Breast Health Global Initiative

Global Summit on International Breast Health and Cancer Control:

Improving Breast Health Care through Resource-Stratified Phased Implementation

Novel Technology for Detection and Diagnosis

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Low-Cost Automated Ultrasound for Triage of Palpable Breast Lumps in LMICs

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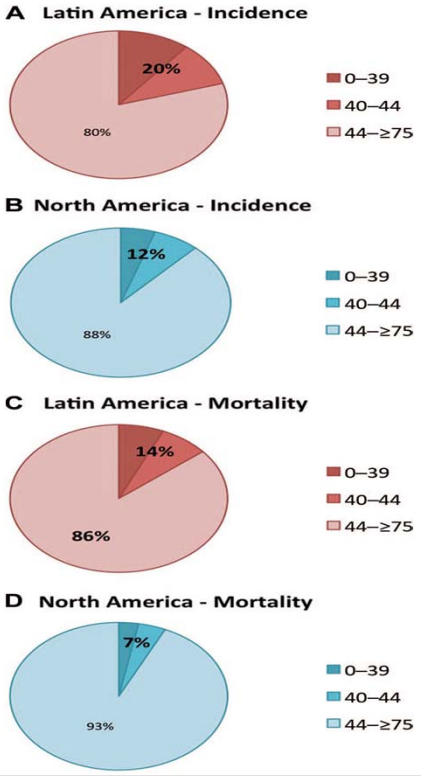
In developing countries breast cancer is more common in young women



- Most breast cancer in women under 50 presents as a palpable mass
- Mammographic screening less effective and available
  - Breast tissue more dense obscuring lesions
  - Biology of breast cancer may well be different with more women presenting with triple negative and Her 2 positive disease
- Most palpable breast masses in women are benign
  - 80% are benign
  - Current medical practice requires biopsy or cyst aspiration to confirm benignity monopolizing scarce medical resources

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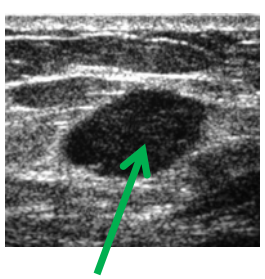
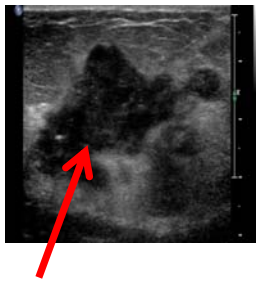
The Solution: Low-Cost Portable Ultrasound with CAD that can be used by non-radiologist health care workers to triage palpable breast lesions

An easy to use portable ultrasound system with CAD that will indicate which palpable lumps are

- Clearly benign: reassure
- Clearly malignant: biopsy
- Probably benign: follow up in six months



benign



suspicious

Stressed healthcare delivery systems could focus their resources on women most likely to benefit from their efforts

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Features and Benefits

- Ultrasound is non-ionizing, non-invasive, less expensive, and more comfortable than mammograms
- *Triage-CAD software is device-agnostic: works with any ultrasound imaging device*
  - User friendly and intuitive interface that requires very little training or experience by local caregivers.
  - Software to assist in diagnosis can be run locally on a low-cost system in environments where there is limited access to high bandwidth, reliable networks for data transfer
  - Computer-aided diagnosis with triage recommendation
- Novel AI algorithms based on deep learning platform
- Triage-software can run as a stand-alone system on DICOM files or JPEG images

Low-Cost Portable US with Triage-CAD

- Portable, low-cost device that is suitable for LMIC environments (all study devices donated by GE)
  - Study device for Phase I validation studies at County USC and Harbor-UCLA Medical Center – **GE Logiq e™**
  - Study device for pilot study with minimally trained operators in Guadalajara: **GE Vscan Dual Probe™**
  - Study device for Phase II studies in Guadalajara: **GE Vscan Extend™**
- **Goal**
  - Portable ultrasound/phone with CAD app that can be applied to image

US Study Device: GE Logiq e

Mexico Study Device: GE Vscan Extend Ultrasound

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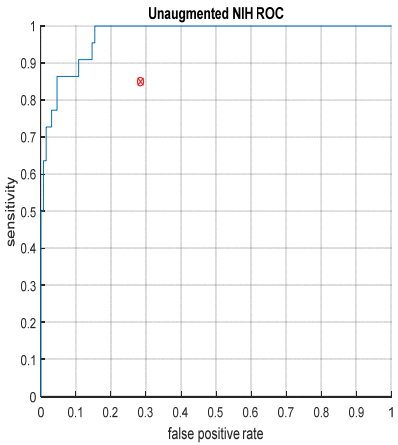
Phase I Validation Study

- Validation study at USC Norris Cancer Center and Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center to assess performance of the triage software compared to standard-of-care and biopsy-confirmed cancers and false positives
- Women 61 years of age or younger with a palpable mass were studied on the study machine as well as the standard of care machine.
- Lesions assessed as BI-RADS 2 by radiologists were designated as benign while any lesions assessed as BI-RADS 4a or higher were sent for biopsy
- Triage software was compared to the performance by radiologists using conventional standard of care

Phase I Validation Study



- Original milestones for study:
  - Achieve a sensitivity of 85%
  - Reduce the number of benign lesions going to biopsy by 40%
- Images collected during validation study
  - 152 lesions
  - 22 biopsy-proven cancers
  - 130 benign lesions
  - 63 benign lesions categorized as BI-RADS 4a or higher by a radiologist and sent for biopsy
- Validation study
  - **Showed an actual sensitivity of 100%**
  - **Reduced the number of benign lesions going to biopsy by 69%**

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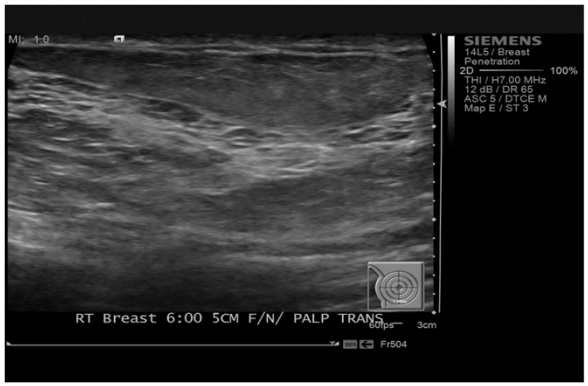
Phase I Validation Study – Image Comparison



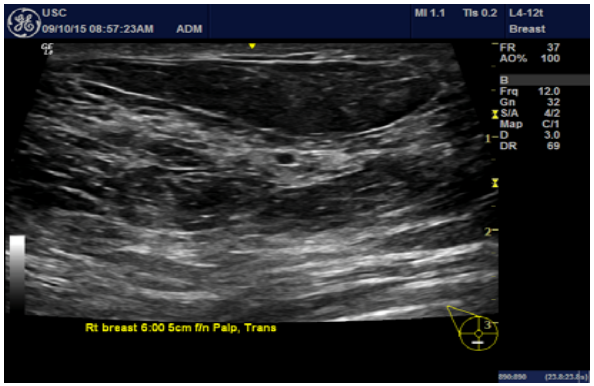


Image comparison – Siemens S2000 vs GE Loqiq e:
Images were collected with the Study Machine (GE Logiq e) and the conventional machine (USC only; Siemens S2000)

Palpable Breast Lump Triage by Minimally Trained Operators in Mexico Using Computer-Assisted Diagnosis and Low-Cost Ultrasound

- Recruited and trained three nonradiologist health care workers in Jalisco, Mexico for pilot study to determine whether they could use the portable ultrasound (GE Vscan Dual Probe) to acquire images of palpable breast lumps of adequate quality for accurate computer analysis
- Images from 32 women with 32 breast masses were then analyzed with the triage-CADx system, generating an output of benign or suspicious (biopsy recommended)
- Triage-CADx outputs were compared with radiologist readings
- Love SM, Berg WA, Podilchuk, C, et al: Palpable Breast Lump Triage by Minimally Trained Operators in Mexico Using Computer-Assisted Diagnosis and Low-Cost Ultrasound. J Glob Oncol. 2018 Aug;(4):1-9.

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CADx-Triage Testing on Data from Pilot

- GE Vscan
  - Is image quality adequate for CAD-Triage Analysis SW? **yes**
  - Are images collected by trainees compared to radiologists adequate for CAD-Triage Image Analysis? **yes**
- The BIRADS scores of the cases break down as follows:
  - 13 BI-RADS 2
  - 5 BI-RADS 3
  - 11 BI-RADS 4A
  - 1 BI-RADS 4B
  - 1 BI-RADS 5
  - 1 confirmed cancer

	Rad-scanned	Trainee-scanned	Rad assessment	Ground truth
Rank	Case #	Case #	BI-RADS	Biopsy Results
1	28	28	Known cancer	Cancer
2	27	27	5	Cancer
3	19	19	4B	Cancer

- CAD-Triage was used to rank the cases by suspicion of malignancy. The table shows the top 3 most suspicious lesions, and their corresponding BI-RADS scores. All three cases are cancers. All other lesions are benign.

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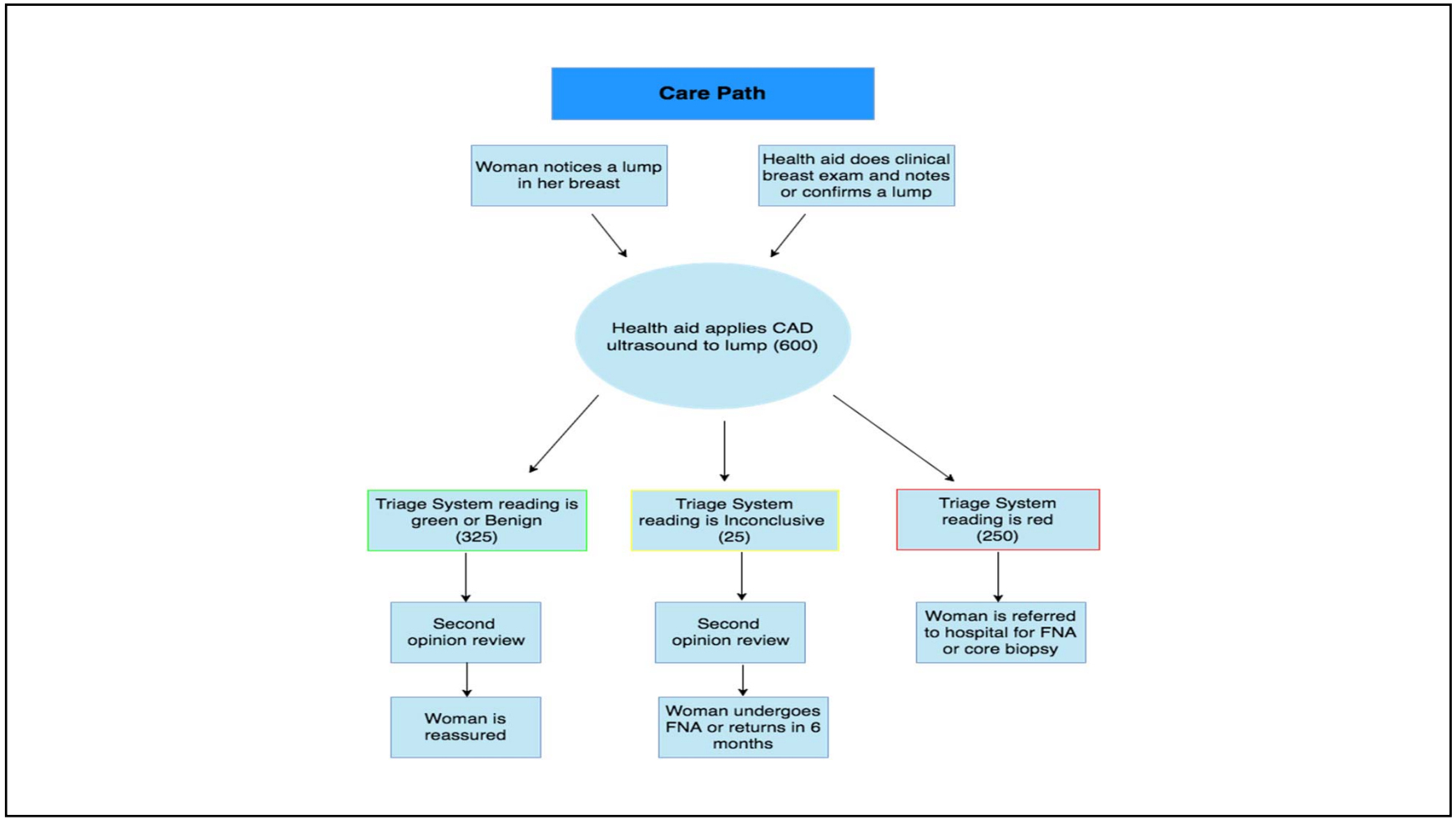
Phase II Data Collection and Validation Studies

Phase	Data Collection Validation Study
Methodology	Non-blinded
Study Duration	1 year 1 year
Study Centers	Hospital Valentin Gomez Farias (ISSSTE) Zapopan, Jalisco, Mexico Instituto Mexicano del Seguro Social (IMSS) Tijuana, Mexico
Principal Investigator	Dr. Susan Love Local PI: Dra Ana Lila Lopez Aldrete, Dr Jorge F. Tokunaga Fujigaki
Objectives	*Objective I:* Determine sensitivity and specificity of CAD Ultrasound System in use in a LMIC environment with a low-cost portable device *Objective II:* Determine the acceptability and feasibility of ultrasound for breast cancer triage in LMIC environment, with expert radiologist oversight
Number Subjects	Phase 1: 500 (data collected to train/test Triage System) Phase 2: 600 (Validation Study – measure Triage performance in clinical setting)
Diagnosis and Inclusion Criteria	Women with a palpable breast lump Ages: 18 years of age and older
Study Product	Triage System with low-cost portable ultrasound imaging device



Goal

- Readily available portable ultrasounds in the women's clinics, to be used by first level health care providers in LMIC countries with potential to migrate to primary care providers in US
- Develop a CAD app that can be incorporated into either a smartphone-based handheld ultrasound device or a phone/tablet paired with a portable ultrasound
- Test app in appropriate clinical setting
- Identify hardware partner(s)

Potential: Immediate treatment of palpable benign lumps by needle aspiration or cryotherapy
Needle biopsy of suspicious lumps for molecular analysis using methylation followed by cryotherapy

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iBreastExam
Specificity in a Screening Population

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October 15, 2018

Disclosure

- I am a co-inventor of this technology
- Drexel University College of Medicine owns the patent
- I have no financial relationship with UE LifeSciences (the parent company of the iBreastExam)
  - But they did buy my plane tickets and lend me a room in the Airbnb

Statement of the problem

- Mammogram screening is excellent in resource rich countries (in resource rich parts of…)
- First line mammography is very expensive.
- First line mammography reduces sensitivity.
- Pre-screening (triage) can reduce reliance on mammography (or clinician operated ultrasound).
- Classic strategies for triage in low resource populations include:
  - Breast self awareness
  - Clinical Breast Exam (health worker breast exam)
  - Risk assessment

iBreastExam Solution

- 4x4 piezoelectric (PZT) sensor array measures elastic modulus in RT.
- Sensors measure tissue compression and stiffness by making top-down tactile palpations from skin surface.
- Applies a gentle force and measure subtle displacements electrically, all within the sensor - electronic palpation device.

- Standardized & objective breast exam to identify clinically relevant lumps at the POC.
- Enables resource-conscious pre-screening.
- Usable by CHWs w/ minimal training.

iBE USA studies to date

- 1st study Feasibility[1]
  - 40 pts with clinically significant lesions
  - 4 finger prototype probe
  - 46 lesions
  - 15 cancers
  - 87% sensitivity for lesion detection

- 2nd study* Sensitivity[2] FN rate
  - 78 pts with clinically significant lesions
  - 16 finger iBE device
  - 77 lesions (quadrant w/abnl findings)
  - 12 cancers
  - 86% sensitivity for lesion detection
  - 83% sensitivity for cancer
  - 89% specificity (compared to negative quadrants)

*Funded by State of PA CURE Grant # 4100059198

•1.JACS 2013 216: 1168-73

2. WJSO 2016 14:277

Global Implementations & Validations

- ***150,000+ enrolled in multiple implementation projects globally***
- *5-7% are positive on iBreastExam*
- *Follow-up rate is appx. 70–80%*
- *120 confirmed diagnoses*
- *Single largest implementation in Maharashtra, India (75,000+)*

- ***10,000+ enrolled in 11 IRB cleared clinical and implementation studies***
- *Studies aim to assess:*
  - *Efficacy to detect clinically relevant lumps (BIRAD 0, 3, 4, 5)*
  - *Detection rate, Follow-up rate, Usability, Feasibility & Acceptability*

iBE 3rd United States study*

- In a screening population with best chance of true diagnosis:
  Specificity (False Positive Rate) and Negative Predictive Value (NPV)
- All women for screening mammography or additional images after screening mammography
- Enrolled women get CBE, iBE, and Mammograms
- Follow up based on Mammo or symptoms (dx mammo, ultrasound, MRI, biopsy)
- Mammogram results defined as:
  Birads 1-2 = Negative Birads 0,3,4,5,6 = Positive
- Stats: CBE, iBE to each-other and Mammogram findings
  Sensitivity, Specificity, PPV, NPV Kappa - agreement

Funded by State of PA CURE grant # 4100059198

iBE 3rd United States study

- 516 women enrolled
- 490 iBE completed
- 501 had Mammo and CBE
- 48 had Ultrasound
- 22 biopsies
- 7 MRI
- 5 women with cancer identified (2 bilateral)

Can iBE tell who needs a mammogram?

•*iBE vs. Mammogram*

Sensitivity: 80%

Specificity 35%

NPV: 99.5%

Kappa 0.08 (low)

	Mammogram negative (1,2)	**Mammogram positive (0,3-6)**
iBE negative	363	22
iBE positive	90	12

•*iBE vs. CBE*

Kappa 0.5 (good)

	CBE negative	**CBE positive**
iBE negative	373	15
iBE positive	50	51

Can iBE tell who doesn't have cancer?

•*Mammogram vs. Cancer*

Sensitivity 100%

Specificity 94%

NPV 99.8%

•*iBE vs. Cancer*

Sensitivity 60%

Specificity 80%

NPV 99.5%

•*CBE vs. Cancer*

Sensitivity 60%

Specificity 87%

NPV 99.5%

	Not Cancer	Cancer
Mammogram negative	467	0(1)
Mammogram positive	29	5(6)

	Not Cancer	Cancer
iBE negative	386	2(3)
iBE positive	99	3(4)

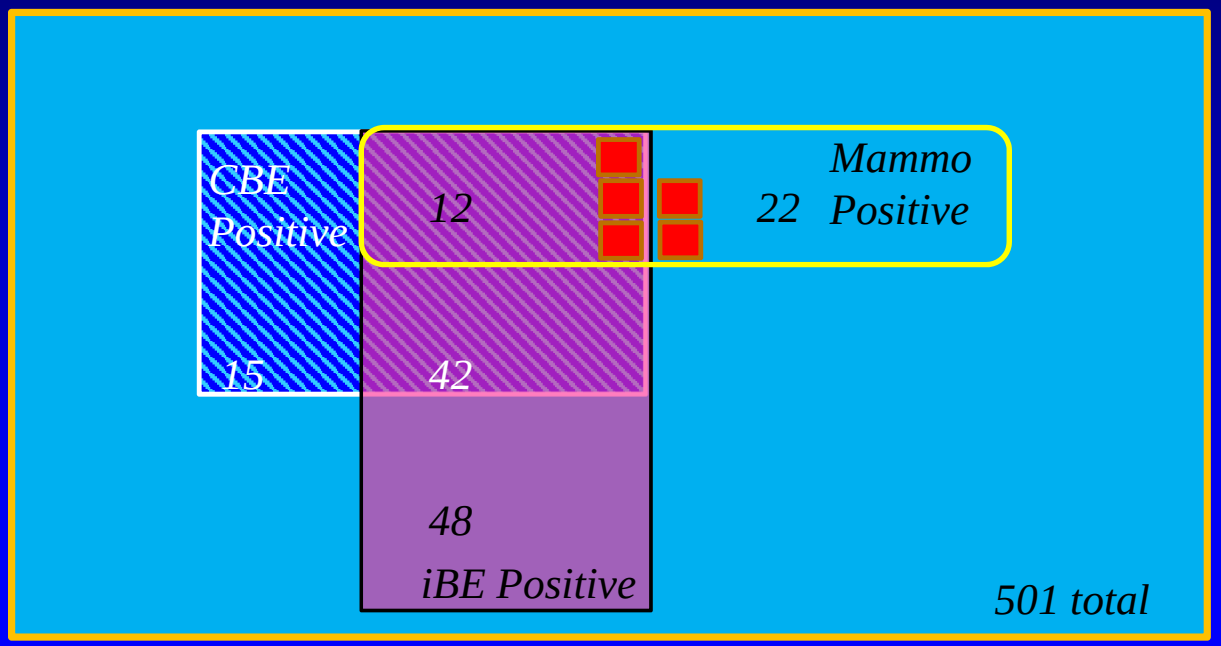
	Not Cancer	Cancer
CBE negative	430	2(3)
CBE positive	66	3(4)

iBE 3rd United States study

- Cancer Detected by iBE, CBE, :
  1. 3cm Left palpable. Right DCIS mammo only
  2. 1.2cm Right invasive and 1.7cm Left invasive both palpable
  3. 2.7cm Right invasive palpable retro-areolar

- Cancer Not Detected by iBE or CBE:
  1. 3mm Right invasive
  2. 1.3cm Right invasive

iBE, CBE, Mammo Results Map



Other screening studies

- Bangalore, India 2016

989 asymptomatic & 20 symptomatic

Median age 47 yrs.

All received iBE, CBE and MMG/USG

8 cancers diagnosed

iBE Vs. screening MMG

Sensitivity 84 %

Specificity 94 %

NPV 98 %

- Rio, Brazil 2018

226 asymptomatic at 2 primary care clinics.

Median age 54 Yrs.

217 rcvd. MMG, 161 rcvd. US, 152 rcvd. MMG & US

9 cancers diagnosed

iBE Vs. MMG + USG

Sensitivity 82 %

Specificity 87 %

NPV 99 %

Summary

- iBE provides excellent NPV and performed equivalent to CBE
- iBE has a record of sensitivity over 80% for clinically significant lesions.
- 150,000 exams in LMIC, iBE has proven to be practical in our target population and compatible with multiple types of delivery models.
- iBE and CBE can synergize as pre-screening tools to significantly reduce the population that needs additional screening.
- Increasing the accuracy of CBE and building a program around a portable and inexpensive device can help with participation.
- Technology is only part of the answer to the problem of access to screening.
- Once a breast problem is identified, there is still the need for diagnostic imaging, biopsy and treatment…

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