Reliability of the Xpert HPV Assay to Detect High-Risk Human Papillomavirus DNA in a Colposcopy Referral Population

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Key Words: Microbiology; Virology; Molecular diagnostics

ABSTRACT

Objectives: The Xpert HPV Assay (Xpert; Cepheid, Sunnyvale, CA) was developed for the multianalytic GeneXpert platform.

Methods: In a colposcopy referral population of 708 women living in the United States, two cervical specimens, A and B, were collected, and both were tested by the Xpert assay for high-risk human papillomavirus (hrHPV) DNA, permitting an evaluation of its test reliability. Specimen B was also tested by Hybrid Capture 2 (hc2; Qiagen, Germantown, MD) and the cobas HPV Test (cobas; Roche Molecular Systems, Pleasanton, CA).

Results: The κ and percent agreement for any hrHPV for the two Xpert results were 0.88 and 94.5%, respectively. There was no statistical difference in testing positive on both specimens by Xpert (P = .62). The sensitivity for detection of cervical intraepithelial neoplasia grade 2 or more severe (CIN2+) was 89.0% using specimen A and 90.4% using specimen B for Xpert, 90.4% for cobas, and 81.6% for hc2.

Conclusions: The Xpert assay was sensitive and reliable for the detection of hrHPV and the identification of women with CIN2+.

High-risk human papillomavirus (hrHPV) testing is now recommended for use in the United States with cytology (“cotesting”) for cervical cancer screening every 5 years in women aged 30 to 64 years,1 for triage of atypical squamous cells of undetermined significance Papanicolaou (Pap) test result,2 and for follow-up of women who underwent colposcopy regardless of whether they were diagnosed with and treated for cervical precancerous lesions (cervical intraepithelial neoplasia [CIN] 2, CIN3, or adenocarcinoma in situ).2 The World Health Organization (WHO) recently recommended hrHPV testing as an alternative to Pap/cytology screening where Pap/cytology has not been successfully implemented.3

Prior to widespread endorsement of hrHPV testing for cervical cancer screening, experts proposed several key criteria for clinically useful hrHPV testing, including a requirement that new testing must be at least comparable to the first US Food and Drug Administration (FDA)-approved test, Hybrid Capture 2 (hc2; Qiagen, Germantown, MD), having good reproducibility.4,5

The GeneXpert Platform from Cepheid (Sunnyvale, CA) is a versatile, easy-to-use, scalable, and accessible laboratory test platform. It is a multianalyte, random-access, molecular diagnostic platform ranging in capacity from one to 80 test-processing modules. GeneXpert platforms are widely available in high-income countries and in a growing number of low- to middle-income countries. The latter is associated with endemic tuberculosis (TB) for which the Cepheid’s Xpert MTB/RIF Assay received endorsement by the WHO in 2010 for molecular detection of TB and drug-resistant TB.6

The Cepheid Xpert HPV Assay (Xpert), on the GeneXpert platform, is a new, qualitative, real-time polymerase chain reaction (PCR) assay for the detection of
hrHPV DNA. In addition to providing partial genotyping, as a quantitative, real-time PCR assay, the Xpert HPV assay can also provide quantitative HPV viral load information. The assay is formatted in a single-use GeneXpert Test cartridge and requires 1 mL of cervical specimen collected in PreservCyt (ThinPrep; Hologic, Bedford, MA).

We recently completed the first evaluation of Xpert for clinical performance in a colposcopy referral population living in the United States. Here, we evaluated its reliability by comparing the agreement of the Xpert test results on paired specimens collected from all participants in the aforementioned study.

Materials and Methods

Study Population and Design

This study was a two-stage, multicenter (seven US sites), prospective study that enrolled women of all ages referred for colposcopy evaluation based on one or more prior abnormal Pap test results, an abnormal Pap test result in combination with a positive hrHPV test result, or clinical suspicion of cervical cancer. Two Pap specimens (specimen A and specimen B) were collected and placed into PreservCyt from each participant at the time of colposcopy to support cytology review and comparator testing with Xpert, hc2 (Qiagen), and the cobas HPV Test (Roche Molecular Systems, Pleasanton, CA). Specimen A was processed for cytology review, followed by analysis with the Xpert. Specimen B was reserved for hrHPV analysis with hc2, cobas, and, finally, the Xpert assay; this specimen mimics a prealiquot testing modality. Both specimens were collected using an endocervical brush/spatula combination per the ThinPrep package insert (http://www.thinprep.com/pdfs/thinprep_package_insert.pdf). A minimum of two cervical punch biopsy specimens were collected from each participant as well as an endocervical curettage in cases of unsatisfactory colposcopy evaluations. This study was approved by the institutional review board at each site.

Laboratory Testing

The Xpert HPV Assay includes reagents for the simultaneous detection of 13 hrHPV types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) and one possible hrHPV type (HPV66), a human reference gene (hydroxymethylbilane synthase [HMBS]), and an internal probe check control (PCC). The 14 targeted HPV types are detected in five fluorescent channels: (1) HPV16; (2) HPV18 and HPV 45 (HPV18/45); (3) HPV31, 33, 52, and 58 (HPV31/33/52/58); (4) HPV51 and HPV59 (HPV51/59); and (5) HPV39, 56, 66, and 68 (HPV39/56/66/68). The specimen adequacy control, HMBS, is detected in a sixth fluorescent channel. The PCC verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability. In total, the assay uses six fluorescent channels for the detection of individual types of HPV, groups of HPV, and the human reference gene. Each fluorescent channel has its own cutoff parameters for target detection/validity. Assay results are reported as an overall “positive” if any type of targeted HPV is detected, but in addition, HPV16, HPV18/45, and collectively the other high-risk types of HPV detected by the assay are reported specifically as “positive” or “negative.” For this analysis, Xpert testing of both specimens A and B was used.

Stage I recruited 144 participants with 31 cases of CIN2 or more severe (CIN2+). Data from stage I were used to estimate a set of clinical cutoffs for the assay relative to CIN2+ (and CIN3 or more severe [CIN3+]) disease end points using a receiver operating characteristic (ROC) curve approach. Stage II recruited 564 participants with 111 cases of CIN2+. Data from stage II were used to refine the clinical cutoffs relative to CIN2+ (and CIN3+) disease end points using an ROC curve approach. Retrospectively, a homogeneity analysis was conducted to examine both participant characteristics and specimen characteristics to confirm that the results from stage I and stage II could be pooled. No substantial differences were detected, so the stage I and stage II data were pooled for the analyses presented here.

Xpert results were compared with hc2 and cobas testing, which was conducted per their respective US in vitro diagnostic package inserts and using their FDA-approved cutoffs. hc2 was performed at the Wishard Hospital (Indianapolis, IN), and cobas was performed at Purdue University (Indianapolis, IN). The cobas assay targets the same 14 HPV types targeted by Xpert. hc2, a signal amplification DNA test for the same 13 hrHPV types as Xpert and cobas, is known to detect HPV66 due to cross-reactivity. Thus, for this analysis, we considered that all three tests detect 14 hrHPV types. All testing was done masked to the diagnosis or the results of the other hrHPV tests.

Pathology Review

Biopsy and endocervical curettage specimens were reviewed locally for standard of care/patient management and then retrospectively, in blinded fashion, by a panel of three expert review pathologists (M.H.S., T.C.W., and A.F.) to determine a consensus final cervical disease status, which was used as the end point in this analysis.

Statistical Analysis

Of the 708 participants enrolled in the study, 658 (92.9%) had Xpert test results on both specimens as well as hc2 and cobas results. Percent total agreement, percent positive agreement, and k values were calculated for each HPV channel and hrHPV detection by any channel for Xpert results.
on specimens A and B, overall and stratified on disease status (<CIN2 or CIN2+). Test results were also categorized by the number of channels positive and hierarchically according to a priori cancer risk⁵ (HPV16 positive, else HPV16 negative and HPV18/45 positive, else HPV16 and HPV18/45 negative and positive for other hrHPV types, else hrHPV negative), and the same statistics were applied. An exact version of a symmetry χ² test was used to test for differences in binary (positive, negative) and categorical test results. For continuous cycles to threshold (Ct) values, Spearman coefficients were calculated for correlations, and a sign rank test was used as a test for difference in the median value. A P value of less than .05 was considered statistically significant.

The clinical performance (sensitivity, specificity, positive predictive value, and negative predictive value) for CIN2+ of Xpert HPV test results on both specimens was calculated. The results for cobas and hc2 testing on specimen B, previously reported for 697 women (along with Xpert HPV testing results on specimen B, previously reported), are shown for this subset of 658 women included in this analysis for reference.

**Results**

Of the 658 women included in this analysis, 45.0% were African American, 28.3% were non-Hispanic white, and 21.7% were Hispanic. The mean, median, and range of ages were 35.2, 33, and 18 to 75 years, respectively.

**Table II** shows the agreement statistics, overall and stratified by disease status (CIN2+ vs <CIN2), for hrHPV detection and for each detection channel. Overall, the κ values ranged from 0.68 to 0.96, the percent agreement ranged from 94.1% to 98.9%, and the percent positive agreement was from 72.7% to 98.2%. The κ (95% confidence interval [CI]), percent agreement, and percent positive agreement for any hrHPV were 0.88 (95% CI, 0.84-0.92), 94.5%, and 95.3%, respectively. Among those with less than CIN2, the κ values ranged from 0.88 to 0.94, the percent agreement ranged from 94.6% to 98.9%, and the percent positive agreement was from 84.2% to 95.6%. Among those with CIN2+, the κ values ranged from 0.68 to 0.96, the percent agreement ranged from 94.1% to 98.5%, and the percent positive agreement was from 72.7% to 98.2%. There was no significance difference in testing hrHPV positive overall and for any detection of any subgroup of high risk in each of the five channels. The κ values of the two Xpert results and the cobas results were 0.85 and 0.83, and the hc2 results were 0.72 and 0.74 (data not shown).

**Figure II** shows the correlation of the raw signal strength (number of cycles) for each measurement. The HMBS, a marker for cellularity, had a Spearman coefficient of only 0.58. There were significantly higher levels of HMBS (eg, lower number of Ct) in specimen A than in specimen B (median, 29.20 vs 30.60, respectively; P < .0001), suggesting that the cellularity in specimen B was lower than in specimen A. The correlation between measures of HPV

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**Table II**

Agreement Statistics for Xpert Results on Paired Specimens (A and B) for All High-Risk HPV and Each HPV Channel, Overall and Stratified on Disease Status, Less Than CIN2, and CIN2 or More Severe Diagnoses (CIN2+)

<table>
<thead>
<tr>
<th>Specimen A/Specimen B, No. (%)</th>
<th>HPV Category</th>
<th>Pos/Pos</th>
<th>Pos/Neg</th>
<th>Neg/Pos</th>
<th>Neg/Neg</th>
<th>Total</th>
<th>κ (95% CI)</th>
<th>% Agreement</th>
<th>% Pos Agreement</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>High-risk HPV</td>
<td>405 (61.6)</td>
<td>20 (3.0)</td>
<td>16 (2.4)</td>
<td>217 (33.0)</td>
<td>658 (100)</td>
<td>0.88 (0.84-0.92)</td>
<td>94.5</td>
<td>95.3</td>
<td>.62</td>
</tr>
<tr>
<td></td>
<td>HPV16</td>
<td>102 (15.5)</td>
<td>5 (0.8)</td>
<td>4 (0.6)</td>
<td>547 (83.1)</td>
<td>658 (100)</td>
<td>0.95 (0.92-0.98)</td>
<td>98.6</td>
<td>95.3</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>HPV18/45</td>
<td>60 (9.1)</td>
<td>10 (1.5)</td>
<td>4 (0.6)</td>
<td>584 (88.8)</td>
<td>658 (100)</td>
<td>0.88 (0.82-0.94)</td>
<td>97.9</td>
<td>85.7</td>
<td>.18</td>
</tr>
<tr>
<td></td>
<td>HPV31/23/25/52/58</td>
<td>182 (27.7)</td>
<td>10 (1.5)</td>
<td>10 (1.5)</td>
<td>456 (69.3)</td>
<td>658 (100)</td>
<td>0.93 (0.90-0.96)</td>
<td>97.0</td>
<td>94.8</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>HPV51/59</td>
<td>54 (8.2)</td>
<td>9 (1.4)</td>
<td>8 (1.2)</td>
<td>587 (89.2)</td>
<td>658 (100)</td>
<td>0.85 (0.78-0.92)</td>
<td>97.4</td>
<td>85.7</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>HPV39/56/66/68</td>
<td>98 (14.9)</td>
<td>13 (2.0)</td>
<td>7 (1.1)</td>
<td>540 (82.1)</td>
<td>658 (100)</td>
<td>0.89 (0.84-0.94)</td>
<td>97.0</td>
<td>88.3</td>
<td>.26</td>
</tr>
<tr>
<td>&lt;CIN2</td>
<td>High-risk HPV</td>
<td>287 (55.0)</td>
<td>17 (3.3)</td>
<td>11 (2.1)</td>
<td>207 (39.7)</td>
<td>522 (100)</td>
<td>0.89 (0.85-0.93)</td>
<td>94.6</td>
<td>94.4</td>
<td>.34</td>
</tr>
<tr>
<td></td>
<td>HPV16</td>
<td>46 (8.8)</td>
<td>4 (0.8)</td>
<td>2 (0.4)</td>
<td>470 (90.0)</td>
<td>522 (100)</td>
<td>0.93 (0.89-0.99)</td>
<td>98.9</td>
<td>92.0</td>
<td>.69</td>
</tr>
<tr>
<td></td>
<td>HPV18/45</td>
<td>48 (9.2)</td>
<td>9 (1.7)</td>
<td>2 (0.4)</td>
<td>463 (88.7)</td>
<td>522 (100)</td>
<td>0.89 (0.82-0.95)</td>
<td>97.9</td>
<td>94.2</td>
<td>.07</td>
</tr>
<tr>
<td></td>
<td>HPV31/23/25/52/58</td>
<td>129 (24.7)</td>
<td>6 (1.1)</td>
<td>7 (1.3)</td>
<td>380 (72.8)</td>
<td>522 (100)</td>
<td>0.94 (0.90-0.97)</td>
<td>97.5</td>
<td>95.6</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>HPV51/59</td>
<td>46 (8.8)</td>
<td>6 (1.1)</td>
<td>5 (1.0)</td>
<td>465 (89.1)</td>
<td>522 (100)</td>
<td>0.88 (0.81-0.95)</td>
<td>97.9</td>
<td>88.5</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>HPV39/56/66/68</td>
<td>87 (16.7)</td>
<td>12 (2.3)</td>
<td>6 (1.1)</td>
<td>417 (79.9)</td>
<td>522 (100)</td>
<td>0.89 (0.84-0.94)</td>
<td>96.6</td>
<td>87.9</td>
<td>.24</td>
</tr>
<tr>
<td>CIN2+</td>
<td>High-risk HPV</td>
<td>118 (86.8)</td>
<td>3 (2.2)</td>
<td>5 (3.7)</td>
<td>10 (7.4)</td>
<td>136 (100)</td>
<td>0.68 (0.48-0.89)</td>
<td>94.1</td>
<td>97.5</td>
<td>.73</td>
</tr>
<tr>
<td></td>
<td>HPV16</td>
<td>56 (41.2)</td>
<td>1 (0.7)</td>
<td>2 (1.5)</td>
<td>77 (56.6)</td>
<td>136 (100)</td>
<td>0.96 (0.90-1.0)</td>
<td>97.8</td>
<td>98.2</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>HPV18/45</td>
<td>12 (8.8)</td>
<td>1 (0.7)</td>
<td>2 (1.5)</td>
<td>121 (89.0)</td>
<td>136 (100)</td>
<td>0.88 (0.74-1.0)</td>
<td>97.8</td>
<td>92.3</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>HPV31/23/25/52/58</td>
<td>53 (39.0)</td>
<td>4 (2.9)</td>
<td>3 (2.2)</td>
<td>76 (55.9)</td>
<td>136 (100)</td>
<td>0.89 (0.82-0.97)</td>
<td>94.9</td>
<td>93.0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>HPV51/59</td>
<td>8 (5.9)</td>
<td>3 (2.2)</td>
<td>2 (2.2)</td>
<td>122 (89.7)</td>
<td>136 (100)</td>
<td>0.70 (0.48-0.93)</td>
<td>95.6</td>
<td>72.7</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>HPV39/56/66/68</td>
<td>11 (8.1)</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
<td>123 (90.4)</td>
<td>136 (100)</td>
<td>0.91 (0.78-1.0)</td>
<td>98.5</td>
<td>91.7</td>
<td>1.0</td>
</tr>
</tbody>
</table>

CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; Neg, negative; Pos, positive.
Figure 1  Correlation in Xpert measurements (number of cycles to threshold, Ct) between specimens A and B for all six channels: hydroxymethylbilane synthase (HMBS) measurements for all specimens (A) and the five human papillomavirus (HPV) measurements among those specimens in which either or both were above the positive cut point (B-F). The Spearman correlation, median value for both specimens, and the results of the sign rank test for differences in the median Ct values are as follows:  

A, \( r = 0.58 \); median, 29.20 (specimen A) and 30.60 (specimen B); \( P < .0001 \).  
B, \( r = 0.78 \); median, 29.1 (specimen A) and 30.3 (specimen B); \( P = .001 \).  
C, \( r = 0.76 \); median, 32.95 (specimen A) and 32.40 (specimen B); \( P = .006 \).  
D, \( r = 0.72 \); median, 30.65 (specimen A) and 31.05 (specimen B); \( P = .004 \).  
E, \( r = 0.48 \); median, 31.10 (specimen A) and 31.70 (specimen B); \( P = .22 \).  
F, \( r = 0.78 \); median, 33.25 (specimen A) and 33.30 (specimen B); \( P = .05 \).
Correlation in Xpert measurements (number of cycles to threshold, Ct) between specimens A and B of the five human papillomavirus (HPV) measurements normalized by the hydroxymethylbilane synthase measurement (A–E) among those specimens in which either or both were above the positive cut point. The Spearman correlation and the results of the sign rank test for differences in the median values are as follows: 

- **A**, \( r = 0.86; P = .4 \)
- **B**, \( r = 0.84; P = .03 \)
- **C**, \( r = 0.88; P = .0001 \)
- **D**, \( r = 0.90; P = .009 \)
- **E**, \( r = 0.88; P = .05 \)
in the five other channels in which either one or both specimens was positive for HPV (above the positive Ct cutoff) was better, with Spearman coefficients in the range of 0.48 to 0.78. Normalizing the specimens on cellularity using the HMBS measurement improved the correlation for the HPV measures noticeably, with Spearman coefficients in the range of 0.84 to 0.90 Figure 2.

The \( \kappa \) value was 0.82 (95% CI, 0.78-0.85), the percent agreement was 89.4%, and there was no significant difference in the number of positive channels \( (P = .95) \) between specimens. The \( \kappa \) value was 0.91 (95% CI, 0.87-0.93), the percent agreement was 93.5%, and there was no significant difference in ranking the HPV test results hierarchically \( (P = .86) \) between specimens.

The paired test results for hrHPV and HPV16 were compared with comparable measures of specimen B by cobas and hc2, as well as cobas, respectively Table 2. The percent hrHPV positive by cobas or hc2 was highest (~90%) if both specimens tested positive, intermediate (~70%-35%) if only one specimen tested positive, and lowest (~10%) if both specimens tested negative by Xpert. Similar results were observed comparing HPV16 detection by Xpert on the paired specimens and by cobas.

The HMBS measurements were notably different among those specimens with discordant results compared with those with concordant results. The HMBS Ct median values were 29.1 for specimen A and 30.4 for specimen B for paired positives and 29.4 for specimen A and 30.7 for specimen B for paired negatives. By comparison, for specimen A positive and specimen B negative, the HMBS Ct median values were 28.1 for specimen A and 31.9 for specimen B; for specimen A negative and specimen B positive, the HMBS Ct median values were 31.1 for specimen A and 30.1 for specimen B.

Finally, we compared the clinical performance for detection of CIN2+ for Xpert on both specimens and cobas and hc2 on specimen B for reference Table 3. The Xpert assay had similar performance on either specimen and was similar to cobas testing on specimen B, with approximately 90% sensitivity and 40% specificity in this colposcopy referral population. hc2 was a little less sensitive but more specific than Xpert on either specimen or cobas on specimen B. Similar results between assays were observed using a CIN3+ end point (data not shown).

Discussion

One of the hallmarks of HPV testing is its good reliability despite the use of a heterogeneous Pap specimen with significant variability in cellularity. Here, we demonstrated that Xpert has very good analytic reproducibility for the detection of any hrHPV and for each subgroup of hrHPV detected in the five HPV-reporting channels of the assay on consecutive specimens. The good analytic reproducibility translated to good clinical performance reproducibility.

We noted that the signal strength (ie, Ct, which for quantitative PCR is a measure of HPV viral load) was well correlated between the Xpert results on the two specimens collected from each participant. Thus, Xpert may be able to provide quantitative HPV viral load measures. Although the evidence of HPV viral load as a predictor of cervical precancer and cancer has been mixed,\(^ {10-18} \) these data have been limited by using only semiquantitative measures that were not HPV type specific and other internal controls that may not accurately measure the cellularity of the specimen.

HMBS measurement proved to be a useful marker of specimen cellularity. As shown in Figure 1, HMBS measurement varied approximately 15 Ct, suggesting that there is in fact significant variability in the cellularity of specimens, as previously discussed.\(^ {19} \) We noted that correlations of HPV signal strengths between specimens A and B improved when the signal strength was normalized for cellularity using the HMBS measurement, suggesting that the misclassification of HPV viral load was reduced. Consistent with this finding, discordant test results on
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Paired specimens were associated with lower HMBS measurements (higher Ct) for the specimen that tested negative.

We acknowledge an important limitation in this analysis. This was a population referred to colposcopy due to an abnormal cytology, which is associated with higher HPV loads.\(^{20,21}\) Thus, we expect that the interspecimen agreement is better in this population than in the general screening population,\(^{22-25}\) which is the intended-use population for this test. We also did not have a second result from the same specimen to determine how much discordance between results is the variability in testing results vs those introduced by testing a second, sequentially collected specimen. As a consequence, the agreement reported here is less than would be expected for repeat testing on the same specimen.

In conclusion, we demonstrated that Xpert is a reliable, sensitive test for identifying women with CIN2+. Given its reliability shown here and comparable performance to FDA-approved tests, as previously reported on a larger set of specimens,\(^7\) along with test attributes such as a multianalyte platform, test results in 1 hour, scalability from one to 80 test-processing modules, and ease of use, Xpert is a promising new cervical cancer screening test that warrants further evaluation.

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**References**


