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LETTER

# Diagnostic sensitivity for invasive cervical carcinoma of high risk HPV tests performed on SurePath™ liquid-based pap specimens

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## Dear Editor

Recently I communicated with the Editor regarding Drs Naryshkin and Austins' article entitled "Limitations of widely used high-risk human papillomavirus laboratory-developed testing in cervical carcinoma screening."[1,2] As noted previously, this article is based on a single case report of squamous cell carcinoma of the cervix diagnosed in a patient who had abnormal Pap results but had negative Hybrid Capture 2 (HC2)(Qiagen NV, Hilden, Germany) high risk human papillomavirus (hrHPV) testing from SurePath™ (Becton-Dickinson, Franklin Lakes, NJ, USA) samples. The authors concluded that such testing should not be done using this collection medium. Interestingly, they also mentioned a 10% false negative rate for similar testing performed on FDA-approved Preservcyt® media on three of 31 invasive cervical carcinoma patients at Dr Austin's own laboratory.

In their response to my letter they noted that a 10% false negative rate for women with invasive cervical carcinoma tested by the HC2 method using US Food and Drug Administration (FDA)-approved collection media tested within one year of the cancer diagnosis is the norm and is consistent with previous estimates of achievable HPV test sensitivity. This is most likely due to a low HPV viral load in the negative samples. They also correctly pointed out that such data is available for only a limited number of cases tested using HC2 on SurePath™ samples. They then reiterated their call for a nationwide data collection effort to document the likelihood of false negative hrHPV test results for all HPV testing methods over the 5–10 year period preceding histopathologic cervical cancer diagnoses.[3]

In this communication I respond to their call. Our laboratory uses the FDA-approved HC2 hrHPV method on SurePath™ Pap media which does not have FDA-approval for hrHPV testing. This testing methodology is used based on the results of an in-house validation performed under Clinical Laboratory Improvement Amendments (CLIA) guidelines and has enjoyed excellent College of American Pathologists (CAP) hrHPV proficiency testing results. This retrospective study focuses on the sensitivity of this testing for invasive cervical squamous carcinoma in our low risk patient population. Our methodology included identifying all histologically confirmed cervical squamous carcinoma cases at our institution from 2002–2012. Prior Pap test and hrHPV test records were reviewed for each patient. The results include 48 cases of carcinoma. Thirty-one of the 48 (65%) had Pap tests and seven of 48 (15%) had hrHPV tests within 5 years of diagnosis. All seven hrHPV tests were performed by HC2 on SurePath™ samples.

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All seven (100%) were positive. During the study period the laboratory performed 496,859 Pap tests with an overall ASC-H (atypical squamous cells - cannot exclude high grade squamous intraepithelial lesion) or higher Pap diagnosis rate of 0.5%. hrHPV tests were performed on 63,726 of the Pap tests (12.8%). The percentage of Pap tests with concurrent hrHPV tests increased from 0.65% in 2002 to 42.7% in 2012. In conclusion, based on a limited number of cases, no false negative hrHPV tests performed on SurePath™ samples from patients with cervical carcinoma were identified at our institution. Since current cervical cancer screening guidelines recommend increasing screening intervals which are dependent upon hrHPV test results, it is essential that the testing methodology is reliable. A large-scale national or international study, as suggested by Drs Naryshkin and Austin, is recommended in order to establish false negative rates for all hrHPV testing methods and sample types.

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# Authors' response

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We thank Dr Nance for providing additional data on his experience with Hybrid Capture 2 (HC2) (Qiagen NV, Hilden, Germany) Laboratory Developed Testing (LDT) from the SurePath™ (Becton-Dickinson, Franklin Lakes, NJ, USA) vial. As mentioned previously, we believe this is the kind of retrospective data that the laboratory profession should be monitoring nationwide,[1,2] especially given proposed extended five year screening intervals for many women with negative high risk (hr) HPV test results.[3]

The SurePath™ HC2 hrHPV LDT data cited by Dr Nance differs significantly from published data reported by several US academic centers. A study from Emory University of patients with ASC-H (atypical squamous cells - cannot exclude high grade squamous intraepithelial lesion) SurePath™ cytologic findings, for example, reported positive hrHPV HC2 LDT results from the SurePath™ vial in only 11 of 21 patients (52%) with follow-up CIN3 biopsy findings of 48 of 61 patients (79%) with follow-up CIN2 biopsy findings.[4] More recently, Johns Hopkins University, reported positive hrHPV HC2 LDT results from the SurePath™ vial in 48 of 57 patients (84%) with HSIL SurePath™ cytology results, zero of six patients with SurePath™ cytologic findings of adenocarcinoma, and one of two patients with SurePath™ cytologic findings of squamous cell carcinoma.[5] Since current achievable standards have been proposed that an HPV test should have clinical sensitivity to detect at least 89%–95% of existing CIN3+ lesions,[6] these published findings and a number other cautionary observations we made in our initial report[7] should be of concern regarding this widespread LDT.

Furthermore, since SurePath™ HPV testing is not standardized according to any US Food and Drug Administration (FDA)-validated protocol, it is not possible to reliably extrapolate findings from any one laboratory to others. In fact, we are not aware of any published SurePath™ hrHPV LDT validation study which has published its methodology in sufficient detail so that it might be independently implemented and verified by other laboratories. Under current regulations, SurePath™ hrHPV LDT methods cannot be promoted by the manufacturers. LDT methods used in practices appear to vary quite widely, based on conversations with individual laboratories. Therefore, we applaud Dr Nance's recent announcement to introduce in his laboratory co-collection of HPV test specimens in a separate FDA-approved collection vial. This, of course, is the approach the SurePath™ manufacturer itself recommended in its June 8, 2012 Technical Bulletin (BD Diagnostics, personal communication, June, 2012).

Dr Nance's report of positive hrHPV SurePath™ vial LDT results in seven of seven patients with HPV testing within 5 years of a diagnosis of cervical squamous cell carcinoma is itself somewhat surprising. Available international data indicate that negative hrHPV test results increase significantly as testing is less proximate to the time of diagnosis, probably due to increased difficulty in sampling infected lesional cells (sampling false negatives).[8] In the largest available US study, baseline HC2 hrHPV test results collected in FDA-approved Specimen Transport Medium (STM) vials within 5 years of cervical cancer diagnoses were positive at baseline in only 60 of 87 cervical cancer patients (69%).[9] It would be useful to know the full details of the LDT method(s) used by Dr Nance's laboratory during the time periods mentioned, who originally developed this methodology, when the methodology was developed, and to have more information on the proximity of the seven HPV tests to the final diagnoses of squamous carcinoma.

Ideally, in our opinion, what is needed is an FDA-approved SurePath™ hrHPV methodology based on supporting clinical trial data, so that user laboratories nationwide that wish to perform HPV testing from the SurePath™ vial can implement a standardized FDA-validated HPV testing method. Both the American Cancer Society and the American College of Obstetricians and Gynecologists now recommend that only FDA-approved HPV test methods be relied on in cervical screening.[3] Laboratories choosing not to follow professional organization and manufacturer recommendations should make their validation data available upon request for independent review along with detailed information on the precise HPV testing method(s) they have used. Only then can findings be scientifically tested and independently scrutinized for validity and reproducibility. Patients deserve to be tested using scientifically sound methods. Clinicians should be able to trust that HPV testing used for patient care has been determined to meet current standards established

through rigorous FDA trials and independent review. Until laboratories using LDT for HPV testing are willing to share their detailed methods and data so that their testing results are open to scientific scrutiny, reliance on FDA-approved testing methods is prudent.

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