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## Review

# What is the role of HPV typing in the United States now and in the next five years in a vaccinated population?

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## ABSTRACT

**Objective.** To review the current state of HPV typing of the vaccinated population in the United States and potential for typing of this population over the next 5 years.

**Methods.** An expert forum conducted on September 12–13, 2008, by the Society of Gynecologic Oncologists including 56 experts in cervical cancer and titled “Future strategies of cervical cancer prevention: what do we need to do now to prepare?”

**Results.** In principle, screening with HPV DNA testing for oncogenic genotypes followed by cytologic triage has attractive features that may serve well the screening needs of a post-vaccination era in the US. Particularly in light of the recent FDA approval of a HPV genotyping test, the group focused on how typing could be used to assist clinical decisions and whether its implementation would be cost-effective. Furthermore, it was agreed upon that HPV typing should not be used to determine who should be vaccinated against HPV. There was considerable discussion regarding the potential misuse and overuse of HPV typing in low risk women among healthcare providers.

**Conclusions.** As HPV typing technologies gain traction in the United States, its appropriate use will depend on the evolving natural history of the vaccinated cohort, continued educational efforts of healthcare providers, and most importantly, creating an integrated approach to cervical cancer prevention that will lead to a greater decrease in the incidence of cervical disease in the US while allowing for cost equipoise.

On September 12–13, 2008, the Society of Gynecologic Oncologists (SGO) convened a symposium of 56 cervical cancer experts titled “Future strategies of cervical cancer prevention: what do we need to do now to prepare?” to discuss evidence-based strategies in cervical cancer prevention and control, including HPV vaccination. This paper is the second in a series of manuscripts which highlight concepts, information, obstacles and approaches discussed during the Forum’s sessions and focuses on the current state of HPV typing of the vaccinated population in the United States and typing of this population over the next 5 years.

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## Introduction

Molecular testing for DNA of high-risk genotypes of human papillomavirus (HPV), the necessary cause of cervical cancer, has

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become an integral part of algorithms for management of equivocal cytology in the screening of women for precancerous cervical lesions. HPV natural history studies have shown that infection with oncogenic, high-risk HPV types is associated with progression to cervical disease and that a persistent infection is a strong predictor of the development of high grade precancerous lesions and cancer of the cervix [1–3]. HPV DNA testing has been implemented as an adjunct to cytology screening in females aged 30 years and older [4]. In conjunction with Papanicolaou (Pap) testing, HPV testing not only improves the sensitivity and negative predictive value of screening but provides the reassurance of extended intervals between screening tests. Reflex HPV testing is also cost-effective in the detection of high grade lesions in women with equivocal cytologic abnormalities, when used as recommended [5–7]. With the implementation and widespread use of HPV vaccines targeting the most common oncogenic HPV types (HPV 16/18), the burden of precancerous lesions is expected to diminish over time. This vaccine impact is likely to be further increased following incorporation into clinical practice of a second generation of prophylactic HPV vaccines that will likely extend the range of prevention of additional HPV genotypes.

It is clearly accepted that cervical cancer screening is necessary in the vaccine era and that guidelines put forth by the American Society for Colposcopy and Cervical Pathology (ASCCP) are evidence-based and practical. These guidelines rely largely on the use of cytology tests but, if available and depending on regulatory approval, HPV testing could become instrumental in screening for and in determining the future risk of high grade lesions. Questions also arise with regard to the use of more advanced technologies, such as HPV genotyping, and their clinical value. This review summarizes the content discussed in the September 2008 SGO Forum and considers the feedback obtained from the presenters, moderators, and general audience. Although this review does not establish a particular point of view, it does give suggestions and guidance to fellow clinicians with respect to the screening technologies that may become mainstream in the post-vaccination era and discusses future research needs. The following sections examine the potential for competing or complementary strategies that have attractive features in screening women who have been vaccinated.

#### Candidate strategy: HPV followed by Pap screening strategy

HPV types 16/18 account for 77% of cervical cancers and 54% of high grade lesions in the US [8]. HPV 18 is also associated with the development of adenocarcinoma, the second most common form of cervical cancer, which is often not easily detected by Pap tests [9]. As successive cohorts of women are vaccinated, there will be a reduction in the prevalence of cytologic abnormalities. In the short term, and in settings where there is organized or opportunistic Pap testing, it is plausible to expect a reduction in the cases of atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesions (LSIL), and high grade intraepithelial lesions (HSIL), as well as the number of referrals for colposcopy [10]. Plausible estimates from meta-analyses of etiologic fraction studies suggest a reduction in LSILs by as much as 40% for those vaccinated against HPV types 16/18, and 50% for those protected against HPV types 6/11/16/18 [11]. These proportions are likely to further increase once the next generation of multivalent HPV vaccines is adopted in clinical practice. As an increasing proportion of the population is vaccinated against an increasing number of HPV types, the prevalence of cervical abnormalities will inevitably continue to decrease, which will adversely affect the positive predictive value (PPV) (a major driver of screening costs) of any screening test for cervical cancer. However, as an objective assay not prone to the vagaries of subjective interpretation, HPV testing is likely to suffer less from this effect than Pap cytology. The latter is based on the subjective assessment of abnormalities by a cytotechnician workforce that is used to seeing many abnormal smears during a day's workload. As the successive cohorts of

vaccinated women reach screening age, the very low abnormality rate may lead to an increase in human error due to the monotony of reading of negative smears. Consequently, with more false negative results, the already low sensitivity of the Pap test (relative to HPV) will further decline. Furthermore, a decline in specificity is also likely to occur because of a decrease in the relative proportion of squamous abnormalities including koilocytosis (signal) to inflammation and reactive atypias (noise) in most smears. This may lead to more false-positive results in overcalling benign abnormalities (noise), particularly if the cytotechnician is fearful of missing any relevant abnormalities due to the threat of malpractice litigation. As lesion prevalence continues to decrease over time, the compounded effects of losses in sensitivity and specificity of Pap cytology will exact further penalties on the PPV of this test if used as the sole primary screening test. Use of liquid-based cytology may offset some of the problems if combined with computerized optical instrumentation to recognize cellular abnormalities. However, because of the rarity of relevant lesions, the altered signal-to-noise ratio that is expected post-vaccination may require recalibration of the computer-assisted recognition algorithms. Therefore, the negative impact on the PPV can be expected even with heightened quality control and improved cytology systems.

Under this scenario, a more sensible strategy to screen for cervical cancer is to use a highly sensitive HPV DNA test as a first line screen and to take advantage of the well known high specificity of the Pap test as a second line triage in women who test HPV DNA positive; in essence a HPV followed by Pap triage schema. Despite its potential for much greater accuracy and efficiency in detecting existing high grade cervical lesions, the HPV/Pap triage paradigm has not yet been adopted for primary screening because of lack of long-term follow-up studies on the safety of extended screening intervals. However, a recent pooled analysis of European studies has shown that the risk of interval precancer in women with negative HPV DNA tests is, in fact, much lower than that conferred by a negative Pap test. In other words, a negative HPV DNA test provides more reassurance to a woman that she is at low risk for a true cervical cancer precursor lesion while she awaits the next screening opportunity [12]. This body of new evidence will assist policymakers in defining acceptable screening intervals based on HPV testing.

An additional rationale for using HPV testing as the primary screening test is the benefit it will bring in “enriching” the cytology case load with smears that have a high probability of containing relevant abnormalities. If instead of Pap cytology we assume that HPV DNA testing will serve as a primary screen, we may expect that in any group of HPV positive cases the prevalence of cytological abnormalities will be considerably greater, exceeding 20% or more. It has been shown in modeling studies [13–16] that cytology will have its highest PPV and thus greatest clinical utility if lesion prevalence can be maintained at a high level. This “enriched” cytology caseload is “artificially” created in women who are screened first with the HPV test and then triaged by cytology. Under these conditions, it is also expected that the screening work conditions will be substantially improved, as the cytotechnician will be fully aware that the Pap smears to be read have been “flagged” as originating from women who are HPV positive and are thus more likely to have a lesion. This in turn will make for less tedious work in sifting through multiple normal Pap tests and improve accuracy in identifying clinically-relevant lesions. Moreover, if HPV testing alone is used for primary screen, there will be a substantial reduction in smear reading workload for cytotechnicians. This, in addition to reducing costs, will improve the attention and thoroughness with which each smear will be read. Another major advantage of using HPV testing as the primary screen is the opportunity for extended screening intervals compared with a cytology-centered screening program, which inevitably will help with cost-containment. The safety afforded by a negative HPV test result after even up to 4 years is equivalent to that of a negative Pap test result after 1 year, in terms of the cumulative

risk of high grade lesions [12]. However, even in a mostly vaccinated cohort of women who have been vaccinated against HPV 16/18 vaccine, it would not be prudent to space intervals for a Pap-based program (beyond what is currently recommend by the American College of Obstetricians and Gynecologists [17]) because the lesions that are caused by oncogenic HPV types other than those covered by the vaccines will continue to occur. On the other hand, this requirement would not exist for HPV testing because lesions caused by any HR-HPVs would be detectable by any of the approved HPV tests [18].

The HPV/Pap triage strategy for cervical cancer screening can also play an important role in post-HPV vaccination surveillance with the creation and linkage of vaccination and screening databases. This allows an efficient and low-cost strategy to monitor long-term protection among vaccinated women while providing a cervical cancer screening service to the population. Other advantages of this approach are the improved screening efficacy relative to cytology in detecting glandular lesions and the opportunity to use self-collected samples to increase the screening coverage of women in remote areas, such as aboriginal populations.

A recently published trial from Finland has demonstrated the advantage of the HPV followed by Pap algorithm and may represent the best screening strategy for the vaccination era [19]. A randomized controlled trial in Canada is underway to address this screening approach as well.

#### How does HPV genotyping fit into current us cervical cancer screening and guidelines?

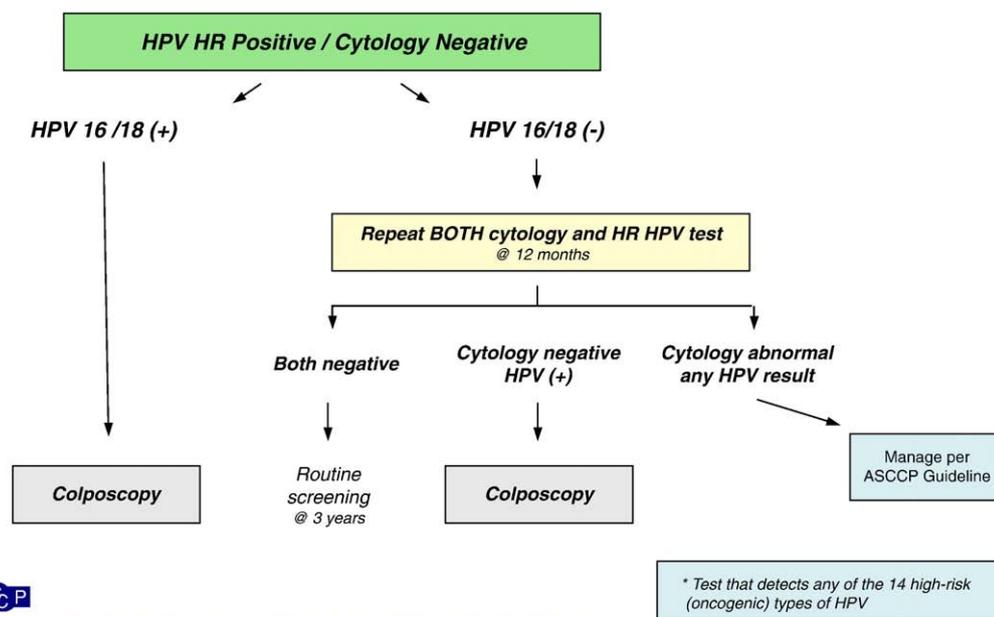
As discussed above, the inevitable loss in the PPV of cytology suggests a need to rely on molecular markers of HPV infection and technologies, such as HPV genotyping. Genotyping for specific oncogenic HPV types has also been shown to increase the PPV and specificity in predicting CIN2/3 and carcinoma in women with ASCUS and LSIL, thus possibly tailoring clinical management of these women [20,21]. A HPV 16/18 specific DNA test should be considered for specific cohorts. For instance, until a generation of females is vaccinated, a HPV DNA type specific test may be considered in the future as a co-test for females aged

21 to 29 years of age; however, this will require further study and validation. Also, due to the increased risk of HPV 16/18 ASCUS and LSIL progressing to a high grade lesion [22,23], HPV 16/18-specific genotyping and co-testing may be considered for LSIL triage. In the vaccine era, HPV testing may be considered useful for assessing the prevalence of specific HPV types and to determine genotype unmasking (i.e., an increase in prevalence of non-vaccine HPV types) in registries and population-based studies. In vaccinated women, type specific testing can also allow for easier assessment of persistent HPV infection and assess their contribution to the development of cervical intraepithelial neoplasia [CIN].

Women who test positive for specific oncogenic HPV types are considered to be at a higher risk for developing cervical disease. For women identified as HPV DNA positive with negative cytology, there is still a considerable risk of developing CIN 2+ [22,23]. In such cases, HPV genotyping could be useful for triage as a HPV 16/18 negative test should allow a safe conservative interval of screening used. Recently this guideline has been offered as a potential strategy by the ASCCP [24]. However, implementation of HPV 16/18 genotyping as part of testing could lead to increased anxiety and overtreatment in women who are positive for high-risk HPV DNA yet only transiently infected. Also, an additional test available for clinical use can add considerable confusion to already complicated guidelines and potentially a considerable amount of over-testing in some women who are at little risk for cervical neoplasia.

On March 12, 2009, the FDA approved the first HPV 16 and 18 genotyping test under the trade name Cervista (Hologic, Marlborough, MA). This test is currently approved for the following indications: 1) in women 30 years and older the Cervista HPV 16/18 test can be used adjunctively with the Cervista HPV HR™ test in combination with cervical cytology to assess the presence or absence of high-risk HPV types 16 and 18 and 2) to be used adjunctively with the Cervista HPV HR test in patients with atypical squamous cells of undetermined significance (ASCUS) cervical cytology results, to assess the presence or absence of high-risk HPV types 16 and 18 [25]. The ASCCP has recently released recommendations on the use of this assay (Fig. 1). These guidelines suggest that in women 30 years or older

#### Use of HPV Genotyping to Manage HPV HR \* Positive / Cytology Negative Women 30 Years and Older



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Fig. 1. American Society of Colposcopy and Cervical Pathology (ASCCP) HPV genotyping algorithm (management of HPV HR positive/cytology negative women 30 years and older).

with normal cytology and positive high-risk HPV results (i.e., co-testing approach), a subsequent HPV 16/18 genotyping test should be considered at that time. With a positive HPV 16/18 result, women should be referred to colposcopy. In women with a negative HPV 16/18 result, it is suggested that cytology and the high-risk HPV test be repeated in 12 months [24].

### HPV testing should not be used to help decide whether or not to vaccinate

Its attractive features notwithstanding, HPV genotyping should not be considered a tool for determining whether or not a woman should be vaccinated against HPV. The reasons for this position are clear. A positive or negative test result does not provide the certainty required in ascertaining previous exposure to specific HPV types and the potential for protection by vaccination. Furthermore, it will add an unnecessary cost on an already costly preventive health measure. Also, a negative HPV test may occur not only in women without exposure to HPV infection but also in those who have previously been exposed to HPV but were able to clear their infection. As a preventive health measure, guidelines are meant to help the most, while harming few. As such, recommendations are simple and should be based on age alone. Adding HPV typing for prescreening only adds cost without offering direction on clinical benefit and should be discouraged, particularly since it could create an inappropriate barrier to vaccination. Professional guidelines should be clear in this regard because of the potential for misperception by the biotechnology sector that an entirely new market niche for HPV testing now exists. Pre-vaccination HPV testing may lead to emotional distress and will inevitably cause confusion to many women.

### Conclusions

Discussion at this session of the SGO's "Future strategies of cervical cancer prevention: what do we need to do now to prepare?" meeting generated the greatest polarity in thinking as well as opportunities for considerable discussion regarding the future of HPV technologies in the vaccine era. The lack of an FDA-approved HPV test for genotyping (at the time of the symposium) fueled dissent over the future role of HPV genotyping, which has changed since the meeting. When HPV genotyping was supported, it seemed important to question how the information acquired would impact clinical decisions, and whether this clinical implementation would be cost-effective as well. The anticipated loss of PPV with cytology in a vaccinated cohort underscores the importance of molecular markers such as HPV genotyping. It was also agreed that HPV genotyping should not be used to determine who to vaccinate against HPV, particularly as it would not offer additional clinical decision-making benefit and may deter what currently is in the US, opportunistic vaccine uptake. HPV genotyping could create misuse and potentially overuse in low risk women among healthcare providers and therefore, parallel emphasis should be placed on education.

There will be a need to develop screening algorithms with HPV genotyping which take into account the natural history of HPV, (i.e., transient vs. persistent infection, and progression to cervical disease.) There may also be a need to tailor such guidelines to specific age groups since the use of molecular markers or a high-risk HPV test to predict risk of cervical cancer precancerous lesions may vary with age. For future research, focus should be placed on registries of vaccinated populations, such that findings from prospective longitudinal studies are linked to decision-making tools to estimate the risk of developing cervical cancer. It may also be helpful to clearly determine the contribution of other high-risk types to the development of precancerous lesions, and to obtain more data on screening intervals and follow-up in large prospective cohorts. Alternate screening tests should be evaluated as well their usefulness when combined with imaging and automated systems. Considerable emphasis should be

placed on educational and risk assessment tools as well as education regarding current recommendations and guidelines. This will continue to create an integrated approach to cervical cancer prevention that will lead to a greater decrease in the incidence of cervical disease in the US while creating cost equipoise.

### Conflict of interest statement

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The authors for this manuscript disclose the following conflicts of interest:

Warner K. Huh: consultant for GSK, Merck, Hologic, Roche, and Helix Biopharma; speaker for Merck; and contracted research GSK, Merck, and Roche  
 Thomas J. Herzog: honorary for educational programs, Merck, Hologic, and GSK  
 Mark H. Einstein: consultant, speaker and advisor for Merck, GSK, Roche, Hologic, and Qiagen; contracted research through Hologic, Roche, GSK, and Merck (Dr. Einstein does not receive direct honorarium from these companies.)  
 Eduardo L. Franco: consultant for GSK, Merck, Roche, Gen-Probe, Qiagen, Ikonisys, and Cytyc

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- [25] Cervista Package Insert. <http://www.cervista.com>.