

ASCUS LSIL Triage Study (ALTS) Conclusions Reaffirmed: Response to a November 2001 Commentary

Diane Solomon, MD,
Mark Schiffman, MD, MPH, and
Robert Tarone, PhD, for the ALTS Group

Divisions of Cancer Prevention and Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland

We are writing to correct misinterpretations raised in the November 2001 Commentary by Drs. Herbst, Pickett,

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Address reprint requests to: Diane Solomon, MD, National Cancer Institute, Division of Cancer Prevention, EPN, Room 2130, MSC 7333, 6130 Executive Boulevard, Bethesda, MD 20892-7333; E-mail: ds87v@nih.gov.

Members of the ALTS Group: **University of Alabama at Birmingham, AL**, E.E. Partridge, Principal Investigator, L. Kilgore, Co-Principal Investigator, S. Hester, Study Manager; **University of Oklahoma, Oklahoma City, OK**, J.L. Walker, Principal Investigator, G.A. Johnson, Co-Principal Investigator, A. Yadack, Study Manager; **Magee-Womens Hospital of the University of Pittsburgh Medical Center Health System, Pittsburgh, PA**, R.S. Guido, Principal Investigator, K. McIntyre-Seltman, Co-Principal Investigator, R.P. Edwards, Investigator, J. Gruss, Study Manager; **University of Washington, Seattle, WA**, N.B. Kiviat, Co-Principal Investigator, L. Koutsky, Co-Principal Investigator, C. Mao, Investigator; **Colposcopy Quality Control Group**, J.T. Cox, Co-Investigator, University of California at Santa Barbara, Santa Barbara, CA; **HPV Quality Control Group**, C.M. Wheeler, Principal Investigator, University of New Mexico Health Sciences Center, Albuquerque, NM, C. Peyton-Goodall, Lab Manager, University of New Mexico Health Sciences Center, Albuquerque, NM; **Pathology Quality Control Group**, R.J. Kurman, Principal Investigator, Johns Hopkins Hospital, Baltimore, MD, D.L. Rosenthal, Co-Investigator, Johns Hopkins Hospital, Baltimore, MD, M.E. Sherman, Co-Investigator, Johns Hopkins Hospital, Baltimore, MD, M.H. Stoler, Co-Investigator, University of Virginia Health Science Center, Charlottesville, VA; **Cost Utility Analysis Group**, D.M. Harper, Investigator, Dartmouth Hitchcock Medical Center, Lebanon, NH; **Westat, Coordinating Unit, Rockville, MD**, J. Rosenthal, Project Director, M. Dunn, Data Management Team Leader, J. Quarantillo, Senior Systems Analyst, D. Robinson, Clinical Center Coordinator.

Follen, and Noller,¹ which questioned some of the conclusions of the ASCUS LSIL Triage Study (ALTS).² Based on two significant misapplications of ALTS data and factual errors about ALTS study design, those authors reached incorrect conclusions about the significance of the study findings. In the following, we discuss these misinterpretations and reaffirm the fundamental conclusion of the original paper: ALTS data show human papilloma-virus (HPV) testing is a viable option for managing women with an atypical squamous cells of undetermined significance (ASCUS) cytology finding.

THE REASON FOR ALTS

At the time of the development of the ALTS protocol, standard management of ASCUS or low-grade squamous intraepithelial lesion (LSIL) included two options: 1) direct referral to (immediate) colposcopy; or 2) follow-up by repeat cytology with referral to colposcopy for another ASCUS or worse (ASCUS+) cytologic finding.³ Although immediate colposcopy with referral of all women with ASCUS provided the greatest sensitivity for detecting underlying CINIII or cancer (CINIII+), this approach was criticized as costly and anxiety-provoking, given that only 5% of women with ASCUS had CINIII+. It was also recognized that management by repeat cytology was far from ideal: a single repeat Papanicolaou lacked sensitivity for CINIII+, while a program of following women with multiple repeat cytology samplings raised problems of loss-to-follow-up, as well as significant costs associated with multiple office visits.

Cervical neoplasia is etiologically related to cancer-associated HPV. The development of a robust clinical assay for HPV suggested that testing for HPV DNA might provide the sensitivity of immediate colposcopy for identifying CINIII+, while reducing the number of women referred to colposcopy. Accordingly, ALTS was designed to compare management strategies for women with community cytology results of ASCUS or LSIL.

The three ALTS management approaches were 1) immediate colposcopy (IC); 2) HPV triage with referral to colposcopy triggered by a positive HPV DNA test or repeat cytology showing high-grade squamous intraepithelial lesion (HSIL); and 3) conservative management (CM) with follow-up by repeat cytology and referral to colposcopy triggered only by an HSIL (not ASCUS or LSIL) cytology. The goal was to determine whether there was a triage strategy with sensitivity comparable to universal colposcopy, but that spared women at minimal

risk of CINIII+ from the cost and anxiety of unnecessary colposcopy and biopsy.

REPORTED ALTS RESULTS

To date, we have published two reports of enrollment results from ALTS. First, an interim analysis of women referred to ALTS with LSIL cytology demonstrated very high HPV positivity (83%), limiting the utility of HPV testing to inform clinical management of these women.⁴ Second, the enrollment results for women referred to ALTS with ASCUS cytology were recently reported by Solomon et al.² The conclusions of this paper were questioned in the November 2001 Commentary.¹

The ALTS ASCUS publication included comparisons of the sensitivity and referral percentage of various strategies for clinical management based on the triage test performance of enrollment cytology and HPV among women with histologically confirmed CINIII+.*

The findings may be summarized as follows:

1. An HPV test would triage 96% of cases of prevalent, colposcopy-detected CINIII+, while referring 56% of women to colposcopy.
2. Repeat cytology with colposcopy triggered at a threshold of HSIL (not ASCUS or LSIL) would refer only 7% of women to colposcopy, but would identify only 44% of prevalent CINIII+ cases.
3. Management by repeat cytology with colposcopy triggered at a threshold of ASCUS+ would identify 85% of cases of CINIII+, but would refer 59% of women to colposcopy.

INAPPROPRIATE COMPARISONS

The first, and most significant, misapplication of the ALTS data presented in the November Commentary begins with the statement that there was “. . . a large excess of colposcopies and biopsies in the HPV arm in comparison with the conservative management ([HSIL] cytology) arm.” Apparently based on this assertion, the Commentary takes issue with the conclusion that HPV testing is a viable management option for ASCUS cytology findings.

Unfortunately, simply comparing the number of colposcopies ignores the critical issue of sensitivity. Referral to colposcopy based on a repeat cytology of HSIL detects only 44% of CINIII+, which would be considered unsafe for clinical management outside the setting of a closely monitored clinical trial such as ALTS. We are

*For this simulation, cases of CINIII+ in the IC and HPV triage arms—in which there was relatively complete ascertainment of disease—were combined. The CM arm was not included in this analysis because of a deficit of detected CINIII+.

concerned that by highlighting this approach, the Commentary might be read as implying it is a currently accepted standard of practice—it is not. The conservative management arm deliberately used a high threshold of HSIL for triage to colposcopy to determine if high sensitivity for CINIII+ could be achieved while greatly minimizing the number of women requiring colposcopy and biopsy, and to allow for study of the natural history of untreated LSIL under conditions of close follow up.

While we noted (in the manuscript) the theoretical possibility that sensitivity would improve substantially with multiple follow-up cytologic samplings, unpublished longitudinal ALTS data now confirm that cytologic follow-up with referral to colposcopy based on an HSIL threshold is insensitive for detection of CINIII+, even with multiple repeat cytology assessments. These ALTS data were presented in early September 2001 at the American Society for Colposcopy and Cervical Pathology Consensus Conference for the Management of Cytological Abnormalities and Cervical Cancer Precursors. Publication of these findings is forthcoming.

The Commentary also proposed an alternative outcome measure for comparing management strategies, “. . . the yield of LEEP and CINIII+ per colposcopy performed. . . .”¹ This is analogous to “positive predictive value” or in other words, the percentage of women found to have CINIII+ among those who were referred to colposcopy by a positive triage test.

While positive predictive values were presented in the publication by Solomon et al.,² using such a metric to evaluate a triage strategy without the context of sensitivity is very misleading. The following example illustrates this problem. Suppose colpo-biopsy was limited only to those lesions with a high-grade colposcopic appearance suggestive of CINIII. This strategy would obviously have a higher yield of histologically-confirmed CINIII compared to an approach that called for biopsy of lesions colposcopically suggestive of any grade of CIN; however, the high threshold for biopsy would miss many cases of true CINIII that colposcopically might appear less severe. This example illustrates it is quite possible for a strategy to achieve high positive predictive value (in this case, high yield of CINIII+ per colposcopy performed), but at a cost of low sensitivity.

We maintain that to be considered acceptable, an ASCUS management strategy should have a level of sensitivity to detect CINIII+ that is comparable to the current standard(s) of practice. Among adequately sensitive triage strategies, other factors should then be considered such as referral percentage, positive predictive value, patient acceptability, and cost.

COMPARISON OF HPV TRIAGE TO CURRENT ASCUS MANAGEMENT OPTIONS

The performance of HPV triage should be compared to the two current standards of ASCUS management: 1) immediate colposcopy of all women and 2) follow up by cytology with referral to colposcopy at a threshold of repeat ASCUS+. Thus, the 96% sensitivity for CINIII+ with 56% of women referred to colposcopy based on HPV triage should be compared to immediate colposcopy (presumed 100% sensitivity with 100% referral) and also to repeat cytology with referral based on a second ASCUS+ finding (85% sensitivity with 59% referral). With this comparison, HPV triage refers approximately the same number of women to colposcopy as follow up cytology at the ASCUS+ threshold, but with greater sensitivity than cytology for identifying women with CINIII+. Compared to immediate colposcopy of all women, HPV triage reduced the number of colposcopic referrals by about half, while preserving safe and sensitive detection of CINIII+. Longitudinal analyses in ALTS will undoubtedly demonstrate that serial repeat cytologic tests increase cumulative sensitivity for CINIII+, but this will come at the cost of even more women being referred to colposcopy and biopsy. Attendant concerns related to costs for repeat visits and the danger of loss-to-follow-up must also be considered.

APPLICABILITY OF ALTS RESULTS TO CLINICAL PRACTICE

Another misinterpretation of ALTS data by the Commentary relates to the question of applicability of ALTS results to clinical practice. The Commentary cites diagnostic variability in ALTS reported by Stoler and Schiffman⁵ as evidence that the validity of the diagnoses on which the trial is based is open to question. The Commentary further suggests that applying more stringent criteria with less frequent diagnosis of ASCUS would be a solution.

ALTS is the largest randomized clinical trial addressing management of women with ASCUS and LSIL cytology results. The geographic and demographic diversity of the four clinical centers that participated in the trial allow the findings of the study to be generalized. While ALTS analyses do demonstrate interobserver diagnostic variability, there is no evidence that such variability is unique to this study. Virtually every study that has evaluated inter- (and intra-) observer diagnostic concordance has found only moderate reproducibility.⁵

The suggestion in the Commentary that “more stringent criteria and less frequent diagnosis of the ASCUS

category [would be of greater value]” is an unfortunate oversimplification. Even expert cytopathologists do not agree on ASCUS interpretations with any greater reproducibility than observed in ALTS.⁶ ASCUS interpretations represent cases that are difficult to evaluate, often because of scant numbers of abnormal cells or limited specimen adequacy. Total elimination of ASCUS based on review by expert cytopathologists is not feasible. (Pitman BM, Cibas ES, Powers CN, Frable WJ. Consequences of eliminating ASCUS. *Cancer Cytopathol* [in press].) Finally, substituting the review diagnoses rendered by the expert Pathology QC group did not significantly alter the performance of cytology in ALTS, in terms of sensitivity for detection of CINIII+ or the percentages of women referred for colposcopy.

FACTUAL ERRORS

The Commentary includes three factual errors concerning the procedures of the ALTS trial that are addressed by the following corrections:

1. The Commentary states “in the conservative management arm, colposcopy was done if the entry smear showed an LGSIL reading or worse.” In fact, the threshold for colposcopy in the conservative management arm was a finding of HSIL.
2. The Commentary states “patients in arms 2 and 3 also underwent cervicography.” Rather, all women in the ALTS trial had cervicography performed at all routine visits in the trial.
3. The Commentary states “authors of the ALTS report did not publish any estimates of specificity for either the HPV arm or the repeat conservative management arm.” In fact, the ALTS paper reported both the percentage of women referred to colposcopy and the positive predictive value—more clinically meaningful surrogate measures of specificity—for all triage strategies evaluated.

CONCLUSION

Careful and critical reanalysis of published data can often bring a valuable fresh perspective and useful insights to clinical findings. Unfortunately, the reanalysis presented in the Commentary is more confusing than informative. While many questions remain to be answered, the ALTS data clearly establish that HPV testing is a viable option to be considered in the management of women with ASCUS cytology results. Assertions to the contrary presented in the Commentary are simply wrong and any suggestion that ASCUS should be man-

aged by followup cytology with an HSIL threshold for referral to colposcopy (as in the conservative management arm of ALTS) is unsupported by objective evidence and is potentially dangerous.

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Human papillovirus (HPV) testing in patients with abnormal cytology is controversial and borders on contentious. The bottom line for physicians and their patients is whether it is practical, cost effective, and will actually reduce the rate of invasive carcinoma of the cervix. We published a commentary by Arthur Herbst, MD, and colleagues and an editorial comment by Raymond Kaufman, MD, in the November 2001 issue of the *Green Journal* that argued against its routine clinical use. Diane Solomon, MD, and colleagues, lead authors on the ALTS trial papers, present a different viewpoint.

James R. Scott, MD

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