The Accuracy of Colposcopic Grading for Detection of High-Grade Cervical Intraepithelial Neoplasia

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■ **Abstract**

Objective. To relate aspects of online colposcopic image assessment to the diagnosis of grades 2 and 3 cervical intraepithelial neoplasia (CIN 2+).

Methods. To simulate colposcopic assessment, we obtained digitized cervical images at enrollment after acetic acid application from 919 women referred for equivocal or minor cytologic abnormalities into the ASCUS-LSIL Triage Study. For each, 2 randomly assigned evaluators from a pool of 20 colposcopists assessed images using a standardized tool online. We calculated the accuracy of these assessments for predicting histologic CIN 2+ over the 2 years of study. For validation, a subset of online results was compared with same-day enrollment colposcopic assessments.

Results. Identifying any acetowhite lesion in images yielded high sensitivity: 93% of women with CIN 2+ had at least 1 acetowhite lesion. However, 74% of women without CIN 2+ also had acetowhitening, regardless of human papillomavirus status. The sensitivity for CIN 2+ of an online colpophotographic assessment of high-grade disease was 39%. The sensitivity for CIN 2+ of a high-grade diagnosis by Reid Index scoring was 30%, and individual Reid Index component scores had similar levels of sensitivity and specificity. The performance of online assessment was not meaningfully different from that of same-day enrollment colposcopy, suggesting that these approaches have similar utility.

Conclusions. Finding acetowhite lesions identifies women with CIN 2+, but using subtler colposcopic characteristics to grade lesions is insensitive. All acetowhite lesions should be assessed with biopsy to maximize sensitivity of colposcopic diagnosis with good specificity. ■

Key Words: colposcopy, acetowhite lesion, biopsy, Pap test, cervical intraepithelial neoplasia

Cervical cancer prevention in the developed world currently relies on cytology screening and treatment of high-grade cervical intraepithelial neoplasia (CIN 2 or 3, CIN 2+), a cancer precursor. However, cytologic screening fails to identify women with cancer precursors with sufficient specificity to justify treatment of all cytologically abnormal women. The problem with specificity is especially acute when screening is supplemented by testing for the human papillomavirus (HPV), the etiologic agent of cervical cancer, to improve sensitivity. Current approaches to cervical cancer prevention interpose colposcopy as a triage test to define better which women need treatment. Optimal use of colposcopy requires that it improve specificity by identifying women with CIN 2+ without substantial loss of sensitivity.

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The accuracy of colposcopy has been increasingly questioned. Studies of loop excision after colposcopy have identified women with CIN 2+ and cancer missed colposcopically [1]. Biopsy of colposcopically normal areas may reveal unsuspected CIN 2+ [2]. Colposcopic lesion grade may predict histology poorly [3, 4]. Women with negative colposcopy remain at substantial risk for subsequent detection of CIN 2+, suggesting that lesions were missed [5]. In the ASCUS-LSIL Triage Study (ALTS), only 53% of women found to have CIN 3 over 2 years of follow-up were identified at intake colposcopy, although most missed lesions were small and presumably early in their natural history and so at low risk of imminent progression to invasive cancer [6]. Our group has shown recently that interobserver agreement among experienced colposcopists is moderate to poor for critical components of colposcopic assessment, including lesion grade, lesion characteristics, and even the presence of a lesion [7, 8]. If colposcopy is inaccurate, then prevention algorithms may need to change.

We set out to estimate the accuracy of colposcopy in the identification of CIN 2+ using online assessment by experienced colposcopists of digitized cervical images obtained from women enrolled in ALTS. In addition to assessing the accuracy of colposcopy overall among women referred for atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesion (LSIL), we attempted to estimate the utility for CIN 2+ detection of components of the commonly used Reid Index system for colposcopic grading [9]. Finally, we compared the accuracy of assessments of digitized images to results of actual colposcopy performed on the same day to ensure that conclusions based on image assessment were valid.

METHODS

Details of ALTS have been previously described [10]. Briefly, 5,060 women were enrolled between November 1996 and December 1998 at 4 clinical settings: the Magee-Women's Hospital of the University of Pittsburgh Medical Center Health System (Pittsburgh, PA), the University of Oklahoma (Oklahoma City, OK), the University of Alabama (Birmingham, AL), and the University of Washington (Seattle, WA). Eligibility required a cytologic report of ASCUS or LSIL. The study involved randomization to management using immediate colposcopy, triage using HPV DNA testing, and serial cytology and was approved by local institutional review boards and in accordance with the US Department of Health and Human Services standards. Each woman signed a written informed consent at enrollment before randomization. Samples were obtained for liquid-based cytology and for HPV testing. Questionnaire data were collected. Once all samples were collected, the cervix was washed with 5% acetic acid for 1 minute and 2 Cervigrams® (National Testing Laboratories Worldwide, Fenton, MO) were taken. These images, when digitized, were the basis of the image assessments in this study. For women randomized to the immediate colposcopy arm of ALTS, the enrollment examination was followed by a conventional colposcopy examination. Colposcopic impressions were recorded after real-time colposcopic assessment, and biopsies were obtained when indicated. Women in ALTS were followed with semiannual visits for 2 years.

Women were tested for carcinogenic HPV using the Hybrid Capture 2 assay (Qiagen, Gaithersburg, MD). Women also were tested for at least 27 HPV genotypes using a line blot assay (Roche Molecular Systems, Alameda, CA) [11]. HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 were considered carcinogenic.

The histologic outcome was defined as the highest grade lesion identified at initial colposcopy or during subsequent follow-up. Grading was adjudicated by a pathology quality control group as previously described [6]. Women with less than CIN 2 were subcategorized according to the HPV type found at entry as having HPV 16, other carcinogenic types, only noncarcinogenic types, or no HPV.

Image selection has also been described [7]. We selected 1,000 enrollment cervical images based on initial Cervigram diagnosis, including all women with images rated as high grade or cancer (n = 117), a 10% random sample of all negatives (n = 278), and a random sample (about one fourth) of all images read as atypical or low grade (n = 605) to achieve a total of 1,000 images. This sample size was chosen as the practical limit for the collaborating colposcopist reviewers. After excluding 21 lost and 40 poor-quality images, the final sample included 939 images. Demographic characteristics of these women also have been published [7]. Twenty images were evaluated by all evaluators. The remaining 919 images were randomly assigned so that each had 2 evaluators. Each evaluator reviewed 112 images, and each shared the same number of images with each one of the peer colposcopists. The images were assigned in a stratified randomization sequence to ensure that each evaluator viewed comparable images. These included 668 (73%) cases of CIN 1 or negative histology (<CIN 2),

83 (9%) with CIN 2,and 168 (18%) with CIN 3+. We did not distinguish between CIN 1and negative histology due to poor reproducibility in doing so [12] and the lack of importance of this distinction in ALTS in predicting risk of CIN 3 in ALTS follow-up [13]. After excluding assessments not done because evaluators considered images uninterpretable, 1,789 interpretations remained. For an unbiased analysis comparing the performance of online image assessment to that of live colposcopic impression performed the same day, we used 299 images from the immediate colposcopy arm of the study, yielding 582 evaluations after excluding those few images in this subgroup considered uninterpretable by some online evaluators.

After digitization and compression [14], images were evaluated online using software developed by the National Institutes of Health [15]. The evaluators were 20 colposcopists (12 general gynecologists and 8 gynecologist-oncologists) with at least 10 years of experience in colposcopy and previous research in cervical cancer prevention. Evaluators were not provided clinical data and were unaware of others' responses.

During evaluation, performed between January and April 2006, evaluators first determined whether images were evaluable. For evaluable images, evaluators determined whether acetowhite lesions were present and whether lesions were completely evaluable. Each lesion was then scored for color, vascularity, and margins according common definitions similar to those described by Ferris and Litaker [3] and Reid and Scalzi [9] that were provided by the prompting software. Finally, each lesion was assessed for the presence of atypical blood vessels. Summed scores were created from the colposcopic components. To correspond with conventional scoring for modified Reid Index [3], we added scores for color and margin to the higher score for the 2 vascular components (mosaicism or punctation). When multiple lesions were present, the highest score for each variable was recorded, which tended to increase the total score compared with the alternative of taking the score of the worst lesion. Using this alternative analytic approach, with slightly lower total scores, did not alter the conclusions. When an evaluator considered an acetowhite lesion to be absent, all grading scores were considered to be zero. Images with missing evaluations were excluded from final analysis.

All proportions are estimated by logistic regression or multinomial regression with an identity link within SAS 9.1.3 (SAS Institute Inc., Cary, NC). All statistical tests and 95% confidence intervals (CIs) account for the fact that the same image was evaluated multiple times by different evaluators by fitting each model using generalized estimating equations with an independence working correlation matrix to produce robust empirical standard errors [16].

To assess whether live colposcopic impression and online assessment of static Cervigrams yield equivalent information about final histology, we fitted an ordinal logistic regression model [17] comparing the predictive value of these 2 techniques for worsening state of final histology. To minimize confusion, "colposcopy" and "colposcopic impression" referred in this model to real-time, dynamic colposcopic assessment of a live patient, whereas "image assessment" or "online assessment" refers to assessment of static colpophotographs over the Internet. Covariates included colposcopic impression, online assessment, and age. The model yielded odds ratios (ORs) associating each technique with worsening grade of final histology ranked as follows: <CIN 2 and negative for HPV, <CIN 2 and positive only for non-carcinogenic HPV, <CIN 2 and positive for carcinogenic HPV types other than HPV 16, and <CIN 2 and positive for HPV 16, CIN 2, or CIN 3+. We conducted a 3 degree of freedom test for equality of the 2 ORs (for colposcopic impression and for online assessment) for equivalent grade of assessment, jointly across all 3 possible nonnormal assessments. For colposcopy, these 3 were atypical, low grade or high grade, whereas for online assessment, they were metaplasia, low grade, or high grade.

We conducted ancillary analyses regarding the sensitivity of acetowhitening, online global assessment of lesion severity, and Reid Index. We restricted the disease definition to the most stringent one available in ALTS: cases of histologically confirmed CIN 3+ diagnosed during the 2 years of the study for which the apparently causative HPV type was already present at enrollment. This group is most likely to represent prevalent CIN 3+, even if not identified by colposcopy at enrollment.

RESULTS

Characteristics of women who contributed images to the study are listed in Table 1. The median age was 24 years (range = 18–73 years). We first compared the accuracy of the identification in the online image of an acetowhite lesion for the diagnosis of CIN 2+ during up to 2 years of follow-up (Table 2). Acetowhite lesions were identified in 1,421 (79%, 95% CI = 74–85%) reviewed images. Using the identification of any acetowhite lesion as a diagnostic cutpoint had a sensitivity for disease diagnosed over the subsequent 2 years that was 94%

Table 1. Characteristics of 919 Women Contributing Images

	N	%[a]
Age (y)		
<20	132	14
20–29	577	63
30–39	142	15
>39	68	7
Parity		
0	422	46
1–2	398	43
>2	98	11
Unknown	1	
Ethnicity		
White/Hispanic		
White/non-Hispanic	24	3
African American	579	63
Asian/Pacific Islander	256	28
Other/unknown	24	2
Referral Pap		
ASCUS	564	61
LSIL	355	39
Study site		
Alabama	268	29
Oklahoma	190	21
Pennsylvania	163	18
Washington	298	32
Histology		
<CIN 2/HPV negative	145	16
<CIN 2/nononcogenic HPV positive	108	12
<CIN 2/oncogenic HPV positive	313	34
<CIN 2/HPV 16 positive	102	11
CIN 2	83	9
CIN 3	165	18
Cancer	3	<1

Categories of HPV are exclusive, such that women with nononcogenic HPV did not have oncogenic HPV and women with oncogenic HPV did not have the most oncogenic genotype, HPV 16.
ASCUS indicates atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; LSIL, low-grade squamous intraepithelial lesion.
[a]Some percentage columns do not add to 100% due to rounding.

(95% CI = 90–98%) for CIN 3+ and 93% (95% CI = 88–97%) for CIN 2+. The corresponding specificity (finding no acetowhitening when no CIN 2+ is present) was low: 67% (95% CI = 60–75%) of HPV-negative women without CIN 2+ had acetowhitening, as did 74% (95% CI = 68–81%) of those without CIN 2+ regardless of HPV, and 75% (95% CI = 70–82%) of women in whom CIN 3+ was not found, for a specificity for less than CIN 3 of only 24% (95% CI = 18–30%). Although the stratified sampling of images from the total ALTS population prevented direct and simple calculation of predictive values, the great majority of women with acetowhite lesions did not have CIN 2+.

We next calculated χ^2 statistics for all comparisons between disease outcome and online colposcopic features, including the presence of an acetowhite lesion, overall assessment, color, margin, punctation, mosaic, and derived Reid Index score. All were highly significant

Table 2. Online Identification of an Acetowhite Lesion and the Development of CIN Within 2 Years of Study Enrollment

	<CIN 2/HPV-[a]	<CIN 2/HPV+	CIN 2	CIN 3	Total
No lesion	145 (33)	186 (22)	16 (10)	21 (6)	368
Lesion seen	298 (67)	664 (78)	149 (90)	310 (94)	1421
Total	443 (100)	850 (100)	165 (100)	331 (100)	1789

Results given as *n* (%).
CIN indicates cervical intraepithelial neoplasia; HPV, human papillomavirus.
[a]Detection of carcinogenic HPV at enrollment.

($p < .0001$), suggesting that these factors reflect underlying biologic differences. However, correlation may not mean clinical utility if the variation is substantial. To estimate the utility of these factors, we next calculated the accuracy of global online colpophotographic assessment in the diagnosis of subsequent CIN 3+ and CIN 2+ (Table 3). The sensitivity of a global online assessment using a diagnostic threshold of high-grade disease was only 43% for CIN 3+ and 39% for CIN 2+. For each component of the Reid Index system, including color, margin, punctation, and mosaic, the sensitivity of a high Reid component score for CIN 3+ and for CIN 2+ ranged between 9% and 24%. The specificity of a low Reid Index score for each component ranged between 39% and 69% for CIN 3+ and between 41% and 70% for CIN 2+. Results for summed Reid Index scores were similar (Table 4). The sensitivity of a high-grade result by summed Reid Index score was 32% (95% CI = 25–39%) for CIN 3+ and 30% (95% CI = 23–37%) for CIN 2+. The specificity of a negative or low-grade (0–3) Reid Index score was 87% (95% CI = 84–90%) for all women without CIN 2+.

Assessment of the accuracy of colposcopy using static images has been criticized because real-time colposcopy allows skilled examiners to assess dynamic acetowhitening and fading as well as to manipulate the

Table 3. Online Global Assessment of Cervigrams Assessed Online and the Development of CIN Within 2 Years of Study Enrollment ($p < .0001$)

Online Assessment	Histology				
	<CIN 2/HPV	>CIN 2/HPV	CIN 2	CIN 3	Total
Negative	136 (31)	161 (19)	13 (8)	11 (3)	321
Metaplasia	118 (27)	191 (22)	39 (24)	45 (14)	393
Low grade	140 (32)	347 (41)	63 (38)	132 (40)	682
High grade	49 (11)	151 (18)	50 (30)	143 (43)	393
Total	443 (100)	850 (100)	165 (100)	331 (100)	1789

Results given as *n* (%).
Abbreviations as in Table 1.

Table 4. Correlations Between an Online Assessment of Modified Reid Index Score of Negative or Low-Grade Disease (Scores 0–3) and High-Grade Disease (Scores 4–6) Against the Development of CIN Within 2 Years of Study Enrollment ($p < .0001$)

Reid index score	<CIN 2/HPV−	<CIN 2/HPV+	CIN 2	CIN 3	Total
0–3	399 (90)	730 (86)	124 (75)	225 (68)	1478
4–6	44 (10)	120 (14)	41 (25)	106 (32)	311
Total	443 (100)	850 (100)	165 (100)	331 (100)	1789

Results given as *n* (%), with results for all HPV types aggregated for brevity.
Abbreviations as in Table 1.

cervix [18]. To assess the possible impact that static image assessment had on colposcopic diagnosis, we compared overall assessment derived online by our study group with impressions recorded at the time of intake colposcopy in the immediate colposcopy arm of ALTS. There were 582 reviews of images from 299 women with both a same-day colposcopic impression and a cervical image evaluated online. In this subgroup, intake Pap results were ASCUS in 167 (56%) and LSIL in 132 (44%). Diagnostic outcomes after 2 years of follow-up included CIN 3+ in 54 women (18%), CIN 2 in 37 (12%), <CIN 2 with HPV16 in 33 (11%), <CIN 2 with other oncogenic HPV in 96 (32%), <CIN 2 with nononcogenic HPV in 27 (9%), and <CIN 2 without HPV in 52 (17%). The online evaluations and the corresponding same-day colposcopic impressions are presented in Table 5. Differences in the distribution of diagnoses between the 2 modalities were significant ($p < .0001$) because many colposcopic impressions were low grade rather than atypical whereas metaplasia was more commonly diagnosed online. More importantly, however, Table 5 shows that the proportions of the total that were interpreted as normal (13% vs 16%) and high grade (15% vs 20%) were statistically ($p = .02$) but not substantially different between same-day colposcopy and online assessment, respectively.

The ordinal logistic regression model yielded ORs as measures of association of the same-day impression or online assessment with ordered categories of disease severity. Failure to find differences in the ORs for each equivalent impression/assessment category demonstrated that that colposcopic impression and online assessment were similar in their ability to predict the severity of final diagnostic category. For high grade versus negative, the ORs of association between impression/assessment category and increasing disease severity were strong and statistically significant for both methods: 5.4 (95% CI = 2.3–12.9) for same-day impression and 4.3 (95% CI = 2.4–7.9) for online assessment (p for equality = .63). These ORs can be interpreted as meaning that a woman with a colposcopic impression or high-grade online assessment, for example, was respectively 5.4 or 4.3 times more likely to have a more serious disease outcome than one with a negative impression/assessment. For low-grade versus negative, the ORs of associations were weaker but still substantial: 1.8 for same-day impression and 1.8 for online assessment (p for equality = .94). For metaplasia/atypia versus negative, the ORs of association with increasing disease severity were virtually null: 1.3 for same-day impression and 1.2 for online assessment (p for equality = .81); these near-null values suggest that the distinction between metaplasia or atypia and normal is not clinically important. Of importance for our research, the colposcopy and the online assessments were not significantly different from each other at each level for predicting the severity of disease during follow-up (p = .95 by 3 degree of freedom test that each pair of ORs is equal when considered as a set).

We addressed the possibility that some cases of CIN 2+ or even CIN 3+ diagnosed during the 2 years of ALTS follow-up might have been incident and not diagnosable by colposcopy. In other words, the lesions might have been due to HPV infections from after enrollment and might not have been present at enrollment when the images were taken and same-day colposcopy was performed. Therefore, in an ancillary analysis, we considered only the 295 images from those women with CIN 3+ whose enrollment specimen contained the same carcinogenic type found at the time of CIN 3+ diagnosis. The results were almost identical to the main analysis. Of the 295 images from this most stringent case group, 96% (95% CI = 93–99%) were judged to have at least 1 acetowhite lesion at enrollment. The percentage with high-grade online assessments was 45.1%

Table 5. Online Global Assessment of Cervigrams Assessed Online Versus Same-Day Colposcopic Assessment ($p < .0001$)

	Assessment type	
Assessment	Same day	Online
Negative	39 (13, 9–17)	95 (16, 12–21)
Metaplasia/atypical	30 (10, 4–16)	141 (24, 18–31)
Low grade	185 (62, 55–68)	229 (39, 35–44)
High grade	45 (15, 10–20)	117 (20, 16–24)
Total	299 (100)	582 (100)

Results given as *n* (%, 95% CI).
Abbreviations as in Table 1.

(95% CI = 37.3–52.9%). The sensitivity of a Reid Index of 4 to 6 was low: 33% (95% CI = 25–40%). Choosing lower thresholds for a "positive" Reid Index did not yield improved accuracy because many of the stringently defined cases had a total score of 1.

DISCUSSION

Our results show that the identification of an acetowhite lesion is a highly sensitive indicator for the subsequent identification of CIN 2+. However, the specificity of this finding seems to be low, and directed biopsy is required to guide subsequent therapy, as most women with acetowhite lesions do not have CIN 2+. In addition, the sensitivity of more detailed colposcopic analysis is substantially lower. The clinical colposcopic impression and the modified Reid Index components that contribute to it, including color, margin, vascularity, and total score, do not discriminate between acetowhite lesions that harbor CIN 2+ and those that do not.

There are several clinical implications to these observations. First, CIN 2+ in women with ASCUS and LSIL cytology presents as acetowhite lesions visible colposcopically. Although others have found a high yield to random biopsy in largely unscreened women [2], this suggests that biopsy of colposcopically normal tissue in US women with ASCUS or LSIL cytology is likely to increase yield minimally when acetowhite lesions have been assessed comprehensively. However, formally determining the utility of random biopsy requires prospective studies such as one we have initiated. Second, sensitive detection of CIN 2+ requires biopsy of acetowhite lesions even when the colposcopic impression is low grade or metaplasia. Third, Reid Index scores cannot be used to differentiate low from high-grade lesions in women with borderline cytology, nor can Reid Index scores distinguish a subgroup of women at sufficiently low risk for CIN 2+ to be followed without biopsy or treatment. Patient management cannot be based on colposcopic impression unless confirmed by biopsy. Finally, in a patient with multiple acetowhite lesions, Reid Index scoring should not be used to restrict biopsy number to those areas that seem most suspicious colposcopically. Lesions that were missed colposcopically in ALTS were generally subtle and small [19].

As recently reviewed [20], these results are broadly consistent with previous work. In ALTS, the sensitivity of initial colposcopy for the subsequent development of CIN 3 was only 53% [6]. However, results were better when more biopsies were taken, and results were worst for the most experienced clinicians, who may have used lesion characteristics to forego biopsy of early high-grade lesions [21]. Some women with negative or low-grade colposcopy findings after abnormal Pap tests have CIN 2+ identified at loop excision [1, 22] or later develop cervical disease, suggesting that significant lesions were missed or underestimated colposcopically [23]. Previous work has also shown that using lesion characteristics to define lesion grade is problematic because experienced colposcopists disagree over how terms should be applied [8] and how grading should be derived from observed images [7]. Our results also extend the findings of Sideri et al. [4], who showed that interobserver correlations and sensitivity are best when the identification of an acetowhite lesion rather than detailed colposcopic grading is the trigger for biopsy.

Our study was limited to women with antecedent ASCUS or LSIL cytology reports. The Reid Index and similar grading systems may still be useful in women with high-grade SIL, who may present with larger or more colposcopically advanced lesions. In fact, colposcopic grading systems were developed soon after the wide dissemination of cytology screening and before the development of current cytology classification systems, when many women undergoing colposcopy had more advanced disease. However, at present, most cytologic abnormalities requiring colposcopy are ASC or LSIL, and most CIN 2+ is found among women with these cytology results [24], so our results should apply to current colposcopic practice.

Previous work from our study group has been criticized for using static images [16]. Colposcopy involves longitudinal assessment of acetowhite changes, and in vivo assessment may be more accurate because it allows observation of the time course of onset and fading of acetowhitening. Colposcopy and online assessment differ in their distribution of diagnoses, but this occurs mostly in how the 2 modalities distinguish low grade from atypical or metaplastic changes. We found no clinically meaningful difference between same-day impression and online assessment for predicting final histology. However, the ORs for same-day colposcopic impressions were equal to or slightly larger than the ORs for online assessment. If colposcopy is more accurate than assessment of still images in identifying CIN 2+, a far larger study will be required to substantiate the small, but possibly clinically irrelevant, differences.

Our findings have particular relevance for education because most colposcopy teaching depends on projection of static images. The lack of significant difference between the ability of real time colposcopy and static

image assessment to identify CIN 2+ suggests that use of static images should continue. In fact, ASCCP and staff from the National Institutes of Health have been collaborating to develop online teaching and evaluation tools. The significant association between Reid Index components such as vascularity, margin, color, and total score indicate that these visual characteristics have biologic significance and should be included in curricula. However, learners should be instructed that these factors are too inaccurate to be used in clinical management, including determining biopsy site or the need for treatment without histologic confirmation.

The role of colposcopy in the prevention of cervical cancer continues to evolve. As the threshold for abnormal screening results has shifted from Papanicolaou Class III cytology to mild dysplasia to ASCUS and now to detection of persistent oncogenic HPV in the face of normal cytology, the task of identifying increasingly subtle preinvasive lesions has become more difficult. Until better strategies are developed to find CIN 2+ in women with borderline changes, biopsy of all acetowhite lesions will yield the greatest sensitivity for detecting cervical precancer. Toward this end, we are now studying a protocol that attempts to balance sensitivity against patient discomfort and costs.

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