New Generation Colposcopies and AI

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THE ARCHITECTURE TO ELIMINATE CERVICAL CANCER:

VISION: A world without cervical cancer

THRESHOLD: All countries to reach < 4 cases 100,000 women-years

2030 CONTROL TARGETS

90%

of girls fully vaccinated with HPV vaccine by 15 years of age

70%

of women screened with an high precision test at 35 and 45 years of age

HPV DNA

90%

of women identified with cervical disease receive treatment and care

SDG 2030: Target 3.4 – 30% reduction in mortality from cervical cancer

The 2030 targets and elimination threshold are subject to revision depending on the outcomes of the modeling and the WHO approval process

World Health Organization

Future of Colposcopy

- ✓HPV DNA and Vaccination
  - High Sensitivity and low specifity
  - Colposcopy TSUNAMI ?
- ✓A NEED FOR HIGH RE-ASSURENCE AFTER COLPOSCOPY IS A MUST
  - 1063 hrHPV + women with Borderline or Mild Dyskaryosis with Negative Colposcopy -Evidence from HPV pilots,
  - Outcome measure CIN2+
  - Cumulative rate of CIN2+ at three years 4.4%
  - No difference with Age or initial grade of dyskaryosis
  - Rate of subsequent high grade sufficiently low to justify normal recall 3 yearly screening
  - Difficult protocole for many colposcopists

Kelly RS, BJOG. 2012 Jan;119(1):20-5.

COMPARATIVE STANDARDS of Pap-Smear, HPV DNA, Colposcopy

Comparative Standards for Low and High Grade Lesions-CIN2+

Colposcopy is a Big Gap For the Whole World

	Sensivity (%)	Specifity (%)
Pap-Smear Screening [A 1-4]	53	97
HPV DNA Screening[A 1-4]	96	92
Colposcopy[B 1-4]		
Old Studies	80	63
New Studies	50-60..(**30%)**	70-85

UK: Quality Standard PPV: Minimal %65 for CIN2+

A: 1) Mayrand MH et al. Int J Cancer 2006 119;615-623, 2) PALMS STUDY, Cancer Cytopathol, 2015 3) Ikenberg, JNCI, 2013 4) Cuzick, PVR 2016

B: 1) M Underwood et al. Br J Obstet Gynaecol 2012; 119:1293-130, 2) Pretorius et al Am J Obstet Gynecol 2004; 191: 430-4. 3) Bekkers et al Eur J Obstet Gynecol Reprod Biol 2008; 141; 430-4 4) Massad et al, J Lower Gen Tract Dis 2009 Jul;13(3):137-44

Increasing Number of Biopsies

- ✓Gage 2006: Increasing the number of biopsies from abnormal areas increased detection of CIN2+ within ALTS study.
  - Sensitivity: One biopsy 68%, two 81%, three 83%
- ✓Wentzensen 2015: US Biopsy study, 690 women,4 directed biopsies or non directed biopsy to a total of 4 .
  - Sensitivity : One biopsy 61%, two 85%, three 95%
    - **Recommendation: Taking additional biopsies when multiple lesions present should be standard US practice**

GAGE JC, Obstet Gynecol. 2006 Aug;108(2):264-72
.Wentzensen N, J Clin Oncol. 2015 Jan 1;33(1):83-9.

Training

Quality Assurence

Biopsy Numbers

New Generation Colposcopies

For Developing Countries (AI, Smart Phone, Telemedicine)

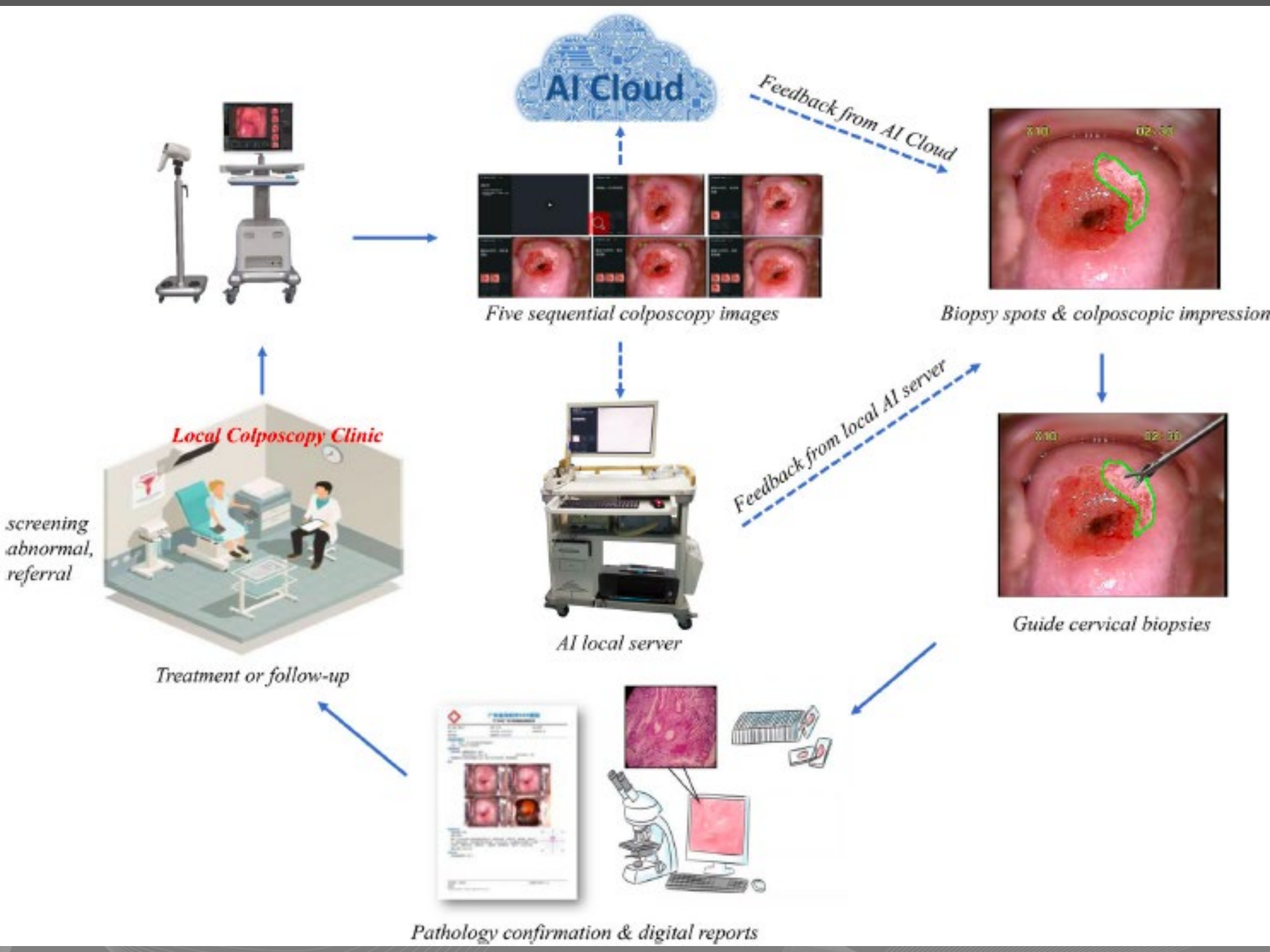
For Developed Countries (Colposcopy Adjunts)

Challenges of Colposcopy in LMIC

- ✓ Diagnostic performance of colposcopy strongly depends upon the **subjective experience** of operators- (thickness, color, border irregularity, surface smoothness, the timing of appearing and fading, solution quality, operation, and observation ways etc.)
- ✓ Due to the lack of experienced colposcopists in LMICs, the **workload** increases along with the expanded cervical cancer screening programs, exacerbating the diagnostic inaccuracy of colposcopy
- ✓ Implementing **colposcopy courses** in practice may not always be feasible to improve the overall diagnostic performance in a short period of time
- ✓ Although uniform diagnostic standards and strict **quality control for colposcopy** practice are released by relevant official organizations, many colposcopic practitioners due to the limited diagnostic ability and lacking professional training from LMICs are having a hard time to follow standardized recommendations to practice
- ✓ The diagnostic performance of colposcopy may be adversely affected by changes in screening modality from cytology, cytology-HPV cotesting to **primary HPV screening**, since cervical lesions related to HPV infections are likely to be mild and harder to be identified than cytological abnormalities

How Artifical Intelligence be Helpfull ?

- ✓Digital Colposcopy
  - Better accuracy with cervical images but still big inter and intra-observer variability
- ✓Artifical Intelligence
  - Different AI methods (such as the deep learning-based algorithms) can learn features of cervical lesions from annotated colposcopy images which can then be integrated into the digital for automated colposcopy and may imrove the subjectivity of the colposcopy
  - Works in real time, opposite to telemedicine and may be very usefull in busy colposcopy clinics
  - Cloud based AI platforms decrease the gap between rural and uban areas
    - Both for training nd consultation purposes


AI Cloud
Feedback from AI Cloud
Five sequential colposcopy images
Biopsy spots & colposcopic impression
Local Colposcopy Clinic
screening
abnormal,
referral
AI local server
Feedback from local AI server
Guide cervical biopsies
Treatment or follow-up
Pathology confirmation & digital reports

Incredible Progress of AI in Medicine Still results can not be generalized..

Table 1 The advancements in computer algorithms applying to cervical images

Reference	Publish year	Aim of the study	Study design	Number of subjects	Image-generating devices	Type of algorithms	Outcomes
Simoes et al. [18]	2014	Classification of colposcopy images	Retrospective	170 images (training set 48; test and internal validation set 122)	Digital colposcopy	ANN	Accuracy 72.15%
Kim and Huang [19]	2013	Detection of CIN2+ from normal/CIN1	Retrospective	2000 images (normal/CIN2 1000; CIN2+ 1000)	Cervicography (discontinued)	SVM	Sensitivity 75% Specificity 75%
Asiedu et al. [20]	2019	Detection of CIN1+ against normal	Retrospective	134 patients (training set 107; internal validation set 27)	Digital colposcopy	SVM	Accuracy 80% Sensitivity 81.3% Specificity 78.6%
Miyagi et al. [21]	2019	Classification of CIN1 and CIN2+	Retrospective	310 images (both using in training and internal validation set)	Traditional colposcopy	Convolutional neural networks	Accuracy 82.3% Sensitivity 80% Specificity 88.2%
Song et al. [22]	2015	Detection of CIN2+	Retrospective	7669 patients with < CIN2, 142 patients with CIN2+ (training set 7531; internal validation set 280)	Cervicography (discontinued)	Multimodal convolutional neural networks	Accuracy 89% Sensitivity 83.21% Specificity 94.79%
Schiffman et al. [23]	2019	Detection of CIN2+	Retrospective	9127 patients with < CIN2, 279 patients with CIN2+ (training set 744, internal validation set 324, rest in screening set)	Cervicography (discontinued)	Faster R-CNN	AUC 0.91

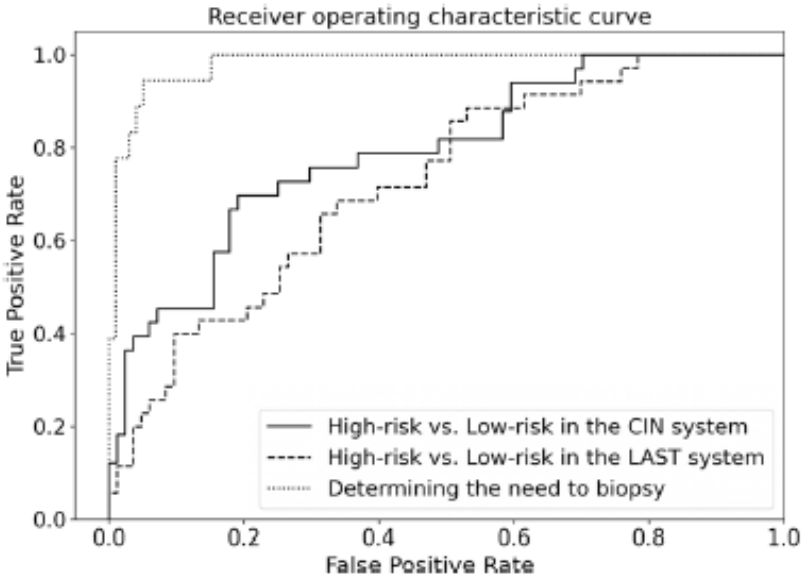
Artificial neural networks, support vector machine (SVM), AI classifier multimodal convolutional neural network, Faster region-based convolutional neural network (Faster R-CNN)

Cho et. al, Korean AI, 2020

- ✓ AUC for discriminating Low vs. High Grade Lesions
  - 0.78 for CIN system
  - 0.70 forLAST system
- ✓ AUC for detection of lesions requiring biopsy
  - 0.94

Model	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC
High-risk lesions vs. Low-risk lesions in the CIN system						
Inception-Resnet-v2	69.3 ± 4.8	66.7 ± 3.1	70.6 ± 6.1	47.2 ± 6.0	84.0 ± 1.8	0.739 ± 0.024
Resnet-152	68.9 ± 4.0	66.7 ± 3.1	69.9 ± 4.5	46.7 ± 5.0	84.2 ± 2.0	0.781 ± 0.020
High-risk lesions vs. Low-risk lesions in the LAST system						
Inception-Resnet-v2	63.2 ± 9.4	62.9 ± 7.6	63.5 ± 10.3	42.7 ± 9.3	79.9 ± 6.1	0.685 ± 0.072
Resnet-152	66.9 ± 3.4	65.7 ± 2.9	67.9 ± 3.7	46.1 ± 3.9	82.3 ± 2.0	0.708 ± 0.024
Determining the need to biopsy						
Inception-Resnet-v2	87.7 ± 0.5	83.3 ± 0.0	88.6 ± 0.6	57.0 ± 0.0	96.7 ± 0.0	0.932 ± 0.031
Resnet-152	87.7 ± 5.7	85.2 ± 3.2	88.2 ± 6.2	58.9 ± 15.4	97.0 ± 0.8	0.947 ± 0.030

Table 2. Diagnostic performance of the machine learning models in the binary classification of cervical neoplasms on colposcopic photographs. *PPV* positive predictive value, *NPV* negative predictive value, *AUC* area under the curve, *CIN* cervical intraepithelial neoplasia, *LAST* lower anogenital squamous terminology.



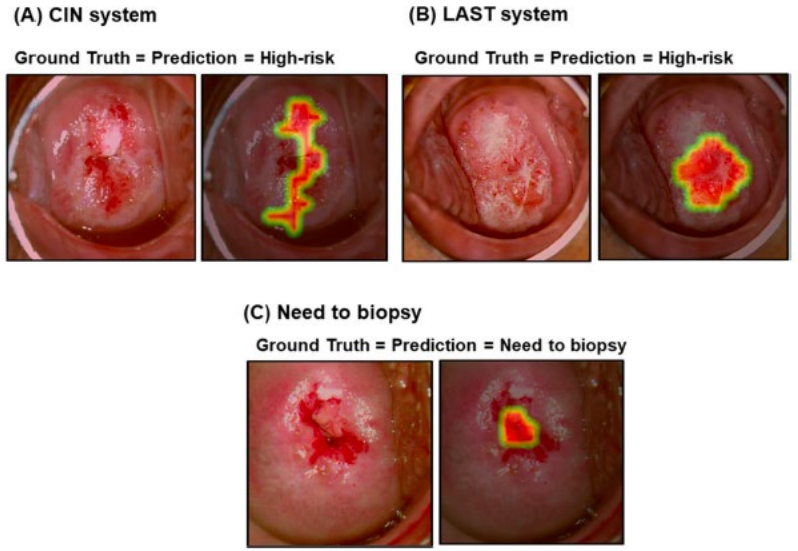


Figure 5. Class activation map for the classification of high-risk and low-risk cervical lesions on colposcopic photographs using a convolutional neural network based on (**A**) the CIN system or (**B**) the LAST system.

Ongoing Challlenges for Further Progress

- ✓However, large colposcopic image datasets are rarely well managed for labeling, annotation, classification, and quality control due to different types of colposcopy equipment used for data collection and non-uniform descriptive terminology in colposcopy practice, which makes it difficult for the data to be used for training and validating AI-guided digital colposcopy.
- ✓AI do not include dynamic acetowhite changes
- ✓Accceptence of AI by clinicians
- ✓Rare cervical cancers or lesions?

Automated Visual Evaluation (AVE) as An Adjunct to VIA for LMIC ?

- ✓A deep learning computer application for cervical cancer screening, can be used on cervix images taken by a contemporary smartphone camera
- ✓Using AVE on smartphones could be a useful adjunct to health-worker visual assessment with acetic acid(VIA)
- ✓Probabilities generated by AVE were strongly associated with evaluation of the same cervix images by experienced oncologists.
  - 7587 filtered images from 3221 women
  - Area under the curve values for the discrimination of the most likely precancer cases from least likely cases (most likely controls) were above 0.90
- ✓Commercial MobileODT EVA system uses Samsung Galaxy J5 smartphone camera

Xue Zhiyun, Int. J. Cancer. 2020;147:2416–2423

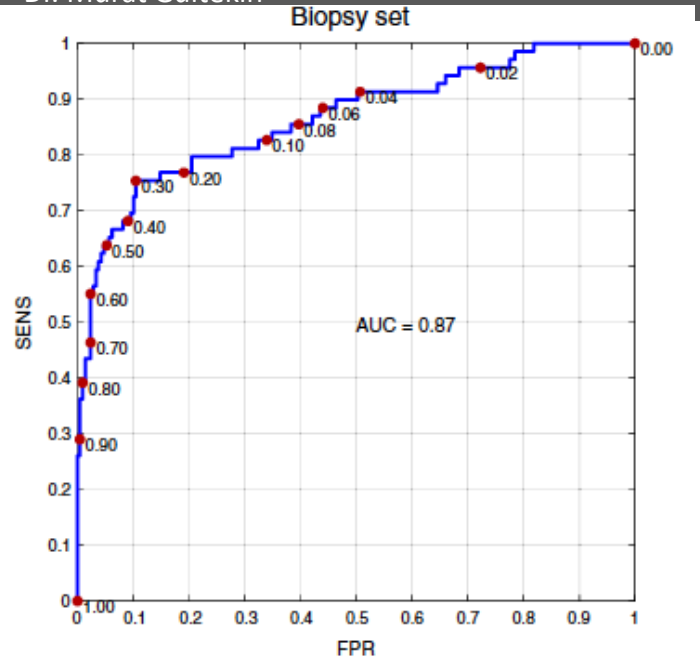
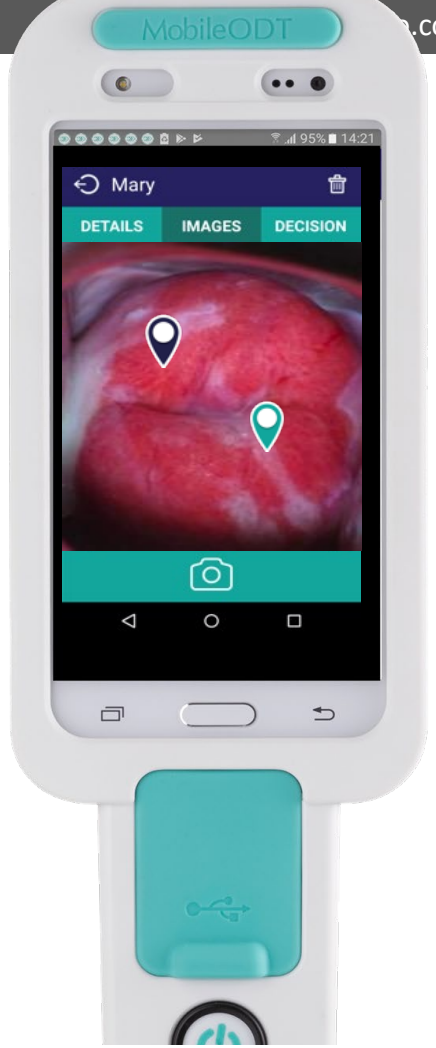
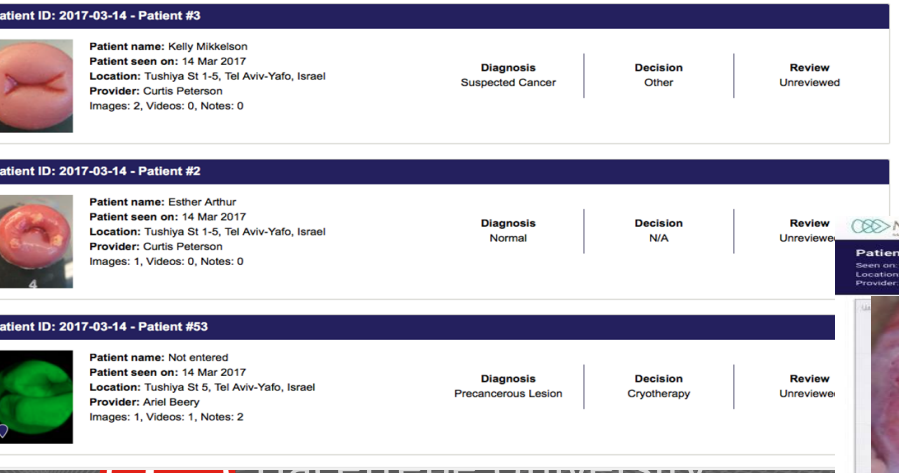
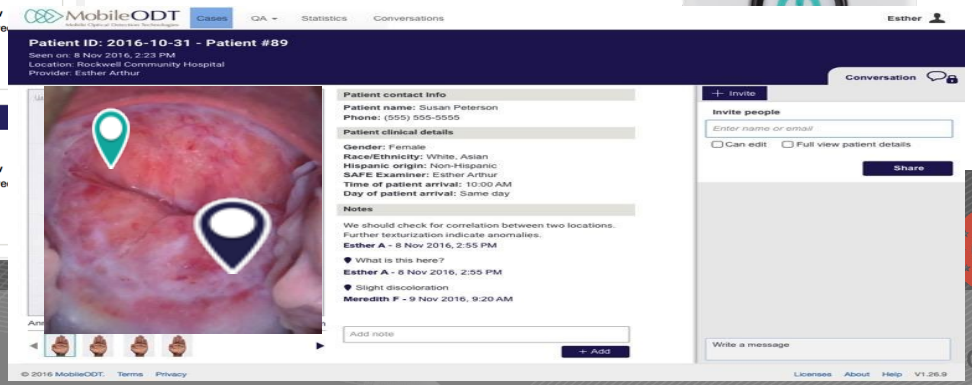


FIGURE 4 ROC curve for test set in the biopsy validated dataset (CIN2+ vs CIN1/normal) and the area under the curve value is 0.87 (95% CI 0.81-0.92) [Color figure can be viewed at wileyonlinelibrary.com]







"The EVA System is one of the greatest things to happen to women's cervical health. It is really amazing to go back and review results versus my initial impression of individual lesions."
Bonnie Betts, Nurse Practitioner

Streamlined cervical screening

The FDA-cleared EVA COLPO is a portable, internet connected colposcope designed to simplify workflow during and after a colposcopy procedure. The EVA System combines advanced hardware with integrated software with a user-friendly set up for easy adoption for novice to expert clinicians.

User-friendly

The EVA System's intuitive software and portable device are designed to be easy-to-use by clinicians at any level of experience.

Integrated documentation

Complete your procedure notes within the EVA System at the point-of-care, and annotate images collected with relevant findings and biopsy locations. The EVA software walks you through the documentation process enabling your procedure note to be completed by the time you finish your exam, ready to export to your EMR.

Case review

All data is automatically transferred to the HIPAA and GDPR compliant EVA Web Storage, which can be accessed through the EVA Portal. Review procedure notes and annotated images, export them securely to print or upload to your local EMR, and enable quality review by program administrators and residency directors for training.

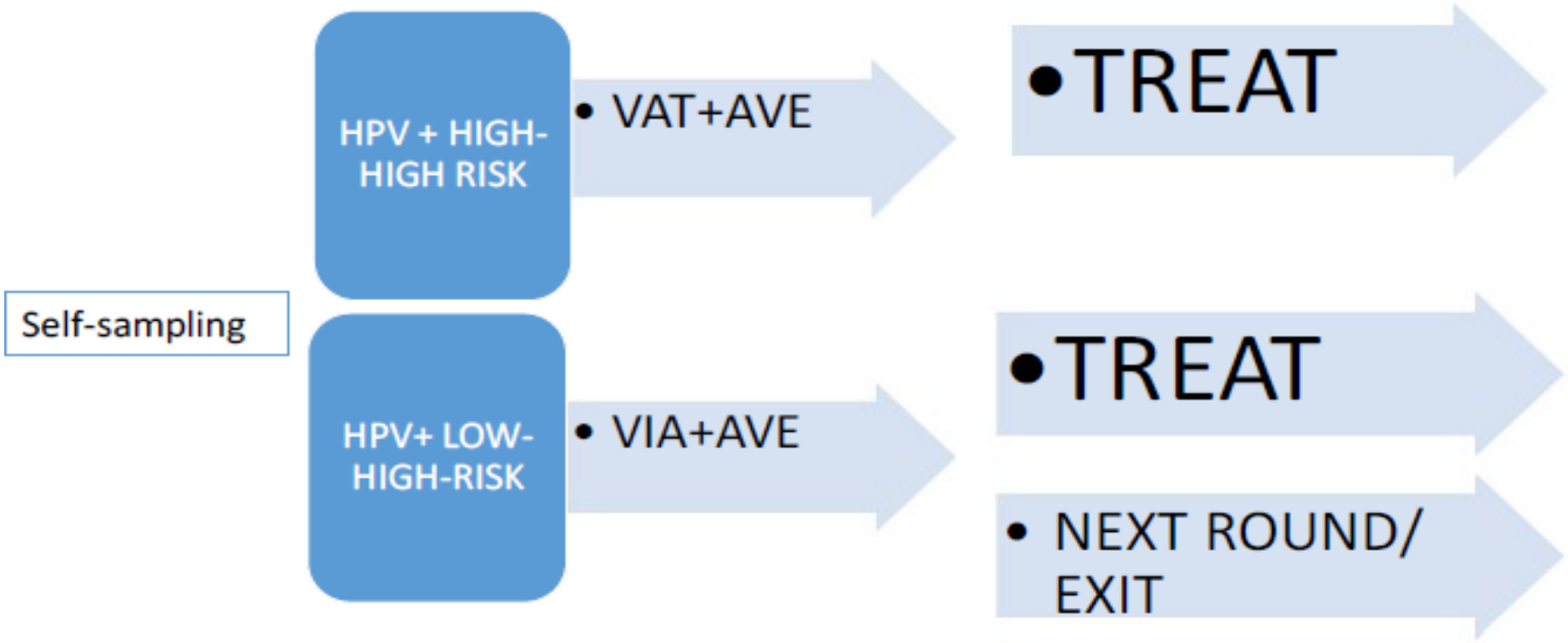
Teleconsultation

Share a HIPAA-compliant and secure video feed of the procedure in real-time with an off-site expert, with the EVA System teleconsultation feature. Colposcopies can be remotely supervised in real time, directing the clinician at the point-of-care throughout the consultation.

Patient Education

Enhance your patients' understanding of their anatomy and the colposcopy procedure by showing them the images directly on the device or by videocasting to an external monitor.

Scenario with high accuracy, minimizing overtreatment and potential low cost



VAT Visual assessment for treatment
VIA Visual evaluation necked eye
AVE Automated visual evaluation
HIGH/HIGH 16,18,45,31,33,35,52,58
LOW-HIGH 39,51,56, 59,68

New Generation Colposcopies For Developed Countries

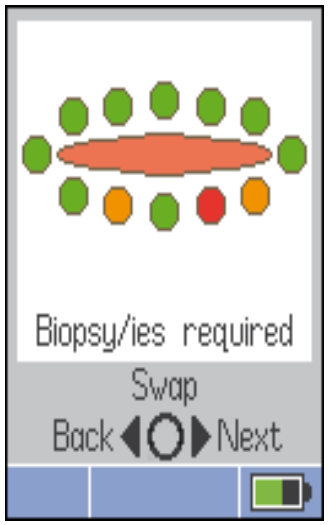
- ✓ **ZedScan : Electrical Impedance Spectroscopy**
- ✓ **Dysis: Dynamic Spectral Imaging System**
- ✓ **Luviva: Multimodal hyperspectroscopy**
- ✓ **(Niris: Optical Coherence Tomography) : Not on the Market Anymore**
- ✓ **Truscreen/Polarprobe: Optoelectric device**

Electrical Impedance Spectroscopy (EIS)

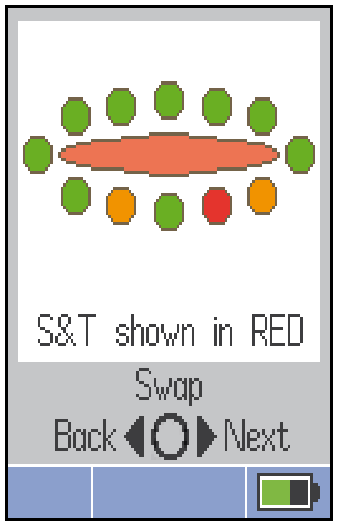
ZedScan

Electrical Impedance Spectroscopy (EIS)

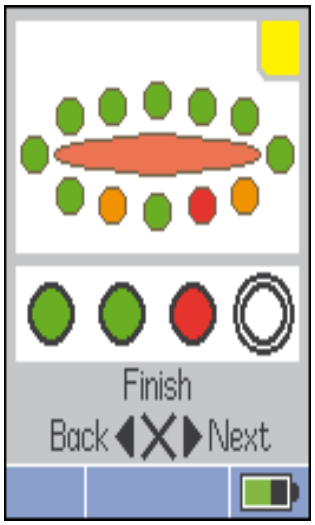
Real time data processing and displayed on hand set



Identifies areas to biopsy



Identifies areas that pass threshold for 'see & treat



Single point mode to accurately identify site to biopsy

Electrical Impedance Spectroscopy (EIS)

UPDATED RESULTS: Key Points

- ✓ Clinical Evaluation 1570 patients at Sheffield Colposcopy Clinic

- ✓ 429 high Grade diagnosed: ZedScan diagnosed extra 59 = 13.25% increase

Cytology	HG CIN Colposcopy +Zedscan	Additional Cases detected by Zedscan	Increased detection rate Sensitivity
High Grade	337	10	3.1%
Low Grade	129	43	50%
Other Referrals	38	6	18.8%

Electrical Impedance Spectroscopy (EIS)

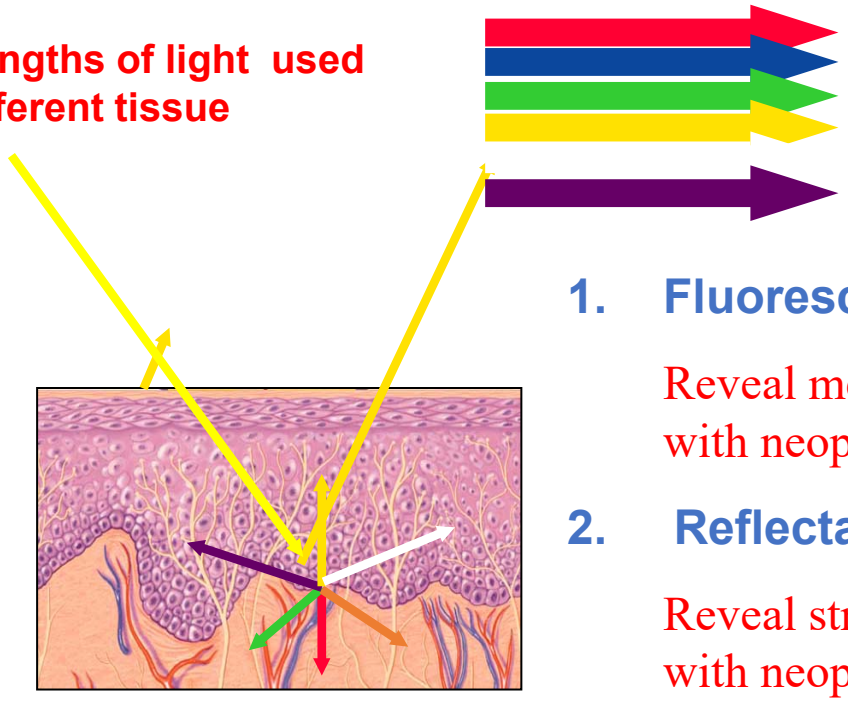
'See & Treat'

- ✓401 women referred with high grade cytology
- ✓259 women had 'see and treat' after ZedScan dictated passed the threshold for treatment
- ✓PPV for high grade disease on LLETZ 94%

Multimodal Spectroscopy (MMS)

Light In –

Multiple wavelengths of light used to penetrate different tissue depths



Spectrometer Results

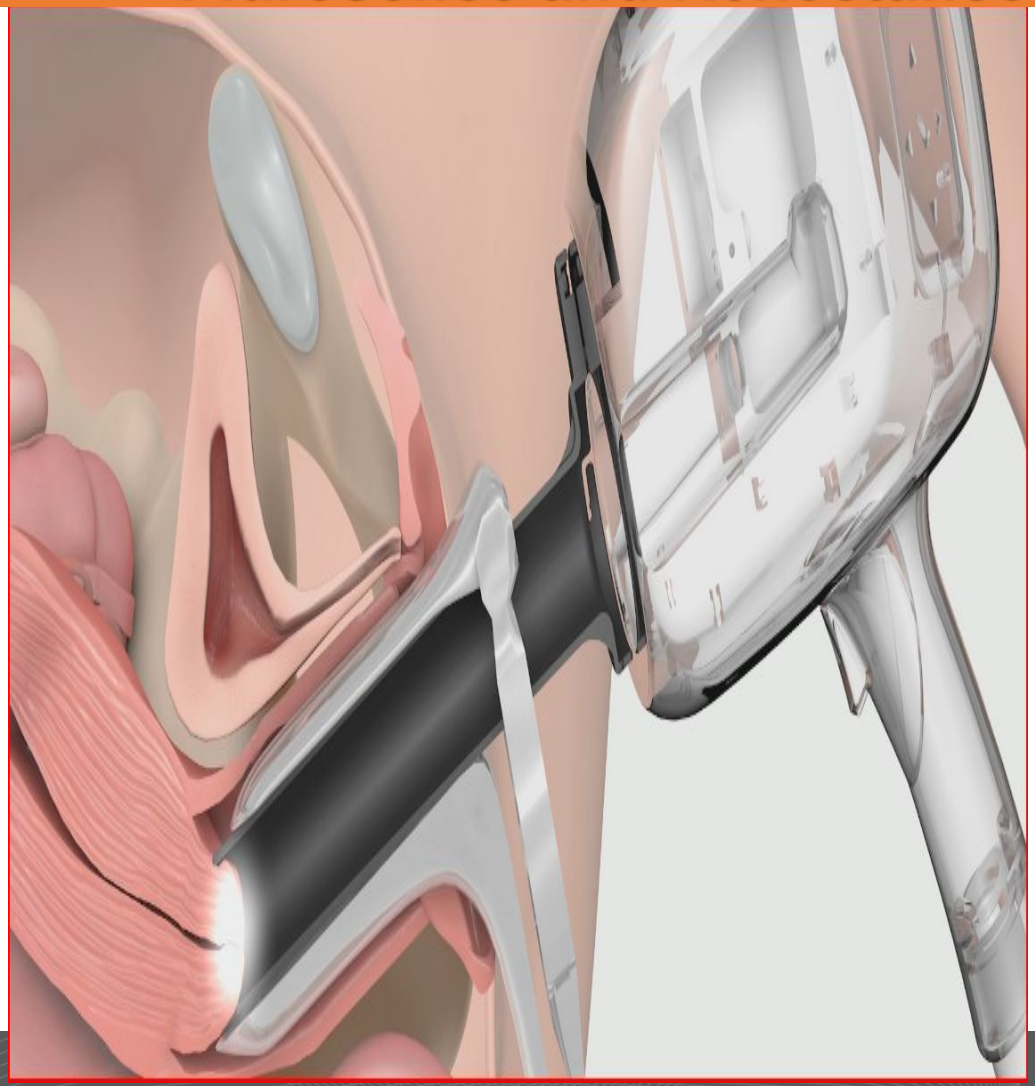
1. **Fluorescence Spectra -**

   Reveal metabolic changes associated with neoplasia

2. **Reflectance Spectra –**

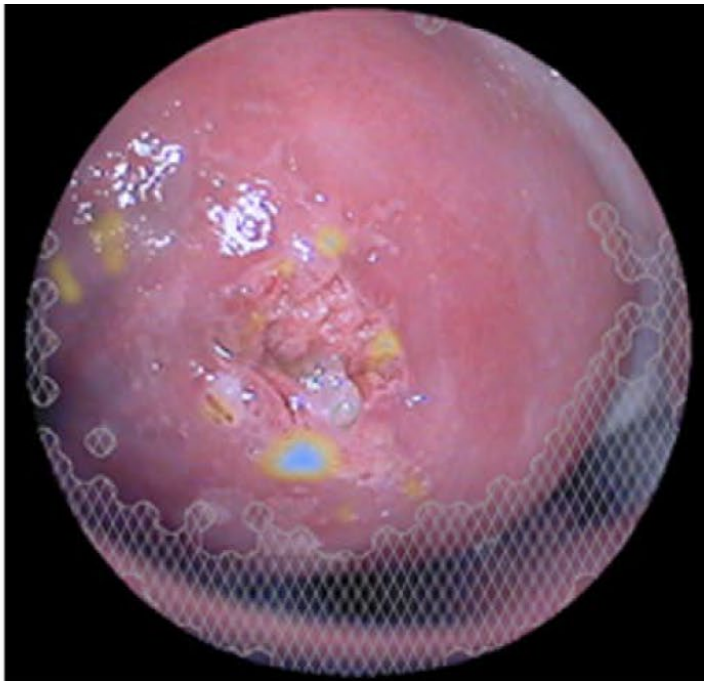
   Reveal structural changes associated with neoplasia

Multimodal Spectroscopy (MMS) : Luviva Flurosence and Reflectance Spectra



Multimodal Spectroscopy (MMS)

Colposcopy with Acetic Acid



Optical spectroscopy demonstrating area of high grade disease

Multimodal Spectroscopy (MMS)

Multimodal Spectroscopy as a Triage Test For Women at Risk For Cervical Neoplasia: Results of a 1,607 Subject Pivotal Trial

- 1607 women referred with an Abnormal Pap smear / HPV test
- All patients had colposcopy, biopsy of abnormal areas and endocervical curretage
- All patients had Spectroscopy and the results were blinded from the colposcopists

Gynecol Oncol. 2013 Jul;130(1):147-51

Multimodal Spectroscopy (MMS)

Standard of Care : Pap Smear, HPV and Colposcopic Impression

Identified 202 CIN2+ (202/266)

%76

CIN3 NPV 99%

Light Touch: MMS

Identified 242 CIN2+; 40 More Identified (242/266)

%91

MDS Detected 20% more for CIN2+

May even Be Used as Primary Screening ??

Gynecol Oncol. 2013 Jul;130(1):147-51

Multimodal Spectroscopy (MMS)

For CIN2+	n	Sensitivity	Specifity
Ebisch, 2017	125	93.6%	42.3%
Twiggs, 2013	1607	91.3%	38.9%
Desantis, 2008	572	95.1%	55.2%
Systematic Review, 2016	2530	93%	62%

- VERY GOOD SENSITIVITY (TRIAGE)
- NO NEED For COLPOSCOPY : Can be Used for Primary Screening –Kenya ??
- PAIN DURING EXAM
- 15% INABILITY TO COMPLETE EXAM
- CAN MISS LESIONS ın ONE SINGLE SCAN

Gynecol Oncol. 2013 Jul;130(1):147-51

Opto-electronic Spectral Impedence (True Scan)

Opto-electronic Spectral Impedence

Value for Biopsy Confirmed CIN2+ (Low and High Grade Lesions)

Author (Year)	Sensitivity	Specifity	n
Singer, 2003	70%	??	671
Abdul, 2006	74%	53%	176
Pruski, 2008	78%	78%	293
Long, 2013	67%	68%	181
Ozgu, 2015	86%	35%	285
Campos, 2019	33%	86%	32

Dynamic Spectral Imaging System

DySIS digital colposcope

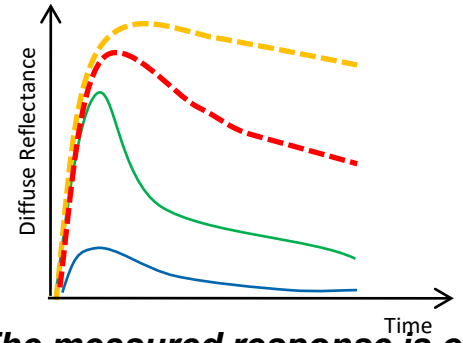
- **Hi-resolution digital colposcopy**
- **DySISmap: mapping the cervix (acetowhitening measurement)**
- **It produces a quantitative measurement of the rate, extent and duration of the acetowhitening.**
- **Image & video capture, biopsy annotation & video**
- **Longer duration of exam and if fails can not be repeated**

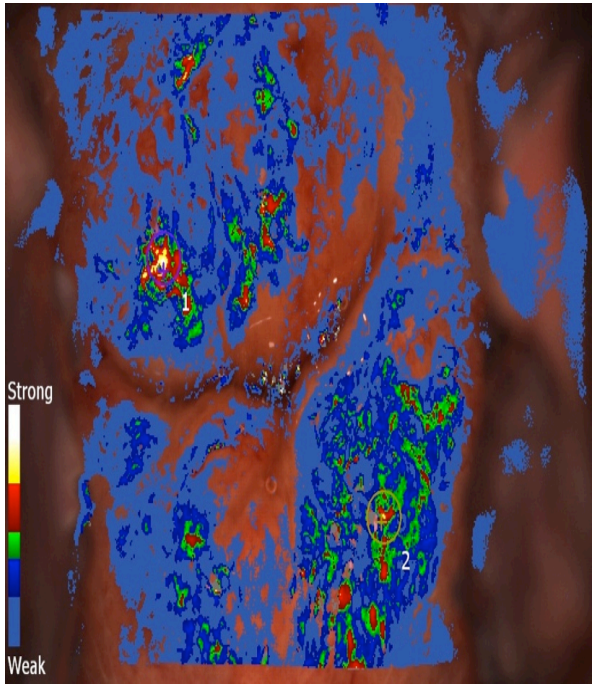
Dynamic Spectral Imaging System

DySIS Mapping Method

Dynamic Spectral Imaging

Standardised measure of acetowhitening intensity and duration





Red, yellow, white suggest high grade

The measured response is colour-coded & summarised to build the DYSISmap

Dynamic Spectral Imaging System

- ✓ No difference in patient satisfaction between conventional colposcopy and Dysis
- ✓ Dysis consistently higher sensitivity compared to colposcopy but lower specificity diagnosing CIN2+

	Soutter* All Referrals	Lowers All referrals	Zaal HPV 16+ Cases
Sensitivity			
Colposcopy	49%	55%	53%
Dysis	79%	88% Combined 79% Map Alone	97% Combined
Specifity			
Colposcopy	89%	85%	90%
Dysis	76%	69% Combined 77% Map Alone	100% Combined

*Early UK study Soutter et al used pre-production model and not combined with dynamic colposcopy

Soutter P, Clin Cancer Res. 2009 Mar 1;15(5):1814-20.

Louwers JA, Gynecol Oncol. 2015 Dec;139(3):452-7.

Zaal A, BJOG. 2012 Apr;119(5):537-44

Dynamic Spectral Imaging System

CIN2+ Detection on ASCUS/LSIL IMPROVE-COLPO Study

- ✓39 community clinics in US
- ✓1788 patients retrospectively, 1857 patients prospectively (Compares outcomes before and after DYSIS)

	Before	After	Difference	p
Biopsy Number	1.03	1.25	(21.6%), One extra per five women	0.05
CIN2+ Yield	7.21%	9.48%	2.27% (31.4%)	0.01
CIN3+ Yield	2.07%	3.23%	1.16% (56.1%)	0.03
False + Rate	64.4%	62.0%		>0.05

MORE CIN2+ DETECTION WITH SIMILIAR BIOPSY RATES UPON LOW GRADE REFERRALS

Cholkeri-Singh A, J Low Genit Tract Dis. 2018 Jan;22(1):21-26

THANK YOU SO MUCH….