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

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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

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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

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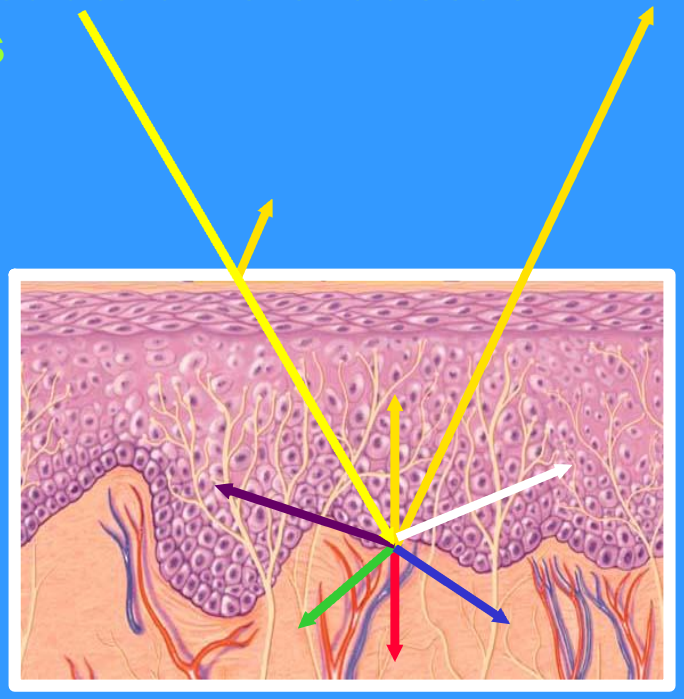
Multimodal Spectroscopy

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

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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

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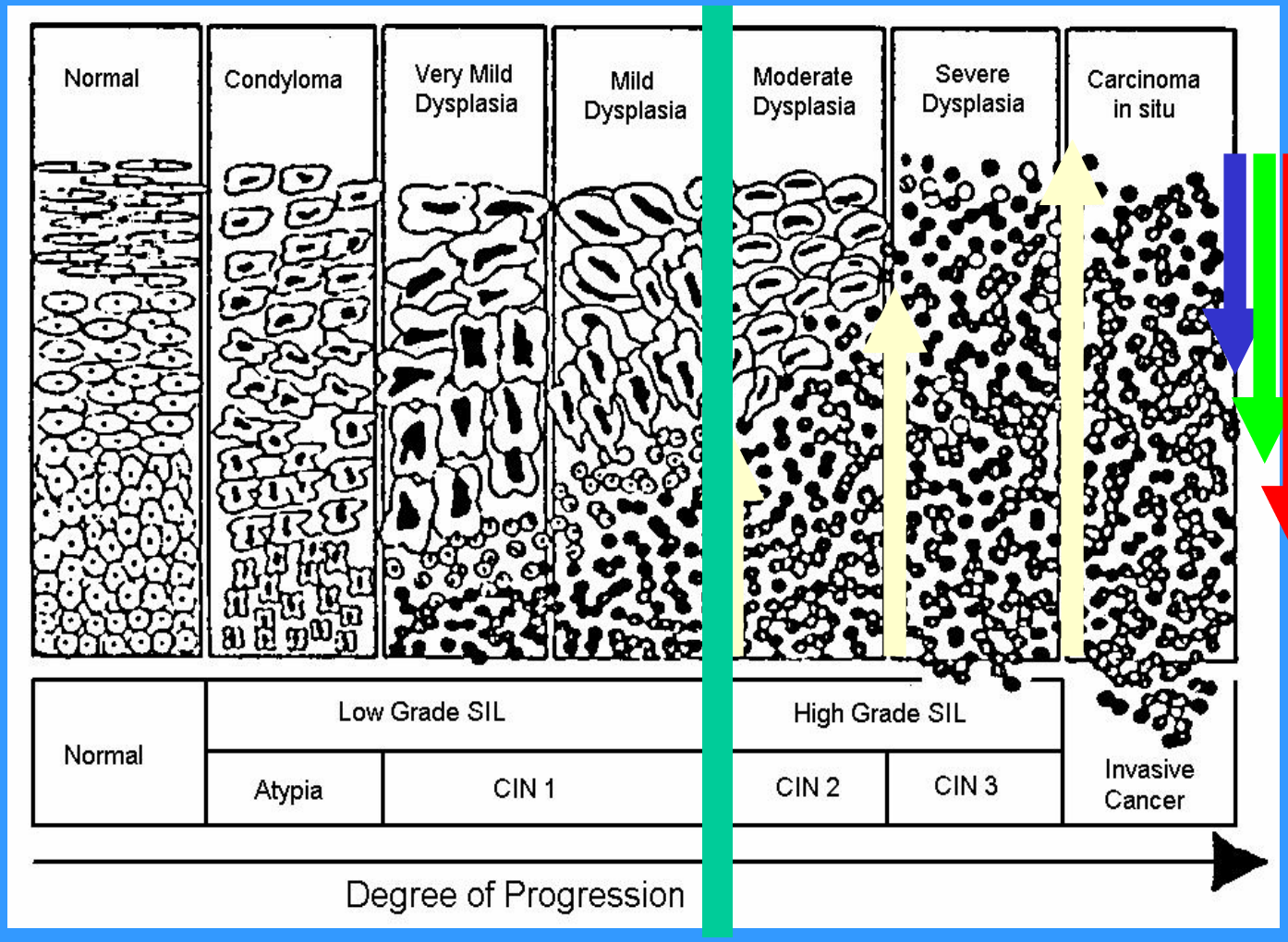
Precursors to Invasive Cervical Cancer



Spectroscopy light penetrates below surface layer

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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

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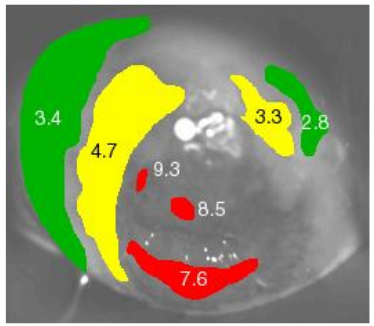
Benefits of Cervical Spectroscopy

- 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



LuViva Advanced Cervical Scan

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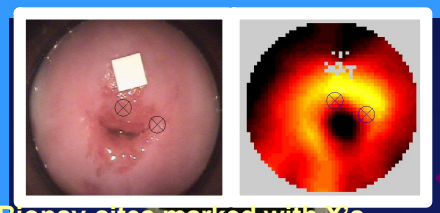
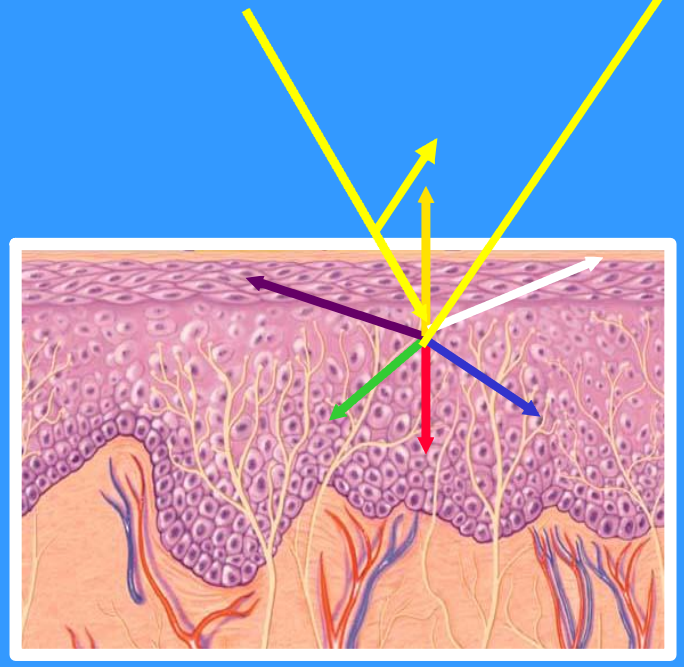
Multimodal Spectroscopy

Cervical Maps of Patient with Dysplasia



Biopsy sites marked with X's

HOLD CONTACT TUBE AGAINST CERVIX



Results

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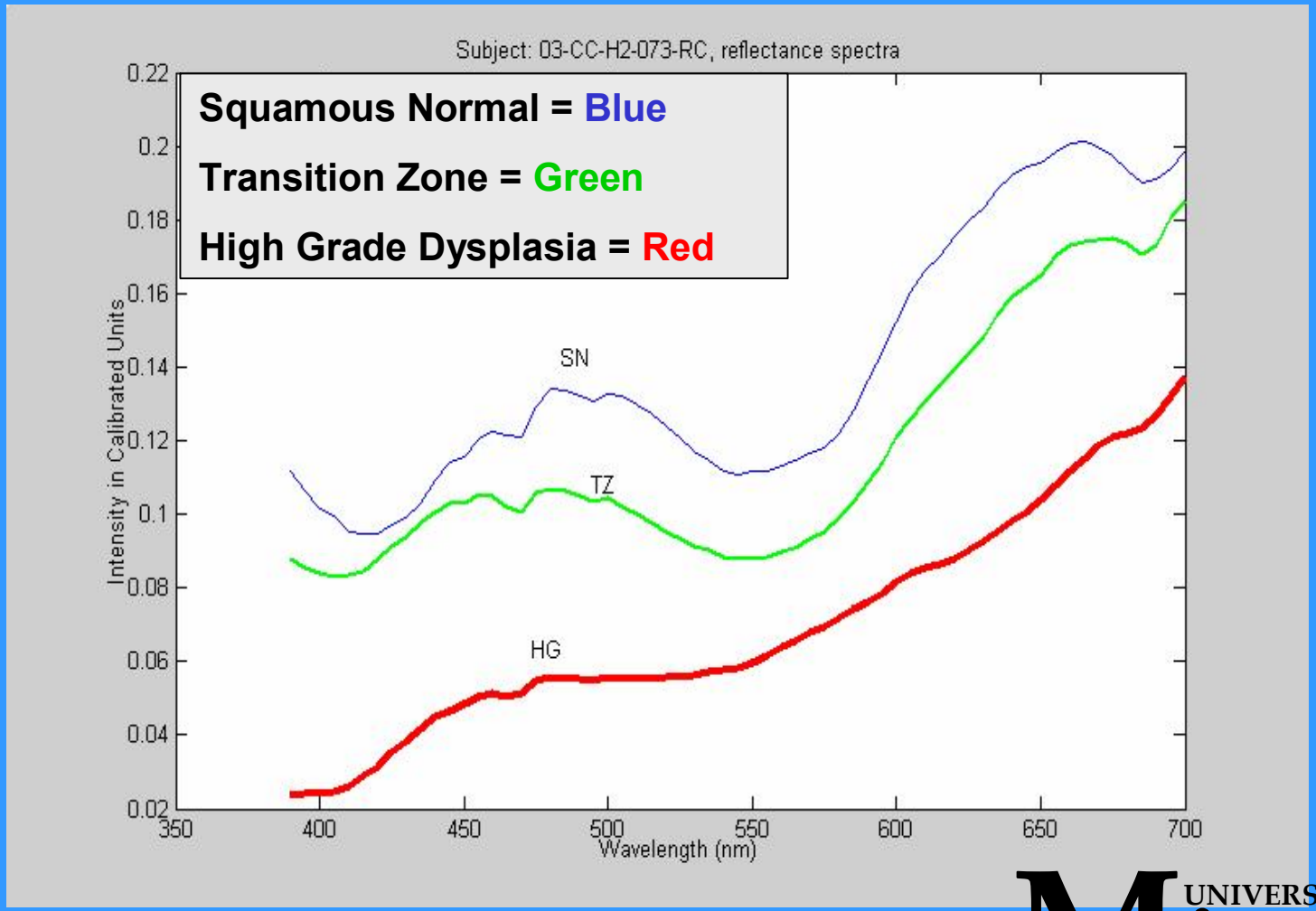
Spectral Output of Cervical Tissue



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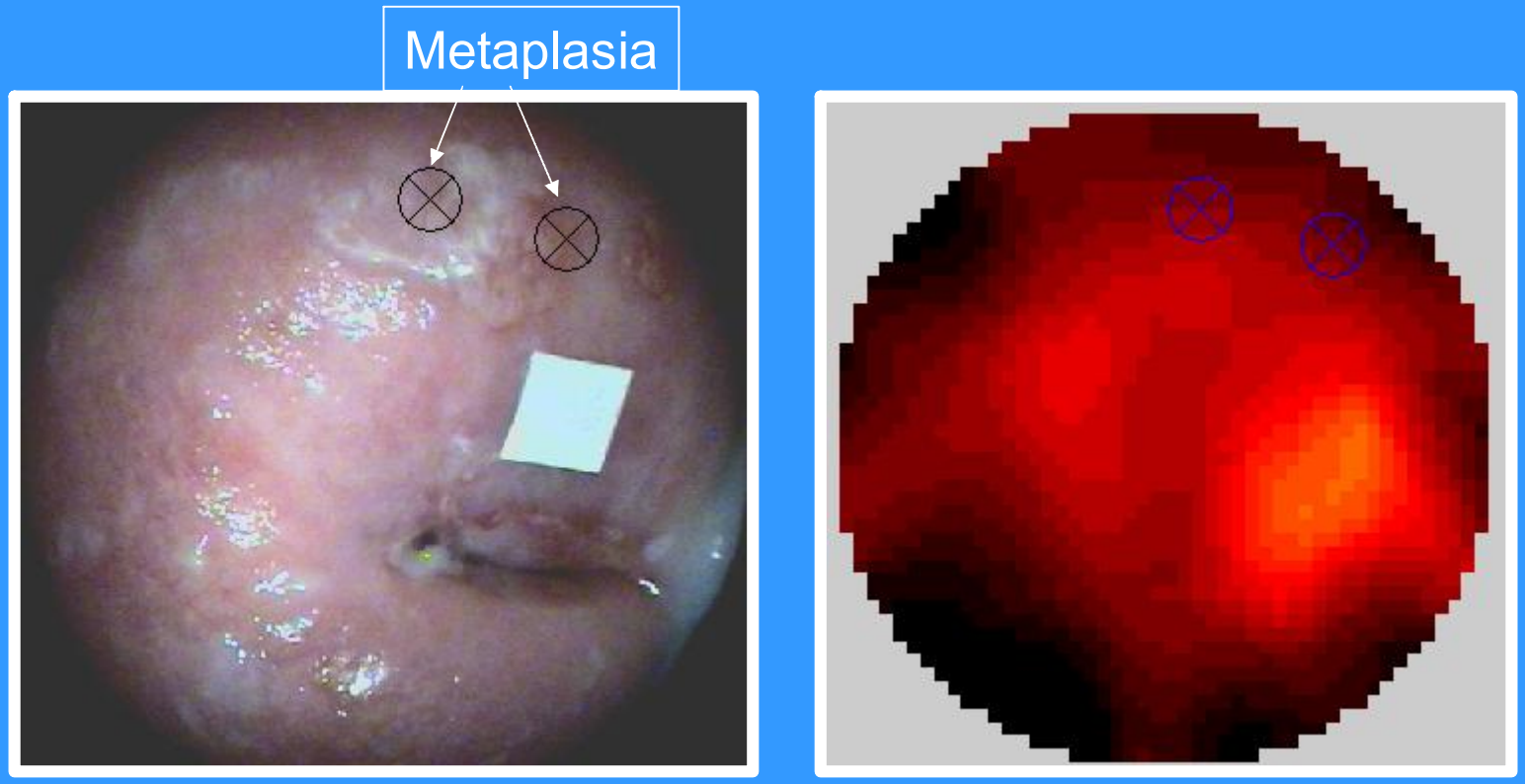
Cervical Maps of Patient with Metaplasia



Biopsy sites marked with X's

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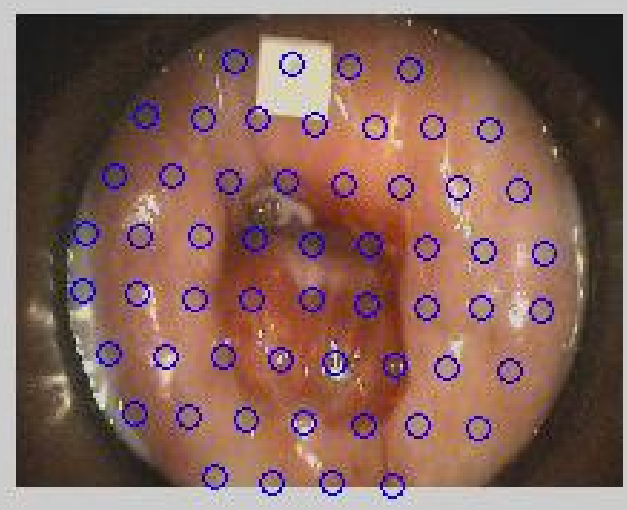
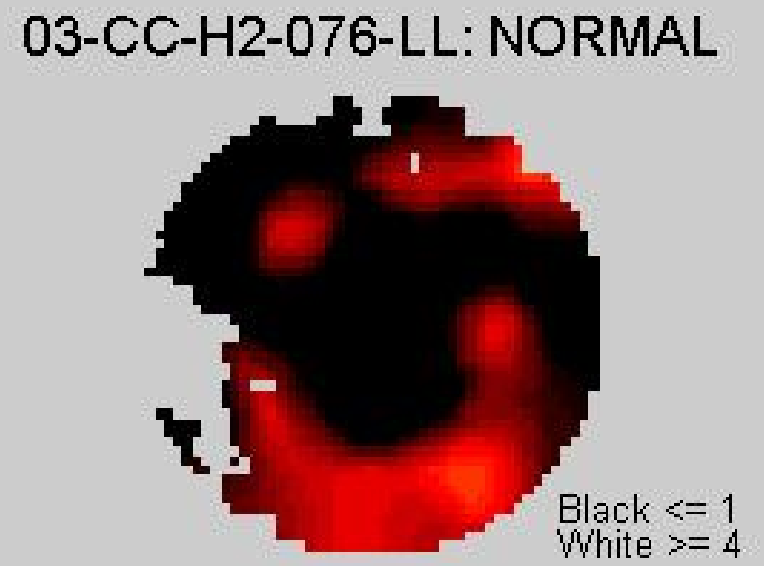
Cervical Maps of Patient with Normal Cervix





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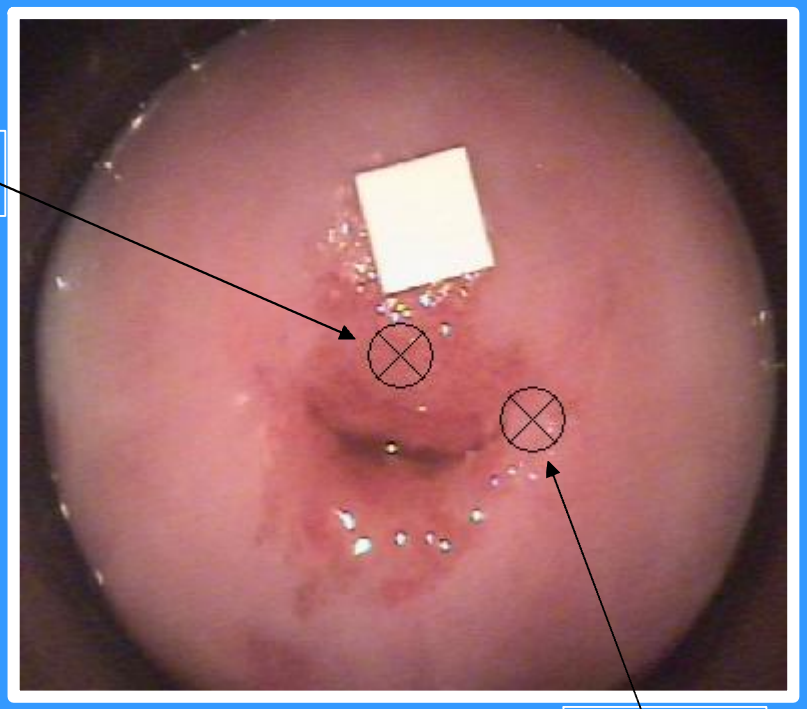
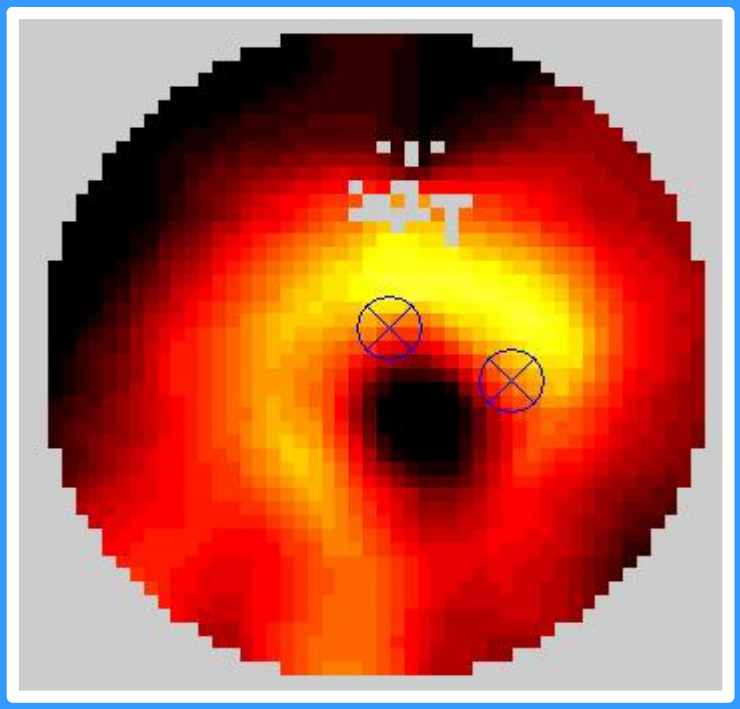
Cervical Maps of Patient with CIN 2+





Biopsy sites marked with X's

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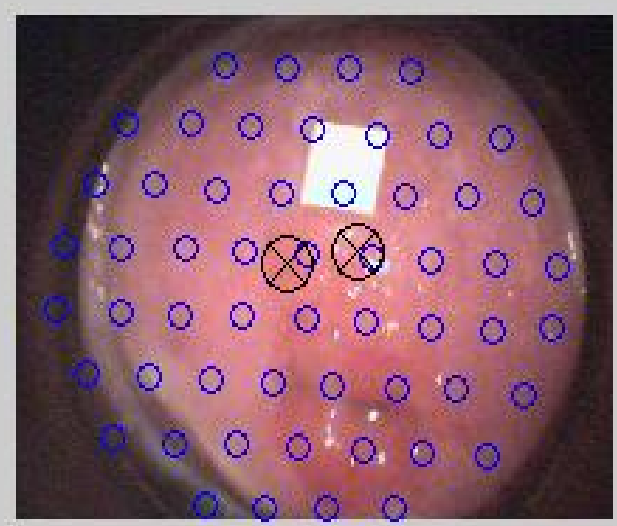
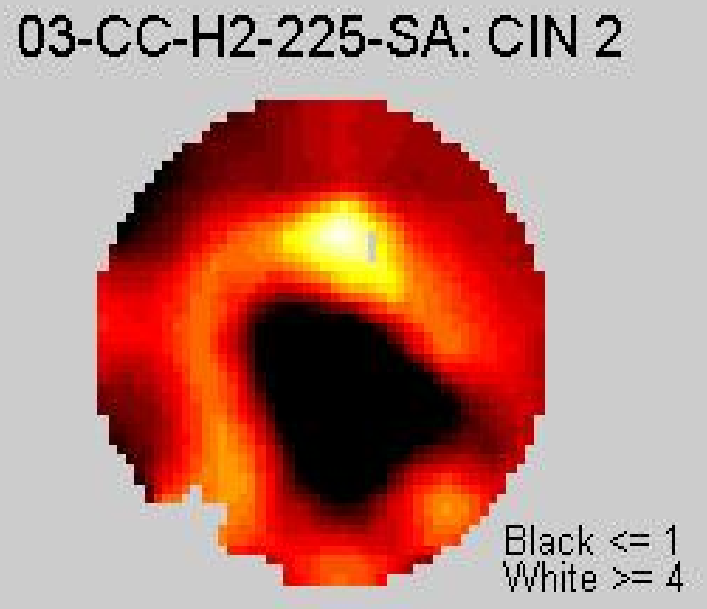
Cervical Maps of Patient with CIN 2





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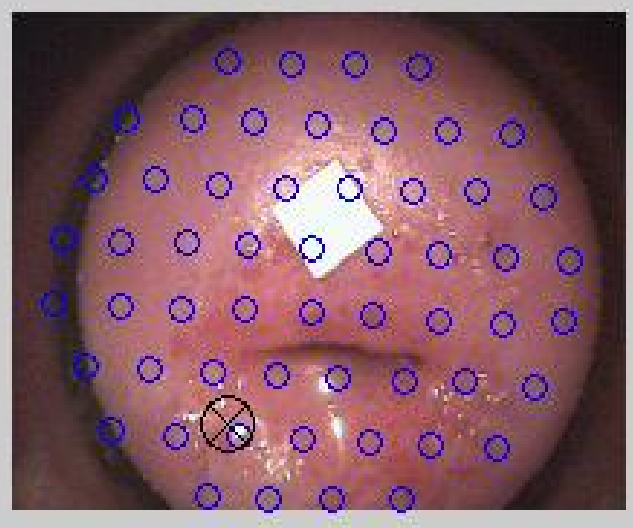
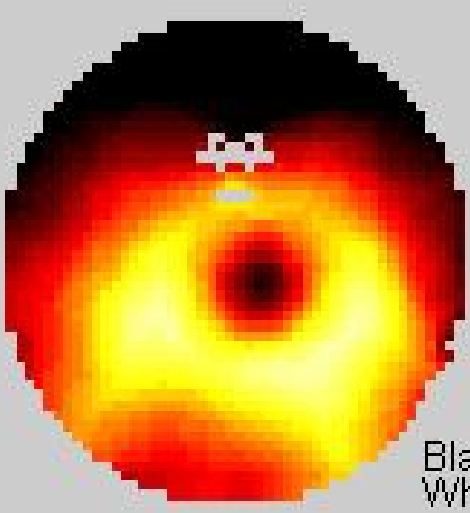
Cervical Maps of Patient with CIN 3



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



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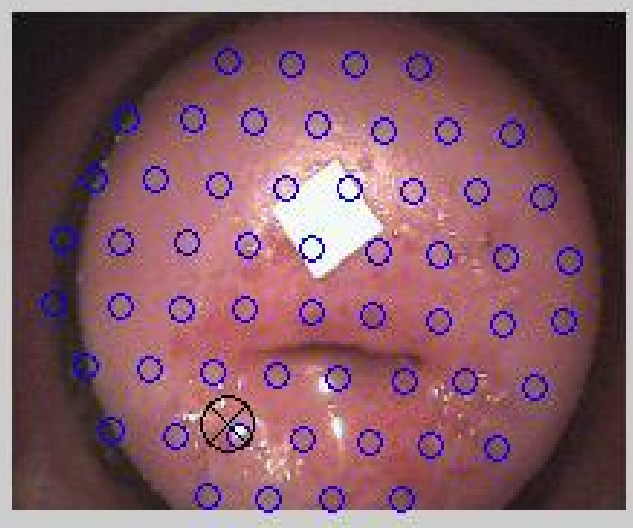
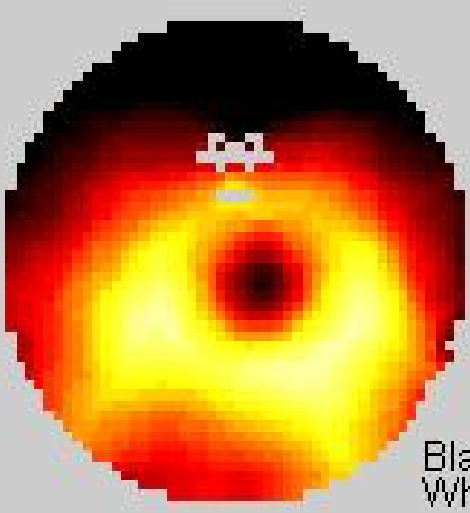
Cervical Maps of Patient with CIN 3



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



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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

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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)

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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

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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)

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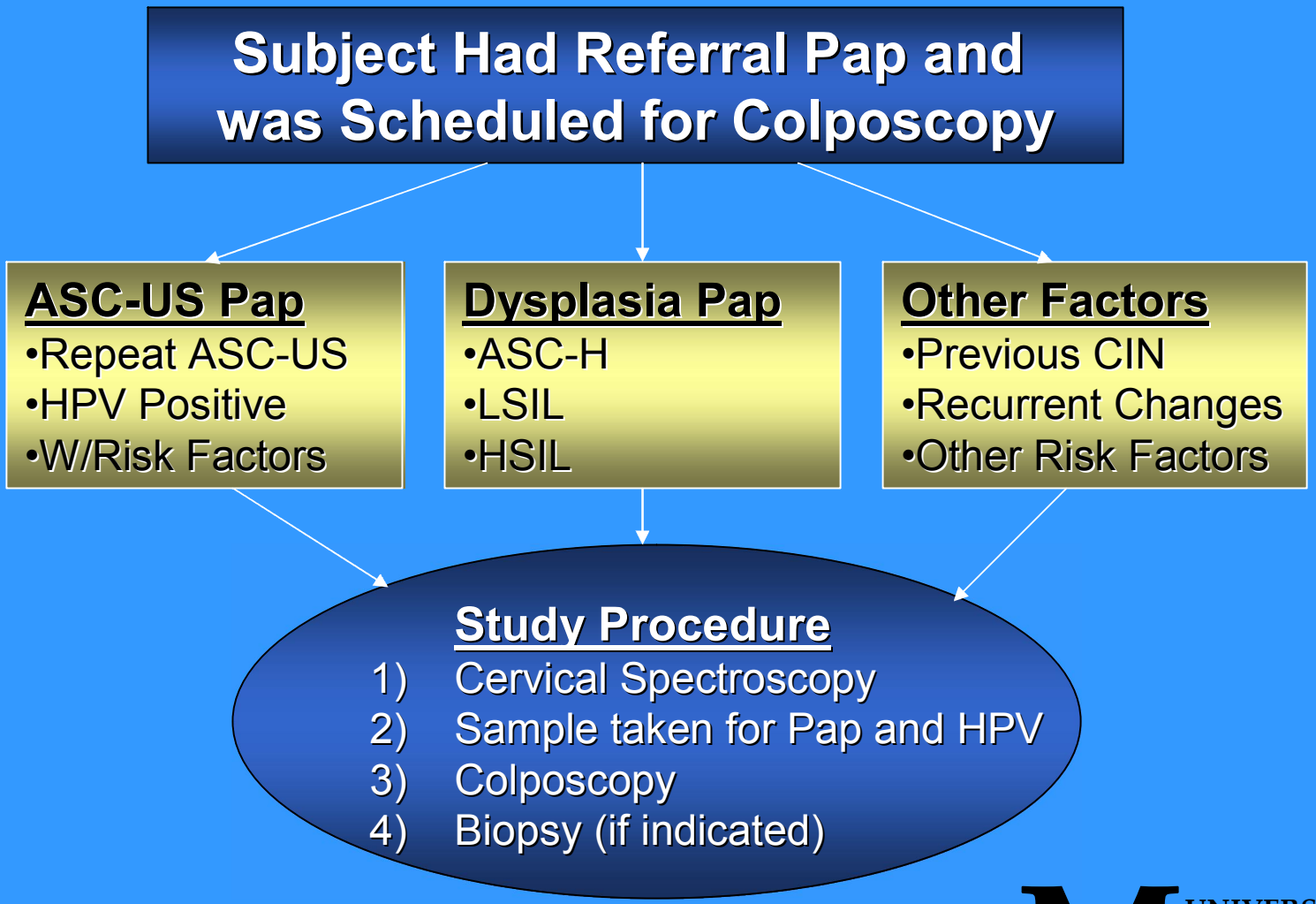
Study Design Flow Chart



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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

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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**

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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**

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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**

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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

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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%)

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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)

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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

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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

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