Multimodal Spectroscopic Imaging of the Cervix for Triaging Patients to Colposcopy

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Clinical Rationale

- Current triage methods miss disease and result in excessive false positive rate
  - ALTS trial showed that current triage of colposcopy after referral for ASC-US/HPV+ and LSIL patients would still miss 30% to 40% of CIN3 disease
  - Only about 5% of ASCUS Pap tests and 10% of LSIL Pap tests will actually detect CIN3 disease
  - Use of HPV testing adjunctive to Pap will increase referrals to colposcopy and biopsy
- Need exists for pre-colposcopy triage technique with high negative predictive value and specificity

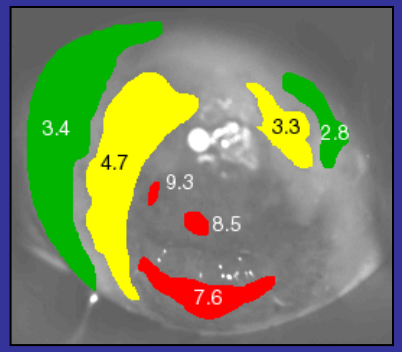
Triage Background: ALTS Data Key Results*

- Adjunctive test would be useful because of the following findings:
  - ASCUS/HPV+ would boost colposcopy referral rate to 56%
  - ASCUS/HPV+ (26% CIN2/3) was nearly equivalent to LSIL (28% CIN2/3)
  - Sensitivity of immediate colposcopy for CIN3 was 53.6%
  - No utility for HPV in triaging LSIL
  - HPV is an acceptable alternative to conservative management for ASCUS
  - However, current triage of colposcopy after referral for ASC-US/HPV+ and LSIL patients would still miss 30% to 40% of CIN3 disease

* Walker J. Cervical cancer chemoprevention and biomarkers. Presentation given at 2nd International Conference on Cervical Cancer. April 11-14, 2002. Houston, TX. Includes analysis of follow-up data.

Multimodal Spectroscopy Potential Benefits

- Immediate result
- Objective, more accurate test
- Less discomfort



- Time
  - Exam time: 3-5 minute test vs. 20-30 minute colposcopy
  - Patient time lost due to repeated office visits
- Reduced cost to patient and healthcare system
- Underserved populations

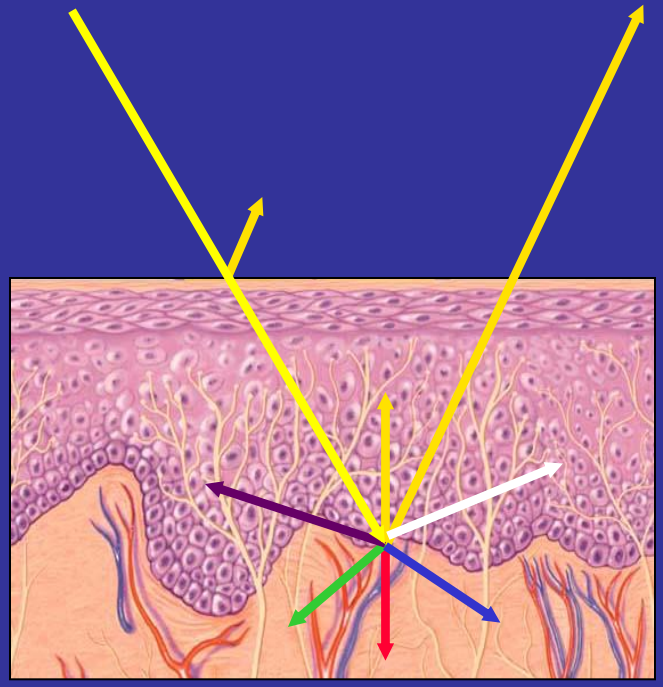
Multimodal Spectroscopy

Light In –

Multiple wavelengths used to penetrate different tissue depths

Spectrometer

Results



1. *Fluorescence Spectra* -

   Reveal metabolic changes associated with neoplasia

2. *Reflectance Spectra* –

   Reveal structural changes associated with neoplasia

Technology developed by SpectRx, Inc. Norcross, GA USA

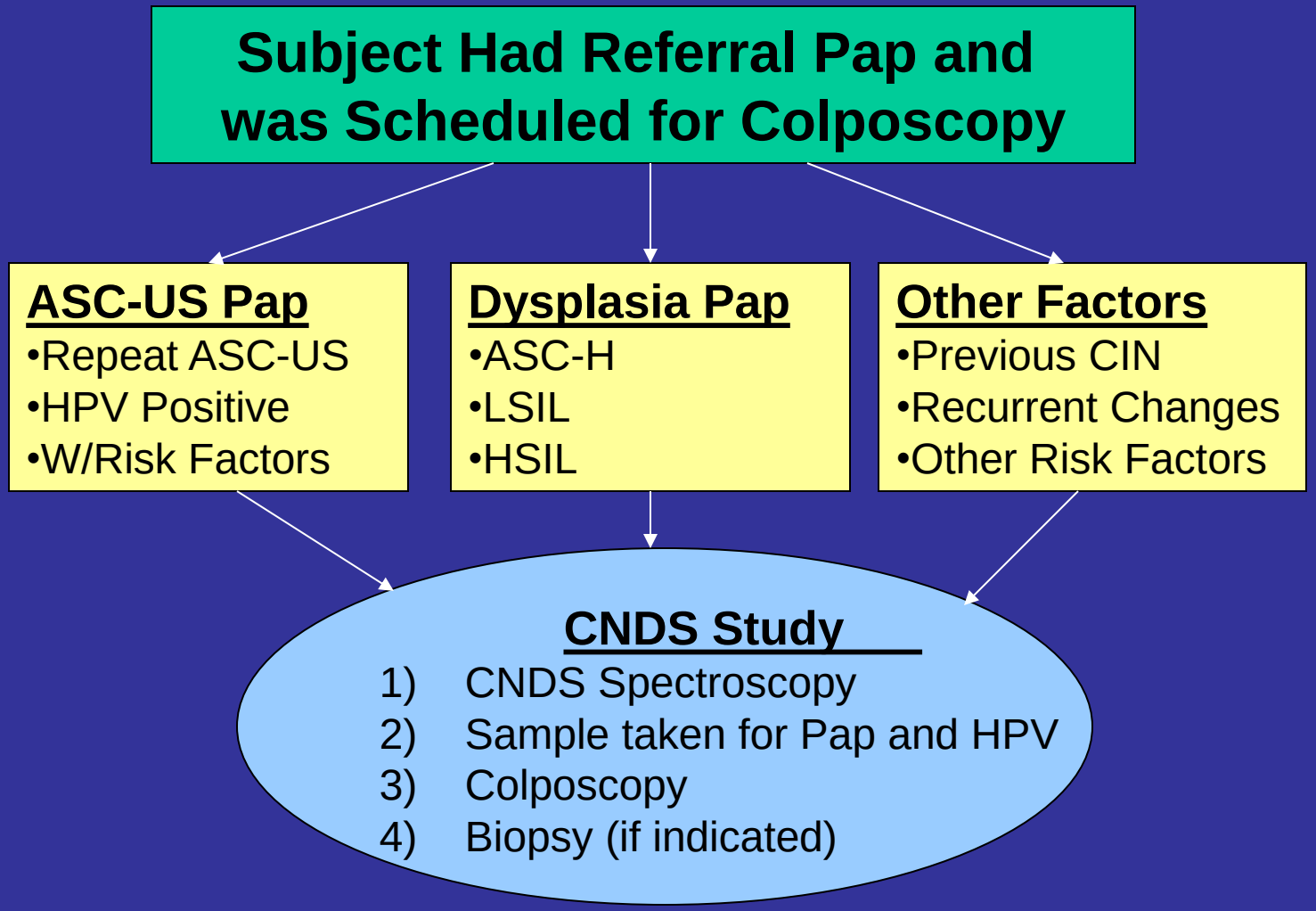
Clinical Trial Objectives

- Evaluate Multimodal Spectroscopy at four U.S. centers with diverse population
  - 414 subjects enrolled, 398 with evaluable cytology and histology
  - Age range 18-72, Median 27
- Primary goal: Develop and validate diagnostic algorithm for use in commercial system
- Additional goals:
  - Further evaluate patient acceptability for procedure
  - Estimate CNDS performance, especially ability to rule out CIN2+ disease

Study Hypotheses

- At equal sensitivity (90%), Multimodal Spectroscopy will produce a significant increase in specificity compared to the Pap test
- At equal specificity (70%), Multimodal Spectroscopy will produce a significant increase in sensitivity compared to the Pap test
- Additional analyses (still ongoing) involve using the spectroscopic information to localize suspected disease sites on the cervix

Patient Flow Chart



Study Inclusion Criteria

- Age 18 or above
- Able to read or understand and give informed consent
- Scheduled for colposcopy
- Pap test within 120 days
- Willing to undergo a Pap test and HPV test on day of study

Study Exclusion Criteria

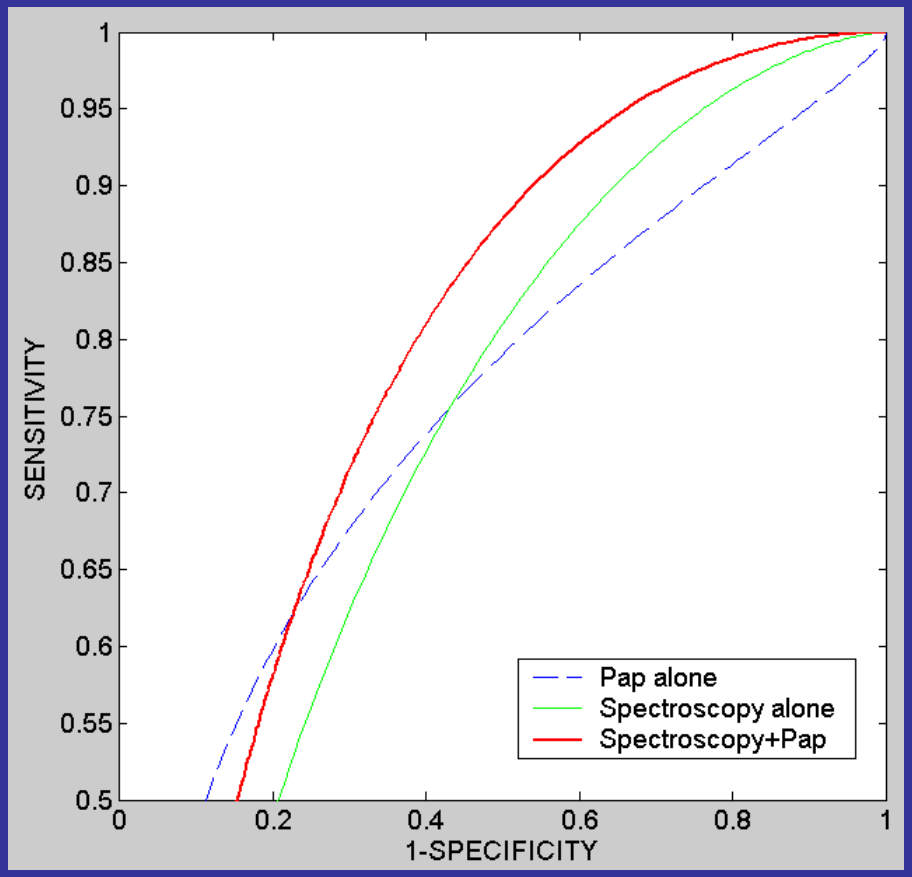
- Pregnancy
- Menstruating on the day of study
- Radiation to genitourinary system within 1 year
- Prior hysterectomy
- Congenital anatomical cervical variant (e.g., double cervix)

Cytology and Histology Results

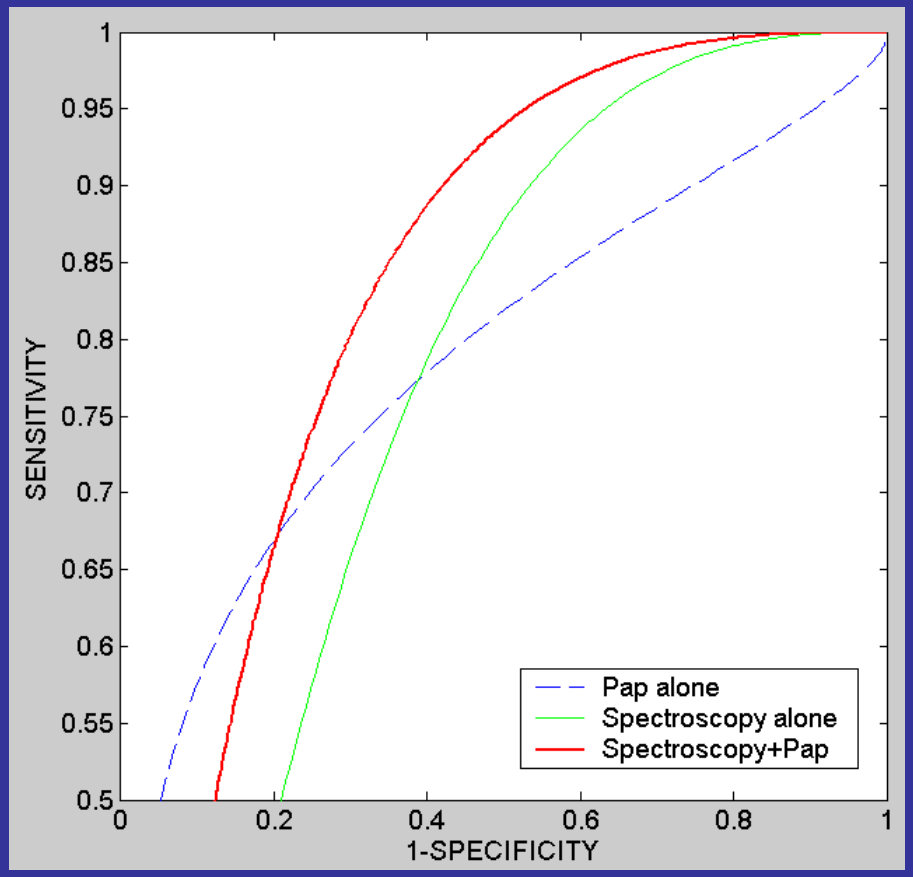
		HISTOLOGY			
CYTOLOGY	Normal	Benign	CIN 1	CIN 2+	**Total**
Within Normal Limits	62	19	13	11	**105**
Benign changes	17	10	6	3	**36**
ASCUS	41	27	19	15	**102**
LSIL	18	31	31	26	**106**
HSIL+	3	3	6	37	**49**
Total	**141**	**90**	**75**	**92**	**398**

Smoothed ROC Curves for Training and Validation

Training (n=258)



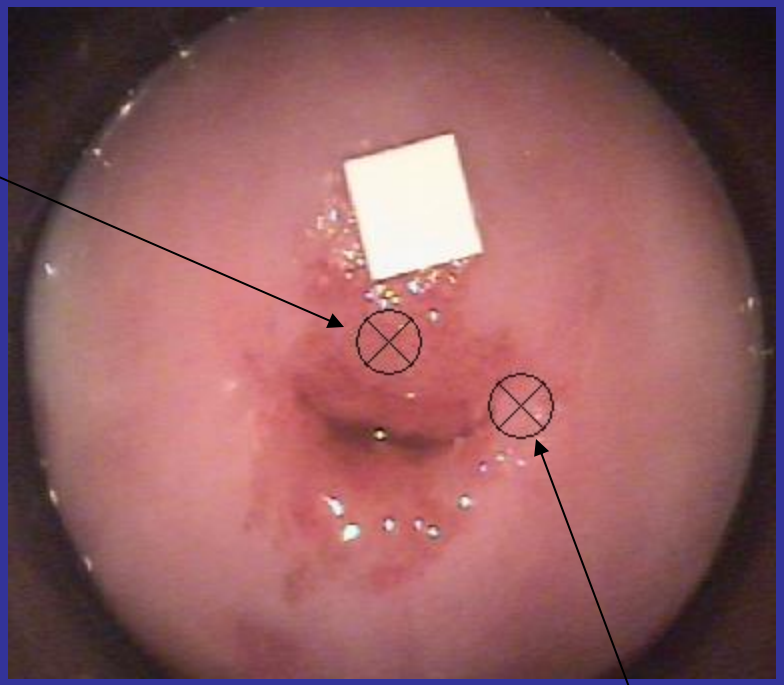
Validation (n=140)

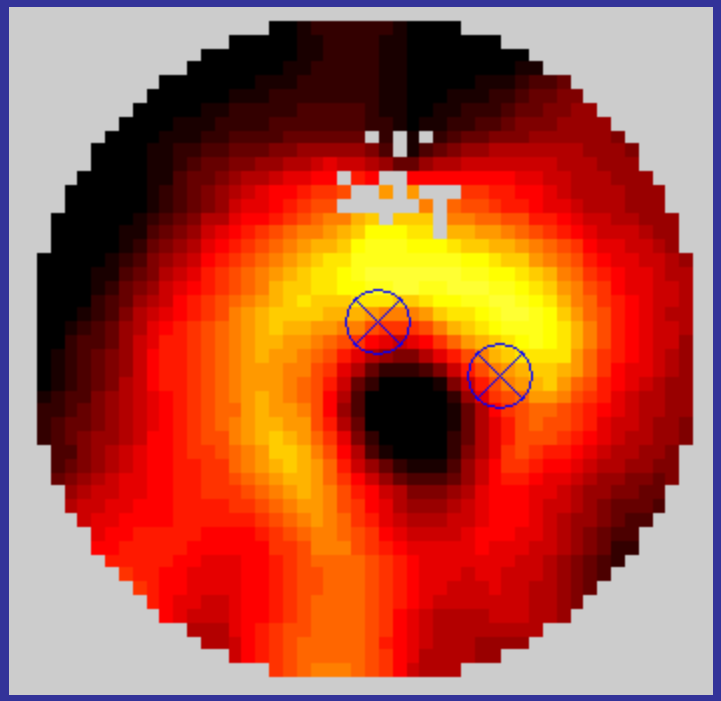


Comparative Diagnostic Performance:
Combined Training and Validation Sets
(at 90% Sensitivity for CIN2 Threshold)

Modality	Sensitivity	Specificity	NPV	PPV
Pap Alone	90%	25%	89%	27%
Spectro-scopy alone	90%	41%	93%	32%
Pap + Spectroscopy	90%	55%	95%	38%

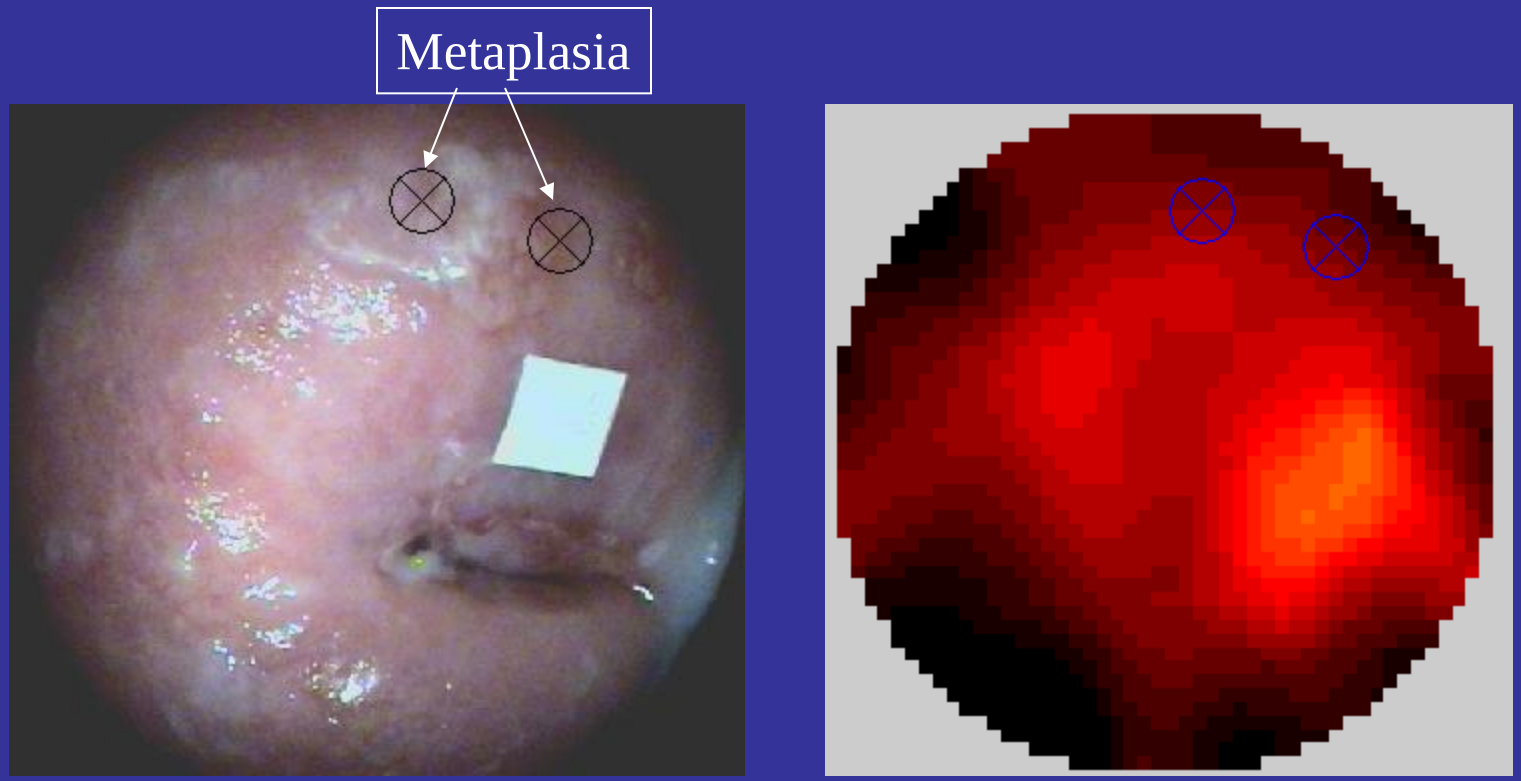
Cervical Maps of Patient with Dysplasia





Biopsy sites marked with X's

Cervical Maps of Patient with Metaplasia



Biopsy sites marked with X’s

PSA Test – Analogy to CNDS Results

PSA Result (ng/mL)	Category	Triage Recommendation	Percent Men with PCA
0 - 4	Normal	Re-test in one year	Less than 20%
4 – 10	Borderline	Ultrasound or biopsy	20% to 30%
> 10	High	Ultrasound guided or random biopsies	40% to 60%

Note: PSA result is used in combination with digital rectal exam, patient age, prostate size by ultrasound and as a bound PSA/free PSA ratio

References: 1) American College of Physicians (1997). Clinical Guideline. Part III. Screening for prostate cancer. Annals of internal medicine, 126(6): 480-484. 2) Coley CM et al (1997). Clinical Guideline. Part I: Early detection of prostate cancer Part I: Prior probability and effectiveness of tests. Annals of Internal Medicine, 126(5):394-406.

Predictive Values of SpectRx Results
(Adds New Data and Processing; N =420)

CNDS Result	Risk Level	% Benign N=214	% CIN1 N=106	% CIN2 N=47	% CIN3 N=53	Triage Strategy
0-35 N=141	Low Risk	85%	12%	2%	1%	Return to Screening
36-50 N=122	Borderline Low	53%	30%	11%	6%	Follow-up in 6 months or colposcopy
51-65 N=117	Borderline High	24%	37%	16%	23%	Immediate colposcopy
66-100 N=40	High Risk	5%	22%	28%	45%	Immediate colposcopy/ biopsy/DEP

Notes: The CNDS test result includes the Pap test result and should be interpreted within the overall context of patient history and other risk factors.

Study Conclusions

- At 90% sensitivity, Multimodal Spectroscopy increased specificity of Pap test by 30%
- Diagnostic algorithm trained on first 258 cases validated on the remaining 140 cases
- There were no adverse events and patient acceptance of the procedure was excellent