Clinical Commentary

Use of primary high-risk human papillomavirus testing for cervical cancer screening: Interim clinical guidance ☆

Warner K. Huh [a,*], Kevin A. Ault [b], David Chelmow [c], Diane D. Davey [d], Robert A. Goulart [e], Francisco A.R. Garcia [f], Walter K. Kinney [g], L. Stewart Massad [h], Edward J. Mayeaux [i], Debbie Saslow [j], Mark Schiffman [k,1], Nicolas Wentzensen [k,1], Herschel W. Lawson [l], Mark H. Einstein [m]

[a] University of Alabama at Birmingham, Birmingham, AL, USA
[b] University of Kansas Medical Center, Kansas City, KS, USA
[c] Virginia Commonwealth University Medical Center, Richmond, VA, USA
[d] University of Central Florida, Orlando, FL, USA
[e] New England Pathology Associates, Springfield, MA, USA
[f] Pima County Health Department, Tucson, AZ, USA
[g] Kaiser Permanente, Sacramento, CA, USA
[h] Washington University School of Medicine, St. Louis, MO, USA
[i] University of South Carolina School of Medicine, Columbia, SC, USA
[j] American Cancer Society, Atlanta, GA, USA
[k] National Cancer Institute, Bethesda, MD, USA
[l] American Society of Colposcopy and Cervical Pathology, Frederick, MD, USA
[m] Albert Einstein College of Medicine, Bronx, NY, USA

H I G H L I G H T S

• This interim guidance provides information for healthcare providers who are interested in primary hrHPV testing for cervical cancer screening.
• Primary hrHPV screening can be considered as an alternative to current US cytology-based cervical cancer screening methods.
• The potential advantages and disadvantages of this strategy are reviewed and discussed.

A R T I C L E   I N F O

A B S T R A C T

In 2011, the American Cancer Society, the American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology updated screening guidelines for the early detection of cervical cancer and its precursors. Recommended screening strategies were cytology and cotesting (cytology in combination with hrHPV testing). These guidelines also addressed the use of hrHPV testing alone as a primary screening approach, which was not recommended for use at that time. There is now a growing body of evidence for screening with primary hrHPV testing, including a prospective US-based registration study. Thirteen experts including representatives from the Society of Gynecologic Oncology, American Society for Colposcopy and Cervical Pathology, American College of Obstetricians and Gynecologists, American Cancer Society, American Society of Cytopathology, College of American Pathologists, and the American Society for Clinical Pathology, convened to provide interim guidance for primary hrHPV screening. This guidance panel was specifically triggered by an application to the FDA for a currently marketed HPV test to be labeled for the additional indication of primary cervical cancer screening. Guidance was based on literature review and review of data from the FDA registration study, supplemented by expert opinion. This document aims to provide information for healthcare providers who are interested in primary hrHPV testing and an overview of the potential advantages and disadvantages of this strategy for screening as well as to highlight areas in need of further investigation.

© 2014 the Society of Gynecologic Oncology and the American Society for Colposcopy and Cervical Pathology. Published by Elsevier Inc. All rights reserved.

Introduction

It is well recognized that persistent infection of the uterine cervix with high-risk types of human papillomavirus (hrHPV) is required for the development of invasive cervical cancer [1]. While infection with hrHPV is common, especially in sexually active young women, most infections are transient and spontaneously clear without clinical consequences. However, some women develop persistent hrHPV infections and are at risk for cervical cancer and its precursors. Previously approved Food and Drug Administration (FDA) labeling for hrHPV testing included triage of equivocal cytology (i.e., atypical squamous cells of undetermined significance or ASC-US) and as an adjunct to cytology when screening women 30 years and older (cotesting). These two uses are widely recommended by numerous stakeholder societies and organizations, as well as the United States Preventive Services Task Force (USPSTF) [2]. Triage via identification of specific high-risk types of HPV, including types 16 and 18, is also an FDA approved use of hrHPV testing in selected settings. In April 2014, the FDA approved the modified labeling of an hrHPV assay to include primary hrHPV screening [3] for women 25 years and older.

hrHPV screening is highly sensitive, but specificity depends on subsequent evaluation strategies and screening frequencies. FDA approval does not include specific recommendations for applying hrHPV screening in the US. Clinical practice guidelines for primary hrHPV screening do not yet exist in the US. In 2011, the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology substantially updated screening guidelines for the early detection of cervical cancer and its precursors [4]. At that time, the guideline stated "in most clinical settings, women aged 30 years to 65 years should not be screened with hrHPV testing alone as an alternative to cotesting at 5-year intervals or cytology alone at 3-year intervals." Despite stating "most clinical settings", the guidelines did not suggest any settings in which use would be appropriate. This recommendation was primarily based on substantial concerns about the specificity of primary hrHPV screening and the potential harms such as excess colposcopy and treatment for non-neoplastic HPV lesions that can be detected by primary hrHPV screening [4]. Additional concerns included lack of a well-defined and evaluated strategy to manage hrHPV-positive women, inadequate information to define appropriate screening intervals for women who are hrHPV-negative, and lack of data on testing errors due to specimen inadequacy, cost-effectiveness, and adherence to implementation within the current US opportunistic screening setting. Furthermore, at the time of the screening guideline update, several screening studies had reported on only a single round of screening, limiting the evaluation of primary hrHPV screening over multiple rounds of screening. Since the screening guidelines were developed in 2011, several additional large studies have been published, including new primary screening data and updates on subsequent rounds of screening from previously published trials.

While these reports do not fully address all of the concerns raised in the 2011 screening guideline update, they substantially strengthen the evidence supporting primary hrHPV screening. They consistently demonstrate an improved sensitivity of primary hrHPV screening for detecting cervical cancer precursor lesions (cervical intraepithelial neoplasia grades 2 and 3 (CIN2 and CIN3)) compared to cytology alone [5–10]. Some of these trials reported that primary hrHPV screening continues to have a sensitivity advantage over cytology after multiple rounds of screening. Although the majority of these studies were conducted in Europe, a large prospectively-conducted US FDA registration trial of primary hrHPV screening with recently published end-of-study results [23] demonstrated improved sensitivity against CIN2 and CIN3 over cytology alone in a single round of screening and sheds light on the utility of various triage strategies for women who are hrHPV-positive.

This document provides guidance for the clinical use of primary hrHPV screening, an overview of the potential advantages and disadvantages of hrHPV testing for primary screening and a discussion of questions and concerns that still need further investigation.

Methods

An interim guidance panel was convened to review the recent evidence and address specific questions and concerns regarding using a hrHPV test for primary screening. The guidance panel was co-sponsored and funded by the Society of Gynecologic Oncology (SGO) and the American Society for Colposcopy and Cervical Pathology (ASCCP) and included thirteen experts that represented SGO, ASCCP, American College of Obstetricians and Gynecologists, American Cancer Society, American Society of Cytopathology, College of American Pathologists, and the American Society for Clinical Pathology. Financial conflicts of interest (both direct and indirect) were examined and reviewed by the Chair (WKH) and Co-Chair (MHE) of this panel and are fully disclosed in this document. Observers from the Centers for Disease Control and Prevention and the U.S. Food and Drug Administration (FDA) were invited as well. Members participated in conference calls and a face-to-face meeting in Atlanta, GA on February 17, 2014. In addition, panel members were invited to a scientific summary presentation provided by Roche Diagnostics of the Addressing the Need for Advanced HPV Diagnostics (ATHENA) trial including data and findings related to the primary hrHPV screening components of this trial. Panel members were given the opportunity to submit questions both before and after the discussion. Participation by Roche Diagnostic's staff and affiliated experts was limited to presentation of ATHENA data including answering specific questions regarding the ATHENA trial data from panel members.

The MEDLINE database was queried on January 14, 2014 for relevant English language papers using the search terms "Human Papillomavirus", "HPV", "Cervical Cancer", "Screening", and "Tests" after November 2011, when the ACS–ASCCP–ASCP Cervical Cancer Screening Guideline group met in Bethesda, MD. The review of abstracts yielded eleven papers that were reviewed by panel members [5–15]. In addition, significant papers published prior to November 2011 were evaluated. Each article was reviewed by at least 3 panel members. Members of the panel commented on the relevance of articles to this clinical update and how they should be considered in the guidance document. The contribution of several articles to the primary objectives of this guidance panel was limited due to the following characteristics: limited follow-up of the study population, management strategies that were not generalizable to the United States, and limited data on the number of colposcopies and other relevant outcomes.

At the panel meeting, members were asked to address two main questions: 1) Is hrHPV testing for primary screening as safe and effective as cytology-based screening? and 2) Can primary hrHPV screening be considered as an alternative to current US cervical cancer screening methods? Additional questions addressed by the group included comparisons between cotesting and primary hrHPV testing, management of women with positive and negative hrHPV tests, age of initiation of screening, and targeted areas of future research. All voting was web-based and anonymous, with two-thirds majority constituting agreement.

Similar to the 2011 screening guideline update, the interim guidance is based on several guiding assumptions:

- No cancer screening test has the ability to detect all cases of prevalent or incipient cervical cancer.
- Higher detection of CIN3 + at the baseline screening round and reduced detection of CIN3 + at subsequent screening rounds are considered as benefits.
- Increased number of colposcopies is considered a surrogate for harms of screening [17].

Interim guidance panel recommendations and discussion

Is hrHPV testing for primary screening as safe and effective as cytology-based screening?

Table 1
CIN3 + and cancer risks 3 and 5 years after negative hrHPV and cytology.

Author	Population/study	Age	N	Negative test at entry	3-year CIN3 +	5-year CIN3 +	3-year cancer[a]	5-year cancer[a]
Gage	Kaiser Permanente Northern California	30–64	1,011,092[b]	HPV	0.07	0.14	0.011	0.017
				Cytology	0.19	0.31	0.02	0.031
Wright	ATHENA	25–93	42,209[c]	HPV	0.34			
				Cytology	0.78			
Ronco	4 European trials	20–64	176,464[d]	HPV			0.0046	0.0087
				Cytology			0.0154	0.036
Dillner	7 European studies	20 +	24,295[d]	HPV	0.12	0.25		
				Cytology	0.51	0.83		

The Swedish study (Swedescreen) is included in both the analyses by Ronco and Dillner.
  [a] 3.5 and 5.5 years in the analysis by Ronco et al.
  [b] Restricted to HPV-negative or cytology-negative women.
  [c] All women; only 2.8% of 31,548 HPV-negative and HPV-negative women were referred to colposcopy and followed up for disease; results from sample are weighted back to full population.
  [d] All women.

A negative hrHPV test provides greater reassurance of low CIN3 + risk than a negative cytology result.

Several large trials have evaluated the performance of primary hrHPV screening (Table 1). Dillner et al. combined follow-up data from several European screening trials to compare the risk of CIN3 + in women testing negative for cytology, hrHPV, or both. In a pooled analysis of five studies, the 3-year cumulative incidence rate (CIR) of CIN3 + in women with a negative cytology was 0.5% compared to 0.11% for women who were hrHPV negative [16]. A similar reduction was seen in the Netherlands VUSA-Screen study that was not included in the pooled analysis by Dillner et al. [6] A somewhat smaller, but nevertheless statistically significant difference was seen in the U.K. trial of Kitchener et al. after 6 years of follow-up and three rounds of screening [17]. In agreement with these clinical trials, Katki et al. reported risk estimates from over 300,000 women undergoing cotesting at Kaiser Permanente Northern California showing significantly lower 3-year risk in hrHPV-negative women compared to cytology-negative women [18].

A 2014 publication by Ronco et al. analyzed follow-up data of women from four previously published randomized controlled screening trials of hrHPV-based screening including the NTCC (Italy), ARTISTIC (United Kingdom), Swedescreen (Sweden), and POBASCAM (Netherlands). Over 176,000 women were followed in the four studies. The studies used either liquid based or conventional cytology and either a clinically validated PCR assay or Hybrid Capture 2 testing (Qiagen, Gaithersburg, MD) to detect hrHPV [5]. HPV-based screening included hrHPV testing alone in one part of one study and co-testing in all of the others. It is important to recognize that these studies were not specifically designed to test primary hrHPV screening. While no difference in cancer detection between study arms was seen in the first 2.5 years, after extended follow-up (median: 6.5 years), the incidence of invasive cervical cancer was significantly lower in women initially screened with hrHPV based testing compared to those screened with cytology alone (RR: 0.45, 95% CI: 0.25–0.81). Of note, these results were primarily driven by the Italian and Dutch trials; no significant difference in cancer rates was observed in the Swedish and UK trials. As expected given the known limitations of cytology for the identification of glandular lesions, there was a more pronounced benefit of hrHPV-based testing for detection of adenocarcinoma compared to squamous cell carcinoma with hrHPV-based screening with a pooled rate ratio of 0.31 (95% CI: 0.14–0.69) and 0.78 (95% CI: 0.49–1.25) for adenocarcinoma and squamous cell carcinoma, respectively.

In the ATHENA trial, there was a substantially lower 3-year CIR of CIN3 and cancer (CIN3 +) in women 25 years and older who were hrHPV-negative at enrollment (0.34%; 95% CI: 0.10–0.65) compared to women who were cytology-negative at enrollment (0.78%; 95% CI: 0.53–1.09). For comparison, among women who were both cytology and hrHPV (cotest) negative at enrollment, the 3-year cumulative incidence risk of CIN3 + was 0.30% (95% CI: 0.05–0.62). ATHENA was not powered to show differences in cancer detection between the different screening strategies and did not follow women beyond three years. While primary hrHPV screening detected approximately 50% more CIN3 + compared to cytology, it also resulted in approximately double the number of colposcopies compared to cytology.

Based on the data from European randomized controlled screening trials and the US-based data from the ATHENA trial, primary hrHPV screening is at least as effective as cytology, a currently accepted standard for screening in the US, at the same screening intervals.

Can primary hrHPV screening be considered as an alternative to current US cervical cancer screening methods?

Because of equivalent or superior effectiveness, primary hrHPV screening can be considered as an alternative to current US cytology-based cervical cancer screening methods. Cytology alone and cotesting remain the screening options specifically recommended in major guidelines.

Additional questions, recommendations, and discussion

How should one manage a positive hrHPV result?

Based on limited data, triage of hrHPV-positive women using a combination of genotyping for HPV 16 and 18 and reflex cytology for women positive for the 12 other hrHPV genotypes appears to be a reasonable approach to managing hrHPV-positive women.

Data from ATHENA and other studies support the use of genotyping for HPV 16 and 18 as a way to triage hrHPV-positive women. In ATHENA, the 3-year CIR of CIN3 + for HPV 16/18-positive women was 21.16% (95% CI: 18.39–24.01). In contrast, the CIR of CIN3 + was only 5.4% (95% CI: 4.5–6.4) after 3 years in women with HPV genotypes other than 16 and 18. These results were consistent with those from Rijkaart et al. from the Netherlands. They observed a 3-year CIN3 + CIR of 26.1% for women who were HPV 16/18-positive compared to 6.6% in women with hrHPV genotypes other than 16 and 18 [6].

A modeling study of triage options for hrHPV-positive women, based on the ATHENA trial, was reviewed by the guidance panel [23]. The post-hoc analysis compared triage strategies that utilized cytology alone or genotyping alone to a combination of genotyping and cytology as reflex tests. Specific parameters that were modeled included total CIN3 + detected, missed CIN3 + (through two rounds of screening), number of screening tests, and the number of colposcopies required to detect one case of CIN3 +. Triaging positive hrHPV tests with genotyping for 16/18 and reflex cytology for women positive for the 12 other hrHPV genotypes (Fig. 1) achieved an appropriate balance between safety and test utilization. The strategy missed few cases of CIN3 + and required reasonable numbers of screening tests and colposcopies compared to other strategies. Importantly, several studies evaluating triage strategies for hrHPV-positive women are currently ongoing. As more data become available from these studies, guidance regarding triage of hrHPV-positive women will be updated.
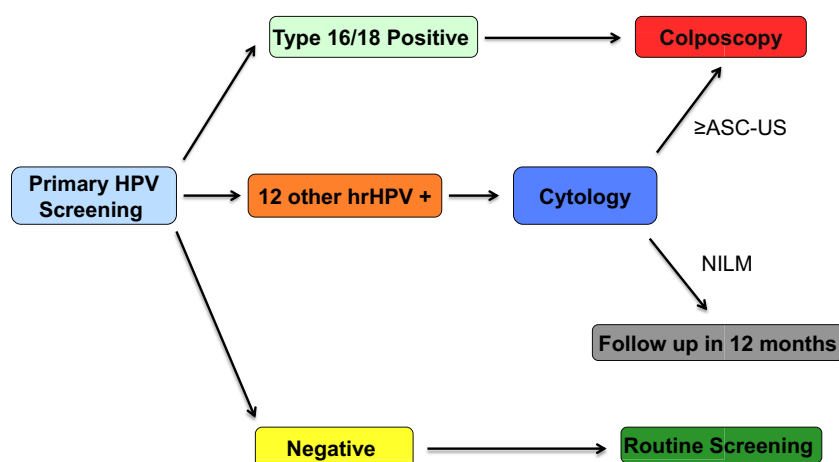
Fig. 1. Recommended primary HPV screening algorithm.

What is the optimal interval for primary hrHPV screening?

Re-screening after a negative primary hrHPV screen should occur *no sooner* than every 3 years.

Current screening interval recommendations for cervical cancer screening include every 3 years for cytology and every 5 years for cotesting. There are limited data to select the optimal screening interval for primary hrHPV screening. According to Ronco et al., a screening interval of at least 5 years for hrHPV screening is safer than cytology every 3 years. Three of the four European screening trials used for the Ronco, et al. analysis utilized 3-year screening intervals [5].

Follow-up data in the ATHENA trial was restricted to 3 years, and the cumulative incidence of CIN3 + over 3 years was less than 1%. Thus, screening should not occur at intervals shorter than 3 years among women with negative screening results. Although the rate is unlikely to increase sharply after 3 years, the panel believed that there are currently insufficient prospective U.S. data to recommend screening intervals beyond 3 years. Therefore, re-screening after a negative primary hrHPV screen should occur *no sooner* than every 3 years.

At what age should one initiate primary hrHPV screening?

Primary hrHPV screening should not be initiated prior to 25 years of age.

Current screening guidelines recommend initiation of screening at 21 years of age with cytology alone and initiation of cotesting at 30 years of age. In ATHENA, approximately 30% of CIN3 + cases were found in women between 25 and 29 years of age and 37% of cases were found in women 30–39 years of age [23,24]. More than half of women 25–29 years of age with CIN3 + were found to have normal cytology [23,24].

Primary hrHPV screening with genotyping for HPV 16 and 18 and reflex cytology for women with the 12 other hrHPV genotypes, starting at 25 years of age, doubled the number of colposcopies but resulted in a 54% greater detection of CIN3 + when compared to the same strategy starting at 30 years of age [23,24].

The panel had concerns regarding the potential harms of beginning primary hrHPV screening at age 25 years, particularly with regard to the number of colposcopies, despite the increased detection of disease. Progression to cancer is uncommon, and detection of most of the disease found in the 25–29 year age group can be safely deferred until age 30 and older. It is unclear that identification of these women with CIN3 + would translate into a meaningful reduction of cervical cancer. Transitioning from current guidelines for 21–24 year olds requires care. According to current guidelines, if a woman initiates screening at 21 years of age and is re-screened at age 24 years, the next time she would require screening would be at age 27. Primary hrHPV screening should begin 3 years after the last negative cytology and should not be performed only one or two years after a negative cytology result at 23 to 24 years of age.

How does the performance of primary hrHPV screening compare to cotesting?

In the largest comparison to date, Gage et al. estimated the 3- and 5-year risks of invasive cervical cancer following a negative primary hrHPV screen and negative cotest. The data are from approximately 1 million women screened at Kaiser Permanente Northern California. The analysis demonstrated that most of the reassurance of safety provided by a cotest is derived from the HPV test component. More specifically, the 3-year risk following an hrHPV-negative result was lower than the 5-year risks following a cytology-negative/hrHPV-negative cotest result (CIN3 +: 0.069% v. 0.11%, p < 0.0001; cancer: 0.011% v. 0.014%, p = 0.21) and of note, lower than the 3-year risks following a cytology-negative result (CIN3 +:0.069% v. 0.19%, p < 0.0001; cancer: 0.011% v. 0.020%, p < 0.0001). These results suggest that primary hrHPV testing with a negative result with a 3-year screening interval is at least as effective as five-year cotesting [19].

Other considerations and areas of future research

As with all new advances that enter clinical practice, the introduction of primary hrHPV screening raises a number of questions and concerns. Despite the improved sensitivity associated with primary hrHPV testing compared to cytology, clinicians should be aware that false negative results will continue to occur. Retrospective analyses of cervical cancer tissues have shown that a small proportion of invasive cancer cases will test negative using various hrHPV assays [20,21]. A recent study published by Hopenhayn et al. systematically evaluated 777 cervical cancer tissues from several US-based cancer registries and found carcinogenic HPV in 91% of the cases [22]. A proportion of the hrHPV-negative cases could not be distinguished from endometrial carcinomas based on the histology, suggesting that these may not be primary cervical cancers. While false-negative hrHPV test results cannot be ruled out, it is difficult to extrapolate the findings from these retrospective, tissue-based studies to performance of hrHPV testing in cervical samples in screening populations.

Specimen adequacy, appropriate internal controls, and the impact of potential interfering substances (e.g., lubricants) are also important considerations when applying primary hrHPV testing to a screening population. Assay internal controls may not always reflect adequate sampling and do not completely obviate the risk of false negatives without the added morphologic control offered by cotesting. Data in this area are limited and further research is necessary.

The 2011 ACS/ASCCP/ASCP Cervical Cancer Screening Guidelines stressed the importance of using FDA-approved tests that also met specific criteria for clinical performance. At present, there are four FDA-approved hrHPV assays that are commercially available, but only one of these assays is now FDA-approved specifically for primary screening. Since the performance characteristics vary somewhat among these

four FDA-approved assays, assumptions of comparability should not be made. As such, clinicians should not use an FDA-approved test without a specific primary hrHPV screening indication. Although this recommendation does restrict primary hrHPV screening to one assay at the present, it is expected that other assays will become rigorously validated and approved for the primary screening setting in the near future. Clinicians who wish to offer primary hrHPV screening to their patients are advised to inquire with their respective testing laboratories as to which hrHPV test is currently used and whether it is FDA-approved for primary screening.

Comparative effectiveness studies that consider projected lifetime number of screening tests, colposcopies, and follow-up visits are needed. Moreover, direct cost comparisons of primary hrHPV screening to cytology and cotesting are a priority. Further information is also needed regarding cancer risks over extended screening intervals such as 5 years (versus 3 years), the impact of multiple cumulative negative hrHPV tests on absolute risk of CIN3 +, and risk of CIN3 + among women who are HPV 16/18-positive yet colposcopy-negative. Concerns regarding harmonizing primary hrHPV screening algorithms with published screening, management, and treatment guidelines and the inherent confusion this alternate strategy might create for both patients and providers exist. Further investigation is also needed on understanding how women might transition in and out of different algorithms of cytology, cotesting, and primary hrHPV screening. Finally, there remain a number of questions with regard to adoption, implementation, and acceptance.

Conclusions

Primary hrHPV screening is an important scientific and clinical advance in cervical cancer screening since it offers better reassurance of low cancer risk compared to cytology-only screening conducted at the same interval. Primary hrHPV screening can be considered as an alternative to current US cytology-based cervical cancer screening approaches including cytology alone and cotesting. The use of HPV 16/18 genotyping and reflex cytology for women positive for the 12 other hrHPV genotypes achieves a reasonable balance of disease detection with the number of screening tests and colposcopies required to achieve that detection. It is expected that more data on triage options will be available soon that could lead to updated triage recommendations. Primary hrHPV screening at 25–29 years of age may lead to increased CIN3 detection, but the impact of increased number of colposcopies, integration with screening prior to age 25, and actual impact on cancer prevention need further investigation. While there continue to be numerous practical and research questions, primary hrHPV testing has the potential to further reduce morbidity and mortality of cervical cancer in the US. However, to achieve the maximum benefit of screening, we need to continue to identify women who are either unscreened or under-screened.

References

[1] Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999;189(1):12–9.

[2] Moyer VA, U.S.P.S.T.F. Screening for cervical cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2012;156(12):880–91 [W312].

[3] Wright Jr TC, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D, et al. 2006 consensus guidelines for the management of women with abnormal cervical screening tests. J Low Genit Tract Dis 2007;11(4):201–22.

[4] Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. CA Cancer J Clin 2012;62(3):147–72.

[5] Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJ, Arbyn M, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet 2014;383(9916):524–32.

[6] Rijkaart DC, Berkhof J, van Kemenade FJ, Coupe VM, Rozendaal L, Heideman DA, et al. HPV DNA testing in population-based cervical screening (VUSA-Screen study): results and implications. Br J Cancer 2012;106(5):975–81.

[7] Leinonen MK, Nieminen P, Lönnberg S, Malila N, Hakama M, Pokhrel A, et al. Detection rates of precancerous and cancerous cervical lesions within one screening round of primary human papillomavirus DNA testing: prospective randomised trial in Finland. BMJ 2012;345:e7789.

[8] Malila N, Leinonen M, Kotaniemi-Talonen L, Laurila P, Tarkkanen J, Hakama M. The HPV test has similar sensitivity but more overdiagnosis than the Pap test — a randomised health services study on cervical cancer screening in Finland. Int J Cancer 2013;132(9):2141–7.

[9] Gyllensten U, Gustavsson I, Lindell M, Wilander E. Primary high-risk HPV screening for cervical cancer in post-menopausal women. Gynecol Oncol 2012;125(2):343–5.

[10] Ogilvie GS, Krajden M, van Niekerk DJ, Martin RE, Ehlen TG, Ceballos K, et al. Primary cervical cancer screening with HPV testing compared with liquid-based cytology: results of round 1 of a randomised controlled trial — the HPV FOCAL Study. Br J Cancer 2012;107(12):1917–24.

[11] Ronco G, Giorgi-Rossi P, Carozzi F, Confortini M, Dalla Palma P, Del Mistro A, et al. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. Lancet Oncol 2010;11(3):249–57.

[12] Anttila A, Kotaniemi-Talonen L, Leinonen M, Hakama M, Laurila P, Tarkkanen J, et al. Rate of cervical cancer, severe intraepithelial neoplasia, and adenocarcinoma in situ in primary HPV DNA screening with cytology triage: randomised study within organised screening programme. BMJ 2010;340:c1804.

[13] Zhao FH, Lin MJ, Chen F, Hu SY, Zhang R, Belinson JL, et al. Performance of high-risk human papillomavirus DNA testing as a primary screen for cervical cancer: a pooled analysis of individual patient data from 17 population-based studies from China. Lancet Oncol 2010;11(12):1160–71.

[14] Petry KU, Luyten A, Scherbring S. Accuracy of colposcopy management to detect CIN3 and invasive cancer in women with abnormal screening tests: results from a primary HPV screening project from 2006 to 2011 in Wolfsburg, Germany. Gynecol Oncol 2013;128(2):282–7.

[15] Rijkaart DC, Berkhof J, van Kemenade FJ, Coupe VM, Hesselink AT, Rozendaal L, et al. Evaluation of 14 triage strategies for HPV DNA-positive women in population-based cervical screening. Int J Cancer 2012;130(3):602–10.

[16] Dillner J, Rebolj M, Birembaut P, Petry KU, Szarewski A, Munk C, et al. Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study. BMJ 2008;337:a1754.

[17] Kitchener HC, Gilham C, Sargent A, Bailey A, Albrow R, Roberts C, et al. A comparison of HPV DNA testing and liquid based cytology over three rounds of primary cervical screening: extended follow up in the ARTISTIC trial. Eur J Cancer 2011;47(6):864–7118.

[18] Katki HA, Kinney WK, Fetterman B, Lorey T, Poitras NE, Cheung L, et al. Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population-based study in routine clinical practice. Lancet Oncol 2011;12(7):663–72.

[19] Gage J, Katki HA, Schiffman M, Castle PE, Fetterman B, Poitras NE, et al. Reassurance against future risk of precancer and cancer conferred by a negative human papillomavirus test. J Natl Cancer Inst 2014;106(8):1–4.

[20] Liebrich C, Brummer O, Von Wasielewski R, Wegener G, Meijer C, Iftner T, et al. Primary cervical cancer truly negative for high-risk human papillomavirus is a rare but distinct entity that can affect virgins and young adolescents. Eur J Gynaecol Oncol 2009;30(1):45–8.

[21] Li N, Franceschi S, Howell-Jones R, Snijders PJ, Clifford GM. Human papillomavirus type distribution in 30,848 invasive cervical cancers worldwide: variation by geographical region, histological type and year of publication. Int J Cancer 2011;128(4):927–35.

[22] Hopenhayn C, Christian A, Christian WJ, Watson M, Unger ER, Lynch CF, et al. Prevalence of human papillomavirus types in invasive cervical cancers from 7 US cancer registries before vaccine introduction. J Low Genit Tract Dis 2014;18(2):182–9.

[23] 2014 meeting materials of the Food and Drug Administration (FDA) microbiology devices panel. http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/MicrobiologyDevicesPanel/ucm388531.htm; March 12, 2014. [Accessed July 2014].

[24] Wright TC, Stoler MH, Behrens CM, Sharma A, Zhang G, Wright TL. Primary cervical cancer screening with human papillomavirus: end of study results from the ATHENA study using HPV as the first-line screening test. Gynecol Oncol 2015;136(2):187–95.