

**Re: Comparison of Three Management Strategies for Patients With Atypical Squamous Cells of Undetermined Significance: Baseline Results From a Randomized Trial**

In their study of alternative management strategies for women with equivocal Pap smears, Solomon et al. (1) concluded that "HC 2 [Hybrid Capture 2™] testing for cancer-associated HPV [human papillomavirus] DNA . . . has greater sensitivity to detect CIN3 [cervical intraepithelial neoplasia grade 3] or above and specificity comparable to a single additional cytologic test indicating ASCUS [atypical squamous cells of undetermined significance] or above."

Solomon et al. (1) reported that the HPV test had a 96.3% sensitivity to detect CIN3 or higher (CIN3+) and a 10.0% positive predictive value in a population with a 5.1% prevalence of CIN3+. However, these data imply that the specificity of the HPV test was only 53.4%. Solomon et al. further reported that a repeat Pap smear based on the LSIL+ (i.e., low-grade squamous intraepithelial lesion or higher) had a 64.0% sensitivity to detect CIN3+ and a 14.3% positive predictive value in the same population. From the latter data, I calculate that the specificity of the follow-up Pap smear based on the LSIL+ criterion was actually 79.4%.

My calculations are given in Table 1, which shows the distributions of HPV test results (panel A) and follow-up Pap smear results based on the LSIL+ criterion (panel B) in a standard population of 10 000 women with atypical squamous cells on initial Pap smear.

The trade-off between the higher sensitivity of the HPV test and the higher specificity of the repeat cytology based on LSIL+ becomes especially important when the prevalence of disease is as low as 5.1%. For every 10 000 women with equivocal Pap smears, comparison of panels A and B shows that the HPV test will correctly identify 165 additional cases of high-grade cervical neoplasia (i.e., 491 – 326). However, at the same time, the test will mistakenly send to colposcopy an additional 2465 women who do not have precancerous or can-

**Table 1.** Relationship between test results and the presence of cervical intraepithelial neoplasia of grade 3 or higher (CIN3+) in a population of 10 000 women with atypical squamous cells of undetermined significance\*

A) HPV test results versus presence of CIN3+			
	Negative HPV test	Positive HPV test	Total
Disease (CIN3+) present	19	491	510
Disease (CIN3+) absent	5071	4419	9490
Total	5090	4910	10 000

Prevalence of CIN3+ = 510/10 000 = 5.1%†  
Sensitivity of HPV test = 491/510 = 96.3%‡  
Positive predictive value = 491/4910 = 10.0%§  
Negative predictive value = 5071/5090 = 99.6%||  
Specificity of HPV test = 5071/9490 = 53.4%¶

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B) Follow-up Pap test results versus presence of CIN3+			
	Negative Pap test#	Positive Pap test#	Total
Disease (CIN3+) present	184	326	510
Disease (CIN3+) absent	7536	1954	9490
Total	7720	2280	10 000

Prevalence of CIN3+ = 510/10 000 = 5.1%†  
Sensitivity of follow-up Pap test = 326/510 = 63.9%‡  
Positive predictive value = 326/2280 = 14.3%§  
Negative predictive value = 7536/7720 = 97.6%||  
Specificity of follow-up Pap test = 7536/9490 = 79.4%¶

\*HPV = human papillomavirus.

†The prevalence of a disease is the proportion of the population with the disease (4). Solomon et al. (1) reported a prevalence of CIN3+ of 5.1% among women with initially equivocal Pap smears.

‡The sensitivity of a test is the proportion of diseased persons with a positive test (4). Solomon et al. [Table 5 in (1)] reported sensitivities of 96.3% and 64.0%, respectively, for the HPV test and follow-up cytology based upon LSIL+ (i.e., low-grade squamous intraepithelial lesion or higher).

§The positive predictive value is the proportion of persons with a positive test who have the disease (4). Solomon et al. [Table 5 in (1)] reported positive predictive values of 10.0% and 14.3%, respectively, for the HPV test and follow-up cytology based on LSIL+.

||The negative predictive value is the proportion of persons with a negative test who are disease free (4). Solomon et al. [Table 5 in (1)] reported negative predictive values of 99.5% and 97.1%, respectively, for the HPV test and cytology based on LSIL+.

¶The specificity of a test is the proportion of disease-free persons with a negative test (4).

#In panel B, a follow-up Pap test is positive if an LSIL+ is detected.

cerous cervical lesions (i.e., 4419 – 1954).

The results reported by Solomon et al. (1) were widely misinterpreted by the media (2,3), which highlighted the finding that the HPV DNA test had a negative predictive value of 99.5% in the detection of high-grade cervical neoplasia. However, the negative predictive value is the probability that a patient with a negative HPV test did not have high-grade cervical neoplasia. By contrast, the specificity is the probability that a woman without high-grade cervical neoplasia had a negative HPV test (4).

Unless the HC 2 test can be improved to identify the specific oncogenic subtypes of HPV DNA, it may not be superior to repeat cytology. Barring such improvements, we will need to balance the benefits of early detection of cervical neoplasia in 165 additional cases per 10 000 women against the higher costs

of the HC 2 test and the costs and trauma of unnecessary colposcopy in 2465 additional cases per 10 000 women.

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## NOTE

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The Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Epithelial Neoplasia (ASCUS/LSIL) Triage Study (ALTS) is a milestone in efforts to determine the utility of human papillomavirus (HPV) DNA assays as an adjunct to primary cervical cytologic screening. Reporting for the ALTS investigators, Solomon et al. (1) present important data regarding the sensitivity of the Hybrid Capture 2™ (HC 2) HPV DNA test in detecting high-grade cervical intraepithelial neoplasia (CIN) following a borderline cytologic finding. Solomon et al. (1) conclude that, “[HC-2] sensitivity, combined with reasonable specificity for triage, makes HPV testing a viable option for the management of ASCUS [lesions found to be borderline by cytology].”

There is reason for concern, though, that these encouraging findings might be misinterpreted by nonexpert readers. The *New York Times* (2), for example, reported, “The NCI [National Cancer Institute] said that women who receive borderline abnormal results should be tested for HPV . . .” If the perception that HPV DNA testing is the “standard of care” were to become widespread in the general public, it could be difficult to change, even if further investigation demonstrates that conservative management is more appropriate. Recent conversations with physicians have indicated that they too often fail to appreciate the preliminary nature of the findings to date.

Secondly, it is important to point out that the utility of HPV triage could possibly vary by age group and specific population characteristics, because of differences in positive predictive value. In sexually active college-aged women, for example, HPV DNA cumulative prevalence is very high (40%–60%), but the prevalence of CIN3 or higher (CIN3+), which increases with age, is very low (3). Few true positives (CIN3+), relative to other groups, and greater potential for false-positive findings (i.e., accurate positive HPV DNA results but no detectable morphologic changes present) could result in a lower

positive predictive value (true positives/true positive + false positives) (4). In fact, an increase in the false-positive rate would mean reduced specificity (true negatives/true negatives + false positives). Thus, the performance of the assay itself, in terms of detecting cervical disease, could potentially vary among populations. In keeping with this concern, the investigators reported that the prevalence of HPV varied among clinical centers (patient groups) from 31% to 60%, a nearly twofold difference. It will be important, therefore, for physicians to know the positive likelihood ratio (sensitivity/1 – specificity) for HPV DNA testing in a given age group and population, as well as the pretest probability of disease, before choosing to use HPV triage with a given patient. In populations that vary substantially from the ALTS cohort (e.g., human immunodeficiency virus-positive women), it may be necessary to conduct separate studies. Similar considerations apply to suggestions that HPV triage be used to determine the frequency of cervical cancer screening following a normal cytologic finding (5). Because of its strong study design and exceptional clinical work, the ALTS will carry special weight in the medical community. To begin to address the above issues, it would be helpful for the investigators to present the age- and population-specific data from the current investigation.

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## NOTES

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## RESPONSE

Both letters raise important points regarding the utility of HPV testing as a triage modality following an ASCUS cytology result. Harris correctly points out that there is an inevitable trade-off between specificity and sensitivity. The tests and test thresholds used in medical practice for follow-up and/or treatment of cervical abnormalities depend not only on available technology, but also on prevailing management paradigms, medicolegal issues, economic factors, and societal expectations. In the United States, sensitivity has generally been emphasized over specificity and other issues in the context of cervical cancer screening.

In our recent publication (1) comparing management strategies for women with ASCUS, we reported the sensitivity for detecting CIN3 and the percentage of women referred to colposcopy (as a proxy for specificity) for HPV DNA testing performed using an analytical threshold of 1 pg/mL and for repeat cytology at several cutpoints. We were careful not to suggest that our results establish a new “standard of care.” Rather, it is the purview of the relevant medical organizations to develop guidelines for medical practice based on the available data. In fact, a conference is already planned for September 2001 under the aegis of the American Society for Colposcopy and Cervical Pathology to develop evidence-based “Consensus Guidelines for the Management of Cytological Abnormalities and Cervical Cancer Precursors.” In the future, when longitudinal data from our study become available, we will consider the cost-effectiveness and patient acceptance of the different management strategies in ALTS to further inform development of practice guidelines.

We also agree with Strickler and Shah that population characteristics may

affect the utility of HPV testing as a strategy for triage of ASCUS cytology. A detailed analysis of age and other factors on the performance of both cytology and HPV testing is the subject of a forthcoming ALTS publication.

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## NOTES

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