

Quantitative Optical Spectroscopy of the Uterine Cervix: A cost effective way to detect and manage cervical disease

Nahida Chakhtoura, MD, Leo Twiggs, MD, Timothy DeSantis, MD
Claudia Werner, MD, William Griffith III, MD, Lisa Flowers, MD
Manocher Lashgari, MD, Daron Ferris, MD,
Edward Wilkinson, MD, Stephen Raab, MD, Shabbir Bambot, Ph.D.
Brenda Schultz, David Mongin

Clinical Rationale

Cervical Cancer Screening

Current triage methods are not optimal

- Misses significant disease
 - Delays in diagnosis
- Excessive false positive rate
 - Result in unnecessary cost and morbidity

Clinical Rationale

Cervical Cancer Screening

- Need for new technology
- Evaluate the efficacy of quantitative optical spectroscopy
- Compare the efficacy of our approach with that of the current standard of care in the US
 - HPV + Pap
 - Colposcopy + Biopsy

Objective

Cervical Cancer Screening

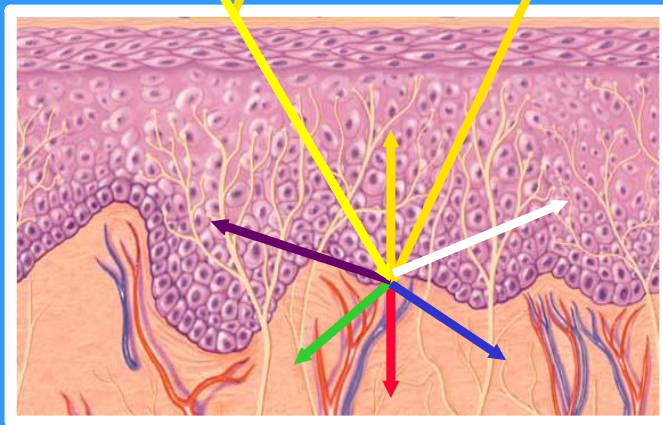
Pre-colposcopy triage techniques need high negative predictive values and specificity

- ALTS Trial showed that current triage of colposcopy after referral for ASC-US/HPV+ and LSIL patients would still miss between 30% to 40% of CIN3 disease
- ALTS Trial-Only about 5% of ASCUS Pap tests and 10% of LSIL Pap tests will actually detect CIN3 disease

Multimodal Spectroscopy

Light In –

Multiple wavelengths used to penetrate different tissue depths



Spectrometer



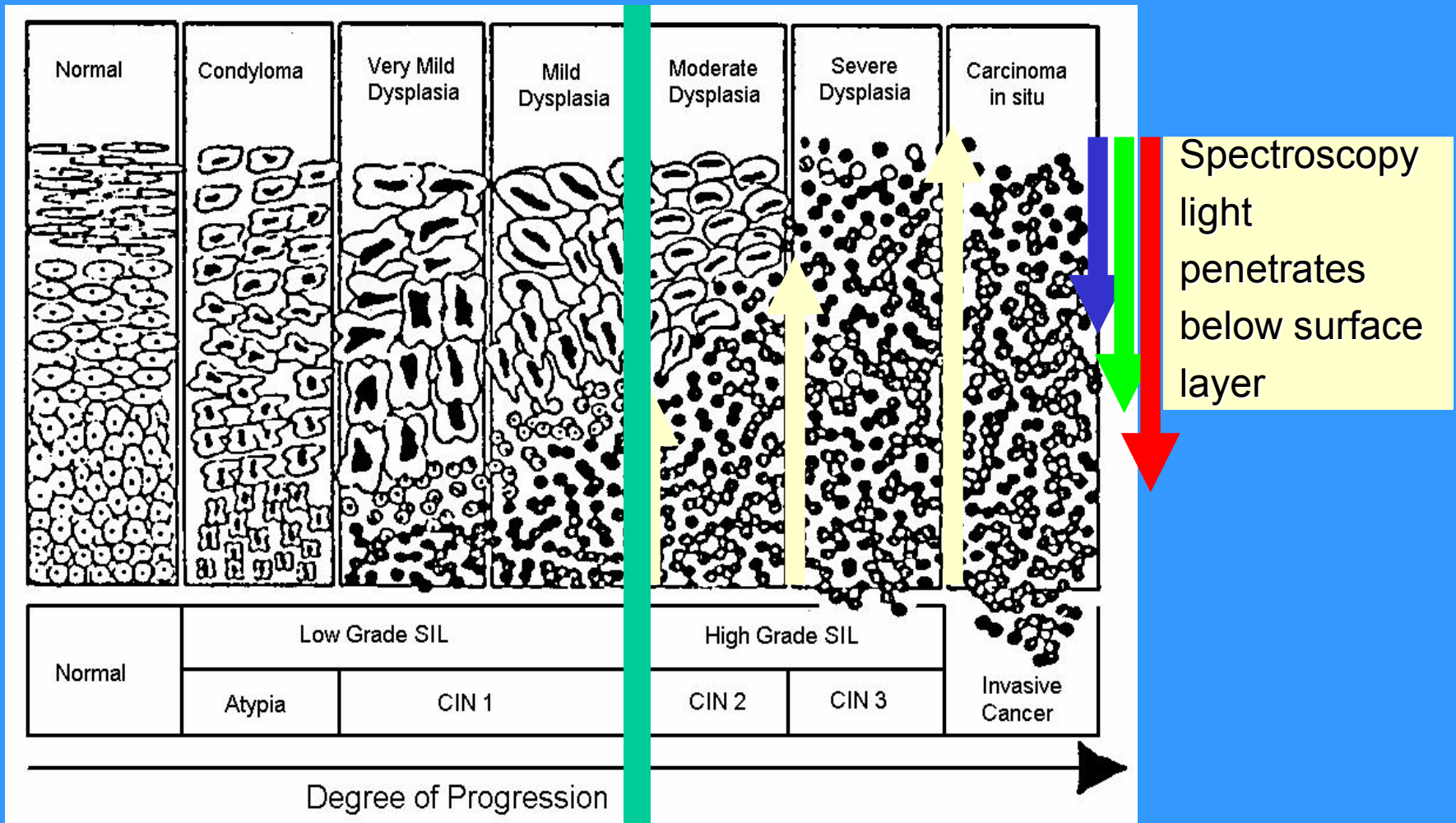
Results

1. *Fluorescence Spectra* -
Reveal metabolic changes associated with neoplasia
2. *Reflectance Spectra* –
Reveal morphological changes associated with neoplasia

What do we measure?

- Biochemistry: Fluorescence 300-500 nm excitation
 - NADH, FAD, Tryptophan
 - Collagen, Elastin
 - Porphyrin
- Morphology: Reflectance 350-900 nm
 - Increase in Nuclear/Cytoplasmic ratio
 - Hyperchromasia
 - Loss of cellular differentiation
 - Angiogenesis

Precursors to Invasive Cervical Cancer



Cervical Spectroscopy Device

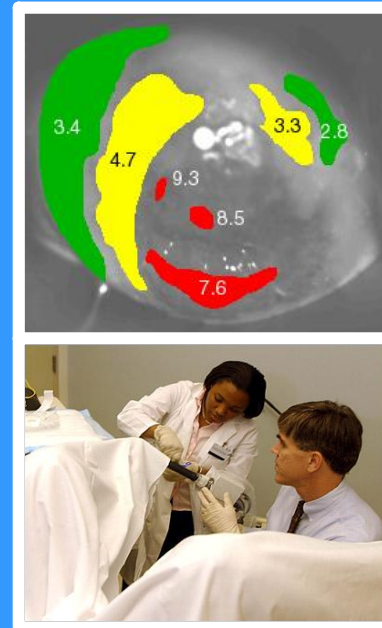
Cervical Neoplasia Detection System (CNDS)

- Measures fluorescence and reflectance spectra at multiple points on the cervix
- Low cost device and single patient use disposable
- Built in video colposcope – permits see and treat in the same visit and reimbursable in US using colposcopy CPT 57452
- Provides a color map of the cervix highlighting areas of high disease probability
- CNDS Manufactured by Guided Therapeutics, Inc. / Norcross, Georgia, USA



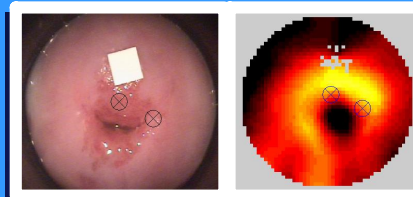
Benefits of Cervical Spectroscopy

- Immediate results
- Objective, more accurate test
- Less discomfort
- Saves Time
 - Exam time: 1-2 minute test
 - vs. 15-20 minute colposcopy
 - Less time chasing patients for return visits
- Reduced cost to patient and healthcare system
- Underserved populations



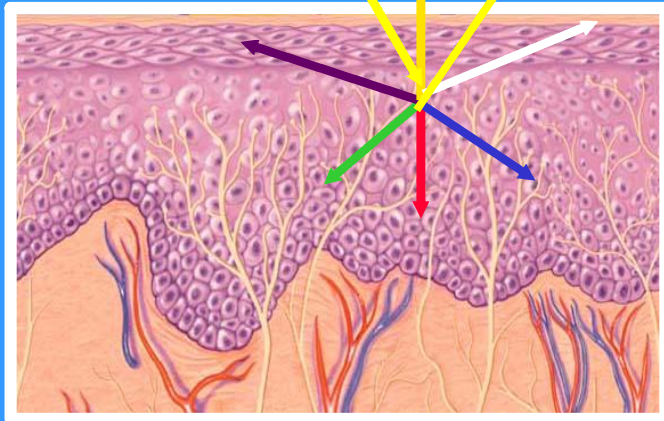
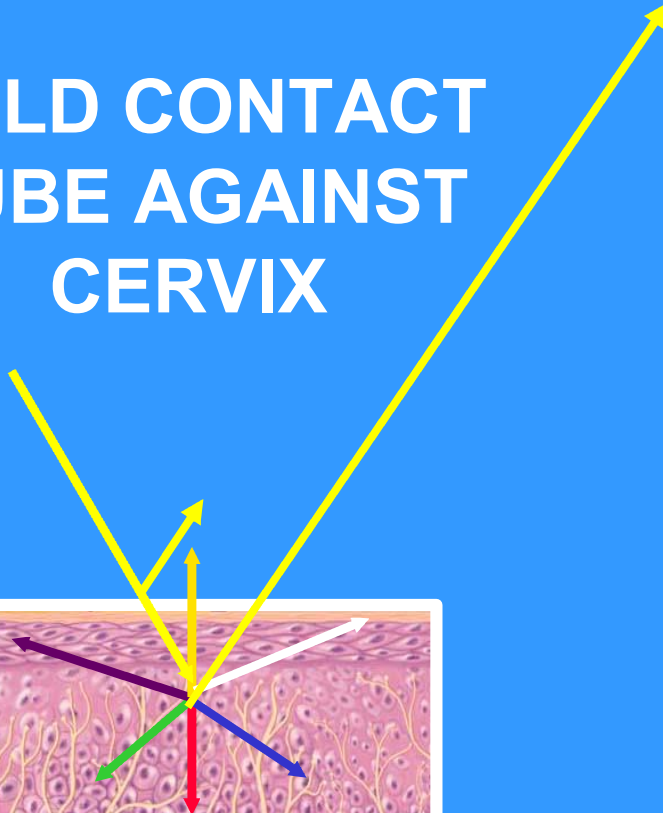
Multimodal Spectroscopy

Cervical Maps of Patient with Dysplasia



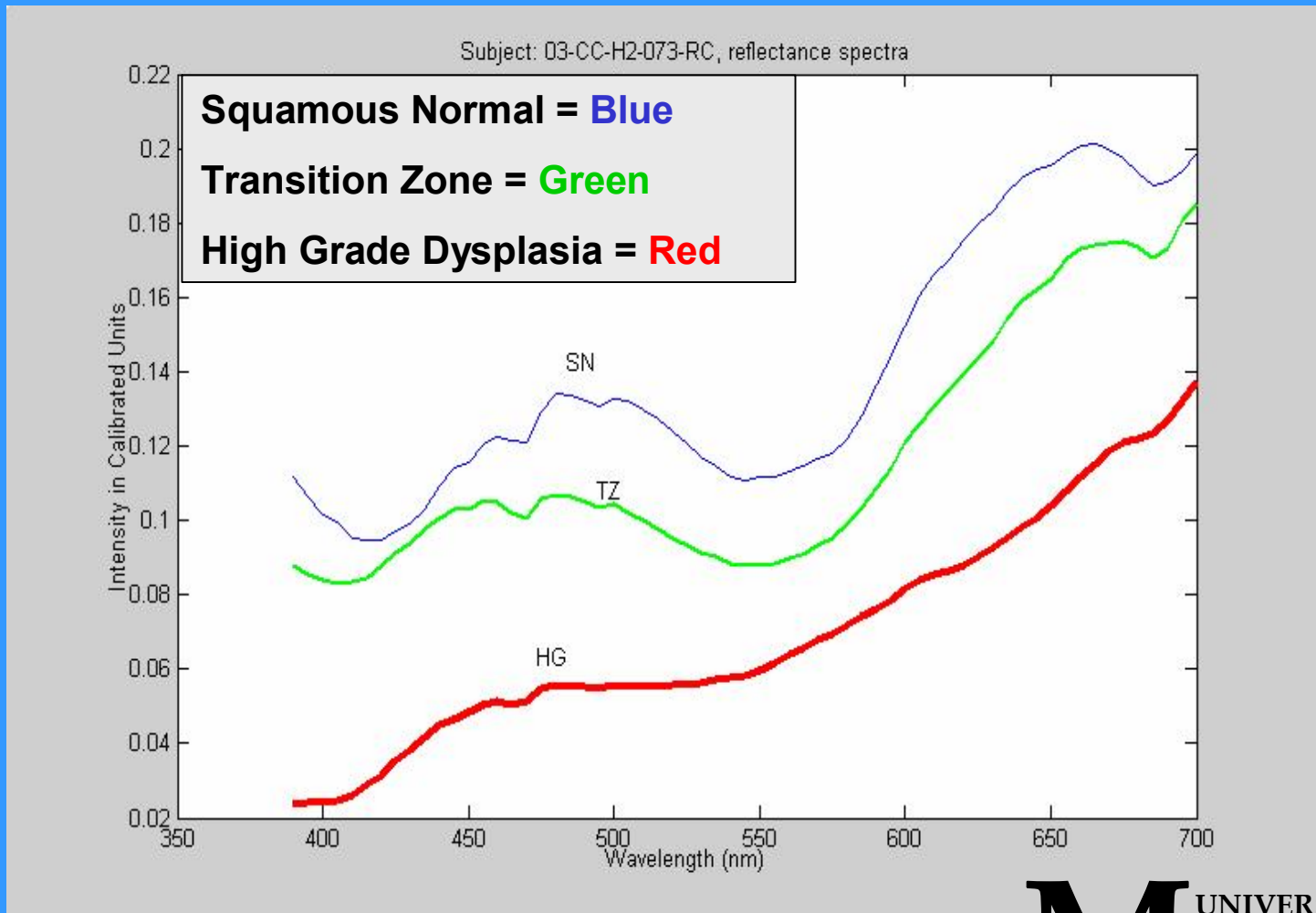
Biopsy sites marked with X's

**HOLD CONTACT
TUBE AGAINST
CERVIX**

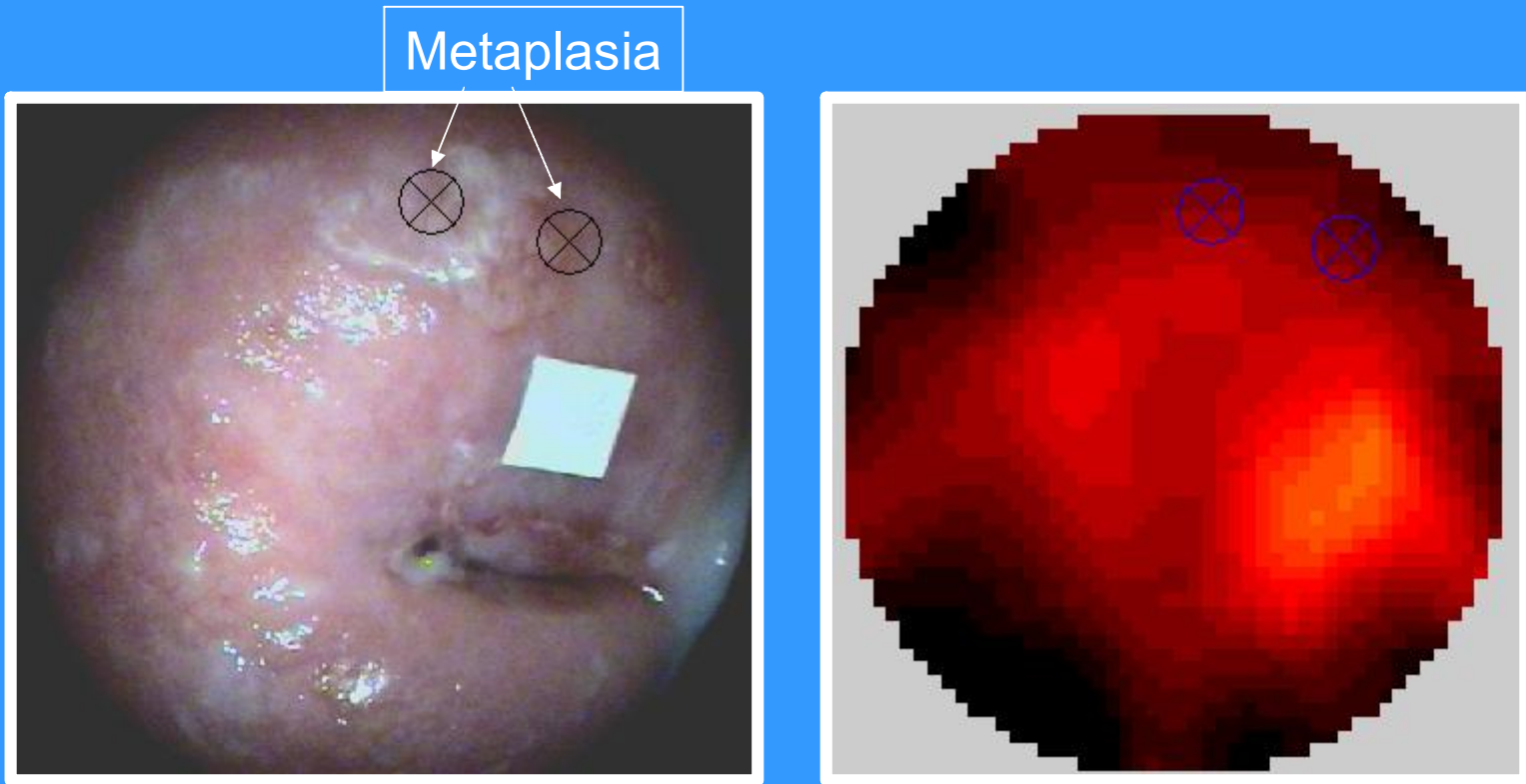


Results

Spectral Output of Cervical Tissue



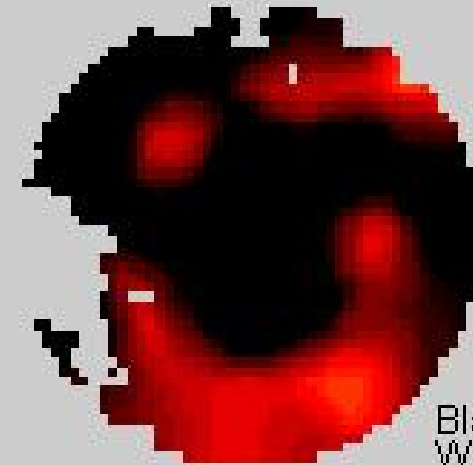
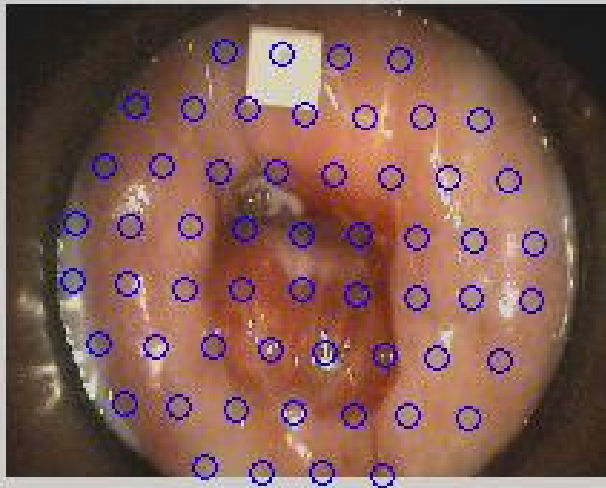
Cervical Maps of Patient with Metaplasia



Biopsy sites marked with X's

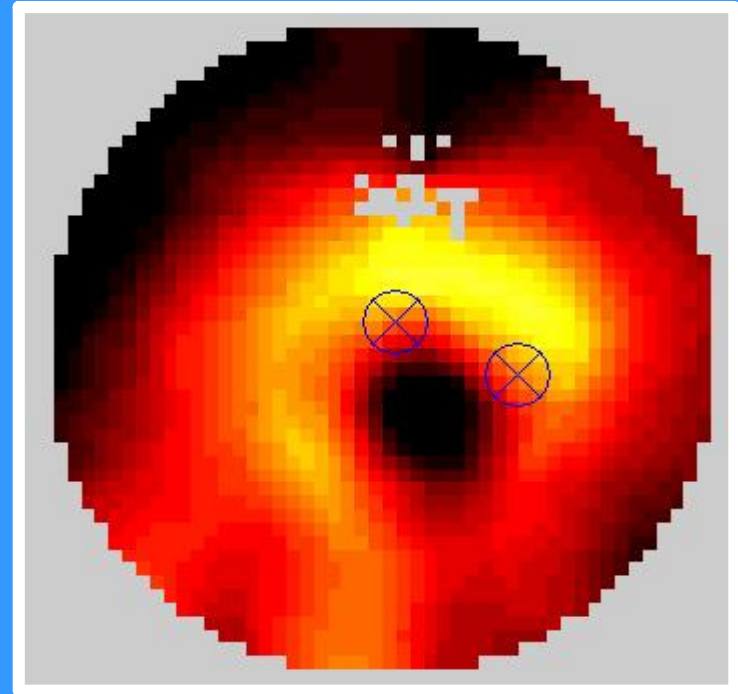
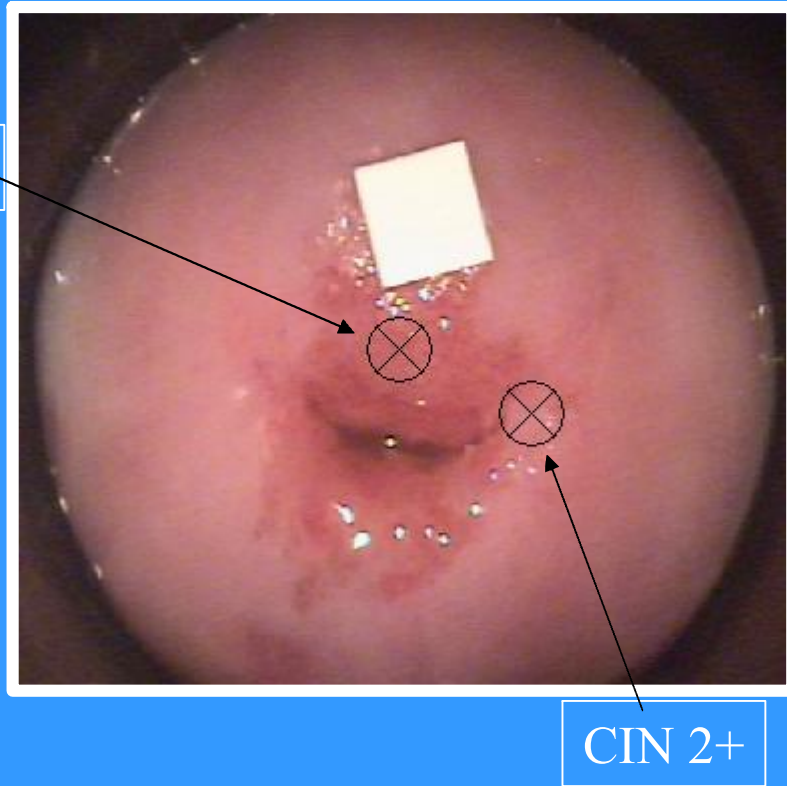
Cervical Maps of Patient with Normal Cervix

03-CC-H2-076-LL: NORMAL



Black ≤ 1
White ≥ 4

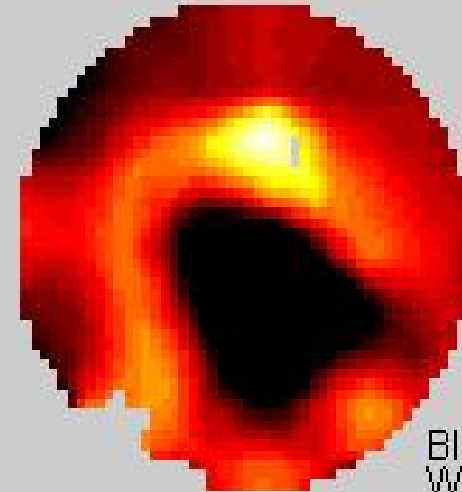
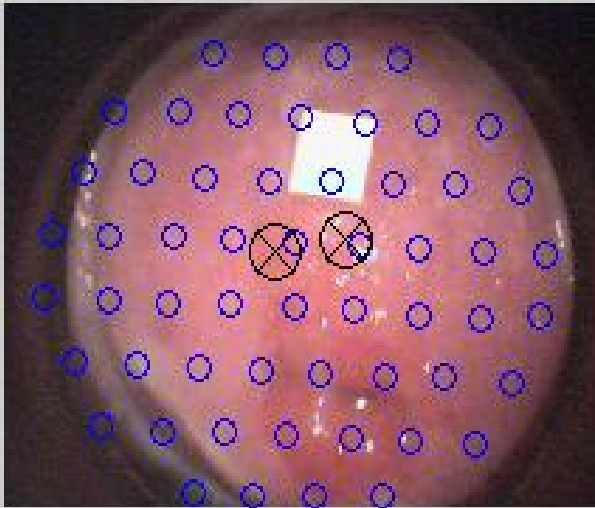
Cervical Maps of Patient with CIN 2+



Biopsy sites marked with X's

Cervical Maps of Patient with CIN 2

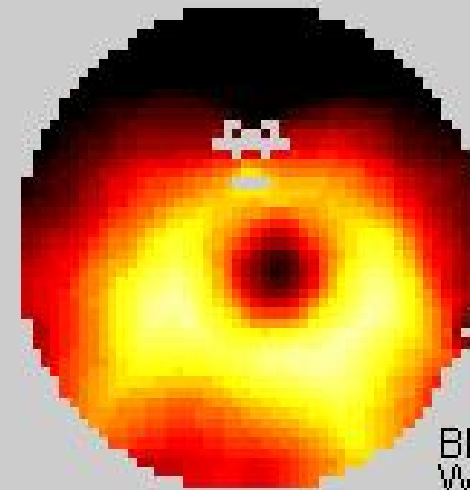
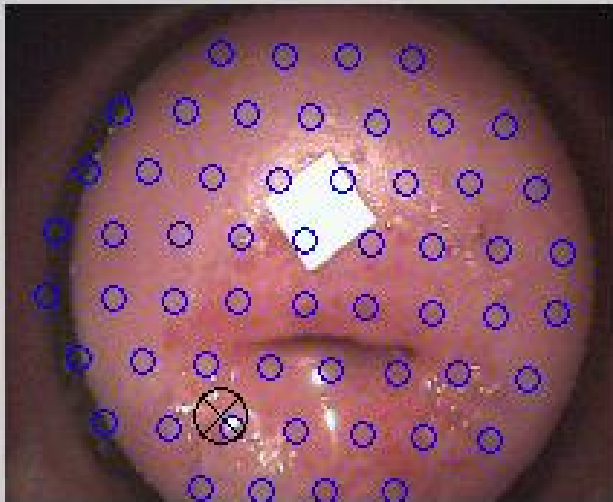
03-CC-H2-225-SA: CIN 2



Black ≤ 1
White ≥ 4

Cervical Maps of Patient with CIN 3

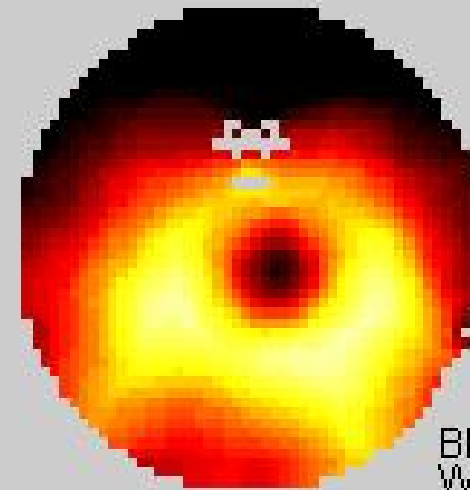
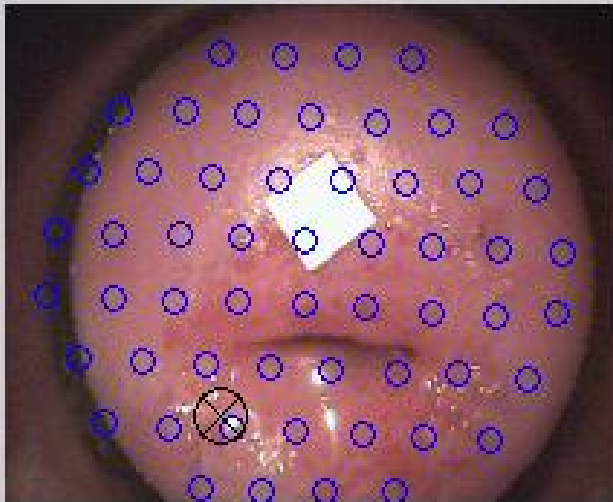
03-CC-H2-232-TG: CIN 3+



Black ≤ 1
White ≥ 4

Cervical Maps of Patient with CIN 3

03-CC-H2-232-TG: CIN 3+



Black ≤ 1
White ≥ 4

Methodology

Study Design 1

- Prospective double-blinded pivotal trial
 - Clinicians blinded to spectral output
 - Technical team blinded to clinical results (history, colposcopy, cytology, histology, HPV test)
- IRB approval at
 - University of Texas Southwestern Medical Center, Dallas
 - **University of Miami, Miami, FL.**
 - Medical College of Georgia, Augusta, GA.
 - St. Francis Hospital, University of Connecticut, Hartford, CT,
 - Emory University School of Medicine, Grady Memorial Hospital



Methodology

Study Design 2

- All colposcopies performed by one of 2 experienced colposcopists
- Pathology QA: agreement by 2 of 3 pathologists (1 site / 2 outside pathologists)

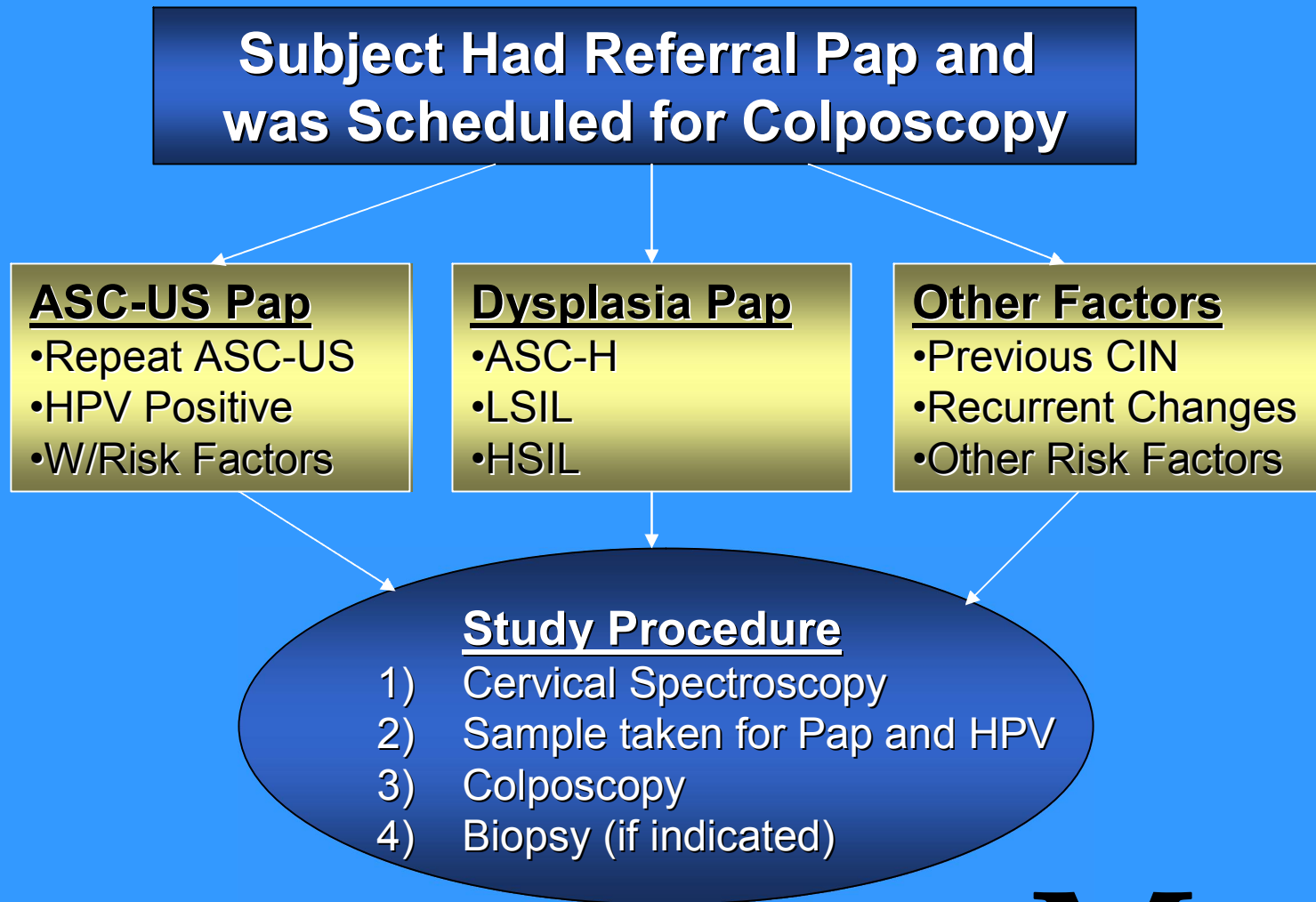
Study Inclusion Criteria

- Age 18 or above
- Able to read or understand and give informed consent
- Scheduled for colposcopy
- Pap test within 120 days
- Had a referral Pap test or willing to undergo a Pap test on day of study

Study Exclusion Criteria

- Pregnancy
- Menstruating on the day of study
- Radiation to genitourinary system within 1 year
- Prior hysterectomy
- Congenital anatomical cervical variant (e.g., double cervix)

Study Design Flow Chart



Clinical Trial Objectives

- Evaluate Multimodal Spectroscopy at five U.S. centers with diverse population
 - 648 subjects enrolled, 574 evaluable with valid cytology and QA pathology
 - Age Range: 18 – 73
- Additional goals:
 - Further evaluate patient acceptability for procedure
 - Estimate spectroscopy performance, especially ability to rule out significant pre-invasive disease (CIN 2+)

Quality Assurance (QA) Histopathology Procedure

- Site pathology renders diagnosis which is assigned to one of three categories
 - Normal
 - CIN1
 - CIN2+
- Site pathology sends original or representative slide to QA 1
 - If QA 1 agrees with site, diagnosis confirmed
 - If QA 1 disagrees with site diagnosis, specimen sent to QA 2 pathologist
- If 2 out of 3 diagnoses agree – case is included in analysis
- 3 way disagreements are not included in the analysis

Algorithm Performance

Sensitivity and Specificity of Spectroscopy by Disease Category for All 572 Evaluable Subjects

ALL CASES (N=572)	SENSITIVITY		SPECIFICITY
DISEASE	CIN2+	CIN1	No CIN
NUMBER TESTED	142	180	250
NUMBER CORRECT	135	135	138
PERCENT CORRECT	95.1	75.0	55.2
95% CONFIDENCE INTERVAL	91.55, 98.65	68.67, 81.33	49.04, 61.36

University of Miami

Algorithm Performance

Sensitivity and Specificity of Spectroscopy by Disease Category
for 151 Evaluable Subjects enrolled at the University of Miami

Miami CASES (N=151)	SENSITIVITY		SPECIFICITY
DISEASE	CIN2+	CIN1	No CIN
NUMBER TESTED	48	50	53
NUMBER CORRECT	45	43	34
PERCENT CORRECT	93.8	86	64.2

Histopathology Agreement Analysis

	Site / QA 1	Site / QA 2	QA 1 / QA 2
NUMBER OF SUBJECTS	424	213	213
AGREE (both positive)	101	59	56
AGREE (both negative)	260	105	106
PERCENT AGREEMENT	85%	77%	76%
KAPPA STATISTIC*	0.65	0.52	0.50

***Kappa value of at 0.41 to 0.60 indicates moderate agreement, above 0.60 indicates substantial agreement**

Algorithm Performance-Without 6 Interferences “Clean Cases”

ALL CASES (N=510)	SENSITIVITY		SPECIFICITY
DISEASE	CIN2+	CIN1	No CIN
NUMBER TESTED	133	151	226
NUMBER CORRECT	127	119	128
PERCENT CORRECT	95.5	78.8	56.6
95% CONFIDENCE INTERVAL	91.98, 99.02	72.28, 85.32	50.14, 63.06

These results suggesting that spectroscopic measurements and the interpretive algorithm used to produce the test result are relatively robust

University of Texas Southwest Clinical Trial

- UTSW one of largest clinics in US – Over 90,000 Paps handled each year
- Trial, completed in 2004, nearly identical to current FDA pivotal trial
- 113 Subjects scheduled for colposcopy: 18 CIN2+ and 84 sub-CIN2 cases
- Study compared Pap+HPV and Pap+Cervical Spectroscopy (CS)
- Sensitivity 95% (19/20 high grade cases detected by both)
- Specificity 65% (compared with HPV specificity of 27%)

CNDS Ability to Detect Cases Missed by Pap and Site Histopathology

- 19 cases that were missed or mis-classified by Pap
 - All 19 detected by CNDS (100% sensitivity)
- 18 cases that were mis-classified as low grade or normal by colposcopically-directed site biopsy
 - QA histopathology (two independent experts) determined these to be CIN 2+
 - CNDS detected 18 out of 18 (100% sensitivity)

Clinical Benefits of Cervical Spectroscopy Compared with Current Standard of Care

Triage Modality	Sensitivity	Specificity	Immediate Result	Time to Acquire Data	Lab Turn-around	All Ages	Easy to Train and Use
HPV/ Colposcopy	65% (combined)	26% (combined)	NO YES	< 1 min 15 min	2-4 weeks for biopsies	NO YES	YES NO
Cervical Spectroscopy	95%	55%	YES	<1 min	None	YES	YES
Pap	51%	97%	NO	1-2 min	1-2 weeks	YES	YES

Conclusions

Cervical Spectroscopy

- Improves detection of high-grade dysplasia
- Eliminates unnecessary colposcopy & biopsy
- The test is relatively simple
 - Less discomfort
 - Well accepted by subjects
- Provides immediate and more accurate results
- Reduces cost to patients and healthcare system

Thank You

The National Cancer Institute
The Georgia Research Alliance

