

New diagnostic tests for HPV in the developed and the developing world

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Human papillomavirus (HPV) infection is one of the most common sexually transmitted infections worldwide, affecting up to 80% of women by the age of 50.¹ Increasing evidence shows that men have a similar risk of HPV infection.² There are over 100 different types of HPV; about 40 of these affect the anogenital area. Certain types such as HPV type 16 and type 18 cause the majority of cervical cancers worldwide. These and other “high-risk” or oncogenic types act in contrast to the “low-risk” or non-oncogenic HPV types such as HPV types 6 and 11, which cause the majority of non-cancerous lesions such as anogenital warts. HPV-associated malignancies include most cervical cancers, the most common cancer in women in many developing countries, as well as some vulvar and vaginal cancers.³ HPV is also an important cause of other anogenital cancers including most anal and a proportion of head and neck cancers in both men and women.^{4,5}

Screening strategies have traditionally relied on the detection and treatment of pre-cancer lesions — not infection. In general, in communities able to implement systematic cervical Papanicolaou (Pap) screening, this has been a very successful approach. Combining data from national programs in eight countries, the International Agency for Research on Cancer (IARC) described a 90% reduction in cervical-cancer incidence if periodic screening of the entire adult female population is undertaken.⁶ In most of the developing world, however, the cost of cervical-cancer screening infrastructure is prohibitive. Recent research has focused on the utility of alternative screening approaches in resource-poor environments including the use of rapid HPV testing to triage high-risk women.⁷ Molecular identification of HPV has been used to increase the interval of Pap screening in the United States or to triage women with atypical squamous cells of undetermined significance (ASCUS) on Pap testing to immediate colposcopy or to repeat Pap at a one year’s interval instead of at three to six months (see Figure 1 online).⁸ Note that recent guidelines for Pap screening in adolescents now de-emphasize HPV testing (see Figure 2 online), given the high-prevalence of high-risk HPV types and observation that most of these infections are transient.^{9,10}

The development and licensure of the HPV bivalent (types 16, 18)¹¹ [not FDA cleared in the United States currently] and quadrivalent (types 6, 11, 16, 18) prophylactic vaccines¹² has led to further discussions regarding the clinical use of type-specific HPV-testing to identify already HPV-exposed women who may benefit from vaccine.¹³ Currently, the Centers for Disease Control and Prevention (CDC)/Advisory Committee on Immunization Practices (ACIP) and the American College of Obstetricians and Gynecologists (ACOG) guidelines *do not recommend routine HPV screening prior to the administration of the vaccine for females aged 9 to 26 years old*.¹⁴ Adjunctive molecular tests are increasingly being used to risk stratify women with abnormal biopsies.

We will review some testing methodologies currently used in the field and discuss the potential place in screening algorithms for new and existing HPV-diagnostic tests. Although there has been much headway in developing screening and treatment guidelines for other HPV-associated malignancies, such as anal cancer,^{15,16} this article will focus on cervical cancer.

Diagnostic tests for HPV disease

Traditionally, these tests have been the focus of cervical-cancer screening programs in the developed world. These programs have been successful largely because cervical cancer has such a long pre-cancer state (typically, more than 10 years) and these pre-cancer states are treatable. The cornerstone of most cervical-cancer screening programs is the Pap test.¹⁷ The Pap test can be done in two ways; both methods use cells sampled from the cervix and the vagina using a brush or spatula. The conventional method is the Pap smear introduced in the United States in 1941. The sensitivity of the Pap test to detect high-grade cervical intraepithelial neoplasia (\geq CIN2) ranges from 44% to 99% and specificity from 91% to 98%.¹⁸ Providers place cells on a glass slide and chemically fix them in the office. In the newer thin-layer liquid preparations (e.g., ThinPrep; CYTYC, Boxborough, MA), providers suspend cells in liquid transport media, which is subsequently spun down and filtered in the laboratory and then placed on slides for the pathologist to review. Both methods have similar test characteristics.¹⁹ If an abnormal result is obtained on cytology (see Figure 1 online), colposcopy, together with topical chemicals, such as acetic acid and Lugol’s iodine, is used to identify lesions that might have contributed to the abnormal cells seen on cytology. Biopsies of these lesions permit the pathologist to confirm the cytologic diagnosis and set the stage for the treatment modality based on the findings. In resource-poor countries, visual inspection using acetic acid (in lieu of Pap testing) can be used by trained nurses to triage patients to colposcopy and biopsies as needed.²⁰

Diagnostic tests for HPV infection

Incorporation of testing for HPV infection in cervical-cancer screening programs has several potential roles both in the developed world and in resource-poor countries. As a primary modality, HPV testing is generally thought to be more sensitive than cytology for detecting cervical intraepithelial neoplasia. In one Canadian study of more than 10,000 women aged 30 to 69 years old, HPV testing as a primary-screening modality was compared to conventional cervical Pap testing. The sensitivity to detect biopsy proven \geq CIN2 lesions using HPV testing was higher compared with the sensitivity of Pap testing (95% vs. 55%). The corresponding specificity was similar (94% vs. 97%).²¹ These results support an increased future reliance on molecular HPV testing over traditional Pap testing, particularly in resource-poor environments where populations are infrequently screened. Currently, HPV testing in the developed world is incorporated in two ways in existing screening programs. The first is the use of HPV testing to triage women with ASCUS to immediate colposcopy if positive for high-risk HPV infection (see Figure 1 online); if negative for a high-risk HPV type, repeat Pap testing can be performed in one year instead of three to six months.⁸ The second scenario where HPV testing is recommended is in low-risk women over 30 years old. If found to have a negative Pap test and negative for a high-risk HPV type, then the interval can be increased from annual screening to every three years.¹⁸

Three principal methods exist in the laboratory to detect HPV: 1)

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direct probe methods (e.g., Southern transfer hybridization and *in situ* hybridization [ISH]); 2) signal amplification (e.g., hybrid capture second-generation [HC2] assay [QIAGEN, Gaithersburg, MD, USA]); and 3) target amplification (polymerase chain reaction [PCR] variants). Newer test development has focused on signal and target amplification. Of these methods, only HC2 is U.S. FDA cleared for use in HPV testing, and in the cervix only. HC2 is also approved for use in Europe (Conformité Européenne (CE) marked).

Signal amplification

Hybrid Capture HPV DNA assay (Digene, Gaithersburg, MD): The HC2 assay uses RNA probes specific for the identification of certain high-risk (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) or low-risk HPV types (6, 11, 42, 43, 44). These long RNA probes are separated into two testing cocktails based on whether high-risk or low-risk types are to be identified. First, the patient's specimen (as whole HPV DNA) is separately hybridized to each of the two testing cocktails. In each case, specific HPV DNA-RNA hybrids are formed. This is then added to a microtiter plate coated with antibodies specific to RNA-DNA hybrids so that the HPV DNA-RNA hybrids previously formed can be "captured" or immobilized on the plate. Immobilized hybrids are then bound to antibodies conjugated to alkaline phosphatase. Excess antibodies and non-hybridized probes are removed, and a chemiluminescent substrate is added. A luminometer is then used to detect the remaining immobilized hybrids. A semi-quantitative measure of the viral load can be obtained based on the intensity of the light emitted by the sample divided by the light emitted by a positive control (expressed as relative light units) since this is proportional to the quantity of target DNA in the patient's specimen. To reduce cost and time, often only high-risk probes are used in clinical evaluation and a result of positive or negative (but not the specific HPV type) for a high-risk group is provided.

CareHPV (QIAGEN, Gaithersburg, MD): This is a new test specifically developed for use in the developing world and broadly based on the HC2 assay. It is meant to be rapid (results in less than 2.5 hours in contrast to six hours with HC2), requires minimal infrastructure, and is anticipated to be inexpensive. The features that facilitate these differences include unique reagents in the patient-collection device that contains non-toxic surfactants that can quickly and directly solubilize cervical specimens without a requirement for prolonged mechanical agitation. In addition, microtiter plates in HC2 are replaced by magnetic beads, and temperature requirements are altered in some steps compared to HC2. In the first

comprehensive study evaluating careHPV, more than 2,500 women in Shanxi province in rural China were evaluated with the screening tests careHPV, HC2, and simple visual inspection with acetic acid (VIA) using a gold standard of colposcopy with biopsy. The sensitivity and specificity to detect high-grade CIN (CIN 2 and higher) in cervical specimens was 90% and 84% for careHPV, 97% and 86% for HC2, and 41% and 95% for VIA.⁷ This test has enormous potential for use in the developing world as it is specifically designed to be rapidly processed by inexperienced personnel under constraints of space and temperature while women wait for results (see Figure 2 online).

Target amplification

There are two principal approaches used in the detection of HPV by polymerase chain reaction (PCR): consensus PCR and type-specific PCR. Consensus primers such as PGM09/11 can generate a variety of primers that can amplify and identify a wide variety of HPV types typically in one reaction. Examples of other consensus primers used are GP5+/6+ and short PCR fragment (SPF). The result is whether there is HPV present or not, but not the specific HPV type. In contrast, type-specific PCR tests target-specific sequences of viral genes, which result in the amplification of a single HPV genotype. Therefore, multiple PCR reactions (one per type evaluated) must be carried out on a single specimen to determine which HPV type is present. Of these type-specific HPV tests, only the Roche Linear Array HPV genotype test has been developed for commercial use.

Line blot (Roche Molecular Systems, Alameda, CA): This is an L1 consensus primer-based PCR assay using PGM09/11 followed by a line blot assay. In the line blot assay, multiple probes are fixed as lines on a membrane strip. Reverse line blot hybridization detects 27 HPV genotypes (6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51 to 59, 66, 68, 73, 82, 83, 84). An expanded version of the test including detection of an additional 11 non-oncogenic types has also been used (additionally types 61, 62, 64, 67, 69 to 72, 81, 82, 89). This test is primarily used in the research setting and has been used in multiple previous research studies examining the molecular epidemiology of HPV.

Linear array (Roche Molecular Systems, Alameda, CA): The Linear Array HPV Genotyping Test is a commercial version of the line blot assay that has been submitted for review but not as yet U.S. FDA cleared. It detects 37 of the 38 types included in the line blot assay (except the non-oncogenic HPV type 57). One study compared the linear array to the HC2 test in 3,488 women with ASCUS on Pap testing at baseline. The sensitivity (93% vs. 93%), specificity (48%

vs. 51%), negative predictive value (99% vs. 99%), and positive predictive value (15% vs. 15%) of the baseline detection of high-risk HPV types (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52) to predict biopsy-proven cervical intraepithelial neoplasia (CIN) grade 3 at two years were similar when comparing linear array and HC2 testing, respectively.²²

INNO-LiPA HPV test (Innogenetics, Gent, Belgium): The INNO-LiPA HPV test is a reverse hybridization line probe assay (LiPA) which is approved for use in Europe (Conformité Européenne (CE) marked) but not U.S. FDA-cleared for specific HPV typing of clinical specimens. The LiPA test permits the use of amplimers generated by SPF as well as MY 09/11 primers. The test uses specific probes for HPV genotypes 6, 11, 16, 18, 31, 33 to 35, 39, 40, 42 to 45, 51 to 54, 56, 58, 59, 66, 68, 70, 74. Like the line blot and linear array assays, the probes are immobilized as parallel lines on membrane strips.

AMPLICOR (Roche Molecular Systems, Alameda, CA): The Roche AMPLICOR HPV test amplifies target DNA by PCR followed by nucleic-acid hybridization to various HPV types. AMPLICOR detects the same 13 high-risk HPV types detected by HC2 and also uses amplification of the β -globin gene as an internal measure of sam-

ple integrity and adequacy. The performance characteristics to determine the presence or absence of any high-risk HPV type (but not the specific HPV genotype) is similar to that of the HC2 test.²³ AMPLICOR, approved in Europe, is not currently U.S. FDA-cleared for clinical use.

Other selected diagnostic tests

P16-INK4A is a cyclin-dependent kinase inhibitor, which is overexpressed in cell lines where the HPV-induced E7 oncogenic protein product has inactivated the retinoblastoma protein RB. The RB protein normally arrests growth and induces cell apoptosis in response to DNA damage. If RB is inactivated, then unregulated cell growth may lead to malignant transformation. P16-INK4A can be identified by immunohistochemistry (CINtech P16-INK4A cytology kit [Dako A S, Glostrup, Denmark]) or enzyme-linked immunosorbent assay, making it a potential marker for risk stratification of HPV-positive women. In a study of 24,661 women in Italy, the sensitivity and specificity of P16-INK4A to detect CIN2 or greater was 88% and 61%, respectively. Using a strategy of HPV testing and P16-INK4A triage compared to cervical Pap tests in the 25- to 60-year-old age group, the relative sensitivity was 1.53. There was also no large increase in referrals

to colposcopy.²⁴ **HPV viral load** in a cervical sample (the amount of HPV DNA) can be determined by real-time PCR methods. Studies have been inconsistent in showing a prospective relationship between HPV viral load and the subsequent development of high-grade CIN.²⁵ For now, this is not a standard test that is used or recommended to risk stratify women with HPV-associated disease. **HPV DNA sequencing** is also a potential method to identify specific HPV types. Its use is limited by the inability to sequence multiple HPV genotypes.²⁶ Finally, because of poor standardization and reproducibility, HPV serology as a marker of past and/or cumulative exposure to HPV-associated disease is not widely used outside of clinical trials.

HPV is a common sexually transmitted infection that causes a large burden of disease including various anogenital cancers and external genital warts worldwide. In industrialized countries, screening for pre-cancer lesions using Pap tests has resulted in a substantial decrease in cervical-cancer incidence. The development of molecular-based diagnostics such as HC2 has led to screening strategies that incorporate cytology and HPV testing to risk-stratify women to less or more frequent screening. New evidence also suggests that HPV testing may be a viable alternative to traditional cytologic screening. The decrease in cervical cancer incidence in the West is in contrast to many developing countries where cervical cancer is one of the top two causes of cancer-related deaths in women. This difference in cervical-cancer incidence is largely thought to be due to the absence of cervical-cancer screening programs in many developing countries. HPV testing may have enormous impact in the developing world as a means to rapidly, more economically, and more easily risk stratify women who need further evaluation and treatment. The development and incorporation into screening of type-specific HPV testing as well as other molecular methods (i.e., P16-INK4A might further help to more specifically identify the smaller group of women who need intervention. Ultimately, the widespread uptake of currently available and next-generation HPV prophylactic vaccines will be the most effective measure to reduce the HPV-associated disease burden worldwide. □

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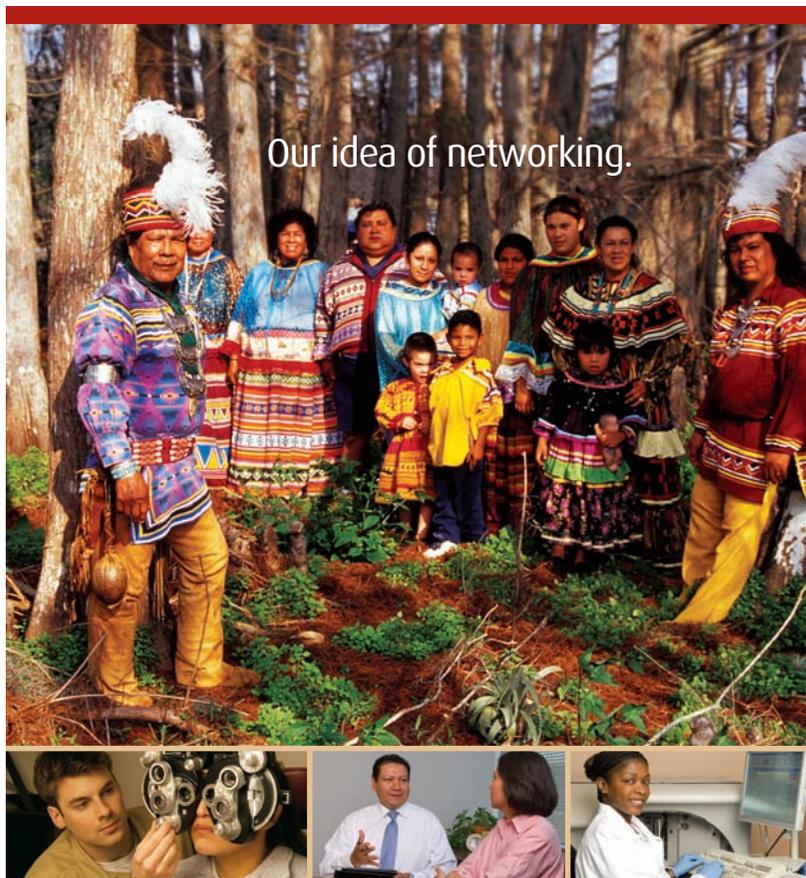
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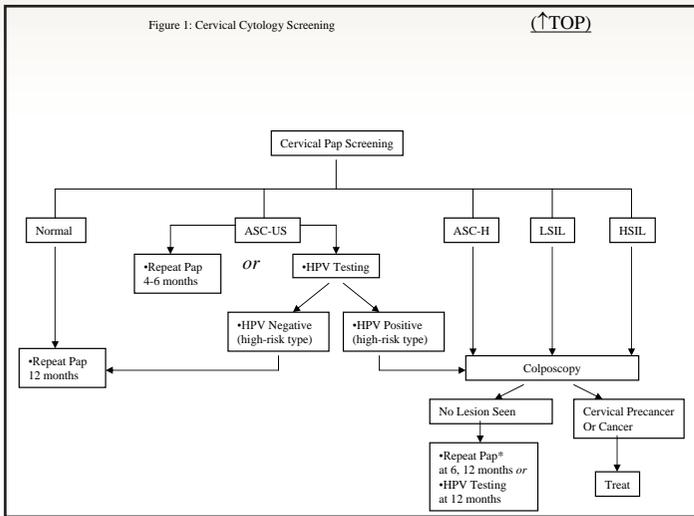


Figure 1. Cervical cytology screening

Key:

ASCUS: atypical squamous cells of undetermined significance
 ASC-H: atypical squamous cells: cannot exclude high-grade SIL
 LSIL: low-grade squamous intraepithelial lesions
 HSIL: high-grade squamous intraepithelial lesions

*If HSIL and no lesion seen on colposcopy, most guidelines recommend diagnostic excisional procedure.

Figure 2. Cervical cytology screening in adolescent women (under age 20)

Key:

ASCUS: atypical squamous cells of undetermined significance
 ASC-H: atypical squamous cells: cannot exclude high-grade SIL
 LSIL: low-grade squamous intraepithelial lesions
 HSIL: high-grade squamous intraepithelial lesions

*If HSIL and no lesion seen on colposcopy, most guidelines recommend diagnostic excisional procedure.

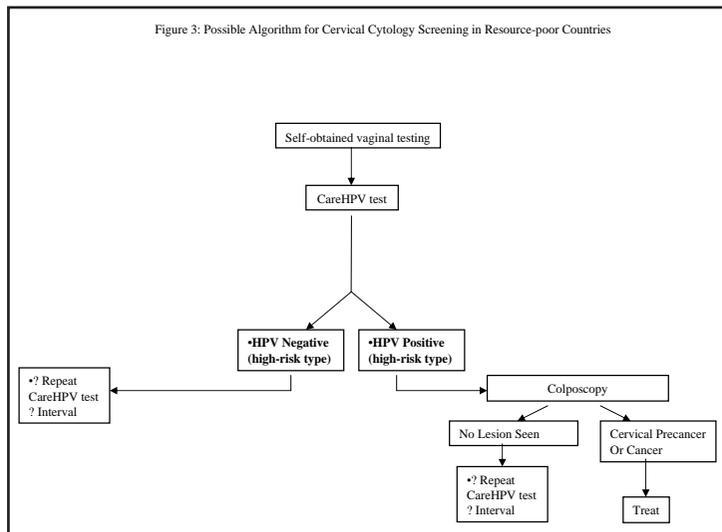
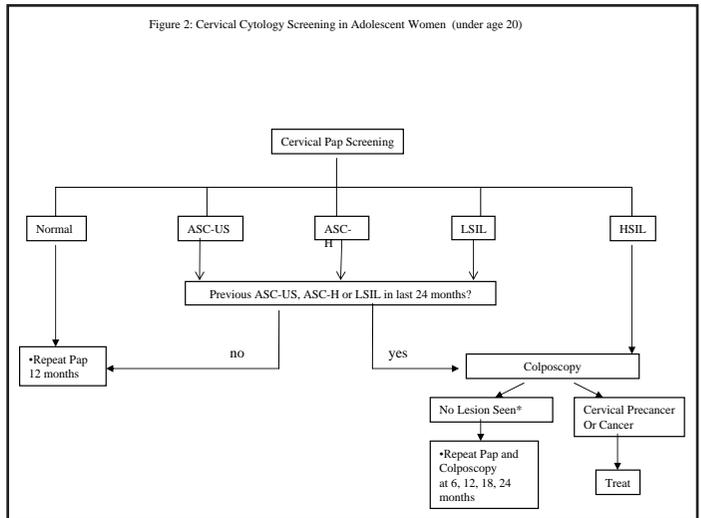


Figure 3. Possible algorithm for cervical cytology screening in resource-poor countries