MP 2.04.07 Cervical Cancer Screening Technologies with Pap and HPV

Medical Policy

<table>
<thead>
<tr>
<th>Section</th>
<th>Original Policy Date</th>
<th>Last Review Status/Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicine</td>
<td>12:2013</td>
<td>Reviewed with literature search/12:2013</td>
</tr>
</tbody>
</table>

Issue
12:2013

Disclaimer

Our medical policies are designed for informational purposes only and are not an authorization, or an explanation of benefits, or a contract. Receipt of benefits is subject to satisfaction of all terms and conditions of the coverage. Medical technology is constantly changing, and we reserve the right to review and update our policies periodically.

Description

Data suggest that cytological screening for cervical cancer reduces the incidence of cervical cancer by up to 50%. Several technologies have been investigated for their role in detecting cancerous and precancerous cervical lesions.

It is estimated that there will be 12,200 new cases, and 4210 deaths from cervical cancer in the United States in 2010. The high prevalence and natural history of cervical cancer, as well as the ability to cure patients in pre-invasive stages, create ideal conditions for wide-spread screening. Cytological screening, through the sampling of cells of the cervix, has been the gold-standard since the introduction of the the Papanicolaou (Pap) smear in the 1940s. The Pap smear involves sampling cells of the transformation zone of the cervix, the area most prone to malignant transformation.

False-negative Pap smears are troubling, because a patient with undetected pre-invasive cancer may progress to invasive disease before she undergoes another Pap test, particularly if the patient does not undergo regular Pap smear screening. Pap smear cytology is associated with a false negative results ranging from 15% to 55%. False negative results may be explained by various factors, including sampling errors, errors in slide preparation, and errors in slide interpretation. Different approaches to reducing the false negative rate have targeted each step in the process. This policy addresses the technologies that attempt to improve the accurate detection of cervical abnormalities.

Appreciation of the causative effect of human papilloma virus (HPV) infection in most cervical cancers has led to the development of screening techniques for the presence of certain high-risk HPV strains in an attempt to improve the specificity of traditional Pap smears.

The Bethesda classification system assigns a degree of atypia to cells seen on Pap smear; however a biopsy is necessary to gain information on the tissue structure, or histology, of lesions. The correlation between cytological grade and histological grade, and the natural history of cervical cancer, has been an area of rapidly evolving understanding. While HPV infection has been associated with the development of cervical cancer, many infections are
clearly spontaneously and low grade lesions may regress or disappear, particularly in younger women.

**Regulatory Status**
Several liquid-based preparations have received premarket approval from the FDA. For example, in May 1996, “ThinPrep® Pap Test” (Hologic, Bedford, MA) was approved by the FDA through the premarket approval process for use in collecting and preparing cervical cytology specimens for Pap stain-based screening for cervical cancer.

Several automated screening systems have received premarket approval through the FDA. For example, in September 1995, “AutoPap® Automatic Pap Screener, now FocalPoint™” (BD Diagnostics, Franklin Lakes, NJ) was approved by the FDA through the premarket approval process for use in initial screening of cervical cytology slides. The device is intended to be used on both conventionally-prepared and prepstain system cervical cytology slides.

In March 2003, test kit “digene® HPV test” (Qiagen Inc, Valencia, CA) was approved by the FDA through the premarket approval process for use in diagnostic testing for the qualitative detection of DNA from 13 high-risk human papillomavirus types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) in cervical specimens.

In March 2009, test kit “Cervista® HPV HR” (Hologic, Bedford, MA) was approved by the FDA through the premarket approval process for use in diagnostic testing for the qualitative detection of DNA from 14 high-risk human papillomavirus types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) in cervical specimens.

**Policy**
The following refers to average-risk asymptomatic women aged 21 to 65:

Preparation of Papanicolaou (Pap) smears using conventional or a monolayer slide preparation system may be considered **medically necessary** every 2 to 3 years.

Primary screening and rescreening of Pap smears using the FocalPoint™ or ThinPrep® automated slide reading systems may be considered **medically necessary**.

HPV testing, in conjunction with Pap smears, for the purpose of screening women over age 30 for cervical abnormalities may be considered **medically necessary**.

The following refers to high-risk or symptomatic women or those with a prior abnormal Pap:

Human papillomavirus (HPV) testing of Pap smears that have an interpretation of atypical cells of undetermined significance (ASCUS) may be considered **medically necessary**.

HPV testing for the purpose of following-up prior positive HPV tests in women over age 30 may be considered **medically necessary**.

Primary screening and rescreening of Pap smears using the FocalPoint™ system automated slide reading system in high-risk patients is **investigational**.

**Policy Guidelines**

42 Memorial Drive ● Suite 1 ● Pinehurst, N.C. 28374 ● Phone (910) 715-8100 ● Fax (910) 715-8101

FirstCarolinaCare Insurance Company, Inc. is a wholly-owned subsidiary of FirstHealth of the Carolinas, Inc.
CPT codes 88142-88143 and 88174-88175 refer to the use of monolayer preparation (i.e., collected in preservative fluid) with various different screening options. CPT codes 88147 and 88148 refer to conventionally prepared slides with automated screening while CPT codes 88152, 88154, 88166, and 88167 refer to conventionally prepared slides with computer-assisted rescreening with or without cell selection.

CPT codes 87620-87622 refer to the DNA probe techniques for detecting HPV.

Rationale

This policy was originally created in 1998 and was regularly updated with searches of the MEDLINE database. The most recent literature search was performed for the period of July 2008 through August 2010. Following is a summary of key literature to date:

Monolayer slide preparation/Liquid-based cytology

Initial literature focused on the goal of improved sensitivity of liquid based cytology when compared to conventional cytology. In 2008, Arbyn and colleagues produced a systematic review and meta-analysis of studies published between 1991 and 2007 comparing conventional and liquid-based cytology in patients who subsequently had histological biopsy, including one randomized controlled trial (RCT). (1) Of the remaining 8 studies, 7 were concomitant testing (samples for both methods taken at the same time from the same subject) with blinding of the identities of each sample. For the concomitant studies, sensitivity and specificity could be calculated from pooled data. Data were analyzed from three cut-off points for the decision to proceed to biopsy: high- and low-grade squamous intraepithelial lesions and ASCUS. For the first two cut-off levels, liquid-based and conventional Pap smears performed similarly. However, when ASCUS was used as the cut-off to further testing (biopsy), liquid-based Pap showed a lower specificity compared to conventional Pap (ratio 0.91, 95% confidence interval 0.84 - 0.98). Specificity at that level was 64.6% compared to 71.3% for conventional cytology. Lower specificity leads to a larger number of false-positive samples. An accompanying editorial asserts that this increase in false positives is unlikely to be off-set by any advantage gained in the ability to perform HPV testing on the same sample. (2)

In 2009, Siebers and colleagues published a RCT comparing the effectiveness of liquid-based cytology to conventional Pap smear in the detection of histological abnormalities. (3) In this Dutch study, 89,784 women were assigned to conventional or liquid-based cytology screening, based on the cluster randomization of 246 participating family physician practices (the unit of randomization). Women with baseline cytological abnormalities were prospectively followed, and repeat cytology or biopsy was completed within the 18 month study period. The cytology specimens were obtained in the same manner as the initial sample. Cytopathologists and histopathologists interpreting the follow up samples were blinded to initial Pap result. The positive predictive values of the paired results were analyzed under three cut-off scenarios of initial cytopathology: ASCUS or worse, LSIL or worse and HSIL or worse. The ratios of the positive predictive values (PPV) of the two methodologies approached unity at all cut-off values. At the ASCUS cut-off and at 95% confidence interval, no significant differences between the two methodologies was observed (PPV ratio 0.97, 95% confidence interval 0.81 -1.18).

Automated Slide Reading Systems

This policy is based in part on a 1998 TEC Assessment (4) that focused on monolayer slide preparation and automated slide reading systems. Automated screening of the Papanicolaou
(Pap) smear was only evaluated for rescreening in the original TEC Assessment, as there was no FDA approval for initial automated screening at that time. Subsequently, the FocalPoint™ and ThinPrep® systems were approved for automated initial screening. Both monolayer and automated rescreening technologies were found to increase the sensitivity of an individual Pap smear and thus are considered medically necessary based on this limited outcome.

In 1999, and again in 2002, Wilbur and colleagues published performance data of the FocalPoint™ system to traditional manual reading and rescreening. (5-6) Over 25,000 slides were analyzed in the study. Depending on the cutoff used to determine a positive slide, reading assisted by FocalPoint™ was between 4% and 7% more sensitive than traditional manual reading. FocalPoint™-assisted reading was also 1% more specific than traditional manual reading in identifying normal slides. Studies of the ThinPrep® imaging system have shown diagnostic performance equivalent or better than manual reading. (7-8)

HPV Testing
Regarding HPV testing, data from the ASCUS-LSIL Triage Study (ALTS) (9) showed that triage of smears with atypical squamous cells of unknown significance (ASCUS) using HPV testing for triage to immediate colposcopy was more sensitive and equally specific in identifying cervical intraepithelial neoplasia grade 3 (CIN 3) as repeat Pap smear using ASCUS as the threshold for colposcopy referral. Based primarily on the results of this trial, guidelines issued by the American Society for Colposcopy and Cervical Pathology recommend either repeat Pap smear, immediate colposcopy, or HPV testing for women who have ASCUS Pap smears. (10) HPV testing can be performed on the remaining liquid media used as part of the preparation of monolayer slides. Otherwise, if the original Pap smear was prepared conventionally, HPV testing would require an additional office visit to perform an additional Pap smear.

In March 2003, the FDA approved HPV testing, in conjunction with Pap smear screening, for primary screening of women over age 30. Both the American Cancer Society (11) and the American College of Obstetricians and Gynecologists (ACOG) (12) have endorsed combined screening in women over age 30, under the condition that, among women who test negative for both tests, screening should not be repeated for 3 years. It was not clear how women with negative Pap smears and positive HPV tests should be managed. However, the U.S. Preventive Services Task Force (USPSTF), in its 2003 report on screening for cervical cancer, (13) found insufficient evidence to recommend for or against the routine use of HPV testing. As of September 2010, these recommendations are under review by the USPSTF. The basis for the recommendations in support of HPV screening is a consensus of a large body of evidence demonstrating that HPV infection is a strong etiologic factor for cervical abnormalities. However, in women under age 30 years, infection is often transient and nonspecific. Thus, screening women in this age group with HPV would be inefficient. However, the absence of HPV infection in conjunction with a normal Pap smear has an extremely high negative predictive value and identifies a group of women at low risk for cervical abnormalities. Screening intervals in these women who are over age 30 can be safely extended to 3 years. (10) HPV screening is not recommended for women under age 30 because infections are most likely to be transient in this group.

Regarding HPV testing, a later ACOG Practice Bulletin recommended that both tests (HPV and cervical cytology) be repeated at 6–12 months, and a persistently positive HPV test should be followed up with colposcopy regardless of cytology results. (14) Recent practice guidelines reiterate but do not change the recommendations for HPV testing. A consensus document sponsored by the American Society for Colposcopy (15) reiterates the use of HPV to follow up
abnormal Pap smears and the use of HPV in combination with Pap smears to screen women over age 30; HPV testing for women under age 20 was discouraged. This document suggests that follow-up with repeat cytology and HPV testing at 12 months is the best management approach for cytology-negative, HPV-positive women. Women who on repeat testing are persistently HPV positive should undergo colposcopy, whereas women who are negative on HPV and cytology can be rescreened in 3 years.

Summary
The evidence regarding the use of liquid-based cytological screening methods for cervical cancer demonstrates similar sensitivity to conventional cytology, possibly at the expense of specificity. The liquid-based system may add to the convenience of subsequent HPV testing, and in some locations alternatives are not supported by pathology laboratories. Evidence firmly supports the use of HPV testing for both initial screening in women over 30, and in triage of ASCUS results for all women. The use of automated slide reading systems is supported by a small body of evidence that the systems may increase sensitivity.

Technology Assessments, Guidelines and Position Statements
In August 2009, the American College of Obstetricians and Gynecologists published a practice bulletin on cervical cytology screening. (16) A systematic review of the MEDLINE database for the period of June 1985 to July 2009 was described and graded recommendations provided. However, details of the strength of evidence and quality of included studies were not provided. Level A recommendations (good and consistent evidence) were:

- Cervical cancer screening should begin at 21 years, and avoided prior.
- Cervical cancer screening is recommended every two years for women between the ages of 21 and 29 years.
- Screening interval may be increased to every three years in women 30 years and older who have had three consecutive negative pap smears and no history of Cervical Intraepithelial Neoplasia (CIN) grade 2 or 3, immunosuppression or HIV, and who have not been exposed to diethylstilbestrol in utero.
- Both liquid-based and conventional methods of cervical cytology are acceptable.
- Cervical screening should be discontinued in women after total hysterectomy for benign indications (non-cancerous).
- Co-testing cytology with HPV DNA testing is an acceptable strategy in women over 30 years. Patients testing negative for both should not be rescreened for 3 years.

Medicare National Coverage
The Centers for Medicare and Medicaid Services (CMS) currently have the following national coverage decisions:

National Coverage Decision on Screening Pap Smears (210.2)
A screening pap smear and related medically necessary services provided to a woman for the early detection of cervical cancer (including collection of the sample of cells and a physician’s interpretation of the test results) and pelvic examination (including clinical breast examination) are covered under Medicare Part B when ordered by a physician (or authorized practitioner) under one of the following conditions:
• She has not had such a test during the preceding two years or is a woman of childbearing age

• There is evidence (on the basis of her medical history or other findings) that she is at high risk of developing cervical cancer and her physician (or authorized practitioner) recommends that she have the test performed more frequently than every two years.

National Coverage Decision on Diagnostic Pap Smears (190.2)
A diagnostic pap smear and related medically necessary services are covered under Medicare Part B when ordered by a physician under one of the following conditions:

• Previous cancer of the cervix, uterus, or vagina that has been or is presently being treated;

• Previous abnormal pap smear;

• Any abnormal findings of the vagina, cervix, uterus, ovaries, or adnexa;

• Any significant complaint by the patient referable to the female reproductive system; or

• Any signs or symptoms that might in the physician's judgment reasonably be related to a gynecologic disorder.

References:


4. TEC Assessment 1998; Tab 1.


<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT Codes</td>
<td>88142</td>
<td>Cytopathology, cervical or vaginal (any reporting system), collected in preservative fluid, automated thin layer preparation; manual screening under physician supervision</td>
</tr>
<tr>
<td></td>
<td>88143</td>
<td>; with manual screening and rescreening under physician supervision</td>
</tr>
<tr>
<td></td>
<td>88147</td>
<td>Cytopathology smears, cervical or vaginal; screening by automated system under physician supervision</td>
</tr>
<tr>
<td></td>
<td>88148</td>
<td>; screening by automated system with manual rescreening under physician assistance</td>
</tr>
<tr>
<td></td>
<td>88152</td>
<td>Cytopathology, slides, cervical or vaginal; with manual screening and computer-assisted rescreening under physician supervision</td>
</tr>
<tr>
<td></td>
<td>88154</td>
<td>; with manual screening and computer-assisted rescreening using cell selection and review under physician supervision</td>
</tr>
<tr>
<td></td>
<td>88166</td>
<td>Cytopathology, slides, cervical or vaginal (the Bethesda System); with manual screening and computer-assisted rescreening under physician supervision</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>88167</td>
<td>Cytopathology, cervical or vaginal (any reporting system), collected in preservative fluid, automated thin layer preparation; screening by automated system, under physician supervision</td>
<td></td>
</tr>
<tr>
<td>88174</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); papillomavirus, human, direct probe technique</td>
<td></td>
</tr>
<tr>
<td>88175</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); papillomavirus, human, amplification probe technique</td>
<td></td>
</tr>
<tr>
<td>87620</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); papillomavirus, human, direct probe technique</td>
<td></td>
</tr>
<tr>
<td>87621</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); papillomavirus, human, amplification probe technique</td>
<td></td>
</tr>
<tr>
<td>87622</td>
<td>Infectious agent detection by nucleic acid (DNA or RNA); papillomavirus, human, quantification</td>
<td></td>
</tr>
<tr>
<td>ICD-9 Procedure</td>
<td>91.46 Microscopic examination of specimen from female genital tract</td>
<td></td>
</tr>
<tr>
<td>ICD-9 Diagnosis</td>
<td>180.0 – 180.9 Malignant neoplasm of cervix uteri, code range</td>
<td></td>
</tr>
<tr>
<td></td>
<td>198.82 Secondary malignant neoplasm of genital organs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>236.0 Neoplasm of uncertain behavior of uterus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>239.5 Neoplasms of unspecified nature of other genitourinary organs</td>
<td></td>
</tr>
<tr>
<td>HCPCS</td>
<td>P3000 – P3001 Screening Papanicolaou smear, cervical or vaginal, up to three smears, code range</td>
<td></td>
</tr>
</tbody>
</table>

**Index**

- Autopap
- Focal Point Rescreening, Pap Smear
- HPV Testing
- Human Papillomavirus (HPV) Testing
- PAPNET
- Pap Smears, New Technologies
- SurePath, Pap Smear
- ThinPrep
- TriPath, Pap Smear