Cost-effectiveness of Alternative Triage Strategies for Atypical Squamous Cells of Undetermined Significance

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Context Every year approximately 2 million US women are diagnosed as having a cervical cytological result of atypical squamous cells of undetermined significance (ASC-US).

Objective To determine the most efficient and cost-effective management strategy for women in the United States diagnosed as having ASC-US.

Design and Setting Cost-effectiveness analysis of data from clinical trials, prospective studies, and other published literature. A computer-based model was used to compare 4 management strategies for a cytological result of ASC-US: immediate colposcopy; human papillomavirus (HPV) triage, which includes colposcopy if high-risk HPV types are detected; repeat cytology, which includes follow-up cytology at 6 and 12 months and referral for colposcopy if a repeat abnormal result occurs; and reclassifying ASC-US as normal in which a cytological result of ASC-US is ignored. Reflex HPV DNA testing uses either residual liquid-based cytological specimens or samples collected at the time of the initial screening for conventional cytology. Another method, referred to as the 2-visit HPV DNA triage, requires a woman with an ASC-US result to return within 1 month to provide another specimen sample.

Main Outcome Measures Years of life saved (YLS), quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios.

Results The least costly strategy for biennial screening was to reclassify ASC-US as normal, resulting in a reduction in total cancer incidence of 75% for conventional cytology and 84% for liquid-based cytology compared with no screening. The next least costly strategy was HPV DNA testing resulting in a reduction in total cancer incidence of 86% for conventional cytology and 90% for liquid-based cytology, followed by immediate colposcopy with a reduction of 87% and 91%, respectively. Compared with reflex HPV DNA testing, a strategy of repeat cervical cytology or delayed HPV testing costs more but is less effective. When all strategies were compared simultaneously, varying frequency and type of cytological test, biennial (vs every 3 years) liquid-based cytology with reflex HPV testing had a cost of $174,200 per YLS. In a similar comparison, liquid-based cytology with reflex HPV testing conducted every 3 years (vs every 5 years) had a cost of $59,600 per YLS and was more effective and less costly than a strategy of conventional cytology incorporating repeat cytology or immediate colposcopy conducted biennially.

Conclusion Reflex HPV DNA testing provides the same or greater life expectancy benefits and is more cost-effective than other management strategies for women diagnosed as having ASC-US.
professional organizations developing national guidelines for the optimal management of ASC, we conducted a comprehensive cost-effectiveness analysis comparing different strategies.

METHODS

Natural History Model

We modified a previously developed computer-based mathematical model, which simulates the natural history of cervical carcinogenesis using a sequence of monthly transitions among health states (FIGURE 1). HPV infection is defined as either detectable or undetectable to accurately represent the proportion of CIN 1 and CIN 2-3 that would be detectable in a clinical practice setting. This structure was chosen to permit calibration to cross-sectional data on the distribution of detectable HPV DNA within low-grade squamous intraepithelial lesions (LSILs) and high-grade squamous intraepithelial lesions (HSILs). Biopsy-confirmed cervical disease is defined as either CIN 1 or CIN 2-3, whereas cytological results are classified as ASC, LSIL, or HSIL. Invasive cervical cancer is stratified according to the cancer staging system of the National Cancer Institute’s Surveillance, Epidemiology, and End-Results Program (local, regional, and distant cancer). For our analyses, a hypothetical cohort of adolescent girls were entered into the model at age 13 years. They have never had sex, are free of disease, but at each month face an age-dependent risk of acquiring HPV. Females with detectable high-risk types of HPV (defined as HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 61 detected using a sensitive molecular assay) have a greater risk of CIN 2-3 and invasive cancer than those with undetectable HPV.

Women with HPV infection or established cervical lesions can regress to normal, progress to HSILs or cervical cancer, or stay the same. Unique health states are defined to distinguish women with previously abnormal screening results, prior treatment for CIN, and detected cervical disease (through symptoms or screening). Women may die at any age due to a cervical cancer-related illness.

Strategies

We discuss 3 main strategies to manage ASC: (1) immediate colposcopy (all women receive colposcopy); (2) HPV DNA triage (colposcopy only if high-risk HPV types are detected); (3) repeat cytology (follow-up cytology at 6 and 12 months and referral for colposcopy for a repeat cytological result of ASC, LSIL, HSIL, or cancer). We also evaluate the implications of using a higher threshold on repeat cytology (eg, HSIL for referral to colposcopy, and of a fourth strategy in which ASC is reclassified as normal (ie, a cytological result of ASC is ignored).

We used the new 2001 Bethesda System, which subcategorizes ASC into atypical squamous cells of undetermined significance (ASC-US) and atypical squamous cells that cannot exclude HSIL (ASC-H) for our base case. The ASC-H category constitutes approximately 5% of all ASC, but includes women at greatest risk for CIN 2-3. Women who are treated for CIN 2-3, or have biopsy-confirmed CIN 1 return for a repeat cytological test every year; (4) women with ASC-US in whom no CIN is identified at colposcopy return to routine screening; (5) compliance with primary screening and follow-up is 100%.

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and (6) disease status is confirmed by colposcopy and biopsy. The implications of alternative assumptions were evaluated in sensitivity analyses. We compared the different options within each possible screening frequency for both liquid-based and conventional cytology separately. Next, to identify the most efficient screening options not conditional on any particular screening interval or cytological technique, we simultaneously compared ASC-US management options, screening frequencies, and type of cytology.

We adopted a societal perspective and followed the recommendations of the Panel on Cost-effectiveness in Health and Medicine. Costs are expressed in 2000 US dollars and clinical benefits are expressed as years of life saved and quality-adjusted life-years (QALYs) gained. Future costs and life-years are discounted at an annual rate of 3%. The performance of alternative screening strategies is measured using the incremental cost-effectiveness ratio, defined as the additional cost of a specific screening strategy, divided by its additional clinical benefit, compared with the next most expensive strategy.

### Clinical Data

Selected data used for the base case are summarized in Table 1.9-11,21-61 To check the face validity of our model, we projected the age-specific prevalence of HPV, CIN, and invasive cervical cancer and compared these outputs with population-based data not used to create the model.62-72 Model corroboration was assessed by comparing the projected lifetime risk of invasive cervical cancer with estimates from other published analytic models.11,27,28,73

### Natural History

Our model requires parameters for the natural history of cervical disease conditional on a woman’s HPV DNA status. Since some of the required model parameters were not available directly from the literature, average probabilities of progression and regression of CIN were derived using data that were not stratified by HPV status.32,33 Using an independent mathematical model, we applied the relative risk of CIN with detectable HPV and the prevalence of detectable HPV to split the overall average probabilities of progression and regression of cervical lesions for women with detectable high-risk HPV DNA and women without detectable high-risk HPV DNA.

To achieve consistency with the age-specific cross-sectional data reported in the literature, the model was first used to project a series of intermediate and long-term outcomes for which there were suitable data in the absence of screening (eg, lifetime risk and age-specific cancer incidence, stage distribution of inva-

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### Table 1. Model Variables: Baseline Values and Ranges Used in Sensitivity and Specificity Analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base Case</th>
<th>Plausible Range</th>
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</thead>
<tbody>
<tr>
<td><strong>Natural History</strong></td>
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</tr>
<tr>
<td>Probability of disease progression</td>
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<tr>
<td>Normal to HPV DNA</td>
<td>0.0007-0.0209†</td>
<td>0.0004-0.0418†</td>
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<td>HPV DNA to CIN grade 1‡</td>
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<td>0.0023-0.0092</td>
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<tr>
<td>CIN grade 1 to grade 2-3</td>
<td>0.0011-0.0039†</td>
<td>0.0006-0.0078†</td>
</tr>
<tr>
<td>CIN grade 2-3 to local invasive cancer</td>
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<td>0.0020-0.0080</td>
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<tr>
<td>Local invasive cancer to regional invasive cancer</td>
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<td>0.0100-0.0400</td>
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<tr>
<td>Regional invasive cancer to distant invasive cancer</td>
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<td>0.0125-0.0500</td>
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<tr>
<td>Probability of disease regression</td>
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<td>HPV DNA to normal</td>
<td>0.0028-0.0397†</td>
<td>0.0014-0.0794†</td>
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<td>CIN grade 1 to normal</td>
<td>0.0068-0.0128†</td>
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<td>CIN grade 2-3 to normal</td>
<td>0.0029</td>
<td>0.0015-0.0058</td>
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<tr>
<td>Probability of cytology result41,42 among women with abnormal cytology and CIN grade 2-3§</td>
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<td>Atypical squamous cells</td>
<td>0.380</td>
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<td>ASC-US</td>
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<td>Annual probability of symptom detection13</td>
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<td><strong>Test Characteristics27,31-33,45-55</strong></td>
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<td>ThinPrep cervical cytology, %</td>
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<tr>
<td>Sensitivity</td>
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<td>LSIL</td>
<td>70</td>
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<tr>
<td>HSIL</td>
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<td>50-100</td>
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<tr>
<td>Specificity</td>
<td>95</td>
<td>90-100</td>
</tr>
<tr>
<td>Conventional cervical cytology, %</td>
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<tr>
<td>Sensitivity</td>
<td></td>
<td></td>
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<tr>
<td>LSIL</td>
<td>56</td>
<td>40-100</td>
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<td>HSIL</td>
<td>64</td>
<td>50-100</td>
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<tr>
<td>Specificity</td>
<td>95</td>
<td>90-100</td>
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<tr>
<td>Repeat cervical cytology</td>
<td>60</td>
<td>40-80</td>
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<tr>
<td>HPV DNA test, %</td>
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<td></td>
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<tr>
<td>Sensitivity</td>
<td></td>
<td></td>
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<tr>
<td>LSIL</td>
<td>83</td>
<td>50-100</td>
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<tr>
<td>HSIL</td>
<td>93</td>
<td>50-100</td>
</tr>
<tr>
<td>Specificity</td>
<td>75/85¶</td>
<td>50-100</td>
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</table>

(continued)
sive disease). The model was then calibrated to the approximate distribution of detectable HPV within LSIL and HSIL. The calibration required (1) approximately 20% of acquired HPV in each monthly Markov cycle to be undetectable; (2) the probability of developing LSIL among women residing in the detectable and undetectable HPV sectors of the model to be the same; and (3) the transition of LSIL to HSIL among women residing in the undetectable HPV sector to be reduced by 80% relative to those in the detectable sector. Our model projected that approximately 5% of invasive cervical cancer would appear to be HPV-negative (ie, arising from the undetectable HPV sector).

### Screening Tests

The distribution of abnormal cytological results based on cervical disease status was estimated using data from several different studies (Table 1). Data from the Columbia University Family Planning Colposcopy Clinic (1997-2001) provided probabilities of each cytological test result (ASC-US, ASC-H, LSIL, HSIL), which were conditional on the underlying disease status (normal, CIN 1, CIN 2-3, invasive cancer) (T. C. W., written communication, September 6, 2001). We then applied the relative distributions for ASC-US and ASC-H to published data that were not stratified.41,42

Estimates for the sensitivity and specificity of cervical cytology (when used for population screening) were obtained from recent published comprehensive reviews,27,44,45 while those for repeat cervical cytology and HPV DNA testing of women with ASC-US were obtained from a formal literature review conducted for the American Society of Colposcopy and Cervical Pathology national consensus conference on management of cytological abnormalities.4,5,7,8,74

### Health-Related Quality of Life

In the sensitivity analysis, the quality weights for the base case (and their plausible ranges) were 0.68 (0.60-1.00) for local cancer, 0.56 (0.40-1.00) for regional cancer, and 0.48 (0.35-1.00) for distant cancer.75 Age-specific quality weights from the Beaver Dam Health Outcomes study76 were used for noncancer states because these data were only available for women aged 40 years or older. We assumed a quality weight of 1.00 for women aged 39 years or younger.

### Costs

Selected costs are shown in Table 1.9-11,27,56-61 Direct medical costs included: screening (eg, Papanicolaou test, HPV test, treatment visit); clinician’s fee(s); workup following an abnormal cytological result (eg, colposcopy) and any necessary treatment; and inpatient and/or ambulatory medical facility. Direct medical costs for screening and treatment were derived from 3 sources.27,56-58

Cytological costs were estimated by having the model directly calculate a weighted average of normal and abnormal cervical cytological costs since abnormal results require physician review and their evaluation is reimbursed at a higher rate.37 For example, the total cost for liquid-based cytology when used for general screening ranged from $71 to $107 depending on whether physician review was required. We assumed a unit HPV DNA testing cost of $48.50 based on current Centers for Medicare and Medicaid Services (formerly the Health Care Financing Administration) reimbursement rate, but this var-

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Table 1. Model Variables: Baseline Values and Ranges Used in Sensitivity and Specificity Analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Direct Medical Costs, US $ in 20009-11,27,56-61</th>
</tr>
</thead>
<tbody>
<tr>
<td>ThinPrep cervical cytology</td>
<td>71-107</td>
</tr>
<tr>
<td>Normal Papanicolaou test result</td>
<td>28 14-100</td>
</tr>
<tr>
<td>Abnormal Papanicolaou test result with physician review</td>
<td>64 32-150</td>
</tr>
<tr>
<td>Office visit</td>
<td>22 11-50</td>
</tr>
<tr>
<td>Time cost</td>
<td>21 11-200</td>
</tr>
<tr>
<td>Conventional cervical cytology</td>
<td>58-94</td>
</tr>
<tr>
<td>Normal Papanicolaou test result</td>
<td>15 0-100</td>
</tr>
<tr>
<td>Abnormal Papanicolaou test result with physician review</td>
<td>51 0-150</td>
</tr>
<tr>
<td>Office visit</td>
<td>22 0-50</td>
</tr>
<tr>
<td>Time cost</td>
<td>21 0-200</td>
</tr>
<tr>
<td>HPV DNA test (Hybrid Capture II)</td>
<td>48.50 25-200</td>
</tr>
<tr>
<td>Co-collection fee with conventional cytology</td>
<td>2 0-10</td>
</tr>
</tbody>
</table>

**Aggregate Costs, US $ in 2000**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Base Case</th>
<th>Plausible Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colposcopy and biopsy</td>
<td>436</td>
<td>200-600</td>
</tr>
<tr>
<td>CIN grade 1</td>
<td>1264</td>
<td>800-1706</td>
</tr>
<tr>
<td>CIN grade 2-3</td>
<td>2833</td>
<td>1500-3275</td>
</tr>
<tr>
<td>Local invasive cervical cancer</td>
<td>21 533</td>
<td>9439-21 946</td>
</tr>
<tr>
<td>Regional invasive cervical cancer</td>
<td>23 046</td>
<td>11 734-29 089</td>
</tr>
<tr>
<td>Distant invasive cervical cancer</td>
<td>36 912</td>
<td>12 670-81 549</td>
</tr>
</tbody>
</table>

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Cost-Effectiveness of Management Strategies for ASC-US

Biennial screening using liquid-based cytology

No screening 210 28.69869

Biennial screening using liquid-based cytology

Ignore ASC-US 1423 1213 28.78741 84.03 12 300 13 700

Reflex HPV DNA testing 1712 1213 28.79370 90.45 13100 14 500

Repeat cytology 1820 51 28.79370 90.45 Dominated| Dominated

Immediate colposcopy 1867 155 28.79411 90.54 667 300 905 300

Biennial screening using conventional cytology

Ignore ASC-US 1199 960 28.78186 78.87 10 500 11 900

HPV DNA testing† 1472 273 28.78997 86.39 28 200 33 600

2-Visit HPV DNA testing 1479 7 28.78997 86.39 Dominated| Dominated

Repeat cytology 1523 108 28.78589 84.97 Dominated| Dominated

Immediate colposcopy 1595 132 28.79019 86.56 433 800 570 900

Biennial screening using conventional cytology

Ignore ASC 1170 960 28.77807 74.52 11 100 12 100

HPV DNA testing† 1461 292 28.78987 86.30 20 400 24 700

2-Visit HPV DNA testing 1471 109 28.78987 86.30 Dominated| Dominated

Repeat cytology 1520 596 28.78807 84.28 Dominated| Dominated

Immediate colposcopy 1594 133 28.79019 86.56 312 000 411 500

†HPV indicates human papillomavirus; ASC-US, atypical squamous cells of undetermined significance; and ASC, atypical squamous cells. Base case analyses were performed using data from Kaiser Permanente. Costs expressed in dollars are based on US values.

‡Incremental costs represent the difference between the strategy and the next best nondominated strategy.

§The difference in cost divided by the difference in quality-adjusted life expectancy or life expectancy for each strategy compared with the next best strategy. All strategies are assumed to be equally available.

‖Incremental tests for dominated strategies.

*This strategy assumes co-collection of a second specimen at the time of the initial Papanicolaou test, which is stored until the patient’s cervical cytology result is available and used only if the initial cytology result is ASC.

#Results reflect the traditional unstratified cytological category of ASC. See “Methods” for details.
screening using liquid-based cytology, the least costly strategy was to reclassify ASC-US as normal (ie, ignore a result of ASC-US), followed sequentially by HPV DNA testing, repeat cytology, and then immediate colposcopy. Compared with no screening, a strategy in which ASC-US was ignored increased discounted life expectancy by 32 days with a cost of $13,700 per year of life gained. Compared with ignoring ASC-US, reflex HPV DNA testing was associated with an incremental life expectancy benefit of 2 days with a cost of $4,440 per year of life gained. In comparison, repeat cytology was more expensive and less effective than HPV testing. Compared with HPV testing, immediate colposcopy provided an additional 2 hours in life expectancy and had an incremental cost-effectiveness ratio of $905,300 per year of life gained. Results in which life expectancy was quality-adjusted were similar (Table 2).

We repeated these analyses in the context of conventional cytology and evaluated these testing strategies: (1) reflex HPV testing using samples co-collected at the time of conventional cytology and (2) 2-visit HPV DNA testing in which a woman with an ASC-US result has to return for an HPV test. Provided that compliance with the repeat visit was 100%, the 2-visit HPV DNA testing strategy was just as effective as reflex HPV testing using co-collected samples. As estimates of compliance with the second visit decreased, the reflex HPV testing strategy using co-collected samples became more effective. As expected, under the base-case assumptions, the 2-visit HPV DNA testing was more costly than reflex HPV testing using co-collected samples. To quantify the trade-off between the cost of co-collection vs the cost of a second visit, we determined the monetary threshold at which the cost-effectiveness ratios for the 2 HPV testing strategies converge. We found that unless the cost of a repeat visit was less than $32 (including the cost of medical staff, office visit, transportation, and patient time), the co-collection strategy would be preferred.

Results were similar for analyses in which the categories of ASC-US and ASC-H were not segregated but grouped under the single traditional cytological diagnosis of ASC (lower third of Table 2). HPV DNA testing with biennial screening using conventional cytology had a cost of $24,700 per year of life gained and immediate colposcopy exceeded $400,000 per year of life gained, making it more expensive than other strategies. The life-expectancy gains associated with all strategies except immediate colposcopy were somewhat lower than in the base case; however, these differences were almost immeasurable. Stratification of ASC had a significant impact only in the context of ignoring an ASC result. Biennial screening with conventional cytology provided a 79% reduction in cancer incidence using the new stratified terminology (ASC-US and ASC-H) compared with a 75% reduction using a single cytological category of ASC.

Figure 3 shows the relationship between the discounted costs and life expectancies for all 37 potential screening strategies. This analysis assumes all strategies are available and are feasible options. The cost-effectiveness of moving from one screening strategy to a more costly alternative is represented by the difference in cost divided by the difference in life expectancy associated with the 2 strategies (this is expressed as a cost-effectiveness ratio and is shown for each nondominated strategy). Strategies on the efficiency curve dominate those to the right of the curve because they are more effective, and either cost less or have a more attractive cost-effectiveness ratio than the next best strategy.

Every 5-year screening using conventional cervical cytology and ignoring an ASC-US result had a cost-effectiveness ratio of $7,100 per year of life gained compared with no screening. Every 5-year screening with reflex HPV DNA testing yielded an incremental cost-effectiveness ratio of

YLS indicates years of life saved; ASC, atypical squamous cells; and HPV, human papillomavirus.

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$12,100 per year of life gained compared with ignoring ASC-US. Every 5-year screening with liquid-based cytology and reflex HPV DNA testing was substantially more effective and cost $20,300 per year of life gained. The costs for the same strategy conducted per year of life gained are $59,600 for every 3 years and $174,200 for every 2 years. All strategies that relied on annual screening, regardless of the ASC-US management option, provided minimal incremental life-expectancy gains and had cost-effectiveness ratios exceeding $500,000 per year of life gained.

The inconvenience of co-collection may preclude its widespread adoption in settings where liquid-based cytology is considered too expensive for routine use. However, a longer screening interval of 3 years using the liquid-based cytology strategy of reflex HPV testing is more effective and less costly than a screening interval of every 2 years using the conventional cytology strategies of repeat cytology or immediate colposcopy.

**Sensitivity Analyses**

These general results were not sensitive to analyses of screening test performance, alternative management options for CIN 1, cost of the workup for an abnormal screening test result, and the costs of CIN 2-3 and cervical cancer treatment. Repeat cytology was no longer dominated when the cost of HPV DNA testing exceeded $190. The rank ordering of strategies did not change despite varying the costs of colposcopy of between $200 and $600.

When noncompliance was assumed to be random (ie, all women are equally likely to be noncompliant), lower rates of compliance resulted in lower costs and more attractive cost-effectiveness ratios. For example, when compliance was decreased to 60% for each return visit in the strategies of repeat cytology, reflex HPV testing no longer dominated repeat cytology because the cost savings associated with losing patients to follow-up was relatively greater than the loss in clinical benefits. When noncompliance was assumed to be systematic (ie, women at greater risk for cervical cancer are more likely to be noncompliant), this counterintuitive result was somewhat blunted—lower rates of compliance were still associated with lower costs, but the loss in clinical benefits resulting from women at high risk being lost to follow-up were greater than when women were at average risk. In both situations, however, HPV DNA testing remained more effective than repeat cytology and had an attractive cost-effectiveness ratio of between $19,000 and $29,000 per year of life gained compared with repeat cytology strategy when using biennial screening with liquid cytology. This pattern was similar for noncompliance with screening, follow-up visits, and colposcopy.

**COMMENT**

Managing the approximately 2 million US women with equivocal cervical cytological results each year is a significant clinical and public health problem. This year a national consensus conference was held to develop evidence-based guidelines for the management of women with cervical cytological abnormalities. To provide information for the guideline process, we conducted a comprehensive cost-effectiveness analysis of alternative strategies for women with ASC.

We first assessed the best option for ASC-US management given a particular clinical screening practice, since all possible strategies evaluated in this article may not be universally accessible and feasible. Our results indicate that a policy of ignoring a cytological result of ASC-US reduces the effectiveness of cervical cancer screening compared with HPV testing, repeat cytology, or immediate colposcopy, especially when longer screening intervals or less sensitive screening methods are used. There are extremely small differences between the 3 ASC-US management strategies in terms of cancer incidence reduction, although under all conditions repeat cervical cytology is somewhat less effective than either HPV DNA testing or immediate colposcopy. In contrast, the costs associated with ASC-US management strategies differed substantially. Immediate colposcopy was always more costly than either repeat cervical cytology or HPV DNA testing. Regardless of the clinical scenario evaluated, referral of all women with ASC-US for colposcopy had incremental cost-effectiveness ratios exceeding $200,000 per year of life gained compared with HPV DNA testing. Reflex HPV DNA testing was always less costly than repeat cytology, in part because it eliminates the need for a repeat clinical examination to obtain a cervical specimen in the case of ASC-US and reduces the number of colposcopic examinations by 40% to 60% compared with immediate colposcopy. Our results were not affected by reasonable changes in screening costs, performance of HPV testing, and cytology, and time costs. Our base case incorporated the new 2001 Bethesda System that subcategorizes ASC into ASC-US and ASC-H. Recent clinical practice guidelines recommend that since women with ASC-H are at increased risk for having CIN 2-3, they should have immediate colposcopy. However, our analyses indicate that subcategorizing ASC makes little difference in terms of clinical benefits, provided some follow-up of ASC-US occurs.

We then assessed the most efficient screening options by considering alternative strategies to manage ASC-US while simultaneously varying all possible screening frequencies and type of cytological tests. This was done from a broad health policy perspective and assuming all strategies are equally available and feasible. Similar to others, we found that all strategies that rely on annual screening, regardless of the ASC-US management option, provide minimal incremental life-expectancy gains compared with less frequent screening strategies and have extremely high and unattractive cost-effectiveness ratios (> $500,000 per year of life gained). A biennial screening program using liquid-based cytology combined with reflex HPV DNA testing for women with ASC-US is more effective and less costly than annual conventional cytology coupled with either repeat cervical cytology or colposcopy for women with ASC-US. However, the cost-
effectiveness ratio of this strategy ($174,200 per year of life gained) is higher than many clinical preventive interventions that have been adopted in the United States.\textsuperscript{87} There is no consensus that defines the cost per QALY and represents an acceptable value for money, however, cost-effectiveness ratios are often placed in context by comparisons with interventions that are widely mandated, such as hemodialysis for end-stage renal disease of between $60,000 and $128,000 per year of life gained.\textsuperscript{88} In our model, screening performed every 3 years, using liquid-based cytology coupled with reflex HPV DNA testing, has an incremental cost-effectiveness ratio of approximately $60,000 per year of life gained over screening performed every 5 years and would be considered a cost-effective intervention. It is important to emphasize, however, that in the context of current cervical cancer screening practices in the United States, shifting women currently being screened annually with conventional cytology coupled with repeated cytology for an ASC-US result to biennial liquid-based cytology and reflex HPV DNA testing would save more than $15 billion over the lifetime of a typical cohort of 18-year-old to 24-year-old women.\textsuperscript{89}

Our analysis has a number of limitations. There is considerable uncertainty with respect to the longitudinal nature of HPV infection and our results may be further refined as better data become available. There is also considerable variability with respect to the distribution of cytological results in women with CIN 2-3, although our results did not change significantly despite using parameters from 3 different clinical studies.\textsuperscript{40,82} Unknown factors that contribute to population heterogeneity and possible cofactors that contribute to an individual’s risk of disease progression could not be modeled,\textsuperscript{82} although we did try to explore the implications of certain heterogeneous behaviors, such as those reflecting noncompliance.\textsuperscript{91}

This analysis provides important insights for both policy makers developing management guidelines for women with ASC results, as well as for clinicians caring for these women. In interpreting these findings, it is important to recognize that not only are women’s relative preferences for a potential outcome important when deciding the best option in a given clinical setting, but other factors must also be considered.\textsuperscript{92} For example, there are settings in which liquid-based cytology is already the standard of care, and others in which conventional cytology is the only option. Some settings will find co-collection suited to their daily operational systems and others will not. However, many of our key findings were robust in a variety of settings. First, in the context of current cervical cancer screening practice in the United States, follow-up for ASC-US provides clinical benefits at a reasonable cost. Second, under the conditions of our base case, reflex HPV DNA testing appears to provide clinical benefits similar to those of immediate colposcopy for women with ASC-US, but is less costly. Finally, a triennial or biennial cervical cancer screening program incorporating liquid-based cytology and reflex HPV DNA testing is more effective and less costly than annual screening with conventional cytology and repeat cytology for women with ASC. Thus, the aggregate health economic costs saved by adopting such a policy would be enormous.

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