

Commentary on Statement on HPV DNA Test Utilization

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Michaela had a Papanicolaou (Pap) test at age 17 years, less than 3 months from her first intercourse. The Pap was interpreted as atypical squamous cells of undetermined significance (ASC-US) and the laboratory automatically “reflexed” this to human papillomavirus (HPV) testing. Michaela tested positive for high-risk (carcinogenic) HPV, underwent colposcopy and biopsy, and had cryotherapy for cervical intraepithelial neoplasia (CIN), grade 1. Her 4-month postcryotherapy Pap was ASC-US HPV+.

So what is the problem with Michaela’s story? Everything! According to national guidelines: (1) She should not have had her first Pap until 3 years after first intercourse or age 21 years.¹⁻³ (2) She should not have had HPV testing for the ASC-US Pap unless she was at least 21 years old.³ (3) As an adolescent, she should not have had colposcopy for a minor Pap test abnormality or cryotherapy to treat CIN 1.³

Why is it so important to adhere to national guidelines? Don’t we (clinicians) know what is best for our patients? Well, clinically we know our patient best, and guidelines cannot foresee every variation in real clinical practice. However, guidelines created through rigorous evaluation of evidence-based data and a consensus process provide a framework for providing care that is optimum for most women at each phase in the timeline of their life. Guidelines cannot, and should not, trump clinical decisions for a unique patient situation.³ But variations from recommended guidelines should be the exception rather than the rule in clinical practice.

Perhaps we need to go back to the beginning—to the dialogue between the King and the white rabbit in Lewis Carroll’s wonderful *Alice in Wonderland*: “Where shall I begin, please, your majesties?” Like the King we will say, “Begin at the beginning and go until you come to the end. Then stop!” So, to understand how we can best protect our patients from cervical cancer, *let’s begin at the beginning....*

Cervical cancer is the first cancer identified to have a single obligatory cause, cervical infection by HPV.⁴ However, HPV is common; cervical cancer is not. Almost everyone who is sexually active has had 1 or more HPV infections in their life.⁴ Some HPV types are associated with cervical precancer and cancer and are, therefore, called high-risk (HR; also carcinogenic or oncogenic) HPV types.

Other types that do not cause cancer are called low-risk HPV types. Most HPV infections, including those caused by HR HPV types, are benign and transient and resolve spontaneously within a year or two. Less commonly, HR HPV infections persist. The longer HR HPV infections persist, the more likely they are to cause a precancerous lesion, which, if not detected and treated in a timely manner, can become cancerous.⁴ Fortunately, cancer is an uncommon outcome for an infection virtually everyone gets. The entire process of cervical carcinogenesis, from causal infection to invasive cancer, is usually slow, taking many years or decades. The success of cervical cytology, despite its limitations in sensitivity,^{5,6} has been the result of repeated screening, detection, and therapeutic intervention during the long sojourn from causal infection to invasion.⁷

So why use HPV testing in cervical cancer prevention? Testing for the virus that causes cervical cancer certainly makes sense because cervical cancer rarely, if ever, occurs without HPV. However, the natural history of HPV-induced carcinogenesis and the ubiquitous nature of HPV must temper and guide how we use HPV testing. Most young women are infected with HPV within a few years of becoming sexually active, but exceedingly few have precancer and far fewer still have cancer. Meanwhile, older women have fewer HPV infections and are at more risk for having precancer and cancer if they test HPV+. Misuse of HPV testing in young women identifies too many women with HPV who are not at risk for cervical cancer.

What is the harm? For Michaela, it was a Pap test when she had no risk of cervical cancer and the likelihood of an abnormal cervical cytologic finding was very, very high; an HPV test at an age when HPV is ubiquitous and carries little prognostic value; the anxiety and discomfort of triage to colposcopy and cervical biopsy for HPV lesions of little risk; and the mental and physical trauma of cervical treatment for often transient CIN 1, a diagnosis that is synonymous with HPV infection. Although cryotherapy has not been shown to cause adverse reproductive outcomes, too many young women with minor abnormalities are being treated by cervical excision procedures (eg, loop electrosurgical excision procedure or laser cone) that may increase the risk 2- to 4-fold of premature delivery and low-birth-weight infants.⁸⁻¹⁰

Such a risk is acceptable if necessary to prevent progression to cervical cancer. But since there is so little cancer risk at Michaela's young age (US rates of cervical cancer in women younger than 25 years are 2 in 100,000, only slightly higher than the rates of vaginal cancer for which there is no screening recommended), our primary consideration is to avoid harm when there is little benefit. This is such an important tenet that if HPV testing is inadvertently performed in an adolescent, the results should be ignored and not used to influence patient management.³

So when is HPV testing clinically useful? As summarized by the Statement on HPV DNA Test Utilization¹¹ (based on the consensus guidelines developed by ASCCP³ and endorsed by the American Cancer Society, American Society for Clinical Pathology, American Society for Colposcopy and Cervical Pathology, American Society of Cytopathology, American Society for Cytotechnology, College of American Pathologists, International Academy of Cytology, and Papanicolaou Society of Cytopathology), there is clear, documented benefit for HPV testing in the circumstances listed in the document.

HPV testing must be for *HR-HPV types only* and should use a Food and Drug Administration (FDA)-approved or equivalent test that has undergone peer review in a rigorous, masked evaluation involving an adequate sample size.¹² Testing for low-risk HPV types that do not cause cervical cancer has no clinical benefit and, therefore, cannot be justified or condoned.¹² Other than the indications listed in the Statement on HPV DNA Test Utilization,¹¹ HR-HPV testing generally should not be done because it potentially creates more harm than benefit. It is important to note that cotesting with the Pap and HPV test in women 30 years or older should not be done more frequently than every 3 years if the results of both tests are negative. This combination of tests provides safety for at least 3 years, with recent studies suggesting safety may extend for at least 6 years.^{13,14} Hence, testing more often in women who are at virtually no risk of having precancer adds cost without benefit. Excessive screening all too often identifies transient HPV infections and minor cytologic abnormalities that would have resolved on their own if given wider screening intervals,¹⁵ adding unnecessary evaluations and procedures that create patient harm.

HPV testing should be avoided as a reflex test to any abnormal Pap test other than ASC-US, except in postmenopausal women with low-grade squamous intraepithelial lesion (LSIL). Fewer than 50% of postmenopausal women have LSIL due to HPV, and women with HPV- LSIL are at low risk for cancer and do not need colposcopy.

Neither should HPV testing be done in the initial management of women with atypical glandular cells (AGC). Women with AGC may not have HPV-induced lesions, ie, tubal metaplasia of the endocervix, reactive endocervical cell changes, atypical endometrial hyperplasia, endometrial carcinoma, glandular lesions in the fallopian tubes, and ovarian and glandular cancers from a variety of sources metastatic to the pelvis. However, once possible sources of a non-HPV-induced lesion have been eliminated and colposcopy has not detected CIN or adenocarcinoma in situ (AIS), HPV testing can provide important information about the best follow-up option for women with AGC "not otherwise specified" (NOS). Women with AGC NOS who are positive for high-risk HPV are at greater risk for subsequent detection of CIN

2/3 or AIS and are best followed up with a repeated Pap and HPV test in 6 months with referral to colposcopy if either result is abnormal. This is 1 of only 2 exceptions to the general rule that a positive HPV test should not be repeated in less than a year. The other exception is in the 6-month surveillance of women treated for CIN 2/3.

There are a number of other areas where HPV testing should not be done that are not mentioned in the Statement on HPV DNA Test Utilization.¹¹ HPV testing should *never* be used as a screening test for sexually transmitted diseases (STDs) because HPV is so common and, unlike most STDs, has no treatment that would follow detection. HPV testing should not be done as screening before administering the HPV vaccine. The FDA-approved HPV test identifies a pool of HR HPV types and is not restricted to the 4 HPV types in the vaccine (6, 11, 16, and 18). In addition, there is no commercially available serologic test that would identify past exposure to these 4 HPV types. The cost of prevaccination screening of all sexually active women would escalate the cost of vaccine administration. HPV vaccination programs should target populations that will glean the greatest benefit for the cost: girls in early adolescence who are mostly naive to HPV infections.¹⁶

The Statement on HPV DNA Test Utilization¹¹ represents a convergence of many professional societies on the best practice of HPV testing in the screening and management of women for prevention of cervical cancer. The underpinnings for these recommendations, based on the ASCCP guidelines,³ are the natural history and epidemiology of HPV and cervical cancer. The underlying principle for using any screening or diagnostic test is to differentiate effectively the people at risk of disease from the people who are not.¹⁷

However, there must be an acknowledgment that no test, diagnostic procedure, or treatment is error-free. No measures can be taken to provide absolute reassurance against cervical cancer. As tests for HR HPV have become available, there is the misconception that its exhaustive use might eliminate all cervical cancer. Yet excessive screening may result in excessive management and harmful treatment for benign conditions while minimally reducing cancer incidence; most cervical cancer (60%) occurs in pockets of underscreened populations (<http://www.cdc.gov/cancer/cervical/>). For women in Michaela's age group (younger than 25 years), it is unproven whether additional or more sensitive screening can eliminate any of the rare cancers.

For the clinicians, laboratories, and pathologists conducting (or promoting) more HPV testing for financial gain,¹⁸ it is important to understand the risks being taken. The Pap test has been the most successful cancer screening test in the history of modern medicine. As a result, we have seen a drop in incidence of cervical cancer and its precursors. Consequently, a "positive" Pap test is more likely to be a false-positive than

a true-positive. The reason that HPV testing is such a powerful adjunct to cervical cytology is that it clarifies risk: women (21 years or older) with HPV– ASC-US are at exceedingly low risk of precancerous lesions¹⁹ and can return to routine screening without further clinical intervention, while women with HPV+ ASC-US have a risk comparable to that of LSIL cytology. Before the advent of HPV testing, patients with equivocal Pap results would most often have repeated Pap tests and multiple colposcopic evaluations with possibly multiple biopsies, all of which could lead to patient morbidity. With HPV testing, we can weigh the risk of having significant cervical disease against the costs of unnecessary intervention and harm.

For HPV testing to fulfill its promise, clinicians must understand where it should be used and where it should not. Laboratories must question their client clinicians when HPV testing is ordered in a situation that is more likely to cause harm than benefit. Clinicians must not threaten to move their business to another laboratory, as has been done when the laboratory refuses to do HPV testing that is not clinically indicated by the guidelines. Clinicians must also question the motives of laboratory professionals who urge HPV testing that is not in accordance with guidelines. We all share in the responsibility of keeping our patients as safe as reasonably possible from harm and making medicine as protective and cost-effective as possible. "Where shall I begin, please, your majesties?" Begin with understanding how common HPV is, yet how it can cause cervical cancer. Use your understanding of the natural history of HPV to make sage decisions that take you to the best choices for your patients that emphasize benefit and minimize harm. When we all get to that goal, we can feel confident that we have fulfilled that promise that we made when we took the Hippocratic Oath. "First do no harm."

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References

1. Saslow D, Runowicz CD, Solomon D, et al. American Cancer Society Guideline for Early Detection of Cervical Neoplasia and Cancer. *CA Cancer J Clin*. 2002;52:342-362.
2. ACOG Practice Bulletin. Clinical Management Guidelines for Obstetrician-Gynecologists: number 61, April 2005: human papillomavirus. *Obstet Gynecol*. 2005;105:905-918.

3. Wright TC Jr, Massad LS, Dunton CJ, et al; for the 2006 ASCCP-Sponsored Consensus Conference. 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. *Am J Obstet Gynecol*. 2007;197:346-355.
4. Schiffman M, Castle PE, Jeronimo J, et al. Human papillomavirus and cervical cancer. *Lancet*. 2007;370:890-907.
5. Cuzick J, Clavel C, Petry KU, et al. Overview of the European and North American studies on HPV testing in primary cervical cancer screening. *Int J Cancer*. 2006;119:1095-1101.
6. Mayrand MH, Duarte-Franco E, Rodrigues I, et al. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. *N Engl J Med*. 2007;357:1579-1588.
7. McCredie MR, Sharples KJ, Paul C, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncol*. 2008;9:425-434.
8. Arbyn M, Kyrgiou M, Simoons C, et al. Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis [published online September 18, 2008]. *BMJ*. 2008;337:a1284. doi:10.1136/bmj.a1284.
9. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, et al. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. *Lancet*. 2006;367:489-498.
10. Albrechtsen S, Rasmussen S, Thoresen S, et al. Pregnancy outcome in women before and after cervical conisation: population based cohort study [published online September 18, 2008]. *BMJ*. 2008;337:a1343. doi:10.1136/bmj.a1343.
11. Solomon D, Papillo JL, Davey DD; on behalf of the Cytopathology Education and Technology Consortium (CETC). Statement on HPV DNA test utilization. *Am J Clin Pathol*. 2009;131:768-769.
12. Stoler MH, Castle PE, Solomon D, et al. The expanded use of HPV testing in gynecologic practice per ASCCP-guided management requires the use of well-validated assays. *Am J Clin Pathol*. 2007;127:335-337.
13. Dillner J, Rebolj M, Birembaut P, et al. Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study [published online October 13, 2008]. *BMJ*. 2008;337:a1754. doi:10.1136/bmj.a1754.
14. Sherman ME, Lorincz AT, Scott DR, et al. Baseline cytology, human papillomavirus testing, and risk for cervical neoplasia: a 10-year cohort analysis. *J Natl Cancer Inst*. 2003;95:46-52.
15. Rodriguez AC, Schiffman M, Herrero R, et al. Rapid clearance of human papillomavirus and implications for clinical focus on persistent infections. *J Natl Cancer Inst*. 2008;100:513-517.
16. Saslow D, Castle PE, Cox JT, et al. American Cancer Society Guideline for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. *CA Cancer J Clin*. 2007;57:7-28.
17. Castle PE, Sideri M, Jeronimo J, et al. Risk assessment to guide the prevention of cervical cancer. *Am J Obstet Gynecol*. 2007;197:356.
18. Moriarty AT. A rock and a hard place: HPV testing and financial gain [editorial]. *Diagn Cytopathol*. 2007;35:463-464.
19. Safaeian M, Solomon D, Wacholder S, et al. Risk of precancer and follow-up management strategies for women with human papillomavirus-negative atypical squamous cells of undetermined significance. *Obstet Gynecol*. 2007;109:1325-1331.