THE UNIVERSITY OF TEXAS
MD Anderson ~~Cancer~~ Center

Making Cancer History®

hospital de amor

MobileODT®
Mobile Optical Detection Technologies

A Multimodal Imaging System for Cervical Pre-Cancer and Cancer Detection

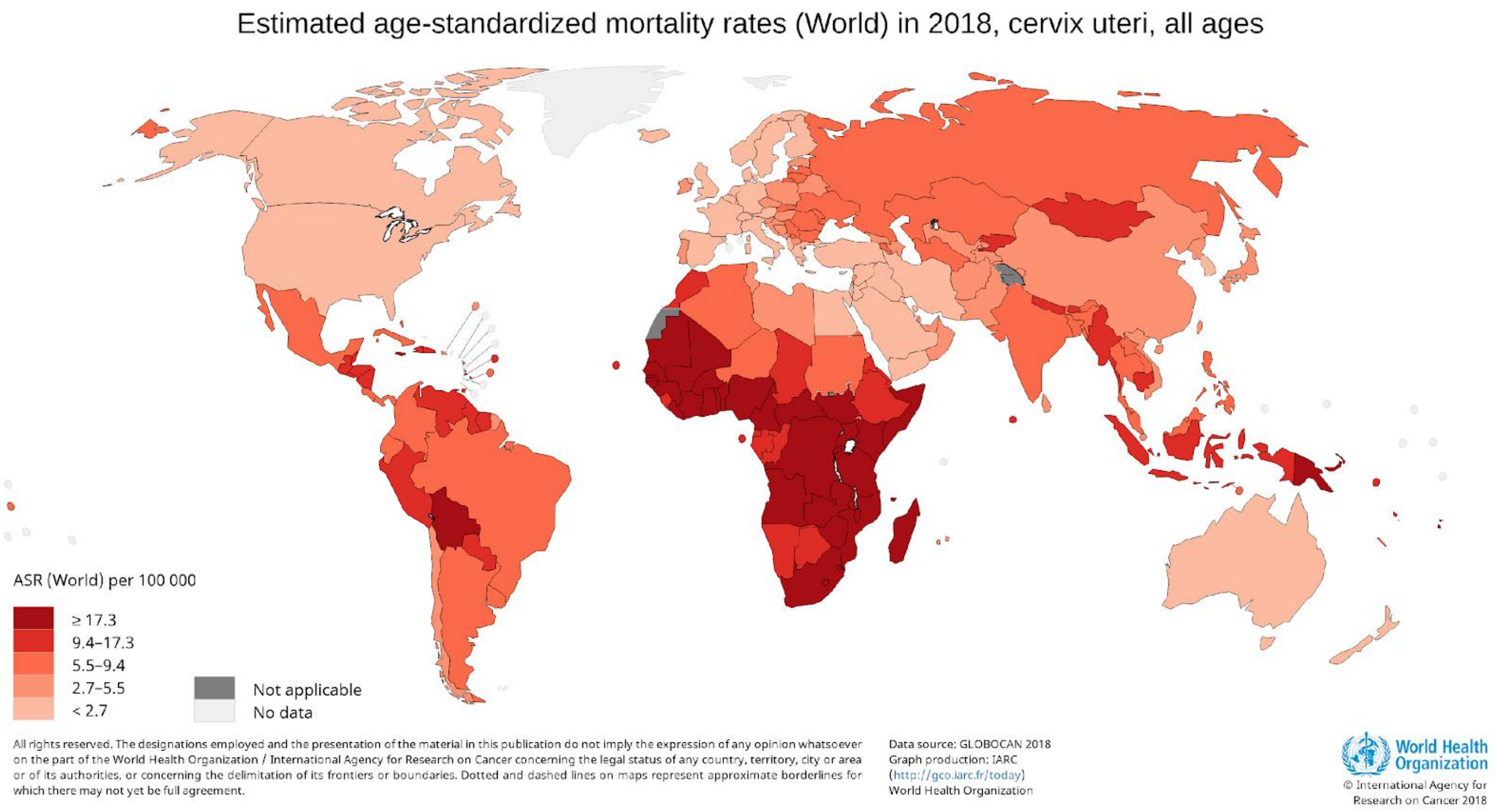
David Brenes, Brady Hunt, Rebecca Richards-Kortum, Kathleen Schmeler, Jose Fregnani, David Levitz

Outline

1. Background
   - Cervical cancer incidence and biology
   - Standard of care
   - Proposed scalable care
2. Multimodal Imaging System
   1. High Resolution Endomicroscopy (HRME)
      - Current algorithm
      - Clinical studies
      - Deep learning
   2. MobileODT Colposcope
      - Automated Visual Evaluation Algorithm
   3. Integration of MobileODT Colposcope and HRME

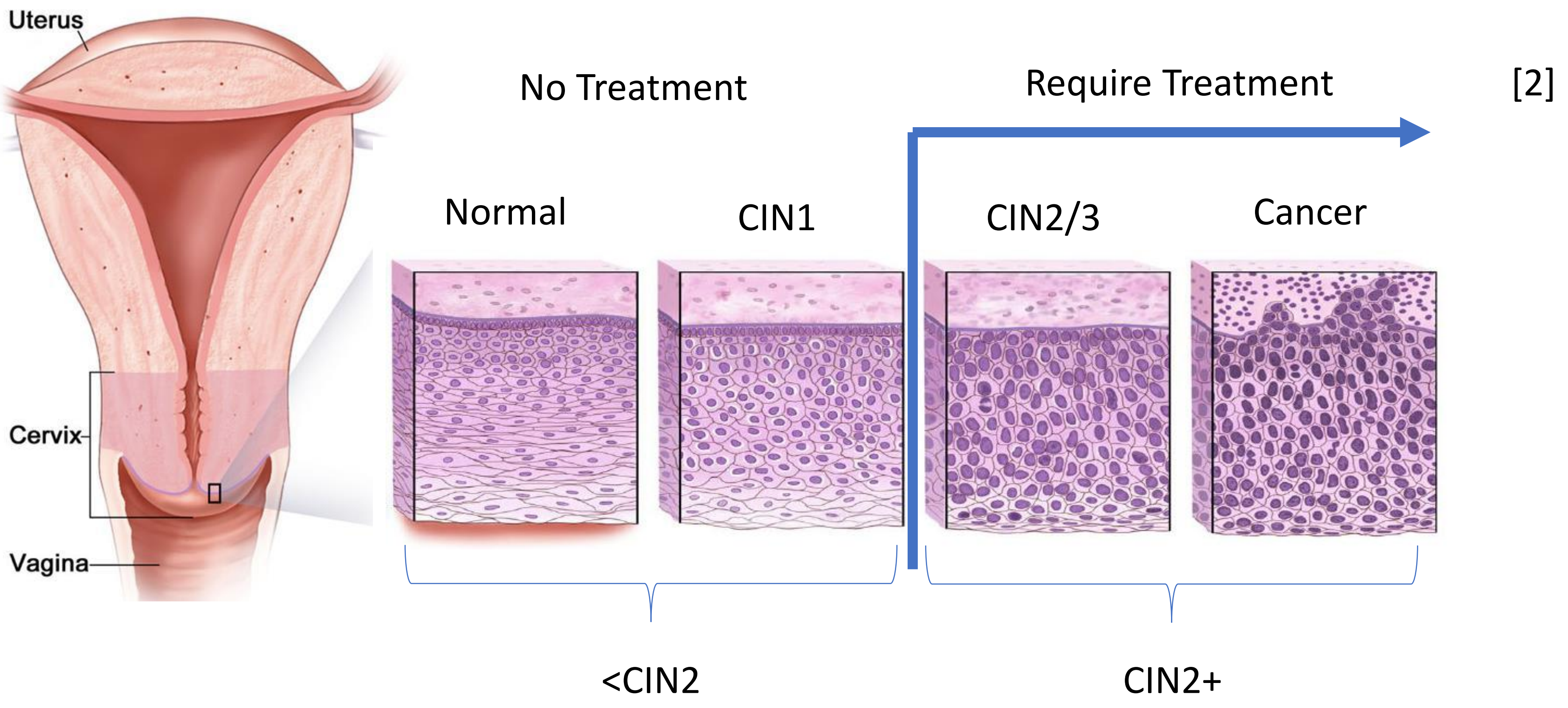
Cervical Cancer: A Global Challenge

- **90%** of cervical cancer deaths occur in low- and lower-middle- income countries (LMICs) [1]
- Early screening and treatment of pre-cancerous lesions can prevent cervical cancer
- **70%** of cervical cancers start with Human Papilloma Virus (HPV) infection [1]
- In 2018, the World Health Organization announced a global call to action towards the elimination of cervical cancer [1]
  - 90% HPV vaccination coverage (age>15)
  - **Management of 90% of lesions**
  - **70% screening coverage (35, 45)**



Early Stage Detection – Cervical Pre-cancer

- Cervical pre-cancer is called cervical intraepithelial neoplasia (CIN)

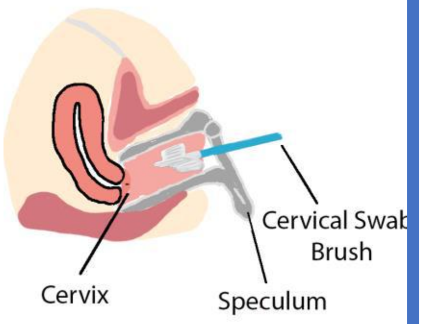


Challenges in Standard of Care for LMICs

Standard of Care

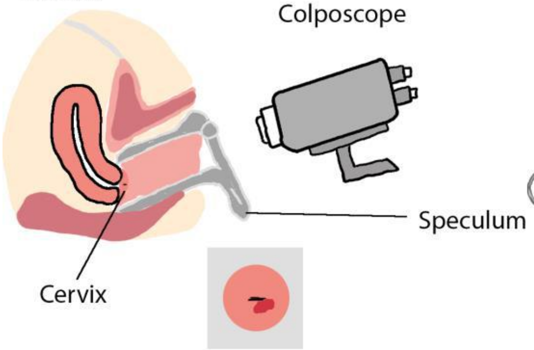
Visit 1 Screen

HPV Test

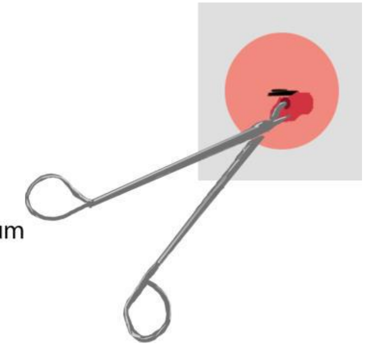


Visit 2 Diagnose

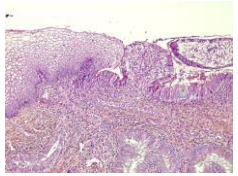
Colposcopy



Punch Biopsy



Histopathology



Visit 3 Treat

CIN2/3

- LEEP Conization

Cancer

- Referred to oncology

Challenges in Standard of Care for LMICs

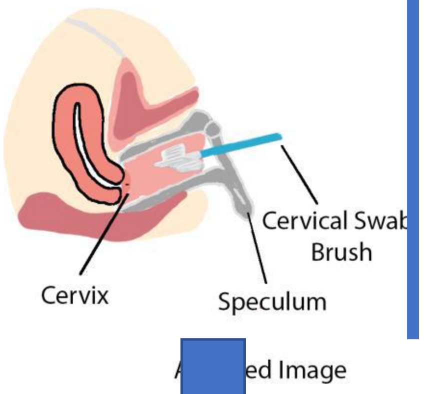
Standard of Care

Visit 1 Screen

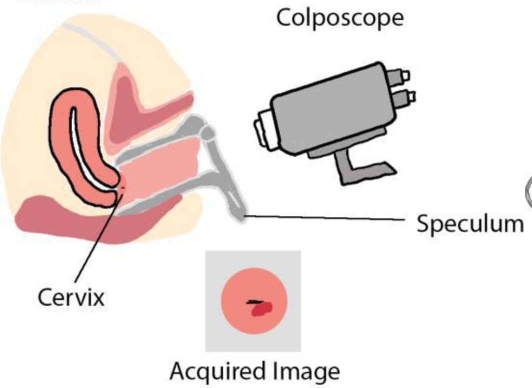
Visit 2 Diagnose

Visit 3 Treat

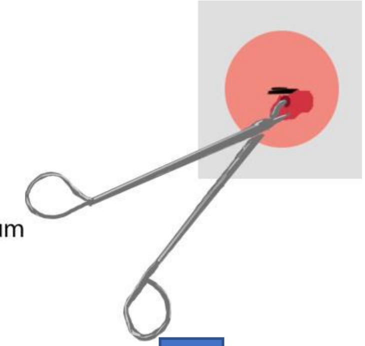
HPV Test



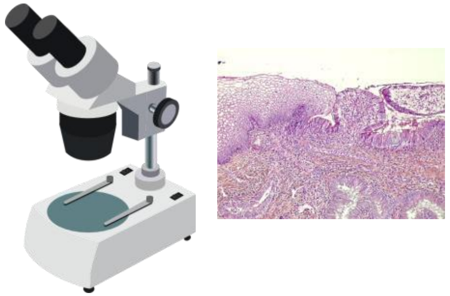
Colposcopy



Punch Biopsy



Histopathology



CIN2/3

- LEEP Conization

Cancer

- Referred to oncology

Limitations

- Scarcity of reagents
- Expensive equipment
- Trained professional

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- Trained professional
- Patient loss to follow-up

- Expensive equipment
- Trained professional
- Patient loss to follow-up

Proposed Workflow for LMICs

A single practitioner can perform all the necessary steps to screen, diagnose, and treat a patient at the point-of-care

Visit 1 Screen Diagnose Treat

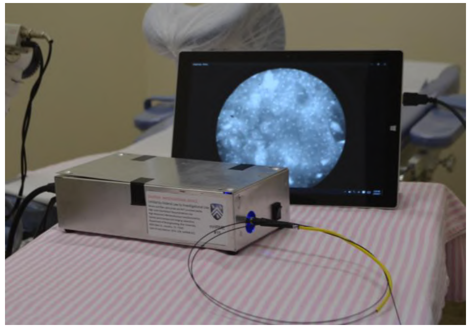
Scalable Care

HPV Lateral Flow Assay
Automated Reader

Automated Multimodal Imaging System

Mobile Colposcope

Mobile
Microendoscopy



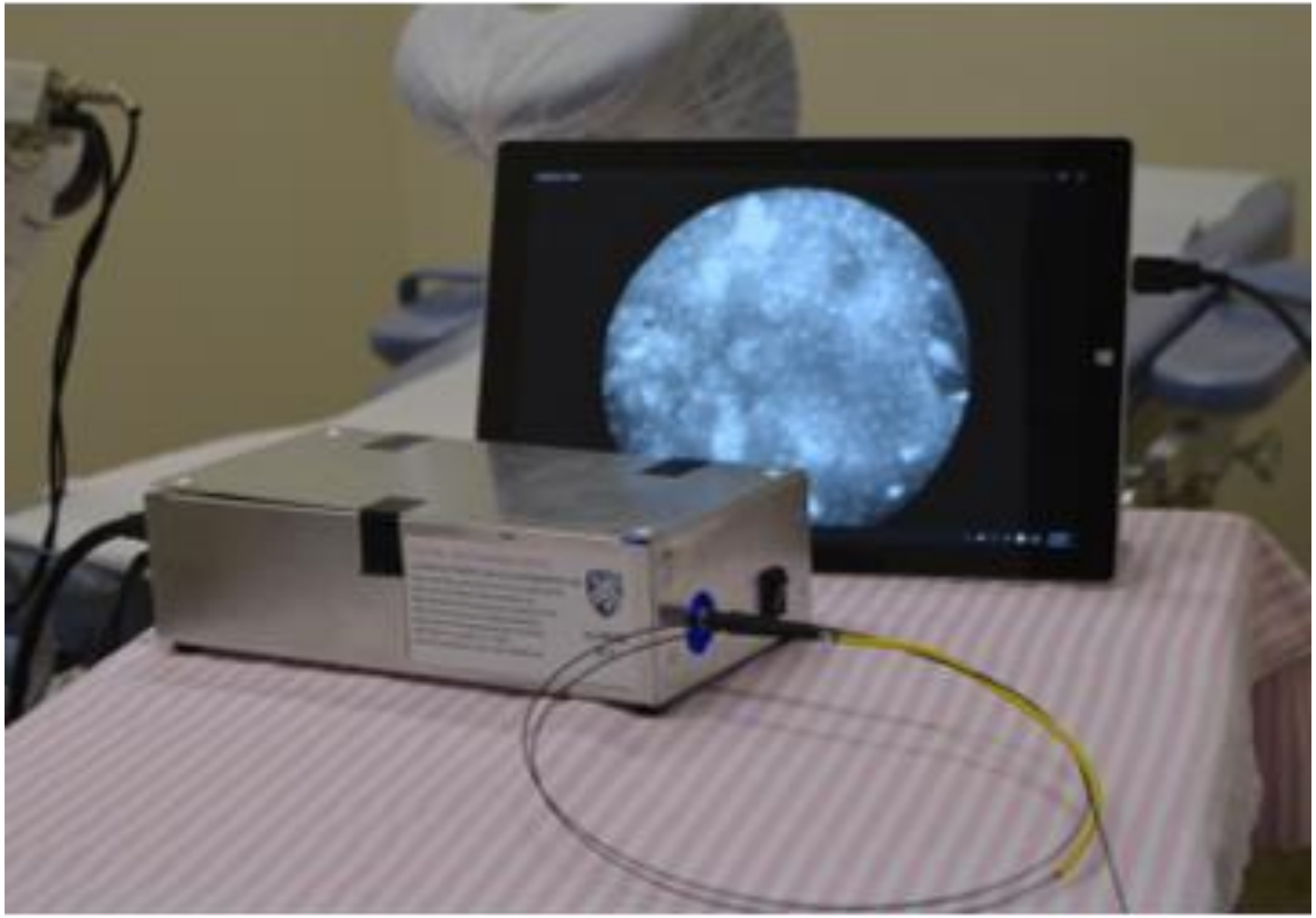
CIN2/3

- Portable Thermocoagulator

Cancer

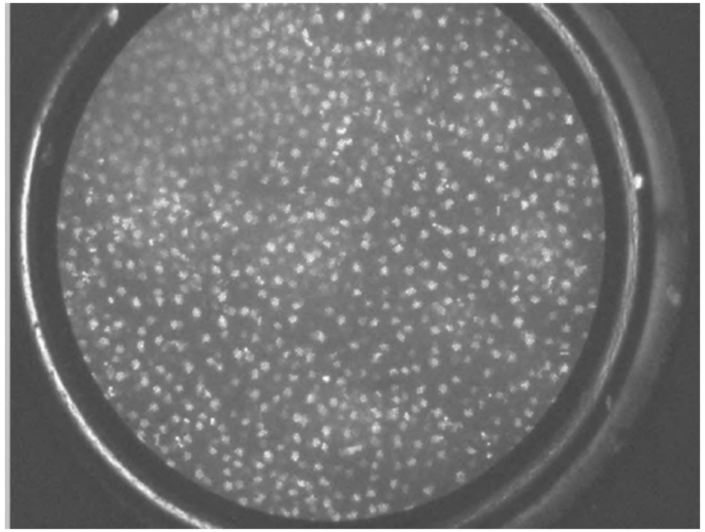
- Referred to oncology

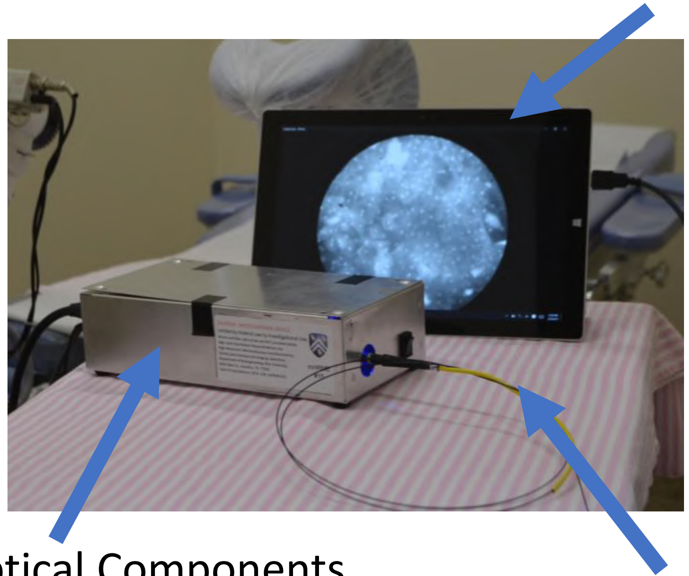
High Resolution Microendoscopy (HRME)



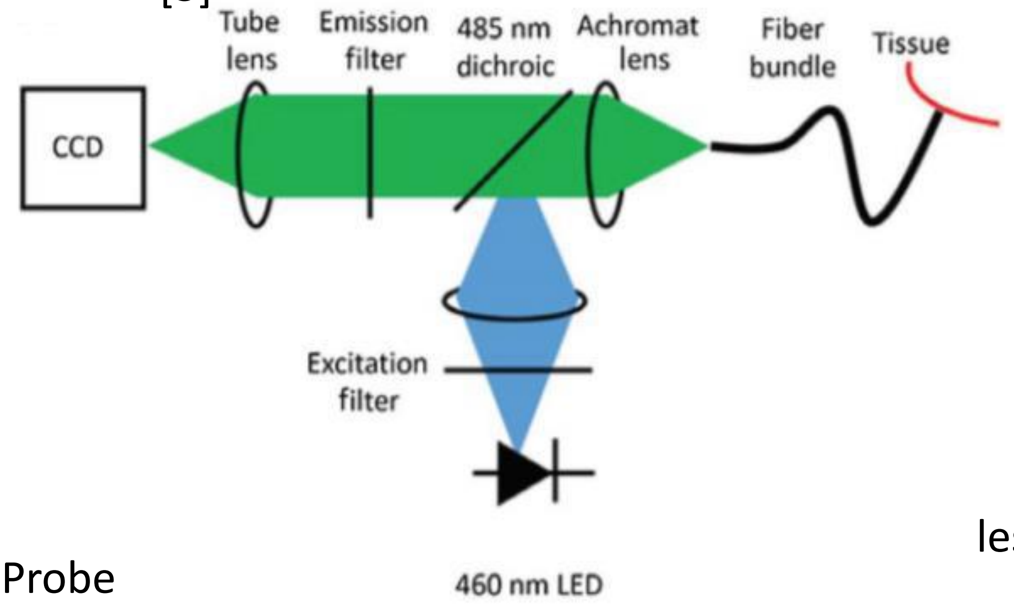
HRME Instrumentation

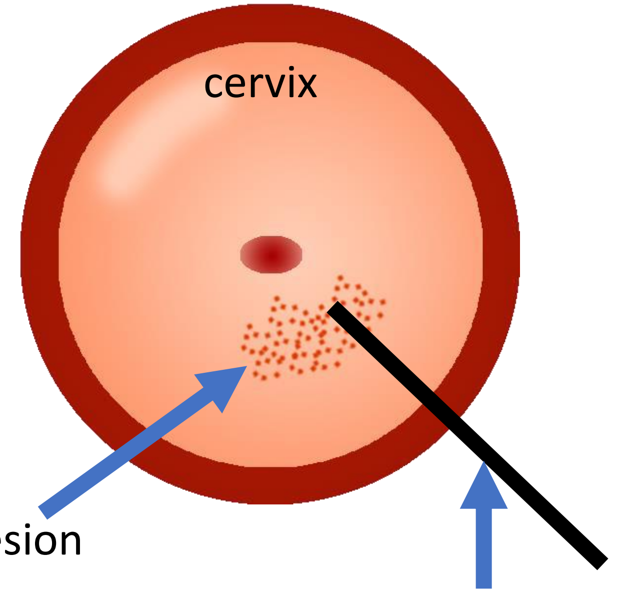
- Fiber optic probe is used to image lesions
- Nuclei are stained with proflavine dye





[3]

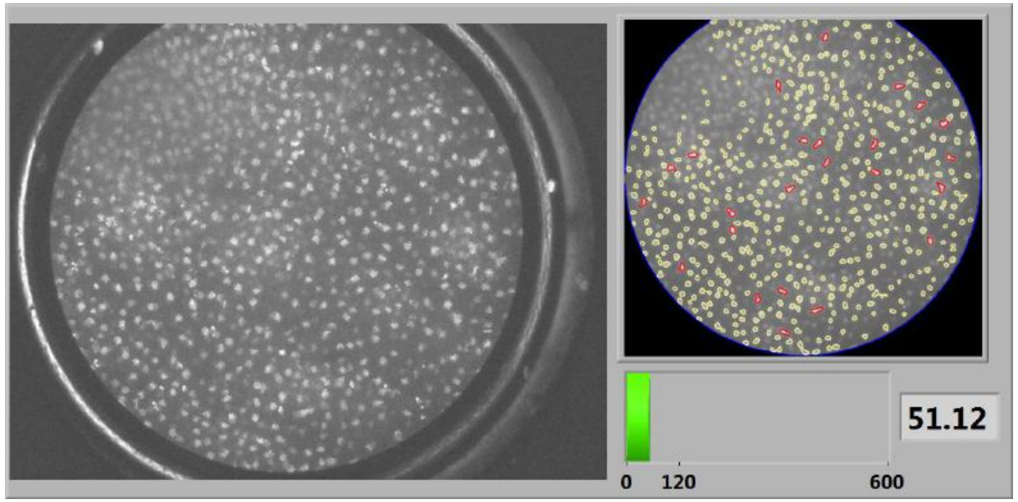




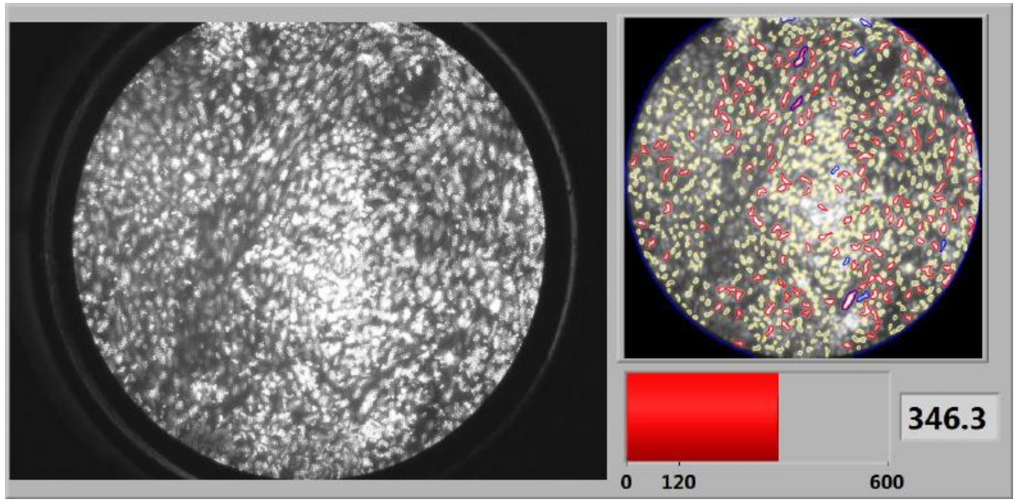
HRME Computer Vision based Algorithm (CVBA) [4]

1. Segment the fiber ROI
2. Saturated and dim regions are found and excluded
3. Nuclear segmentation is performed using Otsu’s method
4. Feature Extraction
   - Nuclear Area
   - Nuclear Eccentricity
5. Nuclei are classified as normal or abnormal based on thresholds on these features
6. **HRME Score = # Abnormal Nuclei/Area**
7. HRME+ >= 120 and HRME- <120

HRME Negative



HRME Positive



HRME Clinical Studies

1. Hospital de Amor
   Barretos, São Paulo, Brazil

Other Studies:

2. El Salvador
3. Mozambique (ongoing)

Clinical Trails in Brazil

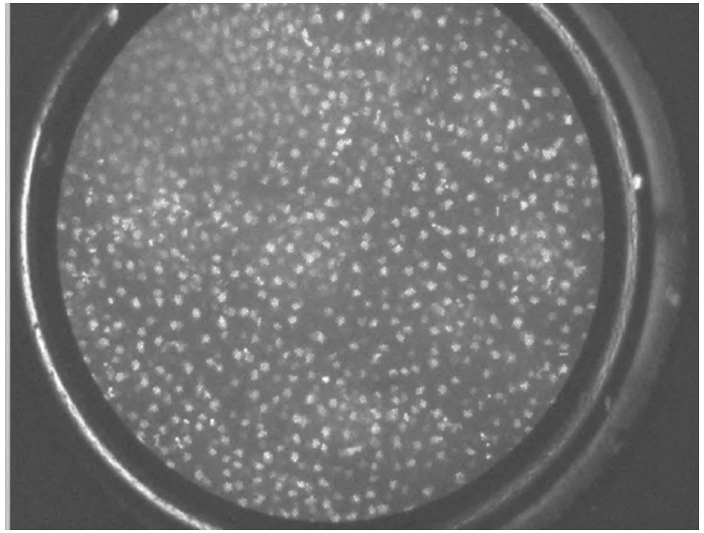
- Conducted 2 studies in Barretos, Brazil
- Each patient undergoes colposcopy, HRME, biopsy, histopathology

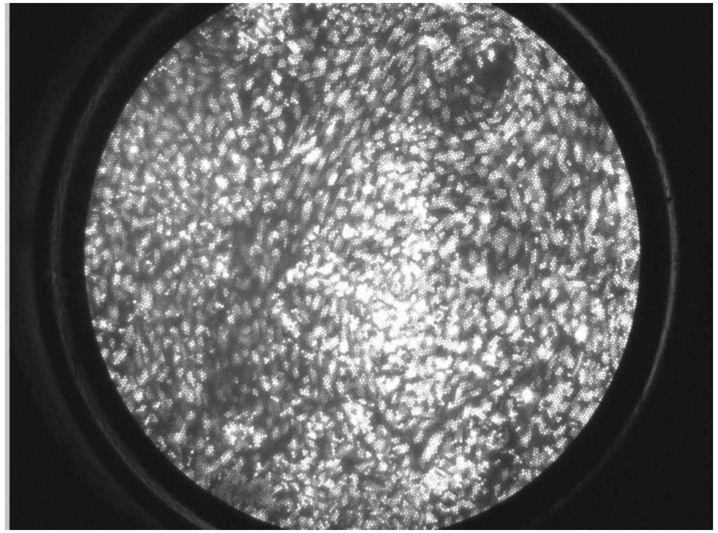
	Clinical Studies – Brazil, Barretos	
	UH2	CLARA
Number of Patients	144	1486
Number of Sites	229	1901
% of CIN2+ Patients	37 %	28 %
Sensitivity (CVBA)	92 %	92 %
Specificity (CVBA)	48 %	60 %
AUC Per Patient (CVBA)	0.87	0.83

- Per patient score = worst image score for that patient

Challenges

- Subtle class variations (<CIN2, CIN2+)
- Difficult to ensure perfect correlation between the biopsy and the HRME image
- Small dataset
- Class imbalance (70% <CIN2, 30% CIN2+)





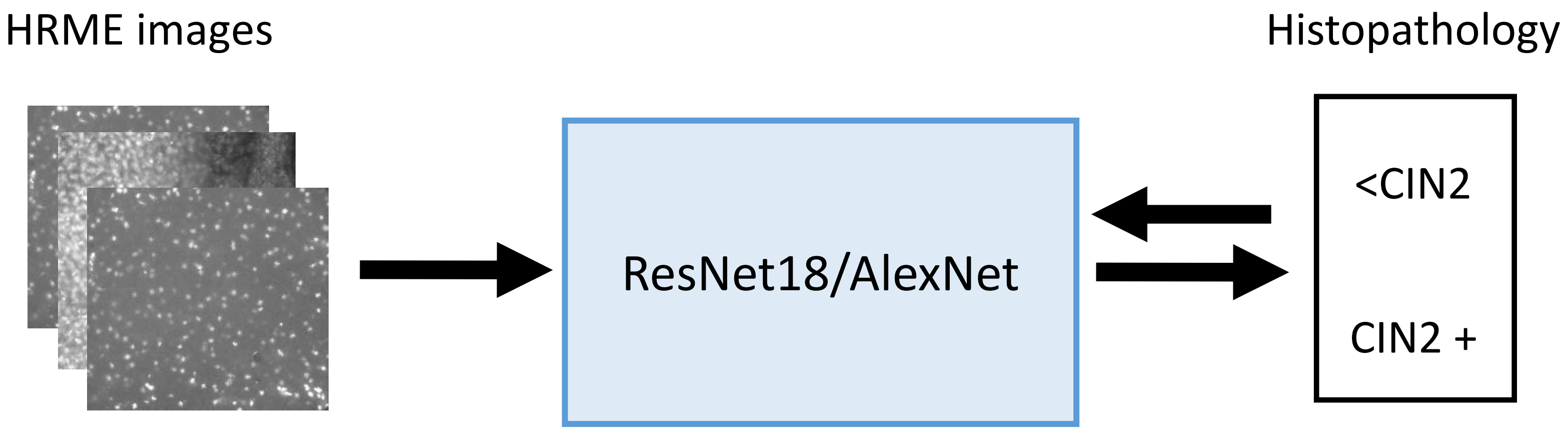
Deep Learning for HRME

Use modern computational methods to further improve the performance of HRME for cervical pre-cancer prediction

UH2 5-Fold Cross Validation Benchmark Study

Model	Ground Truth Training Label	Aggregate Per Patient AUC Validation
AlexNet	**Histopathology**	**0.804**
ResNet18	Histopathology	0.800

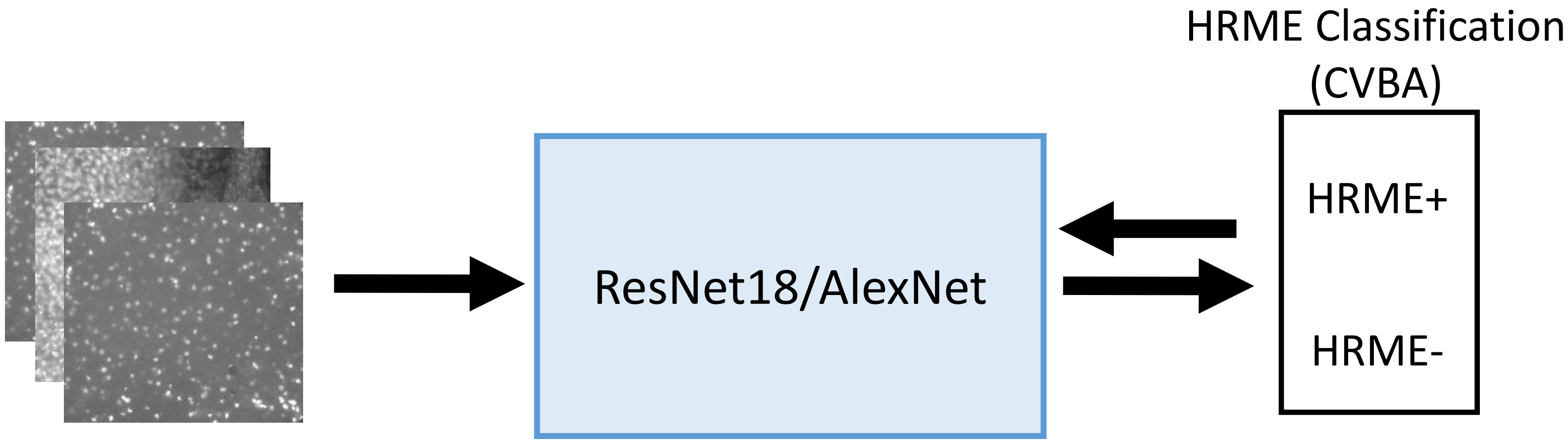
	UH2 – HRME Algorithm
Number of Patients	144
Number of Sites	229
% of CIN2+ Patients	37 %
Sensitivity	92 %
Specificity	48 %
AUC Per Patient (CVBA)	0.87



UH2 5-Fold Cross Validation Benchmark Study

Model	Ground Truth Training Label	Aggregate Per Patient AUC Validation
AlexNet	Histopathology	0.804
ResNet18	Histopathology	0.800
AlexNet	**HRME Prediction**	**0.885**
Resnet	HRME Prediction	0.876

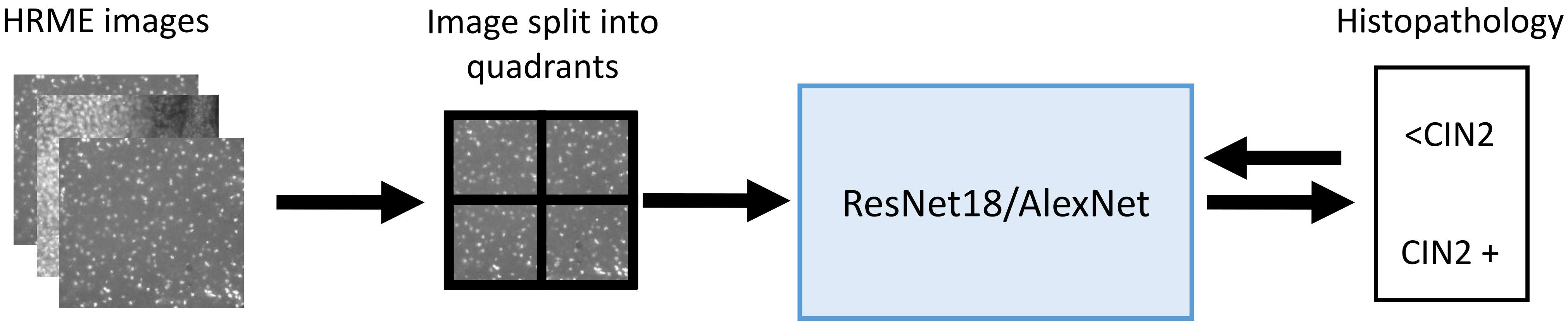
	UH2 – HRME Algorithm
Number of Patients	144
Number of Sites	229
% of CIN2+ Patients	37 %
Sensitivity	92 %
Specificity	48 %
AUC Per Patient (CVBA)	0.87



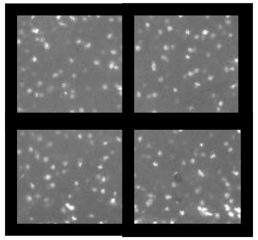
UH2 5-Fold Cross Validation Benchmark Study

Model	Ground Truth Training Label	Aggregate Per Patient AUC Validation
AlexNet	Histopathology	0.804
ResNet18	Histopathology	0.800
AlexNet	**HRME Prediction**	**0.885**
Resnet	HRME Prediction	0.876
AlexNet-Quadrants	**Histopathology**	**0.870**
ResNet18-Quadrants	Histopathology	0.855

	UH2 – HRME Algorithm
Number of Patients	144
Number of Sites	229
% of CIN2+ Patients	37 %
Sensitivity	92 %
Specificity	48 %
AUC Per Patient (CVBA)	0.87



Takeaways Benchmark Study



Training on image quadrants rather than whole images improves performance

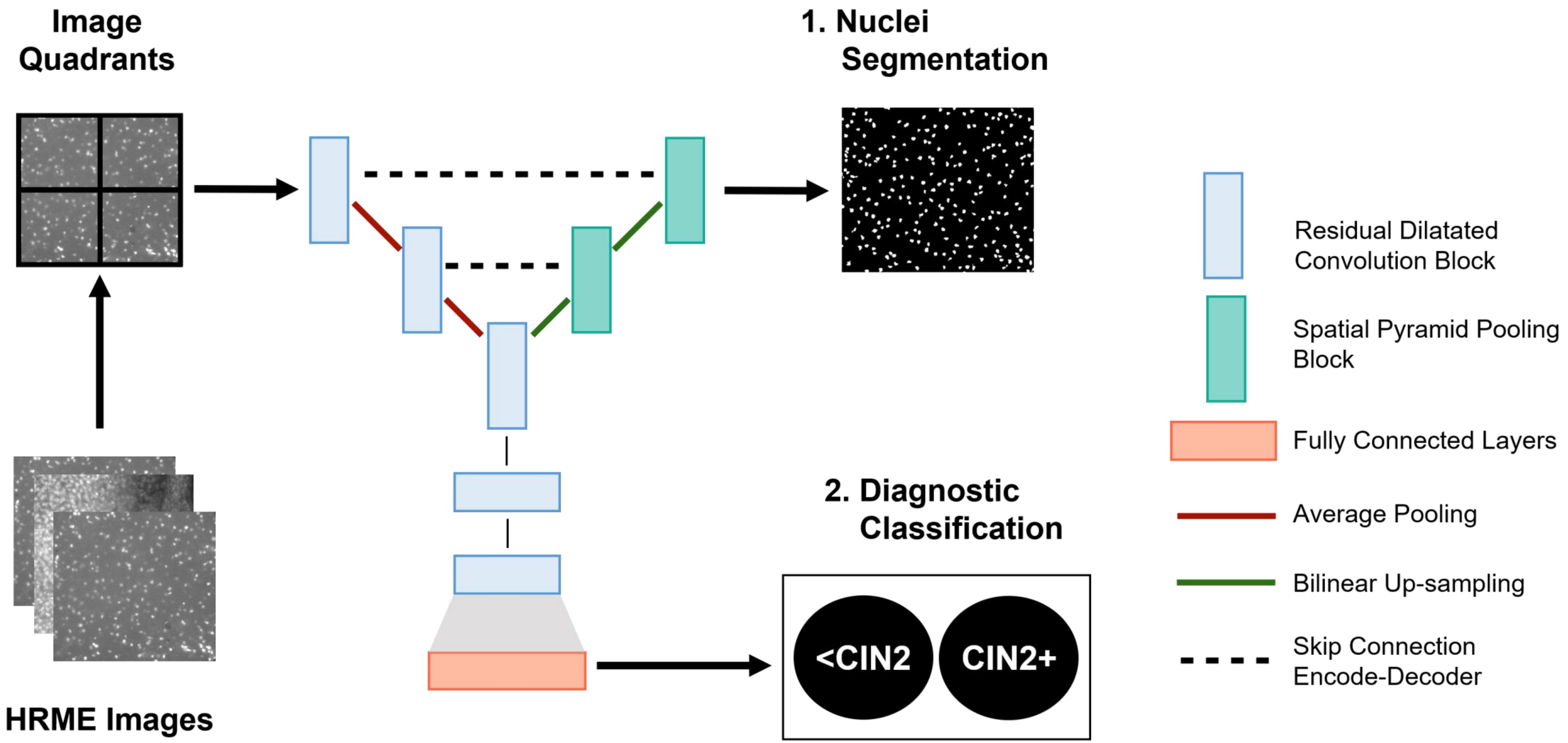
Training on HRME prediction provides a stronger supervision signal than training directly on histopathology

Next Step

Guide the neural network during training to leverage similar features to the CVBA

Multi-Task: Segmentation & Classification

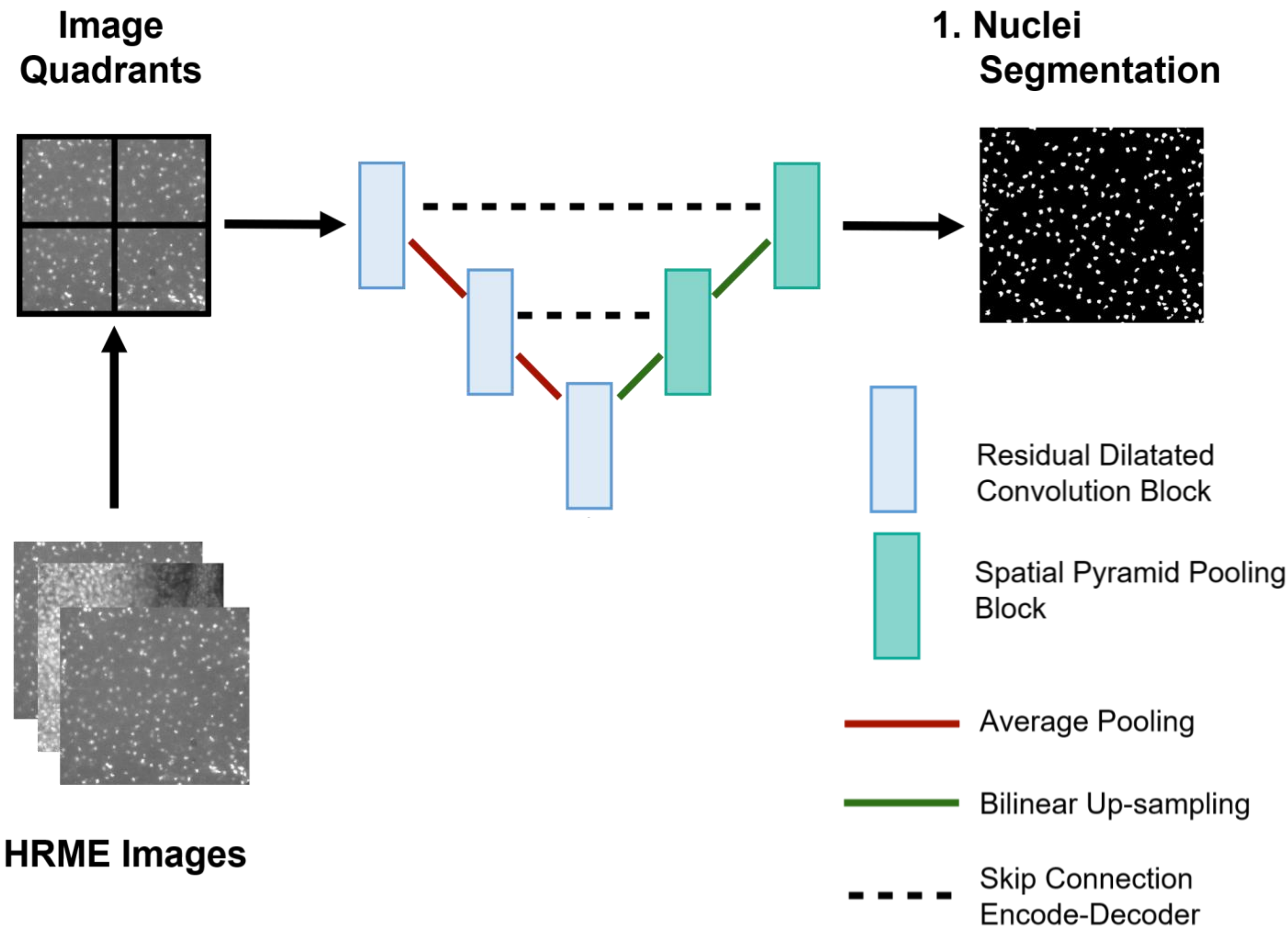
Y-Net architecture developed by Sachin Mehta et al. [5]



[5] Mehta, Sachin, et al. MICCAI, Springer, Cham, 2018.

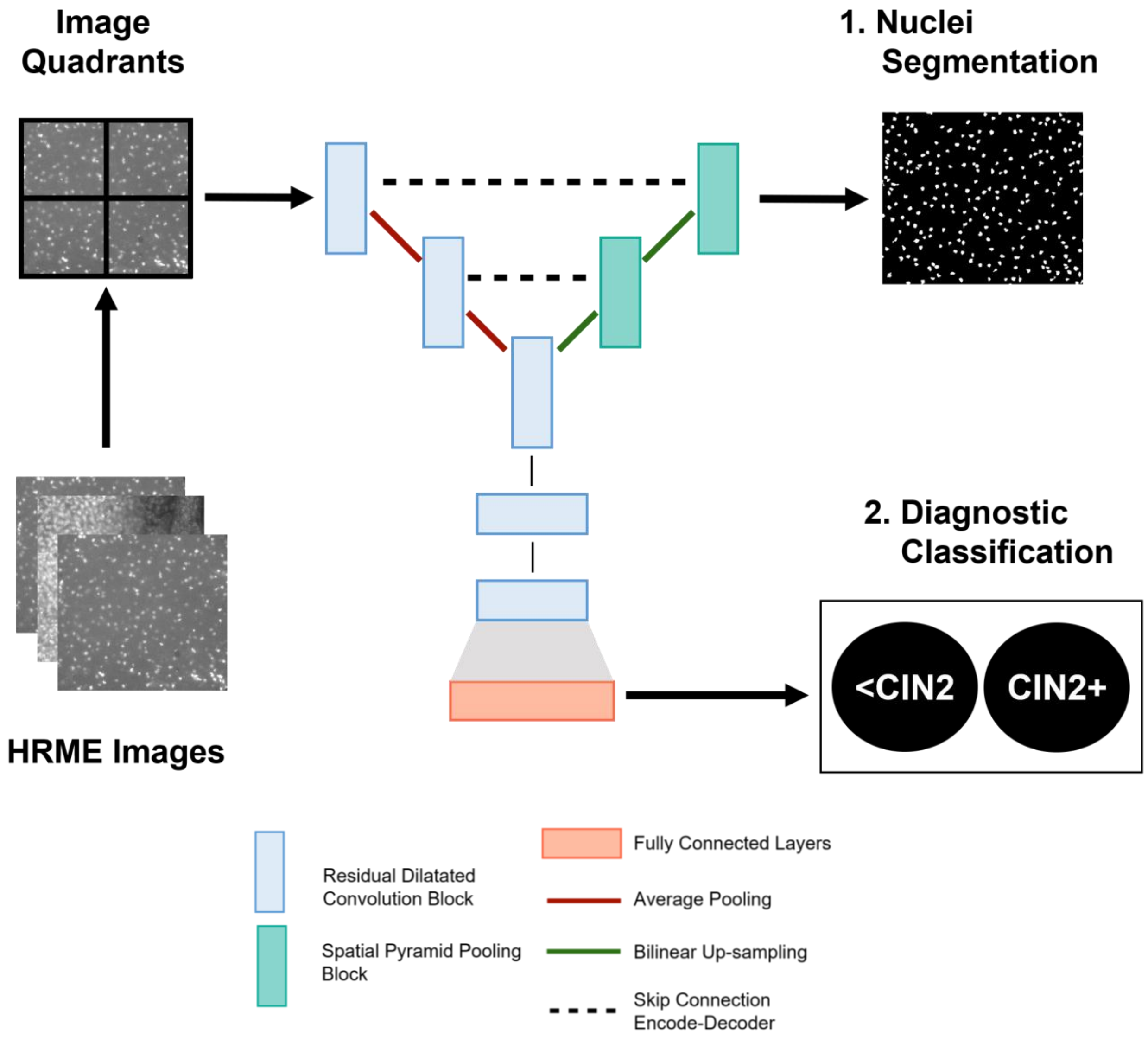
Stage 1: Self-supervised Segmentation

- Handmade segmentations are expensive for HRME images
- Self-supervision:
  - Use traditional computer vision segmentation techniques to generate segmentation and weight masks
- Use this proxy mask to train the network



Stage 2: Diagnostic Branch

Diagnostic Ground Truth:
Histopathology



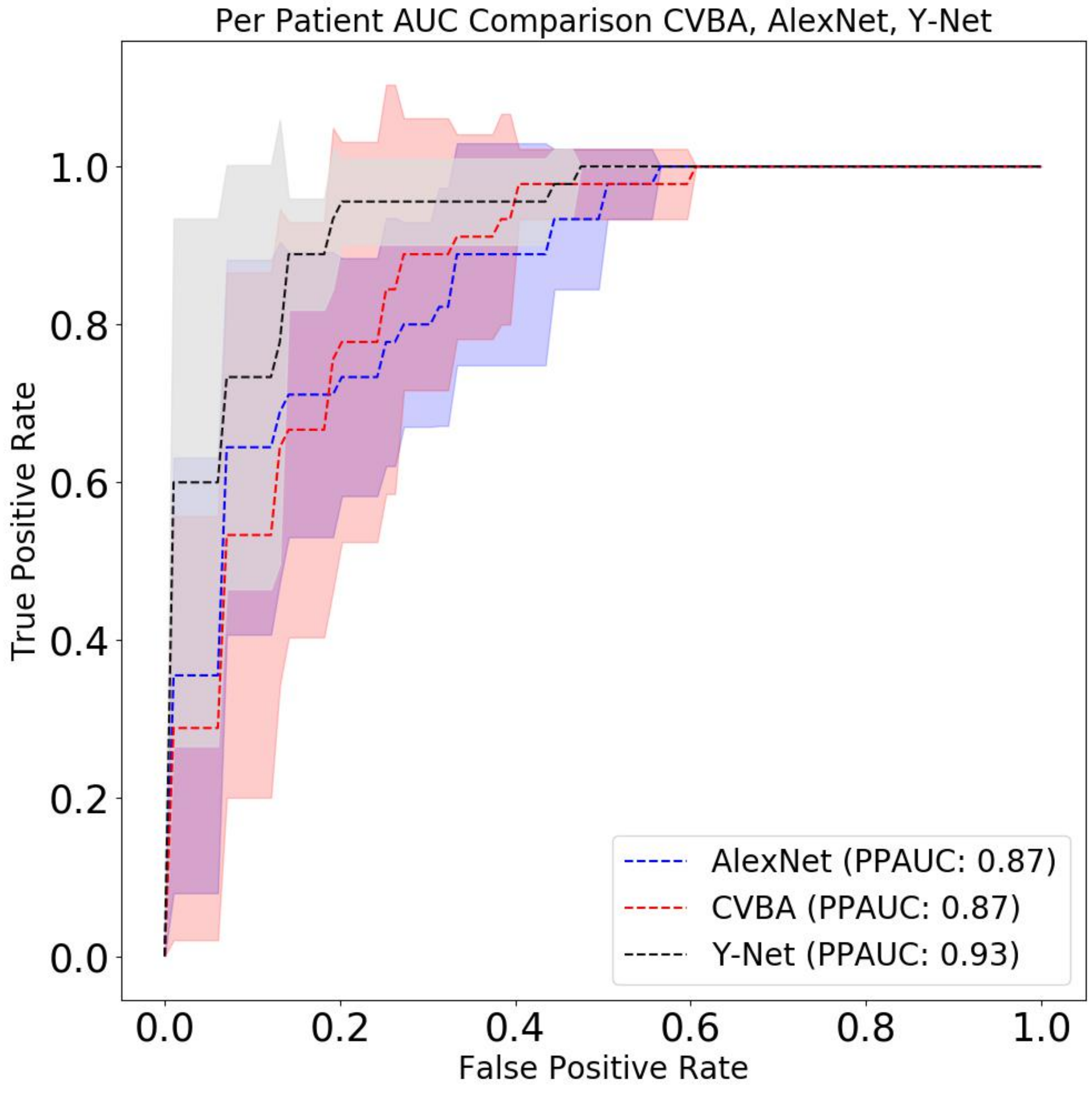
UH2 Cross Validation Results

Y-Net Performance

1. Outperformed all other tested classification architectures

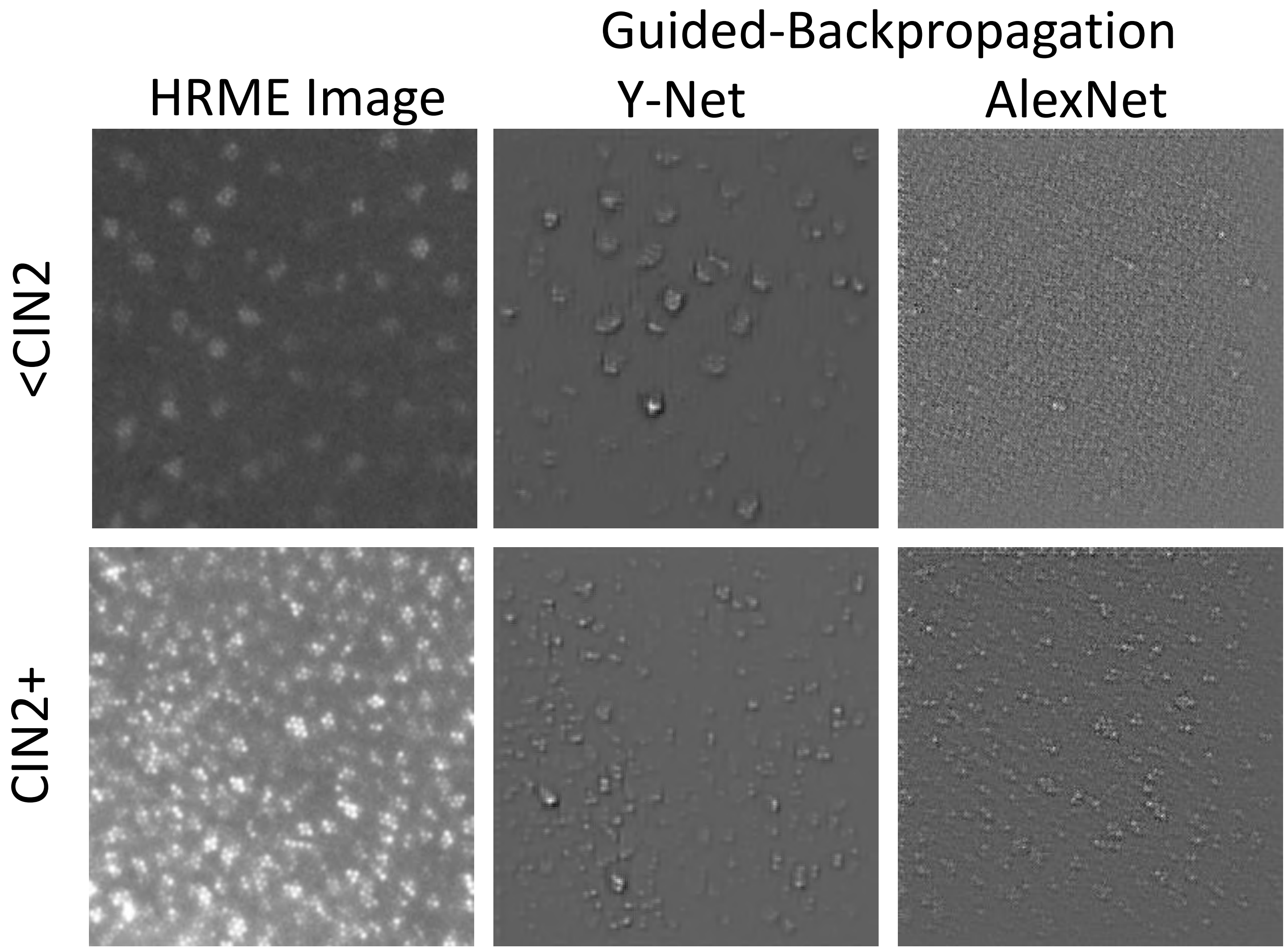
2. Outperformed the current HRME algorithm (traditional computer vision)

3. Had lowest standard deviation across validation folds



Guided Backpropagation

- Relative to our 2nd best performing model trained on histopathology, Y-Net prevents neuron activations originating from non-nuclear pixels



Future Work: Incorporating CLARA Data

	Clinical Studies – Barretos, Brazil		
	UH2	CLARA	UH2+Clara
Number of Patients	144	1486	1630
Number of Sites	229	1901	2130
% of CIN2+ Patients	37 %	28 %	29%

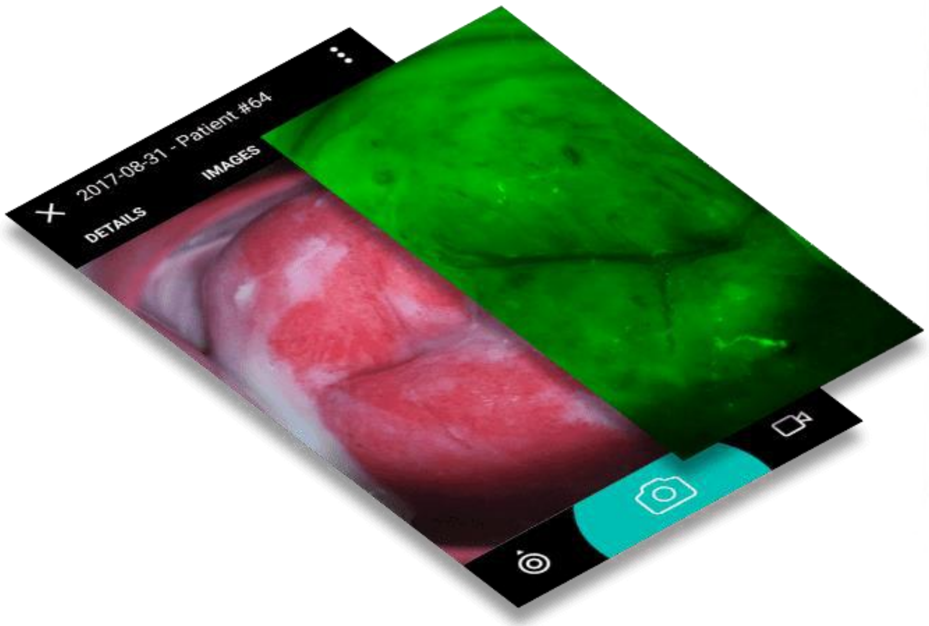
MobileODT
Colposcope System

MobileODT Colposcope

Smartphone based, low-cost colposcope

Features

- White light Images
- Green filtered Images
- Web-portal
- **Automate Visual Evaluation**



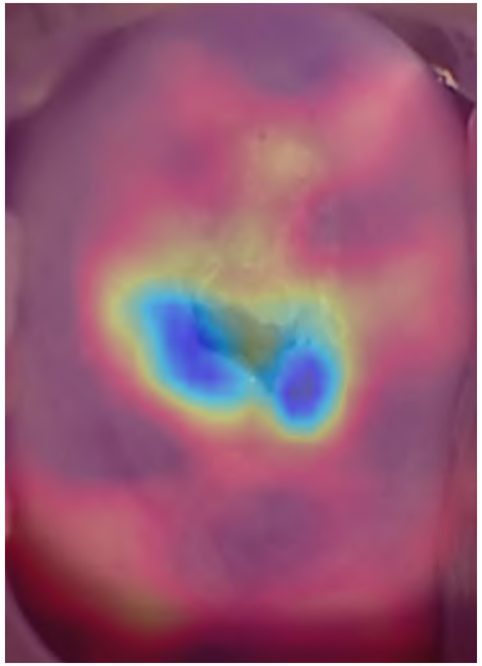
Automated Visual Evaluation Algorithm (AVE)

MobileODT and NCI trained an AVE on digital colposcopy images [6]

- 7,587 images from 3,221 patients
- Colposcopy impression as ground truth
- AUC > 0.9

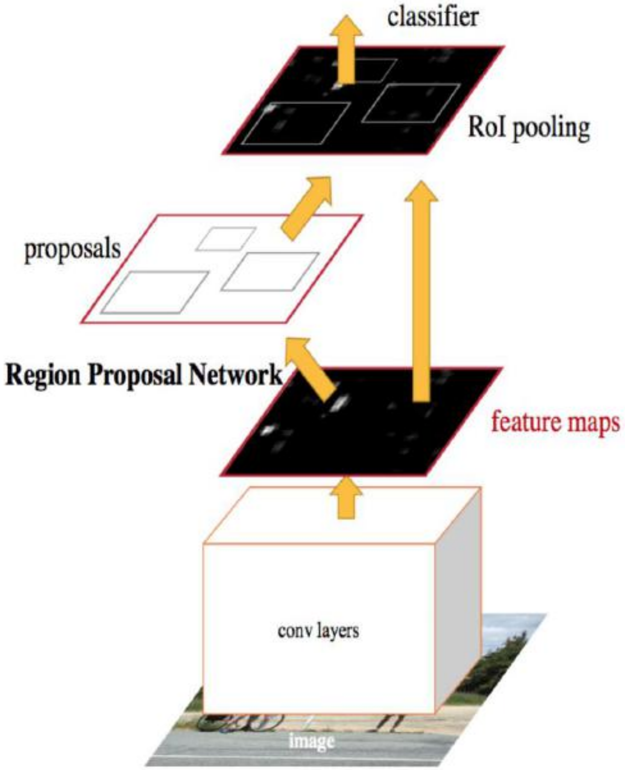
Faster R-CNN built on a VGG-16 backbone

1. Detects the cervix
2. Extracts diagnostic features
3. Predicts lesion or no lesion
4. Returns class activation map

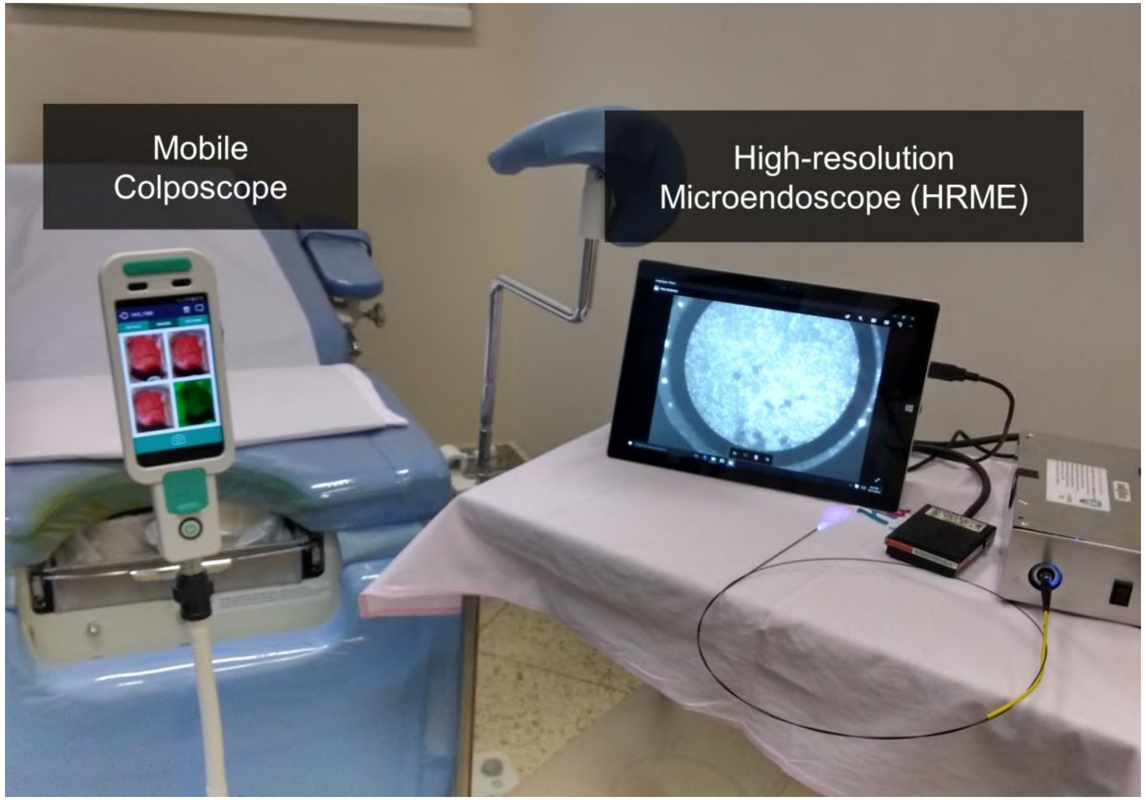


Class Activation Map

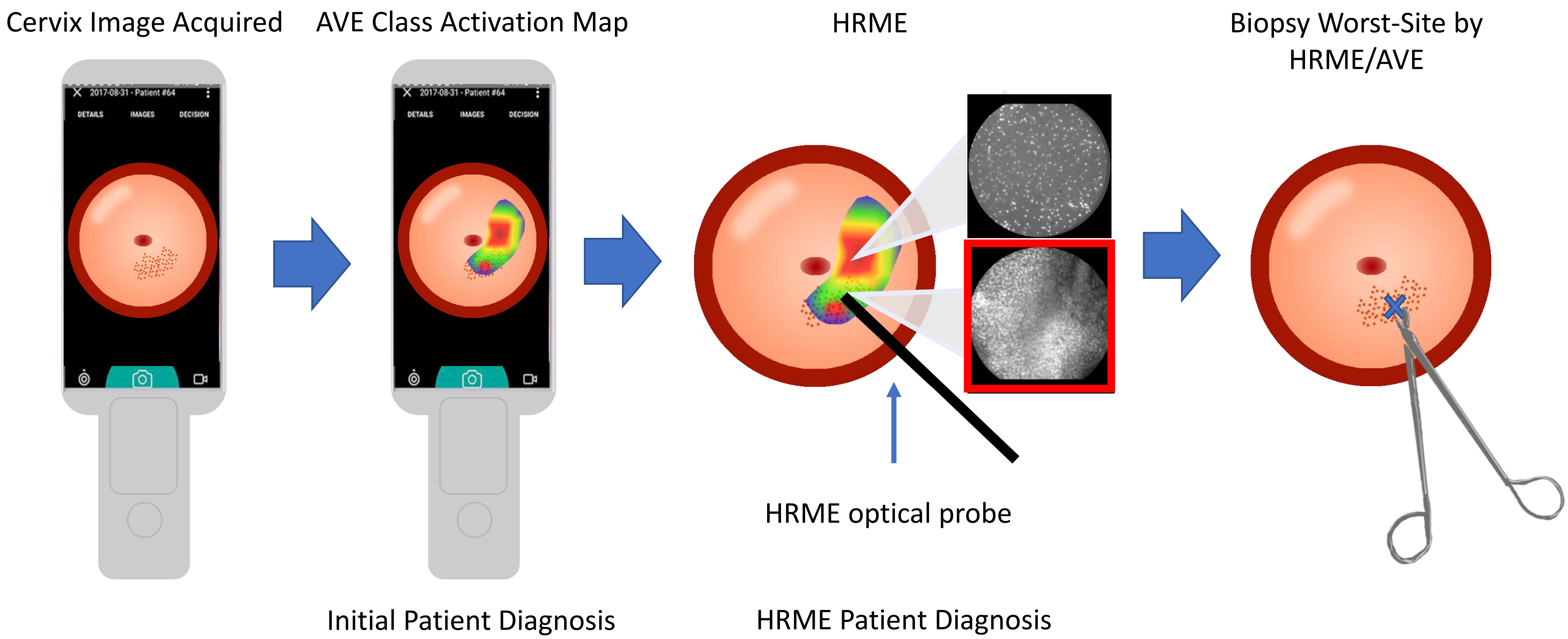
[7]



Multimodal System Integration



EVA System and HRME Sequential Integration



Future Work: Beyond Sequential Integration

Integrating complementary information from both imaging modalities

1. Acquiring a larger dataset of patients with both EVA colposcopy image and HRME images
2. Exploring transfer learning from colposcopy images from other colposcopes to the AVE
3. Developing deep learning architectures to simultaneously learn from colposcopy and HRME images to improve diagnostic performance

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