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Multicenter Evaluation of the Xpert Norovirus Assay for Detection of Norovirus Genogroups I and II in Fecal Specimens

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Norovirus is the most common cause of sporadic gastroenteritis and outbreaks worldwide. The rapid identification of norovirus has important implications for infection prevention measures and may reduce the need for additional diagnostic testing. The Xpert Norovirus assay recently received FDA clearance for the detection and differentiation of norovirus genogroups I and II (GI and GII), which account for the vast majority of infections. In this study, we evaluated the performance of the Xpert Norovirus assay with both fresh, prospectively collected (n = 914) and frozen, archived (n = 489) fecal specimens. A Centers for Disease Control and Prevention (CDC) composite reference method was used as the gold standard for comparison. For both prospective and frozen specimens, the Xpert Norovirus assay showed positive percent agreement (PPA) and negative percent agreement (NPA) values of 98.3% and 98.1% for GI and of 99.4% and 98.2% for GII, respectively. Norovirus prevalence in the prospective specimens (collected from March to May of 2014) was 9.9% (n = 90), with the majority of positives caused by genogroup II (82%, n = 74). The positive predictive value (PPV) of the Xpert Norovirus assay was 75% for GI-positive specimens, whereas it was 86.5% for GII-positive specimens. The negative predictive values (NPV) for GI and GII were 100% and 99.9%, respectively.

Globally, norovirus is the most common cause of endemic and epidemic gastroenteritis in all age groups (1). Within the United States, it is estimated that norovirus infections account for 400,000 emergency room visits, 56,000 to 71,000 hospitalizations, and 570 to 800 deaths annually (2). In countries that have implemented rotavirus vaccination programs, norovirus has become the leading cause of gastroenteritis in young children, in both outpatient and hospitalized individuals (3–6).

Norovirus, originally called Norwalk virus, was identified from a gastroenteritis outbreak in Norwalk, OH, when the viral particles were visualized using electron microscopy (7). Genomic sequence data place norovirus in the genus Norovirus in the family Caliciviridae, which also includes Sapovirus, Lagovirus, Nebovirus, and Vesivirus, which are all small, nonenveloped, positive-sense RNA viruses. Currently, there are 7 known genogroups of norovirus, designated genogroup I (GI) to GVII, and over 40 genotypes (8). The majority of norovirus infections in humans are caused by GI and GII viruses (9). Norovirus can be transmitted via the fecal-oral route, through aerosolization of viral particles in vomitus (10, 11), and through contaminated food, water, and environmental sources (12).

Norovirus infections are characterized by a variety of symptoms, including vomiting, nonbloody diarrhea, abdominal pain, nausea, and a low-grade fever. In otherwise healthy individuals, norovirus infections are typically self-limiting and resolve within a few days of symptom onset. However, norovirus symptoms can be more severe and prolonged in the elderly, young children, and immunocompromised individuals. Currently, there are no U.S. Food and Drug Administration (FDA)-approved treatments or vaccines for norovirus infections, so treatment is chiefly supportive care, such as rehydration.
Although no specific antimicrobial therapy is used to treat norovirus infection, a rapid and accurate diagnosis can expedite appropriate infection prevention measures and reduce the necessity of additional diagnostic procedures and can also facilitate public health measures if the infection is part of an outbreak. Nucleic acid amplification tests (NAATs) for norovirus detection have gone through several iterations and have now become the mainstay for identification of norovirus in clinical specimens. Several commercial multiplex NAAT gastrointestinal pathogen panels which include norovirus as a target have received FDA clearance. These assays include the xTAG Gastrointestinal Pathogen Panel (GPP) (Lumigene, Austin, TX), the FilmArray Gastrointestinal (GI) Panel (Biofire, Salt Lake City, UT), and the Verigene Enteric Pathogens Nucleic Acid test (Nanosphere, Northbrook, IL) (14–18). The Xpert Norovirus assay, which is easy to perform, can be run on demand, and has a short (~90-min) turnaround time, recently received FDA clearance and is the first standalone molecular assay for detection of norovirus. The objective of this multicenter study was to evaluate the laboratory and clinical performance characteristics of the Xpert Norovirus assay.

MATERIALS AND METHODS

Specimens. This study evaluated both prospectively collected, fresh specimens (collected from March to May 2014) and banked, frozen specimens (collected from January 2008 to May 2014). At each study site, specimens were deidentified by a third-party individual who documented basic information, including patient age, gender, and health care setting. Fresh and frozen unprepared and unfrozen fecal specimens were included in the study if they were collected from patients presenting with acute gastroenteritis, if a sufficient amount was available both for Xpert Norovirus assay testing and for the composite reference method, and if the Xpert Norovirus assay could be performed within 24 h of collection for fresh specimens or within 24 h of thawing for frozen specimens. Frozen specimens also had to be stored at ≤−70°C prior to testing. A total of 914 fresh fecal specimens were collected and tested at 6 clinical trial sites, while 489 frozen fecal specimens were tested at 7 clinical trial sites (Table 1). Institutional review board (IRB)/ethics committee approval was obtained at each study site.

Xpert Norovirus assay. The Xpert Norovirus assay was performed according to the manufacturer’s instructions. Briefly, a swab was placed into the fecal specimen to gather a small amount of material, and then the swab was inserted, broken off, and left in a sample reagent vial. The sample reagent vial with the swab tip was then subjected to vortex mixing for 10 s. An appropriate amount of sample was dispensed into the sample chamber of an Xpert Norovirus assay cartridge and loaded on a GeneXpert instrument system platform for testing. If an indeterminate result (an invalid result, an error, or no result) was obtained, then the specimen was tested one additional time. Each day of testing, one negative and two positive controls, including separate GI and GII positive controls, were tested and had to be acceptable prior to testing patient specimens. Xpert Norovirus assay cartridges contain a sample processing control (SPC) and a probe check control (PCC). The SPC controls for adequate specimen processing and the presence of PCR inhibitors, while the PCC controls for reagent rehydration, PCR tube filling within the cartridge, probe integrity, and dye stability. All controls had to perform as expected in all cases for the assay result to be considered valid. After Xpert Norovirus assay testing, all specimens were stored at ≤−70°C prior to shipment on dry ice to the CDC for composite reference method testing.

Composite reference method. As a gold standard for comparison, a composite reference method was used at the CDC. The composite reference method consisted of a real-time reverse transcription (RT)-PCR assay (19) with modifications and a conventional RT-PCR that amplified two distinct regions of the capsid gene (termed regions C and D) followed by bidirectional sequencing (19). The primers used in the composite method were different from the ones used in the Xpert Norovirus assay. The algorithm for the composite method result interpretation is shown in Table 2. Norovirus-positive samples were genotyped by comparisons with reference sequences (9). Testing at the CDC was performed on specimens in batches.

Statistical analysis. A power calculation was performed to determine the requirements for the study to demonstrate that the lower 2-sided 95% confidence interval for positive percent agreement (PPA) was greater than 85% and that the lower 2-sided 95% confidence interval for negative percent agreement (NPA) was greater than 82%. In order to ensure a reasonable probability of meeting the significance criteria, the PPA and NPA targets were 95% and 92%, respectively. Thus, the sample size requirements included a minimum of 124 samples positive for each of GI and GII norovirus and 155 negative specimens. The positive percent agreement (PPA), negative percent agreement (NPA), positive predictive value (PPV), and negative predictive value (NPV) were calculated using standard methods. The 95% confidence interval was calculated using a two-tailed Fisher’s exact method.

RESULTS

Specimens. A total of 1,413 eligible fecal specimens were collected for Xpert Norovirus assay testing. Ten specimens (5 with indeterminate results from the composite reference method, 4 that were not tested within 24 h of collection, and 1 with an indeterminate result by the Xpert Norovirus assay) were excluded from the final analysis, resulting in a total of 1,403 specimens for analysis (Fig. 1). Of the 1,403 specimens analyzed, 914 were fresh specimens (collected from March to May 2014) and 489 were frozen specimens. The frozen specimens were preselected to increase the number of GI-positive specimens. Two frozen specimens were excluded from the GII analysis due to indeterminate Xpert Norovirus assay results, resulting in 1,401 specimens analyzed for GII results (Fig. 1).

<p>| TABLE 1 Number of fresh and frozen specimens tested at each clinical site |
|-----------------------------------------------|-------------------|</p>
<table>
<thead>
<tr>
<th>Study site</th>
<th>No. of specimens tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh</td>
<td>Frozen</td>
</tr>
<tr>
<td>A</td>
<td>119</td>
</tr>
<tr>
<td>B</td>
<td>307</td>
</tr>
<tr>
<td>C</td>
<td>383</td>
</tr>
<tr>
<td>D</td>
<td>38</td>
</tr>
<tr>
<td>E</td>
<td>57</td>
</tr>
<tr>
<td>F</td>
<td>0</td>
</tr>
<tr>
<td>G</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>914</td>
</tr>
</tbody>
</table>

| TABLE 2 Composite reference test algorithm for result interpretation |
|-----------------------------------------------|-------------------|
| CDC norovirus real-time RT-PCR result with BDS | Result from CDC conventional RT-PCR (region C) with BDS | Result from CDC conventional RT-PCR (region D) with BDS | Gold standard result |
| Positive | Positive | NA | Positive |
| Negative | Positive | NA | Positive |
| Positive | Negative | Positive | Positive |
| Positive | Negative | NA | Negative |
| Negative | Negative | NA | Negative |

a BDS, bidirectional sequencing. 

b NA, not applicable.
Study subjects. The numbers of subjects were approximately equal with regard to gender distribution (females, n = 738, 52.6%) (Table 3). Nearly half (n = 675, 48.1%) of all subjects were between 21 to 65 years of age, and over one-third (n = 531, 37.8%) of the subjects were >65 years of age (Table 3). The majority of specimens came from subjects who were hospitalized (n = 907, 64.6%), with outpatients being the next-most-common patient population (n = 272, 19.4%) (Table 3).

![FIG 1](https://example.com/fig1.png)  
**FIG 1** Overview of specimens collected and tested by the Xpert Norovirus assay. Of the 6 specimens that were excluded for indeterminate results, 5 were indeterminate by the composite reference method and 1 was indeterminate by the Xpert Norovirus assay. The true-positive (TP), true-negative (TN), false-positive (FP), and false-negative (FN) results of the Xpert Norovirus assay were determined by the composite reference method.

<table>
<thead>
<tr>
<th>Subject parameter</th>
<th>No. (%) of specimens</th>
<th>Fresha</th>
<th>Frozenb</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>420 (46.0)</td>
<td>225 (46.0)</td>
<td>645 (46.0)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>494 (54.0)</td>
<td>244 (49.9)</td>
<td>738 (52.6)</td>
<td></td>
</tr>
<tr>
<td>Not specified</td>
<td>0 (0.0)</td>
<td>20 (4.1)</td>
<td>20 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Age range (yrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>8 (0.8)</td>
<td>12 (2.4)</td>
<td>20 (1.4)</td>
<td></td>
</tr>
<tr>
<td>&gt;1–5</td>
<td>6 (0.7)</td>
<td>46 (9.4)</td>
<td>52 (3.7)</td>
<td></td>
</tr>
<tr>
<td>&gt;5–12</td>
<td>10 (1.1)</td>
<td>35 (7.2)</td>
<td>45 (3.2)</td>
<td></td>
</tr>
<tr>
<td>&gt;12–21</td>
<td>29 (3.2)</td>
<td>32 (6.5)</td>
<td>61 (4.4)</td>
<td></td>
</tr>
<tr>
<td>&gt;21–65</td>
<td>520 (56.9)</td>
<td>155 (31.7)</td>
<td>675 (48.1)</td>
<td></td>
</tr>
<tr>
<td>&gt;65</td>
<td>341 (37.3)</td>
<td>190 (38.9)</td>
<td>531 (37.8)</td>
<td></td>
</tr>
<tr>
<td>Not specified</td>
<td>0 (0.0)</td>
<td>19 (3.9)</td>
<td>19 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Health care setting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency department</td>
<td>48 (5.2)</td>
<td>13 (2.6)</td>
<td>61 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Hospitalized</td>
<td>561 (61.4)</td>
<td>346 (70.8)</td>
<td>907 (64.6)</td>
<td></td>
</tr>
<tr>
<td>LTCFc</td>
<td>81 (8.9)</td>
<td>14 (2.9)</td>
<td>95 (6.8)</td>
<td></td>
</tr>
<tr>
<td>Outpatient</td>
<td>223 (24.4)</td>
<td>49 (10)</td>
<td>272 (19.4)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.1)</td>
<td>67 (13.7)</td>
<td>68 (4.9)</td>
<td></td>
</tr>
</tbody>
</table>

a Data represent percentages of all fresh specimens (n = 914).
b Data represent percentages of all frozen specimens (n = 489).
c LTCF, long-term-care facility.

### TABLE 3 Demographics of study subjects

Xpert Norovirus assay performance. The Xpert Norovirus assay provided a valid result for 98.6% (1,383/1,403) of the specimens in the first attempt at analysis, with the analyses of 20 (1.4%) specimens showing indeterminate results. Repeat testing resulted in a valid assay result for all 20 repeat specimens. Of the 1,403 specimens tested, 23.7% (n = 333) were positive for GI or GII by the Xpert Norovirus assay (Table 4). Of the norovirus-positive specimens, 41.4% (n = 138) were GI and 58.6% (n = 195) were GII. No dually GI-positive and GII-positive specimens were detected by the Xpert Norovirus assay.

As there is no established gold standard for norovirus testing, the results from the Xpert Norovirus assay were compared to the results from the composite reference testing that was conducted at the CDC. On the basis of the composite method, the Xpert Norovirus assay positive percent agreement (PPA) and negative percent agreement (NPA) for all specimens were 98.3% and 99.4% and 98.2% for GI-positive specimens, respectively (Table 5). The positive predictive value (PPV) and negative predictive value (NPV) for fresh specimens were 75.0% and 100% for GI-positive specimens and 86.5% and 99.9% for GII-positive specimens, respectively (Table 5).

### Analysis of prospective specimens

The fresh prospectively collected specimens were obtained from the clinical trial sites from March to May of 2014, and over this time period 9.9% (n = 90) of specimens tested positive for norovirus by the Xpert Norovirus assay (Table 6). Of these positive specimens, 17.8% (n = 16) were GI and 82.2% (n = 74) GII. Most of the positive specimens were submitted from hospitalized subjects (38.9%), followed by outpatients (27.8%) and patients in long-term-care facilities (25.6%). Finally, while 27.7% (n = 233) of specimens were collected in March, that month accounted for 53.3% (n = 48) of all norovirus-positive specimens (Table 6).

### Norovirus genotypes

A sequence that could be genotyped was obtained from each of the 286 Xpert Norovirus assay-positive samples. The genotypes that were detected by the Xpert Norovirus assay included GI.1 (n = 1), GI.3 (n = 3), GI.3B (n = 23), GI.3C (n = 16), GI.4 (n = 14), GI.5 (n = 1), GI.5A (n = 3), GI.6 (n = 1), GI.6A (n = 28), GI.7 (n = 22), GI.9 (n = 1), GI.11 (n = 3), GI.2 (n = 4), GI.3 (n = 5), GI.4 New Orleans (n = 74), GI.4 Osaka (n = 1), GI.4 Sydney (n = 75), GI.6 (n = 2), GI.6B (n = 1), GI.13 (n = 7), and GI.14 (n = 1).

### DISCUSSION

Norovirus can cause both sporadic gastroenteritis and outbreaks; norovirus outbreaks are associated with health care institutions, cruise ships, schools, and other environments in which people are in close quarters. A meta-analysis of acute gastroenteritis cases worldwide revealed that norovirus accounts for 18% of all diarr-
rheal infections (1). On the basis of the Xpert Norovirus assay, we observed that 9.9% (n = 90) of freshly collected specimens tested positive for norovirus. Given that 78.9% of norovirus cases in the Northern Hemisphere occur between October and March (1), our lower prevalence could reflect the limited time frame (i.e., March to May of 2014) within which fresh specimens were collected. In fact, over half (n = 48, 53.3%) of the positive norovirus specimens reported here were from March, with 70.8% (n = 34) of these specimens from a single clinical site. We also observed a predominance (84%, n = 64) of positive GII specimens in our study, a result which has been noted in a previous study where GII viruses accounted for ~62% of norovirus outbreaks (20).

Control of norovirus outbreaks is complicated by the relatively low infectious dose (21) and by the high level of norovirus shedding in vomitus (21) and feces (22). Routine norovirus prevention and control measures utilize a combination of staff- and patient-level strategies, including hand hygiene, assigning of patient cohorts, use of appropriate protective equipment, and effective environmental disinfection (23, 24). The implementation of such measures requires the prompt identification of norovirus-infected patients. Among the strengths of the Xpert Norovirus assay are the relative ease of performing the test, the ability to run samples on demand without batch processing, and the short turnaround time, which includes less than 5 min of hands-on time and approximately 90 min for a result.

In a study in Hong Kong, the investigators enhanced their standard infection control measures by performing norovirus PCR testing on all specimens submitted for fecal studies, even if norovirus testing was not requested (25). By the use of a laboratory-developed PCR assay for norovirus detection (26), 242 (25%) patients tested positive for norovirus; among them, 114 (47% of positives) were detected only by testing samples for which norovirus testing had not been ordered. The resulting increased detection led to additional patients being identified and given proper precautions. Overall, the authors found that these enhanced measures reduced the number of hospital-acquired norovirus infections from 131 to 16 cases per 1,000 potentially infectious patient-days, relative to the previous 12 months (25).

Asymptomatic carriage of norovirus is an area of unknown significance for infection prevention measures and poses a diagnostic problem for laboratory testing. Real-time RT-PCR testing of fecal specimens of asymptomatic individuals in England revealed a 12% age-adjusted prevalence of norovirus, with the highest prevalence noted for children <5 years of age (27). One source of asymptomatic shedding can be a recently resolved infection. A median of 29 days of norovirus shedding has been documented via real-time RT-PCR in norovirus-infected volunteers (21). The du-
reration of symptoms and norovirus shedding can be much longer in immunocompromised patients than in healthy patients (28, 29). It remains unknown whether asymptomatic norovirus carri-

ers can serve as a reservoir for sporadic cases or outbreaks and whether such individuals require infection prevention measures. Additionally, given the potential for a high prevalence of asym-

ptomatic carriage, the only fecal specimens that should be tested for norovirus are those from individuals with symptoms of gastroen-

teritis, similarly to parameters commonly established by clinical laboratories for Clostridium difficile testing (30).

While there are several FDA-approved assays that include no-

rovirus as a target, the Xpert Norovirus assay is the first FDA-

cleared stand-alone NAA T specifically for norovirus detection. There are currently 3 FDA-cleared multiplex assays for syndromic testing for gastrointestinal pathogens that include norovirus as a tar-
get—the xTAG GPP, the FilmArray GI panel, and the Verigene enteric-pathogen nucleic acid test. The xTAG GPP method detects

15 gastrointestinal pathogens, including GI and GII norovirus. This assay requires a separate nucleic acid extraction prior to am-

plification and target detection. In contrast, the FilmArray GI as-

say is a self-contained test that performs nucleic acid extraction, detection, and interpretation of results for 22 gastrointestinal

pathogens, including GI and GII norovirus. While these assays
detect both GI and GII, they do not differentiate between these
genotypes. Two recent studies (14, 15) evaluated the FilmArray GI panel, using a CDC-based assay as the reference method for no-

rovirus detection (31), and reported sensitivities of 91.7% and

94.5% and specificities of 99.5% and 98.8%, respectively. In the

paper by Khare et al., in addition to evaluating the FilmArray GI panel, the authors reported that the sensitivity and specificity of the xTAG GPP panel for norovirus were 100% and 90.8%, respective-
tively. Two other recent studies (16, 17) used a different reference method (32) to evaluate the xTAG GPP panel and reported sensitivi-
ties of 93.4% to 94.4% and specificities of 98.9% to 100%. The

results for the Xpert Norovirus assay presented here indicate sim-

ilar performance characteristics with the FilmArray GI and xTAG GPP panels, but additional studies are needed to directly compare these methods for norovirus detection. These studies and others

have evaluated coinfections detected by multiplex panels, which

have been reported at rates of 8% to 17.2% (14–18). In most of

these studies, norovirus is commonly a component of these coin-
fec tions. Given the high prevalence of asymptomatic norovirus

shedding, the clinical significance of norovirus detection in coin-
fec tions remains unclear and is an important area for future in-
vestigation.

This study had a number of strengths, including the large num-

ber (n = 914) of prospectively collected specimens from patients

with acute gastroenteritis from multiple medical centers and di-

verse health care settings. Norovirus genotyping data revealed that

specimens in this study represented a variety of distinct GI (n

= 11) and GII (n = 10) genotypes, indicating that the Xpert Noro-

virus assay has the capacity to detect a variety of norovirus geno-
types. The inclusion of frozen specimens improved the power for
evaluating the analytical performance characteristics for geno-
group GI. The limitations of this study included a relative paucity

of specimens from subjects less than 21 years of age (n = 178,

12.7% of total), the limited time frame and time of year (i.e.,

nonpeak) during which the samples were collected, and the low

number of GI-positive prospective specimens. Additionally, while

cecal specimens were submitted for routine studies, limited clini-
cal data are available to correlate the testing results with symptoms

and the presence of other pathogens in these samples.

In summary, the Xpert Norovirus assay is a rapid and accurate

method to detect and differentiate the prominent norovirus geno-

groups. Consistent with previous reports, we found that norovirus

is a frequent cause of acute gastrointestinal infections, and effi-
cient and accurate testing has the potential to rapidly identify in-

fected individuals, minimizing the need for additional diagnostic

testing and prompting infection prevention measures.

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The findings and conclusions in this report are ours and do not nec-

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and Prevention.

Names of specific vendors, manufacturers, or products are included for

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