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Xpert® C. difficile

REF GXCDIFFICILE-CE-10

Cepheid®

In Vitro Diagnostic Medical Device IVD

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Xpert® *C. difficile* (English)

In Vitro Diagnostic Medical Device

Proprietary Name

Xpert® *C. difficile*

Common or Usual Name

Xpert *C. difficile* Assay

Intended Use

The Xpert *C. difficile* Assay, performed on the Cepheid GeneXpert® Systems, is a qualitative *in-vitro* diagnostic test for the rapid identification and differentiation of Toxin B, and Binary Toxin from appropriate stool specimens collected from patients suspected of having *Clostridium difficile* infection (CDI). The test utilizes automated real-time polymerase chain reaction (PCR) to detect Toxin producing *C. difficile*, which is associated with CDI. The Xpert *C. difficile* Assay is intended as an aid in the diagnosis of CDI. Concomitant testing is necessary only if further typing is required.

Summary and Explanation

Clostridium difficile (*C. difficile*) is a Gram-positive, spore-forming anaerobic bacillus that was first linked to disease in 1978.[1] *Clostridium-difficile* infection (CDI) ranges from diarrhoea to severe life-threatening pseudomembranous colitis.[2] Mature colonic bacterial flora in a healthy adult is generally resistant to *C. difficile* colonization.[3] However, if the normal colonic flora is altered, resistance to colonization is lost. The most common risk factor is exposure to antibiotics.[4] *C. difficile*'s primary virulence factors are enterotoxin A and cytotoxin B.[5] The genes coding for toxin A (*tcdA*) and toxin B (*tcdB*) are parts of the pathogenicity locus (PaLoc).[6,7] Most pathogenic strains are toxin A-positive, toxin B-positive (A+B+) strains although toxin A-negative, toxin B-positive (A-B+) variant isolates have been recognized as pathogenic.[8] Some strains of *C. difficile* also produce an actin-specific ADP-ribosyltransferase called CDT or binary toxin. The binary toxin locus contains two genes (*cdtA* and *cdtB*) and is located outside the PaLoc.[9-11] In the last several years, there have been outbreaks of CDI caused by "hypervirulent" and fluoroquinolone-resistant strains belonging to PCR ribotype 027, PFGE type NAP1 and REA Type B1.[8,12] These strains exhibit increased toxin production which is being attributed to deletions in the regulatory gene *tcdC*.[13,14]

The European Centre for Disease Prevention and Control (ECDC) has identified an urgent need for rapid diagnostic tests with better performance than currently available assays for *C. difficile*.[12] *C. difficile* diagnosis is generally based on the detection of toxin A or B. The labor intensive cell cytotoxicity assay is still considered to be the "gold standard" because of its high specificity.[15,16] Several rapid enzyme immunoassays have been developed for detection of toxin A and B. However, these tests have reduced sensitivity and specificity compared to the cell cytotoxicity assay. Recently, PCR methods for the detection of toxin A and/or toxin B have been developed with high sensitivity and specificity as compared to the cell cytotoxicity and immunoassays. However, no commercial standardized PCR assays for detection of toxin A and B are currently available.[17]

Principle of the Procedure

The GeneXpert Instrument Systems automate and integrate sample purification, nucleic acid amplification, and detection of the target sequences in simple or complex samples using real-time PCR and RT-PCR assays. The systems consist of an instrument, personal computer, and preloaded software for running the tests on collected samples and viewing the results. The systems require the use of single-use disposable GeneXpert cartridges that hold reagents for PCR and hosts the processes of DNA extraction and PCR. Because the cartridges are self-contained, cross-contamination between samples is eliminated. For a full description of the system, see the *GeneXpert Dx System Operator Manual* or the *GeneXpert Infinity System Operator Manual*.

Xpert *C. difficile* Assay includes reagents for the detection of Toxin producing *C. difficile* and Toxin producing *C. difficile*, presumptive 027/NAP1/BI respectively as well as the Sample –Processing Control (SPC). The SPC is present to control for adequate processing of the target bacteria and to monitor the presence of inhibitors in the PCR reaction. The Probe Check Control (PCC) verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability.

The primers and probes in the Xpert *C. difficile* assay detect sequences in the genes for Toxin B (*tcdB*), Binary Toxin (*cdt*), and *tcdC* deletion nt 117 (*tcd*CΔ117).

Reagents and Instruments

Material Provided

The Xpert *C. difficile* kit contains sufficient reagents to process 10 specimens or quality control samples.

The kit contains the following:

Xpert *C. difficile* Assay Cartridges with integrated reaction tubes	**10**
Bead 1, Bead 2, and Bead 3 (freeze-dried)	**1 per cartridge**
Reagent 1	**3.0 mL per cartridge**
Reagent 2 (Sodium Hydroxide)	**3.0 mL per cartridge**

Xpert *C. difficile* reagent pouches	**10**
Sample Reagent (Guanidinium thiocyanate)	**10 x 2.0 mL per pouch**
CD	**1 per kit**

- Assay Definition File (ADF)
- Instructions to import ADF into GX software
- Package Insert

Note: Safety Data Sheets (SDS) are available at www.cepheid.com/tests-and-reagents/literature/msds or www.cepheidinternational.com/tests-and-reagents/literature/msds.

Note: The bovine serum albumin (BSA) in the beads within this product was produced exclusively from bovine plasma sourced in the United States. The manufacturing of the BSA is also performed in the United States. No ruminant protein or other animal protein was fed to the animals; the animals passed ante- and post-mortem testing. During processing, there was no commingling of the material with other animal materials.

Storage and Handling

- Store the Xpert *C. difficile* cartridges and reagents at 2 – 28 ˚C.
- Do not use sample reagent or cartridges that have passed the expiration date.
- Do not open a cartridge lid until you are ready to perform testing.
- Use the cartridge and sample reagent within 30 minutes after opening the package.
- Do not use sample reagent that has become cloudy or discolored.

Materials Required but Not Provided

- GeneXpert Dx System or GeneXpert Infinity System (catalog number varies by configuration): GeneXpert instrument, computer, barcode wand reader, and Operator Manual
- Printer (See *GeneXpert Dx System Operator Manual* or the *GeneXpert Infinity System Operator Manual* for compatibility guidelines)
- Vortex mixer
- Disposable, sterile transfer Pipettes
- Dry swab for transfer of the specimen, such as the swab found in the Cepheid Sample Collection Device (Cepheid Catalog Number: 900-0370), Cepheid Single-Use Disposable Swab (Cepheid Catalog Number SDPS-120), or the Copan Dual Swab and Transport System (139CFM LQ STUART)

Warnings and Precautions

- Treat all biological specimens, including used cartridges, as if capable of transmitting infectious agents. Because it is often impossible to know which might be infectious, all biological specimens should be treated with universal precautions. Guidelines for specimen handling are available from the U.S. Centers for Disease Control and Prevention and the Clinical and Laboratory Standards Institute (formerly National Committee for Clinical Laboratory Standards)[18, 19].
- Follow your institution's safety procedures for working with chemicals and handling biological samples.
- The Xpert *C. difficile* Assay does not provide susceptibility results. Additional time is required to culture and perform susceptibility testing.
- Do not substitute Xpert *C. difficile* reagents with other reagents.
- Do not open the Xpert *C. difficile* cartridge lid except when adding sample and reagents or performing a retest.
- Do not use a cartridge that has been dropped or shaken after you have added the sample.
- Do not use a cartridge that has a damaged reaction tube.
- Each single-use Xpert *C. difficile* cartridge is used to process one test. Do not reuse spent cartridges.
- Consult your institution's environmental waste personnel on proper disposal of used cartridges and unused reagents. This material may exhibit characteristics of federal EPA Resource Conservation and Recovery Act (RCRA) hazardous waste requiring specific disposal requirements. Check state and local regulations as they may differ from federal disposal regulations. Institutions outside the USA should check their country hazardous waste disposal requirements.
- Store the Xpert *C. difficile* kit at 2 – 28 °C.
- Do not open a cartridge lid until you are ready to perform testing.
- Reagent 2 contains sodium hydroxide (pH > 12.5); (H302, H315, H319) which is irritating to eyes and skin requiring eye and skin protection.
- Sample Reagent contains guanidinium thiocyanate (H302, H402, EUH031), which is harmful to aquatic life and contact with acid liberates toxic gas.

Specimen Collection and Transport

1. Collect the unformed stool in a sterile container. Follow your institutions guidelines for collecting samples for *C. difficile* testing.
2. Label with Sample ID and send to the laboratory for testing.
3. Store the specimen at –20 °C. The specimen is stable up to 5 days when stored at –20 °C.

Procedure

Preparing the Cartridge

Important: Start the test within 30 minutes of adding the sample to the cartridge.

To add the sample into the cartridge (Xpert *C. difficile*):

1. Remove the cartridge and sample reagent from the package.
2. Immerse swab in the unformed stool sample briefly. The swab does not need to be completely soaked.
3. Insert the swab into the tube containing the Sample Reagent.

Note: Use sterile gauze to minimize risks of contamination.

4. Hold the swab by the stem near the rim of the tube, lift the swab a few millimeters from the bottom of the tube and push the stem against the edge of the tube to break it. Make sure the swab is short enough to allow the cap to close tightly.
5. Close the lid and vortex at high speed for 10 seconds.
6. Open the cartridge lid. Using a clean transfer pipette, transfer the entire contents of the Sample Reagent to the "S" chamber of the Xpert *C difficile* cartridge.
7. Close the cartridge lid.

S = Sample

Figure 1. Xpert *C. difficile* cartridge (top view)

Starting the Test

Important: Before you start the test, make sure the Xpert *C. difficile* assay definition is imported into the software.

This section lists the basic steps for running the test. For detailed instructions, see the *GeneXpert Dx System Operator Manual* or the *GeneXpert Infinity System Operator Manual* depending upon the model that is being used.

1. Turn on the GeneXpert instrument system:
   - If using the GeneXpert Dx instrument, first turn on the instrument and then turn on the computer. The GeneXpert software will launch automatically.

     or
   - If using the GeneXpert Infinity instrument, power up the instrument and double-click the Xpertise software shortcut icon on the Windows® desktop.
2. Log on to the GeneXpert Instrument System software using your user name and password.
3. In the GeneXpert System window, click **Create Test** (GX-I, GX-II, GX-IV GX-XVI) or **Orders** and **Order Test** (Infinity).
4. Scan in the Patient ID (optional).
5. Scan or type in the Sample ID. If typing the Sample ID, make sure the Sample ID is typed correctly. The Sample ID is associated with the test results and is shown in the **View Results** window.
6. Scan the barcode on the Xpert *C. difficile* cartridge. Using the barcode information, the software automatically fills the boxes for the following fields: Select Assay, Reagent Lot ID, Cartridge SN, and Expiration Date.
7. Click **Start Test** (GX-I, GX-II, GX-IV GX-XVI) or **Submit** (Infinity). In the dialog box that appears, type your password.
8. For the GeneXpert Infinity System, place the cartridge on the conveyor belt. The cartridge will be automatically loaded, the test will run and the used cartridge will be placed into the waste container.

   or

   For the GeneXpert Dx Instrument:

   a. Open the instrument module door with the blinking green light and load the cartridge.
   b. Close the door. The test starts and the green light stops blinking. When the test is finished, the light turns off.
   c. Wait until the system releases the door lock before opening the module door and removing the cartridge.
   d. The used cartridges should be disposed in the appropriate specimen waste containers according to your institution's standard practices.

Viewing and Printing Results

For detailed instructions on how to view and print the results, see the *GeneXpert Dx System Operator Manual* or the *GeneXpert Infinity System Operator Manual.*

CONTROL

Quality Control

Each test includes a Sample Processing Control (SPC) and Probe Check (PCC).

Sample Processing Control (SPC)—Ensures the sample was correctly processed. The SPC contains spores of *Bacillus globigii* in the form of a dry spore cake that is included in each cartridge to verify adequate processing of the sample bacteria. The SPC verifies that lysis of *C. difficile* bacteria and a spore have occurred if the organisms are present and verifies that specimen processing is adequate. Additionally this control detects specimen-associated inhibition of the real-time PCR assay. The SPC should be positive in a negative sample and can be negative or positive in a positive sample. The SPC passes if it meets the validated acceptance criteria.

Probe Check Control (PCC)—Before the start of the PCR reaction, the GeneXpert System measures the fluorescence signal from the probes to monitor bead rehydration, reaction-tube filling, probe integrity and dye stability. Probe Check passes if it meets the assigned acceptance criteria.

Interpretation of Results

The results are interpolated by the GeneXpert Instrument System from measured fluorescent signals and embedded calculation algorithms and will be shown in the **View Result**s window. Possible results are:

Toxigenic ***C.*** diff POSITIVE, 027-NAP1-BI PRESUMPTIVE NEG
Toxin producing *C. difficile* target DNA sequences are detected.

- Toxin producing *C. difficile* — the Toxin producing *C. difficile* target(s) (Toxin B or Toxin B plus either Binary Toxin or *tcdC* deletion nt 117) have a Ct within the valid range and endpoint above the minimum setting
- SPC — NA (not applicable); SPC is ignored since *C. difficile* target amplification may compete with this control
- Probe Check — PASS; all probe check results pass.

Toxigenic ***C.*** diff POSITIVE, 027-NAP1-BI PRESUMPTIVE POS
Toxin producing *C. difficile*, presumptive 027/NAP1/BI target DNA sequences are detected.

- Toxin producing *C. difficile*, presumptive 027/NAP1/BI — all Toxin producing *C. difficile*, presumptive 027/NAP1/BI targets (Toxin B, Binary Toxin and *tcdC* deletion nt 117) have Ct within the valid range and endpoint above the minimum setting.
- SPC — NA (not applicable); SPC is ignored since *C. difficile* target amplification may compete with this control.
- Probe Check — PASS; all probe check results pass.

Toxigenic ***C.*** diff NEGATIVE, 027-NAP1-BI PRESUMPTIVE NEG
C. difficile target DNA sequences (Toxin B) are not detected.

NEGATIVE —Toxin producing *C. difficile* DNA sequences (Toxin B) are not detected, other target DNA for toxigenic *C. diff* (Binary Toxin and *tcdC* deletion nt 117) are not detected. SPC meets acceptance criteria.

Toxin producing *C. difficile* DNA sequences (Toxin B) are not detected, other target DNA for toxigenic *C. diff* (Binary Toxin and /or *tcdC* deletion nt 117) are detected.

- NEGATIVE — *C. difficile* target DNA is not detected.
- SPC – PASS; SPC has a Ct within the valid range and endpoint above the endpoint minimum setting.
- Probe Check — PASS; all probe check results pass.

INVALID

Presence or absence of *C. difficile* target DNA cannot be determined, repeat test according to the instructions in the Retest Procedure section below. SPC does not meet acceptance criteria, the sample was not properly processed, or PCR is inhibited.

- INVALID — Presence or absence of *C. difficile* target DNA cannot be determined.
- SPC — FAIL; SPC target result is negative and the SPC Ct is not within valid range and endpoint below minimum setting.
- Probe Check — PASS; all probe check results pass.

ERROR

Presence or absence of *C. difficile* target DNA cannot be determined, repeat test according to the instructions in the Retest Procedure section below. The Probe Check control failed probably due to reaction tube was filled improperly, a probe integrity problem was detected or because the maximum pressure limits were exceeded.

- Toxin B (*tcdB*) — NO RESULT
- Binary Toxin (*cdt*) — NO RESULT
- *tcdC*Δ117 — NO RESULT
- *SPC — NO RESULT

Probe Check — FAIL*; all or one of the probe check results fail

*If the probe check passed, the error is caused by a system component failure.

NO RESULT

Presence or absence of *C. difficile* target DNA cannot be determined, repeat test according to the instructions in the Retest Procedure section below. Insufficient data were collected to produce a test result (for example, the operator stopped a test that was in progress).

- Toxin B (*tcdB*) — NO RESULT
- Binary Toxin (*cdt*) — NO RESULT
- *tcdC*Δ117 — NO RESULT
- SPC — NO RESULT
- Probe Check — NA (not applicable)

Reasons to Repeat the Assay

If any of the test results mentioned below occur, repeat the test according to instructions in the Retest Procedure section below.

- An **INVALID** result indicates that the SPC failed. The sample was not properly processed or PCR was inhibited.
- An **ERROR** result indicates that the Probe Check control failed and the assay was aborted possibly due to the reaction tube being filled improperly, a reagent probe integrity problem was detected, or because the maximum pressure limits were exceeded, or a valve positioning error was detected.
- A **NO RESULT** indicates that insufficient data were collected. For example, the operator stopped a test that was in progress.

Retest Procedure

For retest within 3 hours of an indeterminate result: Use a new cartridge (do not re-use the cartridge) and new reagents. Transfer all remaining contents from Chamber S to a new Sample Reagent. Vortex and add the entire contents of the Sample Reagent to Chamber S of the new Xpert *C. difficile* cartridge. Close the lid and start new test. Retesting can be performed using a new swab sample taken from the original patient specimen.

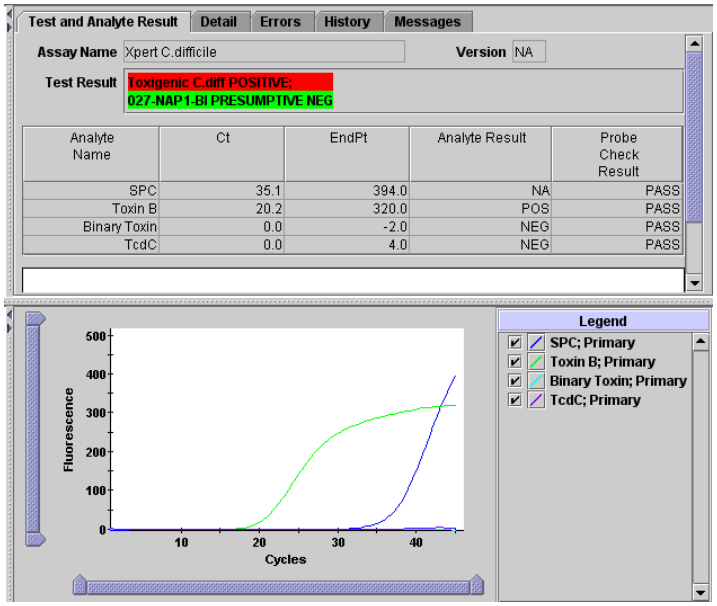

Figure 2. Example of Xpert *C. difficile* positive and 027-NAP1-BI Presumptive negative results

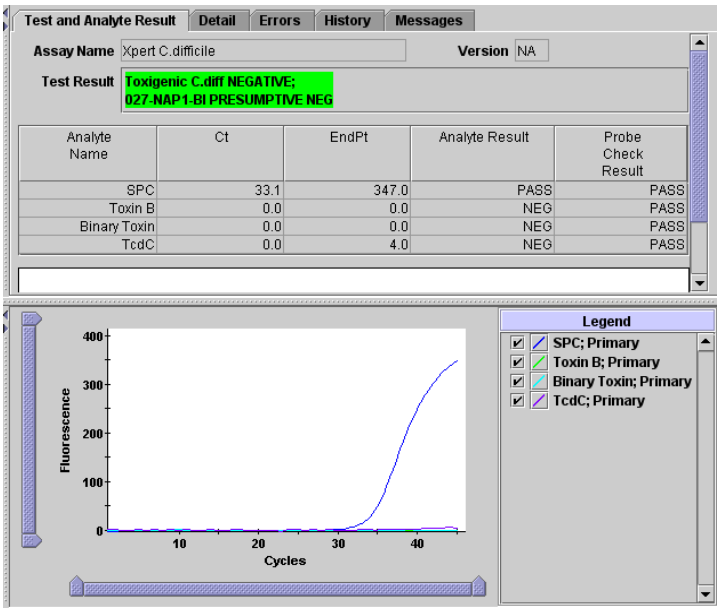

Figure 3. Example of Xpert *C. difficile* negative and 027-NAP1-BI Presumptive negative results

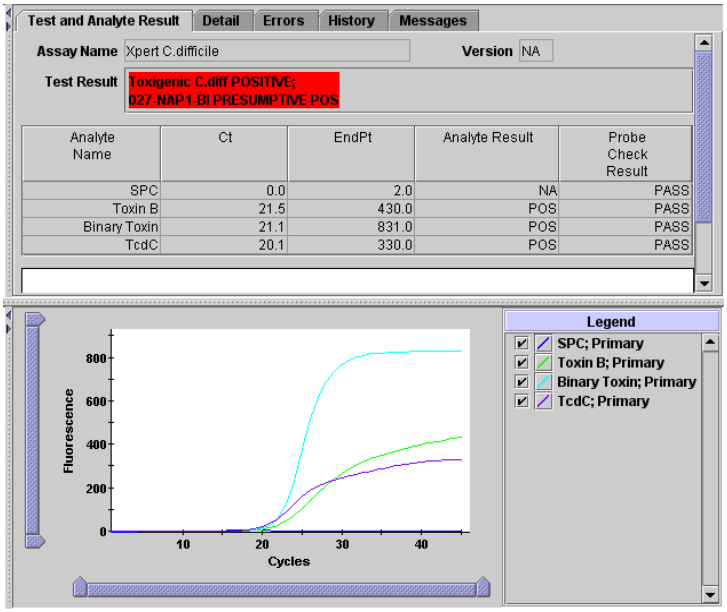

Figure 4. Example of Xpert *C. difficile* positive and 027-NAP1-BI Presumptive positive results

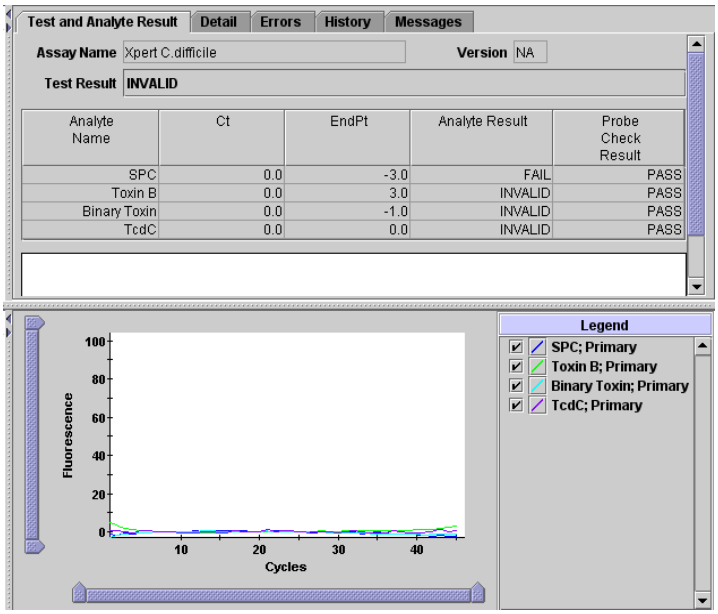

Figure 5. Example of an invalid result

Limitations

The performance of the Xpert *C. difficile* Assay was validated using the procedures provided in this package insert only. Modifications to these procedures may alter the performance of the test. Results from the Xpert *C. difficile* Assay should be interpreted in conjunction with other laboratory and clinical data available to the clinician.

Erroneous test results might occur from improper specimen collection, failure to follow the recommended sample collection, handling and storage procedures, technical error, sample mix-up, or because the number of organisms in the specimen is too low to be detected by the test. Careful compliance with the instructions in this insert is necessary to avoid erroneous results.

Because the detection of *C. difficile* is dependent on the number of organisms present in the sample, reliable results are dependent on proper specimen collection, handling, and storage.

Rerunning the Xpert *C. difficile* assay when results are INVALID, ERROR, or NO RESULT should depend on practices and policies within each facility. Alternate procedures should be available. For culturing, remaining swab specimens should be placed in appropriate transport systems and cultured within 4 days.

A positive test result does not necessarily indicate the presence of viable organism. It is however, presumptive for the presence of *C. difficile*.

Interfering Substances

Potential inhibitory substances tested include blood, excess feces and mucus. Substances were tested in replicates of three with *C. difficile* bacteria strain 027/NAP1/BI spiked near the analytical Limit of Detection (~3x LoD) and higher (~50x LoD). Excess feces material was evaluated with real clinical samples in a multi-site investigation study. Inhibitory effect is occasionally seen in the presence of excess feces on the swab. No significant inhibitory effects were observed in the presence of blood or mucus.

Performance Characteristics

Performance characteristics of the Xpert *C. difficile* Assay were determined in a prospective investigation study at two sites in Europe by comparing the Xpert *C. difficile* Assay on the GeneXpert System (Xpert *C. difficile* Assay) with toxinogenic culture followed by PCR ribotyping of culture positive samples. To be enrolled in the study, specimens had to be from individuals for whom cultures were indicated and/or ordered, according to institutional practices.

Overall Results

A total of 285 specimens were tested for *C. difficile* by the Xpert *C. difficile* Assay and compared to the direct culture method (Table 1).

Table 1. Performance characteristics of the Xpert *C. difficile* Assay as compared to direct culture

		Toxinogenic Culture			
		***C. difficile* pos**	**027/NAP1/BI pos**	**Negative**	
Xpert *C. difficile*	**Toxin B+**	34	0	16	Sensitivity 100%
	027/NAP1/BI	0	0	1	Specificity 93%
	Negative	0	0	234	

Performance Characteristics of the 027/NAP1/BI

To determine the performance characteristics of the 027/NAP1/BI strain, clinical samples were evaluated in-house by Xpert *C. difficile*, cultured and PCR-ribotyped. The data of the study is provided in Table 2. Negative in this case means toxinogenic *C. difficile* strains that are not 027/NAP1/BI.

Table 2. Performance characteristics of the Xpert *C. difficile* Assay as compared to PCR Ribotyping

		Toxinogenic Culture and PCR-ribotyping		
		027/NAP1/BI Pos	**027/NAP1/BI Neg**	
Xpert *C. difficile*	**027/NAP1/BI Pos**	14	1	Sensitivity 100%
	027/NAP1/BI Neg	0	10	Specificity 91%

Analytical Specificity

Cultures from American Type Culture Collection (ATCC) and Culture Collection, University of Göteborg (CCUG) representing organisms closely related to *C. difficile* as well as normal and pathogenic rectal flora were tested in a cross-reactivity study. Two strains of non-toxin producing *C. difficile* were tested using the Xpert *C. difficile* Assay. The organisms tested were represented by 24 aerobic, 14 anaerobic and two microaerophilic species. Three replicates of each isolate were tested at a concentration of at least 10^9 CFU per reaction. Under the conditions of the study, all isolates were reported toxinogenic *C. difficile* negative; none of the isolates were detected by the Xpert *C. difficile* Assay. Positive and Negative controls were included in the study. The Analytical specificity was 100%.

Analytical Sensitivity

Additional studies were performed to determine the 95% confidence interval for the analytical limit of detection (LoD) of this assay. The limit of detection is defined as the lowest number of colony forming units (CFU) per sample that can be reproducibly distinguished from negative samples with 95% confidence. Replicates of 20 were evaluated at six concentrations (100, 300, 600, 1200, 2400 and 4800 CFU/sample).

Under the conditions of the study and using a maximum valid Ct setting of 37, for *tcdB* and *cdt* and 40 for *tcdC* results indicate that the LoD point estimate for toxigenic *C. difficile* is 1657 CFU/swab with a 95% confidence interval ranging from 1157 CFU/swab to 3561 CFU/swab and for toxigenic *C. difficile* strain 027/NAP1/BI 2058 CFU/sample with a 95% confidence interval ranging from 1581 CFU/swab to 3441 CFU/swab.

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Assistance

Before contacting Cepheid Technical Support, collect the following information:

- Product name
- Lot number
- Serial number of the instrument
- Error messages (if any)
- Software version and, if applicable, Computer Service Tag number

Region	Telephone	Email
North America	+1.888.838.3222	
	Sales Support: Option 1	CustomerService@cepheid.com
	Technical Support: Option 2	TechSupport@cepheid.com
	Service Support: Option 3	Cepheid.ServiceSupport@cepheid.com
	Instrument Service Contracts: Option 4	Service.Contracts@cepheid.com
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Contact information for other Cepheid offices is available on our website at http://www.cepheid.com/company/contact-us/.

Table of Symbols

Symbol	Meaning
REF	Catalog number
IVD	*In vitro* diagnostic medical device
	Do not reuse
LOT	Batch code
	Caution, consult accompanying document
	Manufacturer
Σ	Contains sufficient for <n> tests
	Expiration date
CONTROL	Control
CE	CE marking - European Conformity
EC REP	Authorized representative in the European Community
	Temperature limitation
	Biological risks

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Product of Sweden

EC REP

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CE IVD