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
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)
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
Rationale

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

LuViva Advanced Cervical Scan
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)
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
Subjects Referred for Colposcopy

ASC-US (56)
- Repeat ASC-US
- HPV Positive
- W/Risk Factors

LSIL (35)
- ASC-H/ HSIL (7)

Other (4)
- Recurrent Changes
- Previous CIN
- Other Risk Factors

CS Study
1) Spectroscopy
2) Pap and HPV test
3) Colposcopy
4) Biopsy (if indicated)
CS Spectral Output + Concurrent Cytology Algorithm

- Data from previous studies
- Numeric index that correlates with likelihood of CIN2+

Squamous Normal = Blue
Transition Zone = Green
High Grade Dysplasia = Red
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
Results

• Racial diversity
  – 57% African/ American
  – 31% Hispanic
  – 11% Caucasian
  – 1% Asian/ American

• Median age 31 (range 16-57)

• No cases of invasive cancer
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) \( p < 0.0001 \)
  - Pap+CS 65.5% (55/84) McNemar’s test
Study Conclusions

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