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)

\(^1\) The Global Cancer Observatory - All Rights Reserved, March, 2019.
Early Stage Detection – Cervical Pre-cancer

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

![Diagram of cervical regions](Image)

- Normal
- CIN1
- CIN2/3
- Cancer
- Require Treatment
- No Treatment

Challenges in Standard of Care for LMICs

Visit 1 Screen
HPV Test

Visit 2 Diagnose
Colposcopy

Visit 3 Treat
CIN2/3
- LEEP
- Conization
- Cancer
- Referred to oncology

Standard of Care

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cervical Swab Brush</th>
<th>Cervix</th>
<th>Acquired Image</th>
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<table>
<thead>
<tr>
<th>Patient</th>
<th>Colposcope</th>
<th>Cervix</th>
<th>Speculum</th>
<th>Acquired Image</th>
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<table>
<thead>
<tr>
<th>Patient</th>
<th>Punch Biopsy</th>
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<tr>
<th>Patient</th>
<th>Microscope</th>
<th>Cervix</th>
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5
Challenges in Standard of Care for LMICs

Visit 1 Screen
- HPV Test

Visit 2 Diagnose
- Colposcopy
- Punch Biopsy
- Histopathology

Visit 3 Treat
- CIN2/3
- LEEP
- Conization
- Cancer
- Referred to oncology

Limitations
- Scarcity of reagents
- Expensive equipment
- Trained professional
- Expensive equipment
- 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

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

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+ \(\geq 120\) and HRME- <120

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

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<td></td>
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<tr>
<td><strong>Number of Sites</strong></td>
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<tr>
<td><strong>% of CIN2+ Patients</strong></td>
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<tr>
<td><strong>Sensitivity (CVBA)</strong></td>
</tr>
<tr>
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</tr>
<tr>
<td><strong>AUC Per Patient (CVBA)</strong></td>
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- 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

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<th>Aggregate Per Patient AUC Validation</th>
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HRME images → ResNet18/AlexNet → Histopathology

< CIN2
CIN2 +
### UH2 5-Fold Cross Validation Benchmark Study

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### Diagram

- **ResNet18/AlexNet**
- **HRME Classification (CVBA)**
  - HRME+
  - HRME-
UH2 5-Fold Cross Validation Benchmark Study

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<td>ResNet18-Quadrants</td>
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- **HRME images**
- Image split into quadrants
- **ResNet18/AlexNet**

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Histopathology

< CIN2
CIN2 +
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.

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]

Image Quadrants

1. Nuclei Segmentation

Residual Dilatated Convolution Block
Spatial Pyramid Pooling Block

Fully Connected Layers
Average Pooling
Bilinear Up-sampling
Skip Connection Encode-Decoder

2. Diagnostic Classification

< CIN2  CIN2+ >

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

1. Nuclei Segmentation
2. Diagnostic Classification

Image Quadrants

HRME Images

Residual Dilatated Convolution Block
Spatial Pyramid Pooling Block
Fully Connected Layers
Average Pooling
Bilinear Up-sampling
Skip Connection
Encode-Decoder

< CIN2  CIN2+ }
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 2\textsuperscript{nd} best performing model trained on histopathology, Y-Net prevents neuron activations originating from non-nuclear pixels.
Future Work: Incorporating CLARA Data

<table>
<thead>
<tr>
<th></th>
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<th>CLARA</th>
<th>UH2+Clara</th>
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<td>Number of Sites</td>
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<tr>
<td>% of CIN2+ Patients</td>
<td>37 %</td>
<td>28 %</td>
<td>29%</td>
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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
Multimodal System Integration
EVA System and HRME Sequential Integration

Cervix Image Acquired → AVE Class Activation Map → HRME → Biopsy Worst-Site by HRME/AVE

Initial Patient Diagnosis → HRME Patient Diagnosis

HRME optical probe
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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