Cepheid®

Instructions for Use

Xpert® Norovirus

For use with GeneXpert® System with Touchscreen

Catalog Numbers

REF GXNOV-10

303-0938 | Rev. A | 2023-07

℞only IVD *In Vitro* Diagnostic Medical Device

Trademark, Patents and Copyright Statements

See Revision History for a detailed description of changes.

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Product Information

Proprietary Name

Xpert® Norovirus

Common or Usual Name

Xpert Norovirus

Intended Use, Summary, and Principle of Procedure

Intended Use

The Xpert Norovirus test, performed on the GeneXpert® Instrument Systems, is a qualitative *in vitro* diagnostic test for the identification and differentiation of norovirus genogroup I and genogroup II RNA from raw or unpreserved unformed stool specimens collected from individuals with symptoms of acute gastroenteritis. The test utilizes automated real-time reverse transcriptase polymerase chain reaction (RT-PCR) to detect norovirus RNA.

The Xpert Norovirus test is intended to aid in the diagnosis of norovirus infections when used in conjunction with clinical evaluation, laboratory findings, and epidemiological information. The test also aids in the detection and identification of norovirus infections in the context of outbreaks.

Summary and Explanation

Noroviruses are single stranded RNA, non-enveloped viruses in the genus *Norovirus*, family *Caliciviridae*, which cause acute gastroenteritis in humans and other mammals. The prototype norovirus was first identified as the cause of a gastroenteritis outbreak in Norwalk, Ohio in 1968.[1] It is estimated that norovirus may be the causative agent in over 23 million gastroenteritis cases every year in the United States, representing approximately 60% of all acute gastroenteritis cases.[2] Noroviruses can be classified into five different genogroups of which genogroup I (GI) and genogroup II (GII) cause the majority of the infections in humans.

Noroviruses are a major world-wide cause of gastroenteritis. They affect all ages, and are frequently involved in outbreaks in communal facilities, such as nursing homes, hospitals, day nurseries, prisons, and cruise ships.[3–6] Symptoms of norovirus infection are usually diarrhea, vomiting, stomach cramps, nausea, and fever. The disease is normally self-limiting and signs and symptoms may last for several days. In the young, elderly, and immunocompromised, the disease may be life threatening due to dehydration. Common names associated with norovirus gastroenteritis are winter vomiting disease, stomach flu, acute non-bacterial gastroenteritis, and viral gastroenteritis. Norovirus can only be cultured in very specialized cell culture systems.[7] Electron microscopy can be used to directly visualize norovirus in fecal specimens but has poor sensitivity.[8]

Commercially available Enzyme Immunoassays (EIAs) have proven useful during norovirus outbreak situations. However, due to low test sensitivity, commercially available EIAs are useful only when prevalence of norovirus infection is high. In addition, current CDC guidelines recommend all negative EIA results be confirmed by molecular methods.[8] The currently available EIAs are known to have low sensitivity (36–80%) compared to RT-PCR methods and low to good specificity (47–100%) depending on the testing environment.[9–15] In Europe and Japan, where commercially available molecular tests exist, the tests require highly trained molecular technologists and, by design, force testing to be performed in a batched mode, resulting in reporting delays. Under current CDC guidelines, it is recommended that healthcare providers consider the development and adoption of facility policies to enable clinical and virological confirmation of suspected cases of symptomatic norovirus infection while implementing prompt control measures to reduce the magnitude of a potential norovirus outbreak.[16] The Xpert Norovirus test provides an on-demand, fast, accurate molecular test to facilitate confirmation and initiate prompt norovirus control measures, irrespective of prevalence rate.

Principle of the Procedure

The test is automated and utilizes real-time reverse transcriptase polymerase chain reaction (RT-PCR) to detect specific viral gene sequences associated with norovirus genogroup I and genogroup II. The stool specimens are collected from individuals with symptoms of acute gastroenteritis and transported to the laboratory in a clean container. A swab is inserted into the stool specimen and then placed in a tube containing sample reagent. Following brief vortexing, the eluted sample is transferred into the sample chamber of the disposable fluidic cartridge (the GeneXpert cartridge). The GeneXpert cartridge is loaded onto the GeneXpert Instrument System platform, which performs hands-off automated sample processing and real-time RT-PCR for identification and differentiation of norovirus genogroup I and genogroup II.

The GeneXpert Instrument Systems automate and integrate sample preparation, nucleic acid extraction and amplification, and detection of the target sequences in simple or complex samples using reverse transcriptase PCR (RT-PCR) and real-time PCR tests. The systems consist of an instrument, personal computer, and preloaded software for running the tests and viewing the results. The systems require the use of single-use disposable GeneXpert cartridges that hold the RT-PCR and PCR reagents and also host the RT-PCR and PCR processes. Because the cartridges are self-contained, cross-contamination between samples is minimized. For a full description of the systems, see the operator manual.

The Xpert Norovirus test includes reagents for the detection of nucleic acid sequences for norovirus genogroup I and genogroup II from raw or unpreserved unformed stool specimens collected from individuals with symptoms of acute gastroenteritis. A Sample Processing Control (SPC) and a Probe Check Control (PCC) are also included in the cartridge. The SPC is present to control for adequate processing of the target viruses and to monitor for the presence of inhibitors in the PCR reaction. The PCC verifies dry reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability.

Reagents, Instruments, and Materials

Reagents

Materials Provided

The Xpert Norovirus test kit contains sufficient reagents to process 10 specimens or quality control samples. The kit contains the following:

Xpert Norovirus Cartridges with Integrated Reaction Tubes	**10**
Bead 1, Bead 2, and Bead 3 (freeze-dried)	1 of each per cartridge
Elution Reagent	1.5 mL per cartridge
Rinse Reagent	1.0 mL per cartridge
Binding Reagent (Guanidinium thiocyanate)	2.7 mL per cartridge
Sample Reagent (Guanidinium thiocyanate)	**10 x 2.0 mL per bottle**
CD	**1 per kit**

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

Note Safety Data Sheets (SDS) are available at www.cepheid.com or www.cepheidinternational.com under the **SUPPORT** tab.

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

Materials Required but Not Provided

- GeneXpert system with touchscreen: GeneXpert instrument, touchscreen unit with built-in scanner, Cepheid OS software version 2.0 or higher, and operator manual.
- Printer: Contact Cepheid Sales Representative to arrange for the purchase of a recommended printer.
- Vortex mixer
- Disposable transfer pipettes

- Single-use disposable dry rayon tipped swab (SDPS-120) or equivalent rayon swab for transfer of the stool specimen from the specimen container into the sample reagent bottle
- Clean preservative-free specimen container

Materials Available but Not Provided

- ZeptoMetrix® NATtrol™ Rotavirus Stock (catalog no. NATROTA-6MC) as external negative control.
- ZeptoMetrix® NATtrol™ Norovirus GI Stock and NATtrol™ Norovirus GII Stock (catalog no. NATNOVI-6MC and NATNOVII-6MC) as external positive controls.

Warnings and Precautions

General

- For *In Vitro* Diagnostic Use. ℞only
- Treat all biological specimens, including used cartridges and reagents, as if capable of transmitting infectious agents. Because it is often impossible to know which might be infectious, all biological specimens should be treated using standard precautions. Guidelines for specimen handling are available from the U.S. Centers for Disease Control and Prevention[17] and the Clinical and Laboratory Standards Institute.[20]
- Biological specimens, transfer devices, and used cartridges should be considered capable of transmitting infectious agents requiring standard precautions. Follow your institution's environmental waste procedures for proper disposal of used cartridges and unused reagents. These materials may exhibit characteristics of chemical hazardous waste requiring specific national or regional disposal procedures. If national or regional regulations do not provide clear direction on proper disposal, biological specimens and used cartridges should be disposed per WHO [World Health Organization] medical waste handling and disposal guidelines. Consult your institution's environmental waste personnel on proper disposal of used cartridges and unused reagents.

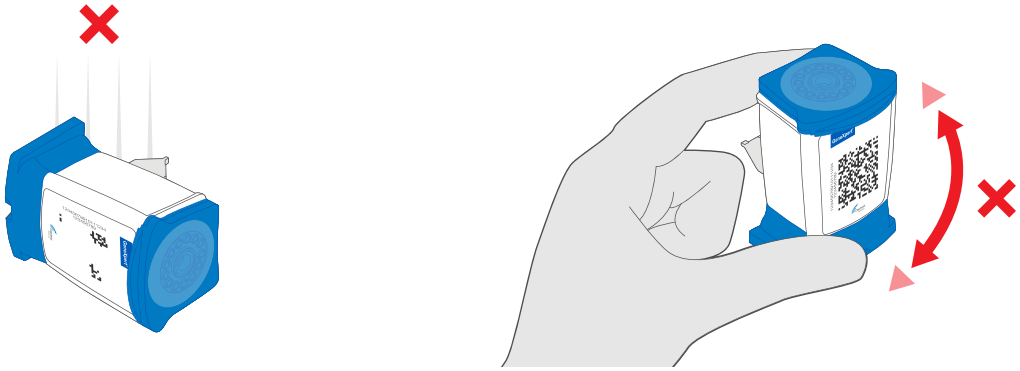
Specimen

- Maintain proper storage conditions during specimen transport to ensure the integrity of the specimen (see Specimen Collection, Transport and Storage). Specimen stability, under shipping conditions other than those recommended, has not been evaluated.
- Proper sample collection, storage, and transport are essential for correct results.

Test/Reagent

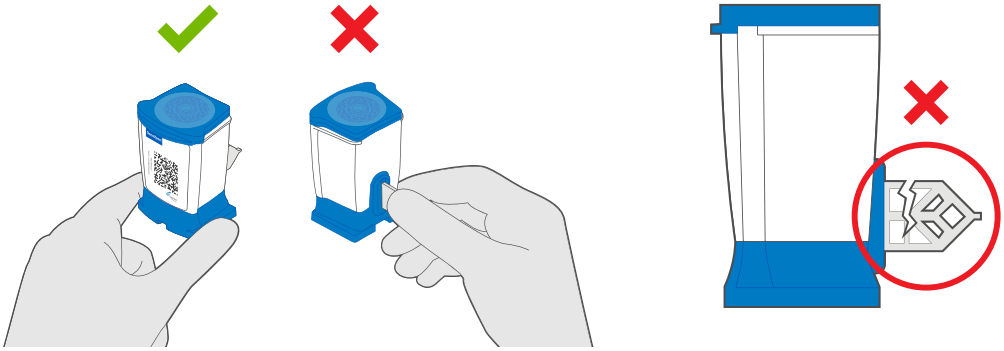
- Do not substitute Xpert Norovirus test reagents with other reagents.
- Do not open the Xpert Norovirus test cartridge lid until you are ready to add a sample.
- Do not use a cartridge that has been dropped after removing from the kit or shaken after the cartridge lid has been opened. Shaking or dropping the cartridge after opening the lid may yield false or non-determinate

results.



- Do not place the sample ID label on the cartridge lid or on the barcode label.

- Do not use a cartridge if it appears wet or if the lid seal appears to have been broken.
- The sample reagent is a clear, colorless liquid. Do not use the sample reagent if it is cloudy or discolored.
- Hold the cartridge by the base. Do not touch the reaction tube at the rear of the cartridge, as this could cause damage that would interfere with light passing through it during the test. Do not use a cartridge that has a damaged reaction tube.



- Each single-use Xpert Norovirus test cartridge is used to process one test. Do not reuse spent cartridges.
- Good laboratory practices should be followed and gloves should be changed between handling each patient specimen in order to avoid contamination of specimens or reagents. Regularly clean the work surface/areas with 10% bleach then wipe the surface again with 70% ethanol or isopropyl alcohol before and after processing Xpert Norovirus specimens.
- Specimens may contain high levels of organisms. Ensure that specimen containers do not contact one another. Change gloves if they come in direct contact with the specimen and after the processing of each specimen to avoid contaminating other specimens.

Chemical Hazards, Storage and Handling

Chemical Hazards[21,22]

- UN GHS Hazard Pictogram

- Signal Word: WARNING
- **UN GHS Hazard Statements:**
  - Harmful if swallowed.
  - Causes mild skin irritation.
  - Causes eye irritation.
- UN GHS Precautionary Statements:
  - **Prevention**
    - Wash thoroughly after handling.
  - **Response**
    - Call a POISON CENTER or doctor/physician if you feel unwell.
    - If skin irritation occurs: Get medical advice/attention.
    - IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
    - If eye irritation persists: Get medical advice/attention.

Storage and Handling

- Store the Xpert Norovirus test cartridges and reagents at 2–8°C.
- Do not use reagents or cartridges that have passed the expiration date.
- Do not open the cartridge lid until you are ready to perform testing.
- Use the cartridge within 30 minutes after opening the lid.

Specimen Collection, Testing, and Results

Specimen Collection

Specimen Collection, Transport and Storage

1. Collect the raw or unpreserved unformed stool specimen in a clean preservative-free container. Follow your institution's guidelines for collecting samples for norovirus testing.
2. Label the stool specimen container with Patient's Name and Sample ID and send to the laboratory.
3. Store specimen at 2–8 °C. The specimen is stable for up to two days when stored at 2–8 °C.

Procedure

Preparing the Cartridge

Note Start the test within 30 minutes of adding the sample reagent to the cartridge.

To add the sample to the cartridge:

1. Remove the cartridge and sample reagent bottle from the kit.
2. Dip a swab in the raw or unpreserved unformed stool sample. See Table 1 for the correct amount of specimen to be used for the Xpert Norovirus test.
   Note Wrap sterile gauze around both the stem of the swab and the mouth of the bottle to minimize the risk of contamination. Do not coat the entire swab fiber tip with stool. See Table 1. Too much stool may result in errors or invalid results.

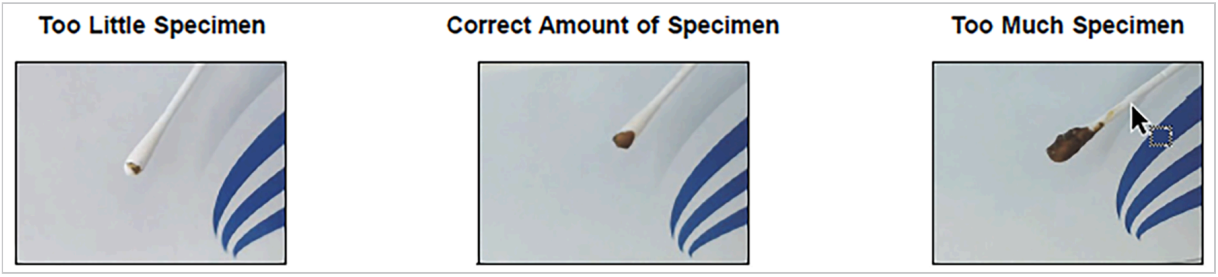


Figure 1 Sample Collection on Swab

3. After removing the cap from the sample reagent bottle, insert the swab with stool sample into the bottle containing the sample reagent.
4. Hold the swab by the stem near the rim of the bottle. Lift the swab a few millimeters from the bottom of the bottle and bend the stem over the edge of the bottle to break it off, leaving the swab short enough to allow the swab to fit into the bottle and the cap to close tightly.
5. Close the cap of the sample reagent bottle and vortex at high speed for ten seconds.
6. Open the cartridge lid. Using a clean transfer pipette (not supplied), transfer the entire contents of the sample reagent bottle to the Sample Chamber of the Xpert Norovirus test cartridge.
7. Close the cartridge lid and start the test within 30 minutes.

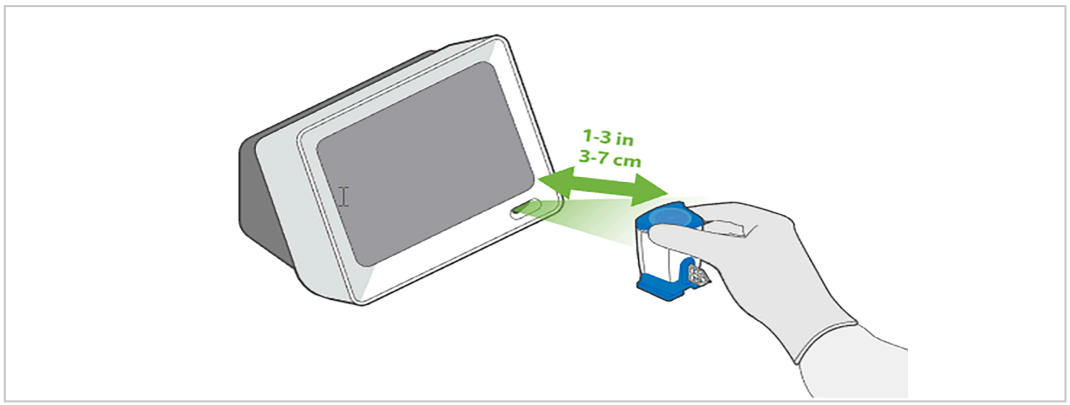
Starting the Test: GeneXpert System with Touchscreen

Important **Before you start the test, make sure that:**

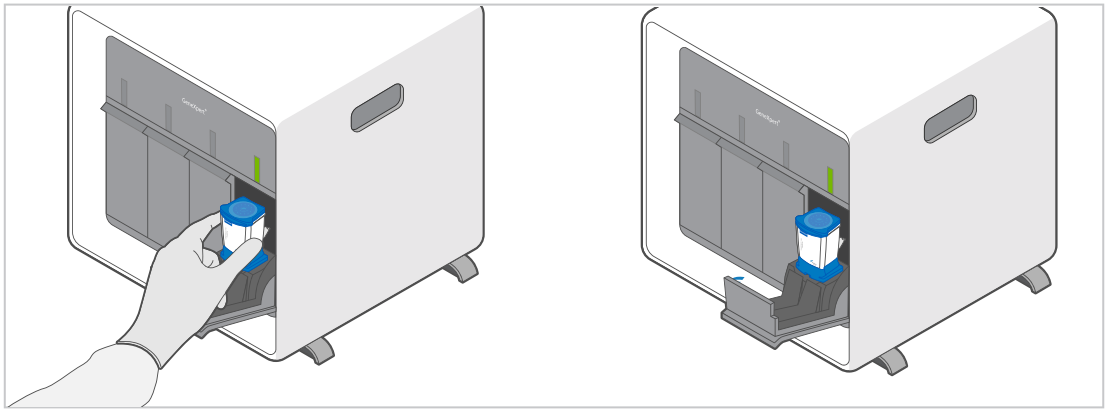
- **The system is running the correct Cepheid OS software version shown in section - Materials Required but Not Provided.**
- **The correct assay definition file is imported into the software.**

Note The default workflow is shown. Your system administrator may alter the workflow.

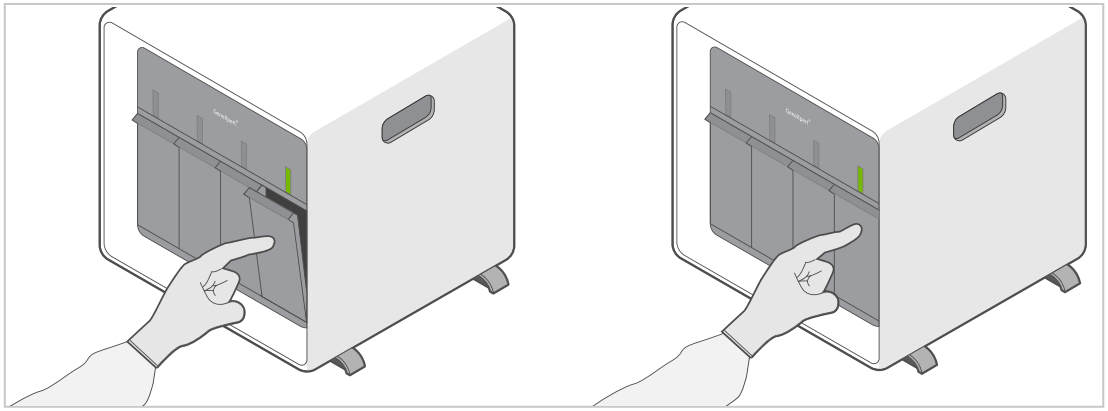
1. Turn on GeneXpert system with touchscreen.
2. Log on to system software using your username and password.
3. On the Modules tab, touch **Start Test**.
4. Follow onscreen prompts to create new test and enter patient and sample information.
5. Scan or manually input the cartridge serial number. If scanning, hold the cartridge about 1-3 inches (3-7 cm) away from the scanner. The scanner projects a green crosshair, which you center on the barcode. Scanning is complete when you hear an audible beep. Touch **Continue**.



6. Select the desired test and touch **Continue**.
7. Watch the cartridge preparation video, if needed.
8. On the Confirm screen, review all data and touch **Confirm**.
9. Open the module door under flashing green light and insert the cartridge.



10. Close cartridge module door completely by pressing until it latches. The test starts.



11. When the test completes, the **Results Summary** screen appears. Open the module door and remove cartridge.
12. Dispose of used cartridge in appropriate waste container according to your institution's standard practices.

Viewing Results: GeneXpert System with Touchscreen

The GeneXpert system with touchscreen results screen will automatically interpret test results for you and clearly show them in the **View Results** window.

1. Tap **Results**.
2. Tap the test to be viewed in the Results screen.
3. Click **OK**.
4. To generate a PDF report file, touch **View Report**. More detailed instructions for viewing and uploading results are available in your system operator manual.

Quality Control

Built-in Quality Controls

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

- **Sample Processing Control (SPC)**: Ensures the sample was processed correctly. The SPC contains an internal control that is included in each cartridge to verify adequate processing of the sample. The SPC verifies that release of RNA from virus has occurred if the organism is present and verifies that the specimen processing is adequate. Additionally, this control detects specimen-associated inhibition of the RT-PCR and PCR reactions. 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 Instrument System measures the fluorescence signal from the probes (SPC, QC1, and QC2, one for each of the two reagent beads) to monitor bead rehydration, reaction tube filling, probe integrity, and dye stability. Probe Check passes if it meets the assigned acceptance criteria.

External Controls

- External Controls: ZeptoMetrix NATtrol Rotavirus Stock (catalog # NATROTA-6MC) as external negative control and ZeptoMetrix NATtrol Norovirus GI Stock and NATtrol Norovirus GII Stock (catalog #

NATNOVI-6MC and NATNOVII-6MC) as external positive controls may be used in accordance with local, state, and federal accrediting organizations, as applicable.

Results

The results are interpreted by the GeneXpert Instrument Systems from measured fluorescent signals and embedded calculation algorithms and will be shown in the View Results window. Possible results are shown in Table 1.

Table 1. Xpert Norovirus Results and Interpretation

Result	Interpretation
`NORO GI DETECTED,NORO GII NOT DETECTED`	Norovirus genogroup I (GI) RNA sequence is detected. • Norovirus genogroup I (GI) target RNA sequence has a Ct within the valid range and endpoint above the threshold setting. • SPC – NA (not applicable); SPC is ignored since norovirus target amplification may compete with this control. • PCC – PASS; all probe check results pass.
`NORO GI NOT DETECTED,NORO GII DETECTED`	Norovirus genogroup II (GII) RNA sequence is detected. • Norovirus genogroup II (GII) target RNA sequence has a Ct within the valid range and endpoint above the threshold setting. • SPC – NA (not applicable); SPC is ignored since norovirus target amplification may compete with this control. • PCC – PASS; all probe check results pass.
`NORO GI DETECTED,NORO GII DETECTED`	Norovirus genogroup I (GI) RNA sequence is detected and Norovirus genogroup II (GII) RNA sequence is detected. • Norovirus genogroup I (GI) target RNA sequence has a Ct within the valid range and endpoint above the threshold setting. • Norovirus genogroup II (GII) target RNA sequence has a Ct within the valid range and endpoint above the threshold setting. • SPC – NA (not applicable); SPC is ignored since norovirus target amplification may compete with this control. • PCC – PASS; all probe check results pass.
`NORO GI NOT DETECTED,NORO GII NOT DETECTED`	Norovirus target RNA sequences are not detected. • Norovirus target RNA sequences are not detected. • SPC – PASS; SPC has a Ct within the valid range and endpoint above the endpoint threshold setting. • PCC – PASS; all probe check results pass.
`INVALID`	Presence or absence of norovirus target RNA sequences cannot be determined. Repeat test according to the instructions in Retest Procedure. • Norovirus GI – INVALID • Norovirus GII – INVALID • SPC – FAIL; SPC Ct is not within valid range and endpoint below threshold setting. • PCC – PASS; all probe check results pass.

Result	Interpretation
ERROR	Presence or absence of norovirus target RNA sequences cannot be determined. Repeat test according to the instructions in Retest Procedure. • Norovirus GI – ERROR • Norovirus GII – ERROR • PCC – FAIL*; one or more of the probe check results failed. * If the probe check passed, the error is caused by the maximum pressure limit exceeding the acceptable range.
NO RESULT	Presence or absence of norovirus target RNA sequences cannot be determined. Repeat test according to the instructions in Retest Procedure. A **NO RESULT** indicates that insufficient data were collected. For example, the operator stopped a test that was in progress or a power failure occurred. • Norovirus GI – NO RESULT • Norovirus GII – NO RESULT • PCC – NA (not applicable).

Reasons to Repeat the Test

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

- An **INVALID** result indicates that the SPC failed. The sample was not properly processed, PCR is inhibited, or the sample was not properly collected.
- An **ERROR** result could be due to, but not limited to, a Probe Check Control failure or the maximum pressure limits were exceeded.
- A **NO RESULT** indicates that insufficient data were collected. For example, the operator stopped a test that was in progress, or a power failure occurred.

Retest Procedure

For retesting of specimens with a result of **INVALID**, **ERROR**, or **NO RESULT**, use a new cartridge (do not re-use the cartridge) and new sample reagent bottle.

1. Remove the cartridge and sample reagent bottle from the Xpert Norovirus test kit.
2. After removing the cap from the sample reagent bottle, briefly dip a swab in the unformed stool sample. See Figure 2 for the correct amount of specimen to be used for the Xpert Norovirus test.
   Note Wrap sterile gauze around both the stem of the swab and the mouth of the bottle to minimize the risk of contamination. Do not coat the entire swab fiber tip with stool. See Figure 2. Too much stool may result in errors or invalid results.

Figure 2 Sample Collection on Swab

3. After removing the cap from the sample reagent bottle, insert the swab with stool sample into the bottle containing the sample reagent.
4. Hold the swab by the stem near the rim of the bottle. Lift the swab a few millimeters from the bottom of the bottle and push the stem against the edge of the bottle to break it. Make sure the swab is short enough to allow the cap to close tightly.
5. Close the cap of the sample reagent bottle and vortex at high speed for ten seconds.
6. Open the cartridge lid. Using a clean transfer pipette (not supplied), transfer the entire contents of the sample reagent to the Sample Chamber of the Xpert Norovirus test cartridge.
7. Close the cartridge lid and start the test within 30 minutes.

Limitations

Limitations of the Procedure

- For *In Vitro* Diagnostic Use Only.
- The performance of the Xpert Norovirus test was validated using the procedures provided in this IFU only.
- Modifications to these procedures may alter the performance of the test. Results from the Xpert Norovirus test should be interpreted in conjunction with other laboratory and clinical data available to the clinician.
- Erroneous test results might occur from improper specimen collection, handling or storage, sample mix-up, or because the number of organisms in the specimen is below the limit of detection of the test. Careful compliance to the instructions in this IFU is necessary to avoid erroneous results.
- With raw or unpreserved unformed stool specimens, test interference may be observed in the presence of Barium sulfate (≥ 1% w/w) and Benzalkonium chloride at all concentrations tested (1% w/v, 0.2%, w/v, and 0.04% w/v).
- Mutations or polymorphisms in primer or probe binding regions may affect detection of new or unknown norovirus variants resulting in a false negative result.
- In the event of a mixed Norovirus GI and GII infection where the titer of one genogroup has a higher titer than the other genogroup, the genogroup with the higher titer of the two infections will be reported as detected; the lower titer genogroup may be reported as not detected.

Expected Values

In the Xpert Norovirus test clinical study, a total of 914 prospectively collected, fresh, raw or unpreserved unformed stool specimens were included from seven study centers. The number and percentage of Norovirus GI and Norovirus GII positive cases, calculated by age group, are presented in Table 2.

Table 2. Observed Prevalence of GI and GII by Age Group

Age (Years)	No. of GI Positives	GI Observed Prevalence %	No. of GII Positives	GII Observed Prevalence %
0-1	0/8	0	0/8	0
>1-5	1/6	16.7	0/6	0
>5-12	0/10	0	1/10	10.0
>12-21	0/29	0	3/29	10.3
>21-65	9/520	1.7	35/520	6.7

Age (Years)	No. of GI Positives	GI Observed Prevalence %	No. of GII Positives	GII Observed Prevalence %
>65	6/341	1.8	35/341	10.3
Total	16/914	1.8	74/914	8.1

Specific Performance Characteristics

Clinical Performance

Performance characteristics of the Xpert Norovirus test were evaluated at seven institutions in the U.S. and E.U. The study specimens consisted of raw or unpreserved unformed stool specimens from subjects with symptoms of acute gastroenteritis. The Xpert Norovirus test performance was compared to a composite reference test method performed at the Centers for Disease Control and Prevention (CDC; Atlanta, GA, US).

A total of 1403 specimens were tested for Norovirus GI by the Xpert Norovirus test and the composite reference test. Of the 1403 specimens, 914 were fresh, prospectively collected and 489 were frozen, archived specimens. A total of 1401 specimens were tested for Norovirus GII by the Xpert Norovirus test and the composite reference test. Of the 1401 specimens, 914 were fresh, prospectively collected and 487 were frozen, archived specimens.

On fresh, prospectively collected specimens, the Xpert Norovirus test demonstrated 100% PPA and 99.6% NPA for detection of Norovirus GI, relative to the composite reference test (Table 3). The Xpert Norovirus test demonstrated 98.5% PPA and 98.8% NPA for detection of Norovirus GII (Table 4).

On frozen, archived specimens, the Xpert Norovirus test demonstrated 98.1% PPA and 94.6% NPA for detection of Norovirus GI, relative to the composite reference test (Table 5). The Xpert Norovirus test demonstrated 100% PPA and 96.8% NPA for detection of Norovirus GII (Table 6).

Table 3. Xpert Norovirus Performance for GI vs. Composite Reference Test – Fresh Specimens

		Composite Reference Test		
		POS	**NEG**	**Total**
Xpert Norovirus	**POS**	12	4	16
	NEG	0	898	898
	Total	12	902	914
PPA% (95% CI)		100% (95% CI: 73.5–100)		
NPA% (95% CI)		99.6% (95% CI: 98.9–99.9)		

Table 4. Xpert Norovirus Performance for GII vs. Composite Reference Test – Fresh Specimens

		Composite Reference Test		
		POS	**NEG**	**Total**
Xpert Norovirus	**POS**	64	10	74
	NEG	1	839	840
	Total	65	849	914
PPA% (95% CI)		98.5% (95% CI: 91.7–100)		
NPA% (95% CI)		98.8% (95% CI: 97.8–99.4)		

Table 5. Xpert Norovirus Performance for GI vs. Composite Reference Test – Frozen Specimens

		Composite Reference Test		
		POS	**NEG**	**Total**
Xpert Norovirus	**POS**	101	21	122
	NEG	2	365	367
	Total	103	386	489
PPA% (95% CI)		98.1% (95% CI: 93.2–99.8)		
NPA% (95% CI)		94.6% (95% CI: 91.8–96.6)		

Table 6. Xpert Norovirus Performance for GII vs. Composite Reference Test – Frozen Specimens

		Composite Reference Test		
		POS	**NEG**	**Total**
Xpert Norovirus	**POS**	109	12	121
	NEG	0	366	366
	Total	109	378	487
PPA% (95% CI)		100% (95% CI: 96.7–100)		
NPA% (95% CI)		96.8% (95% CI: 94.5–98.3)		

Analytical Performance

Analytical Sensitivity (Limit of Detection)

The limit of detection (LoD) study was performed to evaluate the analytical sensitivity of the Xpert Norovirus test with positive clinical stool specimens containing Norovirus GI.3 or Norovirus GII.4 diluted into a pooled negative stool matrix. The LoD is defined as the lowest concentration (copies/mL) per sample that can be reproducibly distinguished from negative samples with 95% confidence. Replicates of at least 23 were evaluated at seven concentrations for Norovirus GI.3 and Norovirus GII.4 and LoDs were estimated by probit analysis. The estimated LoDs were confirmed by testing at least 20 replicate samples with virus diluted to the estimated LoD concentrations.

The LoD point estimates and confirmed LoD for each genogroup tested are summarized in Table 7.

Table 7. Limit of Detection of the Xpert Norovirus test

NorovirusGenogroup/strain	Limit of Detection (95% CI)
GI.3	5.7×10^5(copies/mL)(4.64×10^5 –6.67×10^5)
GII.4	3.0×10^5(copies/mL)(1.25×10^5 –1.78×10^5)

Analytical Reactivity (Inclusivity)

The analytical reactivity of the Xpert Norovirus test was evaluated against thirty-one genotypes representing both norovirus genogroups (GI and GII). The thirty-one norovirus strains evaluated in this study were tested near the LoD concentration of the test (Table 8). Three replicates were tested for each strain.

Table 8. Analytical Reactivity Results of the Xpert Norovirus test

Norovirus Strain	Estimated Concentration (copies/mL)[a]	Result	
		GI	GII
GI.1	9.0×10^6	POS	NEG
GI.2	3.7×10^8	POS	NEG
GI.3	1.4×10^6	POS	NEG
GI.4	1.0×10^5	POS	NEG
GI.5[b]	2.5×10^5	POS	NEG
GI.6[b]	2.5×10^5	POS	NEG
GI.7[b]	2.5×10^5	POS	NEG
GI.8	3.7×10^5	POS	NEG
GI.14	3.0×10^6	POS	NEG
GII.1	3.6×10^6	NEG	POS
GII.2	1.1×10^5	NEG	POS
GII.3[b]	1.3×10^3	NEG	POS
GII.4 (2006a)	1.2×10^5	NEG	POS
GII.4 (2006b)	2.4×10^5	NEG	POS
GII.4 (2008)	4.3×10^5	NEG	POS
GII.4 (2009) New Orleans	1.7×10^5	NEG	POS
GII.4 (2010)	9.6×10^4	NEG	POS
GII.4 (2012) Sydney	1.2×10^5	NEG	POS
GII.5[b]	1.3×10^3	NEG	POS
GII.6[b]	1.3×10^3	NEG	POS
GII.7	8.0×10^4	NEG	POS
GII.8[b]	1.3×10^3	NEG	POS
GII.9[b]	1.3×10^3	NEG	POS
GII.10[b]	1.3×10^3	NEG	POS

Norovirus Strain	Estimated Concentration (copies/mL)[a]	Result	
		GI	GII
GII.11	2.6×10^5	NEG	POS
GII.12	5.7×10^5	NEG	POS
GII.13	6.9×10^5	NEG	POS
GII.14	1.5×10^5	NEG	POS
GII.15	1.7×10^5	NEG	POS
GII.16[b]	1.3×10^3	NEG	POS
GII.17[b]	1.3×10^3	NEG	POS

a. An estimated concentration or titer was provided based on a Ct value (because of the difficulty in culturing norovirus particles, an exact concentration cannot be provided). The Ct value for each clinical specimen in the inclusivity study was extrapolated to the titer obtained from the LoD study for well-characterized GI and GII samples using a standard curve at CDC.

b. Naked RNA transcripts were used for these strains, clinical samples were not available at the time of testing.

Analytical Specificity (Cross-reactivity)

The analytical specificity of the Xpert Norovirus test was evaluated by testing a panel of 68 organisms, consisting of 54 bacteria, 1 fungi, 9 viruses, and 4 parasites representing common gastroenteritis pathogens or those potentially encountered in stool. A minimum of three replicates of all bacterial and fungal strains were tested at concentrations ≥ 10^6 CFU/mL. A minimum of three replicates of all viruses were tested at concentrations ≥ 10^5 TCID50/mL with the exception of two viruses obtained from clinical samples with unknown concentrations. A minimum of three replicates of all parasites were tested at concentrations ≥ 10^6 copies/mL. All organisms tested were correctly reported as **NORO GI NOT DETECTED**; **NORO GII NOT DETECTED** by the Xpert Norovirus test. The analytical specificity was 100%. Results are shown in Table 9.

Table 9. Analytical Specificity of Xpert Norovirus test

Organism	Strain ID	Concentration
Acinetobacter baumannii	CCUG 3477	>3.0×10^8 CFU/mL
Anaerococcus prevotii [a]	ATCC 9321	6.7×10^8 CFU/mL
Bacteriocides fragilis [a]	ATCC 25285	1.4×10^9 CFU/mL
Campylobacter coli	ATCC 43478	1.8×10^8 CFU/mL
Campylobacter jejuni	ATCC 33560	1.3×10^8 CFU/mL
Campylobacter lari	ATCC 35221	3.4×10^7 CFU/mL
Citrobacter freundii	ATCC 33128	1.5×10^9 CFU/mL
Clostridiodes difficile [a]	ATCC 9689	2.2×10^8 CFU/mL
Clostridium sordelli [a]	DSMZ 2141	2.0×10^8 CFU/mL
Eggerthella lenta	ATCC 43055	>3.0×10^7 CFU/mL
Enterobacter cloacae	ATCC 70021	1.0×10^9 CFU/mL
Enterococcus casseliflavus	ATCC 25788	1.0×10^9 CFU/mL
Enterococcus faecalis	ATCC 29212	5.4×10^8 CFU/mL
Enterococcus faecium	ATCC 9756	8.2×10^8 CFU/mL

Organism	Strain ID	Concentration
Enterococcus gallinarium	ATCC 49573	4.5 x 10^8 CFU/mL
Escherichiacoli O157:H7	ATCC 43888	8.4 x 10^8 CFU/mL
Escherichia coli O26:H11	CDC 033014	7.4 x 10^8 CFU/mL
Escherichia coli O45:H2	CDC 003039	3.3 x 10^8 CFU/mL
Escherichia coli O103:H11	CDC 063008	5.4 x 10^8 CFU/mL
Escherichia coli O11	CDC 201114	6.9 x 10^8 CFU/mL
Escherichia coli O121	CDC 023211	1.4 x 10^9 CFU/mL
Escherichia coli O145	CDC 993311	7.1 x 10^8 CFU/mL
Escherichia hermannii	ATCC 33650	1.5 x 10^9 CFU/mL
Fusobacterium necrophorum [a]	ATCC 31647	9.6 x 10^8 CFU/mL
Helicobacter pylori	CCUG 1784	1.5 x 10^8 CFU/mL
Klebsiella pneumoniae	ATCC 70063	1.2 x 10^9 CFU/mL
Lactobacillus jensenii	ATCC 25258	4.0 x 10^8 CFU/mL
Listeria monocytogenes	CCUG 3358	1.2 x 10^9 CFU/mL
Micrococcus luteus	ATCC 4698	1.8 x 10^8 CFU/mL
Morganella morganii	ATCC 49948	1.3 x10^9 CFU/mL
Peptostreptococcus anaerobius [a]	CCUG 7835	1.5 x 10^9 CFU/mL
Plesiomonas shigelloides	ATCC 51903	3.1 x 10^8 CFU/mL
Prevotella oralis [a]	ATCC 33269	1.2 x 10^9 CFU/mL
Proteus mirabilis	ATCC 43071	1.1 x 10^9 CFU/mL
Proteus vulgaris	ATCC 49132	1.8 x 10^9 CFU/mL
Providencia alcalifaciens	CCUG 6325	1.8 x 10^9 CFU/mL
Providencia stuartii	ATCC 49809	1.3 x 10^9 CFU/mL
Pseudomonas aeruginosa	ATCC 27853	6.3 x 10^8 CFU/mL
Pseudomonas fluorescens	ATCC 13525	>3.0 x 10^8 CFU/mL
Pseudomonas putida	ATCC 49128	5.5 x 10^8 CFU/mL
Salmonella agona	ATCC 51957	1.2 x 10^9 CFU/mL
Salmonella bongori	ATCC 43975	1.7 x 10^9 CFU/mL
Salmonella enterica	ATCC 13314	9.2 x 10^8 CFU/mL
Serratia marcescens	ATCC 43862	3.8 x 10^8 CFU/mL
Shigella flexneri	ATCC 12022	8.1 x 10^8 CFU/mL
Shigella sonnei	ATCC 25931	>3.0 x 10^8 CFU/mL
Staphylococcus aureus	ATCC 25923	8.8 x 10^8 CFU/mL
Staphylococcus epidermidis	ATCC 14990	>3.0 x 10^7 CFU/mL
Streptococcus agalactiae (GBS)	ATCC 12386	9.6 x 10^8 CFU/mL
Streptococcus dysgalactiae	ATCC 43078	7.2 x 10^8 CFU/mL

Organism	Strain ID	Concentration
Streptococcus pyogenes	ATCC 19615	5.5 x 10^8 CFU/mL
Vibrio cholerae [b]	CCUG 9118	5.2 x 10^9 copies/ m L
Vibrio parahaemolyticus	ATCC 17802	3.8 x 10^8 CFU/mL
Yersinia enterocolitica	ATCC 9610	7.1 x 10^8 CFU/mL
Adenovirus	Type 31	3.6 x 10^5 TCID50/mL
Adenovirus	Type 40	2.8 x 10^7 TCID50/mL
Adenovirus	Type 41	4.6 x 10^7 TCID50/mL
Astrovirus [c]	--	Not applicable[d]
Coxsackievirus	Type B5	1.4 x 10^5 TCID50/mL
Echovirus	11	3.3 x 10^9 TCID50/mL
Parechovirus	Type 6	1.9 x 10^7 TCID50/mL
Rotavirus	Type Wa	1.0 x 10^6 TCID50/mL
Sapovirus [d]	--	Not applicable[e]
Candida albicans	ATCC 10231	>3.0 x 10^7 CFU/mL
Blastocystis hominis [e]	BT1	1.0 x 10^9 copies/mL
Cryptosporidium parvum [e]	Iowa	6.1 x 10^9 copies/mL
Giardia lamblia [e]	Portland-1	3.05 x 10^9 copies/mL
Entamoeba histolytica [e]	ATCC 30459D	4.9 x 10^6 copies/mL

a. Strictly anaerobic bacteria.

b. Tested as genomic DNA.

c. Clinical sample.

d. The concentration is not known for the Astrovirus clinical samples that were obtained from KUL; the Ct values according to KUL test were in the range of 12-27.

e. The concentration is not known for the Sapovirus clinical samples that were obtained from KUL; the Ct values according to KUL test were in the range of 19-23.

Interfering Substances Study

Potentially interfering substances that may be present in stool were evaluated directly relative to the performance of the Xpert Norovirus test. Potentially interfering substances included hemoglobin, mucin, cholesterol, triglycerides and whole blood, plus additional endogenous and exogenous substances listed in Table 10.

Negative samples were tested in replicates of 8 with each substance in a negative stool matrix to determine the effect on the performance of the sample processing control (SPC). Positive samples were tested in replicates of 8 per substance with one Norovirus GI and one Norovirus GII clinical isolate near the LoD.

All results were compared to positive and negative controls prepared in negative stool matrix. All valid positive and negative control samples were correctly reported using the Xpert Norovirus test.

Inhibition of the Xpert Norovirus test was observed in the presence of Benzalkonium chloride (1% w/v, 0.2% w/v, and 0.04% w/v). False-negative test results were reported for the Norovirus GII target at (1% w/v) Benzalkonium chloride. In the presence of Barium sulfate (5% w/w), a statistically significant inhibitory effect

was observed on the Norovirus GII Ct in positive samples relative to the control (p-value <0.05). No statistically significant effect was observed on the Norovirus GII Ct relative to the control in the presence of Barium sulfate (1% w/w).

No other potential interfering substances were found to be inhibitory and no false-negatives were reported for these substances.

Table 10. Potentially Interfering Substances in Xpert Norovirus

Endogenous Substances		
Substance	Description /Active Ingredient	Concentration Tested
Cholesterol	Fecal fat/Cholesterol	5 % w/v
Hemoglobin	Hemoglobin human	12.5 % w/v
Mucin	purified Mucin protein	5 % w/v
Steric acid/ Palmitic acid (1:1)	Fatty acids/Steric acid, Palmitic acid	5 % w/w
Triglyceride	Fecal fat/Triglyceride Mix	5 % w/v
Whole Blood	Human Whole Blood	10 % v/v
Exogenous Substances		
Substance	Description /Active Ingredient	Concentration Tested
Acetaminophen	Acetaminophen	5 % w/v
Amoxicillin	Antibiotic/Amoxicillin	5 % w/v
Ampicillin	Ampicillin Sodium Salt	152 µmol/L
Aspartame	Aspartame	5 % w/v
Barium sulfate	Contrast medium/Barium sulfate	5 % w/w, 1% w/w
Benzalkonium chloride Commercial alcohol	Antiseptic Towelettes/ Benzalkonium Chloride in ethanol	1 %, 0.2 %, 0.04 % w/v
Bismuth subsalicylate	Bismuth (III) Subsalicylate (an active ingredient in Peptobismol)	1 % w/v
$CaCO_3$	Calcium Carbonate	5 % w/v
Hydrocortisone	Hydrocortisone	50 % w/v
Ibuprofen	Ibuprofen	5% w/v
Imodium	Loperamide HCl	5 % v/v
Kaopectate	Attapulgite	5 mg/mL
Metronidazole	Metronidazole	5 % w/v
Mycostatin	Nystatin	50 % w/w
Naprosyn	Naproxen Sodium	2.2 µmol/mL
Novaluzid	$Mg(OH)_2$, $Al(OH)_3$and $MgCO_3$	5 % w/v
Polymyxin B sulfate Bacitrin zinc	Polysporin/Polymyxin B Sulfate and Bacitracin Zinc	50 % w/v
Pursennid	Sennaglycosides	5 % w/v
Rexall Mineral oil laxative	Mineral Oil	50 % v/v

Carry-over Contamination Study

A study was conducted to demonstrate that single-use, self-contained GeneXpert cartridges prevent carry-over contamination in negative samples run followed by very high positive samples in the same GeneXpert module. The study consisted of a negative sample processed in the same GeneXpert module immediately followed by a highly positive Norovirus GII sample. This testing scheme was repeated 21 times between two GeneXpert modules for a total of 42 runs for 20 positive and 22 negative specimens. All 19 positive samples were correctly reported as **NORO GI NOT DETECTED**; **NORO GII DETECTED** and one positive sample was reported as an **ERROR**. All 22 negative samples were correctly reported as **NORO GI NOT DETECTED**; **NORO GII NOT DETECTED**.

Reproducibility

A panel of 7 specimens with varying concentrations of Norovirus GI and Norovirus GII was tested two times on five different days by two different operators, at each of three sites (7 samples x 2 time/day x 5 days x 2 operators x 3 sites). One lot of Xpert Norovirus test cartridges was used at each of the 3 testing sites. The Xpert Norovirus test was performed according to the Xpert Norovirus test procedure. Results are summarized in Table 11.

Table 11. Summary of Reproducibility Results

Sample ID	Site 1	Site 2	Site 3	Overall
Neg	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
GI - High Neg	30.0% (6/20)	15.0% (3/20)	30.0% (6/20)	25.0% (15/60)
GI - Low Pos	100% (20/20)	85.0% (17/20)	95.0% (19/20)	93.3% (56/60)
GI - Mod Pos	100% (19/19)	100% (20/20)	100% (20/20)	100% (59/59)[a]
GII - High Neg	25.0% (5/20)	30.0% (6/20)	35.0% (7/20)	30.0% (18/60)
GII - Low Pos	100% (20/20)	95.0% (19/20)	90.0% (18/20)	95.0% (57/60)
GII - Mod Pos	95.0% (19/20)	100% (20/20)	100% (20/20)	98.3% (59/60)

a. One sample 2x indeterminate

The reproducibility of the Xpert Norovirus test was also evaluated in terms of the fluorescence signal expressed in Ct values for each target detected. The mean, standard deviation (SD), and coefficient of variation (CV) between-sites, between-days, and between-operators for each panel member are presented in Table 12.

Table 12. Summary of Reproducibility Data

Sample	Assay Channel (Analyte)	N[a]	Mean Ct	Between-Site		Between-Day		Between-Operator		Within-Assay		Total	
				SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
Neg	SPC	60	31.9	0.17	0.5	0.06	0.2	0.06	0.2	0.26	0.8	0.32	1.0
GI - High Neg	GI	60	39.4	0	0	0.46	1.2	0	0	1.80	4.6	1.86	4.7
GI - Low Pos	GI	59	37.9	0.29	0.8	0	0	0.36	1.0	1.03	2.7	1.13	3.0
GI - Mod Pos[b]	GI	57	34.7	0.09	0.2	0.07	0.2	0	0	0.41	1.2	1.01	1.2
GII - High Neg	GII	54	38.9	0	0	0	0	0.77	2.0	1.77	4.5	1.93	5.0

Sample	Assay Channel (Analyte)	N[a]	Mean Ct	Between-Site		Between-Day		Between-Operator		Within-Assay		Total	
				SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
GII - Low Pos	GII	60	37.3	0	0	0	0	0.58	1.6	1.33	3.6	1.45	3.9
GII - Mod Pos[b]	GII	59	34.3	0.22	0.6	0	0	0	0	0.45	1.3	0.50	1.5

a. Results with non-zero Ct values out of 60

b. n=3 sample outliers (2 GI Mod Pos and 1 GII Mod Pos) that were more than 5 standard deviations from the mean were considered outliers and were removed from the analysis.

Instrument System Precision

An in-house precision study was conducted to compare the performance of the GeneXpert Dx and the GeneXpert Infinity instrument systems. A panel of 7 samples with varying concentrations of Norovirus GI and Norovirus GII was tested on 12 different days by two operators. Each operator conducted four runs of each panel samples per day on each of the two instrument systems (7 samples x 4 times/day x 12 days x 2 operators x 2 instrument systems). Three lots of Xpert Norovirus test cartridges were used for the study. The Xpert Norovirus test was performed according to the Xpert Norovirus procedure. Results are summarized in Table 13.

Table 13. Summary of Instrument System Precision Results (Dx vs. Infinity)

Sample	GeneXpert Dx			Infinity			% Total Agreement by Sample
	Op 1	Op 2	Inst	Op 1	Op 2	Inst	
Neg	100% (48/48)	100% (48/48)	100% (96/96)	100% (48/48)	100% (48/48)	100% (96/96)	100% (192/192)
GI - High Neg	14.6% (7/48)	10.4% (5/48)	12.5% (12/96)	14.6% (7/48)	25.0% (12/48)	19.8% (19/96)	16.2% (31/192)
GI - Low Pos	100% (48/48)	97.9% (47/48)	99.0% (95/96)	97.9% (47/48)	97.9% (47/48)	97.9% (94/96)	98.4% (189/192)
GI - Mod Pos	100%[a] (47/47)	100% (48/48)	100% (95/95)	100% (48/48)	100% (48/48)	100% (96/96)	100% (191/191)
GII - High Neg	25.0% (12/48)	29.2% (14/48)	27.1% (26/96)	29.2% (14/48)	31.3% (15/48)	30.2% (29/96)	28.7% (55/192)
GII - Low Pos	89.6% (43/48)	89.6% (43/48)	89.6% (86/96)	83.3% (40/48)	95.7% (44/46)	87.5% (84/96)	88.5% (170/192)
GII - Mod Pos	100% (48/48)	100% (48/48)	100% (96/96)	100% (48/48)	100%[b] (47/47)	100% (95/95)	100% (191/191)

a. One GI Mod Pos sample not tested.

b. One GII Mod Pos sample indeterminate and not retested.

The precision of the Xpert Norovirus test was also evaluated in terms of the fluorescence signal expressed in Ct values for each target detected. The mean, standard deviation (SD), and coefficient of variation (CV) between-instruments, between-lots, between-days, between-operators, and within-tests for each panel member are presented in Table 14.

Table 14. Summary of Precision Data

Sample	Assay Channel (Analyte)	N[a]	Mean Ct	Between-Instrument		Between-Lot		Between-Day		Between-Operator		Within-Test		Total	
				SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
Neg	SPC	192	31.8	0	0	0.44	1.4	0	0	0.08	0.2	0.39	1.2	0.59	1.9
GI - High Neg	GI	188	38.6	0.19	0.5	0.25	0.7	0.18	0.5	0	0	1.40	3.6	1.45	3.8
GI - Low Pos	GI	192	37.1	0.39	1.1	0.26	0.7	0.19	0.5	0	0	0.95	2.6	1.08	2.9
GI - Mod Pos	GI	191	34.0	0	0	0.36	1.1	0.04	0.1	0.08	0.2	0.38	1.1	0.53	1.6
GII - High Neg	GII	178	38.7	0.16	0.4	0	0	0.29	0.7	0	0	2.03	5.3	2.06	5.3
GII - Low Pos	GII	187	37.6	0.10	0.2	0	0	0	0	0.45	1.2	1.65	4.4	1.71	4.6
GII - Mod Pos	GII	191	34.3	0	0	0.09	0.2	0	0	0.17	0.5	0.42	1.2	0.46	1.3

a. Results with non-zero Ct values out of 192.

Appendix

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Table of Symbols

Symbol	Meaning
REF	Catalog number
IVD	*In vitro* diagnostic medical device
	Do not reuse
LOT	Batch code
	Consult instructions for use
	Caution
	Manufacturer
CC	Country of manufacture
Σ	Contains sufficient for *n* tests
CONTROL	Control
	Expiration date
	Temperature limitation
	Biological risks

Symbol	Meaning
	Warning
	For prescription use only

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IVD

Revision History

Description of Changes: 303-0938 Rev. A

Purpose: Initial release