Biophotonic Detection of Cervical Dysplasia: *The Transition from Clinical Trials to Real World Use*

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Presentation Outline

- Brief history of biophotonics (spectroscopy) for cancer detection
- Clinical trial history and study results
- Current evaluations of commercial systems
- Conclusions

Brief History of Biophotonics

- 1990's – Mostly academic research projects
  - City University of New York, MIT, University of Texas, British Columbia
- 2000's – Commercialization of specific applications for:
  - Lung cancer
  - Colorectal cancer
  - Cervical cancer
- Most of these companies did not survive the economic recession of 2007-2009

Biophotonics and Cervical Dysplasia

- Initial application was to assist colposcopists in identifying lesions to biopsy (e.g., Medispectra (defunct) and Dysis)
  - Mostly due to cost and complexity of these systems
- Some companies chose to develop lower cost systems
  - Polartechnics
  - Guided Therapeutics
- Technology advances resulting in lower cost and easy to use systems lend themselves to lower cost triage use

Cancer Markers Identified by Spectroscopy

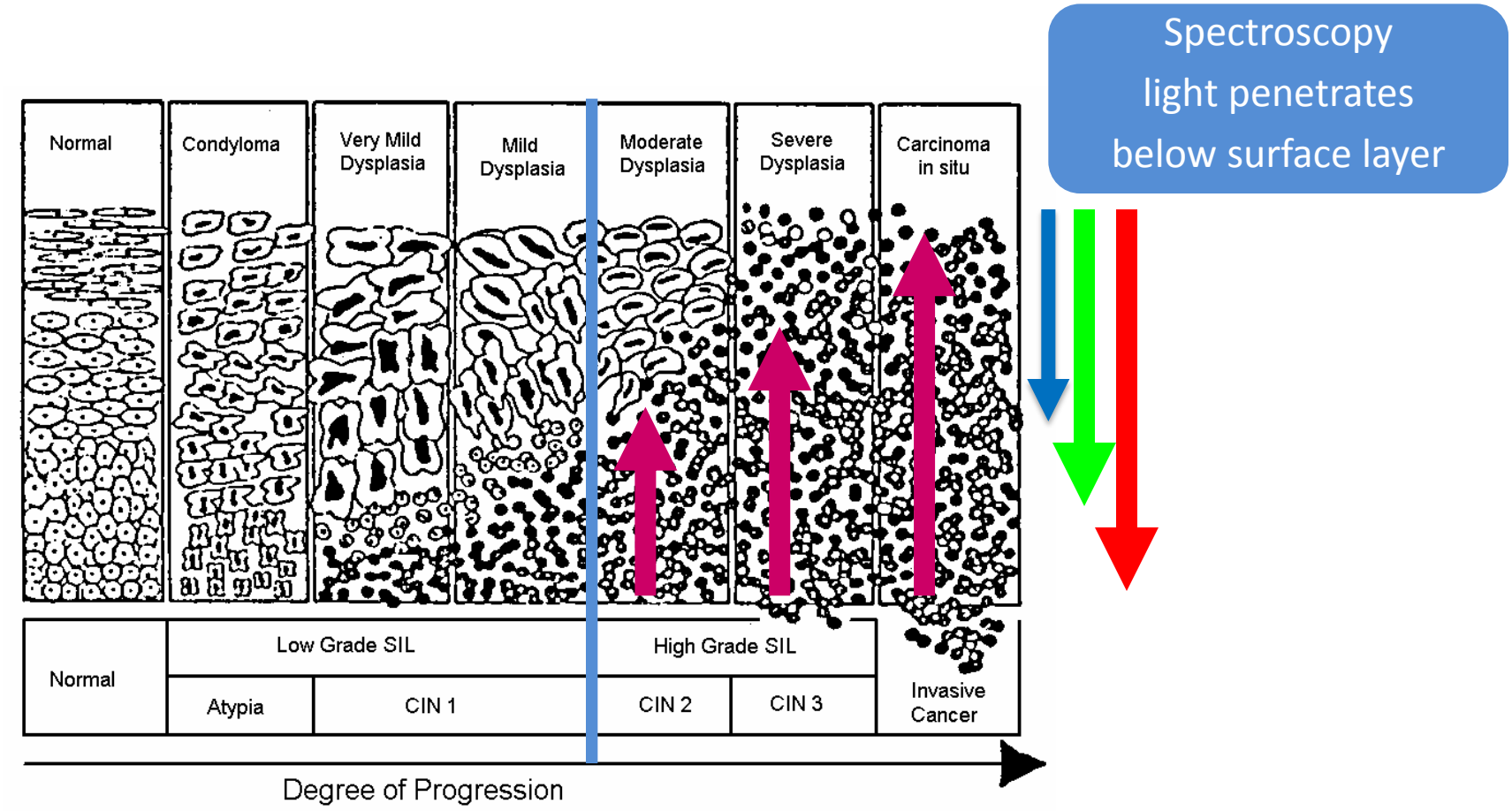
- Biochemistry: Fluorescence 300-500 nm excitation
  - NADH, FAD, Tryptophan
  - Collagen, Elastin
  - Porphyrin
- Morphology: Reflectance 350-900 nm
  - Increase in Nuclear/Cytoplasmic ratio
  - Hyperchromasia
  - Loss of cellular differentiation
  - Angiogenesis

Clinical Rationale

Pre-colposcopy triage techniques need high negative predictive value 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

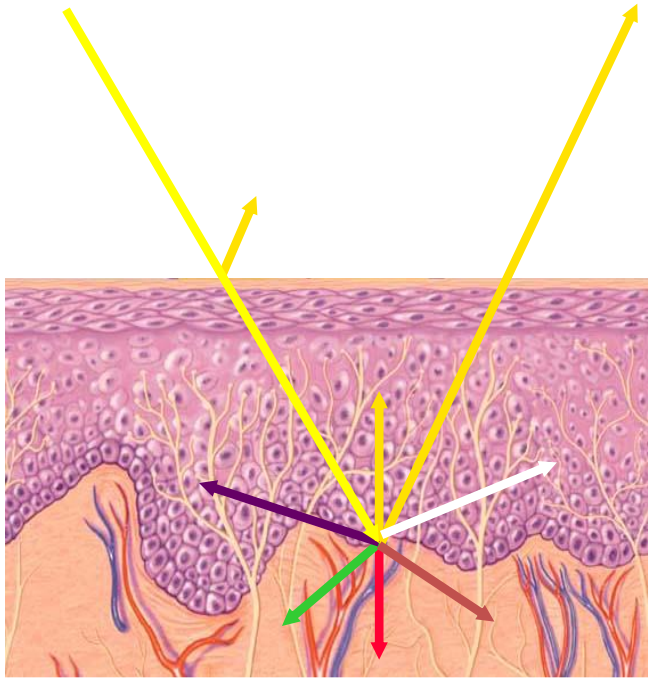
Precursors to Invasive Cervical Cancer



Potential Solution: Better Technology

Light In –

Multiple wavelengths used to penetrate different tissue depths



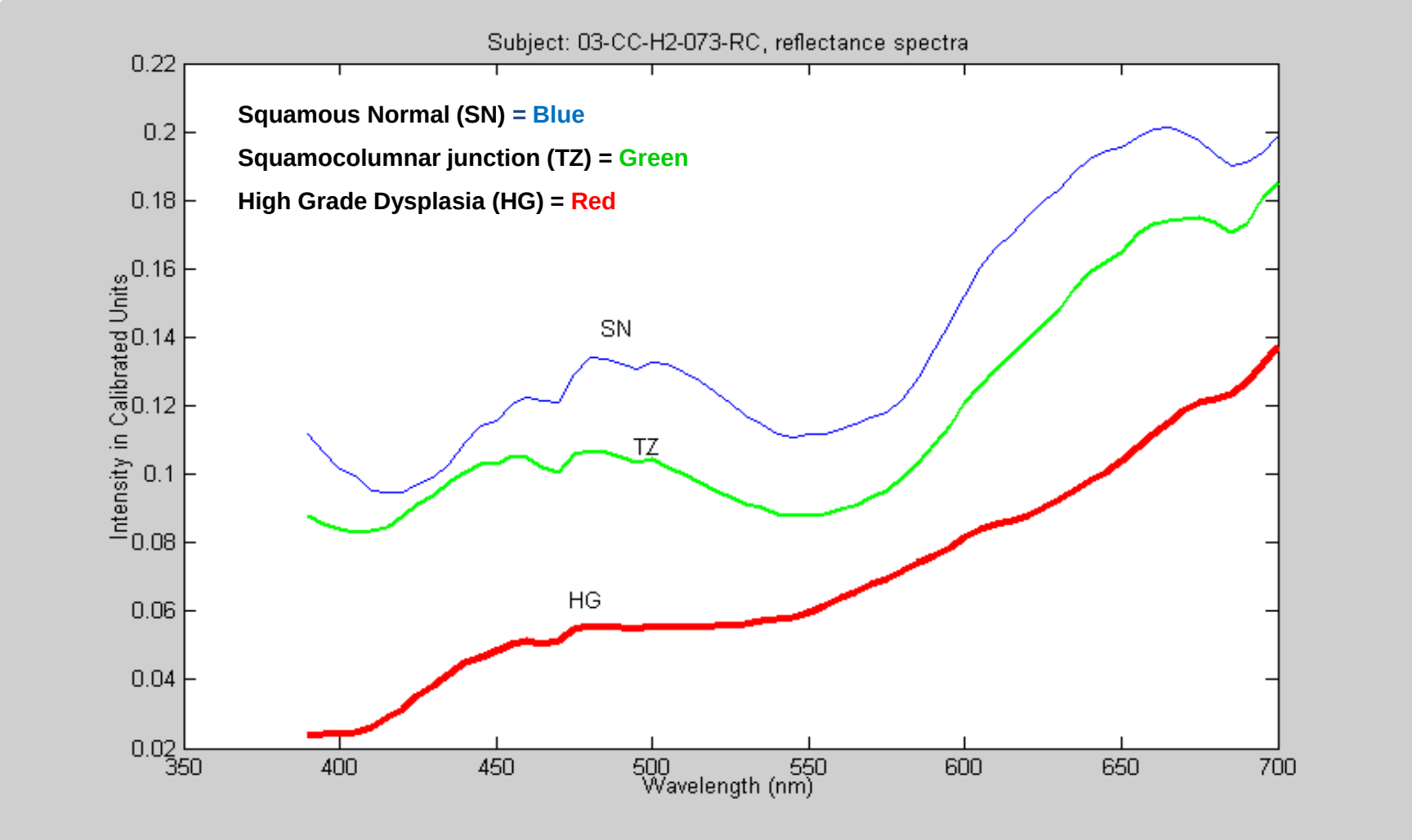
1. *Fluorescence Spectra -*

   Reveal metabolic changes associated with neoplasia

2. *Reflectance Spectra –*

   Reveal morphological changes associated with neoplasia

Spectral Output of Cervical Tissue



Clinical Rationale For Better Triage

Countries with established screening programs, e.g., US, Canada and Western Europe, have seen dramatic reductions in mortality due to cervical cancer

However…

- Significant disease is not detected (false negatives)
- Many women without disease are referred to expensive and invasive procedures (false positives)
- HPV testing increases detection but also results in more false positives

US Pivotal Study Group

- 1607 total enrolled
- 195 excluded (mostly training cases or women with discordant or insufficient histopathology)
- 1447 analyzed for sensitivity and specificity
- 804 subjects with two year follow up
- Study published in Gynecologic Oncology, April 2013

Multimodal Spectroscopy as a Triage Test For Women at Risk For Cervical Neoplasia: Results of a 1,607 Subject Pivotal Trial

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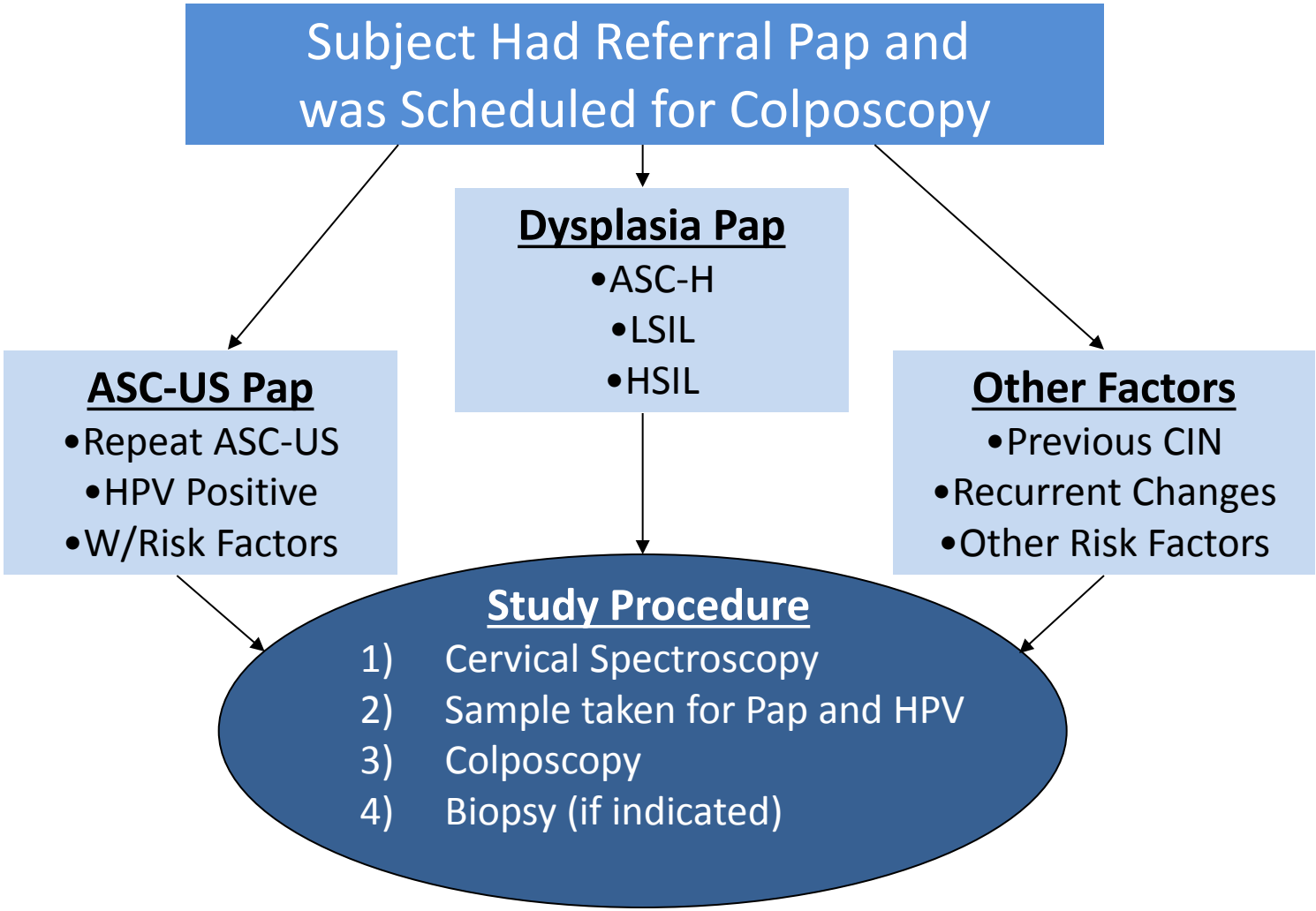
US Pivotal Study Design

- Each subject served as own control
- Referral Pap/HPV or other risk factor to qualify for study
- Day of study, each subject had endocervical samples taken for Pap and HPV, followed by colposcopy and biopsy
- Histology QA procedure used to reach diagnosis for each subject
- Follow up data (two year) collected if available
- 804 returned for follow up, 243 had biopsies

Study Design Flow Chart



US Patient Demographics

Age	Non-Hispanic				Hispanic		Total Enrolled
	American Indian	Asian Pacific Islander	African American	White	African American	White	
16-20	1	2	182	36	6	63	290
21-30	2	13	383	101	6	178	683
31-over	0	5	303	113	2	211	634
						TOTAL	1,607

Definitions

- **Final histology**
  - Pathology QA review involved blinded review by two independent expert pathologists
  - Up to two year histopathology follow-up after study
- **Standard of Care Includes:** Pap cytology, HPV testing and colposcopic impression
- **Sensitivity -** Ability of test to correctly identify patients with disease (CIN2+)
- **Specificity -** Reduction in referral rate to colposcopy and biopsy procedures
- **Negative Predictive Value (NPV)** - Level of confidence that a patient is free from disease (CIN3+)

Study Results

Modality	% Sensitivity CIN2+ (n = 276)	% Specificity CIN1 (n = 570)	% Specificity Normal (601)
Standard of Care for referral*	76**	N/A (all referred to biopsy)	N/A (all referred to biopsy)
LuViva®	91	30	39

* Includes Pap cytology, HPV and colposcopy impression

** As determined by up to two year follow up

Rationale as Rule In Test to Find Cervical Cancer Earlier

Modality	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity P value vs. LuViva
Pap Cytology	72.2% (65.9,78.5)	50.4% (46.3,54.6)	0.0016
Colposcopy*	21.1% (15.4,26.9)	97.5% (96.2,98.8)	<0.0001
Standard of Care**	74.2% (68.1,80.4)	0%	0.0018
LuViva	87.1% (82.4,91.8)	35.5% (32.7,38.3)	NA

* Calculated at High Grade/Low Grade threshold per FDA recommendation

** Consists of referral Pap cytology, HPV, colposcopy and ECC

LuViva Triage Test: Reduction of Unnecessary Colposcopy and Biopsy

- Using the results of LuViva
  - **Normals -** 222/570 (39%) would not need further evaluation
  - **CIN1 -** 182/601 (30%) would not need further evaluation
- Significant cost savings
- Reduced anxiety and complications from overtreatment

US Study Conclusions

LuViva detected 91% of CIN2+ compared with 76% sensitivity for the current standard of care consisting of Pap, HPV and colposcopically directed biopsy

- *Data support use of LuViva to find cervical dysplasia earlier than standard of care*

LuViva would have reduced the number of false positives by 39% for women with normal histology and by 30% for women with low grade dysplasia (CIN1 histology) with 99% confidence (NPV)

- *Data support use of LuViva to safely eliminate a significant number of unnecessary colposcopies and biopsies*

LuViva® Advanced Cervical Scan

LuViva® Advanced Cervical Scan

- Measures fluorescence and reflectance spectra in one minute
- Easy to operate with immediate result
- Single patient use disposable
- Built in video colposcope
- LuViva developed by Guided Therapeutics, Inc. Norcross, Georgia, USA

LuViva® Cervical Guide

- Single-use patient interface
- Attaches to Handheld Unit
- Calibrates spectrograph prior to each test
- Maintains optical distance and blocks ambient light
- RFID Chip assures patient protection by prohibiting use on next patient

Scan Procedure

- Prep subject for gynecological exam
- Remove excessive blood or mucus, nothing is applied
- Activate calibration and internal quality checks (1 minute)
- Insert Cervical Guide(CG) until contact is made with cervix and it is in focus with os centered (15-20 seconds)
- Initiate scan
  - Capture video image (<1 second)
  - Collect spectral data (1 minute)
  - Capture second video image to make sure os is still visible and centered (<1 second)
- Withdraw CG and dispose
- Scan complete and results presented immediately

LuViva Triage Results Screen

LOW RESULT MEANS:

- 99% Confidence (NPV) patient does not have CIN3 or cancer
- 40% without dysplasia or cancer
- Patient return to normal screening

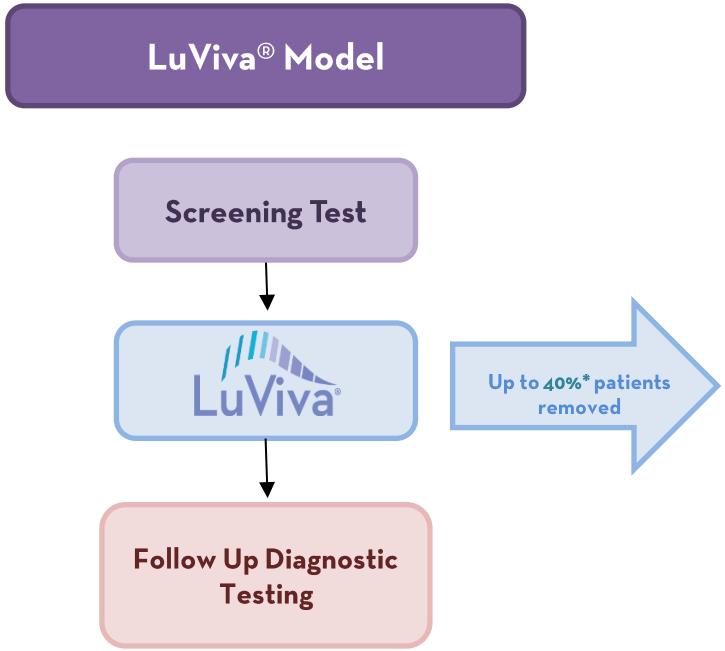
MODERATE RESULT MEANS:

- Moderate Risk of CIN1 or CIN2
- Doctor should consider colposcopy or close follow up based on history

HIGH RESULT MEANS:

- High likelihood of CIN2, CIN3 or cancer
- Doctor should schedule colposcopy and biopsy

LuViva Triage



For triage, LuViva is intended for use after abnormal cytology and/or positive HPV findings and/or other risk factors to triage women aged 16+ for additional evaluation prior to colposcopy and biopsy

Results of Commercial Evaluations

Study	Sensitivity	Specificity**	Number Tested	Researchers
IFCPC* London, UK 2014	100%	44%	55	Bentley and Zane
Nigerian Ministry of Health - 2014	100%	33%	100	Adewole et al
Other International Evaluations (n = 3)	91%	46%	132	Various

* International Federation of Cervical Pathology and Colposcopy
** Normal Histopathology

Results of Commercial Evaluations

Conclusion:

Results of commercial evaluations are consistent with US pivotal study results

- High sensitivity (>90%)
- 30% to 50% of unnecessary colposcopies and biopsies avoided
- LuViva is accepted by physicians and their patients

Cervical Spectroscopy Conclusions

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

Thank You

Areas of Focus Learned from Commercial Evaluations

- The following rules will help avoid false positive and false negative results
- Do make sure the os can be clearly seen and is centered in both the pre- and post-spectroscopy video images
- Do make sure the both the pre- and post-spectroscopy images are in focus
- Do make sure the cervix is free of blood and mucus; check for and remove mucus plugs in the os
- Do not test contra-indicated women
  - Women with recent biopsies or LEEP procedures (wait 3-6 months)
  - Women with obvious infections
  - Women with obvious large lesions
  - Women with abnormal cervical variants
  - Chemo or radiation therapy for one year
- Do not add foreign substances to cervix, for example: Acetic acid, Lugol's stain or lubricants

Technology Advancement

- Advances in the electro-optics, illumination sources and sensors
- Efficiencies in performance and cost of multimodal hyperspectroscopy (MHS)
- ***Development of clinically relevant and convenient devices for the detection of cervical neoplasia***

Pivotal Trial Study Accrual Targets

Estimated Prevalence of CIN 2+ (%)	Number of CIN2+ Cases Required	Number of Benign Cases Required	Total Cases
20.0	165 - 213	414 - 1031	1600-1650

- Enrollment from June 2004 to September 2008 at seven diverse clinical sites
- Follow up data integration starting June 2009

Subject Accountability Tree

2079 (Total number of subjects enrolled) – 70 withdrawn

2009

"Spectroscopic Evaluation of Cervical Neoplasia"

2004 - 2008

418 enrolled – 16 withdrawn

402

Beta Interim and Threshold (BIT) arm

Alpha Device 2 April 2007 – 25 Sep 2007

Beta Device 2 May 2006 – 25 Sep 2007
(Included Equivalence Testing
Sep 2006 – Mar 2007)

Training/Hardware/Software de-bugging	55
No or insufficient Histology (follow-up pending)	18
Histopathology Discordance	32
Device did not produce spectra	17
> ¼ cervix covered w/blood or mucus	36
USED FOR THRESHOLD VALIDATION	**244**

1661 enrolled – 54 withdrawn

1607

Primary Efficacy and Performance (PEP) arm

8 June 2004 – 2 April 2007

25 Sep 2007 – 25 Sep 2008
(Pathology embargo until February 2009)
(Included Repeatability Testing Feb 2008 – Sept 2008)

Alpha and Repeatability Training	54
Referral Pap Test Result Unavailable	1
No or insufficient Histology (Follow up Pending)	31
Histology Discordance	37
Device did not produce spectra	24
User Error	17
> ¼ cervix covered w/blood or mucus	36
USED FOR EFFICACY ANALYSIS	**1407**

Up to Two Year Follow Up Results

Clinical Site	Enrolled	Follow up Data Not Yet Made Available	Lost to Follow Up	Follow up Data
University of Texas Southwest	234	64	125	45
Emory University/Grady Hospital	348	48	81	219
University of Miami	313	0	116	197
University of Connecticut Saint Francis Hospital	394	0	164	230
University of Arkansas	48	48	0	0
Medical College of Georgia	130	126	3	1
Orange County California	140	11	20	109
Total	**1,607**	**297**	**509**	**801**

Clinical Rationale
Cervical Cancer Screening

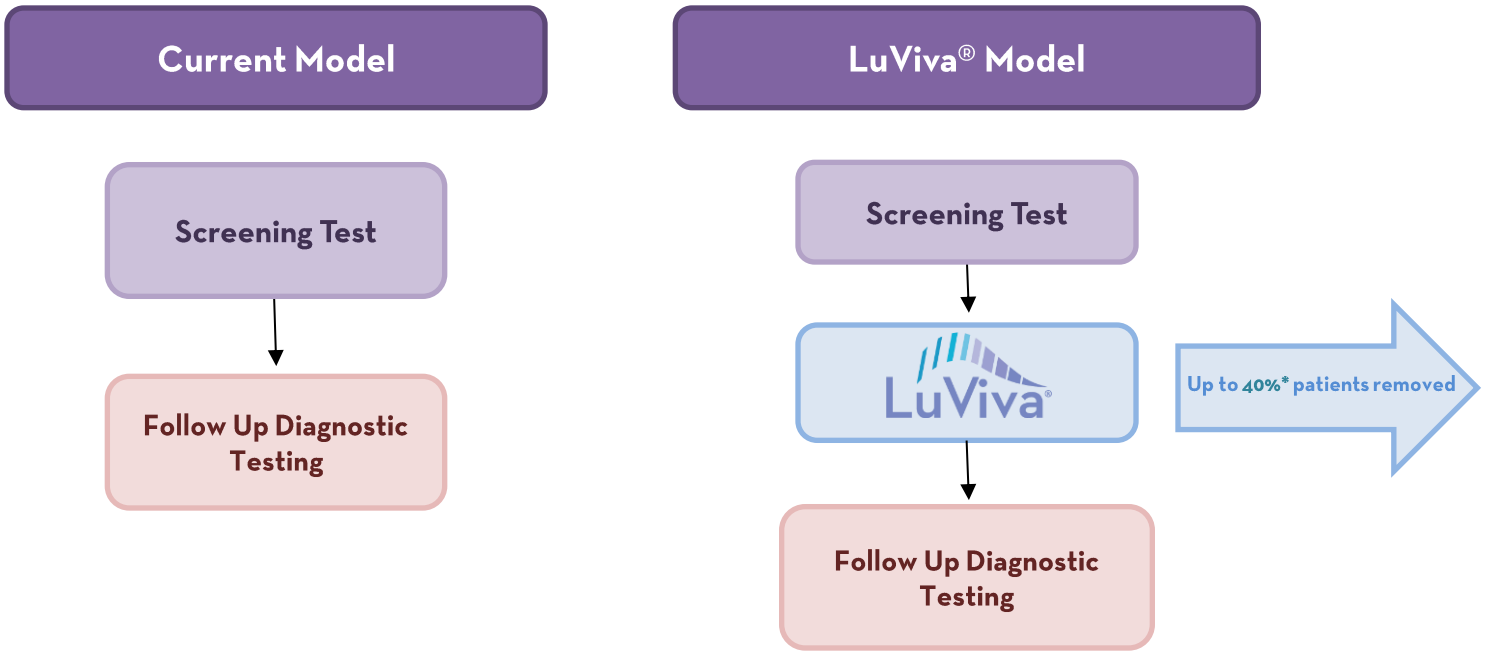
Current screening and triage methods cause:

- **Delays** in diagnosing significant disease
- **Excessive** false positive rate
- **Expensive** billions of dollars of unnecessary cost

Patient Referral and Histopathology Results
Cases with no or indeterminate histopathology excluded (n=74)

Reason for Referral	Normal	CIN 1	CIN 2+	TOTAL	Prevalence CIN 1 (%)	Prevalence CIN 2+ (%)
Negative Pap	23	12	2	37	32.4	5.5
ASC/HPV+**	325	272	71	668	40.7	10.6
LSIL	245	330	134	709	46.5	18.9
HSIL	8	26	85	119	21.8	71.4
Total	**601**	**640**	**292**	**1533**	**41.7**	**19.1**

LuViva Triage



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Study Clinical Sites

University of Texas Southwest – Dallas, Texas

Principal Investigator – Claudia Werner, MD

Emory University School of Medicine – Atlanta, Georgia

Principal Investigator – Lisa C. Flowers, MD

University of Miami – Miami, Florida

Principal Investigator – Leo B. Twiggs, MD / Co PI – Nahida Chakhtoura, MD

Saint Francis Hospital Univ. of CT – Hartford, Connecticut

Principal Investigator – Manocher Lashgari, MD

University of Arkansas – Little Rock, Arkansas

Principal Investigator – Alexander Burnett, MD

Medical College of Georgia – Augusta, Georgia

Principal Investigator – Daron G. Ferris, MD

Orange Coast/SaddleBack Women's Medical Group

Principal Investigators – Marc Winter, MD / Daniel Sternfeld, MD