**Introduction:** Current modalities for detection and management of cervical pre-cancers may miss significant disease and generate false positives. The result of these modalities' inadequacies may lead to mis-diagnosis, delay in diagnosis and/or over treatment of disease. The general current standard of care in the United States is Pap cytology, followed by a human papilloma virus (HPV) test and/or follow up, secondary cytology for slightly abnormal cytology results and higher. In order to overcome these inadequacies, there is a need to develop and evaluate new technologies with operating characteristics that are fundamentally conducive to optimizing the current standard of care in cervical pre-cancer detection. One such technology is multimodal hyperspectroscopy (MHS), an in vivo test, which does not require a tissue sample for laboratory analysis, is easy to perform, provides an immediate and objective result and is a cost effective method for improving the yield of positive biopsies and reducing the overtreatment of false positives. The objective of this study was to compare the results of MHS, used in combination, with the HPV test within the current standard of care.

**Methods:** In this seven-center Phase III study, 1,607 women at risk for cervical neoplasia and who were referred to colposcopy and biopsy were tested using MHS (LuViva Advanced Cervical Scan, Guided Therapeutics, Inc. Norcross, GA) (Image 1), including 804 that returned for follow up. The population consisted of 1,457 women with abnormal Papanicolaou (Pap) cytology, one with no referral Pap result and 149 with normal or benign cytology, but were at risk for other reasons, including positive HPV results, previous dysplasia and/or recurrent benign findings. On the day of study, each woman underwent MHS, had a specimen taken for cytology and HPV testing and colposcopy. Biopsy specimens were reviewed by a panel of histopathologists to determine a final diagnosis, by which MHS and other tests were compared. A subset of the data was analyzed, from the study (subjects excluding all HSIL cytology) for the various modalities, to determine their sensitivity, specificity and negative predictive value (NPV) as a standalone test and combined with other modalities in detecting cervical neoplasia.

Age Category	Number	Percent
Median	27.00	
Range	16-84	
Adolescents – 20 and under	238	18.1
21 - 30	573	43.0
<b>31 - over</b>	519	39.0

Table 1. Age distribution for 1,330 subjects

# **OPTIMAL COMBINATION OF CERVICAL SPECTROSCOPY WITH CYTOLOGY AND HPV: IMPLICATIONS FOR CLINIC EFFICIENCY**



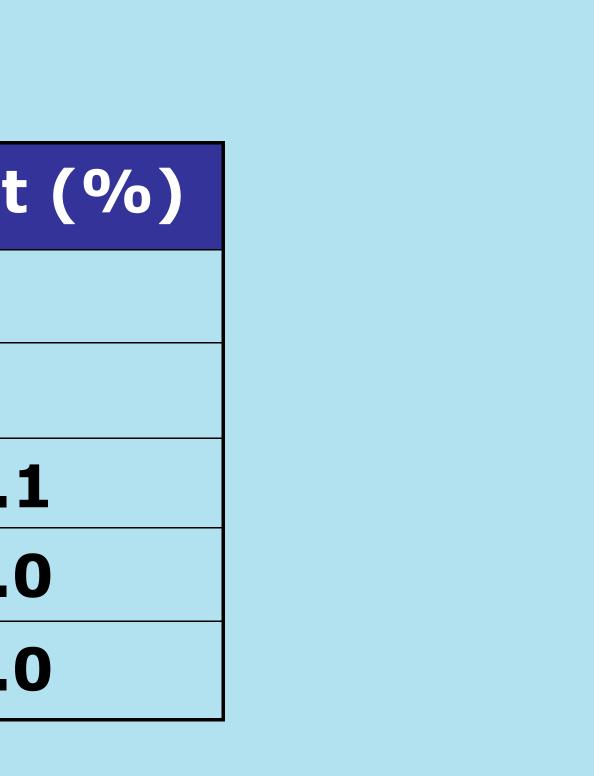
## Winter ML, Orange Coast Women's Medical Group, Laguna Hills, California, Sternfeld DR, Saddleback Women's Medical Group, Laguna Hills, California

Results: Data were analyzed from 1,330 women with abnormal referral cytology (excluding non-evaluable subjects and patients with HSIL cytology)(Table 1) including 561 free of dysplasia, 575 with Cervical Intraepithelial Neoplasia (CIN1) and 194 with Cervical Intraepithelial Neoplasia 2 or 3 (CIN2+)(Table 2), including 21 interval CIN2+ found during two year follow up. The optimal combination of tests, in terms of sensitivity and negative predictive values, was MHS and HPV, with a sensitivity of 99% and NPV of 99% (Table 3). Because of the extremely low likelihood of a false negative, effective implementation of MHS into the current standard of care (Figure 1) could safely reduce the number of unnecessary colposcopies by 33.2% for women free from dysplasia.

According to the National Cancer Institute<sup>1</sup>, approximately 55 million Pap tests are performed each year. Of that 55 million, roughly 7 percent (3.85 million) require additional scrutiny as a result of an abnormal result and/or other factors which would require referral (i.e. positive HPV or follow up from previous disease). Effective application of MHS, in combination with a HPV test, could reduce the number of unnecessary colposcopies by approximately one-third (33.2%). Implementation of MHS would reduce the yearly number of colposcopy procedures by approximately 1.28 million per year and potentially save the healthcare system over \$228 million, according to current California reimbursement rates<sup>2</sup>.

Earlier in 2012, the U.S. Preventative Services Task Force revised the screening recommendations for cervical cancer. The new recommendations stipulate that further clinical investigation of the comparative effectiveness and harms of current screening modalities is warranted<sup>3</sup>. The recommendations suggest HPV testing would be the preferred secondary screening modality, since research indicates HPV infection is associated with nearly all cases of cervical cancer. However, the low specificity of the HPV test alone demonstrates the inability to accurately detect pre-cancerous lesions and suggests the likelihood of over-treatment. Combined with a modality that provided an in vivo, point of care, objective result that is highly sensitive, such as MHS, the HPV test would compensate for this need in the current standard of care.

Image 1. LuViva MHS Device



	REFERRAL PAP CATEGORIES						
Histology	Negative or Benign*	ASC-US	AGC	AGUS	ASC-H	LSIL	TOTAL
Normal	78	205	6	10	30	232	561
CIN1	56	184	2	5	19	309	575
CIN2+	2	52	1	0	12	127	194
* Referred on the basis of Positive HPV, previous dysplasia or other risk factors					1,330		

CAUTION - Investigational device. Limited by federal law to investigational use. The availability of any product in the U.S. developed from these technologies is dependent on FDA marketing approval.

### tology Outcomes for 1,330 subjects

# "MHS provides the convenience of a point of care, objective result that enhances the ability to effectively improve management of cervical neoplasia detection for women, by reducing the number of colposcopies currently being performed on normal and benign cervices."

**Conclusions:** The combination of MHS with HPV testing shows strong potential for reducing the overtreatment of false positives by providing an almost perfect sensitivity and NPV for detection of CIN2+. Use of MHS within a patient management algorithm that includes HPV testing would increase the yield of CIN2+ in the population of women referred to colposcopy and biopsy. This increased efficiency in accurately detecting cervical neoplasia can effectively increase the ability of practices to better manage their time in seeing patients with actual disease and reduce over treatment for those patients who do not necessitate continued investigation, as a result of a false positive. MHS provides the convenience of a point of care, objective result that enhances the ability to effectively improve management of cervical neoplasia detection for women, by reducing the number of colposcopies currently being performed on normal and benign cervices. In adherence with the new USPSTF screening guidelines, further investigation for MHS in combination with the HPV test, is warranted to validate increased sensitivity in detecting cervical neoplasia, while reducing overtreatment of patients without disease in an initial positive screen population.

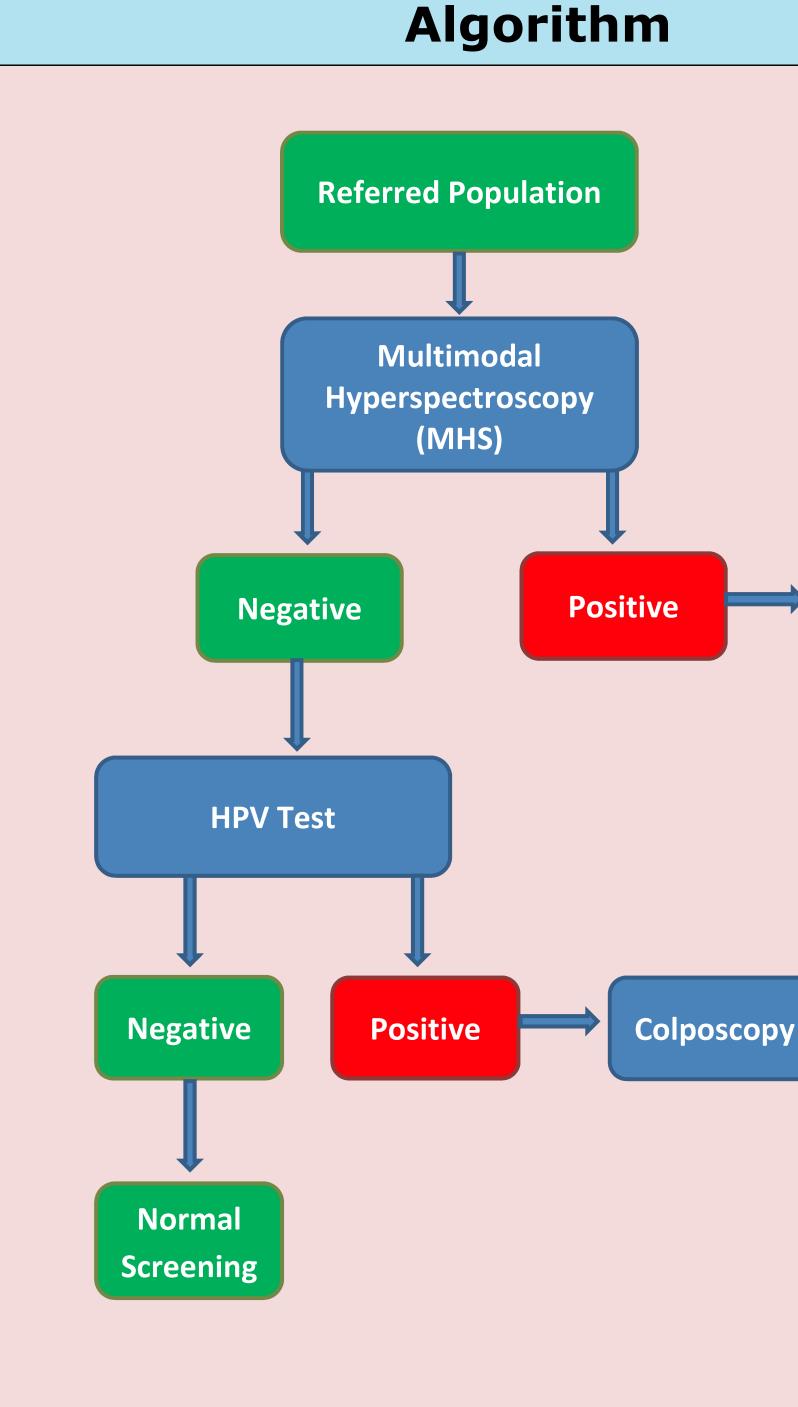


Figure 1. Proposed Patient Management

#### <u>References</u>

1 National Cancer Institute. <u>http://www.cancer.gov/cancertopics/factsheet/Detection/Pap-test</u> 2 Orange County Womens Medical Group (Laguna Hills, CA)/Saddleback Women's Medical Group (Laguna Hills, CA), Based on current reimbursement of CPT 57454. 3 U.S. Preventive Services Task Force. <u>http://www.uspreventiveservicestaskforce.org/uspstf11/</u>

<u>cervcancer/cervcancerrs.htm#clinical</u>

Colposcopy	

Table 3. Sensitivity and Negative Predictive Values
for Various Modalities and Combined Modalities

Modality	Sensitivity (95%CI)	NPV
Pap Cytology	72% (65.9,78.5)	<b>91%</b>
<b>Endocervical HPV</b>	81% (76.0, 86.9)	94%
MHS	87% (82.4, 91.8)	94%
MHS + HPV	99% (96.7, 100.)	<b>99%</b>



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