

Human Papillomavirus Triage of Atypical Squamous Cells of Undetermined Significance: Cost-Effective, But At What Cost?

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Since the introduction of cytology for cervical cancer screening more than 50 years ago, deaths from cervical cancer in the United States have declined by about 75% (1). However, an estimated 3700 women will die from cervical cancer in the United States in 2005 (2). Among the 55 million Pap smears performed in the United States annually, roughly 3 million show atypical cells of undetermined significance (ASCUS), a conundrum for pathologists, clinicians, and patients (3).

Great strides have been made in understanding the underlying biology of cervical cancer. Infection with an oncogenic human papillomavirus (HPV) is necessary but not sufficient for its development. Recent research has attempted to improve the sensitivity of cervical cancer screening to reduce false-negative tests and hence prevent more deaths from cervical cancer. Testing for oncogenic HPV has been shown in the ALTS trial (3) and other studies (4–6) to be an effective triage strategy for women with ASCUS, identifying a great majority of women with underlying cervical intraepithelial neoplasia. In this strategy, women with ASCUS who test positive for oncogenic HPV are referred for colposcopy, whereas those with negative test results return to routine screening.

Kulasingam et al., in their carefully executed cost-effectiveness analysis, compare the relative costs and outcomes of this strategy with alternatives, employing effectiveness data derived from the ALTS trial and direct medical costs derived from Medicare reimbursement rates (7). Estimating the additional cost of HPV DNA testing at \$84 (\$29 for the HPV test and \$55 for an office visit), they compare HPV triage with the use of a single repeat Pap test, and they calculate the incremental average cost per additional case of cervical intraepithelial neoplasia 3 or cancer detected to be \$3514. This is less costly and more effective than serial repeat Pap smears or immediate colposcopy (using the reference colposcopy findings as true positive). The ranking of strategies was robust under a variety of sensitivity analyses.

As the authors acknowledge, however, this type of analysis has limitations. Because of the limitations of the ALTS data and the nature of the model, years of life “saved” cannot be estimated alongside the estimated additional costs. Their findings can be viewed in light of earlier analyses that have applied different datasets to compare the cost-effectiveness of HPV triage strategies in the context of an overall cervical cancer screening program: Kim et al. estimated that screening every 3 years with liquid-based cytology and reflex HPV triage testing of ASCUS (using specimens collected for the liquid-based Pap) had an incremental average cost-effectiveness of \$59 600 per year of life saved compared with ignoring an ASCUS result and was more effective and less costly than alternative strategies for evaluation of ASCUS (8). A variety of screening strategies were also compared from

the perspective of the U.S. Military Health System in an analysis by Maxwell et al. (9). In that analysis, screening with conventional cytology every 3 years cost \$4017 per life-year saved compared with no screening; the addition of liquid-based cytology and reflex HPV triage of ASCUS results to conventional cytology cost on average \$14 263 per life-year saved. Both analyses concluded that serial repeat cytology for ASCUS was more costly and less effective than HPV triage and that annual screening strategies applying any follow-up method were prohibitively costly and added little additional effectiveness.

Although these analyses offer important information to health policy makers and clinicians regarding the management of ASCUS, a broader perspective on the problem of reducing morbidity and mortality from cervical cancer is needed. None of these analyses collected information on the preferences of women related to the different strategies for cervical cancer screening or ASCUS management. Women are not indifferent to alternative screening protocols, and their preferences among protocols are not confined to differences in the outcomes of those protocols (10,11). Failure to consider women’s preferences among different protocols may affect the uptake of or compliance with screening programs. Studies of the effectiveness and costs of alternative strategies should include the preferences of women at risk of cervical cancer. More work that measures women’s preferences for cervical cancer screening is urgently needed.

Although the use of HPV testing for triage of ASCUS may be relatively cost-effective compared with several possible alternatives, the cost-effectiveness ratio fails to impart to the decision maker the impact of the program on the total cost of care. With about 3 million Pap smears diagnosed as ASCUS each year, 3 million HPV DNA tests would be required to implement the program at current levels of screening utilization. At a cost of \$84 per test, an additional \$250 million would be required. If liquid-based testing is routine and HPV testing for ASCUS is done reflexively, the incremental cost is less but the overall cost of screening is greater. Decision makers will need to consider the value of HPV triage in relation to the expected benefits, in terms of the quality and quantity of life-years produced, and weigh these potential benefits against the substantial extra resource

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requirements (i.e., where will these resources be found? What are the potential benefits of using these resources for other programs?). Cost-effectiveness ratios measure the costs of additional effects produced by alternative programs requiring different levels of investments and hence different opportunity costs. The choice facing decision makers is not simply that between one program and another but one between the more costly program on the one hand and, on the other hand, the less costly program plus other programs that together use the same resources as the more costly program.

High opportunity costs are well illustrated by the mounting evidence regarding high costs for annual screening with very minimal additional benefit over screening every 3 years (8,9,12). An overall shift in recommendations in the United States now supports screening for cervical cancer every 2–3 years for most women rather than annually (13–15). Despite this consensus to move away from routine annual screening, American women continue to expect and receive annual screening (16). In fact, 69% of American women without a cervix had a Pap smear between 1999 and 2002, despite extensive evidence of no benefit and recommendations by respected authorities not to screen (17). Health care resources consumed by overscreening could be applied to programs targeting unscreened or underscreened women, with much greater benefits. The recommendations for cervical cancer screening will likely change again when HPV vaccines under development (18–20) become available. For a vaccine-based strategy to be effective, however, girls and young women will need to have access to the vaccine and to be accepting of its use.

Finally, taking a step back, the persistence of cervical cancer mortality, for which effective screening has been available longer than for any other cancer, has been identified as a sentinel marker for health care disparities in the United States. Mortality from cervical cancer shows strong geographic clustering, with higher risks for African American women and those with lower income, less education, and less access to health care. Women in areas of high cervical cancer mortality also have higher rates of mortality from breast and colorectal cancers, cardiovascular disease, and stroke (1). Reducing and eliminating these disparities will require a systems perspective, taking into account opportunity costs, preferences, cultural issues, organization of and, most importantly, access to care. Investing the \$250 million it would cost to support HPV triage (together with additional resources that could be conserved by limiting overscreening) to provide improved access to health care, including cervical cancer screening, for all American women might have greater impact on cervical cancer mortality than applying those resources to HPV triage of ASCUS.

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