

# Limitations of widely used high-risk human papillomavirus laboratory-developed testing in cervical cancer screening

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## Dear editor

I read with interest the recently published article by Naryshkin and Austin entitled “Limitations of widely used high-risk human papillomavirus laboratory-developed testing in cervical cancer screening”.<sup>1</sup> The article is a single case report of squamous cell carcinoma of the cervix diagnosed in a patient who had negative Hybrid Capture 2 (Qiagen NV, Hilden, Germany) high-risk human papillomavirus testing from SurePath™ (Becton-Dickinson, Franklin Lakes, NJ) samples. The authors then discuss several valid points regarding the use of human papillomavirus testing and cervical cancer screening not approved by the US Food and Drug Administration (FDA). Their conclusion is that such testing should not be done using the SurePath collection medium.

Of equal interest is that the article mentions that in Dr Austin’s own laboratory, three of 31 (10%) patients diagnosed with invasive cervical carcinoma and tested within 12 months for high-risk human papillomavirus by Hybrid Capture 2 from FDA-approved Preservcyt® (ThinPrep®) vials also had negative Hybrid Capture 2 results. All three of these patients subsequently had human papillomavirus 18 and/or 16 detected by polymerase chain reaction in paraffin sections of the carcinoma. Should there not have been elaboration on this point with further discussion and perhaps caution regarding use of Hybrid Capture 2 testing using liquid-based cytology specimens of any type, regardless of FDA approval?

## Disclosure

The author reports no conflict of interest in this work.

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## Reference

1. Naryshkin S, Austin RM. Limitations of widely used high-risk human papillomavirus laboratory-developed testing in cervical cancer screening. *Drug Healthc Patient Saf.* 2012;4:167–172.

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## Dear editor

We appreciate Dr Nance's letter to the editor of December 20, 2012 concerning the important (and understudied) issue of false-negative high-risk human papillomavirus (HPV) test results in women developing invasive cervical carcinoma. Given that current scientific consensus holds that "virtually all" (99.7%)<sup>1</sup> invasive cervical carcinomas are caused by persistent carcinogenic HPV infection,<sup>2,3</sup> we regard any negative high-risk HPV screening test result reported within 5–10 years of a histopathologic diagnosis of invasive cervical carcinoma in women aged 30 years and older as a false-negative HPV screening test result, most likely due to low viral load associated with a subset of developing invasive cervical carcinomas.<sup>4</sup> Using the Hybrid Capture 2 method in collection medium approved by the US Food and Drug Administration (FDA), the false-negative high-risk HPV test rate in women with invasive cervical carcinoma tested near the time of cancer diagnosis (less than one year) has been about 10%.<sup>5–7</sup> This figure is consistent with previous estimates of achievable HPV test sensitivity using FDA-validated methods.<sup>8</sup> Some patients and physicians may undoubtedly be unaware of these published sensitivity data. In contrast, in the limited number of reported Hybrid Capture 2-tested SurePath™ samples associated with cervical cancer diagnoses reported from leading US research universities, a majority of Hybrid Capture 2 high-risk HPV test results reported to date have, as in our case report, been unexpectedly negative.<sup>9,10</sup> To date, these institutions have not consented to report or share institutional data on high-risk HPV test results preceding larger numbers of cervical cancer cases. Furthermore, when we approached the medical director of another large national laboratory, one which would be reasonably expected to have hundreds of cervical cancer cases with prior HPV test results

from the SurePath vial, we were informed that these results were "medically legally sensitive and confidential".

Given the currently available data and recommendations of one manufacturer and professional organization guidelines, advice to co-collect high-risk HPV test samples in an FDA-approved vial when using SurePath screening appears to represent a conservative patient safety practice. We are also aware of at least one case where a false-negative Hybrid Capture 2 HPV test result obtained on a SurePath vial collected 5 years before a diagnosis of an HPV16-positive advanced-stage cervical cancer appears to have contributed to a delayed cervical cancer diagnosis and a fatal outcome.<sup>11</sup>

Our case report in *Drug Healthcare and Patient Safety*<sup>12</sup> further reviews a number of other worrisome "red flags" associated with HPV testing from the formaldehyde-containing SurePath vial,<sup>13</sup> still not FDA-approved for HPV testing by any method after over a decade of unsuccessful premarket approval trials. These include issues we have mentioned in several other published articles exploring the limitations of FDA-approved cervical screening test methods.<sup>6,14,15</sup> Most recently, we have again specifically called for a targeted nationwide data collection effort to document better the likelihood of false-negative high-risk HPV test results by all HPV test methods over the 5–10 years preceding histopathologic cervical cancer diagnoses.<sup>15</sup> We formally made this proposal back in 2011 at the College of American Pathologists and Centers for Disease Control and Prevention-sponsored GYN Practices Consensus Conference, but the meeting leaders elected to refer the proposal for "further study". Patients have high and sometimes even unrealistic expectations for cervical screening outcomes.<sup>16</sup> When clinicians and patients are asked to rely on HPV LDT, they should be informed of alternative recommended FDA-validated methods. Laboratory validation data should be publicly available.

## Disclosure

The authors report no conflicts of interest in this work.

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