product accumulation by monitoring the emission intensity of fluorescent dyes released during the amplification process. The probes include CT cryptic plasmid, CT *ompA*, NG DR-9, NG DR-9var and CT/NG Internal Control-specific oligonucleotides, all labeled with a reporter dye and a quencher. When the fluorescent dye-labeled probes are intact, the reporter fluorescence is suppressed by the proximity of the quencher due to Förster-type energy transfer effects. During PCR, the probes hybridize to their respective target sequence and are cleaved by the 5' to 3' nuclease activity of the thermostable Z05 DNA polymerase. Once the reporter and quencher are separated, quenching no longer occurs, and the fluorescent emission of the reporter dyes increases. The amplification of CT targets,

NG targets and the CT/NG Internal Control are measured independently and at different wavelengths. This process is repeated for a designated number of cycles, each cycle increasing the emission intensity of the individual reporter dyes.

REAGENTS

cobas® 4800 System Sample Preparation Kit — **c4800 SMPL PREP** — **240 Tests**
(P/N: 05235782190)

MGP — 10 x 4.5 mL
(**cobas®** 4800 System Magnetic Glass Particles)

Magnetic glass particles
93% Isopropanol

Xi  93% (w/w) Isopropanol

Irritant

F  93% (w/w) Isopropanol

Highly Flammable

R: 11-36-67, S: 7-16-24/25-26

EB — 10 x 18 mL
(**cobas®** 4800 System Elution Buffer)

Tris-HCl buffer
0.09% Sodium azide

cobas® 4800 System Sample Preparation Kit — **c4800 SMPL PREP** — **960 Tests**
(P/N: 05235804190)

MGP — 10 x 13.5 mL
(**cobas®** 4800 System Magnetic Glass Particles)

Magnetic glass particles
93% Isopropanol

Xi  93% (w/w) Isopropanol

Irritant

F  93% (w/w) Isopropanol

Highly Flammable

R: 11-36-67, S: 7-16-24/25-26

EB — 10 x 18 mL
(**cobas®** 4800 System Elution Buffer)

Tris-HCl buffer
0.09% Sodium azide

cobas® 4800 System Wash Buffer Kit — **c4800 WB** — **240 Tests**
(P/N: 05235863190)

WB — 10 x 55 mL
(**cobas®** 4800 System Wash Buffer)

Sodium citrate dihydrate
0.05% N-Methylisothiazolone HCl

cobas® 4800 System Wash Buffer Kit — **c4800 WB** — **960 Tests**
(P/N: 05235871190)

WB — 10 x 200 mL
(**cobas®** 4800 System Wash Buffer)

Sodium citrate dihydrate
0.05% N-Methylisothiazolone HCl

cobas® 4800 System Liquid Cytology Preparation Kit **240 Tests**
(P/N: 05235812190)

c4800 LIQ CYT

PK 10 x 0.9 mL
(**cobas®** 4800 Proteinase K)

Tris-HCl buffer
EDTA
Glycerol
Calcium chloride
Calcium acetate
< 2% Proteinase K

SDS 10 x 3 mL
(**cobas®** 4800 System SDS Reagent)

Tris-HCl buffer
0.2% SDS
0.09% Sodium azide

LYS 10 x 10 mL
(**cobas®** 4800 System Lysis Buffer)

Tris-HCl buffer
37% (w/w) Guanidine HCl
< 5% polydocanol

Xn  37% (w/w) Guanidine HCl
Harmful
R: 22-36/38, S: 13-26-36-46

N  < 5 % Polydocanol
Dangerous For
The Environment
R: 22-41-50, S: 26-39-61

cobas® 4800 System Liquid Cytology Preparation Kit **960 Tests**
(P/N: 05235839190)

c4800 LIQ CYT

PK 20 x 1.2 mL
(**cobas®** 4800 Proteinase K)

Tris-HCl buffer
EDTA
Glycerol
Calcium chloride
Calcium acetate
< 2% Proteinase K

SDS 10 x 9 mL
(**cobas®** 4800 System SDS Reagent)

Tris-HCl buffer
0.2% Sodium dodecyl sulfate
0.09% Sodium azide

LYS 10 x 36 mL
(cobas® 4800 System Lysis Buffer)

Tris-HCl buffer
37% (w/w) Guanidine HCl
< 5% polydocanol

Xn  37% (w/w) Guanidine HCl
Harmful
R: 22-36/38, S: 13-26-36-46

N  < 5% Polydocanol
Dangerous For
The Environment
R: 22-41-50, S: 26-39-61

cobas® 4800 CT/NG Amplification/Detection Kit — c4800 CT/NG AMP/DET — **240 Tests**
(P/N: 05235952190)

CT/NG MMX — 10 x 0.5 mL
(**cobas®** 4800 CT/NG Master Mix)

Tricine buffer
Potassium acetate
Potassium hydroxide
Glycerol
< 0.01% dATP, dCTP, dGTP, dUTP
< 0.01% Upstream and downstream CT and NG primers
< 0.01% Fluorescent-labeled CT and NG probes
< 0.01% Fluorescent-labeled Internal Control probes
< 0.01% Oligonucleotide aptamer
< 0.10% Z05 DNA polymerase (microbial)
< 0.10% AmpErase (uracil-N-glycosylase) enzyme (microbial)
0.09% Sodium azide

CT/NG Mn — 10 x 1.5 mL
(**cobas®** 4800 CT/NG Manganese Solution)

< 1.0% Manganese acetate
< 0.02% Glacial acetic acid
0.09% Sodium azide

cobas® 4800 CT/NG Amplification/Detection Kit — c4800 CT/NG AMP/DET — **960 Tests**
(P/N: 05235979190)

CT/NG MMX — 20 x 1.0 mL
(**cobas®** 4800 CT/NG Master Mix)

Tricine buffer
Potassium acetate
Potassium hydroxide
Glycerol
< 0.01% dATP, dCTP, dGTP, dUTP
< 0.01% Upstream and downstream CT and NG primers
< 0.01% Fluorescent-labeled CT and NG probes
< 0.01% Fluorescent-labeled Internal Control probes
< 0.01% Oligonucleotide aptamer
< 0.10% Z05 DNA polymerase (microbial)
< 0.10% AmpErase (uracil-N-glycosylase) enzyme (microbial)
0.09% Sodium azide

CT/NG Mn — 10 x 1.5 mL
(**cobas®** 4800 CT/NG Manganese Solution)

< 1.0% Manganese acetate
< 0.02% Glacial acetic acid
0.09% Sodium azide

cobas® 4800 System Control Diluent Kit — c4800 CDIL — **10 Sets**
(P/N: 05235847190)

CDIL — 10 x 4.3 mL
(**cobas®** 4800 System Control Diluent)

Tris-HCl buffer
37% Guanidine HCl

Xn  37% (w/w) Guanidine HCl

Harmful

R: 22-36/38, S: 13-26-36-46

cobas® 4800 CT/NG Controls Kit — c4800 CT/NG CTLS — **10 Sets**
(P/N: 05235928190)

CT/NG (+) C — 10 x 0.5 mL
(**cobas®** 4800 CT/NG Positive Control)

Tris-HCl buffer
EDTA
0.05% Sodium azide
< 0.002% Poly rA RNA (synthetic)
< 0.01% Non-infectious plasmid DNA (microbial) containing *C. trachomatis* sequences
< 0.01% Non-infectious plasmid DNA (microbial) containing *N. gonorrhoeae* sequences

(–) C 10 x 0.5 mL
(**cobas**® 4800 System Negative Control)

Tris-HCl buffer
EDTA
0.05% Sodium azide
< 0.002% Poly rA RNA (synthetic)

CT/NG IC 10 x 0.3 mL
(**cobas**® 4800 CT/NG Internal Control)

Tris-HCl buffer
EDTA
0.05% Sodium azide
< 0.002% Poly rA RNA (synthetic)
< 0.01% Non-infectious plasmid DNA (microbial) containing
C. trachomatis primer binding sequences and a unique probe binding region
< 0.01% Non-infectious plasmid DNA (microbial) containing
N. gonorrhoeae primer binding sequences and a unique probe binding region

WARNINGS AND PRECAUTIONS

A. **FOR *IN VITRO* DIAGNOSTIC USE.**

B. This test is for use with endocervical swab and vaginal swab specimens collected using the **cobas**® PCR Female Swab Sample Kit, male and female urine collected using the **cobas**® PCR Urine Sample Kit and cervical specimens collected in PreservCyt Solution.

C. Do not pipette by mouth.

D. Do not eat, drink or smoke in laboratory work areas. Wear protective disposable gloves, laboratory coats and eye protection when handling specimens and kit reagents. Wash hands thoroughly after handling specimens and test reagents.

E. Avoid microbial and DNA contamination of reagents.

F. Dispose of unused reagents and waste in accordance with country, federal, state and local regulations.

G. Do not use reagents after their expiration dates.

H. Do not pool reagents.

I. Material Safety Data Sheets (MSDS) are available on request from your local Roche office.

J. Gloves must be worn and must be changed between handling specimens and **cobas**® 4800 reagents to prevent contamination.

K. Specimens should be handled as infectious using safe laboratory procedures such as those outlined in *Biosafety in Microbiological and Biomedical Laboratories*[23] and in the CLSI Document M29-A3[24].

L. **cobas**® PCR Media (from primary specimen tube), **LYS and CDIL** contain guanidine hydrochloride. **Do not allow direct contact between guanidine hydrochloride and sodium hypochlorite (bleach) or other highly reactive reagents such as acids or bases. These mixtures can release a noxious gas**. If liquid containing guanidine hydrochloride is spilled, clean with suitable laboratory detergent and water. If the spilled liquid contains potentially infectious agents, **FIRST** clean the affected area with laboratory detergent and water, and then with 0.5% sodium hypochlorite.

M. **MGP** contains isopropanol and is highly flammable. Keep away from open flames and potential spark producing environments.

N. **EB, SDS, CT/NG MMX, CT/NG Mn, (–) C, CT/NG (+) C** and **CT/NG IC** contain sodium azide. Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. While disposing of sodium azide containing solutions down laboratory sinks, flush the drains with a large volume of cold water to prevent azide buildup.

O. Wear eye protection, laboratory coats and disposable gloves when handling any reagents. Avoid contact of these materials with the skin, eyes or mucous membranes. If contact does occur, immediately wash with large amounts of water. Burns can occur if left untreated. If spills occur, dilute with water before wiping dry.

P. All disposable items are for one time use. Do not reuse.

Q. Do not use sodium hypochlorite solution (bleach) for cleaning the **cobas x** 480 instrument or **cobas z** 480 analyzer. Clean the **cobas x** 480 instrument or **cobas z** 480 analyzer according to procedures described in the **cobas**® 4800 System Operator's Manual.

R. For additional warnings, precautions and procedures to reduce the risk of contamination for the **cobas x** 480 instrument or **cobas z** 480 analyzer, consult the **cobas**® 4800 System Operator's Manual.

STORAGE AND HANDLING REQUIREMENTS

A. ***Do not freeze reagents.***

B. Store the Sample Preparation Kit **(MGP**, **EB)**, Liquid Cytology Preparation Kit **(PK**, **SDS**, **LYS)**, CT/NG Amplification/Detection Kit **(CT/NG MMX**, **CT/NG Mn)** and CT/NG Controls Kit **(CT/NG (+) C**, **(–) C** and **CT/NG IC)** at 2-8ºC. These reagents are stable until the expiration date indicated.

C. Store Wash Buffer Kit **(WB)** and Control Diluent Kit **(CDIL)** at 15-25°C. These reagents are stable until the expiration date indicated.

MATERIALS PROVIDED

A. cobas® 4800 System Sample Preparation Kit (P/N: 05235782190) **MGP** (**cobas**® 4800 System Magnetic Glass Particles) **EB** (**cobas**® 4800 System Elution Buffer)	c4800 SMPL PREP	**240 Tests**
B. cobas® 4800 System Sample Preparation Kit (P/N: 05235804190) **MGP** (**cobas**® 4800 System Magnetic Glass Particles) **EB** (**cobas**® 4800 System Elution Buffer)	c4800 SMPL PREP	**960 Tests**
C. cobas® 4800 System Wash Buffer Kit (P/N: 05235863190) **WB** (**cobas**® 4800 System Wash Buffer)	c4800 WB	**240 Tests**
D. cobas® 4800 System Wash Buffer Kit (P/N: 05235871190) **WB** (**cobas**® 4800 System Wash Buffer)	c4800 WB	**960 Tests**
E. cobas® 4800 System Liquid Cytology Preparation Kit (P/N: 05235812190) **PK** (**cobas**® 4800 Proteinase K) **SDS** (**cobas**® 4800 System SDS Reagent) **LYS** (**cobas**® 4800 System Lysis Buffer)	c4800 LIQ CYT	**240 Tests**
F. cobas® 4800 System Liquid Cytology Preparation Kit (P/N: 05235839190) **PK** (**cobas**® 4800 Proteinase K) **SDS** (**cobas**® 4800 System SDS Reagent) **LYS** (**cobas**® 4800 System Lysis Buffer)	c4800 LIQ CYT	**960 Tests**
G. cobas® 4800 CT/NG Amplification/Detection Kit (P/N: 05235952190) **CT/NG MMX** (**cobas**® 4800 CT/NG Master Mix) **CT/NG Mn** (**cobas**® 4800 CT/NG Manganese Solution)	c4800 CT/NG AMP/DET	**240 Tests**
H. cobas® 4800 CT/NG Amplification/Detection Kit (P/N: 05235979190) **CT/NG MMX** (**cobas**® 4800 CT/NG Master Mix) **CT/NG Mn** (**cobas**® 4800 CT/NG Manganese Solution)	c4800 CT/NG AMP/DET	**960 Tests**
I. cobas® 4800 System Control Diluent Kit (P/N: 05235847190) **CDIL** (**cobas**® 4800 System Control Diluent)	c4800 CDIL	**10 Sets**
J. cobas® 4800 CT/NG Controls Kit (P/N: 05235928190) **CT/NG (+) C** (**cobas**® 4800 CT/NG Positive Control) **(–) C** (**cobas**® 4800 System Negative Control) **CT/NG IC** (**cobas**® 4800 CT/NG Internal Control)	c4800 CT/NG CTLS	**10 Sets**

MATERIALS REQUIRED BUT NOT PROVIDED

Specimen and Reagent Handling

- **cobas**® PCR Female Swab Sample Kit (Roche P/N 05170516190)
- **cobas**® PCR Urine Sample Kit (Roche P/N 05170486190)
- CO-RE Tips, 1000 µL, rack of 96 (Roche P/N 04639642001 or Hamilton P/N 235905)
- 50 mL Reagent Reservoir (Roche P/N 05232732001)
- 200 mL Reagent Reservoir (Roche P/N 05232759001)
- **cobas**® 4800 System Extraction (deep well) Plate (Roche P/N 05232716001)
- **cobas**® 4800 System AD (microwell) Plate 0.3 mL and Sealing Film (Roche P/N 05232724001)
- Solid waste bag [Roche P/N 05530873001 (small) or 04691989001 (large)]
- Hamilton STAR Plastic Chute (Roche P/N 04639669001)
- Tubes 13 mL Round Base, (Sarstedt P/N 60.540.500) for use as secondary sample tubes
- Caps, neutral color (Sarstedt P/N 65.176.026; for recapping post-run specimens in 13 mL Round Base Sarstedt tubes
- Disposable gloves, powderless

Instrumentation and Software

- **cobas x** 480 instrument
- **cobas z** 480 analyzer
- **cobas**® 4800 System Control Unit with System Software version 1.1 or higher
- **cobas**® 4800 Work Order Editor version 1.1.0.1016 or higher

OPTIONAL EQUIPMENT AND MATERIALS

- Pipettes: capable of delivering 1000 µL
- Aerosol barrier DNase-free tips: capable of delivering 1000 µL
- Centrifuge equipped with a swinging bucket rotor with minimum RCF of 1500
- Stand-alone magnetic plate (Roche P/N 05440777001)
- Vortex Mixer (single tube)
- Multi-tube vortexer [e.g. VWR P/N 58816-116]

SPECIMEN COLLECTION, TRANSPORT AND STORAGE

NOTE: Handle all specimens as if they are capable of transmitting infectious agents.

A. Specimen Collection

Endocervical swab and vaginal swab specimens collected with the **cobas**® PCR Female Swab Sample Kit, male and female urine collected with the **cobas**® PCR Urine Sample Kit and cervical specimens collected in PreservCyt Solution have been validated for use with the **cobas**® 4800 CT/NG Test. Follow the manufacturer's instructions for collecting endocervical swab and vaginal swab, and urine specimens with the **cobas**® PCR Female Swab Sample Kit and **cobas**® PCR Urine Sample Kit, respectively. Follow the manufacturer's instructions for collecting cervical specimens into PreservCyt Solution.

B. Specimen Transport

Endocervical swab and vaginal swab specimens collected with the **cobas**® PCR Female Swab Sample Kit, male and female urine collected with the **cobas**® PCR Urine Sample Kit and cervical specimens collected in PreservCyt Solution can be transported at 2-30ºC. Transportation of CT/NG specimens in **cobas**® PCR Media and PreservCyt Solution must comply with country, federal, state and local regulations for the transport of etiologic agents[25].

C. Specimen Storage

Endocervical swab specimens collected with the **cobas**® PCR Female Swab Sample Kit and male and female urine collected with the **cobas**® PCR Urine Sample Kit may be stored at 2-30°C for up to 12 months once the specimens have been stabilized in **cobas**® PCR Media. Vaginal swab specimens collected with the **cobas**® PCR Female Swab Sample Kit may be stored at 2-30°C for 90 days once the specimens have been stabilized in **cobas**® PCR Media and cervical specimens collected in PreservCyt Solution may be stored at 2-30°C for 90 days.

INSTRUCTIONS FOR USE

NOTE: All reagents except CT/NG MMX and CT/NG Mn must be at ambient temperature prior to loading on the cobas x 480 instrument. The CT/NG MMX and CT/NG Mn may be taken directly from 2-8°C storage as they will equilibrate to ambient temperature on board the cobas x 480 instrument by the time they are used in the process.

NOTE: Specimens in cobas® PCR Media and PreservCyt Solution must be equilibrated to ambient temperature for at least 30 minutes before loading on the cobas x 480 instrument.

NOTE: If transfer of specimens from their primary cobas® PCR Media collection tube to properly barcoded secondary tubes is required, use pipettors with aerosol-barrier or positive-displacement tips to handle specimens. Exercise care to avoid contamination.

NOTE: Refer to the cobas® 4800 System Operator's Manual for detailed operating instructions.

Run Size:

The **cobas**® 4800 System is designed to support the **cobas**® 4800 CT/NG Test with run sizes from 1 to 22 specimens plus controls (up to 24 tests per run) and from 1 to 94 specimens plus controls (up to 96 tests per run). Each **cobas**® 4800 System Sample Preparation

Kit, **cobas**® 4800 System Liquid Cytology Preparation Kit, **cobas**® 4800 System Wash Buffer Kit and **cobas**® 4800 CT/NG Amplification/Detection Kit contains reagents sufficient for 10 runs of either 24 tests (240 tests per kit) or 96 tests (960 tests per kit). The **cobas**® 4800 System Control Diluent Kit and the **cobas**® 4800 CT/NG Controls Kit contain reagents sufficient for a total of 10 runs of either 24 or 96 tests (10 sets per kit). The minimum run size on the **cobas**® 4800 System is 1 specimen plus controls. One replicate of the **cobas**® 4800 System Negative Control [**(–) C**] and one replicate of the **cobas**® 4800 CT/NG Positive Control [**CT/NG (+) C**] are required to perform each test run (see *"Quality Control"* section).

Workflow:

NOTE: Although not an optimal use of reagents, a 960 Test Kit can be used for a 24 sample run.

The **cobas**® 4800 CT/NG Test can be run using either of two workflows, referred to as "Full workflow" or "PCR only workflow" within the **cobas**® 4800 Software.

CT/NG Full Workflow:

The "CT/NG Full Workflow" consists of sample preparation on the **cobas x** 480 instrument followed by amplification/detection on the **cobas z** 480 analyzer. Run size can be a 24-test format (from 1 to 22 specimens plus 2 controls) or a 96-test format (from 1 to 94 specimens plus 2 controls). Refer to the "Performing a Full Workflow" section below and the **cobas**® 4800 System Operator's Manual for details.

CT/NG PCR Only Workflow:

The "CT/NG PCR Only Workflow" consists of amplification/detection on the **cobas z** 480 analyzer. Run size can be from 1 to 94 specimens plus 2 controls. Refer to the "Performing a PCR Only Workflow" section below and the **cobas**® 4800 System Operator's Manual for details.

Specimens:

The following specimen types have been validated using the **cobas**® 4800 CT/NG Test: a) endocervical swab specimens in **cobas**® PCR Media (UT), b) clinician collected and clinician-instructed self-collected vaginal swab specimens in **cobas**® PCR Media (UT), c) male and female urine specimens stabilized in **cobas**® PCR Media (UUT) and d) cervical specimens collected in PreservCyt Solution (PC). Endocervical swab, vaginal swab and urine specimens must be in the **cobas**® PCR Media tube containers with a proper barcode or in a properly barcoded 13 mL round-based Sarstedt tube for processing on the **cobas x** 480 instrument. Cervical specimens must be in the PreservCyt Solution primary container with a proper barcode or in a properly barcoded 13 mL round-based Sarstedt tube for processing on the **cobas x** 480 instrument. Consult the **cobas**® 4800 System Operator's Manual for proper barcoding procedures and the list of acceptable barcodes for the **cobas**® 4800 System.

Endocervical Swab and Vaginal Swab Specimens:

NOTE: The reagent kits required for processing endocervical swab and vaginal swab specimens on the cobas x 480 instrument include: cobas® 4800 System Sample Preparation Kit, cobas® 4800 System Control Diluent Kit, cobas® 4800 System Wash Buffer Kit, cobas® 4800 CT/NG Amplification/Detection Kit and cobas® 4800 CT/NG Controls Kit.

NOTE: Use only the cobas® PCR Female Swab Sample Kit to collect endocervical swab and vaginal swab specimens for the cobas® 4800 CT/NG Test. The cobas® 4800 CT/NG Test has not been validated with other swab collection devices or media types.

NOTE: To avoid cross-contamination of processed specimens, additional caps for cobas® PCR Media tubes in an alternate color (neutral; see Materials Required But Not Provided) should be used to recap specimens after processing.

NOTE: Endocervical swab and vaginal swab specimens containing a single swab in the cobas® PCR Media tube can be directly processed on the cobas® 4800 System. If necessary, the swab may be removed before the specimen tube is loaded onto the instrument (see the cobas® 4800 System Operator's Manual for details).

NOTE: A properly collected endocervical swab and vaginal swab specimen, should have a single swab with the shaft broken at the scoreline. Swab shafts which are broken above the scoreline will appear longer than normal and may also be bent over to fit into the cobas® PCR Media tube. This can produce an obstruction to the system which may cause the loss of test results. In the event that a swab specimen has an improperly broken shaft, remove the swab prior to sample processing on the cobas x 480 instrument.

NOTE: Incoming primary endocervical and vaginal specimen tubes with no swabs or with two swabs have not been collected according to the instructions in the cobas® PCR Female Swab Sample Kit and should not be tested.

NOTE: Do not process endocervical and vaginal swab specimens that appear bloody or have a dark brown color.

NOTE: Occasionally, incoming stabilized endocervical swab or vaginal swab specimens contain excessive mucus which may induce a pipetting error (e.g. clot or other obstruction) on the cobas x 480 instrument. Prior to retesting of specimens that exhibited clots during initial processing, remove and discard the swab, then re-cap and vortex these specimens for 30 seconds to disperse the excess mucus.

NOTE: Endocervical swab and vaginal swab specimens can be assayed twice on the cobas x 480 instrument while the swab is in the collection tube. If additional testing is required, or if the first test fails due to specimen pipetting error (e.g. clot or other obstruction), the swab must be removed and the remaining fluid must have a minimum volume of 1.0 mL.

The **cobas**® PCR Media tube containing the swab specimen can be uncapped and loaded directly onto the **cobas x** 480 instrument or an aliquot of at least 1.0 mL of the specimen can be delivered into a properly barcoded 13 mL round-based Sarstedt tube and then loaded onto the **cobas x** 480 instrument.

NOTE: Use caution when transferring specimens from primary containers to 13 mL round-based secondary tubes. Mix primary specimens prior to transfer. Change pipet tips for each specimen.

Male and Female Urine Specimens:

NOTE: The reagent kits required for processing urine specimens on the cobas x 480 instrument include: cobas® 4800 System Sample Preparation Kit, cobas® 4800 System Control Diluent Kit, cobas® 4800 System Wash Buffer Kit, cobas® 4800 CT/NG Amplification/Detection Kit and cobas® 4800 CT/NG Controls Kit.

NOTE: Use only the cobas® PCR Urine Sample Kit to collect urine specimens for the cobas® 4800 CT/NG Test. The cobas® 4800 CT/NG Test has not been validated with other urine collection devices or media types.

NOTE: To avoid cross-contamination of processed specimens, additional caps for cobas® PCR Media tubes in an alternate color (neutral; see Materials Required But Not Provided) should be used to recap specimens after processing.

NOTE: Untested urine specimens must show the top of the liquid level between the two black lines on the cobas® PCR Media tube label window. If the liquid level is above or below these lines, the specimen has not been collected properly and cannot be used for testing.

NOTE: Do not process urine specimens that appear bloody or have a dark brown color.

The **cobas®** PCR Media tube containing the urine specimen can be uncapped and loaded directly onto the **cobas x** 480 instrument or an aliquot of at least 1.5 mL of the specimen can be delivered into a properly barcoded 13 mL round-based Sarstedt tube and then loaded onto the **cobas x** 480 instrument.

NOTE: Use caution when transferring specimens from primary containers to 13 mL round-based secondary tubes. Mix primary specimens prior to transfer. Change pipet tips for each specimen.

A single run may have any combination of endocervical, vaginal and urine specimens (UT for swab and UUT for urine) and each specimen can be tested for CT or NG or both CT and NG.

Cervical Specimens:

NOTE: The reagent kits required for processing cervical specimens on the cobas x 480 instrument include: cobas® 4800 System Sample Preparation Kit, cobas® 4800 System Liquid Cytology Preparation Kit, cobas® 4800 System Wash Buffer Kit, cobas® 4800 CT/NG Amplification/Detection Kit and cobas® 4800 CT/NG Controls Kit.

NOTE: The cobas® 4800 CT/NG Test is validated for cervical specimens collected in PreservCyt Solution. The cobas® 4800 CT/NG Test has not been validated for cervical specimens obtained in other media types. Using the cobas® 4800 CT/NG Test with other media types may lead to false negative, false positive and/or invalid results.

NOTE: The cobas® 4800 System can process cervical specimens in both primary and secondary containers. When aliquoting specimens from primary containers into barcoded 13 mL round-based Sarstedt tubes for processing on the cobas x 480 instrument, use pipettors with aerosol-barrier or positive-displacement tips to handle specimens. To avoid cross-contamination, additional caps for these tubes in an alternate color (neutral; see Materials Required but not Provided) should be used to recap these specimens after processing.

NOTE: Use caution when transferring specimens from primary containers to 13 mL round-based secondary tubes. Vortex primary specimens prior to transfer. Change pipetting tips after each specimen.

NOTE: Do not process specimens collected in PreservCyt Solution that appear bloody or have a dark brown color.

For cervical specimens, the minimum volume required in the PreservCyt Solution primary containers is 3.0 mL. When using 13 mL round-based secondary tubes, fill to a minimum volume of 1.0 mL and a maximum volume of 10 mL.

A single run of cervical specimens may have any combination of primary or secondary container racks and each specimen can be tested for CT or NG or both CT and NG.

NOTE: Cervical specimens cannot be processed with endocervical, vaginal or urine specimens in the same run. To maximize reagent use, run batches of 22 cervical specimen tests per run (plus one cobas® 4800 System negative control and one cobas® 4800 CT/NG positive control) using 240 Test Kits or batches of 94 cervical specimen tests per run (plus one cobas® 4800 System negative control and one cobas® 4800 CT/NG positive control) using 960 Test Kits.

Workflows

Performing a Full Workflow:

A. The **cobas®** 4800 CT/NG Test may be used for runs of 1 to 22 specimens plus one **cobas®** 4800 System negative control and one **cobas®** 4800 CT/NG positive control (24-test format) and from 1 to 94 specimens plus one **cobas®** 4800 System negative control and one **cobas®** 4800 CT/NG positive control (96-test format).

B. Perform the system startup and maintenance procedures by following the instructions in the **cobas®** 4800 System Operator's Manual in the Operation section.

C. Create a Work Order file for a full run by following the instructions in the **cobas®** 4800 System Operator's Manual. Consult the **cobas®** 4800 System Operator's Manual if an LIS is to be used.

D. Start the New Run by following the software wizard guide.

E. For endocervical swabs, vaginal swabs and urine specimens select the test type "CT/NG workflow". For PreservCyt specimens select the test type "CT/NG cytology workflow".

F. Select the test subtype and media type for each specimen.
   - Choose test subtype "CT/NG" to report both CT and NG test results.
   - Choose test subtype "CT" to report only CT test results.
   - Choose test subtype "NG" to report only NG test results.

NOTE: Endocervical, vaginal and urine specimens can be loaded in barcoded primary or secondary tubes in any order as long as their barcodes match those in the Work Order.

NOTE: Cervical specimens in PreservCyt Solution can be processed in racks of primary specimen vials or secondary tubes in the same run. If primary PreservCyt vials are used for processing, vortex each vial prior to loading.

G. Follow the software wizard guide to load all consumables.

H. Follow the software wizard guide to load all reagents.

NOTE: Controls [CT/NG (+) C, CT/NG IC and (–) C] are not loaded together with specimens. They are loaded onto the reagent carrier during reagent loading. Two positions (A1 and B1) on each of the extraction plate and AD plate are reserved for the CT/NG (+) and (–) controls, respectively.

NOTE: The cobas® 4800 System has an internal clock to monitor the length of time the reagents are on-board. Once the WB is scanned, 1 hour is allowed to complete the loading process and click on the Start button. A countdown timer is displayed on the Workplace Tab. The system will not allow the run to start if the on-board time has expired.

I. Load the sample preparation reagents into the barcoded reagent reservoirs using the "scan-scan-pour-place" method:
- Scan the reagent bottle barcode
- Scan the reagent reservoir barcode
- Pour the reagent into the reservoir
- Place the filled reagent reservoir onto the reagent carrier

NOTE: To assure the accurate transfer of MGP, vortex or vigorously shake the MGP vial prior to dispensing into the reagent reservoir.

J. The reagent reservoirs are available in two sizes: 200 mL and 50 mL. Follow the software wizard guide to select the appropriate reagent reservoir sizes. The reagent reservoir barcodes must face to the right of the carrier.

NOTE: Amplification/detection reagents (CT/NG MMX and CT/NG Mn), Controls [CT/NG (+) C, CT/NG IC and (–) C] and Control Diluent (CDIL) are loaded directly onto the reagent carrier and scanned by the cobas x 480 instrument automatically.

NOTE: All reagents and reagent reservoirs are barcoded and designed for one time use. The cobas® 4800 Software tracks the use of the reagents and reagent reservoirs, and rejects previously used reagents or reagent reservoirs. The software also verifies that reagents from appropriately sized kits are loaded on the instrument, i.e. preventing 240 test kit reagents from being used in a run with more than 22 patient specimens.

K. Start sample preparation by clicking on "Start Run".

L. After successful completion of sample preparation, click **'Unload' to unload the plate carrier.

** The status of sample preparation can be reviewed at this point, prior to clicking "Unload". See the **cobas®** 4800 System Operator's Manual.

M. Follow the instructions in the **cobas®** 4800 System Operator's Manual to seal the microwell plate, transport the plate to the **cobas z** 480 analyzer and start the amplification and detection run.

NOTE: The cobas® 4800 System has an internal clock to monitor the length of time after addition of the prepared samples to working master mix. Amplification and detection should be started as soon as possible but no later than 90 minutes after the end of the cobas x 480 instrument run. A countdown timer is displayed on the Workplace Tab. The system will abort the run if the timer has expired.

N. When the amplification and detection run is completed, unload the microwell plate from the **cobas z** 480 analyzer.

O. Follow the instructions in the **cobas®** 4800 System Operator's Manual to review and accept results.

<u>Performing a PCR Only Workflow</u>

NOTE: The PCR Only Workflow is available as a recovery option in the event that the full workflow cannot be completed due to circumstances beyond the user's control (e.g. power failure during amplification/detection run).

NOTE: Only samples successfully processed on the cobas x 480 instrument can be amplified/detected using the PCR Only run. System surveillance for reagents and consumables is limited during the PCR Only run. No sample position tracking is provided when using the PCR Only workflow – the end user must ensure that the actual position of a sample on the microwell plate corresponds to the one designated in the Work Order file. Extreme care must be exercised while preparing the microwell plate to ensure proper PCR set-up and to avoid contamination.

NOTE: Samples processed on the cobas x 480 instrument have limited stability. They must be amplified/detected using the PCR Only workflow within 24 hours if stored at 15°C to 30°C and within 7 days if stored at 2°C to 8°C.

NOTE: Follow the instructions in the cobas® 4800 System Operator's Manual for renaming of Positive and Negative Control barcodes.

A. Create a Work Order file for a PCR Only Workflow run by following the instructions in the **cobas®** 4800 System Operator's Manual.

a. Refer to the result printout or the result export file for sample barcodes, media types, sub-test types and positions in the **cobas®** 4800 extraction plate for the run which requires a repeat of the amplification/detection.

b. For the positive and negative controls, edit the last 4 digits to identify a reuse of the control barcodes for amplification and detection only workflow by following the instructions in the **cobas®** 4800 System Operator's Manual.

B. Prepare the **cobas®** 4800 CT/NG working master mix:

a. For a run of up to 24 tests, add 240 µL of **CT/NG Mn** to one vial of **CT/NG MMX** (0.5 mL vial from 240 Test Kit).

b. For a run of up to 96 tests, add 450 µL of **CT/NG Mn** to each of two vials of **CT/NG MMX** (1.0 mL vials from 960 Test Kit).

NOTE: The PCR only run must be started within 90 minutes of addition of CT/NG Mn to the CT/NG MMX. The system does not monitor the length of time after addition of the prepared samples to working master mix in the PCR only workflow. The end user must ensure that amplification and detection is started within the allotted time.

C. Thoroughly mix working master mix by carefully inverting the vial(s). Do not vortex the working master mix.

D. Transfer 25 µL of working master mix to the required wells in the microwell plate.

E. Place the extraction plate from the run to be repeated onto the stand-alone magnetic plate.

F. Manually transfer 25 µL of eluate from the extraction plate wells to the corresponding wells in the microwell plate. Ensure that well positions are maintained (e.g. eluate in A1 well in extraction plate is transferred to A1 on the microwell plate). Ensure that no MGP is carried over to the microwell plate.

G. Follow the instructions in the **cobas**® 4800 System Operator's Manual to seal the microwell plate.

H. Centrifuge the microwell plate using a swinging bucket rotor for at least 5 seconds at 1500 RCF.

I. Transport the plate to the **cobas z** 480 analyzer and start the amplification and detection run.

J. When the amplification and detection run is completed, unload the microwell plate from the **cobas z** 480 analyzer.

K. Follow the instructions in the **cobas**® 4800 System Operator's Manual to review and accept results.

Interpretation of Results

NOTE: All assay and run validation is determined by the cobas® 4800 Software.

NOTE: A valid run may include both valid and invalid specimen results.

For a valid run, specimen results are interpreted as shown in Table 1:

Table 1
Result Interpretation of the cobas® 4800 CT/NG Test

cobas® 4800 CT/NG Test	**Result Report and Interpretation**
SubTest CT/NG:	
CT POS, NG POS	**CT Positive, NG Positive.** Specimen is positive for the presence of both CT and NG DNA.
CT NEG, NG NEG	**CT Negative*, NG Negative*.** Neither CT nor NG DNA, if present, could be detected.
CT POS, NG NEG	**CT Positive, NG Negative*.** Specimen is positive for the presence of CT DNA. NG DNA, if present, could not be detected.
CT POS, NG Invalid	**CT Positive, NG Invalid.** Specimen is positive for the presence of CT DNA. NG result is Invalid. Original specimen should be re-tested to obtain valid NG result.
CT NEG, NG POS	**CT Negative*, NG Positive.** CT DNA, if present, could not be detected. Specimen is positive for the presence of NG DNA.
CT Invalid, NG POS	**CT Invalid, NG Positive.** CT result is Invalid. Original specimen should be re-tested to obtain valid CT result. Specimen is positive for the presence of NG DNA.
CT Invalid, NG NEG	**CT Invalid, NG Negative*.** CT result is Invalid. Original specimen should be re-tested to obtain valid CT results. NG DNA, if present, could not be detected.
CT NEG, NG Invalid	**CT Negative*, NG Invalid.** CT DNA, if present, could not be detected. NG result is Invalid. Original specimen should be re-tested to obtain valid NG result.
Invalid	**CT Invalid, NG Invalid.** Both CT and NG results are Invalid. Original specimen should be re-tested to obtain valid CT and NG results.
Failed	**No Result for Specimen** Consult the **cobas®** 4800 System Operator's Manual for instructions to review run flags and recommended actions. Original specimen should be re-tested to obtain valid CT and NG results.
SubTest CT:	
CT POS	**CT Positive.** Specimen is positive for the presence of CT DNA.
CT NEG	**CT Negative*.** CT DNA, if present, could not be detected.
Invalid	**CT Invalid.** CT result is Invalid. Original specimen should be re-tested to obtain valid CT result.
Failed	**No Result for Specimen** Consult the **cobas®** 4800 System Operator's Manual for instructions to review run flags and recommended actions. Original specimen should be re-tested to obtain valid CT result.
SubTest NG:	
NG POS	**NG Positive.** Specimen is positive for the presence of NG DNA.
NG NEG	**NG Negative*.** NG DNA, if present, could not be detected.
Invalid	**NG Invalid.** NG result is Invalid. Original specimen should be re-tested to obtain valid NG result.
Failed	**No Result for Specimen** Consult the **cobas®** 4800 System Operator's Manual for instructions to review run flags and recommended actions. Original specimen should be re-tested to obtain valid NG result.

*A negative result does not preclude the presence of CT and/or NG infection because results depend on adequate specimen collection, absence of inhibitors, and sufficient DNA to be detected.

QUALITY CONTROL

One set of **cobas®** 4800 CT/NG Test Positive and Negative Controls are included in each run. For any run, valid results must be obtained for both the Positive and Negative Control for the **cobas®** 4800 Software to display the reportable **cobas®** 4800 CT/NG Test results from that run.

Positive Control

The CT/NG (+) Control result must be 'Valid'. If the CT/NG (+) Control results are consistently invalid, contact your local Roche office for technical assistance.

Negative Control

The (–) Control result must be 'Valid'. If the (–) Control results are consistently invalid, contact your local Roche office for technical assistance.

PROCEDURAL PRECAUTIONS

As with any test procedure, good laboratory technique is essential to the proper performance of this assay. Due to the high analytical sensitivity of this test, care should be taken to keep reagents and amplification mixtures free of contamination.

PROCEDURAL LIMITATIONS

1. Test only the indicated specimen types. The **cobas**® 4800 CT/NG Test has only been validated for use with female endocervical swab and clinician collected vaginal swab and clinician-instructed self-collected vaginal swab specimens collected in **cobas**® PCR Media (UT), female and male urine specimens stabilized in **cobas**® PCR Media (UUT) and cervical specimens collected in PreservCyt Solution (PC).
2. Interfering substances include, but are not limited to the following:
   - The presence of mucus in endocervical and cervical specimens may inhibit PCR and cause false negative test results. Mucus free specimens are required for optimal test performance. Use a sponge or an additional swab to remove cervical secretions and discharge before obtaining the specimen.
   - Urine specimens stabilized in **cobas**® PCR Media containing greater than 0.35% (v/v) blood may give false negative results.
   - Endocervical swab specimens, vaginal swab specimens and cervical specimens, each containing up to 5% (v/v) whole blood exhibited no interference effects. Whole blood levels above 5% (v/v) may give invalid or false negative results.
   - Endocervical swab specimens, vaginal swab specimens and urine specimens, all stabilized in cobas PCR Media and containing greater than 1×10^5 PBMC cells/mL, and cervical specimens containing greater than 1×10^7 PBMC cells/mL may give invalid or false negative results.
   - Urine specimens taken from patients who have used the over-the-counter product Replens® vaginal moisturizer may give invalid or false negative results.
3. Detection of *C. trachomatis* and *N. gonorrhoeae* is dependent on the number of organisms present in the specimen and may be affected by specimen collection methods, patient factors (i.e., age, history of STD, presence of symptoms), stage of infection and/or infecting *C. trachomatis* and *N. gonorrhoeae* strains.
4. False negative results may occur due to polymerase inhibition. The CT/NG Internal Control is included in the **cobas**® 4800 CT/NG Test to help identify the specimens containing substances that may interfere with nucleic acid isolation and PCR amplification.
5. Prevalence of infection in a population may affect performance. Positive predictive values decrease when testing populations with low prevalence or individuals with no risk of infection. Because the prevalence of *C. trachomatis* and *N. gonorrhoeae* may be low in some populations or patient groups, a false positive rate can exceed the true positive rate so that the predictive value of a positive test is very low. Since some patients that are truly infected will not be identified by testing a single specimen, the true rate of false positives cannot be determined or presumed from the clinical data. The rate of false positive test results may depend on training, operator ability, reagent and specimen handling or other such factors in each laboratory.
6. Reliable results are dependent on adequate specimen collection, transport, storage and processing. Follow the procedures in this Package Insert, Package Inserts for the **cobas**® PCR Media collection kits and the **cobas**® 4800 System Operator's Manual.
7. The addition of AmpErase enzyme into the **cobas**® 4800 CT/NG Master Mix enables selective amplification of target DNA; however, good laboratory practices and careful adherence to the procedures specified in this Package Insert are necessary to avoid contamination of reagents.
8. Use of this product must be limited to personnel trained in the techniques of PCR and the use of the **cobas**® 4800 System.
9. Only the **cobas x** 480 instrument and **cobas z** 480 analyzer have been validated for use with this product. No other sample preparation instrument or PCR System can be used with this product.
10. Due to inherent differences between technologies, it is recommended that, prior to switching from one technology to the next, users perform method correlation studies in their laboratory to qualify technology differences.
11. The **cobas**® 4800 CT/NG Test is not recommended for evaluation of suspected sexual abuse and for other medico-legal indications.
12. The **cobas**® 4800 CT/NG Test provides qualitative results. No correlation can be drawn between the Ct value reported for a positive **cobas**® 4800 CT/NG Test and the number of *C. trachomatis* and *N. gonorrhoeae* cells within the infected specimen.
13. The **cobas**® 4800 CT/NG Test for male and female urine testing is recommended to be performed on first catch urine specimens (defined as the first 10 to 50 mL of the urine stream). The effects of other variables such as first-catch vs. mid-stream, post-douching, etc. have not been evaluated.
14. Improperly collected endocervical swab specimens are likely to contain excess mucus, which may cause clots on the **cobas**® 4800 System. If this occurs at an unusually high rate, endocervical swab specimens may be vortexed prior to loading onto the **cobas x** 480 instrument to disperse excess mucus. Vortex specimens for 30 seconds at 1,700 – 1,800 rpm. Use a multi-tube vortexer for greater efficiency [see **OPTIONAL EQUIPMENT AND MATERIALS** section].
15. The effects of other potential variables such as vaginal discharge, use of tampons, douching, etc. and specimen collection variables have not been evaluated.

16. The **cobas**® 4800 CT/NG Test is not intended to replace cervical exam and endocervical sampling for diagnosis of urogenital infection. Patients may have cervicitis, urethritis, urinary tract infections, or vaginal infections due to other causes or concurrent infections with other agents.
17. Though rare, mutations within the highly conserved regions of the cryptic plasmid or genomic DNA of *C. trachomatis* or the genomic DNA of *N. gonorrhoeae* covered by the **cobas**® 4800 CT/NG Test's primers and/or probes may result in failure to detect the presence of the bacterium.
18. The presence of PCR inhibitors may cause false negative or invalid results.

PERFORMANCE CHARACTERISTICS

Correlation Studies

Correlation Study with Endocervical Swab and Male and Female Urine Specimens

The performance of the **cobas**® 4800 CT/NG Test and CE Mark comparator tests were compared by analysis of endocervical swab and urine (male and female) specimens collected from CT and/or NG infected and healthy patients. All endocervical swab specimens were co-collected using the **cobas**® PCR Female Swab Sample Kit for the **cobas**® 4800 CT/NG Test and the comparator test's collection kits. Specimens were collected in Europe and North America and tested in the United States and The Netherlands.

A total of 1318 urine specimens were tested by the **cobas**® 4800 CT/NG Test subsequent to laboratory standard-of-care testing with the comparator tests. A total of 37 specimens were removed from the analysis. Thirty specimens were mislabeled during NAT 1 testing, two failed on the **cobas**® 4800 CT/NG Test due to clots generated during sample processing and five specimens due to repeated inhibition (four specimens repeatedly invalid by the NAT 1 Test and 1 specimen repeatedly invalid by the **cobas**® 4800 CT/NG Test). A total of 656 co-collected endocervical swab specimens were tested by the **cobas**® 4800 CT/NG Test and comparator tests. A total of 1 specimen was removed from the analysis due to repeated inhibition by the NAT 1 test. All results are shown in Tables 2-10, including percent agreements for positive, negative and total specimens along with their 95% Confidence Interval Lower Bound (LB) values.

The results for *Chlamydia trachomatis* testing of urine specimens are shown in Tables 2-4. The percent positive agreement for all urine specimens was 100.0%. The percent negative agreement for all urine specimens was 99.7% and the total percent agreement (see Table 2) for all urine specimens was 99.7% between the **cobas**® 4800 CT/NG Test and the comparator test. When urine results were separated by gender (see Tables 3 and 4), the percent positive agreement was 100.0% for male urine specimens and 100.0% for female urine specimens [Fisher's Exact test (p value ~ 1.0)], the percent negative agreement was 99.8% for male urine specimens and 99.4% for female urine specimens [Fisher's Exact test (p value = 0.9668)] and the total percent agreement was 99.9% for male urine specimens and 99.5% for female urine specimens [Fisher's Exact test (p value = 0.9683)]. Fisher's Exact test indicates no statistically significant differences were found in correlation of male, female or total urine specimens between the two testing methods.

The results for *Chlamydia trachomatis* testing of endocervical swab specimens are shown in Table 5. The percent positive agreement for endocervical swab specimens was 96.2%. The percent negative agreement for endocervical swab specimens was 100.0% and the total percent agreement for endocervical swab specimens was 99.5% between the **cobas**® 4800 CT/NG Test and the comparator test.

The results for *Neisseria gonorrhoeae* testing of urine specimens are shown in Tables 6-8. The percent positive agreement for all urine specimens was 100.0%. The percent negative agreement for all urine specimens was 99.8% and the total percent agreement (see Table 6) for all urine specimens was 99.8% between the **cobas**® 4800 CT/NG Test and the comparator test. When urine results were separated by gender (see Tables 7 and 8), the percent positive agreement was 100.0% for male urine specimens and 100.0% for female urine specimens [Fisher's Exact test (p value ~ 1.0)], the percent negative agreement was 99.9% for male urine specimens and 99.8% for female urine specimens [Fisher's Exact test (p value = 1.0)] and the total percent agreement was 99.9% for male urine specimens and 99.8% for female urine specimens [Fisher's Exact test (p value = 1.0)]. Fisher's Exact test indicates no statistically significant differences were found in correlation of male, female or total urine specimens between the two testing methods.

Neisseria gonorrhoeae testing of endocervical swab specimens was compared to two CE Mark comparator tests (NAT 1 and NAT 2) and are shown in Tables 9 and 10. From comparison to NAT 1, the percent positive agreement for endocervical swab specimens was 100.0%. The percent negative agreement for endocervical swab specimens was 99.3% and the total percent agreement for endocervical swab specimens was 99.3% between the cobas® 4800 CT/NG Test and the comparator test NAT 1. From comparison to NAT 2, the percent positive agreement for endocervical swab specimens was 100.0%. The percent negative agreement for endocervical swab specimens was 100.0% and the total percent agreement for endocervical swab specimens was 100.0% between the cobas® 4800 CT/NG Test and the comparator test NAT 2.

Table 2
Summary of cobas® 4800 CT/NG Test Results for CT Compared to a CE Mark Comparator Test (NAT 1) with Urine Specimens from Healthy and CT Infected Patients

Total Urine N = 1281		Comparator Test (NAT 1)		
		Positive	Negative	Total
cobas® 4800 CT/NG Test	Positive	115	4*	119
	Negative	0	1162	1162
	Total	115	1166	1281

Positive Agreement = 115/115 = 100.0% (95% CI LB[§] 97%)
Negative Agreement = 1162/1166 = 99.7% (95% CI LB[§] 99%)
Total Agreement = 1277/1281 = 99.7% (95% CI LB[§] 99%)

*Subsequent CT amplification results indicate 2 of 4 discrepant urine specimens were positive.

[§]95% Confidence Interval Lower Bound (LB) value

Table 3
Summary of cobas® 4800 CT/NG Test Results for CT Compared to a CE Mark Comparator Test (NAT 1) with Male Urine Specimens from Healthy and CT Infected Patients

Male Urine N = 700		Comparator Test (NAT 1)		
		Positive	Negative	Total
cobas® 4800 CT/NG Test	Positive	70	1*	71
	Negative	0	629	629
	Total	70	630	700

Positive Agreement = 70/70 = 100.0% (95% CI LB[§] 95%)
Negative Agreement = 629/630 = 99.8% (95% CI LB[§] 99%)
Total Agreement = 699/700 = 99.9% (95% CI LB[§] 99%)

[*]Discrepant specimen remained discrepant after further testing.

[§]95% Confidence Interval Lower Bound (LB) value

Table 4
Summary of cobas® 4800 CT/NG Test Results for CT Compared to a CE Mark Comparator Test (NAT 1) with Female Urine Specimens from Healthy and CT Infected Patients

Female Urine N = 581		Comparator Test (NAT 1)		
		Positive	Negative	Total
cobas® 4800 CT/NG Test	Positive	45	3*	48
	Negative	0	533	533
	Total	45	536	581

Positive Agreement = 45/45 = 100.0% (95% CI LB[§] 92%)
Negative Agreement = 533/536 = 99.4% (95% CI LB[§] 98%)
Total Agreement = 578/581 = 99.5% (95% CI LB[§] 99%)

*Subsequent CT amplification results indicate 2 of 3 discrepant female urine specimens were positive.

[§]95% Confidence Interval Lower Bound (LB) value

Table 5
Summary of cobas® 4800 CT/NG Test Results for CT Compared to a CE Mark Comparator Test (NAT 1) with Endocervical Swab Specimens from Healthy and CT Infected Patients

Endocervical Swab N = 399		Comparator Test (NAT 1)		
		Positive	Negative	Total
cobas® 4800 CT/NG Test	Positive	50	0	50
	Negative	2*	347	349
	Total	52	347	399

Positive Agreement = 50/52 = 96.2% (95% CI LB[§] 87%)
Negative Agreement = 347/347 = 100.0% (95% CI LB[§] 99%)
Total Agreement = 397/399 = 99.5% (95% CI LB[§] 98%)

[*]All discrepant specimens remained discrepant after further testing.

[§]95% Confidence Interval Lower Bound (LB) value

Table 6
Summary of cobas® 4800 CT/NG Test Results for NG Compared to a CE Mark Comparator Test (NAT 1) with Urine Specimens from Healthy and NG Infected Patients

Total Urine N = 1281		Comparator Test (NAT 1)		
		Positive	Negative	Total
cobas® 4800 CT/NG Test	Positive	46	2*	48
	Negative	0	1233	1233
	Total	46	1235	1281

Positive Agreement = 46/46 = 100.0% (95% CI LB[§] 92%)
Negative Agreement = 1233/1235 = 99.8% (95% CI LB[§] 99%)
Total Agreement = 1279/1281 = 99.8% (95% CI LB[§] 99%)

*All discrepant specimens remained discrepant after further testing.

§95% Confidence Interval Lower Bound (LB) value

Table 7
Summary of cobas® 4800 CT/NG Test Results for NG Compared to a CE Mark Comparator Test (NAT 1) with Male Urine Specimens from Healthy and NG Infected Patients

Male Urine N = 700		Comparator Test (NAT 1)		
		Positive	Negative	Total
cobas® 4800 CT/NG Test	Positive	30	1*	31
	Negative	0	669	669
	Total	30	670	700

Positive Agreement = 30/30 = 100.0% (95% CI LB[§] 88%)
Negative Agreement = 669/670 = 99.9% (95% CI LB[§] 99%)
Total Agreement = 699/700 = 99.9% (95% CI LB[§] 99%)

*Discrepant specimen remained discrepant after further testing.

§95% Confidence Interval Lower Bound (LB) value

Table 8
Summary of cobas® 4800 CT/NG Test Results for NG Compared to a CE Mark Comparator Test (NAT 1) with Female Urine Specimens from Healthy and NG Infected Patients

Female Urine N = 581		Comparator Test (NAT 1)		
		Positive	Negative	Total
cobas® 4800 CT/NG Test	Positive	16	1*	17
	Negative	0	564	564
	Total	16	565	581

Positive Agreement = 16/16 = 100.0% (95% CI LB[§] 79%)
Negative Agreement = 564/565 = 99.8% (95% CI LB[§] 99%)
Total Agreement = 580/581 = 99.8% (95% CI LB[§] 99%)

*Discrepant specimen remained discrepant after further testing.

§95% Confidence Interval Lower Bound (LB) value

Table 9
Summary of cobas® 4800 CT/NG Test Results for NG Compared to a CE Mark Comparator Test (NAT 1) with Endocervical Swab Specimens from Healthy and NG Infected Patients

Endocervical Swab N = 445		Comparator Test (NAT 1)		
		Positive	Negative	Total
cobas® 4800 CT/NG Test	Positive	15	3*	18
	Negative	0	427	427
	Total	15	430	445

Positive Agreement = 15/15 = 100.0% (95% CI LB[§] 78%)
Negative Agreement = 427/430 = 99.3% (95% CI LB[§] 98%)
Total Agreement = 442/445 = 99.3% (95% CI LB[§] 98%)

*Subsequent NG amplification results indicate 2 of 3 discrepant endocervical swab specimens was positive.

§95% Confidence Interval Lower Bound (LB) value

Table 10
Summary of cobas® 4800 CT/NG Test Results for NG Compared to a CE Mark Comparator Test (NAT 2) with Endocervical Swab Specimens from Healthy and NG Infected Patients

Endocervical Swab N = 210		Comparator Test (NAT 2)		
		Positive	Negative	Total
cobas® 4800 CT/NG Test	Positive	11	0	11
	Negative	0	199	199
	Total	11	199	210

Positive Agreement = 11/11 = 100.0% (95% CI LB[§] 72%)
Negative Agreement = 199/199 = 100.0% (95% CI LB[§] 98%)
Total Agreement = 210/210 = 100.0% (95% CI LB[§] 98%)
[§]95% Confidence Interval Lower Bound (LB) value

Correlation Study with Vaginal Swab and Cervical Specimens Collected in PreservCyt Solution

Clinician-collected and self-collected vaginal swab specimens collected into the **cobas®** PCR Female Swab Sample device and PreservCyt specimens were obtained from symptomatic and asymptomatic female subjects attending OB/GYN, sexually transmitted disease (STD) and family planning clinics at 12 geographically diverse locations in the United States. In addition to vaginal and PreservCyt specimens, each subject donated 3 endocervical swab specimens collected with the **cobas®** PCR Female Swab Sample device and two reference NAAT (Nucleic Acid Amplification Test) collection devices. One of these NAATs was also used to evaluate PreservCyt specimens. All specimen types were tested by the **cobas®** 4800 CT/NG Test.

The performance of vaginal swab specimens and PreservCyt specimens was based on the total number of **cobas®** 4800 CT/NG Test results for these specimen types compared to the performance of the **cobas®** 4800 CT/NG Test (with previously CE Mark approved) endocervical swab specimens. The results of the two reference NAATs with endocervical swab and PreservCyt specimens was used to resolve discrepant vaginal and PreservCyt specimens in the correlation study.

A total of 3238 subjects were used to collect either clinician-collected or self-collected vaginal swab specimens and an endocervical swab specimen, which were assayed by the **cobas®** 4800 CT/NG Test. Sixty-five specimens (28 endocervical swabs, 37 vaginal swabs) were removed from the analysis due to insufficient volume, clots generated during sample processing or other unknown system errors. There were no invalid results in the analysis. The final total of subjects used in the analysis was 3173[1]. The results for *Chlamydia trachomatis* testing and *Neisseria gonorrhoeae* testing of all vaginal swab specimens are shown in Tables 11 and 12, respectively. For *Chlamydia trachomatis,* the percent positive agreement for all vaginal specimens was 94.6%. The percent negative agreement for all vaginal specimens was 99.6% and the total percent agreement (see Table 11) for all vaginal specimens was 99.3% compared to endocervical swab specimen results using the **cobas®** 4800 CT/NG Test. For *Neisseria gonorrhoeae,* the percent positive agreement for all vaginal specimens was 97.7%. The percent negative agreement for all vaginal specimens was 99.9% and the total percent agreement (see Table 12) for all vaginal specimens was 99.9% compared to endocervical swab specimen results using the **cobas®** 4800 CT/NG Test.

PreservCyt specimens were tested using a 1 mL aliquot in secondary tubes prior to cytology processing (pre-quot) and using the original PreservCyt specimen primary vial after cytology processing (post-quot). Pre-quot and post-quot PreservCyt test results were compared to endocervical swab test results collected from the same subjects, using the **cobas®** 4800 CT/NG Test. A total of 3235 subjects were used to collect PreservCyt pre-quot specimens and endocervical swab specimens. Eighty specimens (29 endocervical swabs, 51 PreservCyt pre-quot specimens) were removed from the analysis due to clots generated during sample processing or other unknown system errors leaving a total of 3155 subjects. There were no invalid results in the analysis. For the post-quot testing, a total of 3228 subjects were used to collect PreservCyt post-quot specimens and endocervical swab specimens. Ninety-seven specimens (28 endocervical swabs, 69 PreservCyt post-quot specimens) were removed from the analysis due to insufficient volume, clots generated during sample processing or other unknown system errors leaving a total of 3131 subjects. There were no invalid results in the analysis.

The results for *Chlamydia trachomatis* testing and *Neisseria gonorrhoeae* testing of pre-quot PreservCyt specimens are shown in Tables 13 and 14, respectively. For *Chlamydia trachomatis,* the percent positive agreement for all pre-quot PreservCyt specimens was 95.2%. The percent negative agreement for all pre-quot PreservCyt specimens was 99.5% and the total percent agreement (see Table 13) for all pre-quot PreservCyt specimens was 99.3% compared to endocervical swab specimen results using the **cobas®** 4800 CT/NG Test. For *Neisseria gonorrhoeae,* the percent positive agreement for all pre-quot PreservCyt specimens was 95.6%. The percent negative agreement for all pre-quot PreservCyt specimens was 99.9% and the total percent agreement (see Table 14) for all pre-quot PreservCyt specimens was 99.8% compared to endocervical swab specimen results using the **cobas®** 4800 CT/NG Test. The results for *Chlamydia trachomatis* testing and *Neisseria gonorrhoeae* testing of post-quot PreservCyt specimens are shown in Tables 15 and 16, respectively. For *Chlamydia trachomatis,* the percent positive agreement for all post-quot PreservCyt specimens was 94.5%. The percent negative agreement for all post-quot PreservCyt specimens was 99.7% and the total percent agreement (see Table 15) for all post-quot PreservCyt specimens was 99.5% compared to endocervical swab specimen results using the **cobas®** 4800 CT/NG Test. For *Neisseria gonorrhoeae,* the percent positive agreement for all post-quot PreservCyt specimens was 95.6%. The percent negative agreement for all post-quot PreservCyt specimens was 99.9% and the total percent agreement (see Table 16) for all post-quot PreservCyt specimens was 99.9% compared to endocervical swab specimen results using the **cobas®** 4800 CT/NG Test. All results are shown in Tables 11 through 16, including 95% Confidence Interval Lower Bound (LB) values.

Endocervical swab specimen test results from reference tests NAAT1 and NAAT2 were used for vaginal specimen resolution analysis. A positive endocervical swab specimen result from either reference test indicated a true positive result for the discrepant vaginal swab specimen.

[1] Of the 3173 vaginal swab specimens tested, 51.4% were clinician-collected and 48.6% were self-collected by the patient.

Endocervical swab specimen results from reference test NAAT1 and endocervical swab and PreservCyt specimen results from reference test NAAT2 were used for PreservCyt (pre-quot and post-quot) specimen resolution analysis. A minimum of two positive results from a possible three from NAAT1 and NAAT2 indicated a true positive result for the discrepant PreservCyt pre-quot or post-quot specimen.

Table 11
Summary of cobas® 4800 CT/NG Test Results for CT Comparing Vaginal Swab Specimens with Endocervical Swab Specimens from Healthy and CT Infected Patients

cobas® 4800 CT/NG Test CT Infection N = 3173		Endocervical Swab		
		Positive	Negative	Total
Vaginal Swab	Positive	158	13**	171
	Negative	9*	2993	3002
	Total	167	3006	3173

Positive Agreement = 158/167 = 94.6% (95% CI LB[§] 90%)
Negative Agreement = 2993/3006 = 99.6% (95% CI LB[§] 99%)
Total Agreement = 3151/3173 = 99.3% (95% CI LB[§] 99%)

*Resolution of discrepant results using NAAT1 and NAAT2 indicates 6 of 9 are true positive

**Resolution of discrepant results using NAAT1 and NAAT2 indicates 8 of 13 are true positive

[§]95% Confidence Interval Lower Bound (LB) value

Table 12
Summary of cobas® 4800 CT/NG Test Results for NG Comparing Vaginal Swab Specimens with Endocervical Swab Specimens from Healthy and NG Infected Patients

cobas® 4800 CT/NG Test NG Infection N = 3173		Endocervical Swab		
		Positive	Negative	Total
Vaginal Swab	Positive	42	2**	44
	Negative	1*	3128	3129
	Total	43	3130	3173

Positive Agreement = 42/43 = 97.7% (95% CI LB[§] 88%)
Negative Agreement = 3128/3130 = 99.9% (95% CI LB[§] 99%)
Total Agreement = 3170/3173 = 99.9% (95% CI LB[§] 99%)

*Resolution of discrepant result using NAAT1 and NAAT2 indicates true positive

**Resolution of discrepant results using NAAT1 and NAAT2 indicates 1 of 2 is true positive

[§]95% Confidence Interval Lower Bound (LB) value

Table 13
Summary of cobas® 4800 CT/NG Test Results for CT Comparing PreservCyt (pre-Quot) Specimens with Endocervical Swab Specimens from Healthy and CT Infected Patients

cobas® 4800 CT/NG Test CT Infection N = 3155		Endocervical Swab		
		Positive	Negative	Total
PreservCyt (pre-quot)	Positive	159	15**	174
	Negative	8*	2973	2981
	Total	167	2988	3155

Positive Agreement = 159/167 = 95.2% (95% CI LB[§] 91%)
Negative Agreement = 2973/2988 = 99.5% (95% CI LB[§] 99%)
Total Agreement = 3132/3155 = 99.3% (95% CI LB[§] 99%)

*Resolution of discrepant results using NAAT1 and NAAT2 indicates 4 of 8 are true positive

**Resolution of discrepant results using NAAT1 and NAAT2 indicates 6 of 15 are true positive

[§]95% Confidence Interval Lower Bound (LB) value

Table 14
Summary of cobas® 4800 CT/NG Test Results for NG Comparing PreservCyt (pre-Quot) Specimens with Endocervical Swab Specimens from Healthy and NG Infected Patients

cobas® 4800 CT/NG Test NG Infection N = 3155		Endocervical Swab		
		Positive	Negative	Total
PreservCyt (pre-quot)	Positive	43	3**	46
	Negative	2*	3107	3109
	Total	45	3110	3155

Positive Agreement = 43/45 = 95.6% (95% CI LB[§] 85%)
Negative Agreement = 3107/3110 = 99.9% (95% CI LB[§] 99%)
Total Agreement = 3150/3155 = 99.8% (95% CI LB[§] 99%)

*Resolution of discrepant results using NAAT1 and NAAT2 indicates 1 of 2 is true positive

**Resolution of discrepant results using NAAT1 and NAAT2 indicates 1 of 3 is true positive

[§]95% Confidence Interval Lower Bound (LB) value

Table 15
Summary of cobas® 4800 CT/NG Test Results for CT Comparing PreservCyt (post-Quot) Specimens with Endocervical Swab Specimens from Healthy and CT Infected Patients

cobas® 4800 CT/NG Test CT Infection N = 3131		Endocervical Swab		
		Positive	Negative	Total
PreservCyt (post-Quot)	Positive	155	8**	163
	Negative	9*	2959	2968
	Total	164	2967	3131

Positive Agreement = 155/164 = 94.5% (95% CI LB[§] 90%)
Negative Agreement = 2959/2967 = 99.7% (95% CI LB[§] 99%)
Total Agreement = 3114/3131 = 99.5% (95% CI LB[§] 99%)

*Resolution of discrepant results using NAAT1 and NAAT2 indicates 6 of 9 are true positive

**Resolution of discrepant results using NAAT1 and NAAT2 indicates 2 of 8 are true positive

[§]95% Confidence Interval Lower Bound (LB) value

Table 16
Summary of cobas® 4800 CT/NG Test Results for NG Comparing PreservCyt (post-Quot) Specimens with Endocervical Swab Specimens from Healthy and NG Infected Patients

cobas® 4800 CT/NG Test NG Infection N = 3131		Endocervical Swab		
		Positive	Negative	Total
PreservCyt (post-Quot)	Positive	43	1**	44
	Negative	2*	3085	3087
	Total	45	3086	3131

Positive Agreement = 43/45 = 95.6% (95% CI LB[§] 85%)
Negative Agreement = 3085/3086 = 99.9% (95% CI LB[§] 99%)
Total Agreement = 3128/3131 = 99.9% (95% CI LB[§] 99%)

*Resolution of discrepant results using NAAT1 and NAAT2 indicates 1 of 2 is true positive

**Resolution of discrepant result using NAAT1 and NAAT2 indicates true negative

[§]95% Confidence Interval Lower Bound (LB) value

Reproducibility

A Reproducibility Study was performed across lot, testing site, operator, run, and day for the **cobas®** 4800 CT/NG Test for detection of *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoeae* (NG) using 3 panels prepared from swabs and urine collected in **cobas** PCR Media, and PreservCyt® Solution. A run for **cobas** PCR Media (urine *or* swab) included 3 replicates of each of 5 panel members and 1 positive and 1 negative control (17 tests total). If **cobas** PCR Media panels were combined in a run, only 1 positive and 1 negative control were included (32 tests total). A run for the PreservCyt panel included 6 replicates of each of 5 panel members and 1 positive and 1 negative control (32 tests total). The 2 operators at each site performed 2 runs per day, for a total of 3 days of testing per operator per panel type (6 days of testing total for each panel type and reagent lot). For the PCR Media/urine panel and the **cobas** PCR Media/swab panel, testing was performed with 2 reagent lots (6 days of testing per lot); the PreservCyt panel was tested with 1 reagent lot.

Overall, 74 runs were performed, and 72 valid runs were obtained for urine and swab panel types. The 2 invalid runs were due to instrument errors. For PreservCyt, 36 runs were performed, and all runs were valid. A total of 1,080 tests were performed on the 5 panel

members for each panel type in the valid runs. There was 1 invalid test result in the urine panel type, 2 invalid test results in the swab panel type, and 0 in the PreservCyt panel type. These invalid tests were due to instrument errors.

All valid test results were included in the analyses that reported the percent agreement for *C. trachomatis* and *N. gonorrhoeae* for each panel type separately. There were no false positive results for either analyte (CT and NG) for all 3 panel types for negative panel members, thus giving negative percent agreement (NPA) of 100% for each analyte.

C. trachomatis (Tables 17, 18, 19)

Percent agreement for the positive panel members was excellent across all panel types and panel members. The lowest overall positive percent agreement (PPA) was 98.1% for the "1 X LOD CT, Negative NG" panel member for PreservCyt panel type.

Analysis of variance components of the Ct values from valid tests performed on positive panel members yielded overall CV (%) ranges from 1.1% to 1.5% for the urine panel type; 1.6% to 1.8% for the swab panel type; and 1.7% to 2.6% for the PreservCyt panel type.

Table 17
C. trachomatis: Percent Agreement by Panel Member for Lot, Site/Instrument, and Day - PCR Media/Urine

Panel Member	Ct SD	Ct CV %	Percent Agreement *								
			Lot			Site/ Instrument			Day		
Negative CT, Negative NG	n/a	n/a	2	100.0	108/108	1	100.0	71/71	1	100.0	72/72
			3	100.0	107/107	2	100.0	72/72	2	100.0	71/71
						3	100.0	72/72	3	100.0	72/72
1 X LOD CT, Negative NG	0.54	1.5	2	100.0	108/108	1	100.0	72/72	1	100.0	72/72
			3	100.0	108/108	2	100.0	72/72	2	100.0	72/72
						3	100.0	72/72	3	100.0	72/72
Negative CT, 1 X LOD NG	n/a	n/a	2	100.0	108/108	1	100.0	72/72	1	100.0	72/72
			3	100.0	108/108	2	100.0	72/72	2	100.0	72/72
						3	100.0	72/72	3	100.0	72/72
1 X LOD CT, 2.5 X LOD NG	0.48	1.3	2	100.0	108/108	1	100.0	72/72	1	100.0	72/72
			3	100.0	108/108	2	100.0	72/72	2	100.0	72/72
						3	100.0	72/72	3	100.0	72/72
2.5 X LOD CT, 1 X LOD NG	0.40	1.1	2	100.0	108/108	1	100.0	72/72	1	100.0	72/72
			3	100.0	108/108	2	100.0	72/72	2	100.0	72/72
						3	100.0	72/72	3	100.0	72/72

* For Negative samples, Percent Agreement = (number of negative results/total valid results);
For Positive samples, Percent Agreement = (number of positive results/total valid results)

Table 18
C. trachomatis: Percent Agreement by Panel Member for Lot, Site/Instrument, and Day - PCR Media/Swab

Panel Member	Ct SD	Ct CV %	Percent Agreement *								
			Lot			Site/ Instrument			Day		
Negative CT, Negative NG	n/a	n/a	2	100.0	108/108	1	100.0	72/72	1	100.0	72/72
			3	100.0	108/108	2	100.0	72/72	2	100.0	72/72
						3	100.0	72/72	3	100.0	72/72
1 X LOD CT, Negative NG	0.61	1.6	2	100.0	107/107	1	100.0	72/72	1	100.0	72/72
			3	100.0	108/108	2	100.0	71/71	2	100.0	72/72
						3	100.0	72/72	3	100.0	71/71
Negative CT, 1 X LOD NG	n/a	n/a	2	100.0	108/108	1	100.0	72/72	1	100.0	72/72
			3	100.0	107/107	2	100.0	71/71	2	100.0	71/71
						3	100.0	72/72	3	100.0	72/72
1 X LOD CT, 2.5 X LOD NG	0.66	1.8	2	100.0	108/108	1	100.0	72/72	1	100.0	72/72
			3	100.0	108/108	2	100.0	72/72	2	100.0	72/72
						3	100.0	72/72	3	100.0	72/72
2.5 X LOD CT, 1 X LOD NG	0.59	1.6	2	100.0	108/108	1	100.0	72/72	1	100.0	72/72
			3	100.0	108/108	2	100.0	72/72	2	100.0	72/72
						3	100.0	72/72	3	100.0	72/72

* For Negative samples, Percent Agreement = (number of negative results/total valid results);
For Positive samples, Percent Agreement = (number of positive results/total valid results)

Table 19
C. trachomatis: Percent Agreement by Panel Member for Lot, Site/Instrument, and Day – PreservCyt

Panel Member	Ct SD	Ct CV %	Percent Agreement *								
			Lot			Site/ Instrument			Day		
Negative CT, Negative NG	n/a	n/a	1	100.0	216/216	1	100.0	72/72	1	100.0	72/72
						2	100.0	72/72	2	100.0	72/72
						3	100.0	72/72	3	100.0	72/72
1 X LOD CT, Negative NG	0.96	2.6	1	98.1	212/216	1	100.0	72/72	1	98.6	71/72
						2	95.8	69/72	2	97.2	70/72
						3	98.6	71/72	3	98.6	71/72
Negative CT, 1 X LOD NG	n/a	n/a	1	100.0	216/216	1	100.0	72/72	1	100.0	72/72
						2	100.0	72/72	2	100.0	72/72
						3	100.0	72/72	3	100.0	72/72
1 X LOD CT, 2.5 X LOD NG	0.86	2.4	1	99.5	215/216	1	100.0	72/72	1	100.0	72/72
						2	98.6	71/72	2	98.6	71/72
						3	100.0	72/72	3	100.0	72/72
2.5 X LOD CT, 1 X LOD NG	0.59	1.7	1	100.0	216/216	1	100.0	72/72	1	100.0	72/72
						2	100.0	72/72	2	100.0	72/72
						3	100.0	72/72	3	100.0	72/72

* For Negative samples, Percent Agreement = (number of negative results/total valid results);
For Positive samples, Percent Agreement = (number of positive results/total valid results)

N. gonorrhoeae (Tables 20, 21, 22)

Percent agreement for the positive panel members was excellent across all panel types and panel members. The lowest overall PPA was 97.2% for the "Negative CT, 1 x LOD NG" panel member for PreservCyt panel type.

Analysis of variance components of the Ct values from valid tests performed on positive panel members yielded overall CV (%) ranges from 1.2% to 1.5% for the urine panel type; 1.4% to 1.9% for the swab panel type; and 1.9% to 4.1% for the PreservCyt panel type.

Table 20
N. gonorrhoeae: Percent Agreement by Panel Member for Lot, Site/Instrument, and Day – PCR Media/Urine

Panel Member	Ct SD	Ct CV %	Percent Agreement [1]								
			Lot			Site/ Instrument			Day		
Negative CT, Negative NG	n/a	n/a	2	100.0	108/108	1	100.0	71/71	1	100.0	72/72
			3	100.0	107/107	2	100.0	72/72	2	100.0	71/71
						3	100.0	72/72	3	100.0	72/72
1 X LOD CT, Negative NG	n/a	n/a	2	100.0	108/108	1	100.0	72/72	1	100.0	72/72
			3	100.0	108/108	2	100.0	72/72	2	100.0	72/72
						3	100.0	72/72	3	100.0	72/72
Negative CT, 1 X LOD NG	0.53	1.5	2	99.1	107/108	1	100.0	72/72	1	100.0	72/72
			3	100.0	108/108	2	100.0	72/72	2	98.6	71/72
						3	98.6	71/72	3	100.0	72/72
1 X LOD CT, 2.5 X LOD NG	0.41	1.2	2	100.0	108/108	1	100.0	72/72	1	100.0	72/72
			3	100.0	108/108	2	100.0	72/72	2	100.0	72/72
						3	100.0	72/72	3	100.0	72/72
2.5 X LOD CT, 1 X LOD NG	0.54	1.5	2	100.0	108/108	1	100.0	72/72	1	100.0	72/72
			3	100.0	108/108	2	100.0	72/72	2	100.0	72/72
						3	100.0	72/72	3	100.0	72/72

[1] For Negative samples, Percent Agreement = (number of negative results/total valid results);
For Positive samples, Percent Agreement = (number of positive results/total valid results)

Table 21

N. gonorrhoeae: Percent Agreement by Panel Member for Lot, Site/Instrument, and Day – PCR Media/Swab

Panel Member	Ct SD	Ct CV %	Percent Agreement [1]								
			Lot			Site/ Instrument			Day		
Negative CT, Negative NG	n/a	n/a	2	100.0	108/108	1	100.0	72/72	1	100.0	72/72
			3	100.0	108/108	2	100.0	72/72	2	100.0	72/72
						3	100.0	72/72	3	100.0	72/72
1 X LOD CT, Negative NG	n/a	n/a	2	100.0	107/107	1	100.0	72/72	1	100.0	72/72
			3	100.0	108/108	2	100.0	71/71	2	100.0	72/72
						3	100.0	72/72	3	100.0	71/71
Negative CT, 1 X LOD NG	0.68	1.8	2	100.0	108/108	1	100.0	72/72	1	100.0	72/72
			3	100.0	107/107	2	100.0	71/71	2	100.0	71/71
						3	100.0	72/72	3	100.0	72/72
1 X LOD CT, 2.5 X LOD NG	0.49	1.4	2	100.0	108/108	1	100.0	72/72	1	100.0	72/72
			3	100.0	108/108	2	100.0	72/72	2	100.0	72/72
						3	100.0	72/72	3	100.0	72/72
2.5 X LOD CT, 1 X LOD NG	0.71	1.9	2	100.0	108/108	1	100.0	72/72	1	100.0	72/72
			3	100.0	108/108	2	100.0	72/72	2	100.0	72/72
						3	100.0	72/72	3	100.0	72/72

[1] For Negative samples, Percent Agreement = (number of negative results/total valid results);
For Positive samples, Percent Agreement = (number of positive results/total valid results)

Table 22

N. gonorrhoeae: Percent Agreement by Panel Member for Lot, Site/Instrument, and Day – PreservCyt

Panel Member	Ct SD	Ct CV %	Percent Agreement *								
			Lot			Site/ Instrument			Day		
Negative CT, Negative NG	n/a	n/a	1	100.0	216/216	1	100.0	72/72	1	100.0	72/72
						2	100.0	72/72	2	100.0	72/72
						3	100.0	72/72	3	100.0	72/72
1 X LOD CT, Negative NG	n/a	n/a	1	100.0	216/216	1	100.0	72/72	1	100.0	72/72
						2	100.0	72/72	2	100.0	72/72
						3	100.0	72/72	3	100.0	72/72
Negative CT, 1 X LOD NG	0.94	2.5	1	97.2	210/216	1	100.0	72/72	1	95.8	69/72
						2	93.1	67/72	2	97.2	70/72
						3	98.6	71/72	3	98.6	71/72
1 X LOD CT, 2.5 X LOD NG	0.69	1.9	1	100.0	216/216	1	100.0	72/72	1	100.0	72/72
						2	100.0	72/72	2	100.0	72/72
						3	100.0	72/72	3	100.0	72/72
2.5 X LOD CT, 1 X LOD NG	1.52	4.1	1	98.6	213/216	1	98.6	71/72	1	98.6	71/72
						2	98.6	71/72	2	100.0	72/72
						3	98.6	71/72	3	97.2	70/72

* For Negative samples, Percent Agreement = (number of negative results/total valid results);
For Positive samples, Percent Agreement = (number of positive results/total valid results)

Analytical Performance

Analytical Sensitivity

Analytical sensitivity (Limit of Detection or LOD) for the **cobas**® 4800 CT/NG Test was determined by analyzing dilutions of quantified *Chlamydia trachomatis* and *Neisseria gonorrhoeae* cultures. CT and NG cultures were diluted into **cobas**® PCR Media, negative vaginal swab specimen in **cobas**® PCR Media, negative urine specimen plus **cobas**® PCR Media and negative PreservCyt specimen to determine the LOD for endocervical swab, vaginal swab, urine and PreservCyt specimens, respectively. All levels were analyzed using the full **cobas**® 4800 CT/NG Test workflow across 3 unique lots of **cobas**® 4800 CT/NG Test reagents. LOD for this test is defined as the target concentration which can be detected as positive in ≥ 95% of the replicates tested. Since LOD evaluation is done with samples stabilized in **cobas**® PCR Media, the LOD for untreated urine will be twice the level reported in Table 23.

The LOD for the CT serovar D culture and NG strain 19424 in **cobas**® PCR Media, vaginal swab specimens stabilized in **cobas**® PCR Media, urine specimens diluted into **cobas**® PCR Media and PreservCyt specimens are shown in Table 23. When analyzed separately, male and female urine results were equivalent for both CT and NG cultures.

Table 23
cobas® 4800 CT/NG Test Limit Of Detection

Specimen Types	*C. trachomatis*			*N. gonorrhoeae*		
	Levels Tested	Replicates/Level	LOD (IFU/mL)	Levels Tested	Replicates/Level	LOD (CFU/mL)
cobas® PCR Media (Endocervical Swabs)	7	192*	3.00	7	192*	9.00
Vaginal Swabs	5	192**	10.00	5	192**	100.00
Urine	7	192*	0.75	7	192*	2.25
PreservCyt	5	189-192**	0.60	5	189-192**	3.50

*Testing included one negative level with 167-168 replicates
**Testing included one negative level with 82-84 replicates

Inclusivity Verification

The sensitivity of the **cobas**® 4800 CT/NG Test was determined for 14 additional *Chlamydia trachomatis* serovars, the new variant (nvCT) Swedish strain and an additional 44 independently isolated strains of *Neisseria gonorrhoeae*. Panels were prepared as described for the LOD study with the number of panel levels varying from 1 to 5, as required. At least 49 replicates were tested for each panel level using one lot of **cobas**® 4800 CT/NG Test reagents. Results are shown in Tables 24 and 25. In Table 25, all NG strains with identical LOD results are presented as a group, shown in the columns labeled "Numbers of NG Strains". Since LOD evaluation is done with samples stabilized in **cobas**® PCR Media, the LOD for untreated urine will be twice the level reported in Tables 24 and 25.

The analytical sensitivity for all 14 CT serovars plus the nvCT variant (Table 24) ranged from 0.2 IFU/mL to 5.0 IFU/mL in **cobas**® PCR Media, from 0.13 IFU/mL to 0.75 IFU/mL in **cobas**® PCR Media plus negative urine and from 0.2 IFU/mL to 2.0 IFU/mL in PreservCyt negative specimen. All CT serovars and the nvCT variant were tested at 10 IFU/mL only in stabilized negative vaginal specimen. All showed 100% positive hit rates at 10 IFU/mL. (IFU = Inclusion Forming Units)

The analytical sensitivity for all 44 NG strains ranged from 3.0 CFU/mL to 20 CFU/mL in **cobas**® PCR Media, was 3.75 CFU/mL in **cobas**® PCR Media plus urine and ranged from 1.5 CFU/mL to 10 CFU/mL in negative PreservCyt specimens. All NG strains were tested at 100 CFU/mL only in stabilized negative vaginal specimen. All showed 100% hit rates at 100 CFU/mL. (CFU = Colony Forming Units)

Table 24
Summary of CT Serovars/Variant Inclusivity Verification Results

Serovar Type or Variant	LOD Results for C. trachomatis							
	cobas® PCR Media (Endocervical Swabs)		Vaginal Swabs*		Urine		PreservCyt Cervical specimen	
	IFU/mL	% Pos	IFU/mL	% Pos	IFU/mL	% Pos	IFU/mL	% Pos
A	3.0	100%	10.0	100%	0.13	98%	0.2	100%
B	3.0	100%	10.0	100%	0.75	100%	0.6	100%
Ba	3.0	100%	10.0	100%	0.75	100%	0.6	100%
C	3.0	100%	10.0	100%	0.75	100%	0.2	98%
E	3.0	100%	10.0	100%	0.75	100%	0.2	99%
F	3.0	100%	10.0	100%	0.75	100%	0.6	100%
G	3.0	100%	10.0	100%	0.75	100%	0.6	100%
H	3.0	100%	10.0	100%	0.75	100%	0.6	100%
I	3.0	100%	10.0	100%	0.75	98%	0.6	100%
J	3.0	100%	10.0	100%	0.13	96%	0.2	98%
K	3.0	100%	10.0	100%	0.75	100%	0.2	100%
LV Type 1	0.2	100%	10.0	100%	0.13	100%	0.2	98%
LV Type 2	0.2	96%	10.0	100%	0.13	100%	0.2	98%
LV Type 3	3.0	100%	10.0	100%	0.13	100%	0.6	100%
nvCT	5.0	96%	10.0	100%	0.75	100%	2.0	100%

*Vaginal swab Inclusivity verified with 10 IFU/mL level only

Table 25
Summary of NG Strains Inclusivity Verification Results

Numbers of NG Strains	LOD cobas® PCR Media (Endocervical Swabs)		Numbers of NG Strains	LOD Urine	
	CFU/mL	% Hit Rate		CFU/mL	% Hit Rate
2	3.0	96%	3	3.75	96%
2	3.0	98%	4	3.75	98%
3	15.0	96%	37	3.75	100%
3	15.0	98%	Total = 44		
33	15.0	100%			
1	20.0	100%			
Total = 44					
Numbers of NG Strains	**LOD Vaginal Swabs***		**Numbers of NG Strains**	**LOD PreservCyt**	
	CFU/mL	**% Hit Rate**		**CFU/mL**	**% Hit Rate**
Total = 44	100	100%	3	1.5	96%
			6	1.5	98%
			16	1.5	100%
			1	3.5	96%
			3	3.5	98%
			11	3.5	100%
			1	10	96%
			1	10	98%
			2	10	100%
			Total = 44		

*Vaginal swab Inclusivity verified with 100 CFU/mL level only

Precision

In-house Precision was examined using panels composed of CT and NG cultures diluted into **cobas**® PCR Media, **cobas**® PCR Media mixed with negative urine and PreservCyt Solution. The precision panel was designed to include members with either CT or NG at approximately the LOD for the panel matrix, members with both CT and NG at approximately the LOD and 2.5 x LOD for the panel matrix and a negative level. Testing was done with three unique lots of **cobas**® 4800 CT/NG Test reagents and three instruments for a total of 24 runs. A description of the precision panels and the study performance in % hit rate are shown in Table 26. All positive panel levels yielded the anticipated hit rates. All negative panel levels tested negative throughout the study.

Table 26
In-House Precision Study Hit Rate Analysis

Panel Number	Panel Matrix	Target Conc.		N Tested	N Pos CT	N Pos NG	Hit Rate	95% CI	
		CT	NG					Lower	Upper
1	**cobas**® PCR Media	Neg	Neg	144	0	0	0%	0.0	2.5
2	**cobas**® PCR Media	1 X LOD	Neg	144	144	0	100%	97.5	100.0
3	**cobas**® PCR Media	Neg	1 X LOD	144	0	144	100%	97.5	100.0
4	**cobas**® PCR Media	1 X LOD	2.5 X LOD	144	144	144	100%	97.5	100.0
5	**cobas**® PCR Media	2.5 X LOD	1 X LOD	144	144	144	100%	97.5	100.0
1	**cobas**® PCR Media + Urine	Neg	Neg	144	0	0	0%	0.0	2.5
2	**cobas**® PCR Media + Urine	1 X LOD	Neg	144	144	0	100%	97.5	100.0
3	**cobas**® PCR Media + Urine	Neg	1 X LOD	144	0	144	100%	97.5	100.0
4	**cobas**® PCR Media + Urine	1 X LOD	2.5 X LOD	144	144	144	100%	97.5	100.0
5	**cobas**® PCR Media + Urine	2.5 X LOD	1 X LOD	144	144	144	100%	97.5	100.0
1	PreservCyt Solution	Neg	Neg	144	0	0	0%	0.0	2.5
2	PreservCyt Solution	1 X LOD	Neg	144	144	0	100%	97.5	100.0
3	PreservCyt Solution	Neg	1 X LOD	144	0	141	97.9%	97.5	100.0
4	PreservCyt Solution	1 X LOD	2.5 X LOD	144	144	144	100%	97.5	100.0
5	PreservCyt Solution	2.5 X LOD	1 X LOD	144	144	143	*99.3%	96.2	99.9

*99.3% Hit Rate for NG. CT Hit Rate is 100%

Analytical Specificity

A panel of 184 bacteria, fungi and viruses, including those commonly found in the female urogenital tract, as well as representatives of *N. cineria, flava, lactamica, perflava* and *subflava* and other phylogenetically unrelated organisms, were tested with the **cobas**® 4800 CT/NG Test to assess analytical specificity. The organisms listed in Table 27 were spiked at high concentrations (microorganisms tested below 1 x 10^6 copies/mL are listed in Table 28) into CT/NG negative **cobas**® PCR Media, pooled negative vaginal specimen and pooled negative PreservCyt specimen and into CT/NG negative **cobas**® PCR Media, pooled negative vaginal specimen and pooled negative PreservCyt specimen spiked with CT and NG cultures at 3 times the limit of detection. Results indicated that none of these organisms interfered with detection of CT and NG or produced a false positive results in the CT/NG negative matrices.

Table 27
Microorganisms Tested for Analytical Specificity

Achromobacter xerosis	*Helicobacter pylori*	*Neisseria sicca*
Acinetobacter calcoaceticus	Hepatitis B virus (HBV)	*Neisseria subflava*
Acinetobacter lwoffi	Hepatitis C virus (HCV)	*Neisseria subflava 6458*
Acinetobacter sp. genospecies 3	Human immunodeficiency virus	*Neisseria subflava 6617*
Actinomyces israelii	Human papillomavirus type 16 (CaSki cells)	*Neisseria subflava 6618*
Actinomyces pyogenes	Human papillomavirus type 18 (HeLa cells)	*Neisseria subflava 7441*
Adenovirus Type 2	Human simplex virus (HSV-1)	*Neisseria subflava 7452*
Aerococcus viridans	Human simplex virus (HSV-2)	*Neisseria weaverii*
Aeromonas hydrophila	*Kingella denitrificans*	*Pantoea agglomerans*
Alcaligenes faecalis	*Kingella kingae*	*Paracoccus denitrificans*
Bacillus subtilis	*Klebsiella oxytoca*	*Pasteurella multocida*
Bacillus thuringiensis	*Klebsiella pneumoniae ss ozaenae*	*Pediococcus acidilactici*
Bacteroides caccae	*Lactobacillus acidophilus*	*Peptostreptococcus anaerobius*
Bacteroides fragilis	*Lactobacillus brevis*	*Peptostreptococcus asaccharolyticus*
Bacteroides ureolyticus	*Lactobacillus crispatus*	*Peptostreptococcus magnus*
Bifidobacterium adolescentis	*Lactobacillus delbrueckii subsp. lactis*	*Plesiomonas shigelloides*
Bifidobacterium breve	*Lactobacillus jensenii*	*Prevotella bivia*
Bifidobacterium longum	*Lactobacillus lactis lactis*	*Prevotella corporis*
Branhamella catarrhalis	*Lactobacillus oris*	*Prevotella intermedia*
Brevibacterium linens	*Lactobacillus parabuchneri*	*Propionibacterium acnes*
Campylobacter gracilis	*Lactobacillus vaginalis*	*Proteus mirabilis*
Campylobacter jejuni	*Lactococcus lactis cremoris*	*Proteus vulgaris*
Candida albicans	*Legionella bozemanii*	*Providencia stuartii*
Candida glabrata	*Legionella pneumophila*	*Pseudomonas aeruginosa*
Candida guilliermondii	*Listeria monocytogenes*	*Pseudomonas fluorescens*
Candida krusei	*Micrococcus luteus*	*Pseudomonas putida*
Candida parapsilosis	*Mobiluncus curtisii subsp. curtisii*	*Rahnella aquatilis*
Candida tropicalis	*Mobiluncus curtisii subsp. holmesii*	*Rhizobium radiobacter*
Chlamydophila pneumoniae	*Mobiluncus mulieris*	*Rhodospirillum rubrum*
Chromobacter violaceum	*Moraxella catarrhalis*	*Ruminococcus productus*
Chryseobacterium meningosepticum	*Moraxella lacunata*	*Saccharomyces cerevisiae*
Citrobacter braakii	*Moraxella osloensis*	*Salmonella choleraesuis*
Citrobacter freundii	*Morganella morganii*	*Salmonella minnesota*
Clostridium innocuum	*Mycobacterium avium*	*Salmonella typhimurium*
Clostridium perfringens	*Mycobacterium gordonae*	*Serratia denitrificans*
Clostridium sporogenes	*Mycobacterium smegmatis*	*Serratia marcescens*
Corynebacterium genitalium	*Mycoplasma genitalium*	*Staphylococcus aureus*
Corynebacterium renale	*Mycoplasma hominis*	*Staphylococcus epidermidis*
Corynebacterium xerosis	*Mycoplasma pneumoniae*	*Staphylococcus saprophyticus*
Cryptococcus neoformans	*Neisseria cinerea 832*	*Streptococcus agalactiae*
Cytomegalovirus	*Neisseria cinerea 3306*	*Streptococcus anginosus*
Deinococcus radiodurans	*Neisseria cinerea 3307*	*Streptococcus bovis*
Deinococcus radiopugnans	*Neisseria cinerea 3308*	*Streptococcus dysgalactiae*
Derxia gummosa	*Neisseria cinerea 6317*	*Streptococcus equinis*
Edwardsiella tarda	*Neisseria denitrificans*	*Streptococcus mitis*
Eikenella corrodens	*Neisseria elongata subsp. nitroreducens*	*Streptococcus mutans*
Enterobacter aerogenes	*Neisseria flava*	*Streptococcus pneumoniae*
Enterobacter cloacae	*Neisseria flavescens*	*Streptococcus pyogenes*
Enterococcus avium	*Neisseria kochii*	*Streptococcus salivarius*
Enterococcus faecalis	*Neisseria lactamica*	*Streptococcus sanguis*
Enterococcus faecium	*Neisseria meningitidis 135*	*Streptomyces griseus*
Epstein Barr Virus	*Neisseria meningitidis Serogroup A*	*Treponema pallidum*
Erwinia herbicola	*Neisseria meningitidis Serogroup B*	*Trichomonas vaginalis*
Erysipelothrix rhusiopathiae	*Neisseria meningitidis Serogroup C*	*Ureaplasma urealyticum*
Escherichia coli	*Neisseria meningitidis Serogroup D*	*Veillonella parvula*
Ewingella americana	*Neisseria meningitidis Serogroup Y*	*Vibrio parahaemolyticus*
Flavobacterium meningosepticum	*Neisseria mucosa*	*Weissella paramesenteroides*
Fusobacterium nucleatum	*Neisseria perflava 837*	*Yersinia enterocolitica*
Gardnerella vaginalis	*Neisseria perflava 911*	
Gemella haemolysans	*Neisseria perflava 6339*	
Gemella morbillorum	*Neisseria perflava 6340*	
Haemophilus ducreyi	*Neisseria perflava 6341*	
Haemophilus influenzae	*Neisseria polysaccharea*	

Table 28
List of Microorganisms Tested Below 1 x 10^6 copies/mL for Analytical Specificity

Microorganism Tested	Concentration Tested in Listed Matrix*		
	cobas® PCR Media	Negative Vaginal Specimen	Negative PreservCyt Specimen
Adenovirus		$8x10^5$ copies/mL	$8x10^5$ copies/mL
Cytomegalovirus (CMV)	$1x10^4$ copies/mL		
Chlamydophila pneumoniae	$1x10^5$ copies/mL	$1.1x10^4$ copies/mL	$1.1x10^4$ copies/mL
Gemella morbillorum		4.5×10^4 copies/mL	4.5×10^4 copies/mL
Hepatitis C virus (HCV)		5.6×10^4 copies/mL	5.6×10^4 copies/mL
Human papillomavirus (HPV) type 16 (SiHa cells)		$1x10^4$ copies/mL	$1x10^4$ copies/mL
Human papillomavirus (HPV) type 18 (HeLa cells)		$1x10^4$ copies/mL	$1x10^4$ copies/mL
Neisseria cinerea 3307		$4x10^5$ copies/mL	$4x10^5$ copies/mL
Prevotella bivia		$9x10^4$ copies/mL	$9x10^4$ copies/mL
Prevotella corporis		$1.4x10^5$ copies/mL	$1.4x10^5$ copies/mL
Treponema pallidum	Not Tested	$1x10^5$ copies/mL	$1x10^5$ copies/mL
Trichomonas vaginalis		$6.5x10^5$ copies/mL	$6.5x10^5$ copies/mL

*Gray cells indicate concentration tested was ≥ 1×10^6 copies/mL in that matrix

Whole System Failure

The whole system failure rate was determined for the **cobas**® 4800 CT/NG Test using **cobas**® PCR Media, **cobas**® PCR Media plus negative urine, negative vaginal specimen (stabilized in **cobas**® PCR Media) and negative PreservCyt specimen spiked with CT and NG cultures at ~ 3 x LOD for each target. A minimum of one hundred replicates representing each of the above matrices were run on the **cobas**® 4800 System using the **cobas**® 4800 CT/NG Test. All results were positive, yielding a whole system failure rate of 0.0% under conditions used to process endocervical swab, vaginal swab, urine and PreservCyt specimens.

Interference

Interference testing was performed using negative endocervical swab specimen (stabilized in **cobas**® PCR Media), **cobas**® PCR Media plus negative urine, negative vaginal swab specimen (stabilized in **cobas**® PCR Media) and negative PreservCyt specimen spiked with CT and NG cultures at ~ 3 x LOD for each target. Eighteen over-the-counter (OTC) products, including contraceptive jelly, lubricants, feminine sprays, anti-fungal cream and anti-itch cream, as well as whole blood, cervical mucus and PBMC cells were tested for interference. Of the 18 OTC products tested, Replens® vaginal moisturizer produced invalid and/or false negative results in the **cobas**® PCR Media plus negative urine panel samples. No interference from Replens® vaginal moisturizer was observed with the other sample matrices tested.

The levels of whole blood, mucus and PBMC cells shown in Table 29 represent maximum allowable concentrations which will not interfere with **cobas**® 4800 CT/NG Test performance. Concentrations in urine samples were determined using total sample volume, including stabilizing media.

Table 29
Results from Endogenous Interference Testing

	Blood (v/v)		PBMC (cells/mL)		Mucus	
	Conc. Tested	Interference Observed	Conc. Tested	Interference Observed	Conc. Tested	Interference Observed
Endocervical Specimen stabilized in **cobas**® PCR Media	0, 1%, 3%, 5%	None	0, 1.0E+05, 1.0E+06, 1.0E+07	> 1×10^5	0.25%, 0.35%, Routine level*	> 0.35% (w/v)
cobas® PCR Media + Urine	0, 0.25%, 0.35%, 0.5%, 1%, 3%	> 0.35%	0, 1.0E+05, 1.0E+06, 1.0E+07	> $1x 10^5$	NT	NT
Vaginal Specimen stabilized in **cobas**® PCR Media	0, 1%, 3%, 5%	None	0, 1.0E+05, 1.0E+06, 1.0E+07	> 1×10^5	Routine level*	None
PreservCyt Specimen	0, 1%, 3%, 5%	None	0, 1.0E+05, 1.0E+06, 1.0E+07	None	Routine level*	None

NT = Not Tested
*Routine level = Quantity of cervical mucus equivalent to amount normally removed prior to sampling

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Document Revision Information	
Doc Rev. 4.0 01/2011	The Intended Use of this test has been updated to include two additional specimen types: • Clinical-collected and clinician-instructed self-collected vaginal swab specimens • Cervical specimens collected in PreservCyt Solution. The package insert text, Workflow Instructions and Performance Characteristics (clinical and analytical) have been updated to support the additional specimen types. Please note that the test does require the use of the **cobas**® 4800 System Control Unit with System Software version 1.1. Please contact your local Roche Representative if you have any questions.

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For **cobas**® 4800 CT Test:

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CE 0088

For **cobas**® 4800 NG Test:

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CE

The following symbols are now used in labeling for Roche PCR diagnostic products.
Die folgenden Symbole werden jetzt bei der Etikettierung von Roche PCR-Diagnoseprodukten verwendet.
Les symboles suivants sont utilisés dans toute la documentation d'accompagnement des produits diagnostiques par PCR de Roche.
I seguenti simboli appaiono su tutte le confezioni di prodotti diagnostici PCR della Roche.
Los siguientes símbolos se emplean actualmente en el rotulado de todos los productos diagnósticos por PCR de Roche.
Os seguintes símbolos são utilizados actualmente em todos os rótulos de produtos de diagnóstico por PCR da Roche.
Følgende symboler er nu i anvendelse på etiketter til Roche PCR diagnostiske produkter.
Följande symboler används för närvarande vid märkning av Roche PCR diagnostiska produkter.
Na etykietach produktów diagnostycznych Roche PCR stosuje się obecnie następujące oznaczenia.
Na označenie diagnostických produktov Roche PCR sa používajú nasledujúce symboly.

Ancillary Software
Zusatz-Software
Logiciel auxiliaire
Software ausiliario
Programa auxiliary
Software Auxiliar
Hjælpesoftware
Stödprogramvara
Oprogramowanie pomocnicze
Prídavný softvér

Distributed by
Vertrieb:
Distributeur
Distribuito da
Distribuido por
Distribuído por
Distribueret af:
Distribueras av
Dystrybucja przez
Distribútor

Authorized representative
Bevollmächtigter
Représentant agree
Rappresentante autorizzato
Representante autorizado
Representante autorizado
Autoriseret repræsentant
Auktoriserad represenant
Autoryzowany przedstawiciel
Autorizovaný zástupca

For *in vitro* diagnostic use
In-vitro-Diagnostikum
Pour diagnostic *in vitro*
Per uso diagnostico *in vitro*
De uso diagnóstico *in vitro*
Para diagnóstico *in vitro*
Til *in vitro* diagnostisk anvendelse
För *in vitro* diagnostiskt bruk
Do stosowania w diagnostyce *in vitro*
Určené na diagnostické použitie *in vitro*

Batch code
Chargen-Bezeichnung
Code du lot
Numero di lotto
Denominación de lote
Número do lote
Batchkode
Batchkod
Kod serii
Číslo šarže

Manufacturer
Hersteller
Fabricant
Produttore
Fabricante
Fabricante
Producent
Tillverkare
Producent
Výrobca

Biological Risk (Potentially biohazardous material)
Biologisches Risiko (Potentiell biogefährliches Material)
Risque biologique (matériel à risque biologique potentiel)
Rischio biologico (materiale potenziale pericoloso sotto il profilo biologico)
Riesgo biológico (Material biológico potencialmente peligroso)
Risco biológico (Material potencialmente perigoso a nível biológico)
Biologisk risiko (potentielt sundhedsfarligt biologisk materiale)
Biologisk risk (potentiellt biologiskt riskmaterial)
Zagrożenie biologiczne (materiał stanowiący potencjalne zagrożenie biologiczne)
Biologické riziko (Potenciálny biologicky nebezpečný materiál)

Store in the dark
Im Dunkeln aufbewahren
Conserver dans un endroit somber
Conservare al buio
Almacenar en la oscuridad
Armazenar no escuro
Opbevares mørkts
Förvaras i mörker
Przechowywać z dala od światła
Skladovať v tmavom prostredí

Catalogue Number
Katalognummer
Numéro de catalogue
Numero di catalogo
Número de catálogo
Número de catálogo
Katalognummer
Katalognummer
Numer katalogowy
Katalógové číslo

Temperature limitation (Store At)
Festgelegte Temperatur (Aufbewahrung bei)
Températures limites de conservation (Conservation à)
Limiti di temperatura (Conservare a)
Temperatura límite (Conservar a)
Limite de temperatura (Conservar a)
Temperaturbegrænsning (Skal opbevares ved)
Temperaturgräns (förvaras vid)
Zakres temperatury (temperatura przechowywania)
Tepelné obmedzenie (Uchovávať pri)

Consult instructions for use
Gebrauchsanleitung beachten
Consulter le mode d'emploi
Vedere le istruzioni per l'uso
Consultar las instrucciones de uso
Consultar as instruções de utilização
Se brugsanvisningen
Läs bruksanvisningen
Przed użyciem należy zapoznać się z instrukcją
Prečítajte si návod na použitie

Test Definition File
Testdefinitionsdatei
Fichier de définition de tests
File di definizione del test
Archivo de definición de pruebas
Ficheiro de Definição de Teste
Testdefinitionsfil
Testdefinitionsfil
Plik definicji testów
Testovací definičný súbor

Contains sufficient for < n > tests
Ausreichend für < n > Tests
Suffisant pour < n > tests
Contenuto sufficiente per < n > test
Suficiente para < n > pruebas
Contém o suficiente para < n > testes
Indeholder tilstrækkeligt til < n > test
Räcker till < n > tester
Wystarcza na < n > testów(-y)
Obsah postačuje na < n > testov

Use by (last day of month)
Verwendbar bis (letzter Tag des Monats)
Utilisable jusqu'au (dernier jour du mois indiqué)
Da utilizzare prima del (ultimo giorno del mese)
Estable hasta (ultimo día del mes)
Data limite de utilização (último dia do mês)
Anvendes inden (sidste dag i måned)
Används senast (sista dagen i månaden)
Zużyć do (ostatniego dnia miesiąca)
Spotrebovať do (posledný deň v mesiaci)

Contents of kit
Inhalt der Packung
Contenu de la nécessaire
Contenuto del kit
Contenido del estuche
Conteúdo do dispositivo
Sættet indholder
Utrustningen innehåller
Zawartość zestawu
Obsah súpravy

This product fulfills the requirements of the European Directive 98/79 EC for *in vitro* diagnostic medical devices.
Dieses Produkt erfüllt die Anforderungen der Europäischen Richtlinie 98/79 EG für *in-vitro*-Diagnostika.
Ce produit répond aux exigences de la Directive Européenne 98/79 CE concernant les dispositifs médicaux de diagnostic *in vitro*.
Questo prodotto è conforme ai requisiti della Direttiva Europea 98/79 CE relativa ai dispositivi medici per uso diagnostico *in vitro*.
El presente producto cumple con los requerimientos previstos por la Directiva Europea 98/79 CE de productos sanitarios para el diagnóstico *in vitro*.
Este produto preenche os requisitos da Directiva Europeia 98/79 CE para dispositivos médicos de diagnóstico *in vitro*.
Dette produkt opfylder kravene fra European Directive 98/79 EC for *in vitro* diagnostisk medicinsk apparatur.
Denna produkt uppfyller kraven i EU:s direktiv 98/79 EC för *in vitro* diagnostiska medic inska produkter.
Produkt spełnia wymagania Dyrektywy Rady Europy 98/79 EC dla urządzeń medycznych do diagnostyki *in vitro*.
Tento produkt spĺňa požiadavky európskej Smernice 98/79 ES pre *in vitro* diagnostické medicínske zariadenia.

US Customer Technical Support 1-800-428-2336

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