MULTIMODAL SPECTROSCOPY AS A TRIAGE TEST FOR WOMEN AT RISK FOR CERVICAL NEOPLASIA: EXPERIENCE WITH A LOW COST COMMERCIAL PROTOTYPE

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OBJECTIVE: We evaluated multimodal hyperspectroscopy (MHS) in a busy private practice setting in Orange County, California. Women enrolled at our clinic and two others were tested with a cost and size reduced version of the MHS device (Image 1.) using a single-use patient interface (Image 2.). In addition, our population consisted mainly of women who are most at need for effective triaging to biopsy, i.e., those with atypical cells of undetermined significance (ASC-US), atypical squamous cells, cannot rule out a high grade lesion (ASC-H) and low grade squamous intraepithelial lesion (LSIL) Papanicolaou (Pap) results and mostly positive human papilloma virus (HPV) results. The objective of the study was to compare the results of MHS with the current standard of care for triage in general and with the Pap test in particular.

METHODS: After initial training and debugging, (n = 61) 444 women were tested at three clinical centers using preproduction prototypes of the MHS device (Guided Therapeutics, Inc. Norcross, GA). A histopathology quality assurance review procedure was used for all subjects in the study along with two year follow up when available to determine histological diagnoses. Data analyses included receiver operating characteristic (ROC) curves along with estimates of sensitivity, specificity and predictive values.

Image 1. LightTouch prototype in a clinical setting.

Image 2. Single-use patient interface.

Pivotal Study Clinical Sites
1-Emory University School of Medicine – Lisa C. Flowers, MD / Talaat S. Tadros, MD
2-University of Miami – Leo Twiggs, MD / Nahida Chakhtoura, MD
3-Orange County California – Marc Winter, MD / Daniel Sternfeld, MD

RESULTS: Accounting for protocol deviations, user/device errors and no or discordant histology results, data from a total of 320 (Table 1.) women were available for analysis, including 14 with normal referral cytology, 153 with atypical squamous or glandular referral cytology, 148 with LSIL referral cytology and five with high grade squamous intraepithelial lesion (HSIL) or malignant referral cytology (Table 2). Histologically, 41 women were diagnosed with cervical intraepithelial neoplasia (CIN2+), 145 with CIN1 and 134 with benign or normal cervices. Using a prospectively set threshold, sensitivity for CIN2+ disease and specificity of normal and benign cervices for MHS alone were 88% and 44% respectively, as compared with 56% and 44% for cytology alone, an improvement of 56% for MHS over Pap cytology. MHS was positive for 69% of CIN1 lesions. Integrating cytology results for each subject with the MHS result did not improve performance, as specificity remained at 44%, but sensitivity of MHS and Pap combined fell to 85%. In both cases, however, the improved sensitivity of MHS compared with the Pap test was statistically significant ($p<0.01$, Fisher's Exact Test). Positive and negative predictive values (excluding CIN1 lesions) for MHS alone were 32% and 92% respectively, as compared with 23% and 77% for cytology (Table 3). Triage value, reflected by area under the ROC curve was 0.54 for cytology, 0.64 for MHS alone and 0.68 for MHS combined with cytology, although the value added by combining cytology with MHS occurred at the low sensitivity end of the ROC curve and thus would have minimal clinical significance (Figure 1). There were no adverse events and, similar to its predecessor prototype, women found the procedure with the new device acceptable.

Table 1. Demographics by age for 320 subjects

Age	Non Hispanic American Indian Alaska Native	Non Hispanic Asian	Non Hispanic Black or African American	Non Hispanic White	Non Hispanic Native Hawaiian/ Pacific Islander	Hispanic Black or African American	Hispanic White	Non Hispanic TOTAL	Hispanic TOTAL	TOTAL ENROLLED
16-20	0	0	14	19	0	0	8	33	8	41
21-30	0	5	41	49	3	0	39	98	39	137
31-over	0	3	38	65	1	0	35	107	35	142
							TOTAL	238	82	320

CONCLUSIONS: In the first clinical evaluation of a lower cost commercial prototype, MHS increased detection of CIN2+ by 56% over the Pap test when both tests were equalized for specificity at 44%, the specificity for MHS using a prospectively determined threshold. The population studied had insignificant numbers of HSIL cytology and thus Pap cytology essentially had negligible triage value when compared with MHS. MHS offers the potential of a cost effective and efficient modality for earlier detection of CIN2+ disease in women at risk for cervical disease, while at the same time reducing the number of colposcopies and biopsies currently performed on normal and benign cervices.

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Figure 1. ROC for Pap cytology and MHS adjunctive to Pap cytology

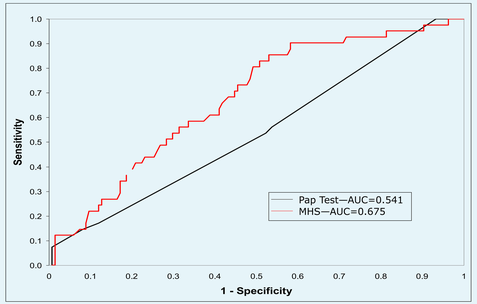

Table 2. Number and Prevalence of final QA histopathology as a function of reason for referral to colposcopy

Referral Cytology	Normal	CIN1	CIN2+	TOTAL	% Prevalence CIN2+
Negative	9	5	0	14*	0.0
ASC-US	73	59	21	153	13.7
LSIL	52	81	15	148	10.1
HSIL	0	0	5	5	100
	134	**145**	**41**	**320**	**12.8**

* Excludes one subject with no histopathology

Table 3. Effectiveness of MHS and Pap cytology for CIN2+ and normal lesions

Value (%)	SENSITIVITY (n=41 CIN2+)	SPECIFICITY (n=134 Normal)	POSITIVE PREDICTIVE VALUE	NEGATIVE PREDICTIVE VALUE
MHS	88	44	32	92
Pap Cytology	56	44	23	77

* Does not include 145 CIN1 lesions

Supported in part by grants from the Georgia Research Alliance and the National Cancer Institute.
Also supported by Guided Therapeutics, Inc.