INTRODUCTION

The California Technology Assessment Forum was requested to review the scientific evidence for the use of human papillomavirus (HPV) testing to screen for cervical cancer. This review was prompted by reports that there are new trials published since this topic was evaluated by the California Technology Assessment Forum in February, 2004.

BACKGROUND

Cervical cancer mortality has dramatically decreased by 70% largely due to the use of routine Papanicolau smear screening. In 2007, an estimated number of 11,150 cases will be diagnosed and an estimated 3,670 women will die from cervical cancer.

The Papanicolau smear (Pap smear) is the current method most commonly used to screen for cervical cancer. Cervical cytology (Pap smear) is used to predict the likelihood of abnormal histology. Histology as determined by biopsy is defined as normal, cervical intra-epithelial level grade 1 (CIN 1), cervical intra-epithelial level, grade 2 (CIN 2) carcinoma in situ (CIN 3 or invasive carcinoma. The current system for reporting cervical cytology in the United States is the Bethesda System that was most recently updated in 2001. The most common cytological findings are listed in Table 1.

Table 1: Classification of Cervical Squamous Cell Pathology

<table>
<thead>
<tr>
<th>Cytology (Papanicolau test)</th>
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<tbody>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>Atypical squamous cells – undetermined significance (ASC-US)</td>
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<tr>
<td>Atypical squamous cells- cannot exclude HSIL (ASC-H)</td>
</tr>
<tr>
<td>Low-grade squamous intra-epithelial lesion (LSIL)</td>
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The reason that cervical cancer screening has been so successful is that cervical cancer has a long preclinical phase. The preclinical or pre-invasive phase is at least ten years so that there are multiple opportunities to detect cervical abnormalities before they become invasive disease. Cervical cytology screening with Pap tests can identify pre-invasive disease which can then be treated to prevent progression to cervical cancer. In addition, the long pre-malignant phase allows repeated tests to reduce the impact of a single false-negative test. The main purpose of screening is to detect and destroy or remove pre-malignant lesions with a high likelihood of invasion (e.g., CIN 3, and in some cases CIN 2) and thus prevent potential progression to cervical cancer.

**Current Screening Recommendations:** Current screening recommendations are for women to have screening performed annually. After age 30, women who have had three or more consecutive normal tests can have screening performed every two to three years. If liquid based cytology is used, biennial screening is recommended by the American Cancer Society.

Cervical cancer screening with cytology has been very successful, but it is not a perfect test. Its sensitivity for detecting high-grade cervical intraepithelial neoplasia (CIN) has been estimated to be 53%-80%.\(^3\,^4\) Factors that limit test sensitivity include the lesion being small, the lesion being inaccessible, the lesion not being adequately sampled, only having a few abnormal cells on the slide, and inflammation or blood obscuring the cells.

**Natural history of cervical cancer:** Cervical cancer takes many years to develop. The time for an initial abnormality to become cervical cancer is approximately ten years. This long preclinical phase provides many opportunities for detecting abnormalities during screening. Many lesions thought to be precancerous (e.g., CIN 2) will regress spontaneously; the utility of finding these and certainly lower grade lesions (CIN 1) is less clear. In addition, regression is age dependent. For LSIL, approximately 65% will regress in three years among women aged 15 to 34, whereas only about ten percent will progress to invasive cancer\(^5\). Regression rates are somewhat lower
in older women. For women aged 35 and older, it has been estimated that 40% will regress in three years, whereas approximately 35% will progress to invasive cancer. For HSIL, overall, it has been estimated that 35% will regress over three years, whereas approximately 40% will progress to invasive cancer.\textsuperscript{5}

Many of the newer strategies for detection of cervical neoplasia lead to an increased detection of low-grade lesions such as CIN1. Given the high rates of regression of low-grade lesions, especially in young women, it is less important to detect these early lesions.

**HPV and cervical cancer:** The primary risk factor for cervical cancer is infection with oncogenic types of HPV. Since HPV infection is transmitted sexually, factors related to sexual behavior have been associated with increased cervical cancer risk including number of sexual partners and age of first intercourse. Cigarette smoking has also consistently been correlated with a two to four fold increased risk of cervical precancer and cancer and appears to decrease clearance of HPV infections\textsuperscript{6-8}. In the United States, the highest incidence and prevalence of HPV infection is in women under age 25.\textsuperscript{9}

Almost all squamous cell carcinoma of the cervix is caused by infection with one of 15-20 types of HPV\textsuperscript{10}. Studies have identified HPV DNA in 95-100% of squamous cell cancers of the cervix and in 75-95% of high grade CIN lesions.\textsuperscript{10-13} More than 100 types of HPV have been identified, but most are not associated with cervical cancer. The HPV types most strongly associated with cervical cancer are HPV16 and HPV18, which cause ~70% of all cervical cancer.\textsuperscript{14} Other HPV types that are considered high-risk include types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. The key viral genes leading to oncogenesis are E6 and E7. They encode proteins that bind to and inactivate tumor suppressor proteins (Rb and p53) in the host genome. Viruses with E6 and E7 proteins that do not inactivate these proteins are not associated with cervical cancer\textsuperscript{15}.

The natural history of HPV infection is complicated. Most women who become infected with HPV clear the infection and have no cytologic abnormalities. In a cohort study of women in college in the United States, 50% of HPV infections resolved within six months after testing positive, and only nine percent of the women continued to be positive for the same HPV type\textsuperscript{16}. Reported regression rates for prevalent cases include 70 percent after two years in a cohort of adolescents and college-age women\textsuperscript{17}, 68 percent over 14 months for women under 25, and 35 percent for women over 30\textsuperscript{18}. 
The presence of intact viral particles within the cell may cause a characteristic peri-nuclear clearing called koilocytosis. Koilocytosis is a defining characteristic of LSIL on cytology and CIN 1 on histology. Given the natural history of HPV infection, it is not surprising that the majority of cases of LSIL resolve without treatment. Development of cervical cancer almost always requires integration of the viral DNA into the host genome. Without integration, low-grade epithelial changes may be observed, but high-grade dysplasia and cancer are rarely observed. Viral integration usually disrupts an important viral gene E2. Thus, high-grade lesions usually do not shed viral particles and do not exhibit koilocytosis. It is estimated that about 60% of untreated high-grade lesions (HSIL, CIN 2 or 3) will progress to invasive cancer. The time from viral infection to oncogenesis is not known. Natural history studies suggest an orderly progression from infection to low grade epithelial changes to high grade changes over a period of many years.

**HPV testing- current indications:** Consensus guidelines published in 2007 recommend the use of HPV testing in the management of abnormal cervical cancer screening tests, in particular some women with ASC-US and LSIL (e.g., HPV testing for LSIL only in post-menopausal women; no HPV testing in women under age 21). Based on a large randomized clinical trial, it is recommended that most women who have ASC-US on liquid-based Pap testing be tested for HPV. Women with ASC-US (n=3488) were randomized to immediate colposcopy, repeat Pap testing, or HPV testing using the Hybrid Capture II method (HC II, see below). Women positive for HPV or HSIL on repeat Pap testing were sent for colposcopy. All women had colposcopy at 24 months. Using a positive HPV test as the threshold for colposcopy, 56% of women were referred and 92% of the women with CIN 3 were identified. Applying these results to theoretical cohorts of women, this approach was estimated to be as sensitive as repeat Pap testing with referral of patients with ASC-US or worse for colposcopy and fewer women required initial colposcopy. When liquid-based cytology is used for initial screening, “reflex” testing can be performed whereby the residual material from the AS-CUS smear can be used to test for oncogenic HPV types. Thus women do not need to return for an additional office visit for HPV testing.

**HPV testing options:** The two available tests for HPV testing are the Hybrid Capture II and a Polymerase Chain Reaction (PCR) test. HC II is currently the only commercially available, FDA-approved test in the United States. The FDA has not approved any PCR-based detection
Hybrid Capture II (HC II): The standard Hybrid Capture II test detects the presence of 13 types of HPV that have been associated with cervical cancer. There is an extended version that detects an additional five HPV types that are less prevalent and lower risk, but this HC II test has not been evaluated in the large trials that evaluated clinical outcomes. The high risk HPV test contains whole genomic RNA probes that detect HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 59, and 68. The probes bind complementary DNA from cervical cells (RNA-DNA complex = “hybrid”). The complexes are detected using an enzyme-linked chemiluminescent assay that uses signal amplification to achieve sensitive detection without DNA amplification. This reduces the risk of interference from materials present in the clinical preparation, which can be a problem for methods that depend on PCR target amplification. The recommended threshold for calling a test positive is 1 pg/ml, which corresponds to approximately 5000 HPV genomes per test well, based on extensive evaluation of the tradeoffs between sensitivity and specificity performed by the manufacturer. However, some authors also report their results using a threshold of 2 pg/ml, which decreases the sensitivity of the test in order to increase specificity, but this is an off-label use of the FDA-approved test and is not recommended. The test can be performed on residual cells from a liquid-based cytology specimen or from a specimen collected using a cervical brush placed in transport medium specifically for the HPV test.

Polymerase Chain Reaction: Other tests available for the detection of high-risk HPV types are based on PCR technology. They are highly sensitive for viral detection and can identify the specific viral type present as well as quantify the viral load, although viral load has not been shown to be clinically useful. These tests use enzymatic amplification of HPV DNA to allow the detection of very low levels of HPV infection. The test has excellent test characteristics in appropriately equipped and experienced laboratories. However, contamination with previously amplified material can lead to false positives and there is currently no standardization between laboratories. The most common PCR systems used in clinical studies are those based on the GP5+/6+ primers and the MY09/MY11 primers. Because of intellectual property issues, no PCR-based test for HPV has been developed commercially. This may change as soon as the Institut Pasteur has recently transferred its HPV intellectual property to F. Hoffmann-La Roche Ltd. Although it is not available in the United States, the PCR GP5+/6+ test is used in
other countries and was used in two of the recent trials of HPV testing in Europe\textsuperscript{26, 27}

\textbf{Summary:} The vast majority of cervical cancers occur in women who have never been screened or who have not been screened in the preceding five years\textsuperscript{28, 29}. Thus, the biggest impact on cervical cancer mortality could be obtained by ensuring that all women who are eligible for screening are regularly screened. However, new technologies for screening may have some improvements over existing tests and hence are being evaluated. The purpose of this report is to evaluate the evidence for the use of HPV testing for primary screening for cervical cancer.

\textbf{TECHNOLOGY ASSESSMENT (TA)}

\textbf{TA Criterion 1:} The technology must have final approval from the appropriate government regulatory bodies.

On March 31, 2003 the FDA Center for Devices and Radiological Health (CDRH) approved a PMA supplement to provide for commercial distribution of the Digene Hybrid Capture\textsuperscript{®} 2 (HC2) High-Risk HPV DNA Test (Digene Corporation, Gaithersburg, MD) as modified in accordance with conditions. The CDRH noted that “this device is indicated for:

1. To triage patients with ASCUS (atypical squamous cells of undetermined significance) Pap smear results to determine the need for referral to colposcopy. The results of this test are not intended to prevent women from proceeding to colposcopy.

2. In women 30 years and older the HC2 High-Risk HPV DNA Test can be used with Pap to adjunctively screen to assess the presence or absence of high-risk HPV types. This information, together with the physician’s assessment of cytology history, other risk factors, and professional guidelines, may be used to guide patient management.”

The PCR tests for HPV are not currently FDA approved.

\textbf{TA Criterion 1 is met.}
TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

Search Methods:

We searched Medline, the Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE) using the search terms of cervical cancer cross references with screening and HPV testing and clinical trials. In addition, we searched the bibliographies of the identified articles and other reviews to identify primary data sources and search strategies to ensure a complete review of the relevant literature.

Criteria:

At the time of the prior CTAF review in 2004, there were no published randomized trials that randomized participants to one strategy that included HPV testing and one that did not. In addition, prior studies focused primarily on test characteristics—what was the sensitivity and specificity of HPV testing when compared with conventional cytologic screening?

Since that time, several clinical trials have been published or are ongoing comparing a strategy including HPV testing with another strategy. Therefore, trials that randomized patients to a strategy including HPV testing versus cytology are the focus of the current review.

A total of seven randomized trials comparing HPV testing to conventional cytology were identified (Table 2: Characteristics of randomized trials comparing strategies that include HPV testing with another strategies) One of these used a different protocol for evaluating women in different age groups who were HPV positive with normal cytology and published its results separately by age category, hence there are eight table entries. Two of the seven trials have published follow-up data and evaluated clinical outcomes, two have published results on test characteristics from the baseline data and three trials are ongoing with no results yet on clinical outcomes or test characteristics. All of these trials are being done within the context of an organized screening program, thus increasing generalizability.

Level of Evidence: 1, 3

TA Criterion 2 is met.
Table 2: Characteristics of Randomized Trials Comparing Strategies that include HPV Testing with another Strategy

<table>
<thead>
<tr>
<th>Trials with follow-up</th>
<th>N</th>
<th>Age</th>
<th>Country</th>
<th>Intervention</th>
<th>Duration of follow-up</th>
<th>Type of HPV test</th>
<th>Verification Bias Avoided</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>POBASCAM Bulkmans, 2007</td>
<td>17,155</td>
<td>29-56</td>
<td>Netherlands</td>
<td>Pap plus HPV vs. Pap alone</td>
<td>7.2 years</td>
<td>PCR GP5+/6+</td>
<td>no</td>
<td>CIN 3 or greater</td>
</tr>
<tr>
<td>SWEDE-SCAN Naucler, 2007</td>
<td>12,527</td>
<td>32-38</td>
<td>Sweden</td>
<td>Pap plus HPV vs. Pap alone</td>
<td>4.1 years</td>
<td>PCR GP5+/6+</td>
<td>yes</td>
<td>CIN2 or CIN 3 or greater</td>
</tr>
</tbody>
</table>

Trials publishing baseline findings

| CCCaST Mayrand, 2007 | 10,154 | 30-69 | Canada       | HPV followed by Pap or Pap followed by HPV       | n/a                   | HC 2              | yes                      | Sensitivity and specificity for detecting CIN 2 or 3 |
| NTCC Ronco, 2006 | 33,364 | 35-60 | Italy        | Pap vs. liquid based cytology and HPV            | n/a                   | HC-2              | no                       | CIN grade 2 or higher  |
| NTCC Ronco, 2006 | 11,810 | 25-34 | Italy        | Pap vs. liquid based cytology and HPV            | n/a                   | HC-2              | no                       | CIN grade 2 or higher  |

Ongoing trials

| ARTISTIC Kitchener, 2006 | 24,510 | 20-64 | England      | Pap alone vs. liquid based cytology plus HPV    | ongoing               | HC-2              | no                       | CIN 3 lesions          |
| Finland trial, Anttila, 2006 | 863,000 | 30-64 | Finland      | 1. automation assisted cytology 2. HPV testing 3. Cytology | ongoing               | HC-2              | no                       | CIN 3 or greater       |
TA Criterion 3: The technology must improve net health outcomes.

All the included studies and their outcomes are described in Table 3. There are three sets of studies- 1) those that have reported clinical outcomes; 2) those that have reported test characteristics from the baseline data and 3) those that are ongoing and have not yet reported outcomes.

Strategies that include HPV testing versus cytology and clinical outcomes: The two most relevant studies are those that had some long term follow-up and evaluated clinical outcomes. When evaluating clinical outcomes, since many CIN 2 lesions will regress on their own anyway, they are less important to include as outcomes than CIN 3 or higher grade lesions. In the POBASCAM study\textsuperscript{26}, the main outcome was CIN 3 or greater lesions, whereas in the SWEDE-SCAN study, the main outcome was CIN 2 or CIN 3 or invasive cancer. In the POBASCAM study, 17,155 women aged 29-56 were randomized to Pap plus HPV or Pap alone and were followed for 7.2 years. HPV testing led to more CIN 3 or higher detected during round one of screening, but after two rounds of screening, the number of CIN 3 lesions did not differ between groups. Thus, the CIN 3 lesions were detected earlier than they would have been without HPV testing. Whether earlier treatment of these lesions led to improved outcomes is not yet known.

In SWEDE-SCAN, 12,527 women aged 32-38 were randomized to Pap plus HPV vs. Pap alone and were followed for 4.1 years. HPV testing also led to the detection of more CIN 2 or greater lesions at baseline, and then a reduced incidence of CIN 2 or higher found in subsequent examinations. Additional analysis showed that there was a reduced incidence of CIN 3 or greater among women who received HPV screening. Again the impact of earlier lesion treatment on subsequent outcomes is not known.

In SWEDE-SCAN, ascertainment bias was avoided by performing a similar number of double blinded Pap smears and colposcopies in randomly selected women in the control group.

Strategies that include HPV testing versus cytology and test characteristics: An important issue in assessing the test characteristics of cervical cancer screening methods is verification bias. In the ideal study of test characteristics (e.g. sensitivity and specificity), all participants
would be tested using the new test and the gold standard. The gold standard for cervical cancer screening is colposcopy with biopsy. Ideally, random four quadrant biopsies would be obtained in addition to biopsy of any suspicious lesions. For ethical and practical reasons, this is rarely done. Of greater concern is the fact that colposcopy is usually not done on women who test negative. Some proportion of women who test negative on the screening test will have cervical dysplasia. Studies with verification bias (not performing the gold standard on patients who test negative) will overestimate the sensitivity of the test. Some studies make statistical corrections for this problem by performing colposcopy on a random sample of women who test negative on the screening test and use these results to extrapolate to the full study population. However, when the outcome is rare (e.g. CIN 2+), the value of finding no disease among a relatively small number of women chosen at random is likely small. Many studies make no attempt to correct for or to eliminate verification bias. Often the most accurate ways to evaluate the test characteristics of a new screening test is to compare them to the test characteristics for the standard test (Pap test) done concurrently with the same patients.

Two randomized control trials (RCTs) have published results on the test characteristics of HPV testing compared with conventional cytology. The CCCaST study, conducted in Canada evaluated the sensitivity and specificity of HPV testing for detecting CIN 2 or CIN 3. A random sample of control group women underwent colposcopy and biopsy to avoid verification bias. HPV testing was more sensitive than conventional cytology (94.6% vs. 55.4%) but less specific (94.1% vs. 96.8%), thus leading to a higher false positive rate. Similar results were seen in the NTCC study, both in women aged 25-34 and those greater than 35, HPV testing was more sensitive than conventional cytology, although HPV testing was less specific and associated with a higher false-positive rate.

**Ongoing Studies:** Three additional ongoing studies have not yet reported results. In England, the ARTISTIC study randomized 28,000 women ages 20-64 years to receive either liquid-based monolayer Pap testing plus HPV testing or Pap testing alone and is following the women for six years. In the Osmanabad Randomized Clinical Trial in India, approximately 120,000 previously unscreened women will be randomized to four arms: HPV testing, Pap testing, visual inspection of the cervix with acetic acid or control and followed for incident cervical cancer. In Finland, 863,000 women have been randomized to automation assisted cytology, HPV testing or conventional cytology and will be followed for incident cancer.
Potential Harms of HPV testing: Although HPV testing is associated with an increase in sensitivity in detecting pre-malignant lesions, there are also potential harms, including a lower specificity with more false positive tests that then lead to additional testing. Any low-grade lesion that is found requires additional follow-up, including additional Pap smears and colposcopies. Given that many of these lesions may regress on their own, over diagnosis of CIN 2 lesions is an important concern since this is the treatment threshold in contemporary guidelines for most women\textsuperscript{19}.

Concerns that have been raised in the literature include increased anxiety and decreased quality of life among women labeled as carrying a sexually transmitted disease that can cause cancer, particularly given the lack of an effective treatment for the infection. Increased anxiety has the potential to decrease follow-up with patients or conversely, to lead to over-treatment. HPV testing could undermine the importance of cytologic screening resulting in decreasing rates of screening in the population and a reversal in the declining incidence of cervical cancer in the population. The diagnosis of HPV infection may also cause conflict between partners. Several qualitative studies have assessed the psychological impact of HPV testing, and some have found increased feelings of stigma and shame, and anxiety\textsuperscript{37,38}. Women who test positive for HPV but have negative cytology are the group most likely to be harmed. They will be told that they are positive for HPV and hence have been infected with a sexually transmitted virus that may cause cancer. This can potentially increase anxiety and may lead to unnecessary colposcopy. Finally, there are economic costs associated with increased surveillance and additional colposcopies.

Potential Benefit: Decreased Screening Interval: HPV testing is intended to identify low-risk women in whom annual testing may be more harmful than beneficial. For example, women over age 30 years with normal cytology tests and negative HPV tests can increase the interval between screening tests to at least three years, but it is unclear if this adds value to current strategies; many women by the age of 30 will have had three or more normal cytology tests and, as current guidelines suggest, extend intervals to up to every three years. Another potential benefit is the increased sensitivity of cervical cancer screening programs with the potential to decrease cervical cancer mortality through earlier detection and treatment and to decrease cervical cancer incidence through the detection and treatment of high-grade dysplasia.
Summary:

HPV testing can lead to earlier detection of CIN 2, CIN3 or higher grade lesions. In particular, the POBASCAM study showed that HPV testing led to earlier detection of CIN3 or higher lesions, which are most clinically significant. Earlier treatment of CIN 3 lesions may result in a reduction in cervical cancer incidence or mortality. Both of these studies were done within the context of an organized cervical cancer screening program, which increases generalizability. However, both of the studies that assessed clinical outcomes used the PCR test that is not commonly used or available in the United States. Increased use of HPV testing will certainly lead to additional testing (Paps and colposcopies), some of which may be unnecessary. In addition, there is the potential for increased anxiety and the stigma of having a sexually transmitted disease. At this time there is insufficient evidence that the benefits outweigh the risks of HPV testing for primary cervical cancer screening.

**TA Criterion 3 is not met**
## Table 3: Outcomes of Randomized Trials Comparing HPV Testing with another Strategy

<table>
<thead>
<tr>
<th>Name</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
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<tbody>
<tr>
<td><strong>Trials with follow-up</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>POBASCAM</td>
<td>Pap plus HPV vs. Pap alone</td>
<td>CIN 3 or greater</td>
<td>More CIN3+ detected during round 1 in HPV group (0.8% vs. 0.5%) Less CIN3+ during round two (0.3% vs. 0.6%) Number of CIN3+ lesions in the two rounds did not differ between groups (1.1% vs. 1.1%)</td>
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<tr>
<td>Bulkmans, 2007</td>
<td></td>
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<tr>
<td>SWEDE-SCAN</td>
<td>Pap plus HPV vs. Pap alone</td>
<td>CIN2 or CIN 3 or invasive cancer</td>
<td>More CIN2+ at baseline in HPV group (1.8% vs. 1.2%) Less CIN 2+ in subsequent exams (0.4% vs. 0.7%)</td>
</tr>
<tr>
<td>Naucler, 2007</td>
<td></td>
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<td></td>
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<tr>
<td><strong>Trials publishing baseline findings</strong></td>
<td></td>
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<td></td>
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<tr>
<td>CCCaST</td>
<td>HPV followed by Pap or Pap followed by HPV</td>
<td>Sensitivity and specificity for detecting CIN 2 or 3</td>
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<tr>
<td>Mayrand, 2007</td>
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<td></td>
<td>HPV</td>
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<td>Sensitivity</td>
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<td></td>
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<td></td>
<td>Specificity</td>
</tr>
<tr>
<td>NTCC Ronco, 2006</td>
<td>Pap vs. liquid based cytology and HPV</td>
<td>CIN grade 2 or higher</td>
<td></td>
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<tr>
<td>Women aged 35-60</td>
<td></td>
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<td>HPV</td>
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<td>Sensitivity</td>
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<td>Specificity</td>
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<tr>
<td><strong>Ongoing trials</strong></td>
<td></td>
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<tr>
<td>ARTISTIC Kitchener, 2006</td>
<td>Pap alone vs. liquid based cytology plus HPV</td>
<td>CIN 3 lesions</td>
<td>None yet</td>
</tr>
<tr>
<td>Finland trial, Anttila, 2006</td>
<td>1. Automation assisted cytology 2. HPV testing 3. Cytology</td>
<td>CIN 3 or greater</td>
<td>None yet</td>
</tr>
</tbody>
</table>
TA Criterion 4: The technology must be as beneficial as any established alternatives.

The standard of care for cervical cancer screening is currently cervical cytology. Thus an important question is whether or not strategies that include HPV testing are as effective as cytology alone. The incorporation of HPV DNA testing into primary screening for cervical cancer will result in millions of women with normal Pap tests being told that they are at increased risk for cervical cancer. If HPV testing is widely adopted, it is important that strategies be put in place to make sure that these women are neither over-treated nor unduly alarmed or stigmatized by their diagnosis.

When comparing HPV testing to the current standard, Pap testing, the key group to focus on is women with normal cytology who test positive for HPV. They represent the group that may benefit, as they are identified as higher risk than they would have been without HPV testing. Without knowing the HPV test results, it is usually recommended that women with normal Pap test results have repeat Pap testing in one year. However, an important question is what follow-up women with normal cytology, but who are positive for HPV, should have. The HART study addressed the issue of how to manage HPV-positive women with negative or borderline cytology. They compared the detection rate and positive predictive values of HPV assay with cytology to determine the best management strategy for HPV-positive women in a multicenter screening study of 11,085 women aged 30-60 years. Women with borderline cytology and women positive for high-risk HPV with negative cytology were randomized to immediate colposcopy or to surveillance by repeat HPV testing, cytology, and colposcopy at 12 months. HPV testing was more sensitive than borderline or worse cytology (97.1% vs. 76.6%, p=0.002), but less specific (93.3% vs. 95.8%, p<0.0001) for detecting CIN 2+. Of 825 randomized women, surveillance at 12 months was as effective as immediate colposcopy. In women positive for HPV at baseline, who had surveillance, 73 (45%) of 164 women with negative cytology and eight (35%) of 23 women with borderline cytology were HPV negative at six to 12 months. No CIN 2+ was found in these women, nor in women with an initial negative HPV test with borderline (n=211) or mild (32) cytology. The authors suggest that HPV testing could be used for primary screening in women older than 30 years, with cytology used to triage HPV-positive women. HPV-positive women with normal or borderline cytology (about six percent of screened women) could be managed by repeat testing after 12 months. This approach could potentially
improve detection rates of CIN 2+ without increasing the colposcopy referral rate.

Women with normal cytology who test positive for oncogenic HPV are also the women most likely to be harmed by the test. They will be told that they are infected with a sexually transmitted virus that can cause cancer. This will undoubtedly increase anxiety significantly for some women, which may lead to poor quality of life, demands for immediate and often unnecessary colposcopy, or avoidance of future cervical cancer screening. On the other hand, the increased knowledge about their risk for cervical cancer could lead to improved compliance with screening recommendations. Given the lack of comparative data, it is not clear that the addition of HPV testing improves cervical cancer screening.

A cost-effectiveness model published before the publication of the recent clinical trials compared the societal costs and benefits of HPV testing, Pap testing, and their combination to screen for cervical cancer. A simulation model of the natural history of cervical dysplasia was used to estimate the societal costs and quality-adjusted life expectancy associated with 18 different general population screening strategies, including Pap plus HPV testing, Pap testing alone, and HPV testing alone every two or three years among hypothetical longitudinal cohorts of US women. Maximal savings in lives were achieved by screening every two years until death with combined HPV and Pap testing at an incremental cost of $76,183 per quality adjusted life year (QALY) compared with Pap testing alone every two years. Stopping biennial screening with HPV and Pap testing at age 75 years captures 97.8% of the benefits of lifetime screening at a cost of $70,347 per QALY. HPV screening alone was equally effective as Pap testing alone at any given screening interval or age of screening cessation, but was more costly and therefore was dominated. In sensitivity analyses, HPV testing would be more effective and less costly than Pap testing at a cost threshold of $5 for an HPV test. The authors argue that screening with HPV plus Pap tests every two years appears to save additional years of life at reasonable costs compared with Pap testing alone. However, expenses higher than $50,000 per QALY are usually not considered cost effective. The model does not allow for the current practice of differential screening intervals based on prior test results nor does it adequately adjust for the changes in the natural history of HPV infection and test characteristics with aging. Newer models including the results of recent RCTs are needed.

Recently, guidelines from the American Cancer Society (ACS) (also adopted by ACOG) were
adopted which support an option of HPV testing combined with cytology for women over age 30. They recommend that women with normal Pap tests who test negative for HPV should be re-screened no more frequently than every three years. However, they specifically label this as a “preliminary recommendation” and call for guidelines to be developed for management of women with normal Pap smears who test positive for HPV DNA. They specifically note that “the prognostic value of a positive test result, especially in the absence of a cytologic abnormality, has not been fully validated in prospective studies.”

HPV testing is more sensitive than Pap cytology and can lead to earlier diagnosis of CIN3 lesions. However, improved sensitivity alone is not sufficient to recommend widespread HPV testing because it is not completely known how often to screen women who test negative for HPV, nor how to manage women with normal Pap cytology who test positive for oncogenic HPV types, although the HART study found that repeat screening after one year in women with normal Pap cytology and a positive HPV test is as safe as immediate colposcopy. Finally, and most importantly, although HPV testing has now been shown to lead to an earlier detection of CIN 3 lesions, whether this earlier detection leads to a reduction in subsequent cervical cancer incidence and mortality is not yet known, but may become apparent after longer term follow-up of the ongoing clinical trials.

TA Criterion 4 is not met

TA Criterion 5: The improvement must be attainable outside of the investigational setting.

Specimen collection for HPV testing with the HC II system is similar to that required for Pap testing and is feasible in routine practice. Similarly, the technical steps required to process and test the specimen are standard in any modern medical laboratory facility. In addition, the clinical trials of HPV testing have been done within the context of routine screening programs, further suggesting feasibility in routine practice. The results that have been seen (increased detection of CIN 2/3 and invasive lesions) are thus potentially attainable outside of the investigational setting.

TA Criterion 5 is met.
CONCLUSION

Many unanswered questions remain about the optimal strategy for incorporating HPV testing into cervical cancer screening programs. Alternative strategies that have been proposed include using HPV as the primary test and performing Pap testing only on patients testing positive for HPV, starting with Pap testing and performing HPV testing only on patients with normal or ASC-US on cytology, or performing both tests concurrently. Current models suggest that Pap and HPV testing every two years would maximize life expectancy, but the approach was not cost-effective by current standards. Furthermore, there are limited data on the best way to manage patients who test positive for HPV, but have normal cervical cytology test. Most women will clear the infection within one to two years, but there are no treatments, no way to predict who will clear the infection, and no data on the impact that a positive “high-risk for cancer” HPV test will have on a woman’s quality of life. It is also not clear what screening interval is appropriate for women who test negative for HPV and have a normal Pap. Current guidelines suggest no more frequently than every three years, but the optimal screening interval has not been determined.

Current evidence suggests that a reasonable way to incorporate HPV testing into current cervical screening programs would be as follows:

1. HPV testing is not recommended for women under the age of 30; an age over which HPV testing should not be performed has not been determined
2. HPV testing may be offered to women 30 years and older in conjunction with Pap testing
   - Women who test negative on both should not be screened again for at least 3 years
   - Women who test positive for HPV, but have normal Pap cytology should have repeat cytology and HPV testing in one year with colposcopy if either is abnormal
   - Women with abnormal Pap cytology should be treated according to current guidelines

Although incorporation of HPV screening can lead to earlier detection of CIN3 lesions, whether or not this will result in reduced cervical cancer incidence and mortality is not known. In addition, the two trials that have published long term follow-up used a PCR test that is not
currently available in the United States. At this time, the evidence is insufficient to recommend for or against the incorporation of HPV testing into cervical cancer screening programs. Finally, it is important to recognize that the majority of the cases of cervical cancer that are diagnosed in the United States are in women who have never received any screening for cervical cancer or have not been screened for over five years. Thus, the potential public health impact of screening with HPV testing will remain small unless there are increases in the proportion of women at risk for cervical cancer who are tested.

RECOMMENDATION

It is recommended that the use of Human Papillomavirus Testing in Cervical Cancer Screening does not meet technology assessment criteria 3 or 4 for improving net health outcomes and being as effective as any established alternatives.

March 5, 2008

*The California Technology Assessment Forum Panel voted to accept the recommendation as written.*
RECOMMENDATIONS OF OTHERS

BLUE CROSS BLUE SHIELD ASSOCIATION (BCBSA)
The BCBSA Technology Evaluation Center has not conducted a review of this technology.

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)
A CMS position specific to the use of HPV testing was not found.

AMERICAN COLLEGE OF OBSTETRICS AND GYNECOLOGY (ACOG)
A representative of ACOG district IX provided testimony at the meeting.
ACOG Practice Bulletin Number 45, August 2003 notes the following:
“The following recommendations are based on limited and inconsistent scientific evidence (Level B):
The use of a combination of cervical cytology and HPV DNA screening is appropriate for women aged 30 years and older. If this combination is used, women who receive negative results on both tests should be rescreened no more frequently than every 3 years.”

AMERICAN CANCER SOCIETY (ACS)
On October 21, 2003 the American Cancer Society revised the Detailed Guide: Cervical Cancer. The following is noted:
“The American Cancer Society recommends the following guidelines for early detection:
Another reasonable option for women over 30 is to get screened every 3 years (but not more frequently) with either the conventional or liquid-based Pap test, plus the HPV DNA test.”

UNITED STATES PREVENTIVE SERVICES TASK FORCE (USPSTF)
In January 2003 the USPSTF issued Recommendations and Rationale for screening for Cervical Cancer and noted that:
“The USPSTF concludes that the evidence is insufficient to recommend for or against the routine use of human papillomavirus (HPV) testing as a primary screening test for cervical cancer. The USPSTF found poor evidence to determine the benefits and potential harms of HPV screening as an adjunct or alternative to regular Pap smear screening. Trials are underway that should soon clarify the role of HPV testing in cervical cancer screening.” The Task Force will be updating their recommendation in 2008.

ASSOCIATION OF NORTHERN CALIFORNIA ONCOLOGISTS (ANCO)
ANCO was invited to provide an opinion and representation at the meeting.

AMERICAN SOCIETY FOR COLPOSCOPY AND CERVICAL PATHOLOGY (ASCCP)
The ASCCP was invited to provide an opinion and representation at the meeting.
MOASC was invited to provide an opinion and representation at the meeting.

CSP was invited to provide an opinion and representation at the meeting.

In the March 2007 revision of the AAFP Summary of Recommendations for Clinical Preventive Services it is noted that “The AAFP concludes that there is insufficient evidence to recommend for or against routine use of human papillomavirus (HPV) testing as a primary screening test for cervical cancer.

**ABBREVIATIONS USED IN THIS REVIEW**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>HPV</td>
<td>Human papillomavirus</td>
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<tr>
<td>BCBSA TEC</td>
<td>Blue Cross Blue Shield Association Technology Evaluation Center</td>
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<tr>
<td>Pap Smear</td>
<td>Papanicolaou smear</td>
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<tr>
<td>AS-CUS</td>
<td>Atypical squamous cells- undetermined significance</td>
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<tr>
<td>ASC-H</td>
<td>Atypical squamous cells- cannot exclude HSIL</td>
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<tr>
<td>PPV</td>
<td>Positive predictive value</td>
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<tr>
<td>LSIL</td>
<td>Low-grade squamous intraepithelial lesion</td>
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<tr>
<td>HSIL</td>
<td>High-grade squamous intraepithelial lesion</td>
</tr>
<tr>
<td>AGC</td>
<td>Atypical glandular cells</td>
</tr>
<tr>
<td>CIN</td>
<td>Cervical intraepithelial neoplasia</td>
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<tr>
<td>Pap C</td>
<td>Conventional Papanicolaou cytology</td>
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<tr>
<td>Pap L</td>
<td>Liquid –based thin layer Papanicolaou cytology</td>
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<tr>
<td>HII</td>
<td>Hybrid Capture II test</td>
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<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
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<tr>
<td>CDRH</td>
<td>FDA Center for Devices and Radiological Health</td>
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<tr>
<td>DARE</td>
<td>Database of Abstracts of Reviews of Effects</td>
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<tr>
<td>RCTs</td>
<td>Randomized controlled trials</td>
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<tr>
<td>QALY</td>
<td>Quality adjusted life year</td>
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<td>ACS</td>
<td>American Cancer Society</td>
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REFERENCES


