

## **MULTIMODAL SPECTROSCOPY AS A TRIAGE TEST FOR WOMEN AT RISK FOR CERVICAL NEOPLASIA: RESULTS OF FOLLOW UP DATA**

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**OBJECTIVE:** The ASCUS/LSIL Triage Study (ALTS) results focused attention on the importance of follow up data when evaluating both existing (colposcopy) and new technology (HPV) for the triage of patients at risk for cervical neoplasia. In the clinical evaluation of multimodal hyperspectroscopy (MHS), follow up data were analyzed to determine the number of women for which diagnoses of cervical intraepithelial neoplasia (CIN)2+ were delayed under the current standard of care (i.e., 2001 Bethesda System: Terminology for Reporting Results of Cervical Cytology, identification of high risk human papillomavirus (HPV) and colposcopy findings). In addition, MHS was evaluated to determine how many of these women with CIN2+ missed by the current standard of care would have been correctly identified by MHS at the time of the study.

**METHODS:** In this seven-center pivotal study, 1,607 women at risk for cervical neoplasia were tested using MHS (LightTouch, Guided Therapeutics, Inc. Norcross, GA), including 125 with high-grade squamous intraepithelial lesion (HSIL) Paps, 71 with atypical squamous cells-cannot exclude high grade squamous intraepithelial lesion (ASC-H) Paps, 737 with low-grade squamous intraepithelial lesion (LSIL) Paps, 523 with atypical squamous cells of undetermined significance (ASC-US)/atypical glandular cells of undetermined significance (AGC-US) Paps, one with no Pap results and 150 with normal or benign cytology but were at risk for other reasons including positive HPV results, previous dysplasia and recurrent benign findings. Of the 1,607 women tested, 200 were excluded prospectively from efficacy analysis for any of several reasons including training subjects, uncertain histopathology and device/user errors. Two types of follow up data were collected. The initial follow up study of the 1,407 evaluable cases consisted of a histopathology review to determine the number of cases called negative for CIN2+ disease by the local (site) pathologist but whose biopsies were later determined by two independent pathologists to harbor CIN2+ disease. The second follow up study included an analysis of 801 available subjects who returned to follow up within approximately two years of their enrollment in the MHS study.

**RESULTS:** There were 38 cases in which histopathology review found CIN2+ missed by the local pathologist at the time of the MHS study. MHS correctly identified 34 (89%) of these cases. For 248 of the 801 women who returned for follow up, biopsies were performed and histopathology results made available. There were 27 women diagnosed with CIN2+ at follow up, and MHS correctly identified 25 (93%) of these at the time of their original enrollment. Combining the two sets of follow up data results in a total of 65 CIN2+ cases missed by the standard of care at the time of the MHS study. MHS correctly identified 59 (91%) of these ( $p < 0.01$ , binomial test). Extrapolating from the 801 cases for which follow up data was available (roughly half of the study population), the true number of cases for which diagnosis of CIN2+ was delayed by the standard of care can be estimated at more than 30%.

**CONCLUSIONS:** The follow up results of the MHS pivotal trial, while incomplete, are consistent with the ALTS results. Specifically, ALTS found that the current standard of care for the triage of women at risk for cervical disease missed approximately 35% of high-grade dysplasia, while the yield of positive biopsies was 26%. In the MHS study, follow up results indicated that the miss rate was over 30% with the yield of positive biopsies at 19%. Of special significance was the ability of MHS to provide an earlier positive identification of CIN2+ disease for 91% of the cases originally missed by the standard of care.

**KEY WORDS:** cervical intraepithelial neoplasia, cervical cancer screening, spectroscopy, cervical cytology, HPV