Primary High-Risk Human Papillomavirus Testing for Cervical Cancer Screening in the United States

Is It Time?

Melina B. Flanagan, MD, MSPH

Context.—The most recent update to cervical cancer screening guidelines offers interim guidance on the use of primary human papillomavirus (HPV) screening, with algorithms for management of results. After decades of screening with pure cytology and a shorter time with adjunctive HPV or cotesting with Papanicolaou (Pap) test and HPV, this is a significant change to our screening methods.

Objective.—To briefly review the history of cervical cancer screening, the evidence upon which these interim guidelines were based, the arguments for and against primary HPV testing, and the current state of the field.

Data Sources.—Primary studies, review articles, and commentaries were reviewed.

Conclusions.—While there is evidence both for and against primary HPV testing, there are a growing number of countries adopting the practice. It would be worthwhile to be informed and prepared for such a change in the United States as well.


A BRIEF HISTORY OF CERVICAL CANCER SCREENING

In 1941, the first peer-reviewed article on the use of cervicovaginal smears as a screening method for cervical cancer was published by Drs George Papanicolaou and Herbert Traut of Weill Medical College.¹ This had been preceded by more than a decade of work by Dr Papanicolaou.² Over time and in conjunction with support from gynecologists, the Papanicolaou (Pap) test was widely implemented in both the United States and throughout the world. There has never been a randomized controlled trial to assess the Pap test; however, evidence of its efficacy comes from population studies demonstrating that areas that implemented strong cervical cytology screening programs have shown a significant decrease in the incidence of cervical cancer relative to those that have not.³

Despite the introduction and establishment of the Pap test for screening, the etiology of cervical cancer was not identified for several more decades. In 1984, Boshart et al⁴ established the causal link between human papillomavirus (HPV) infection and cervical carcinogenesis, and it is now well acknowledged that persistent infection of the cervix with high-risk HPV (hrHPV) types is necessary but not sufficient for the development of cervical cancer. There are approximately 14 hrHPVs; types 16 and 18 are the most prevalent, and most studies indicate that these are associated with approximately 70% of cervical cancers worldwide.⁵ Many young women develop a hrHPV infection after becoming sexually active; however, in most women the infection is cleared with no intervention or clinical consequences.⁶

Pap tests when used alone for cervical cancer screening have certain recognized inherent limitations, including a fairly low sensitivity. Traditionally, this has been overcome by setting the screening interval at 1 year. With the introduction of HPV testing, the past almost 2 decades have been an interplay between advances in HPV research, US Food and Drug Administration (FDA) approval of HPV-related tests and indications, and a rapid series of guideline updates incorporating these into clinical practice.

The current cervical cytology terminology was codified in the 2001 Bethesda system,⁷ and in 2002 for the first time the guidelines for cervical cancer screening recognized the relevance of HPV to cervical cancer without actually recommending HPV testing.⁸ With the results of the ASCUS/LSIL Triage Study (ALTS), reflex hrHPV testing of atypical squamous cell of undetermined significance (ASCUS) Pap results to triage to colposcopy was offered as a viable alternative to Pap testing alone,⁹ and in 2003, the Hybrid Capture 2 HPV test (Digene, Gaithersburg, Maryland) was FDA approved for the indications of both reflex testing of women older than 21 years with ASCUS on cytology and as an adjunctive test for women aged 30 years or older.¹⁰ Management algorithms that incorporated both cytology and hrHPV testing in those 2 settings were published as interim guidelines in 2004¹¹ and fully accepted with the 2006 consensus guidelines.¹² The 2011 consensus
focused on age-appropriate screening strategies and included the use of cotesting with both cytology and hrHPV testing, screening at longer intervals than previously recommended, as well as management of the combined results. Finally, with the increasing evidence that persistent infection with HPV 16 and/or 18 confers a higher risk of cervical carcinogenesis, the 2012 update incorporated HPV genotyping into the algorithm, with positivity for HPV 16 and/or 18 leading directly to colposcopy. The trend throughout these updates and publications has been toward balancing the risk of developing cervical cancer with the risks associated with overtreatment; the age to initiate screening has moved progressively toward a later age, and the screening intervals have gotten longer.

The most recent significant event in cervical cancer screening was the April 2015 FDA approval of the Roche (Gaithersburg, MD) Cobas test for primary HPV screening for women older than 25 years, without concurrent Pap testing. This was based on the Addressing the Need for Advanced HPV Diagnostics (ATHENA) trial, and it was the anticipation of this FDA approval that led to the publication of the interim guidelines for primary HPV screening.

**INTERIM GUIDANCE**

The 2015 interim guidance for primary HPV screening concludes the following: (1) primary hrHPV testing for primary screening is at least as safe and effective as cytology; (2) primary hrHPV screening therefore can be considered as an alternative to current US cervical cancer screening methods; (3) the age to start primary hrHPV screening should be not before 25 years; and (4) the optimal screening interval should be no sooner than every 3 years. In the recommended algorithm, hrHPV testing is the primary screening test, and reflex testing is performed with a combination of genotyping and cytology. Women who test as hrHPV negative remain in the pool of routine screening. Women who are hrHPV positive for types 16 and/or 18 proceed directly to colposcopy, whereas those who are hrHPV positive for any of the 12 other high-risk types have reflex cytology; women with a Pap result of ASCUS or greater proceed to colposcopy, while a negative Pap finding is followed up in 12 months.

To reach this algorithm and these conclusions, representatives from the Society of Gynecologic Oncology, American Society for Colposcopy and Cervical Pathology, American College of Obstetrics and Gynecology, American Cancer Society, American Society of Cytopathology, College of American Pathologists, and the American Society for Clinical Pathology reviewed published data from several large studies, as well as the FDA registration data and expert opinion. These studies looked at results at study entry of either cytology and/or hrHPV testing and followed up patients according to different management algorithms to determine the test performance characteristics for cervical intraepithelial neoplasia 3 (CIN3+) and/or invasive carcinoma. The ATHENA trial included more than 42,000 women aged 25 to 93 years in the United States who were followed up for up to 3 years; the results of this trial led to the FDA approval of the Roche Cobas HPV test for primary HPV screening. Another study at Kaiser Permanente Northern California (Oakland) in the United States followed up more than 1 million women aged 30 to 64 years for a period of 5 years. Two studies were meta-analyses of multiple trials in Europe, including 7 studies with almost 25,000 women and 4 trials with more than 175,000 women, both followed up to 12 years. Studies followed different protocols. Some used liquid-based Pap tests, while others used conventional cytology. Human papillomavirus tests included the Roche Cobas, Digene Hybrid Capture 2, and GP5+/6+ polymerase chain reaction–based assays. Management algorithms varied according to the acceptable practice where studies were performed.

All studies found that a negative hrHPV test result had a lower cumulative incidence rate of CIN3+ than did cytology for follow-up periods of 3 and/or 5 years. Given that primary hrHPV screening shows either superior or equivalent effectiveness to the current methods of cervical cancer screening in the United States (cytology alone or cotesting), it was concluded that it can be considered as an alternative screening method. In the Kaiser Permanente study, the 3-year risk of CIN3+ following a negative hrHPV test result was lower than the 5-year risk following a negative cotest finding, as well as lower than the 3-year risk following a negative Pap test finding; therefore, primary hrHPV testing with a 3-year interval is at least as effective as 5-year cotesting. The A Randomised Trial In Screening to Improve Cytology (ARTISTIC) trial, included in one of the European meta-analyses, showed that cotesting does not improve significantly upon HPV testing alone with cytology triage; more than 95% of clinical utility in cotesting came from the HPV component, whether looking at an outcome of CIN 2, CIN 3, or invasive carcinoma.

The recommended optimal screening interval was derived from the fact that a number of European trials used 3-year intervals; and in the ATHENA trial, the cumulative incidence of CIN3+ during 3 years was less than 1%. These factors suggested that a minimum of 3 years is a safe screening interval, and there is essentially a lack of evidence to recommend either for or against anything longer than that.

Finally, the age to start primary hrHPV screening was determined as being not younger than 25 years. In the ATHENA trial, starting primary hrHPV screening at 25 years doubled the number of colposcopies but with a 53% greater detection of CIN3+ as compared to the same strategy starting at 30 years. There were, however, still concerns that even starting screening at 25 years may result in overtreatment, as progression to cancer at this age is uncommon.

**ARGUMENTS FOR AND AGAINST PRIMARY HPV SCREENING**

The debate over optimal cervical cancer screening currently rests on the comparison between primary HPV testing and cotesting, with screening by pure cytology no longer a consideration. Several arguments have been put forth for and against primary HPV testing, which examine the published study methodologies and data, assumptions underlying these studies, and practical issues. The published data considered for the interim guidance in support of primary HPV screening are fairly robust. Studies have included more than 1.2 million women in 6 countries: the United States, the Netherlands, Sweden, Italy, England, and Canada. Follow-up in these studies has ranged from 3 to 12 years. Despite different study designs, the studies have come to the same conclusions: primary HPV screening provides better and longer-lasting protection against CIN3+
than cytology or cotesting. Additional extended follow-up data from the Canadian Cervical Cancer Screening Trial (CCCaST) published since the interim guidance continue to support primary HPV screening.21

Inherent to any discussion on cervical cancer screening is a consideration of the oft-stated fundamental principle guiding trends in cervical cancer screening guidelines: the balance between benefits and harms. Advocates for primary HPV screening state the concept that excess screening (ie, more frequent screening per older/traditional models) can lead to overtreatment of clinically insignificant disease in the form of both extra procedures and extra cost.5,22 Yet, it has been pointed out that concurrent with the adoption of this paradigm, there has also been a shift toward accepting an increased risk, which is not often acknowledged in most discussions. In 2002, the degree of protection conferred by annual screening with cytology was considered acceptable, and over time and with the implementation of guidelines with longer intervals, the level of risk considered acceptable has increased. When modeled over large population numbers, percentages of risk that may seem low actually result in a significant increase in the numbers of potential authors. Who express these concerns believe that the risk level that different individuals would prefer should be a personal choice, and patients and physicians should be offered a “range of acceptable screening options.”22,23 While this argument was published before the interim guidance for primary HPV screening, the concept is still relevant. Austin24 states that the underlying assumption in the trend toward primary HPV screening—that HPV genomic material is found in almost 100% of cervical cancers—ignores data to the contrary and may be untrue. Some studies have demonstrated that 10% of cervical tissues in US tumor registries do not contain detectible HPV25 and that 37% of cervical adenocarcinomas around the world are HPV negative.26 Similarly, studies following up patients for an extended time have shown higher rates of baseline negative HPV results in patients with cervical cancer,27 a point that questions both the prevalence of HPV positivity in cervical cancers and the length of follow-up time in these studies used to support the interim guidance. If a significant percentage of cervical cancers are not causally related to an HPV infection or do not test HPV positive with current methods, a screening algorithm that keeps HPV-negative women in a general screening pool could miss clinically significant lesions. Yet, this concern does not seem to be borne out by the results of the multiple studies showing that a negative HPV test finding at entry has a lower cumulative incident risk of CIN3+ several years later.

Another concern raised is that most studies did not use invasive carcinoma as the true endpoint, and instead used a precursor (usually CIN3+, and sometimes CIN2+).24,26 This substitution of CIN3+ for invasive cervical cancer increases the statistical power of studies2 and is almost universally accepted; however, despite being considered a direct precursor to invasive carcinoma, many cases of CIN 3+ will resolve without developing into invasive carcinoma. Given the low prevalence of invasive cervical cancer, this is a practical issue that is difficult to overcome. One of the European meta-analyses did use invasive cervical carcinoma as the endpoint and showed that for the first 2.5 years, there was no difference in detection of invasive cervical cancer between HPV-based and cytology-based screening. After this period and for up to 6.5 years of follow-up, the cumulative incidence of invasive cervical carcinoma was significantly lower in the HPV-based arm. This is interpreted as 60% to 70% greater protection by primary HPV screening versus cytology.19

There are, however, modeling studies published subsequently to the interim guidelines that support cotesting rather than primary HPV testing. A Markov analysis performed by Felix et al29 modeled a screening strategy cotesting with primary HPV testing in which women were assumed to be screened once every 3 years. The hypothetical cohort contained 1 million women aged 30 to 70 years. The model predicted that screening with primary HPV testing could result in up to 2141 more cases of invasive cervical carcinoma and 2041 deaths, compared to cotesting. It is, admittedly, difficult to reconcile this model with the data supporting primary HPV testing.27 Another argument against the data supporting primary HPV testing is that many of the European trials used conventional smears, not liquid-based preparations.24 Moreover, in all of the trials and meta-analyses, there were differences not only in the type of Pap preparation, but also in the HPV tests, and the management algorithms followed subsequent to initial screening. The strength of these studies is that despite the different methods and protocols, multiple trials achieved similar results.

In the discussion of primary HPV versus cotest screening, there are other issues to consider aside from comparisons of test characteristics, including whether the Pap test has clinical utility besides the detection of HPV-related cancers, the effect on the cytotechnology workforce, and the difficulty of transitioning between algorithms for all parties involved.

In assessing data on performance characteristics of the Pap test pertaining to the detection or prediction of cervical cancer precursors, consideration of any other information the Pap can provide is lost. Pap tests can detect cancers other than cervical, most notably endometrial. They can also diagnose infectious organisms such as Candida organisms, Trichomonas organisms, and herpesvirus. Although not generally done anymore, vaginal Pap smears historically were used to assess a vaginal maturation index. One could argue that in a test designed as a screening tool, these are incidental findings and there are better tests for each of these entities. Regardless, some clinicians are simply used to their particular practice pattern and are resistant to change.

There is no doubt that primary HPV testing would have a profound effect on the field of cytotechnology. Cytotechnologists have adapted to many changes in the past few decades, including the transition from conventional smears to liquid-based Pap tests, automated imaging, the addition of HPV testing to screening algorithms, and HPV vaccines. With each new set of guidelines there have been longer intervals between cervical cancer screening events, with a concomitant decrease in the number of Pap tests to be screened. There is a real concern that primary HPV testing would lead to a further decrease in the number of Pap tests, further adversely affecting job security for cytotechnologists.30 These changes to the field are not new, and in 2008 the American Society of Cytopathology held a forum on Facing the Future of Cytopathology, which culminated in a white paper addressing, among other things, the changes affecting the cytotechnologist labor force.31 Cytotechnologists increasingly are assisting in the preparation of slides and adequacy assessments during fine-needle aspirations. Also in recognition of their skills in morphologic interpretation, there has been an industry trend to use the ability of
The transition to primary HPV testing has been a significant development in cervical cancer screening. However, the adoption of primary HPV testing faces several challenges, including the need for training cytotechnologists in areas such as analysis of immunohistochemistry, fluorescence in situ hybridization, and other molecular tests, as well as in performing assays such as HPV testing itself or cross-training in areas such as histology.

Cytotechnologist educational programs have adjusted their curricula accordingly, even while the number of schools has declined. Although the field of cytotechnology itself may be salvaged through evolution of cytotechnologists’ work assignments, it will never be what it was several decades ago. In fact, another consideration is whether the impact of the transition to primary HPV testing on the cytotechnology workforce ultimately would have a negative impact on the greater field of cytology. The effect of the trend toward primary HPV testing in areas besides patient care directly related to cervical cancer screening must be considered to prevent unintended consequences.

A very practical concern is the difficulty in transitioning between algorithms. It takes both time and effort to convince clinicians, pathologists, and cytotechnologists of the validity of an updated algorithm. Already in the past decade there have been several changes to the recommended cervical cancer screening algorithms, and these transitions are only making the current potential transition to yet another algorithm even more difficult. Furthermore, patients themselves are not always comfortable breaking longstanding habits. In one study by Silver et al., after the updated 2012 guidelines, patients were resistant to changing from annual to less frequent screening, and preferred cytology to HPV testing. While patients may not be the sole driving force behind the adoption of new guidelines, their resistance makes it more difficult to encourage a change for clinicians who are already resistant to it. That being said, this algorithm is actually much simpler than the 2012 cotesting algorithm, and some physicians may welcome that fact.

Further, although HPV testing is already offered by most laboratories, primary HPV testing requires additional considerations. Currently, the Roche Cobas HPV test is the only HPV test that is FDA approved for the indication of primary HPV testing. Secondly, since cytology and HPV testing are performed by different sections of a laboratory and potentially often reported under different laboratory testing are performed by different sections of a laboratory and potentially often reported under different laboratory systems, the United States does not. Thus, with only the benefit of published interim guidance, it is up to laboratories, clinicians, and even patients whether or not to make the transition. Patients can request primary HPV testing by their physicians, physicians can request primary HPV testing by laboratories, and laboratories can offer it. Until definitive guidelines and algorithms are published by the relevant professional organizations, different practices and laboratories will handle this differently and be in a state of transition.

There is compelling evidence to support the use of primary HPV testing, as well as a few unanswered questions. Regardless, a handful of countries worldwide have taken the leap and are moving away from cytology or cotesting and toward primary HPV screening. In the United States, while there is no unified movement, it would behoove cytologists to be prepared for discussions on the topic with their colleagues both in pathology and other fields related to cervical cancer screening.

References


CURRENT STATUS OF PRIMARY HPV TESTING FOR CERVICAL CANCER SCREENING

Where do we stand now? The United Kingdom began a pilot program for primary HPV primary screening in 2013, and the UK National Screening Committee recommended the adoption of primary HPV screening in January 2016. Australia and the Netherlands have approved switching to primary HPV screening in 2016. Northwest Pathologies of Bellingham, Washington, reportedly was the first to offer primary HPV testing in the United States, but data on the number of laboratories that offer primary HPV testing in the United States are not readily available.

While some of the countries that are moving toward adopting primary HPV screening have national health care systems, the United States does not. Thus, with only the benefit of published interim guidance, it is up to laboratories, clinicians, and even patients whether or not to make the transition. Patients can request primary HPV testing by their physicians, physicians can request primary HPV testing by laboratories, and laboratories can offer it. Until definitive guidelines and algorithms are published by the relevant professional organizations, different practices and laboratories will handle this differently and be in a state of transition.

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