Characteristics of Apparently False-Negative Digene Hybrid Capture 2 High-Risk HPV DNA Testing

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Abstract

This study characterized cases with a negative high-risk Hybrid Capture 2 (HRHC2; Digene, Gaithersburg, MD) test result with concurrent or follow-up biopsy-confirmed high-grade cervical intraepithelial neoplasia (CIN 2/3). From 2,306 HRHC2 tests, 10 negative results were identified with CIN 2/3 (false-negative rate, 4.5%). The majority of the patients had abnormal colposcopic findings and high-grade squamous intraepithelial lesion (HSIL) shown by concurrent cytologic examination, although with few abnormal cells. No trend was evident in the location of the dysplastic epithelium or overall lesion size. In 4 tests, the relative light units over cutoff was more than 0.4 but less than 1.0, suggesting that low quantities of human papillomavirus (HPV) DNA were present in the sample. The negative predictive value for HRHC2 testing may be compromised when the copy number of the HPV DNA is low, and a negative HRHC2 test result may be falsely negative in patients with abnormal colposcopic findings or concurrent cytologic findings showing HSIL.

Testing for the presence of high-risk human papillomavirus (HPV) DNA in cervical samples has become a significant component in triage of patients with equivocal cytologic results in cervical cancer screening.[1] One commercially available test is the high-risk Hybrid Capture 2 test (HRHC2; Digene, Gaithersburg, MD), which has been shown to have high sensitivity for the ultimate detection of cervical intraepithelial neoplasia (CIN) 2/3.[2] The usefulness of the HRHC2 test lies in its high negative predictive value, which has been found in the range of 99%.[3,4]

Despite this high negative predictive value, false-negative results are known to occur but have been detailed by few reports. The ASC-US (atypical squamous cells of undetermined significance)/LSIL (low-grade squamous intraepithelial lesion) Triage Study found a false-negative rate for the HRHC2 HPV test of 3.7%.[5] Other studies have shown higher false-negative rates for HRHC2 tests for histologically confirmed CIN 2/3 cases, ranging from 4.1% to 18.2%.[6,7] The rate of negative HRHC2 test results when histologic evidence of a lesion is present is even greater when CIN 1 cases are included—36.6%.[8]

Although false-negative results are known to arise, to our knowledge, there have been no reports attempting to characterize the cases in which false-negative results have been found. This study was initiated to study cases in which negative HRHC2 test results had occurred in patients with concurrent or immediate follow-up biopsies demonstrating CIN 2/3. The cytologic, histologic, and HRHC2 results were studied to seek the potential sources of false-negative results.

Materials and Methods

Study Population and Testing

This retrospective review of quality assurance data was based on patients visiting a colposcopy unit during a 32-month period, November 2001 through June 2004, and included new referral patients and patients being examined in follow-up. Patients underwent colposcopic examination, repeated cytologic examination (initially conventional and later liquid-based), and colposcopically directed biopsies when indicated. A specific management protocol was not dictated, and the patients were examined and managed at the physician's direction.

The HRHC2 test was performed at the physician's request on separately obtained samples using the Digene Hybrid Capture Cervical Sampler and Specimen Transport Medium. Samples were received within 1 day of collection and stored at –20°C until HRHC2 testing was performed, usually within 2 weeks of collection. HRHC2 HPV tests were performed according to the manufacturer's recommendations using the high-risk probes with the positive and negative control samples run in triplicate and result validation using HC2 software, version 2.0. HRHC2 test results with relative light units over cutoff (RLU/CO) values of less than 1.0 were considered negative.

Inclusion in the study required at least 1 test with an RLU/CO result of less than 1.0 with a concurrent and/or follow-up biopsy within 6 months showing the presence of CIN 2/3 or greater. These cases were considered false-negative HRHC2 test results for the purposes of the study. The clinical, cytologic, histologic, and HRHC2 results from these cases were reviewed.

Case Review and Data Analysis

Cases with false-negative HRHC2 results were divided into 2 groups, new referral and in follow-up. There was no attempt to review the original referral cytologic diagnosis for the new referral cases. The cytologic slides from samples concurrent with the HRHC2 test were reviewed to confirm the cytologic diagnosis. The review was conducted by 2 unblinded pathologists (R.J. and S.B.), and in cases of discordance a third pathologist (W.R.G) reviewed the case.

The number of abnormal cells on the cytologic slide was counted and estimated as few (≤25 abnormal cells), moderate (26-100 abnormal cells), or abundant (>100 abnormal cells), and the proportion of low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL) cells was estimated in each case. The cytologic criteria for LSIL were nuclear enlargement at least 3 times an intermediate cell nucleus, nuclear membrane irregularity, hyperchromasia with a coarse chromatin pattern, and sharp, well-defined perinuclear halos. The cytologic criteria for HSIL were a high nuclear/cytoplasmic ratio, marked nuclear membrane irregularity, and hyperchromasia with chromatin condensation and clearing. The histologic slides from biopsies also were reviewed to confirm the diagnosis. The review was conducted by 2 unblinded pathologists (R.J. and S.B.), and in cases of discordance a third pathologist (W.R.G.) reviewed the case.

The location of the lesion was classified as surface, endocervical glandular space, or both. For all punch biopsy specimens, the lesions were considered focal. For loop electrosurgical excision (LEEP) specimens, the size of the lesion was estimated from the histologic slide as focal (1 lesion ≤0.2 cm), moderate (≥1 lesions >0.2 cm and ≤1.0 cm), or extensive (≥1 lesions >1.0 cm), and the presence or absence of surrounding CIN 1 was noted. The RLU/CO values of the HRHC2 tests were reviewed. No residual samples were available for repeated HPV testing or further studies.

Results

There were 2,306 HRHC2 tests performed for 2,070 patients, with 902 positive and 1,404 negative test results. Of the 2,070 patients, 1,409 (68.1%) had follow-up surgical specimens, including punch biopsy specimens, LEEP specimens, and hysterectomy specimens. There were 739 HPV tests with surgical specimens for patients with a preceding negative HRHC2 test result, of which 677 were negative for CIN. Sixty-two specimens showed CIN, 52 CIN 1 and 10 CIN 2/3 or greater. **Table 1** shows the HRHC2 test results for detecting biopsy-confirmed CIN 2/3. The 10 specimens of biopsy-confirmed CIN 2/3 and negative HRHC2 tests were divided into new referral patients (6 HRHC2 tests from 6 patients), which more closely reflect the screening triage application of HRHC2,

Table 1
Results of Histologic Follow-up on All High-Risk HPV Hybrid Capture Tests With Biopsy Specimens

	CIN 2/3+ Present	CIN 2/3+ Absent	Total
HRHC2 positive	210	460	670
HRHC2 negative	10	729	739
Total	220	1,189	1,409

CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HRHC2, high-risk Hybrid Capture 2 test; +, or greater.

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and patients in follow-up (4 HRHC2 tests from 3 patients). For 6 of the tests, biopsy specimens obtained concurrently with the HRHC2 testing demonstrated the presence of CIN 2/3. For the other 4 tests from 3 patients, biopsy specimens demonstrated CIN 2/3 within 1, 3, and 6 months of the HRHC2 tests. On the basis of histologic follow-up demonstrating CIN 2/3, a false-negative rate of 4.5% was determined for the HRHC2 testing in this population, with a false-positive rate of 38.7%, a sensitivity of 95.5%, a specificity of 61.3%, a positive predictive value of 31.3%, and a negative predictive value of 98.6%.

New Referral Patients

Table 2 shows the referral cytologic diagnosis with the results of colposcopic and pathologic examinations and HRHC2 test results in the 6 new referral patients with negative HRHC2 tests and biopsy-confirmed CIN 2/3. All 6 patients had abnormal cytologic findings and/or abnormal colposcopic results at the time of initial assessment. In 4 patients, the referring cytologic diagnosis had been HSIL, with ASC-US in 1 patient and atypical squamous cells cannot exclude HSIL (ASC-H) in 1 patient. In 2 patients, the initial colposcopic examination was negative; both patients had been referred with a cytologic diagnosis of HSIL.

The cytologic specimens obtained at colposcopy and concurrently with the collection of the sample for HRHC2 testing originally were reported as negative for intraepithelial lesion or malignancy in 2 patients, HSIL in 3 patients, and atypical glandular cells in 1 patient. Review of the concurrent cytologic material **Table 3** revealed HSIL in all 6 specimens but with few abnormal cells in each slide. No LSIL cells were seen in these cytologic samples.

Of the 6 patients, 4 had biopsy specimens obtained concurrently with the negative HRHC2 test result that demonstrated the presence of CIN 3 (Table 2). In 1 patient with a concurrent biopsy result that was negative, follow-up biopsy revealed CIN 3, as did LEEP excision 27 weeks later. The sixth patient underwent LEEP excision that demonstrated microinvasive squamous cell carcinoma 7 weeks after initial examination. Review of histologic samples **Table 4** confirmed the original interpretations in all except 1 case in which the histologic diagnosis was downgraded to CIN 2. In general, the lesions were focal and small, but in 2 cases, a small punch biopsy specimen was the only specimen available for review, and the size of the lesion might have been underestimated. However, in 2 of the cases, the lesions were large and extensive, with most cases demonstrating surface and endocervical glandular space involvement and 1 case in which only a single endocervical glandular space was involved by CIN 3. The concomitant presence of CIN 1 was found in only 1 case. In all the other cases, the only CIN 2/3 was evident in the biopsy.

Table 2
Referral Cytologic Diagnosis and Results of Colposcopic Examination, HRHC2 Testing, and Pathologic Evaluation for Six New Referral Patients With Negative HRHC2 Test Results and Biopsy-Confirmed CIN 2/3 or Greater

Case/ Age (y)	Referral Cytologic Diagnosis	Colposcopic Findings	Concurrent Cytologic Findings	Concurrent Biopsy Findings	HRHC2 (RLU/CO)	Follow-up Biopsy Findings
1/33	ASC-US	Abnormal	HSIL	Cervical biopsy, CIN 3	0.62	None
2/32	HSIL	Abnormal	HSIL	Cervical biopsy, CIN 3	0.42	None
3/59	HSIL	Normal	AGC	ECC, CIN 3	0.13	LEEP, CIN 3
4/30	HSIL	Abnormal	NILM	Negative	0.55	LEEP, CIN 3
5/46	HSIL	Normal	NILM	ECC, CIN 3	0.18	LEEP, CIN 3
6/38	ASC-H	Abnormal	HSIL	None	0.77	LEEP, microinvasive squamous cell carcinoma

AGC, atypical glandular cells; ASC-H, atypical squamous cells cannot exclude HSIL; ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; ECC, endocervical curetting specimen; HRHC2, high-risk Hybrid Capture 2; HSIL, high-risk squamous intraepithelial lesion; LEEP, loop electrosurgical procedure, cervix; NILM, negative for intraepithelial lesion or malignancy; RLU/CO, relative light units over cutoff.

Table 3
Review of Cytologic Samples Obtained During Initial Colposcopic Examination and Concurrently With Samples Obtained for HRHC2 Testing From Six New Referral Patients With Negative HRHC2 Test Results and Biopsy-Confirmed CIN 2/3 or Greater

Case/Age (y)	Original Concurrent Cytologic Diagnosis	Review of Concurrent Cytologic Material	Quantity of Abnormal Cells	Proportion of LSIL vs HSIL Cells
1/33	HSIL	HSIL	Few	All HSIL
2/32	HSIL	HSIL	Few	All HSIL
3/59	AGC	HSIL	Moderate	All HSIL
4/30	NILM	HSIL	Few	All HSIL
5/46	NILM	HSIL	Few	All HSIL
6/38	HSIL	HSIL	Few	All HSIL

AGC, atypical glandular cells; CIN, cervical intraepithelial neoplasia; HRHC2, high-risk Hybrid Capture 2; HSIL, high-risk squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion or malignancy.

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Table 4
Review of Histologic Samples From Six New Referral Patients With Negative HRHC2 Test Results and Biopsy-Confirmed CIN 2/3 or Greater

Case/ Age (y)	Concurrent Biopsy Diagnosis	Follow-up Biopsy Diagnosis	Review of Histologic Material	Location of Lesion	Size of Lesion	Surrounding CIN 1
1/33	Cervical biopsy, CIN 3	None	CIN 2	Surface and gland	Focal	None
2/32	Cervical biopsy, CIN 3	None	CIN 3	Surface and gland	Focal	Focal
3/59	ECC, CIN 3	LEEP, CIN 3	CIN 3	1 Gland only	Focal	None
4/30	Negative	LEEP, CIN 3	CIN 3	Surface and gland	Extensive	None
5/46	ECC, CIN 3	LEEP, CIN 3	CIN 3	Surface and gland	Focal	None
6/38	None	LEEP, microinvasive squamous cell carcinoma	Microinvasive squamous cell carcinoma	Surface and gland	Extensive	None

CIN, cervical intraepithelial neoplasia; ECC, endocervical curetting specimen; HRHC2, high-risk Hybrid Capture 2; LEEP, loop electrosurgical procedure, cervix.

Review of the HRHC2 test results from the new referral patients (Table 2) revealed 2 classes of results: 2 in which the RLU/CO was less than 0.2 and 4 with RLU/CO values of more than 0.4 but less than 1.0.

Patients in Follow-up

Apparent false-negative HRHC2 test results also were identified in 3 patients examined in follow-up in the colposcopy service **Table 5**. In 1 patient, 2 separate negative HRHC2 test results had been obtained. Two patients were undergoing follow-up for persistent low-grade cytologic abnormalities, and the third patient was followed up after primary radiation therapy for invasive squamous carcinoma. Similar to the new referral patients, the follow-up patients had abnormal colposcopic and cytologic findings, and review of cytologic material obtained concurrently with the HRHC2 test showed few HSIL cells **Table 6**. In review of the biopsy specimens **Table 7**, 1 specimen was downgraded to CIN 1, whereas the CIN 3 and invasive squamous cell carcinoma were confirmed in the other 2 specimens. All 4 tests in this group had RLU/CO values of less than 0.3.

Table 5
Clinical Manifestations and Results of Colposcopic Examination, HRHC2 Testing, and Pathologic Evaluation for Three Patients Examined in Follow-up With Negative HRHC2 Test Results and Biopsy-Confirmed CIN 2/3 or Greater

Case/ Age (y)	Reason for Follow-up	Colposcopic Findings	Concurrent Cytologic Findings	Concurrent Biopsy Findings	HRHC2 (RLU/CO)	Follow-up Biopsy Findings
7/56	Persistent LSIL; cervical biopsy and colposcopy negative	Abnormal	HSIL	Cervical biopsy, CIN 3	0.15	Cervical biopsy, CIN 3
8/52	Intermittent ASC-US/LSIL; biopsy negative	Abnormal	HSIL	None	0.20	LEEP, CIN 2
8/52			NILM	None	0.29	
9/35	Primary radiation therapy for invasive squamous cell carcinoma	Abnormal	Insufficient	None	0.15	Vaginal biopsy, invasive squamous cell carcinoma

ASC-US, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HRHC2, high-risk Hybrid Capture 2; HSIL, high-risk squamous intraepithelial lesion; LEEP, loop electrosurgical procedure, cervix; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion or malignancy; RLU/CO, relative light units over cutoff.

Table 6
Review of Cytologic Specimens Obtained During Initial Colposcopic Examination and Concurrently With Samples Obtained for HRHC2 Testing From Three Patients Examined in Follow-up With Negative HRHC2 Test Results and Biopsy-Confirmed CIN 2/3 or Greater

Case/Age (y)	Original Concurrent Cytologic Diagnosis	Review of Concurrent Cytologic Material	Quantity of Abnormal Cells	Proportion of LSIL vs HSIL Cells
7/56	HSIL	NA	NA	NA
8/52	HSIL	HSIL	Moderate	Equal
8/52	NILM	HSIL	Few	All HSIL
9/35	Insufficient	Insufficient	—	—

CIN, cervical intraepithelial neoplasia; HRHC2, high-risk Hybrid Capture 2; HSIL, high-risk squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion or malignancy.

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Table 7
Review of Histologic Samples From Three Patients Examined in Follow-up With Negative HRHC2 Test Results and Biopsy-Confirmed CIN 2/3 or Greater

Case/Age (y)	Follow-up Biopsy Diagnosis	Review of Histologic Material	Location of Lesion	Size of Lesion	Surrounding CIN 1
7/56	Cervical biopsy, CIN 3	CIN 3	Surface only	Moderate	None
8/52	LEEP, CIN 2	CIN 1	Surface only	Focal	CIN 1 only
9/35	Vaginal biopsy, invasive squamous cell carcinoma	Invasive squamous cell carcinoma	Surface and invasive	Focal	—

CIN, cervical intraepithelial neoplasia; HRHC2, high-risk Hybrid Capture 2; LEEP, loop electrosurgical procedure, cervix.

Discussion

HPV DNA testing has been incorporated into cervical cancer screening to triage cases with indeterminate cytologic results. This strategy has met with success because of the high sensitivity and negative predictive value of the Digene HRHC2 test. However, no test is infallible, and false results will occur. In this series, the false-negative rate of the HRHC2 was 4.5%; a false-negative test was defined as an HRHC2 RLU/CO result of less than 1.0 in patients with histologic material demonstrating CIN 2/3 or greater. The false-negative rate in this series is within the lower end of the range reported in the literature, 3.7%[5] to 18.2%[6,7]

Although there are many potential explanations for the false-negative results, it is evident in 4 tests (cases 1, 2, 4, and 6) that HPV DNA was present in the samples, but the level of viral DNA was less than the amount necessary for the result to be considered positive. The RLU/CO result obtained from HRHC2 is related to the actual content of HPV DNA in the sample. An RLU/CO value of 1.0 is equivalent to approximately 1 pg of HPV DNA per 1 mL of sample buffer.[9] Samples with RLU/CO results of less than 1.0 may still contain low quantities of HPV DNA. In 4 of 10 tests, the RLU/CO value for the HRHC2 tests was more than 0.4 but less than 1.0, indicating the presence of low quantities of HPV DNA in these samples.

The cytologic samples from these 4 cases showed few abnormal cells, all of which were HSIL. With few abnormal cells, the amount of HPV DNA in the sample would be less. This situation is made worse by the presence of only HSIL cells, in which the viral DNA load typically is lower.[10] Thus, the false-negative HRHC2 result in these 4 cases with HRHC2 RLU/CO values of more than 0.4 but less than 1.0 originated from samples containing few HSIL cells with a low HPV DNA load, below the cutoff for a positive result.

The question that remains unanswered is why these samples contained so few abnormal cells. In the 4 cases with RLU/CO values of more than 0.4 but less than 1.0, the clinical lesions were sufficiently large to be visualized during colposcopy. Other lesional parameters (Table 4) were studied by histologic examination of the biopsy specimens. No clear explanation was evident from this review. Although some lesions were small and predominantly endocervical, others were large and extensively involved the surface epithelium. Thus, the histologic features of the lesions did not provide a clue to the low cell yield. It is possible that the shedding of abnormal cells during collection reflects some inherent characteristic of the lesion that is not readily apparent morphologically or simply reflects sample collection errors.

In the remaining 6 false-negative tests (cases 3, 5, 7, 8, and 9), the HRHC2 RLU/CO value was less than 0.3, and a definitive explanation for the HRHC2 results cannot be established. It is still possible that a very low level of HPV DNA was present, but other explanations must be considered. In one of these cases, the cytologic sample was unsatisfactory for evaluation and was virtually devoid of cells. Presumably, the HRHC2 sample also would have been unsatisfactory for testing. There are no criteria for evaluating the adequacy of specimens for HRHC2 testing when using specimens obtained separately from a liquid-based cytologic sample. Furthermore, it is not possible to determine whether these samples contain any cellular DNA from the HRHC2 results. It may be postulated that the other 5 tests also were insufficient samples. The concurrent cytologic samples argue against this hypothesis because the other 5 cytologic samples contained abnormal cells, albeit in low numbers.

The false-negative HRHC2 test results in these 6 cases might have been the result of methodologic or reproducibility errors. HRHC2 has been shown to have very good reproducibility, with a κ value of 0.84.[11] However, reproducibility is reduced when the RLU/CO nears 1.0.[12] In these cases in which the abnormal cells are few and the viral DNA load may be low, the HRHC2 results are more likely to be near the cutoff value, and reproducibility may become a significant source of errors.

Histologic interpretation errors must be considered a potential source of the apparent false-negative results in this group of 6 tests. In 2 of the false-negative cases, the biopsy diagnosis was downgraded from CIN 2/3 to CIN 1 after review. These 2 HRHC2 test results may have been true-negative results and not false-negatives. However, it may be argued that most CIN 1 lesions would be expected to be positive by

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HRHC2 testing. CIN 2/3 or greater was confirmed by review in the other 4 cases, indicating that interpretation errors cannot be used to explain the HRHC2 results.

False-negative HRHC2 test results are rare. It would seem that some are the result of samples with a low viral DNA load that falls below the positive cutoff for the test. This situation is likely to arise in samples that contain only a few HSIL cells. Thus, the negative predictive value for HRHC2 testing may be compromised in cases in which the copy number of the HPV DNA is low, as reflected by an RLU/CO less than but near 1.0. HRHC2 test results that are negative may be falsely negative when the concurrent cytologic sample shows the presence of HSIL.

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