Cervical Cancer Screening in Average-Risk Women: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians

George F. Sawaya, MD; Shalini Kulasingam, PhD; Thomas D. Denberg, MD, PhD; and Amir Qaseem, MD, PhD, MHA, for the Clinical Guidelines Committee of the American College of Physicians*

Description: The purpose of this best practice advice article is to describe the indications for screening for cervical cancer in asymptomatic, average-risk women aged 21 years or older.

Methods: The evidence reviewed in this work is a distillation of relevant publications (including systematic reviews) used to support current guidelines.

Best Practice Advice 1: Clinicians should not screen average-risk women younger than 21 years for cervical cancer.

Best Practice Advice 2: Clinicians should start screening average-risk women for cervical cancer at age 21 years once every 3 years with cytology (cytologic tests without human papillomavirus [HPV] tests).

Best Practice Advice 3: Clinicians should not screen average-risk women for cervical cancer with cytology more often than once every 3 years.

Best Practice Advice 4: Clinicians may use a combination of cytology and HPV testing once every 5 years in average-risk women aged 30 years or older who prefer screening less often than every 3 years.

Best Practice Advice 5: Clinicians should not perform HPV testing in average-risk women younger than 30 years.

Best Practice Advice 6: Clinicians should stop screening average-risk women older than 65 years for cervical cancer if they have had 3 consecutive negative cytology results or 2 consecutive negative cytology plus HPV test results within 10 years, with the most recent test performed within 5 years.

Best Practice Advice 7: Clinicians should not screen average-risk women of any age for cervical cancer if they have had a hysterectomy with removal of the cervix.

In 2015, an estimated 12,900 U.S. women will be diagnosed with cervical cancer, and 4,100 will die of the disease (1). Over the past several decades, incidence and mortality have steadily decreased; the current estimated incidence rate is 7.8 cases per 100,000 women per year (2). These decreases have been largely attributed to widespread screening. Although the benefits have been substantial, cervical cancer screening is costly. In 2010, the direct medical cost for screening and follow-up was estimated at $6.6 billion (3) and was probably greater because patient time and out-of-pocket expenditures were not included in the analysis.

Cervical cancer screening is commonly done in the United States; an estimated 89% of the target population of about 70 million women report having been screened in the past 5 years (4). Recent evidence-based guidelines for screening have refined the approach in an effort to minimize harms and maximize benefits. In general, the approach has focused on increasing the age at which to begin screening, lengthening the screening interval, and discontinuing screening in women at low risk for future cervical cancer. Overuse of screening contributes to higher health care costs without improving patient outcomes.

The purpose of this best practice advice article from the Clinical Guidelines Committee of the American College of Physicians (ACP) is to describe the indications for screening for cervical cancer. The target audience is all clinicians, and the target patient population is asymptomatic, average-risk women aged 21 years or older. This article is supported by the American Congress of Obstetricians and Gynecologists (ACOG) and endorsed by the American Society for Clinical Pathology (ASCP).

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* This paper, written by George F. Sawaya, MD; Shalini Kulasingam, PhD; Thomas D. Denberg, MD, PhD; and Amir Qaseem, MD, PhD, MHA, was developed for the Clinical Guidelines Committee of the American College of Physicians. Individuals who served on the Clinical Guidelines Committee from initiation of the project until its approval were Thomas D. Denberg, MD, PhD (Chair); Paul Shekelle, MD, PhD (Immediate Past Chair); Michael J. Barry, MD; Roger Chou, MD; Molly Cooke, MD; Paul Dallas, MD; Nick Fitterman, MD; Mary Ann Forcieria, MD; Russell P. Harris, MD, MPH; Linda L. Humphrey, MD, MPH; Devan Kansagara, MD, MCR; Robert M. McLean, MD; Tanveer P. Mir, MD; Amir Qaseem, MD, PhD, MHA; Holger J. Schünemann, MD, PhD; J. Sanford Schwartz, MD; Donna E. Sweet, MD; and Timothy Wilt, MD, MPH. Approved by the ACP Board of Regents on 15 November 2014.
WHAT ARE THE BENEFITS OF CERVICAL CANCER SCREENING?

Cervical cancer is believed to be the long-delayed consequence of infection with high-risk (or oncogenic) types of human papillomavirus (HPV) (5). Human papillomavirus infections are common, and most are transient. Persistent high-risk HPV infection can lead to cervical precancerous lesions known as cervical intraepithelial neoplasia, which can become invasive. Identification and treatment of CIN lesions through screening lead to reductions in cervical cancer incidence, morbidity, and mortality. Detection of early-stage asymptomatic cancer also contributes to decreased morbidity by making women eligible for treatments with lower morbidity.

WHAT ARE THE HARMS OF CERVICAL CANCER SCREENING?

Harms can occur at any and all points along the sequence of care: collection of cervical specimens, diagnostic evaluation, cervical treatments, and posttreatment surveillance. Collection of cervical samples is generally well-tolerated by women (6, 7). Abnormal screening test results can cause short-term anxiety, including concerns about sexually transmissible infections and their consequences (5).

The likelihood of abnormal test results varies by age, test, and setting. Because the prevalence of high-risk HPV infection peaks shortly after initiation of sexual intercourse, rates of positive HPV test results are highest among women younger than 25 years and decrease with advancing age (5). Positive results occur in about 30% of women aged 21 to 24 years compared with about 12% of those aged 30 to 34 years and 5% of those aged 60 to 64 years (8, 9). Rates of cytologic abnormalities also decrease with age: About 13% of women aged 21 to 24 years have abnormalities (9) compared with about 7% of those aged 30 to 34 years and 3% of those aged 60 to 64 years (8). In the setting of a prepaid health plan, about 9% of women aged 30 to 64 years had either an abnormal cytologic test result or a positive HPV test result (8).

The prevalence of underlying CIN grade 2 or a more severe lesion follows similar age-related patterns, ranging from 12% among women aged 21 to 24 years to 2.4% among those older than 50 years (9). The most severe cytologic abnormalities (squamous cell cancer and high-grade squamous intraepithelial lesion) are uncommon but carry a predicted 5-year risk of about 85% for CIN grade 2 or a more severe lesion. In contrast, the less severe but more common abnormal finding of a normal cytologic test result with a positive HPV test result carries a predicted 5-year risk of about 10% (10).

WHAT ARE THE EVIDENCE-BASED RECOMMENDATIONS FOR CERVICAL CANCER SCREENING?

In 2012, the U.S. Preventive Services Task Force (USPSTF) (22); the ACOG (23); and the American Cancer Society (ACS), in collaboration with the American Society for Colposcopy and Cervical Pathology (ASCCP) and the ASCP (24), released revised recommendations for cervical cancer screening (Table). For the first time, these guidelines agree about the populations to whom the recommendations apply, the ages at which to begin and end screening, the appropriate screening intervals, and the appropriate tests to be used.
The scientific rationale for these recommendations is outlined in detail in all of the guideline documents and can be summarized as follows. Cytologic abnormalities are common in women younger than 21 years, yet clinically important cervical lesions are rare (5). Thus, if screened, many women in this age group will have colposcopy and biopsy, and some will be treated for lesions that have a high likelihood of regression. To minimize this harm, screening before age 21 years is not recommended, regardless of sexual history. Annual screening is no longer recommended because too-frequent screening leads to higher rates of false-positive results, with little effect on subsequent cervical cancer because of the long time between cervical pre-cancerous lesions and invasion. The estimated average time for a high-grade precancerous lesion to progress to cervical cancer is 10 years (25), which allows ample time for identification and treatment of such lesions. Ending screening is important because cervical cancer is uncommon among older women with normal prior screening results, yet the chance of false-positive results and subsequent invasive interventions persists (26). Ending screening before age 65 years in women with life-limiting comorbid conditions seems reasonable, although the process by which an evidence-based recommendation can be made is unclear. Surgical removal of the cervix reduces risk for cervical cancer to zero, making screening after total hysterectomy extremely low-value.

All 3 guidelines endorse the strategy of cytology plus testing for high-risk HPV types (known as cotesting) in women aged 30 to 65 years as an alternative to cytology alone. The rationale behind cotesting is that women with normal cytologic test results and no evidence of high-risk HPV constitute a particularly low-risk group in which screening intervals may be safely lengthened to every 5 years; the cumulative risk for being diagnosed with CIN grade 2 or a more severe lesion over the subsequent 5 years is estimated at 0.34% (27). The guidelines also agree that HPV tests alone (22, 23) or in combination with cytology (22-24) should not be used for primary screening in women younger than 30 years, in part because of the high prevalence of HPV infection among women in this age group. In fact, the USPSTF issued a grade D recommendation for HPV testing in this age group, indicating at least moderate certainty that there is no net benefit or that the harms outweigh the benefits.

Despite these guidelines being largely concordant, a few differences are notable. The ACS/ASCCP/ASCP guideline specifically states that annual testing should not be performed in women of any age. It also states that the strategy of HPV testing plus cytology is preferred to cytology alone among women aged 30 to 65 years, although this is a “weak recommendation,” indicating substantial uncertainty about the balance of benefits and harms. The ACOG agrees that cotesting is preferred, citing evidence that HPV testing improves detection of adenocarcinoma, which comprises about 20% (28) of all cervical cancer histologic types. The USPSTF states that both strategies are acceptable; cotesting is not preferred and should be applied only to women who would like to extend intervals to every 5 years. This recommendation was based in part on a decision analysis showing that these strategies confer similar benefits (cancer cases and cancer deaths prevented) and harms (false-positive test results and colposcopies) (29). From a population perspective, extending intervals to 5 years among cotested women is important to balance the effect of positive HPV test results (30). Of note, the cost-effectiveness of these 2 strategies has not been sufficiently explored to fully understand whether one is preferred from an economic and societal perspective (10).

### DOES PRACTICE FOLLOW THE EVIDENCE?

Clinician surveys have been useful in monitoring adherence to guidelines. Although it is too soon to know how clinician behaviors have changed since the publication of the 2012 guidelines, past results have been discouraging. Clinicians have poor adherence to cervical cancer screening guidelines (31–33) and begin screening too early (34), perform screening too often (34–37), and do not end screening in women who are at low risk on the basis of age criteria (31, 38, 39) or because they have had hysterectomy (40, 41). Moreover, nonadherence to guidelines for the management of women with mild screening test abnormalities—specifically, more intensive surveillance than is deemed necessary—has also been reported (33, 35).

There is much room for improvement. Recent self-reported estimates suggest that approximately 60% of women have been screened by age 21 years (40) and approximately 53% of women aged 75 to 79 years and 38% of those aged 80 years or older have been re-screened.
recently screened (38). Although recent reports have suggested that the age of screening initiation is increasing (42) and cervical cancer screening visits for women aged 65 years or older are decreasing (39), it is unclear whether these changes are due to clinician adherence to guidelines, evolving patient acceptance of less screening, or changes in reimbursement for services that are not endorsed by guidelines.

**WHAT ARE THE ECONOMIC IMPLICATIONS OF OVERUSE OF CERVICAL CANCER SCREENING?**

Increasing the age of first screening from 18 to 21 years has been shown to result in cost savings, with small differences in discounted average quality-adjusted life expectancy (43) due to a higher relative burden of low-grade precancerous lesions, most of which resolve spontaneously (44). Further increasing the age of first screening to 25 years results in additional cost savings and small differences in average quality-adjusted life expectancy (compared with initiating screening at age 18 years) due to a slight increase in cancer incidence among women aged 20 to 24 years compared with those younger than 20 years (43, 45).

The economic implications of screening before age 21 years are substantial. If we assume that screening is restricted to young women who are sexually active and correct for self-reporting (46–48), we estimate that approximately 290,000 women younger than 21 years are screened annually. The estimated annual screening costs range from $21.7 million to nearly $40 million. These estimates are conservative because they do not include costs of follow-up or costs for the small proportion of young women who are not sexually active but may be screened nonetheless (32).

The cost-effectiveness of screening for cervical cancer has been shown to exceed $500,000 per quality-adjusted life-year (QALY) gained when screening is conducted annually, whether with cytology alone or cytology in combination with HPV DNA testing (49, 50). Depending on the type of strategy modeled, biennial screening has been associated with incremental cost-effectiveness ratios of approximately $150,000 to $200,000 per QALY gained (43, 50, 51). The high cost-effectiveness ratios associated with frequent screening are due to a linear increase in costs for screening, follow-up, and treatment (when the same strategy is compared with a fixed sensitivity and specificity) but incrementally smaller gains in averted cervical cancer cases. Most lesions detected at the more frequent intervals would typically regress if left untreated. In contrast, the cost-effectiveness ratio of screening every 3 to 5 years has been shown to be less than $100,000 per QALY gained (43, 52). All QALY analyses, however, are limited by the lack of a comprehensive set of utilities capturing women’s preferences for health states that follow from various strategies, including those incorporating HPV testing (53).

Of the currently recommended strategies, cytology alone has the lowest sensitivity but the highest specificity for detection of CIN grade 2 or a more severe lesion, including cancer. Cost-effectiveness analyses suggest that strategies that include HPV tests and cytology can achieve similar gains in quality-adjusted life expectancy compared with cytology alone at a similar or lower lifetime cost if conducted at a less frequent interval (50). In other words, a strategy with a higher sensitivity and lower specificity can achieve similar or greater reductions in cancer because the costs associated with a lower specificity are offset by fewer overall screening tests.

For women aged 65 years or older who have been screened according to recommendations and have prior normal test results, the burden of continued screening due to false-positive test results (including unnecessary colposcopies) is predicted to be high relative to further benefits (44). After correcting for the high prevalence of hysterectomy in this age group (54), we estimate that the annual cost of screening women aged 65 to 75 years ranges from approximately $50 million to $90 million. This is probably an overestimate because it does not account for the unknown proportion of unscreened and underscreened women for whom screening would be recommended.

For women who have received all 3 doses of an HPV vaccine per the recommended schedule before the onset of sexual activity (when vaccine efficacy is highest), delaying the first screening to age 25 years and using a screening interval of 5 years is predicted to be cost-effective (43). Screening this group at an earlier age (18 or 21 years) and a more frequent interval (1 to 2 years) is predicted to result in incremental cost-effectiveness ratios exceeding $500,000 per QALY (43). However, current recommendations are to continue screening vaccinated women by using the same strategies as those for unvaccinated women given the lack of observed data to confirm model predictions about several key parameters for a vaccinated population, including continued participation in screening, performance of screening tests, and reductions in cancer (55).

**WHAT FORCES PROMOTE OVERUSE OF CERVICAL CANCER SCREENING?**

**Clinician Factors**

The success of public health campaigns promoting cancer screening is bolstered by their ability to deliver clear, simple messages. “Get a Pap test every year” was easy for women to remember and for clinicians to implement as part of an annual well-woman examination. Long-held beliefs are difficult to change. A recent nationwide survey of U.S. obstetrician-gynecologists (42) provides insight into their concerns about lengthening the intervals between gynecologic examinations, including cytologic tests: About three quarters believed that lengthening intervals would decrease patient health, well-being, and satisfaction. Nearly 80% expected financial reimbursements to decrease. Fear of litigation is often cited as a deterrent to less frequent screening, although most lawsuits are not successful as long as care is based on evidence.
Patient Expectations

Although some women prefer less frequent pelvic examination, especially those with a history of sexual trauma (56), many others have expressed a preference for frequent testing to prevent cancer, even if this results in anxiety due to false-positive test results or unnecessary procedures (57, 58). A nationally representative survey of women aged 40 years or older that asked about cytology-based cervical cancer screening revealed that women prefer annual screening and that few expect to stop having cytologic tests before age 80 years (58) or ever (59). Patients also expressed the view that recommendations to screen for cancer less frequently are driven by efforts by insurance companies and government payers to save money (58, 60).

How Can Physicians Reduce Overuse of Cervical Cancer Screening?

Physicians and other health care providers can play a major role in reducing overuse of cervical cancer screening. They must first know current guidelines and should understand the reasoning behind the recommendation for less testing. The desire to find the right balance between benefits and harms should be familiar to all physicians steeped in a tradition of doing no harm. One way to explain these new guidelines to women reluctant to be screened less frequently is to be frank about the expected balance of benefits and harms: “I am concerned that if we screen you more frequently than is recommended, we will be doing more harm than good. In your case, I have a professional obligation to let you know that the harms of screening are likely to outweigh the benefits.” Recent studies have shown that physicians are willing to screen less frequently than every year (36) and that women accept less screening if recommended by their clinicians (59).

Clinicians should be aware of recent statements made by professional societies about less cervical cancer screening. As part of the Choosing Wisely initiative of the American Board of Internal Medicine (61), in which national organizations of medical specialists were asked to identify 5 commonly used tests or procedures in their field that should be questioned, the ASCP suggested that clinicians not order testing for low-risk cervical HPV types because the results have no effect on clinical management. The American Academy of Family Physicians advised against screening women younger than 21 years, women who have had hysterectomy for noncancerous conditions, and low-risk women older than 65 years. It also recommended not using HPV testing alone or in combination with cytology in women younger than 30 years. The ACOG recommended against annual screening of low-risk women aged 30 to 65 years. Finally, the American Society of Nephrology suggested that routine screening for cancer, including cervical cancer, not be performed in patients with end-stage renal disease who are receiving dialysis and have limited life expectancy.

Health care systems can play an important role in encouraging adherence to evidence-based guidelines. Adherence to guidelines seems to be higher in prepaid health plans than in fee-for-service settings, suggesting that characteristics of the practice setting may have an important effect (37). It has long been hoped that adoption of electronic medical records would allow opportunities for clinicians to be reminded of current guidelines and even specifically prompted when ordering tests that have a high likelihood of not being indicated. Electronic medical records have been shown to be useful in identifying low-value cervical cancer screening (62), and evidence suggests that tools based on electronic medical records can decrease inappropriate cervical cancer screening (63).

The National Committee for Quality Assurance has long had a measure for cervical cancer screening in the Healthcare Effectiveness Data and Information Set that addresses whether cervical cancer screening has been performed within the target population. In 2014, a new performance measure was proposed to address inappropriate screening. The measure, entitled “nonrecommended cervical cancer screening in adolescent females,” would capture the percentage of adolescent females aged 16 to 20 years who are unnecessarily screened for cervical cancer (64). This measure is directly derived from the 2012 guidelines that discourage screening before age 21 years. It is hoped that by adding overscreening as a measure of poor-quality care, clinicians and the health systems in which they work will have greater incentives to adhere to current guidelines.

Future Directions

Clinicians can expect future guidelines to include more sophisticated targeting of women at highest and lowest risk for cervical cancer to further maximize screening benefits and minimize harms. Specifically, the age of screening initiation may increase as HPV vaccination becomes widespread. Vaccination should also decrease the incidence of cervical cancer precursors, thus further minimizing screening harms. Screening intervals may be further lengthened and screening may end earlier if women can be stratified by molecular and cytologic test results that can predict even lower risk status. Current guidelines do not address ending screening among women with limited life expectancy due to medical comorbid conditions, but such guidance would be useful.

In 2014, the U.S. Food and Drug Administration approved high-risk HPV testing alone (9) as a primary screening test, and recent interim guidance from a group of experts recommended triennial screening beginning at age 25 years (65). This decision will be controversial given current recommendations to avoid HPV testing in women younger than 30 years, due in part to the relatively high prevalence of HPV among women aged 25 to 29 years (21%) (9). Of note, the major guideline groups cited earlier have not issued recommendations about this strategy.
As new screening strategies emerge, so will a critical need for comparative effectiveness analyses that delineate the economic implications of choosing one strategy over another. Such analyses will be useful in directing clinicians and women to high-value screening options (54). Finally, amid enthusiasm for new screening tests, clinicians should be aware that providing women with affordable and easily accessible screening (regardless of method), coupled with streamlined follow-up of abnormal test results and timely treatment, will realize the highest impact of screening on cervical cancer incidence and mortality.

**CONCLUSION**

As clinicians adhere more strongly to guidelines, it is anticipated that the harms and costs of cervical cancer screening will be minimized and the benefits will be maximized.

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**Figure.** Summary of the American College of Physicians best practice advice on cervical cancer screening in average-risk women.

**SUMMARY OF THE AMERICAN COLLEGE OF PHYSICIANS BEST PRACTICE ADVICE ON CERVICAL CANCER SCREENING IN AVERAGE-RISK WOMEN**

<table>
<thead>
<tr>
<th>Disease/Condition</th>
<th>Cervical precancerous and cancerous lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target Audience</td>
<td>Primary care physicians, family physicians, obstetrician-gynecologists, and other clinicians</td>
</tr>
<tr>
<td>Target Patient Population</td>
<td>Women aged ≥21 y</td>
</tr>
<tr>
<td>Interventions</td>
<td>Cytology tests and tests for high-risk types of HPV</td>
</tr>
<tr>
<td>Benefits of Screening</td>
<td>Decreased cervical cancer morbidity and mortality</td>
</tr>
<tr>
<td>Harms of Screening</td>
<td>Discomfort from speculum examinations and colposcopies, pain and bleeding from cervical biopsies and excisional treatments, prolonged surveillance, and potential adverse obstetric outcomes with some excisional treatments.</td>
</tr>
<tr>
<td>Approaches to Overcome Barriers to Evidence-Based Practice</td>
<td>Adherence to current evidence-based guidelines, electronic health record prompts, and explanations to patients.</td>
</tr>
<tr>
<td><strong>Best Practice Advice</strong></td>
<td></td>
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<tr>
<td>Best Practice Advice 1: Clinicians should not screen average-risk women aged &lt;21 y for cervical cancer.</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Best Practice Advice 7: Clinicians should not screen average-risk women of any age for cervical cancer if they have had a hysterectomy with removal of the cervix.</td>
<td></td>
</tr>
<tr>
<td>Talking Points for Clinicians When Discussing Cervical Cancer Screening With Average-Risk Women</td>
<td>Beginning screening too soon can lead to investigation of transient abnormalities and treatment of cervical lesions that may resolve without treatment.</td>
</tr>
<tr>
<td></td>
<td>Screening more often than every 3 y increases harms of false-positive test results and invasive procedures yet confers little benefit.</td>
</tr>
<tr>
<td></td>
<td>Continued screening of low-risk women after age 65 y provides little or no benefit but can lead to invasive tests and procedures.</td>
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<tr>
<td></td>
<td>After hysterectomy with removal of the cervix, women are no longer at risk for cervical cancer yet may have invasive procedures for test abnormalities.</td>
</tr>
</tbody>
</table>

HPV = human papillomavirus.

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**ACP Best Practice Advice**

Best Practice Advice 1: Clinicians should not screen average-risk women younger than 21 years for cervical cancer.

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Cervical Cancer Screening in Average-Risk Women

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Best Practice Advice 7: Clinicians should not screen average-risk women of any age for cervical cancer if they have had a hysterectomy with removal of the cervix.

The Figure summarizes the recommendations and clinical considerations.

From the University of California, San Francisco, Center for Healthcare Value, San Francisco, California; University of Minnesota School of Public Health, Minneapolis, Minnesota; Carilion Clinic, Roanoke, Virginia; and American College of Physicians, Philadelphia, Pennsylvania.

Note: Best practice advice papers are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment. All ACP best practice advice papers are considered automatically withdrawn or invalid 5 years after publication or once an update has been issued.

Disclaimer: The authors of this article are responsible for its contents, including any clinical or treatment recommendations.

Financial Support: Financial support for the development of this paper comes exclusively from the ACP operating budget.

Disclosures: Dr. Sawaya reports that he was commissioned by the American College of Physicians to write this manuscript and received an honorarium. Dr. Kulasingam reports personal fees from the American College of Physicians during the conduct of the study. Dr. Barry reports grants, personal fees, and nonfinancial support from the Informed Medical Decisions Foundation/Healthwise and personal fees and nonfinancial support from Massachusetts General Hospital/Harvard Medical School outside the submitted work. Dr. Schünemann reports that he played a critical role in the World Health Organization cervical cancer screening and treatment guidelines for low- and middle-income countries. Authors not named here have disclosed no conflicts of interest. Authors followed the policy regarding conflicts of interest described at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M14-2426. A record of conflicts of interest is kept for each Clinical Guidelines Committee meeting and conference call and can be viewed at www.acponline.org/cclinical_information/guidelines/conflicts_cgc.htm.

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Obtaining of funding: A. Qaseem.
Administrative, technical, or logistic support: G.F. Sawaya, A. Qaseem.