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

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Acknowledgements and Disclaimer

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Presenter and Principal Investigators do not have a financial interest in this project
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
  - Hyperchromasias
  - 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

Spectroscopy light penetrates below surface layer

Degree of Progression

<table>
<thead>
<tr>
<th>Normal</th>
<th>Low Grade SIL</th>
<th>High Grade SIL</th>
<th>Invasive Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atypia</td>
<td>CIN 1</td>
<td>CIN 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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

Subject: 03-CC-H2-073-RC, reflectance spectra

Squamous Normal (SN) = Blue
Squamocolumnar junction (TZ) = Green
High Grade Dysplasia (HG) = Red
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

Funding in part by The National Cancer Institute
The Georgia Research Alliance

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- University of Miami Women’s Hospital Center
- University of Texas Southwestern Medical Center
- Emory University School of Medicine
- University of Connecticut – St. Francis Hospital
- Medical College of Georgia
- Orange Coast Women’s Medical Group
- Saddleback Women’s Medical Group
- University of Arkansas
- University of Florida
- University of Colorado
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
Subject Had Referral Pap and was Scheduled for Colposcopy

Dysplasia Pap
- ASC-H
- LSIL
- HSIL

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

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)
# US Patient Demographics

<table>
<thead>
<tr>
<th>Age</th>
<th>Non-Hispanic</th>
<th>Hispanic</th>
<th>Total Enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>American Indian</td>
<td>Asian Pacific Islander</td>
<td>African American</td>
</tr>
<tr>
<td>16-20</td>
<td>1</td>
<td>2</td>
<td>182</td>
</tr>
<tr>
<td>21-30</td>
<td>2</td>
<td>13</td>
<td>383</td>
</tr>
<tr>
<td>31-over</td>
<td>0</td>
<td>5</td>
<td>303</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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

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

* 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

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

* 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
**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
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

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

* 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
  o Less discomfort
  o 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

<table>
<thead>
<tr>
<th>Estimated Prevalence of CIN 2+ (%)</th>
<th>Number of CIN2+ Cases Required</th>
<th>Number of Benign Cases Required</th>
<th>Total Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.0</td>
<td>165 - 213</td>
<td>414 - 1031</td>
<td>1600-1650</td>
</tr>
</tbody>
</table>

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

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

1661 enrolled – 54 withdrawn
1607
*Primary Efficacy and Performance (PEP) arm*

8 June 2004 – 2 April 2007
(Pathology embargo until February 2009)
(Included Repeatability Testing Feb 2008 – Sept 2008)

<table>
<thead>
<tr>
<th>Subject Accountability Tree</th>
</tr>
</thead>
<tbody>
<tr>
<td>Training/Hardware/Software de-bugging</td>
</tr>
<tr>
<td>No or insufficient Histology (follow-up pending)</td>
</tr>
<tr>
<td>Histopathology Discordance</td>
</tr>
<tr>
<td>Device did not produce spectra</td>
</tr>
<tr>
<td>&gt; ¼ cervix covered w/blood or mucus</td>
</tr>
<tr>
<td><strong>USED FOR THRESHOLD VALIDATION</strong></td>
</tr>
</tbody>
</table>

| 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

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

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