A New Generation of Studies of Human Papillomavirus DNA Testing in Cervical Cancer Screening

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“...all zoogles are boogles. You saw a boogle. Is it a zoogle?” Question in an SAT examination (Nassim Nicholas Taleb in “The Black Swan”)

“Not necessarily” is the resounding answer to this thought experiment, in analogy to the central argument in the debate on the clinical utility of human papillomavirus (HPV) testing in cervical cancer screening. Virtually all cervical cancers are caused by infections with oncogenic HPV types (1). However, does a positive HPV DNA test result indicate that cervical cancer or precancerous lesion is present or imminent for a woman attending routine screening? Although most cervical HPV infections, even those with oncogenic types, will be inconsequential, it is also true that a provider will be more likely to find cervical cancers or their precursors if screening is with HPV DNA testing rather than with Papanicolaou cytology (2,3). This extra sensitivity exacts a penalty if screening is with HPV DNA testing rather than with Papanicolaou cytology (2,3). This extra sensitivity exacts a penalty on the specificity of HPV DNA testing, which (by design) detects the presence of viral DNA in cervical cells irrespective of whether or not the molecular changes are in the context of an infection that has already produced morphological abnormalities recognizable by cytology. In other words, HPV DNA testing brings the focus of screening “upstream” in the natural history of cervical neoplasia relative to the decades-old paradigm of Papanicolaou cytology. Returning to the above thought experiment, all cervical cancers arise from cervical intraepithelial neoplasia (CIN), whose grade correlates with the extent of Papanicolaou abnormality. Although it is easier to find a “zoogle” with the HPV DNA “boogle” identifier than with the Papanicolaou “boogle” identifier, the latter will have fewer false positives than the former.

Recognition of the above-described test properties has not been the main rationale for how the scientific community has designed studies to collect evidence on the value of HPV DNA testing in cervical cancer screening and for how professional guidelines emerged in consequence. Although less specific than Papanicolaou cytology, the HPV DNA test was first evaluated and approved to be used conditionally as a triage tool based on the Papanicolaou cytology result exclusively to identify women who need to undergo colposcopy because of an equivocal Papanicolaou diagnosis (4,5). Later, mounting evidence that HPV DNA testing could increase the sensitivity of screening when used in parallel with Papanicolaou cytology led to co-testing as an accepted practice that permitted screening intervals in the United States to be safely extended from annual to triennial (6). The impetus for Papanicolaou and HPV co-testing prompted the initiation of European randomized controlled trials (RCTs) comparing the co-testing strategy with traditional cytology-only screening. The results from these trials have confirmed that 1) more cervical precancerous lesions are detected by co-testing than by cytology (7–9) and 2) the extra detection is beneficial because the excisional treatment given at the time of the discovery lowers the rate of such lesions in subsequent screening rounds, thus proving that many of them would likely persist or progress if left untreated (8–10).

What was not fully appreciated until recently was the fact that although the case was being made for using both tests in parallel for enhanced detection of cervical precancers, the impact of co-testing on the efficiency of screening in permitting safely extended screening intervals (thus reducing costs) was primarily contributed by HPV DNA testing and not by Papanicolaou cytology. A negative HPV DNA test result provides the same confidence that a CIN grade 3 lesion will not ensue during the next 4 years as a negative Papanicolaou finding does for the next year only (11). An RCT in India has also demonstrated that screening with HPV DNA testing reduces mortality from invasive cervical cancer relative to other modalities (12).

In other areas in medicine, screening for disease (eg, syphilis and HIV infection) is first done with a highly sensitive test, and then, if that test is positive, a triage step with a highly specific assay is performed to confirm or increase confidence in the diagnosis. What prevents us from using the same approach in applying the available technologies, that is, Papanicolaou cytology (highly specific) and HPV DNA testing (highly sensitive) in the same fashion, without the costly “security blanket” of parallel co-testing? Replacing Papanicolaou cytology by HPV DNA testing as the primary screen could never have been done without first having all stakeholders (ie, physicians, policy-makers, and patients) gain confidence in the public health utility of HPV DNA testing.

Evidently, Leinonen et al. (13) believe that there is evidentiary and ethical equipoise to justify comparing HPV DNA testing with traditional cytology in Finland, a country that is among the pioneers in using organized cervical screening to reduce morbidity and mortality from cervical cancer. In this issue of the Journal, they (13) report the robust preliminary findings from an RCT that belongs to a new generation of studies that reorder the sequence of screening tests based on the most sensible and empirically valid algorithm, that is, HPV DNA testing as the primary screen and Papanicolaou cytology serving as the triage trigger for clinical management of those who are HPV DNA positive. The intervention arm rests on the premise that only the boogles that look zoogle enough merit further evaluation, thus avoiding referral of large numbers of women for invasive diagnostic procedures.

In addition to being the first RCT that sensibly explores the properties of Papanicolaou and HPV DNA tests as the rationale for designing the intervention algorithm, the Finnish study has

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See “Notes” following “References.”

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the advantage of being conducted within an organized cervical screening program with high participation rates and a well-established infrastructure of cytology laboratories (13). The central finding of this landmark study is that the sequential (rather than parallel) use of HPV DNA screening followed by Papanicolaou triage not only permits enhanced detection of high-grade precancers but also achieves better specificity than the traditional strategy of cytology-only screening (13). Remarkably, the yield of extra lesion detection with fewer false positives for the screening intervention was observed at a comparable rate of colposcopy referrals between arms. Not surprisingly, restricting the analyses to women aged 35 years or older improved the screening indices substantially for the intervention arm relative to standard practice (ie, cytology only). The lesion enrichment effect consequent to assigning to Papanicolaou cytology, the more important triage work of all HPV DNA–positive cases, was impressive; the positive predictive values for CIN 2 or worse or CIN 3 or worse lesions increased more than six times relative to a scenario in which HPV DNA testing would have been used alone (13). This finding underscores the importance of cytology as a triage test in preserving the specificity of the HPV DNA screening approach; the HPV DNA test followed by Papanicolaou boogle was much better at predicting a boogle than the HPV DNA test–alone boogle. Findings from subsequent screening rounds of the Finnish RCT will eventually confirm if this strategy will result in reduced precancer rates with acceptable safety concerning fertility outcomes.

It is noteworthy that the enhanced detection of high-grade CIN in the intervention arm was only slightly less than the equivalent estimates for other European studies (7–9). However, unlike the latter RCTs, which used a co-testing (parallel) intervention, the Finnish study conducted far fewer screening tests because cytology triage was done only for HPV DNA–positive women, thus reducing the costs of screening substantially. An additional benefit of the reduced workload (13-fold in Finland) is the confidence that the time cytotechnicians spend in reading smears is more rewarding because of the expectation of a much greater detection frequency of abnormalities resulting from the initial HPV DNA screen (threefold and sevenfold greater for any abnormality and atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion or worse, respectively) (13), thus reducing boredom and fatigue. The importance of this finding cannot be overemphasized. As successive cohorts of young women immunized with prophylactic HPV vaccines reach screening age, the reduced prevalence of abnormalities may adversely affect the performance of cytology if it is left as the sole screening test. The expectation that lesions will be rare may reduce attention in smear scanning, which may increase the false-negative rate, or as a compensatory effect, result in more overcalls of reactive or repair atypias as squamous abnormalities, thus leading to more false positives (14). Therefore, the strategy (13) of using an automated objective molecular test as initial screening step to artificially increase the prevalence of abnormal smears destined for reading may thus protect the credibility of cytology in the forthcoming era of screening women who were vaccinated against HPV.

References


Notes

The author has served as an occasional advisory board member or consultant to companies involved with HPV vaccines (GlaxoSmithKline [Rixensart, Belgium] and Merck [Whitehouse Station, NJ]), HPV diagnostics (Gen-Probe [San Diego, CA] and Roche [Pleasanton, CA]), or cervical cancer cytology screening (Cytyc [Marlborough, MA] and Ikonisys [New Haven, Connecticut]).