Abnormal Spectroscopy Scans May Presage Persistent or Progressive Cervical Dysplasia

Leo B. Twiggs, M.D.
Professor Emeritus
University of Miami
Miller School of Medicine
Miami Florida USA
Currently- Women's Cancer and Surgical Care
Albuquerque New Mexico USA

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Clinical Challenge of persistent HPV infection

- Usual diagnosis CIN1-Cytologic and Histologic
- Prognosis:
  - Most regress (60% to 80% depending on patient's age)
  - Some (about 10% to 20%) persist from year to year causing multiple call backs and interventions
  - Some (about 10% to 20%) progress to CIN2/3
- Impact on patient
  - Stressful
  - If persistent, increases chances of overtreatment

Current Status of Prognostic Indicators

- Currently no known test can reliably predict progression of CIN1 to more severe disease (CIN2/3)

- Evidence from small studies indicates that *negative* immuno-histochemical staining for tests that assess cell kinetics may be associated with spontaneous regression of CIN1 lesions
  - P-16*
  - Ki – 67**

*del Pino M, Garcia S, Fusté V, et al. Value of $p16^{INK4a}$ as a marker of progression/regression in cervical intraepithelial neoplasia grade 1. Am J Obstet Gynecol 2009;201:488.e1-7.
**Arnold-Jan K, Janssen E, Bol M et al. Low- and high-risk CIN 1 and 2 lesions: prospective predictive value of grade, HPV, and Ki-67 immuno-quantitative variables. Journal of Pathology 2003;199:4,462–470.

Multimodal Cervical Spectroscopy as a Method for Cervical Neoplasia Detection

- 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

LuViva® Advanced Cervical Scan

- Measures fluorescence and reflectance spectra
- Easy to operate with touch screen interface
- Single use disposable, Cervical Guide (CG)
- Provides an immediate result
- Developed by Guided Therapeutics, Inc. Norcross, Georgia, USA

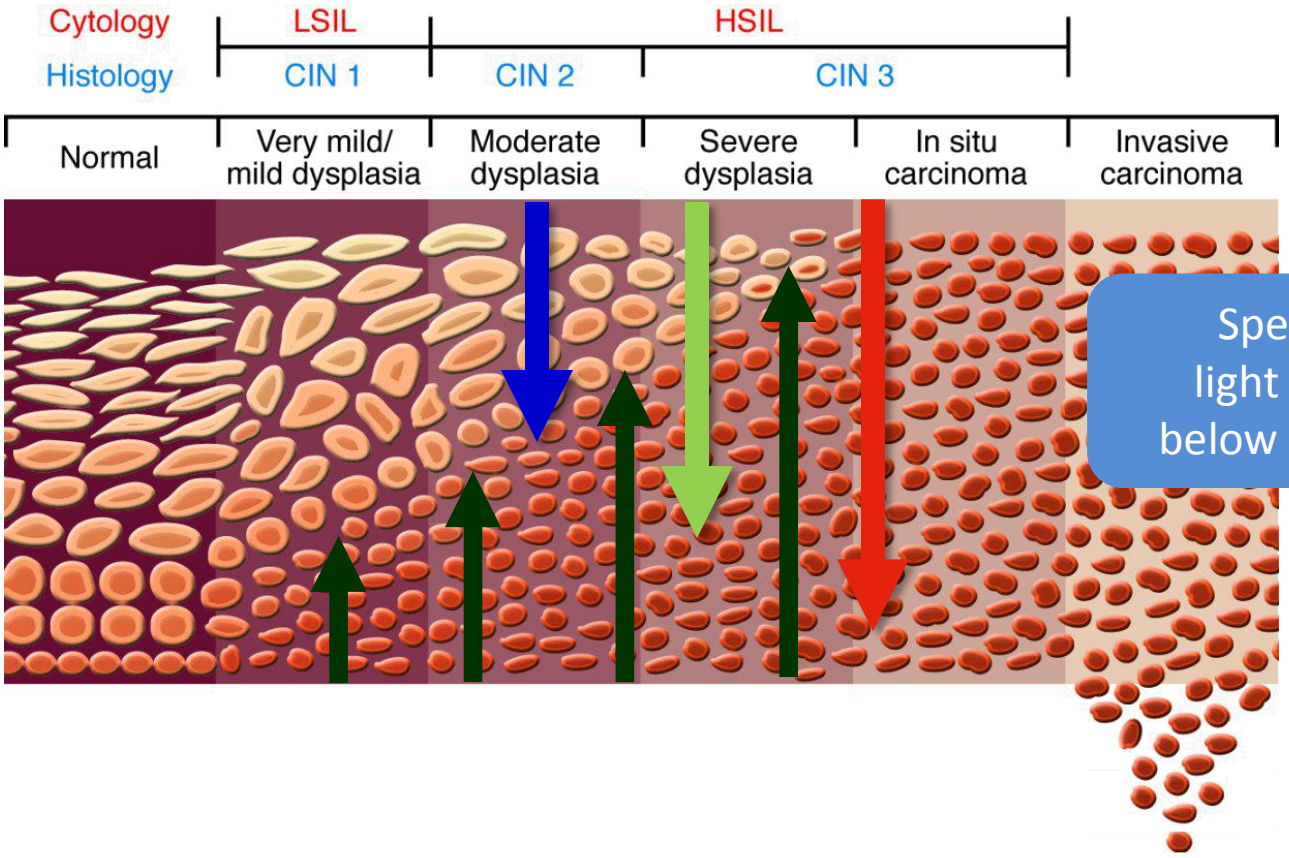
LuViva® Cervical Guide

- 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

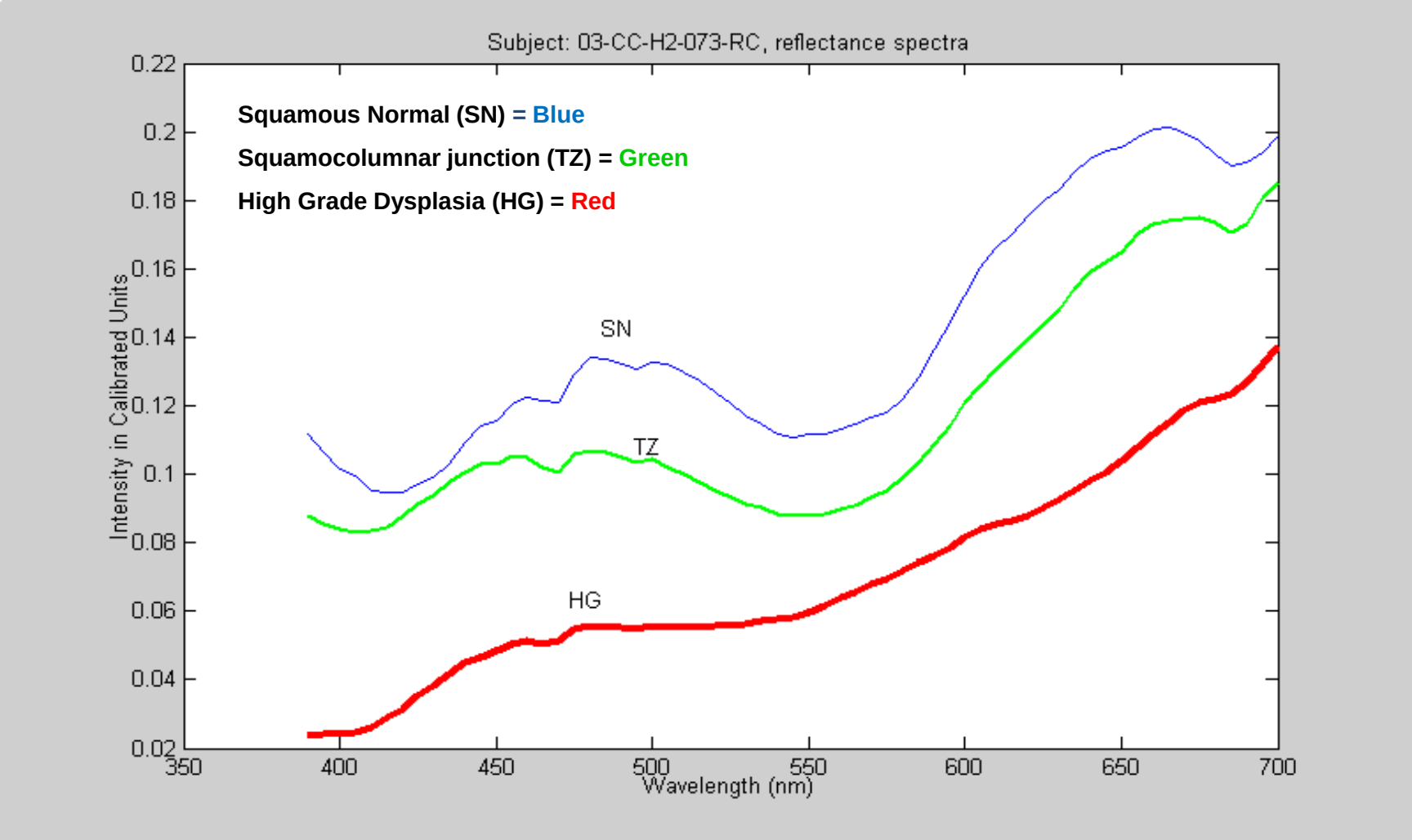
- Activate calibration and internal quality checks
- Prep subject for gynecological exam
  - Remove excessive blood or mucus, nothing is applied
- Using real-time video imaging, insert CG through speculum until contact is made with cervix
- Initiate scan
  - Capture video image
  - Collect spectral data
  - Capture second video image to make sure os is still visible and centered
- Withdraw and dispose CG
- Results displayed on monitor immediately after scan completed
- Entire process takes a few minutes

Precursors to Invasive Cervical Cancer



Spectroscopy light penetrates below surface layer

Spectral Output of Cervical Tissue



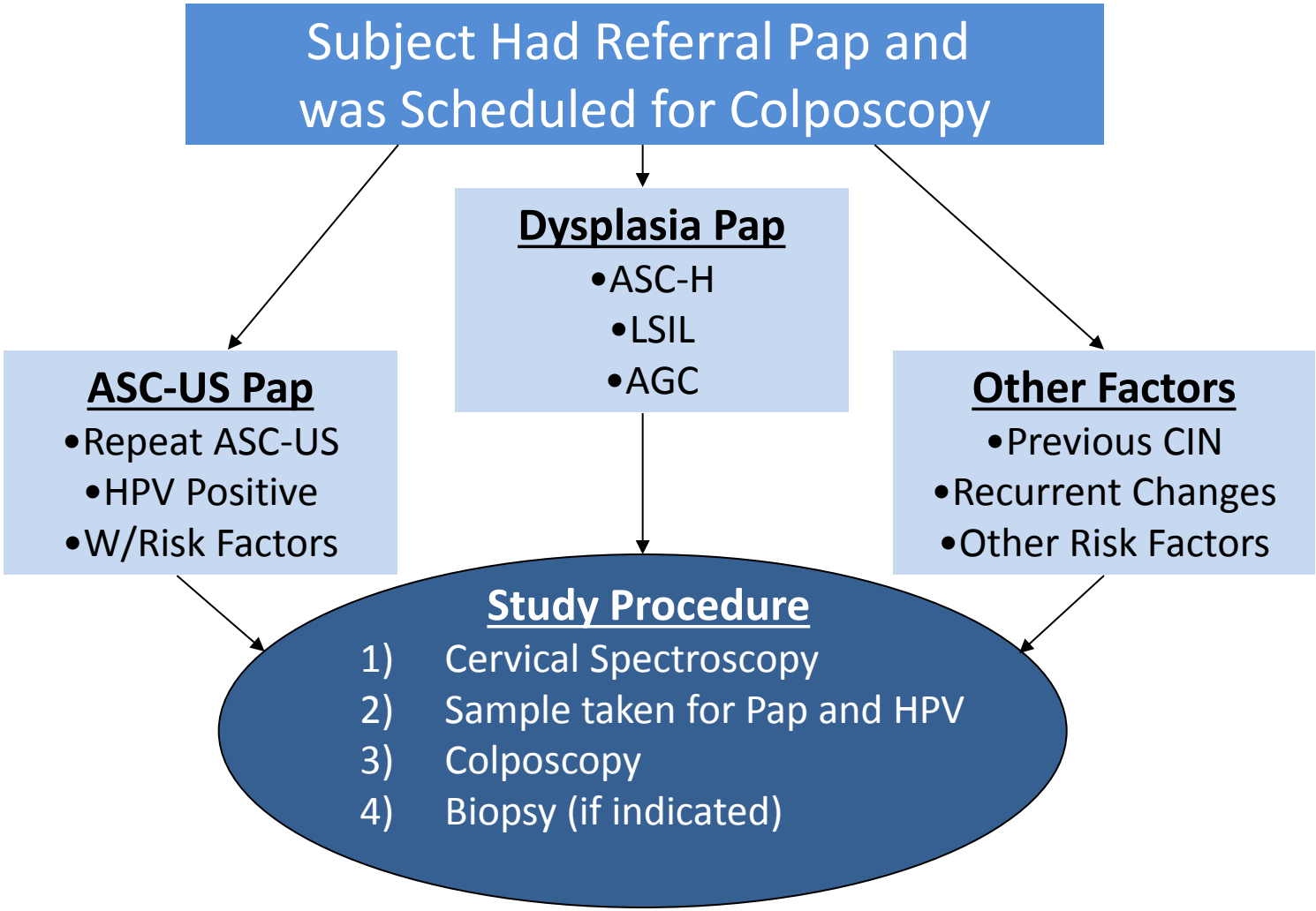
US Pivotal Study

- 1607 total enrolled to study effectiveness of cervical spectroscopy in triaging women referred to colposcopy based on abnormal Pap/HPV
- 195 excluded (mostly training cases or women with discordant or insufficient histopathology)
- 1447 analyzed for sensitivity and specificity
- Study published in Gynecologic Oncology, April 2013

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



Dysplasia Progression Study Subgroup

804 women returned for follow up per management guidelines:

- *222* women with abnormal screening tests leading to colposcopy and biopsy on the day of cervical spectroscopy scan*
- Consensus pathology results-222 pts :
  - ***89 with CIN1***
  - ***46 free of CIN1, 2 or 3 (normal***)
  - 87 with CIN2/3 (treated and therefore not included in analysis of disease progression)

*21 cases excluded from analysis because they were either training cases (n = 10), did not produce a consensus histopathology result from the day of the MHS study (n = 9) or did not produce acceptable spectral data (n = 2).

Progression Study Subject Histopathology by Age

Age	Normal	CIN1	Total Studied
16-20	4	13	17
21-30	12	26	38
31-over	30	50	80
		TOTAL	**135**

Chi Square Results

Table 1. Chi-square table for women with **CIN1** histology at initial visit (p = 0.012)

Follow-up Histology	% Abnormal Initial Spectroscopy Scans
Normal	62.1 (18/29)
CIN1	*86.0 (37/43)*
CIN2+	***94.1 (16/17)***

Table 2. Chi-square table for women with **Normal** histology at initial visit (p = not significant)

Follow-up Histology	% Abnormal Initial Spectroscopy Scans
Normal	65.4 (17/26)
CIN1	35.7 (5/14)
CIN2+	**83.3 (5/6)**

Note: Overall percentage of abnormal scans from referred population is about 60%

Explanation of Chi Square Results

- *Women with CIN1 on the day of their cervical spectroscopy scan were significantly more likely to progress to CIN2/3 within two years if their spectroscopy scan was abnormal*

- Women without dysplasia on the day of their cervical spectroscopy scan were not significantly more likely to progress to CIN1/CIN2/CIN3 within two years if their spectroscopy scan was abnormal

- *Overall, 21 of 23 women (91.3%) with abnormal spectroscopy* scans having either CIN1 or no dysplasia on the day of their scan were *found to progress to CIN2/3 during two year follow up*

- In contrast, only about 60% of spectroscopy scans were found to be abnormal for women who did not progress to CIN2/3 (similar to referred population at large)

Study Caveats

- Some CIN2/3 may have been missed by colposcopically directed biopsy on the day of the spectroscopic scan and therefore do not represent progression
- Study population was small
- Unable to assess whether women with CIN2 progressed to CIN3 because CIN2 was treated

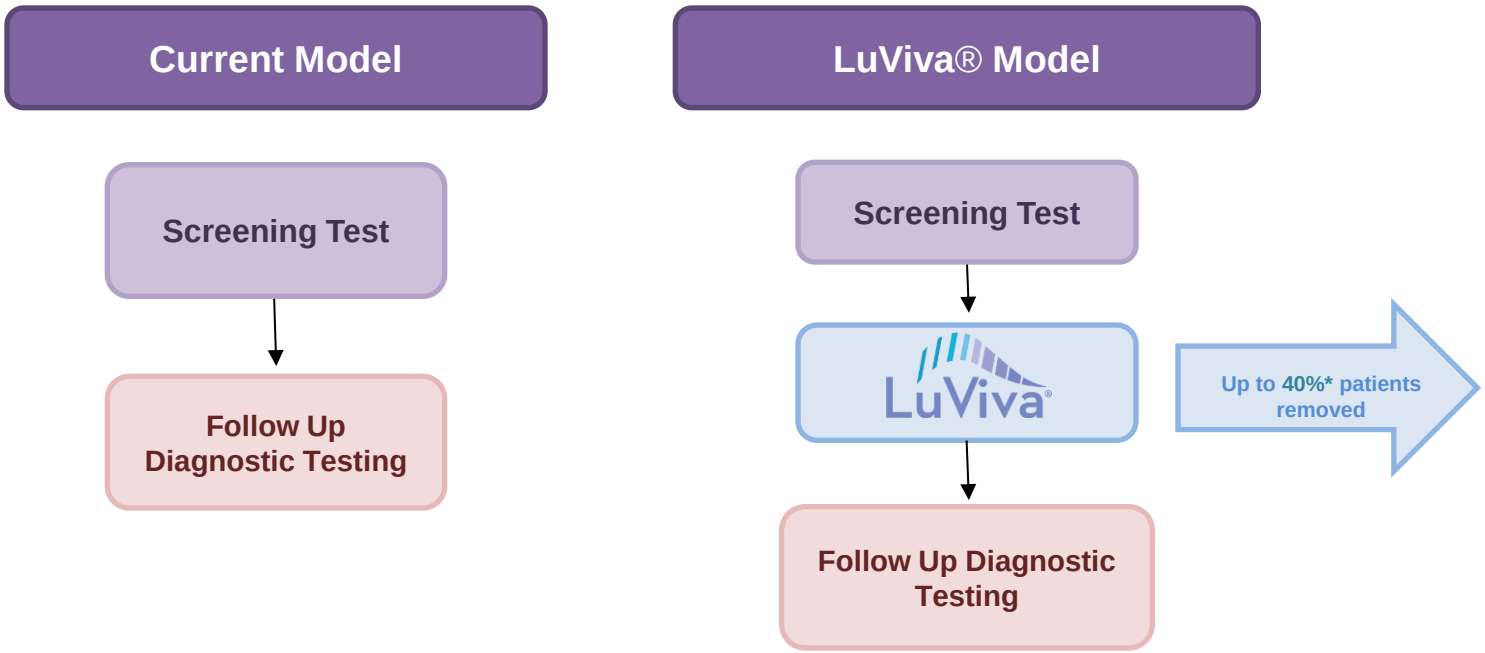
Conclusions

- Cervical spectroscopy is a simple to use test that gives immediate feedback regarding the metabolic and structural changes relating to cervical neoplasia

- Pending confirmatory studies, the existing triage use for cervical spectroscopy as an indicator of whether colposcopy is needed may be supplemented to include its use as a potential prognostic test

Thank You

LuViva 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

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

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

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**

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

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*

Study Design Flow Chart

Subject Had Referral Pap and was Scheduled for Colposcopy

ASC-US Pap
- Repeat ASC-US
- HPV Positive
- W/Risk Factors

Dysplasia Pap
- ASC-H
- LSIL
- AGC

Other Factors
- Previous CIN
- Recurrent Changes
- Other Risk Factors

Study Procedure
1) Cervical Spectroscopy
2) Sample taken for Pap and HPV
3) Colposcopy
4) Biopsy (if indicated)

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