

Assessing Secondary Prevention Methods for Cervical Cancer: Costs and Benefits in Managed Care

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The development of Papanicolaou's cervical smear (Pap test) in the 1930s represents the most important advance in secondary prevention methods for cervical cancer.

The healthcare industry's acceptance and employment of the Pap test have been significant since the 1940s, and it is now the most widely used cancer screening method in the world.¹ Prior to widespread adoption of the Pap test, cervical cancer was the leading cause of cancer death for women in the United States; it now ranks fifteenth, according to the American Cancer Society.¹ Deaths from cervical cancer declined 74% between 1955 and 1992, presumably because of the Pap test's introduction and increased use of organized screening.¹ The rate of death from cervical cancer continues to decline by nearly 4% each year. Although this represents a significant reduction in the death rate, it is estimated that 3870 women will die from cervical cancer in the United States in 2008—more than 10 deaths per day—and countless more will be affected by the disease.¹

Approximately 13,000 cases of invasive cervical cancer and 50,000 cases of in situ cervical carcinoma are diagnosed yearly in this country, imposing a noticeable disease burden on managed care, with important financial implications.¹ Improving screening rates and reducing test errors may decrease cervical cancer deaths in the future, but it appears that managed care is approaching a plateau as to the number of cervical cancer cases that can be prevented using secondary methods.² The continued prevalence of cervical cancer and related cervical disease may be due primarily to the inherent weaknesses associated with the secondary prevention methods (screening) available and their underuse. Enhanced methods of primary prevention are needed to reduce the incidence of cervical cancer further.

Healthcare Communications, LLC Cervical Cancer Screening as Secondary Prevention

Cervical cancer remains one of the most curable cancers, provided it is discovered at an early stage.¹ The 5-year relative survival rate for cervical cancer in its earliest stage is 92%, whereas the 5-year survival rate for all stages of cervical cancer combined is ~72%.¹ This disparity in survival rates according to cervical cancer stage illustrates the benefit of screening in managing the disease and its importance in reducing related mortality. The concept of detecting cervical cancer early in the disease process to improve outcomes is in keeping with one of the premises on which managed care was founded—the

Abstract

Secondary prevention of cervical cancer through regular screening has been very successful since its widespread adoption in the 1940s. The death rate for cervical cancer declined 74% between 1955 and 1992, presumably owing to the introduction of the Papanicolaou's cervical smear (Pap test) and greater use of organized screening. Until now, this is the closest we have come to scoring a win in the ongoing fight against cervical cancer.

Although secondary measures for preventing cervical cancer remain a mainstay in managed care, screening methodologies and processes have several inherent weaknesses, largely because successful screening depends on patient cooperation and adherence. Screening rates have improved, but ~20% of the target population in commercial plans remains unscreened. Weaknesses related to the specificity and sensitivity of cervical screening methodologies compound the problem of preventing cervical cancer through screening.

Secondary prevention methods constitute the greatest proportion of direct costs in cervical disease, by far. Should a patient receive an abnormal test result, costs accelerate significantly. Methods used to resolve test abnormalities, such as repeat screening, colposcopy/biopsy, and human papillomavirus deoxyribonucleic acid testing, add to the overall financial burden of secondary prevention in these cases.

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For author information and disclosures, see end of text.

■ **Table 1.** HEDIS Cervical Cancer Screening Rates in Commercial and Medicaid Health Plans

Cervical Cancer Screening Trends, 1996-2005		
Year	Commercial	Medicaid
2005	81.8	65.0
2004	80.9	64.7
2003	81.8	64.0
2002	80.5	62.4
2001	80.0	61.1
2000	78.1	59.9
1999	71.8	N/A
1998	69.8	N/A
1997	70.9	N/A
1996	70.5	N/A

HEDIS indicates Healthcare Effectiveness Data and Information Set.
Adapted from Reference 2.

prevention of severe disease. Despite the relatively curable nature of cervical cancer if diagnosed at an early stage, under the current paradigm of secondary prevention, detecting the disease early depends entirely on screening adherence and the accuracy of the test results.

Patient Adherence. Improved educational outreach and public health initiatives have emphasized the importance of getting a Pap test. In the United States, it has been estimated that the annual rate of routine cervical cancer screening is 294.7 per 1000 women, with cytologic abnormalities detected in 14.9 per 1000 women.³ Although the rate of detected cytologic abnormalities may appear low, it is important to consider that this figure only takes into account abnormalities detected in the screened population. A lack of patient adherence to recommendations for regular cervical screening further compounds the problem of effective secondary prevention, because abnormalities cannot be detected in patients who do not get screened.²

The National Committee for Quality Assurance’s Healthcare Effectiveness Data and Information Set Cervical Cancer Screening measure provides an accurate look at screening rates in managed care settings. This measure estimates the

percentage of women aged 21 to 64 years enrolled in a health plan who had at least 1 Pap test in the previous 3 years.² The national screening rate in commercial plans rose from ~70% in 1996, when the measure was implemented, to ~80% in 2005 (Table 1).² Nearly 20% of US women covered by commercial insurers still fail to comply with screening recommendations despite a nearly 100% cure rate for cervical cancer detected in its earliest stages.² Between 60% and 80% of American women with newly diagnosed invasive cervical cancer did not undergo a Pap test in the previous 5 years, and many of these women never had a Pap test, which indicates a nationwide lack of adherence to cervical screening recommendations.¹

Nonadherence to cervical screening recommendations can be attributed to numerous socioeconomic and personal factors, but the invasive nature of Pap testing appears to be a driving force.⁴ The conventional Pap test procedure may be uncomfortable for some women because of its invasiveness and the neuroanatomy of the cervix. Patients might experience light bleeding, cramps, and other discomfort after undergoing a Pap test. The presence of side effects varies according to the patient’s anatomy, the skill of the practitioner, psychological factors, and preexisting vaginal conditions. These factors, as well as social and cultural issues, may reduce patient screening adherence.⁴

Effectiveness of Screening. Obviously, cervical cancer cannot be detected at an early stage in patients who do not undergo regular recommended cervical screenings, but even if all patients were compliant, the effectiveness of secondary prevention is partially determined by the accuracy of the screening methods used. Conventional Pap tests have a demonstrated specificity of 94% and a sensitivity of 74%.⁵ McCrory et al found that the Pap test is most accurate when a high-grade squamous intraepithelial lesion detection threshold is used, with the goal of identifying a high-grade lesion.⁶ The use of a high-grade threshold, however, might result in a number of grade 2 or 3 cervical intraepithelial neoplasia (CIN) lesions being missed. Conversely, when lower thresholds are used, such as low-grade squamous intraepithelial lesion (LSIL) and atypical squamous cells of undetermined significance (ASCUS), with the goal of detecting low- or

high-grade dysplasia, test results are less accurate.⁶ This highlights a major shortcoming of Pap testing: the procedure, which is intended to detect cancer in its early stages, is most accurate when targeting high-grade lesions more commonly observed in later-stage cervical dysplasia.

HPV DNA Testing. In addition to concerns about the accuracy of current screening methods, the implications of human papillomavirus (HPV) infection in the development of cervical cancer should be considered. An estimated 76% of cervical cancer cases in North America are linked to HPV types 16 and 18, demonstrating that HPV infection is a significant risk factor for developing cervical cancer.⁷ The value of testing for the presence of HPV infection, therefore, must be weighed. A meta-analysis by de Sanjosé et al found that approximately 10% of HPV cases demonstrate normal cervical cytology and go undetected by conventional Pap tests.⁸ The HPV deoxyribonucleic acid (DNA) test needs to be included as an additional feature of the standard Pap test if patients are to be considered fully screened for cervical cancer risk.⁹ HPV DNA testing is not automatically included as a test option in routine screening examinations.

Although an improvement in the rate of women who undergo screening has led to a decline in cervical cancer deaths, current screening methods and the technologies employed by no means guarantee that cervical cancer or cervical abnormalities will be caught at an early stage using secondary prevention methods alone.^{2,5,6}

Traditional and Emerging Secondary Prevention Methods

Various screening methods for the secondary prevention of cervical cancer are available to clinicians. These include conventional cervical cytology screening (Pap tests), advanced forms of cytology screening (liquid-based and computer-aided tests), and secondary screening in the form of HPV testing. Secondary prevention methods are aimed at early cervical disease detection, thereby increasing opportunities to employ interventions that prevent disease progression and symptoms. Obviously, secondary prevention methods benefit patients because they detect disease at

an earlier stage, improving the likelihood of successful treatment.¹

A major shortcoming of these methods is borne of the very premise on which they are based: they detect in-stage disease. Clinicians employing secondary prevention methods essentially seek to treat disease that is in progress, as opposed to preventing disease. Another downside of secondary prevention methods is their tremendous dependency on patient adherence and clinician accuracy.^{2,10} For some disease states, however, secondary methods constitute the only viable option for prevention.

Papanicolaou Smear Test. The Pap test has been the gold standard of cervical cancer screening since the method was first publicized in 1943. Solid evidence shows that regularly screening the appropriate women for cervical cancer using the Pap test reduces deaths from cervical cancer by at least 80%.¹¹ Screening has been demonstrated to be effective when initiated within 3 years after the first episode of vaginal intercourse.¹¹ Regular screening with the Pap test can lead to additional procedures (eg, colposcopy and subsequent invasive cervical tissue intervention, such as laser conization biopsy or cryosurgery) for diagnosis of LSIL in the event of an ASCUS Pap test result. LSIL will often regress without invasive treatment.¹¹ The risk of undergoing additional diagnostic procedures is greatest for younger women, who have a higher prevalence of LSIL.¹¹ Further diagnostic procedures present notable logistic and financial burdens on managed care. These supplemental procedures are performed in ~50% of women who undergo regular Pap testing, of whom ~5% receive a diagnosis of LSIL.¹¹

In the classic Pap test, cells from the outer opening of the cervix are collected using an Ayre spatula and cervix brush or a plastic-fronded broom.¹² Next, the cell samples are fixed in place on a glass slide and treated with dyes and acids using the Pap smear technique. Then, the slides are evaluated using light microscopy by trained cytopathologists or cytotechnologists.¹²

The adequate and accurate collection of cervical cells during a Pap test is extremely variable and plagued by human error.¹⁰ Whether an error occurs in the collection of the sample by the clinician or in the subsequent analysis of the sample by the techni-

cian, it has great potential to produce an adverse outcome and increase managed care costs. This extends to the point of litigation: Physicians and laboratory technicians in the United States who have failed to diagnose existing cervical cancer from a Pap test have been convicted of negligent homicide.¹³ Karin Smith underwent a Pap test in 1988 and another in 1989. Prosecutors argued that both tests showed “unequivocally” that she had cervical cancer but had not been interpreted properly by laboratory technicians. Following her death on March 8, 1995, from cancer-related complications, a physician and a laboratory technician were convicted of negligent homicide.¹³ As a result, strict quality assurance programs were developed at plants across the nation and emphasis was placed on getting the message out that the Pap test was a screening test, not a diagnostic one. This disclaimer conveys that the Pap test will invariably be associated with a small but inevitable risk of error. No matter how technologically advanced the testing methodology or analysis becomes, until the human element can be better managed, inconsistencies in screening results will remain.¹⁰

The average procedural cost of conventional cervical cytology screening has been estimated to be between \$58 and \$94 (in 2000 US dollars) per test, which includes an average of \$15 for a normal test result and \$51 for an abnormal result with physician review (Figure).¹⁴ Office visit costs and time costs associated with the test have been estimated at \$22 and \$21, respectively.¹⁴ Secondary screening options in the event of an abnormal Pap test result (an ASCUS) and their associated costs will be addressed later in this supplement.

Liquid-based Testing and Computer-aided Analysis. Recent advances in traditional cervical cytology screening include liquid-based testing and computer-aided analysis. The use of liquid-based monolayer cytology, a technique in which the sample is placed in a typical ethanol-based liquid medium, has increased in recent years.¹² This method preserves the cell sample inside the liquid medium, thereby improving the accuracy of conventional Pap testing and preventing inconsistent results.¹² Cytologists process the liquid based samples into a thin layer of cells—hence, monolayer cytology.¹² The slides are then stained and examined using

light microscopy, in a manner similar to that used for conventional samples.¹² This liquid-based technique decreases unsatisfactory specimens by 1.5% (from 4.1% to 2.6%; relative frequency, 0.62; 95% CI, 0.56-0.69).¹⁵ Reducing the percentage of unsatisfactory specimens has economic and patient-centered implications, because it reduces the need for costly and invasive repeat sample collection. Studies have estimated that the sensitivity of liquid-based monolayer cytology is between 61% and 66% and specificity is between 82% and 91%.^{5,16} Some studies report that the liquid-based method has increased sensitivity, but proper sample acquisition is crucial to getting an accurate analysis, which reinforces the point that human errors can never be eliminated completely from secondary prevention methods.^{5,15,16} The newer liquid-based cytologic tests have a false-negative rate of 34% to 39% for detecting abnormal cervical cells, adding to concerns about their efficacy as a secondary prevention method.^{5,16}

In the past 10 years, further attempts to reduce the human error element of secondary prevention methods have resulted in the successful development of a few automated, computer image analysis systems for screening. These include algorithm-based screening methods like AutoPap and computerized rescreening methods such as PapNet.¹⁷ Automation might improve the sensitivity of secondary prevention methods by reducing errors related to technician analysis.¹⁸ This would benefit high-volume reference laboratories the most, where errors arising from human oversight or misinterpretation are more common. It is important to note that neither the liquid-based nor computer-automated advances diminish the conventional method's invasive nature of sample collection and therefore would have little impact on patient adherence to screening guidelines.

Technologic advances in secondary prevention come at an increased cost to managed care on the front end. The average procedural cost of ThinPrep liquid-based monolayer cytology cervical screening has been estimated to be between \$71 and \$107 (in 2000 US dollars) per test, including an average of \$28 for a normal test result and \$64 for an abnormal result with physician review (Figure).¹⁴ The increased specificity (fewer false-positive test results) of these newer techniques may partially offset their

elevated costs in the short term.^{5,16} More importantly, the increased sensitivity of these advancements may produce cost offsets that will not be realized until years later, when fewer legitimate cases of cervical cancer remain undetected as a result of clinician errors. Fewer undetected cases ultimately mean fewer cases of untreated late-stage cervical disease and, therefore, lower rates of treatment complications and mortality. Little data exist, however, that detail these potential cost offsets.

Secondary Screening for HPV Infection.

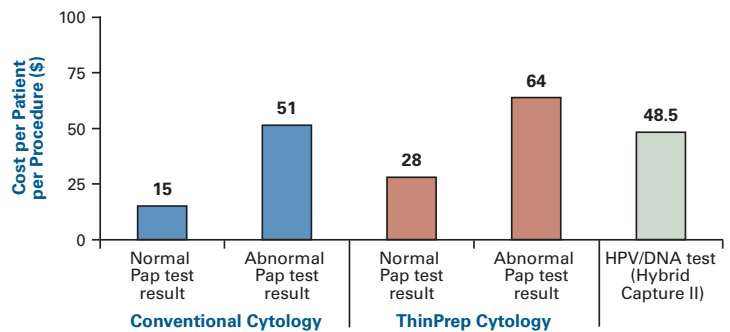
Secondary screening for HPV infection is another useful secondary prevention method, based on the correlation between HPV infection and risk of cervical cancer. The American College of Obstetricians and Gynecologists and the American Society for Colposcopy and Cervical Pathology recommend conducting HPV testing in conjunction with the Pap test for low-risk women aged >30 years.¹⁹ The main advantage of employing this combination method is the 99% negative predictive value of a double-negative test for CIN 2/3 in the subsequent 3 years.

Using the HPV testing method to co-collect cell samples along with the liquid Pap test has a sensitivity ranging from 88% to 91% for detecting CIN 3 or higher lesions and up to 97% for detecting CIN 2 and higher lesions. HPV testing also has a demonstrated specificity of 73% to 79% for detecting CIN 2 or higher lesions and a 93% specificity for detecting CIN 3 or higher lesions.^{16,20} A recent study that incorporated an HPV test with the Pap test when screening women in their mid-30s for cervical cancer reduced the incidence of CIN 2 and CIN 3 lesions detected by 42% and 47%, respectively, and decreased cases of cancer detected by subsequent screening examinations.⁸

The HPV test adds selectivity to screening, but this may come at the expense of specificity, producing more false-positive test results that subsequently increase the number of HPV-infected women who do not have cervical cancer yet undergo unnecessary colposcopy and treatment.²¹ Adding an HPV test to screening would increase managed care costs.

The role of HPV DNA reflex testing has been compared with that of colposcopy (ie, direct observation of the cervical tissue through a high-powered

■ **Figure.** Costs Associated With Various Secondary Prevention Methods for Cervical Cancer



Pap test indicates Papanicolaou's smear test; HPV, human papilloma-virus; DNA, deoxyribonucleic acid.

Source: Reference 14.

microscope or colposcope following the application of a 3% to 5% acetic acid solution, at which time cervical samples of abnormal areas can be taken to make a tissue diagnosis). This type of HPV testing could reduce the number of colposcopies necessitated by increasing the specificity of the cervical testing process.²² Randomized controlled trials suggest that HPV DNA reflex testing should be done for repeat abnormal cervical cytology testing of an ASCUS Pap test result and should precede cervical colposcopy examination.^{16,23} This would reduce unnecessary colposcopy screenings to detect HPV by 40% to 60% for those women initially screened.²² Secondary screening with HPV DNA testing using the Hybrid Capture II method carries an average procedural cost of \$48.50 per case, which is in addition to the costs of traditional cervical cytology screening (Figure).¹⁴

Follow-up Options for Abnormal Test Results

Clinicians have several options when a patient's primary screening test returns an ASCUS result. These options carry different costs and vary in terms of appropriateness on a case-by-case basis. The next steps after a patient receives an abnormal screening test result are primarily based on the patient's level of risk, the certainty of abnormality per the screening test's result, and the type of test used.²³ Because the Pap test is the most common method of primary screening, this test's result typically helps the clinician determine appropriate follow-up care. Follow-up screening options available in the event that a

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Table 2. Comparison of Pap Test Abnormalities in Terms of Follow-up Test and Treatment Options Available

Pap Test Result	Also Known As	Testing and Diagnostic Options
Atypical squamous cells—undetermined significance		HPV testing Repeat Pap test Colposcopy/biopsy Estrogen cream
Atypical squamous cells—cannot exclude high-grade squamous intraepithelial lesion		Colposcopy/biopsy
Atypical glandular cells		Colposcopy/biopsy and/or endocervical curettage
Endocervical adenocarcinoma in situ		Colposcopy/biopsy and/or endocervical curettage
Low-grade squamous intraepithelial lesion	Mild dysplasia CIN 1	Colposcopy/biopsy
High-grade squamous intraepithelial lesion	Moderate dysplasia Severe dysplasia CIN 2 CIN 3 Carcinoma in situ	Colposcopy/biopsy and/or endocervical curettage Further treatment with LEEP, cryotherapy, laser therapy, conization, or hysterectomy

Pap test indicates Papanicolaou's smear test; HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; LEEP, loop electrosurgical excision procedure. Adapted from Reference 24.

patient receives an abnormal Pap test result include repeating the Pap test, HPV testing, or colposcopy/biopsy and/or endocervical curettage.²⁴ **Table 2** outlines follow-up options for various abnormal Pap test results. If a high-risk HPV type is detected, colposcopy/biopsy are recommended because of their ability to facilitate a histologic diagnosis; this combined procedure carries an average aggregate cost of \$436 per patient.¹⁴

Treatment options often vary according to the result of colposcopy/biopsy and may include estrogen cream, loop electrosurgical excision procedure, cryotherapy, laser therapy, conization, or hysterectomy.²⁴ Treatment costs typically correlate to the colposcopy/biopsy result. For example, treatment costs per patient average \$1264 if a CIN 1 lesion is detected (although current guidelines recommend against treating CIN 1, unless it is very persistent)

and \$2833 for CIN 2 to CIN 3 lesions.¹⁴ Invasive cancer costs significantly more to treat and involves more complicated and in-depth surgical procedures, such as hysterectomy. Treatment costs per patient total approximately \$21,533 for local invasive cancer, \$23,046 for regional invasive cervical cancer, and \$36,912 for distant invasive cervical cancer (Figure).¹⁴

Other than colposcopy/biopsy, clinicians can use repeat cytology following ASCUS or LSIL results in adolescents, including tests at 6 and 12 months; they can then refer patients for colposcopy should abnormal results persist.²⁴ The previously cited cytology costs are associated with pursuit of this secondary screening route. As mentioned previously, reflex HPV DNA testing and 2-visit HPV DNA triage are also options for patients with an ASCUS Pap result.²⁴ Reclassifying ASCUS as “normal” is another option for clinicians, but this risks the possibility of overlooking signs of a legitimate case of significant dysplasia or cervical cancer. Such concerns could lead to the practice of “defensive medicine,” in which physicians repeat costly screening procedures to avoid even more costly litigation.

Conclusion

Screening as a secondary prevention method for cervical cancer has had tremendous impact in the last 60 years on lowering mortality rates associated with the disease. Following widespread adoption of the Pap test in the 1940s and 1950s, the mortality rate of cervical cancer dropped by almost 75%. Although secondary prevention through screening has had an important positive impact on managing cervical cancer, the specificity of this methodology in detecting abnormal cytology and HPV infection is flawed. Screening success also relies heavily on patient adherence to primary screening recommendations and follow-up interventions, compounding the likelihood that many cases of cervical cancer remain undetected.

Although many secondary prevention options are available, these methods are often costly in managed care, specifically in cases where repeat screenings and results analyses are needed. An inherent weakness of secondary prevention methods is that they detect existing cervical disease and do not actually prevent cervical disease, which can lead to increased morbidity and mortality and

increased costs resulting from disease complications. The technological advances that have been introduced or will be introduced in the near future are not preventive and instead report on disease already in progress. These advances reduce but do not eliminate the element of human error that is inextricably linked to the accuracy of diagnosis in current secondary prevention methods. In the event that disease is detected, resources have already been spent on screening and diagnosis, and additional financial, clinical, and emotional resources will be expended before the patient's case is resolved.

Secondary prevention remains a key historical component in the battle against cervical cancer, but the new primary prevention methods—namely, vaccines against oncogenic HPV types—will further alter the landscape. Providing access to these vaccines as a covered cost in managed care is essential to promote primary prevention of cervical disease among the highest risk groups, which are young teens and women aged <30 years. Additional public education on the importance of primary prevention needs to be directed at parents, who are the gatekeepers for their daughters' access to this vaccine. Adopting a 2-tiered approach in managed care that uses both primary and secondary prevention methods will be crucial in improving rates of cervical cancer screening and treatment outcomes in the United States. Primary prevention methods can reach those individuals who fail to get screened because of access or financial issues, such as a lack of insurance coverage. For this paradigm shift to be successful, the costs and benefits of primary and secondary prevention methods must be examined from a resource-allocation perspective. This can provide a win-win situation for consumers and the public by reducing the health burden of cervical cancer.

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