

Identifying Women With Cervical Neoplasia Using Human Papillomavirus DNA Testing for Equivocal Papanicolaou Results

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PAPANICOLAOU (PAP) CERVICAL cytology screening has helped reduce cervical cancer rates dramatically since its implementation in the 1950s. Pap test reporting classifications have evolved and been refined, with the current standard being the Bethesda system.¹ The management of equivocal Pap test abnormalities remains a large and complex clinical and public health challenge. The most common abnormal Pap test result is one of uncertainty, atypical squamous cells of undetermined significance (ASCUS). In the United States, about 2 million ASCUS Pap reports occur each year. A survey of Pap smear reporting rates in US cytology laboratories found a median of 2.9% ASCUS results, with 10% of laboratories reporting ASCUS rates of more than 9%.²

See also p 1645 and Patient Page.

Context A Papanicolaou (Pap) test result of atypical squamous cells of undetermined significance (ASCUS) presents a clinical challenge. Only 5% to 10% of women with ASCUS harbor serious cervical disease, but more than one third of the high-grade squamous intraepithelial lesions (HSILs) in screening populations are identified from ASCUS Pap test results.

Objective To determine whether human papillomavirus (HPV) DNA testing of residual material from liquid-based Pap tests and referral of cases found to be HPV-positive directly to colposcopy could provide sensitive detection of underlying HSILs in women with ASCUS Pap results, compared with repeat Pap testing.

Design and Setting Natural history of women with ASCUS Pap smear results, all of whom had liquid-based cytology, HPV testing, and subsequent repeat Pap tests and colposcopy with histologic evaluation, conducted at 12 gynecology clinics in a large managed care organization between October 1995 and June 1996.

Participants From a cohort of 46 009 women who had routine cervical examinations, 995 women with Pap test results of ASCUS who consented to participate were identified.

Main Outcome Measures Cervical histology, HPV test results, and repeat Pap smear results, and sensitivity of HPV testing to identify patients found to have HSIL+ histology.

Results Of 995 participants with ASCUS Pap test results, 973 had both a definitive histologic diagnosis and HPV result. Sixty-five (6.7%) had histologic HSIL or cancer. For women with histologic HSIL+, the HPV test was positive in 89.2% (95% confidence interval [CI], 78.4%-95.2%), and the specificity was 64.1% (95% CI, 60.9%-67.2%). The repeat Pap smear result was abnormal in 76.2% (95% CI, 63.5%-85.7%). Triage based on HPV testing only or on repeat Pap testing only would refer similar proportions (approximately 39%) to colposcopy. The sensitivity of HPV DNA testing for HSIL was equivalent to, if not greater than, that of the repeat Pap test. We further estimated that an HPV-based algorithm including the immediate colposcopy of HPV-positive women, and then repeat Pap testing of all others, would provide an overall sensitivity of 96.9% (95% CI, 88.3%-99.5%).

Conclusions For women with ASCUS Pap tests, HPV DNA testing of residual specimens collected for routine cervical cytology can help identify those who have underlying HSIL. By testing the specimen collected at initial screening, the majority of high-risk cases can be identified and referred for colposcopy based on a single screening.

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A comprehensive study showed that the ASCUS cytology report is not reproducible, even among expert cervical cytopathologists.³ Other research demonstrates that while the majority of ASCUS Pap test results reflect a benign reactive process, 5% to 10% of the women with ASCUS results harbor underlying high-grade squamous intraepithelial lesions (HSILs).⁴⁻⁶ We recently estimated that more than one third of the HSILs in a routine screening population are heralded by ASCUS cytology.⁶

A primary goal of Pap screening and follow-up procedures is to prevent cervical cancer by identifying and treating high-grade precursor lesions. Given the relatively large proportion of HSIL cases that are associated with ASCUS cytology, effective triage of ASCUS re-

ports is essential. Although routine colposcopic evaluation of all ASCUS cases would provide the greatest patient protection, the frequency of ASCUS makes this impractical. Recent guidelines⁷ propose immediate colposcopy, repeat Pap testing, or adjunctive testing for triage of ASCUS cytology.

Researchers have sought diagnostic tools to identify higher-risk ASCUS cases and direct them to colposcopy and in turn, refer those at lower risk for periodic repeat Pap testing. Human papillomavirus (HPV) DNA is associated with virtually all cervical cancers⁸ and their high-grade precursor lesions.⁹ Several studies suggest that the Hybrid Capture test (Digene Corporation, Beltsville, Md) for cancer-associated HPV types is useful for identifying patients with ASCUS Pap results who have underlying HSIL.^{4,5,10,11}

The requirement of a second examination to repeat Pap testing or obtain a specimen for HPV testing raised concerns about the efficiency and cost-effectiveness of these approaches for ASCUS triage.^{5,11} Recent pilot studies using liquid-based cytology (ThinPrep Pap, Cytec Corporation, Boxborough, Mass) demonstrated the utility of a single specimen for cytologic diagnosis and subsequent HPV testing, when indicated.¹²⁻¹⁶ If HPV DNA testing were conducted on residual material collected for routine liquid-based Pap screening, then the second examination could be eliminated and ASCUS patient management decisions could be streamlined.

This study evaluated the utility of a new, more sensitive HPV test, performed on liquid-based cytology specimens, for the triage of women with ASCUS Pap results to colposcopy. We compared the diagnostic value of a triage strategy that bases colposcopy referral on the HPV test result with a strategy based on repeat Pap testing. We used our results to estimate the diagnostic utility of the ASCUS management strategy shown in the FIGURE. The algorithm includes "reflex" HPV DNA testing of all ASCUS cases; the immediate colposcopic examination of women who are HPV-positive; and for

HPV-negative women, repeat Pap testing (again with HPV testing of ASCUS) in about 6 months, with referral to colposcopy if findings are abnormal.

METHODS

Initial cohort study participants (n = 995) were identified from a cohort of 46 009 women belonging to the Kaiser Permanente Medical Care Program, Northern California Region, who had a routine cervical Pap examination at 1 of 12 gynecology clinics at 4 participating medical centers between October 1995 and June 1996. Pregnant women and women treated for cervical neoplasia less than 6 months prior were excluded from the cohort.

Based on data from 34 759 women at 3 of the 4 medical centers, the mean age of the cohort was 40 years (range, 14-92 years).⁶ Kaiser Permanente membership is demographically similar to the US Census-enumerated population in the Bay Area Metropolitan Statistical Area, except for lacking representation of extremes in income.¹⁷ The study was approved by the institutional review board of the Kaiser Foundation Research Institute, Oakland, Calif.

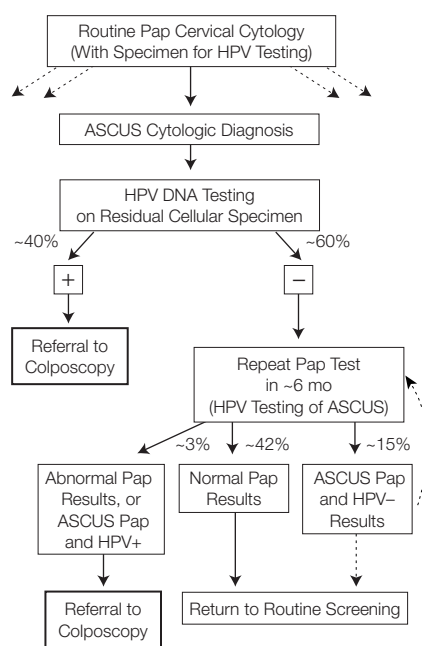
Cohort Screening Examinations

At the routine gynecologic examinations, ectocervical and endocervical specimens were collected with a cervical broom (Papette, Wallach Surgical Devices, Orange, Conn), smeared onto a slide, and spray-fixed for conventional Pap testing. Residual material on the broom was rinsed into PreservCyt fluid (Cytec Corporation). If cervical stenosis precluded endocervical insertion of the broom, a supplementary endocervical cytobrush sample was taken and processed with the broom specimen. After the cytology specimen was collected, another cervical sample was obtained with a conical brush (Medical Packaging Inc, Camarillo, Calif) and placed into specimen transport medium (STM) (Digene Corporation) for HPV testing.

Cytology

Abnormal Pap smear results were recorded on a study report form by the

Figure. Proposed Algorithm for the Triage of Women With ASCUS Papanicolaou Test Results



Routine Papanicolaou (Pap) screening with liquid-based methods (ThinPrep) provides a single specimen appropriate for both cytology and for human papillomavirus (HPV) testing, if indicated. Alternatively, with conventional Pap tests, a specimen specifically for HPV testing can be collected and stored. HPV DNA testing refers to a test for cancer-associated HPV types. Abnormal Pap refers to abnormalities greater than atypical squamous cells of undetermined significance (ASCUS).

Kaiser Permanente pathology department serving the clinic, according to the Bethesda system.¹ ASCUS reports were qualified as “favor reactive,” “favor neoplastic,” or “undetermined.” Pap smears with a result including atypical glandular cells of undetermined significance (AGUS) in addition to ASCUS were considered AGUS cases and were part of a separate study on AGUS. Abnormal Pap history was recorded from the Pap smear request form and computerized cytology records.

Repeat conventional Pap specimens collected at the colposcopy examinations were evaluated by the standard practices of the participating pathology departments and we accessed results from cytology records. Results from these Pap tests were used to estimate the results of a repeat Pap test conducted within 6 months.

ThinPrep Pap Cytology

When the study began in 1995, ThinPrep Pap testing was not yet approved by the US Food and Drug Administration (FDA). Therefore, we were unable to use ThinPrep cytology as the primary screening method for the detection of abnormal Pap cases. Funding limitations made it impossible to conduct ThinPrep Pap testing on the entire screening cohort of 46 000 women, in addition to the conventional Pap test. Therefore, we conducted ThinPrep testing only on specimens from women whose conventional test results were reported as abnormal. Thus, the data from this study cannot be used to compare the performance of ThinPrep with conventional Pap testing, since we did not include cases that had a normal conventional test result and a corresponding ThinPrep that was abnormal.

Within 3 weeks of collection, a ThinPrep Pap slide was prepared from the initial specimen from each of the cohort members with an abnormal conventional Pap test result. A specially trained cytotechnologist (B.J.F.) and pathologist (K.M.M.) at the Kaiser Permanente Regional Laboratory used the Bethesda system and study forms, as de-

Table 1. Histology and Other Test Results for Women With an ASCUS Pap Test Result*

Consensus Histology	No. of Patients	HPV Positive†	ThinPrep Pap Result Abnormal‡	Repeat Pap Result Abnormal§
Normal	783 (80.4)	239 (30.5)	335 (42.8)	245/770 (31.8)
LSIL	125 (12.8)	87 (69.6)	82 (65.6)	79/124 (63.1)
HSIL	64 (6.7)	57 (89.1)	54 (84.4)	47/62 (75.8)
Cancer	1 (0.1)	1 (100)	1 (100)	1/1 (100)
Total	973 (100)	384 (39.5)	472 (48.6)	372/957 (38.9)

*ASCUS indicates atypical squamous cells of undetermined significance; Pap, Papanicolaou test; HPV, human papillomavirus; LSIL, low-grade squamous intraepithelial lesion; and HSIL, high-grade squamous intraepithelial lesion. All data presented as number (percentage).

†DNA testing for HPV of specimens taken at initial visit.

‡From specimens taken at initial visit, result of ASCUS or more severe.

§Result of ASCUS or more severe on Pap smear taken at time of colposcopy. Not available for 16 women. Data presented as number/total specimens for repeat examination.

scribed above, to report ThinPrep Pap results for the ASCUS cases in the study.

Participant Recruitment

Study nurses attempted to contact all women with ASCUS (n = 1632) or greater abnormalities on their conventional Pap tests and asked them to return to their provider for colposcopy. Women were excluded if they were pregnant, were no longer Kaiser Permanente members, had moved, or if their provider deemed them ineligible (eg, due to serious illness). Complete documentation on reasons for exclusions was not available. Informed consent for the study was requested at the colposcopy visit of 1340 eligible women. Efforts of the medical staff to obtain consent varied between the clinics. For participating minors, consent was obtained from their mothers.

Colposcopy Examinations

Repeat Pap collections (including specimens for ThinPrep and HPV testing) were obtained prior to acetic acid application. Colposcopy with biopsy and/or endocervical curettage (ECC) was performed on all participants by experienced staff physicians or nurse practitioners. In cases in which no lesion requiring biopsy was seen, an ECC was performed. In other cases, ECCs were performed at the discretion of the colposcopist. Examinations were conducted without knowledge of the patients' HPV or ThinPrep Pap results.

Participants (n = 995) are defined as consenting, eligible women with ASCUS conventional Pap test results

from whom cervical tissue was obtained for histology.

Histology

Histopathologic diagnoses were made without knowledge of HPV results. Pathology reports were used for patient management decisions. To obtain consensus histologic diagnoses, a study pathologist (M.E.S.) reviewed the slides without knowledge of the diagnosis. If the first 2 diagnoses disagreed, another study pathologist (R.J.K.) reviewed the case, with no knowledge of preceding diagnoses. Consensus diagnoses were determined by two-thirds majority when possible, and remaining discrepancies were resolved by conference review (led by J.E.R.). For cases with both biopsy and ECC results, we report the most severe consensus diagnosis. Specimens from 17 participants were considered insufficient. The low-grade squamous intraepithelial lesion (LSIL) consensus category included diagnoses of condyloma and cervical intraepithelial lesion 1; the high-grade squamous intraepithelial lesion (HSIL) consensus category included cervical intraepithelial lesions 2 and 3 and/or carcinoma in situ. Cases with a consensus histologic diagnosis of HSIL or cancer are denoted “HSIL+.” Thirteen cases with diagnoses of atypia, including atypia in squamous metaplasia, are included in the “normal” category in TABLE 1 (HPV prevalence in atypia and normal cases were identical).

HPV Testing

At the Kaiser Permanente Regional Laboratory, we conducted HPV DNA testing

Table 2. HPV and Repeat Pap Test Results in Women With Histologic HSIL+*

Repeat Pap Test Results	HPV Positive†	HPV Negative‡
Normal	13	2
ASCUS or AGUS	21	2‡
LSIL	8	1
HSIL	14	2
Total	56§	7

*HPV indicates human papillomavirus; Pap, Papanicolaou test; HSIL, high-grade squamous intraepithelial lesion; HSIL+, HSIL or cancer; ASCUS, atypical squamous cells of undetermined significance; AGUS, atypical glandular cells of undetermined significance; and LSIL, low-grade squamous intraepithelial lesion.

†DNA testing for HPV of specimens taken at initial visit (ASCUS Pap results).

‡For both, specimens collected at time of repeat Pap testing for HPV were positive, and both were ASCUS.

§Repeat Pap results were not available for 2 women with HSIL+ histology; both women were HPV-positive.

independently on PreservCyt and the STM specimens that were collected at the initial Pap examination. We used the Hybrid Capture II microplate method¹⁸ and a probe mix for the detection of high-risk HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, and 58. (The HPV test used in this study was a prototype of the now commercially available FDA-approved Hybrid Capture II assay, and did not include probes for types 59 and 68.) Specimen transport medium specimens were processed according to the manufacturer's instructions, using 5% of the cervical specimen for testing. After Thin-Prep slide preparation, aliquots (1.5 mL, 7.5% of specimen) were centrifuged, and the pellets were suspended in 50 μ L of STM and processed as in the STM protocol. Most (990/995) of the PreservCyt specimens had sufficient material for HPV testing after slide preparation. Triplicate assay controls representing 0, 1.0, 2.5, and 5.0 pg/mL of HPV DNA were included. Specimens were considered positive for high-risk HPV types if their assay chemiluminescence was at least that of the three 1.0-pg/mL controls averaged.

When comparing STM specimens with corresponding PreservCyt specimens, we found 89% overall agreement, a κ coefficient of 0.77, and no significant differences ($P = .27$) between 922 matched pairs. We found no differences in HPV prevalence or test sensitivity or specificity for HSIL. Therefore, we present only

the PreservCyt results from the initial Pap examination.

Testing for HPV was also conducted on the STM specimens taken at the repeat Pap examination (at the colposcopy visit). These data are not shown, but are mentioned briefly in the Figure.

Data Analyses

We used statistical software SAS version 6.11¹⁹ and StatXact 3²⁰ for analyses. We calculated 95% confidence intervals (CIs) for proportions,²¹ determined trend significance using the Cochran-Armitage test, compared test performance in matched pairs with the McNemar test, and compared proportions using the Fisher exact test. We applied exact methods when expected cell frequencies were less than 5.

RESULTS

Cytology reports for the 46 009 women who had routine Pap smear screening included 3.5% ASCUS, 0.5% AGUS, 0.9% LSIL, and 0.3% HSIL. The percentage of results reported as ASCUS ranged from 2.7% to 4.9% in the 4 participating facilities. Of the 1632 women with ASCUS Pap smear results, 1340 eligible women (82%) returned for colposcopic examination. Of those, 995 (61% of all ASCUS cases) participated in the study. Participation rates ranged from 44% to 83% (of all ASCUS cases) among the study clinics. As a group, participants were similar to nonparticipants in terms of age, recorded abnormal Pap history, and residential ZIP code (data not shown), suggesting that our participants were representative of all ASCUS cases in the original cohort.

The median age of the participants was 37 years (range, 15-78 years). Of the 850 participants who provided their race/ethnicity, 64% identified themselves as white, 9% as black, 14% as Hispanic, 11% as Asian/Pacific Islander, and the remainder as other categories. Of the 995 initial ASCUS Pap smear reports, 451 (45.3%) were qualified as favor reactive, 273 (27.4%) as favor neoplastic, and 271 (27.2%) as undetermined.

Colposcopy examinations with repeat Pap specimen collection were conducted

a median of 67 days (range, 12-240 days) after the initial Pap examination. Table 1 shows consensus histology and other test results in the 973 patients for whom both a definitive histologic diagnosis and HPV result were available. Normal histology was found in most (79.1%) of the women. One invasive cancer was identified. The ages of women with HSIL ranged from 18 to 63 years (median, 30 years). For the 65 HSIL and cancer cases, the initial ASCUS Pap test results were reported as favor reactive for 10 (15.4%), favor neoplastic for 30 (46.1%), and undetermined for 25 (38.5%) (the 1 cancer case included).

When assessing the cervical specimens collected at the initial screening examination, we detected high-risk HPV DNA in 384 women (39.5%). The sensitivity of the HPV test for identifying patients with ASCUS Pap results with underlying histologically defined HSIL or cancer (HSIL+) was 89.2% (95% CI, 78.4%-95.2%), and the specificity for HSIL+ was 64.1% (95% CI, 60.9%-67.2%).

We compared the diagnostic of the HPV test characteristics (overall prevalence, sensitivity for HSIL, positive and negative predictive values) for the group of 191 women (19.2%) with a previous abnormal Pap result with those for the group without a history of Pap abnormalities. They were essentially identical (data not shown).

We evaluated the results of repeat conventional Pap smears, taken at the time of colposcopy. Based on the 957 cases for whom repeat Pap results were available, 585 (61.1%) had results within normal limits; 279 (29.2%) were ASCUS; 16 (1.7%), AGUS; 54 (5.6%), LSIL; and 23 (2.4%), HSIL. Table 1 shows the distribution of abnormal repeat Pap test results by histologic category. The sensitivity of repeat Pap testing to detect HSIL+ was 76.2% (95% CI, 63.5%-85.7%).

TABLE 2 compares HPV and repeat Pap test results specifically for the 63 available cases with HSIL+ histology. A matched-pairs comparison of these cases suggested the sensitivity of the HPV test was equivalent to, if not higher than, the repeat Pap test ($P = .09$). The

7 women with negative HPV test results were aged 30 to 44 years (median, 33 years). Six of the 7 HSIL histology cases with negative HPV results were evident from colposcopically directed cervical biopsies, and 1 was evident only on ECC. Of note, 4 of those 7 HSIL histology cases were tested within the first weeks of the study, when laboratory procedures were less routine.

Table 1 includes results of the ThinPrep Pap tests taken at the time of the initial Pap test (reported as ASCUS). Overall, the ThinPrep Pap result agreed with the corresponding Pap test result of ASCUS in 299 women (30.7%). In the 65 women with HSIL+ histology, 54 (84.3%) had an abnormal initial ThinPrep Pap result. In that group, the diagnostic characteristics of the microplate assay (overall prevalence, sensitivity for HSIL, positive and negative predictive values) were essentially identical to the entire group of 973 conventional Pap ASCUS cases (not shown).

TABLE 3 compares theoretically the referral of ASCUS cases to colposcopy based on concomitant cervical HPV DNA detection vs referral based on a repeat Pap test abnormality. The results of the Pap specimens taken at colposcopy are used to estimate the results of repeat Pap testing within 6 months of an ASCUS report. The tests would each refer about 39% of women to colposcopy. The positive predictive values for the 2 approaches are similar but are twice as high as the positive predictive value of 6.7% (95% CI, 5.2%-8.5%) for direct referral of all ASCUS cases to colposcopy.

We estimated the diagnostic utility of the ASCUS management strategy shown in the Figure. In addition to the data presented above, we used the repeat Pap and repeat HPV testing (data not shown) results for the subset who were initially HPV-negative. The algorithm includes HPV testing of all ASCUS cases, with immediate colposcopy of those who are HPV-positive. Women who are HPV-negative undergo repeat Pap testing (again with HPV testing of ASCUS) in about 6 months, with referral to colposcopy if results are abnormal. Based on the results from our study, this strategy

Table 3. Predicted Outcomes of Triage Strategies*

Strategy	Referred to Colposcopy†	Sensitivity for HSIL+	Positive Predictive Value for HSIL+	Negative Predictive Value for HSIL+
Triage based on HPV test‡	39.5 (36.4-42.7)	89.2 (78.4-95.2)	15.1 (11.7-19.2)	98.8 (97.4-99.5)
Triage based on repeat Pap test results§	38.9 (35.8-42.1)	76.2 (63.5-85.7)	12.9 (9.8-16.8)	97.4 (95.7-98.5)

*HSIL+ indicates high-grade squamous intraepithelial lesions or cancer; HPV, human papillomavirus. All data presented as percentage (95% confidence interval).
†Prevalence of a positive test result in women with atypical squamous cells of undetermined significance (ASCUS).
‡Referral to colposcopy based on positive DNA test for cancer-associated HPV types. Test conducted on specimen taken at initial visit.
§Referral to colposcopy based on repeat Papanicolaou (Pap) test result of ASCUS or more severe.

would provide a sensitivity (for HSIL+) of about 89.2% in the first set of colposcopy referrals (based on the initial HPV test), and an additional 7.7% from the repeat Pap-based referrals. In our study population of ASCUS cases, this strategy would have resulted in the colposcopic examination of 63 of the 65 women with HSIL+ histology, providing an overall sensitivity of 96.9% (95% CI, 88.3%-99.5%).

COMMENT

In a primary care setting, we found that HPV DNA testing, conducted on a liquid cytology specimen, was sensitive (89.2%) for identifying immediately the subset of women who harbored underlying HSIL+ among those with ASCUS cervical cytology. Overall, a positive HPV test result appeared to be more sensitive than an abnormal repeat Pap diagnosis (76.2%), but this difference was not statistically significant ($P = .09$). The power to observe significance may have been limited by the number of HSIL+ cases. An HPV-based algorithm including the immediate colposcopy of HPV-positive women, and the repeat Pap testing of all others (Figure), would provide an overall sensitivity of 96.9% (95% CI, 88.3%-99.5%).

Most important, our proposed algorithm (Figure) allows HPV testing and a subsequent triage decision based on the initial (ASCUS) Pap specimen. This provides a level of certainty to the ASCUS result, and it may also decrease repeat Pap examinations, reduce patient anxiety, and minimize the loss of high-risk cases during follow-up. The most streamlined approach uses the liquid-based ThinPrep Pap test, which provides a

single specimen appropriate for both cytology and HPV testing. In addition, ThinPrep Pap testing may provide the increased sensitivity for abnormalities, as demonstrated in many studies.²²⁻²⁶ Alternatively, conventional Pap tests can be used if a specimen specifically for HPV testing is collected with each smear and stored. In either case, stored specimens from women with corresponding ASCUS cytology results would be tested for HPV, while others could be discarded.

Our results suggest that HPV-based triage would provide similar results for conventional and for ThinPrep ASCUS Pap cases. Although we were able to assess only the ASCUS ThinPrep cases that were also ASCUS on conventional Pap testing, we found that the proposed HPV-based strategy would perform identically to that found for conventional Pap ASCUS cases. ThinPrep Pap tests provide fewer cases of ASCUS than do conventional tests in some populations^{22,25,26} and may define a more specific group that is more likely to reflect definitive squamous intraepithelial lesions. Regardless, available data suggest that the management of ASCUS ThinPrep results will benefit from HPV-based triage strategies.

The sensitivity of PreservCyt-based Pap and HPV testing may be underestimated somewhat by our results since the cervical specimen was smeared onto a slide for a conventional Pap test and only the residual material was placed into the PreservCyt medium. In addition, sample collection with a cytobrush and spatula combination²⁷ could provide better sampling than the cervical broom in women with a receded squamocolumnar junction, and might

improve the sensitivity of both HPV testing and cytology.

The repeat Pap test and colposcopy occurred on average 10 weeks after the initial Pap test. Repeat Pap smear accuracy is reported to be significantly higher for intervals of at least 4 months than for shorter intervals.²⁸ Perhaps longer intervals would have increased the repeat Pap test sensitivity in our study; however, we did not observe any relationship between sensitivity and interval length.

This large study was conducted in a population and setting that may be widely generalized. Women in the screening cohort represented a broad age range (14-92 years) and racial/ethnic diversity. More than 150 practitioners in 12 gynecology clinics collected the Pap screening specimens, and cytology and histology results were provided by 5 Kaiser Permanente pathology groups.

Based on these results and our assessment of the varied patterns of management of ASCUS Pap tests in this region, we concluded that HPV-based triage would provide equally sensitive detection of HSIL+, fewer colposcopy examinations, and fewer follow-up visits to our membership than do current practices. Furthermore, the savings accrued from decreased visits and procedures were found to be sufficient to offset the costs of implementing ThinPrep Pap testing for all routine screening and subsequent "reflex" HPV testing for all ASCUS cases (Figure) (M.M.M., W.K.K., and L.B.H., unpublished data).

In a corresponding study of women with AGUS Pap test results, we found HPV DNA testing to be highly sensitive for the identification of patients with underlying adenocarcinoma in situ or HSIL.²⁹ Thus, HPV DNA testing may be helpful for the clarification of equivo-

cal squamous and equivocal glandular cervical cytology results.

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