Evaluation of a Digene-Recommended Algorithm for Human Papillomavirus Low-Positive Results Present in a "Retest Zone"

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Abstract

The Digene Hybrid Capture 2 (hc2) high-risk human papillomavirus (HPV) DNA test (Digene, Gaithersburg, MD) is widely used for triage of women with atypical squamous cells of undetermined significance. Results in a "retest zone" (weakly positive tests) are repeated up to 2 times according to the Digene-recommended algorithm.

We studied 56 cervical samples in the retest zone. Specimens were tested by a multiplex polymerase chain reaction (PCR)-based genotyping assay, and relevant cytopathologic results were reviewed. Digene results were compared with a reference standard that combined PCR genotyping and cytopathology results. The first repeated Digene assay yielded a sensitivity of 85.2% and a specificity of 62.1% with false-positive and false-negative rates of 40.0% and 15.4%, respectively. The 22 negative samples underwent a second retest and 18 (82%) were negative by the reference standard. The combined first and second retest sensitivity, specificity, and predictive values remained unchanged from the first retest alone.

Repeating specimens in the retest zone is necessary, but a second retest does not offer advantages over the first retest.

Human papillomavirus (HPV) infection with high-risk (HR) serotypes is highly associated with progression to cervical intraepithelial neoplasia (CIN).[1] Traditional screening by the Papanicolaou (Pap) test is universally used for initial detection of intraepithelial abnormalities such as dysplasia that can be referred for more extensive testing such as colposcopy. In cases of atypical squamous cells of undetermined significance (ASCUS), it has been recommended that reflex HPV DNA testing be performed.[2]

One commercially available test used for reflex testing is the HR Hybrid Capture 2 (hc2) HPV DNA Test (Digene, Gaithersburg, MD).[3] In the ASCUS/LSIL (low-grade squamous intraepithelial lesion) Triage Study trial, the overall sensitivity of the test for detecting CIN 3 was reported at greater than 95%, with a negative predictive value of 99%, although false-negative results have been described.[4] This test is a hybridization assay that does not use HPV target amplification, but instead uses signal amplification and an RNA probe cocktail specific for 13 HR HPV genotypes.[3] The test is approved by the US Food and Drug Administration (FDA), exhibits consistent reproducibility, and has been widely used for triage of women with ASCUS found by Pap smear.[5]

The FDA has recommended a value for reporting positive results of 1.0 relative light units/cutoff light units (RLU/CO), but no consensus exists regarding how to handle low-positive RLU/CO values from 1.0 to 2.5. It is suggested that these samples be retested. The manufacturer (Digene) recently recommended an algorithm on how to treat these values in the retest zone.[6] If the specimen initially tests between 1.0 and 2.5 RLU/CO, the sample should be retested. If the first retest result is greater than or equal to 1.0 RLU/CO, the test is considered positive. If it is less than 1.0 RLU/CO, the specimen is

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retested a second time; and if this result is 1.0 RLU/CO or more, the sample is considered positive.

We sought to evaluate the appropriateness of this algorithm by using a multiplex polymerase chain reaction (PCR)-based Templex HPV genotyping assay (Genaco Biomedical Products, Huntsville, AL) and the presence of changes suggestive of HPV infection by Pap smear as the standards for a positive specimen.

Materials and Methods

Clinical Specimens

Institutional review board approval for this study was obtained. Based on the incidence of sample retests (3%) in our laboratory, an estimation of 2 months of sample collection was sufficient to detect a difference between the first and second Digene retests. We included 56 cervical samples preserved in Cytyc ThinPrep Pap Test PreservCyt solution (Cytyc, Boxborough, MA) and detected in the retest zone (1.0-2.5 RLU/CO) from August to September 2005 at Associated Pathologists, PLC (Nashville, TN). Of these, 37 patient samples had positive cytology results and were reflex tested for HPV by the Digene assay. Four patients had a history of an abnormal Pap test result (ASCUS or dysplasia). Fifteen patients had HPV testing performed without cytology results because of clinician desire for testing. Cases were excluded from the analysis that had insufficient sample or inadequate control results by the Templex PCR methods.

Cytopathology Review

Cytology results were obtained from official cytology reports for each specimen from Associated Pathologists, PLC. Descriptors such as "suggestive of HPV changes," "HPV changes," "HPV effect," and "atypical parakeratosis" were documented. These descriptors were incorporated into the reference standard as specimens that showed positive HPV cytology. Cytology reports that did not contain such descriptors were categorized in the reference standard as negative for HPV changes by cytology.

Digene hc2 Testing

Cervical specimen preparation and the hc2 HR HPV DNA test using only the HR probe set were performed according to the manufacturer's instructions as described previously.[6] For each specimen, RLU/CO values were calculated as the ratio of the specimen luminescence relative to the luminescence of the 1.0 pg/mL of HPV-16 cutoff standard and reflect a semiquantitative value of the cumulative viral burden from 1 or more of 13 HR HPV genotypes (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). An RLU/CO value of 2.5 or more was considered an HR HPV-positive result. Any samples with RLU/CO values from 1.0 to 2.5 were retested. Specimens with an RLU/CO value less than 1.0 were considered negative (product insert).[6]

Genaco Templex HPV Genotyping

DNA was extracted from cervical specimens using an E.Z.N.A. Total RNA Kit II (Omega-Biotek, Doraville, GA) according to the manufacturer's instructions. The Templex HPV genotyping assay was used for HR HPV detection and differentiation as described.[7] Briefly, 6 μL of Templex HPV SuperPrimers (Genaco Biomedical Products) was added to 25 μL of Qiagen Multiplex Master Mix (Qiagen, Valencia, CA). Then, 5 μL of extracted DNA and 14 μL of water were added to the final volume of 50 μL. Amplification was carried out with a unique, 5-stage Templex cycling program.[7] The amplified HPV products were further characterized by using a suspension array for multiplex detection on a Luminex xMAP instrument (Luminex, Austin, TX).

Data Analysis

A reference standard was constructed by using Genaco Templex HPV genotyping data and HPV cytology results. A case was considered positive for HPV genotype and/or cytology if Genaco genotyping was positive for an HR genotype or cytology results showed changes consistent with HPV infection. Paired *t* tests, contingency tables, test performance characteristics, 95% confidence intervals (CIs) for the binomial distribution, *P* values (2-tailed Fisher exact test), receiver operating characteristic (ROC) curve, area under the ROC curve, and *P* values for the area under the ROC curve were generated by using GraphPad Prism, version 4.03, for Windows (GraphPad Software, San Diego, CA). Exact CIs for the binomial distribution were computed by the method of Clopper and Pearson.[8] *P* values and 95% CIs for the area under the ROC curve were calculated by using a nonparametric method described by Hanley and McNeil.[9] *P* values of .05 or less were considered statistically significant.

Results

First, Digene RLU/CO values between the initial test and 2 retests were compared. The data showed a similar distribution of positive and negative results between retest 1 and retest 2 in reference to the FDA-recommended value of 1.0 RLU/CO **Figure 1**. The mean ± SD RLU/CO values for retest 1 and retest 2 were 2.32 ± 3.00 and 1.76 ± 1.97, respectively, and were not significantly different ($P > .05$).

Table 1 illustrates the numbers of positive and negative cases as well as Digene hc2 test performance characteristics using an RLU/CO of 1.0 in comparison with the reference

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standard. We detected 4 false-negatives and 11 false-positives on the first retest of the Digene hc2 assay on samples initially present within the retest zone. During the second retest (third test), results for only 22 of the 56 samples are shown because the other 34 cases were positive and, therefore, did not need to be retested the second time according to the manufacturer's algorithm. Of the 22 cases, 18 were negative and 4 were positive by the reference standard. The first retest with the Digene kit showed fairly good sensitivity but marginal specificity. The Digene assay revealed a good negative predictive value but a modest positive predictive value. These predictive values depended to a large extent on the frequency of positivity in the reference standard, which in our study was high (48%). The difference between cases detected and not detected by the Digene hc2 assay was statistically significant in the first retest (P = .0004), but not in the second retest (P > .05). Assuming that all of the second retest values were treated as negative (in other words, if the second retest was not performed), the overall performance characteristics for the combined data were identical (Table 1).

The ROC curve for the first retest using the Digene hc2 assay is shown in **Figure 2** and compares the sensitivity and specificity of the Digene assay with the reference standard. The arrow illustrates the point on the curve at which the FDA-recommended value for the RLU/CO was 1.0. The area under the curve was modest (0.774) and statistically significantly (P < .001) different from pure chance alone (area under the curve, 0.500). This indicates that on average, 77.4% of patients with HPV by the reference standard will have a higher RLU/CO value compared with control subjects when using the Digene assay. Using an RLU/CO value of greater than 0.96 as positive, the sensitivity improved to 92.6% (95% CI, 75.7-99.1) and the specificity remained unchanged at 62.1% (95% CI, 42.3-79.3).

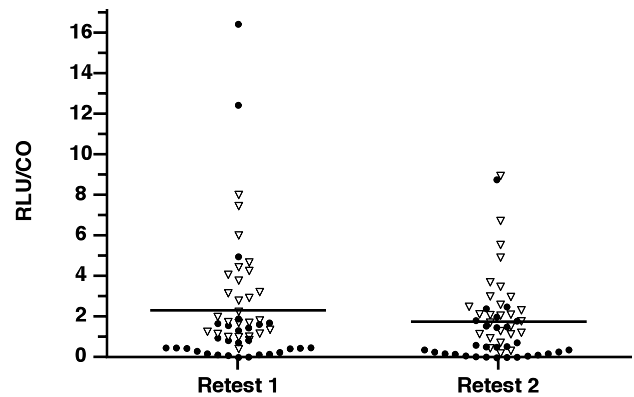

Figure 1 Distribution of relative light units/cutoff light units (RLU/CO) values for the first and second retests. The short horizontal lines represent the mean RLU/CO values of the respective groups. Circles, reference standard negative; triangles, reference standard positive.

The HPV genotype frequencies in relation to the Digene hc2 first retest results are shown in **Table 2**. After the first retesting, 25 specimens were considered positive for HR HPV by the Templex assay, which included 5 (20%), 3 (12%), 0 (0%), 2 (8%), and 6 (24%) for HPV types 16, 18, 31, 45, and 56, respectively. One case was positive by PCR for HR HPV type 56 but classified as negative by the Digene. The Digene assay does not contain a probe to identify types 53, 66, 67, and 82. Five specimens that were positive by the Templex test for these types were all classified as positive on the first retesting by the Digene assay. None of these specimens had cytologic changes indicative of HPV infection (Table 2). Two of these specimens were positive for type 82 by the Templex assay, but only one showed mild dysplasia, and neither showed HPV changes by cytology.

Table 1
Digene Retest Results Compared With the Reference Standard Using the US Food and Drug Administration–Recommended Threshold Value of 1.0 RLU/CO

	Reference Standard*			Test Performance Characteristics†			
RLU/CO	**Negative**	**Positive**	**Total**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
First retest‡				85.2 (66.3-95.8)	62.1 (42.3-79.3)	67.7 (49.5-82.6)	81.8 (59.7-94.8)
<1.0	18 (32)	4 (7)	22 (39)				
≥1.0	11 (20)	23 (41)	34 (61)				
Total	29 (52)	27 (48)	56 (100)				
Second retest†‡				50.0 (67.6-93.2)	94.4 (72.7-99.9)	66.7 (9.4-99.2)	89.5 (66.9-98.7)
<1.0	17 (77)	2 (9)	19 (86)				
≥1.0	1 (5)	2 (9)	3 (14)				
Total	18 (82)	4 (18)	22 (100)				

NPV, negative predictive value; PPV, positive predictive value; RLU/CO, relative light units/cutoff light units.
* Human papillomavirus genotyping and cytology results; given as number (percentage).
† Samples that were negative (<1.0) on the first retest were analyzed in the second retest. Combining the reference standard results of the second retest with those of the first (assuming that all second retest results were negative by the Digene assay) showed no change in the overall sensitivity, specificity, and predictive values. Sensitivity, specificity, and predictive values are given as percentage (95% confidence interval).
‡ First retest, P = .0004. Second retest, P = .0727. P values are for differences between groups within each respective retest.

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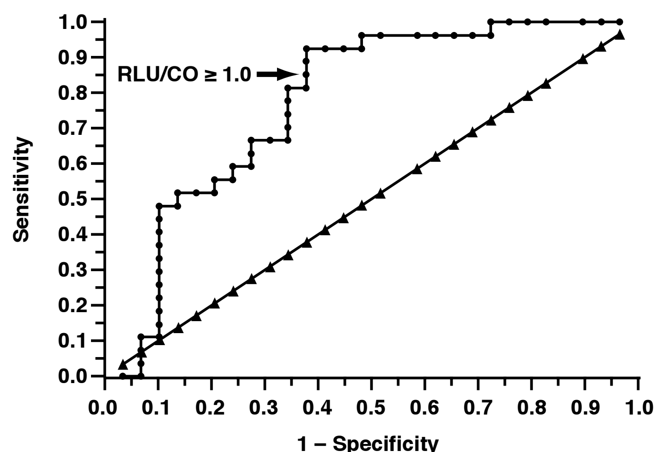

Figure 2 Receiver operating characteristic curve for the first retest using the Digene Hybrid Capture 2 High-Risk HPV DNA test kit. The arrow illustrates the point on the curve at which the positive threshold value was set at the US Food and Drug Administration–recommended relative light units/cutoff light units (RLU/CO) value of 1.0. Area under the curve, 0.774; 95% confidence interval, 0.647-0.901; P = .00044. Circles, sensitivity; triangles, identity.

Table 2
HPV Isolates Typed by Polymerase Chain Reaction and Comparison With Digene First Retest Results Based on the US Food and Drug Administration–Recommended Threshold Value of 1.0 RLU/CO

	Digene First Retest Results*		
High-Risk HPV Type	<1.00 RLU/CO (n = 1)	≥1.00 RLU/CO (n = 24)	Total (n = 25)
16	0 (0)	5 (21)	5 (20)
18	0 (0)	3 (13)	3 (12)
31	0 (0)	0 (0)	0 (0)
39	0 (0)	2 (8)	2 (8)
45	0 (0)	2 (8)	2 (8)
52	0 (0)	2 (8)	2 (8)
53	0 (0)	1 (4)	1 (4)
56	1 (100)	5 (21)	6 (24)
66	0 (0)	1 (4)	1 (4)
67	0 (0)	1 (4)	1 (4)
82	0 (0)	2 (8)	2 (8)

HPV, human papillomavirus; RLU/CO, relative light units/cutoff light units.
* For RLU/CO of 1.00, data are given as number (percentage) of Digene-negative isolates; for RLU/CO ≥1.00, as number (percentage) of Digene-positive isolates; and for total, as number (percentage) of high-risk isolates.

Our data showed 4 false-negative results on the initial retest compared with the reference standard; the characteristics of these patient samples are listed in **Table 3**. None of these specimens had corresponding high-grade dysplasia by cytology. Only 1 of the cases did not have any cytologic findings of HPV infection or dysplasia (case 16). This patient had an HPV genotype (56) that was detectable by the hc2 assay with an RNA probe for HR genotype 56.

Discussion

Our data showed that the RLU/CO value of 1.0 is adequate for delineating positive and negative results from the Digene assay (Figures 1 and 2). On retesting, a value of 1.0 RLU/CO showed the best sensitivity and specificity for the detection of specimens that are infected with HR HPV. By using ROC curve analysis, the optimal value for the cutoff was 0.96 RLU/CO. By using the FDA-established value of 1.0 RLU/CO, the combined results of the first and second retests (when compared with the results of the first retest) showed identical results for the different test parameters when assuming negative Digene results for the second retest. Our data support the use of a positive threshold value of 1.0 RLU/CO for the Digene hc2 assay values that initially test in the retest zone (1.0-2.5 RLU/CO) and that the Digene-recommended algorithm provides no additional benefit for classifying specimens that are in the retest zone. Several studies have evaluated the Digene hc2 assay, comparing the ability of the test to predict the development of CIN.[10-18] These studies all have used the threshold value of 1.0 RLU/CO, and some have used a semiquantitative approach, comparing low, intermediate, and high RLU/CO values as a measure of viral load.

Table 3
Characteristics of Patient Samples Exhibiting a False-Negative Digene Result Compared With the Reference Standard

				RLU/CO Value	
Case No.	Genotype	Bethesda Scoring	Cytologic Descriptor	First Retest 1	Second Retest
16	HR 56	Negative for lesion	—	0.99	1.13
18	Negative	LSIL	Definite HPV changes	0.97	1.13
26	Negative	LSIL	Definite HPV changes	0.81	0.69
36	Negative	ASCUS	Atypical parakeratosis; suggestive of HPV changes	0.38	0.43

ASCUS, atypical squamous cells of undetermined significance; HPV, human papillomavirus; HR, high-risk; LSIL, low-grade squamous intraepithelial lesion; RLU/CO, relative light units/cutoff light units.

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Our study specifically sought to analyze the Digene algorithm using a predefined reference standard that was definitive for HPV infection instead of CIN. Some studies have compared the Digene assay with target amplification-based methods to evaluate the Digene assay's ability to predict the development of CIN.[10-15] Our study sought to characterize the effectiveness of the Digene retest algorithm by using direct measures of HPV infection (PCR-based genotype detection and/or HPV cytology). The first retest showed a high false-positive rate (37.9%) and a somewhat better false-negative rate (14.8%), which are to be expected for specimens that initially test in the retest zone. Lower positive threshold values have shown a significant increase in false-positive results compared with PCR.[19] When comparing with the combined retest results, the first retest classified patient samples equally well, suggesting that the second retest is not needed. Eliminating the need for the second retest would reduce turnaround time and the costs associated with testing.

In general, PCR-based methods have been shown to increase analytic sensitivities from 10- to 500-fold compared with the hc2 assay, and low results with the Templex assay may indicate an early or a transient infection that would favor a positive result.[3] In our study, the Digene hc2 data were compared with the Templex HPV genotyping, and if any potential bias exists, it would lean toward the PCR assay testing positive for some genotypes that were not specifically tested for by the Digene assay (types 26, 53, 66, 67, 69, 70, 73, and 82), thereby causing a higher false-negative rate instead of a higher false-positive rate. Infection with HPV includes periods before and after the presence of HPV-related cytologic changes. Therefore, using cytology in our reference standard might tend to contribute toward a higher false-negative rate in our analysis.[20]

Of note, the relative frequency of HPV types 16, 31, and 45 was relatively low (20%, 0%, and 8%, respectively) and type 56 was high (24%) compared with previously published data.[21,22] The 5 specimens that contained HPV types not tested for by the Digene assay (types 53, 66, 67, and 82) did not exhibit changes indicative of HPV infection by cytology. Only 1 of these specimens showed any evidence of dysplasia (LSIL) and was positive by the Templex assay for types 82 and 39. Of the 5 specimens, 2 (positive for types 53 and 67, respectively) were negative for genotypes that were tested for by the Digene assay. The fact that these 2 Templex-positive samples were also positive by the Digene assay (in the absence of probes specific for types 53 and 67) likely indicates cross-reactivity of probes in the Digene assay with incipient DNA from these HPV types. This type of cross-reactivity has been reported in the literature for types 53, 66, and 67.[23]

Our data showed 4 false-negatives on the initial retest compared with the reference standard. None of these specimens had corresponding high-grade dysplasia by cytology. Only 1 of these cases had no cytologic findings of HPV infection or dysplasia (case 16). This patient had an HPV genotype (56) that was detectable by the hc2 assay (has an RNA probe for HR type 56). Previously published data have shown that false-negative cases occur in the detection of high-grade lesions when using molecular methods.[24] All patients in this study would have likely had routine follow-up, but data are not available as to whether a high-grade (CIN 2/CIN 3) lesion developed.

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