Comparison of HPV Testing and Spectroscopy Combined with Cytology for the Detection of High-grade Cervical Neoplasia

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Current screening and diagnostic strategies have greatly reduced the incidence of cervical cancer, however....

- Significant CIN2+ disease goes undetected (cytology & colposcopy)
- Current management algorithms are multi-stepped and varied combinations of cytology, HPV DNA testing, and colposcopy
- Yield of positive biopsies at colposcopy is low (20% - 30%)
- Continued interest in new technologies with both high sensitivity and high specificity

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HPV DNA Testing

- Currently used for:
  - Primary screening age $\geq$ 30
  - Triage of ASC-US, some LSIL cytologies
  - Post-colposcopy surveillance (histology negative or LSIL)
  - Post-treatment surveillance
- High sensitivity for CIN2+ ($\geq$ 90%)
- Low specificity due to high prevalence in general population (especially in younger women and abnormal cytology)

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Clinical Trial Objective

- Compare performance of cervical spectroscopy (CS) with HPV DNA testing (HPV) when used in conjunction with cytology in detecting CIN2+

- Hypothesis: CS is as sensitive as HPV but more specific

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Rationale

- HPV DNA testing detects HPV infection
- CS detects the metabolic and morphologic changes occurring in neoplastic tissue

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Cervical Spectroscopy Device

• Rated as nonsignificant risk device: FDA

• Base unit and hand-held unit

• Contact tube 1" diameter

• Exam time: 3 to 4 minute test

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Multimodal Spectroscopy

Light In –

•Multiple wavelengths of UV and visible light used to penetrate different tissue depths

•Multiple, non-overlapping, equally distributed points

Spectrometer

Results

1. Fluorescence Spectra -

   Function of metabolic changes

2. Reflectance Spectra –

   Structural changes associated with neoplasia

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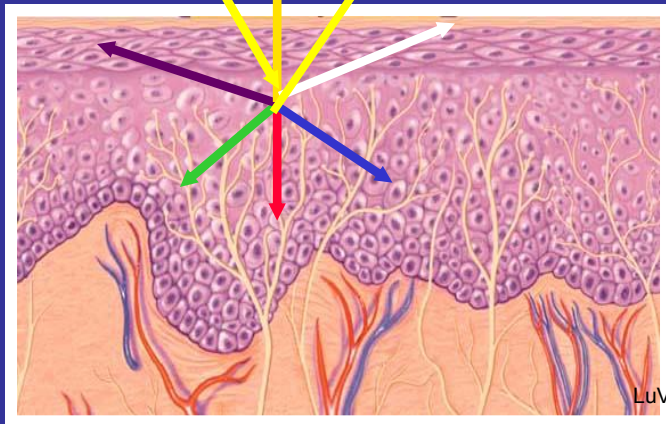
Methodology

- Prospective double-masked trial
  - Clinicians masked to spectral output
  - Technical team masked to clinical results (history, colposcopy, cytology, histology, HPV test)
- Approved by IRB at University of Texas Southwestern Medical Center at Dallas
- Conducted in a gynecology clinic of Parkland Health and Hospital System

Methodology

- All colposcopies performed by one of 2 experienced colposcopists

- Pathology QA: agreement by 2 of 3 pathologists (1 site / 2 outside pathologists)

- Study was funded by a grant from NCI and by Guided Therapeutics (sponsor)

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Study Inclusion/ Exclusion Criteria

- Age 18 or above
- Scheduled for colposcopy
- Able to give informed consent
- Cervix present and cytology within 120 days
- Not pregnant
- Not menstruating

CS Spectral Output + Concurrent Cytology Algorithm

Subject: 03-CC-H2-073-RC, reflectance spectra
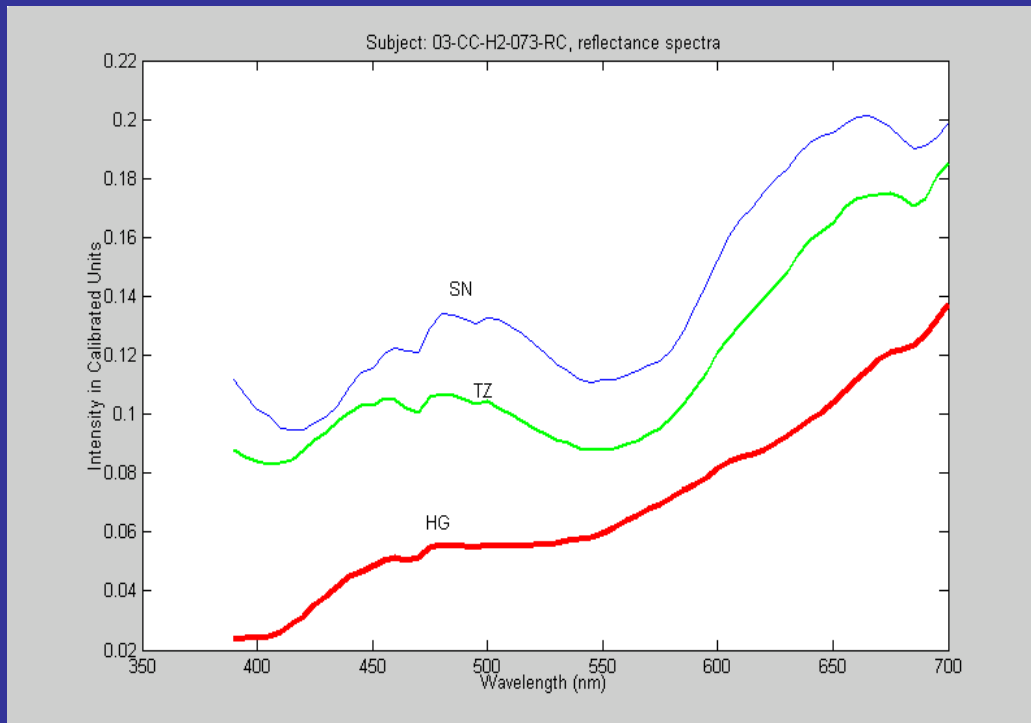
- **Data from previous studies**

- **Numeric index that correlates with likelihood of CIN2+**

Squamous Normal = Blue

Transition Zone = Green

High Grade Dysplasia = Red

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Results

- 109 were enrolled and completed the study

- CS data from 5 (4.6%) cases not evaluable due to device malfunction or operator error

- 104 subjects included in final data analysis

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Results

- Racial diversity
  - 57% African/ American
  - 31% Hispanic
  - 11% Caucasian
  - 1% Asian/ American
- Median age 31 (range 16-57)
- No cases of invasive cancer

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Performance Comparison

- **Sensitivity** of Pap+HPV and Pap+CS were identical
  - **CIN2/ CIN3**   95% (19/20)
  - **CIN3**   100% (10/10)
  - *Single case missed was borderline CIN1/CIN2 lesion*
- **Specificity**
  - **Pap+ HPV   27.4% (23/84)**
  - **Pap+CS   65.5% (55/84)**   p <0.0001
                                         McNemar's test

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Study Conclusions

- Pap+CS demonstrated high sensitivity (95%) and specificity (65%) for detection of CIN 2/ CIN 3 in a population women at high risk for cervical disease

- Specificity was significantly higher than Pap+HPV, which could potentially reduce the number of colposcopy referrals in patients with minor cytological abnormalities

- There were no adverse events and patient acceptance of the procedure was excellent

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Limitations

- Small sample size
    - Limits subgroup analyses
- Inclusion of ASC-H, LSIL, HSIL referral Paps did not mirror current management algorithms exactly

Future Potential

- Alternative triage and surveillance strategy in the management of minor cytological and histological abnormalities

- Localize high grade neoplasia for directing biopsy and /or treatment

- Stand-alone primary screening technology for detection of CIN2+

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