

# Point-of-Care technologies for cervical cancer screening

Carla Chibwasha, MD MSc  
UNC Global Women's Health  
02 October 2018



World Cancer Congress  
Kuala Lumpur, Malaysia  
1–4 Oct 2018

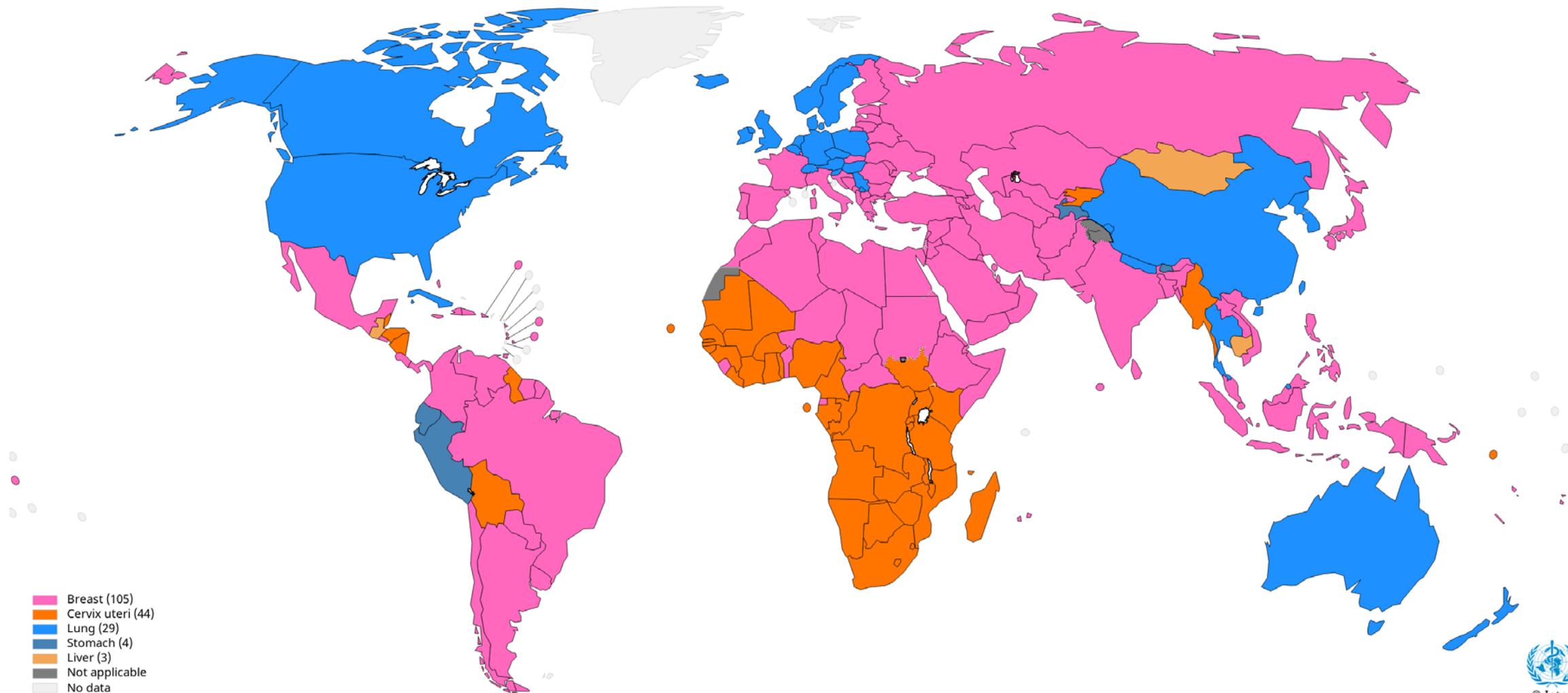
Strengthen  
Inspire  
Deliver



THE UNIVERSITY  
of NORTH CAROLINA  
at CHAPEL HILL

Disclosure of interest: None declared

# Leading cause of cancer death in women – by country (2018)



## Lifetime Risk of Cervical Cancer in South Africa





# Rationale for point-of-care HPV screening

- In randomized trials, HPV screening predicts cervical disease better than VIA or cytology
- The availability of POC molecular testing may expand access to cervical screening through HPV “test-and-treat” strategies
- HPV self-testing may also improve cervical screening coverage

# Methods

- 3 performance validation studies
  - Zambia (CCRCI)
    - 200 HIV-infected women
    - Xpert HPV, OncoE6, VIA, and DC compared to histology
  - South Africa (VICAR)
    - 1,161 HIV-infected women
    - Xpert HPV and Hybrid Capture II compared to histology
  - South Africa (VHX)
    - 350 HIV-infected women
    - Agreement between self- and provider-collected Xpert HPV

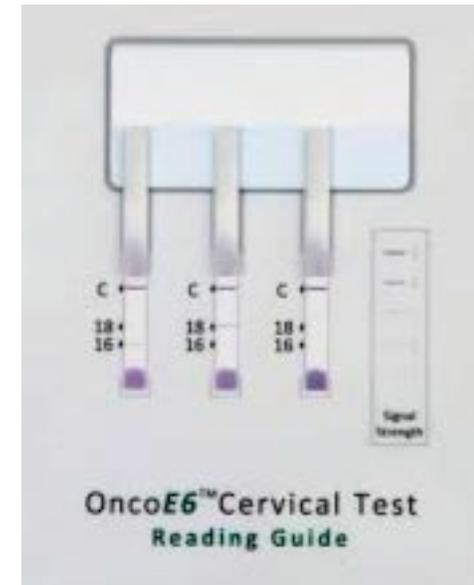
# Xpert HPV

- Qualitative real-time PCR
- Detects 14 hrHPV types
- 1 hour runtime



# OncoE6

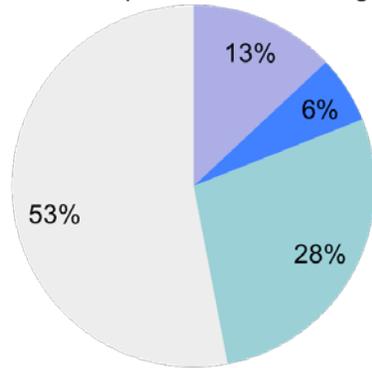
- Oncoprotein lateral flow test
- Detects E6 from 2 hrHPV types
- 1.5 hour runtime



# Results: CCRCI

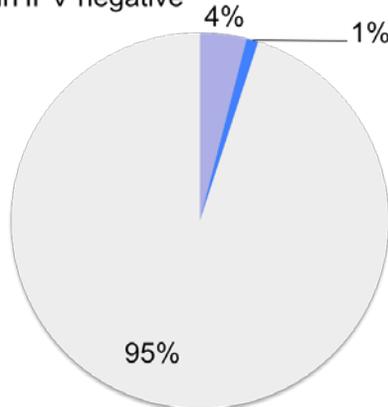
## Xpert HPV

■ HPV-16 positive    ■ HPV-18/45 positive  
■ Other hrHPV positive    ■ hrHPV negative



## OncoE6

■ HPV-16 positive    ■ HPV-18 positive  
■ hrHPV negative



## Clinical Performance Using CIN2+

	Sensitivity (95% CI)	Specificity (95% CI)
Xpert HPV	88 (71-97)	60 (52-68)
OncoE6	31 (16-50)	99 (97-100)
VIA	48 (30-67)	92 (86-95)
DC	59 (41-76)	88 (82-93)

# Results: VICAR

## Clinical Performance Using CIN2+

	<b>Sensitivity (95% CI)</b>	<b>Specificity (95% CI)</b>	<b>PPV (95%CI)</b>	<b>NPV (95% CI)</b>
Hybrid Capture II	92 (87-96)	51 (48-55)	42 (38-46)	94 (91-97)
Any Xpert HPV	88 (84-93)	48 (45-52)	40 (37-44)	91 (88-95)

# Results: VHX

## Agreement Between Self- and Provider-Collected Xpert HPV samples

	<b>Self</b>	<b>Provider</b>	<b>Kappa (95% CI)</b>	<b>Agreement</b>
Any hrHPV	45%	37%	0.65 (0.52-0.77)	83%
HPV16	8%	6%	0.74 (0.53-0.96)	97%
HPV18/45	12%	8%	0.69 (0.48-0.89)	95%
HPV31/33/35/52/58	26%	20%	0.66 (0.51-0.80)	88%
HPV51/59	8%	6%	0.61 (0.34-0.87)	96%
HPV39/68/56/66	18%	15%	0.80 (0.67-0.93)	95%

# Conclusions

- POC testing circumvents the logistic and operational barriers associated with traditional, off-site laboratory testing
- Our validation studies confirm that Xpert HPV performs equivalently to current FDA-approved HPV tests
- We also observed robust agreement between self- and provider-collected Xpert samples, suggesting a role for self-testing in future HPV test-and-treat programs

# Future Directions

- Larger trials and programs are needed to explore optimal implementation strategies for POC technologies, including:
  - HPV screening followed by triage with VIA, cytology, and/or colposcopy
  - Approaches that include same-day treatment
  - The role of mHealth solutions
- Cost-effectiveness analyses are also needed

# Acknowledgements



THE UNIVERSITY  
of NORTH CAROLINA  
at CHAPEL HILL



**GAUTENG PROVINCE**  
HEALTH  
REPUBLIC OF SOUTH AFRICA



TREATING HEALTH SERIOUSLY



**Weill Cornell  
Medicine**  
Medical College



**CIDRZ**



**NATIONAL HEALTH  
LABORATORY SERVICE**



National Institutes  
of Health



**USAID**  
FROM THE AMERICAN PEOPLE



# GE Oncology

Claire Goodliffe  
Global Oncology Director



Dr. Suzette Delalogue  
Gustave Roussy



## One Stop Breast Clinic

*Accelerating access to diagnosis & treatment*



SURA



# GE Oncology

- Provide technology, solutions and service so clinicians can make better decisions for their patients.
- Help make patients cancer care journey more efficient and personalized.

## GEHC Businesses

11 Imaging Businesses

- Surgery & Interventional
- Radiotherapy Planning

Centricity MDT

Cell Therapy

Bioprocessing

GE Partners

Global Design

Service

## Projects

One Stop Clinic

The Symptomatic Clinic

Carepathway  
Management

## Research

Imaging

CAR T Therapy

Treatment Monitoring

Patient Behavior

Risk Assessments

Clinicians Practice  
Behavior

## Partners

Pharma

Scientific Societies

Charities

Governments

Cancer Hospitals



# Delays in diagnosis and treatment

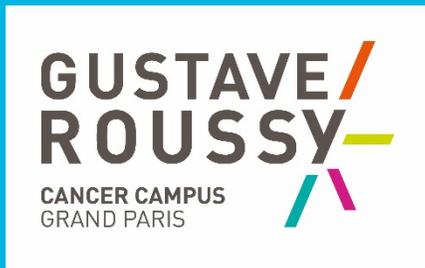
**The low survival rates in developing countries are explained by scarcity of early detection programs, resulting in a high proportion of women presenting with late-stage disease at diagnosis, along with the lack of adequate diagnosis and treatment facilities<sup>1</sup>**

# Gustave Roussy

The premier European Cancer Centre –  
Villejuif France.

Centre for patient care, research and  
teaching, and patients with all types of cancer

The first dedicated One Stop Breast Clinic in  
France



3 500

employees

545

doctors

1400

nursing staff

450

researchers

# One Stop Breast Clinic

Diagnostic Breast Cancer Clinic for women with signs or symptoms of Breast Cancer.

Designed by Dr. S. Delaloge and team in 2004 to receive women from the French screening program.

Organized and efficient care pathway that fosters same day diagnosis

19,000 women have been treated at the clinic since 2004



1. The challenge of rapid diagnosis in oncology: Diagnostic accuracy and cost analysis of a large-scale one-stop breast clinic European Journal of Cancer 66 (2016) 131e137



# Collaboration

GE Healthcare sponsored the data mining of the breast clinic in 2012.

The analysis confirmed the clinic diagnosed 75% of patients the same day

**Oxford Analytica** confirmed Gustave Roussy's findings.

One Stop Clinic breast study published in **European Journal of Cancer 2016**



1. The challenge of rapid diagnosis in oncology: Diagnostic accuracy and cost analysis of a large-scale one-stop breast clinic European Journal of Cancer 66 (2016) 131e137

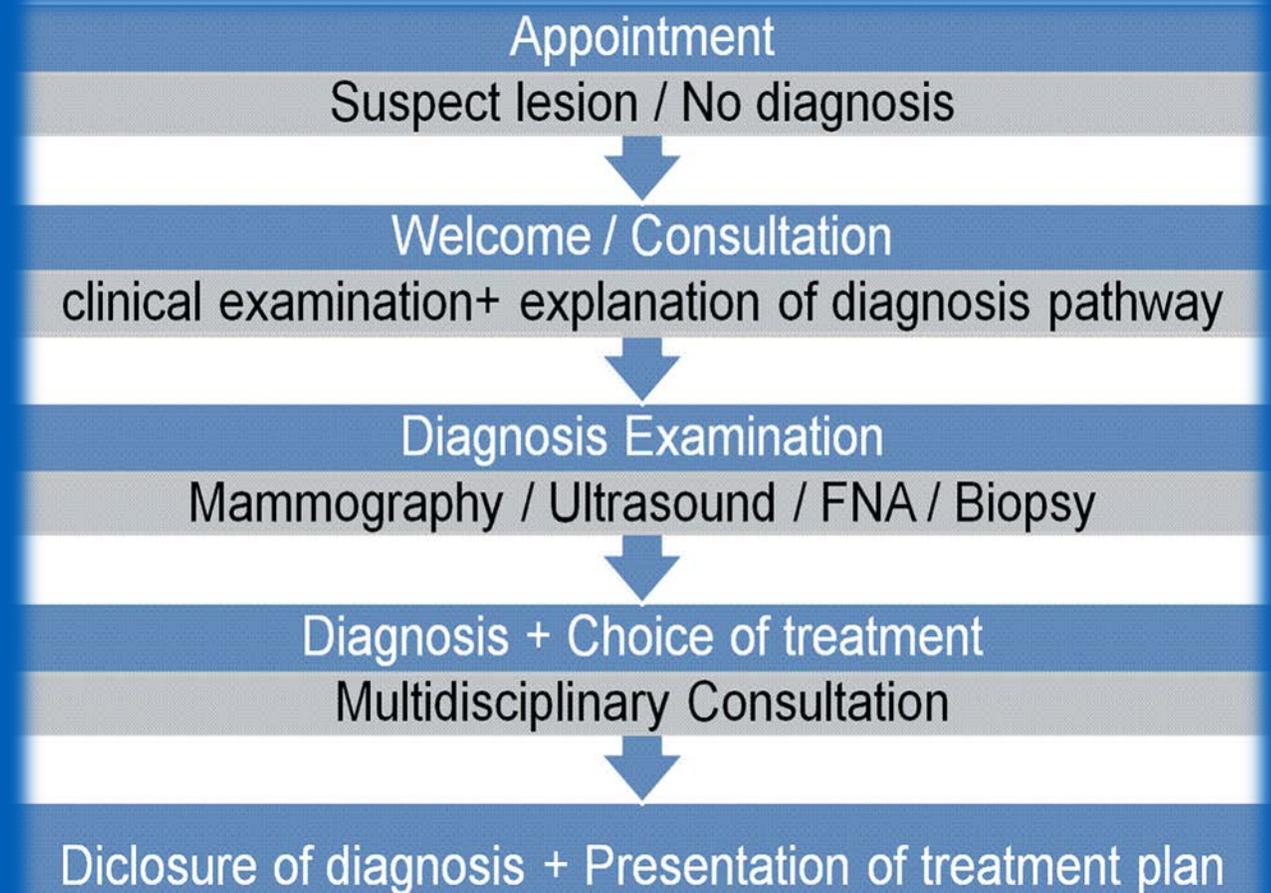


# One Stop Breast Clinic

## Clinic Objectives

- Improve quality of diagnoses
- Reduce time intervals to render diagnoses
- Lower costs of the complete procedures
- Improve patients' satisfaction
- Improve pain management
- Reduce patients' anxiety
- Improve patients' information for recalls

## Patients' Care Pathway



# Clinical Triage of Patients

- **Patients referred to breast center for suspect lesions (BI-RADS 3,4,5)**
- **All patients with solid tumors receive FNA to rule out benign lesions and detect malignancy**
- **Microcalcifications are biopsied with stereotaxy and those patients receive a diagnosis on another day during the week**
- **Malignant patients have core biopsies @ lumpectomy or surgery**

## Multidisciplinary Team Members

3 Radiologists  
1 Breast Surgeon  
1 Oncologist  
1 Cytologist

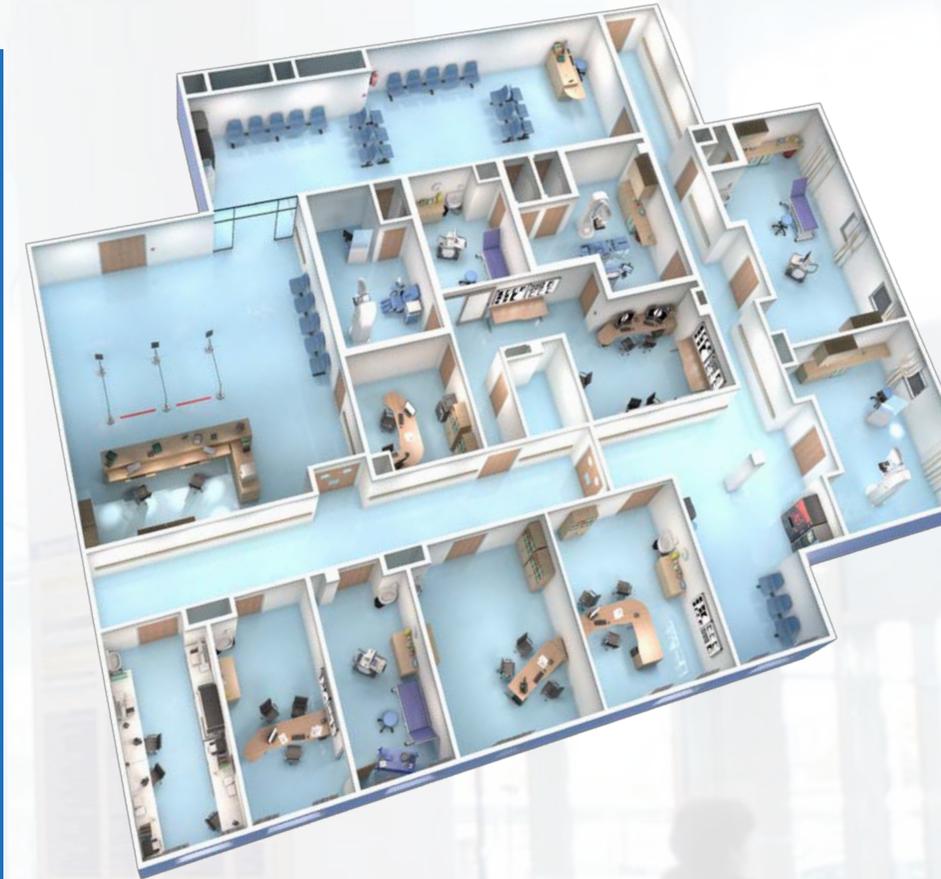
1 coordination nurse  
1 pathology technician  
1,2 nurse  
1,5 imaging technician  
1 person to welcome patients  
3 medical assistants



# Published Results

## Clinical and Economic Outcomes

- 75% of patients have their results on the same day.<sup>1</sup>
- 96% of FNA patients were able to leave with a diagnosis the same day.
- Sensitivity 97,2% & specificity: 99,7% <sup>1</sup>.
- Biopsies avoided in 10% of all patients who underwent a CESM <sup>1</sup>.
- Up to 50% reduced total cost per patient for benign cases and by 33% of costs for malignant cases. <sup>1</sup>
- Patients very satisfied with the one-day diagnosis. <sup>1</sup>



# One Stop Breast Clinic

## Identification of Pilot Sites

Gustave Roussy and GE Healthcare developed a partnership

Set up pilot clinics in countries that would benefit the most from diagnosis in the same day.

GE evaluated pilot sites :

- Colombia
- Mexico
- Algeria
- Kenya

# MEDELLÍN

Colombia

### Medellin

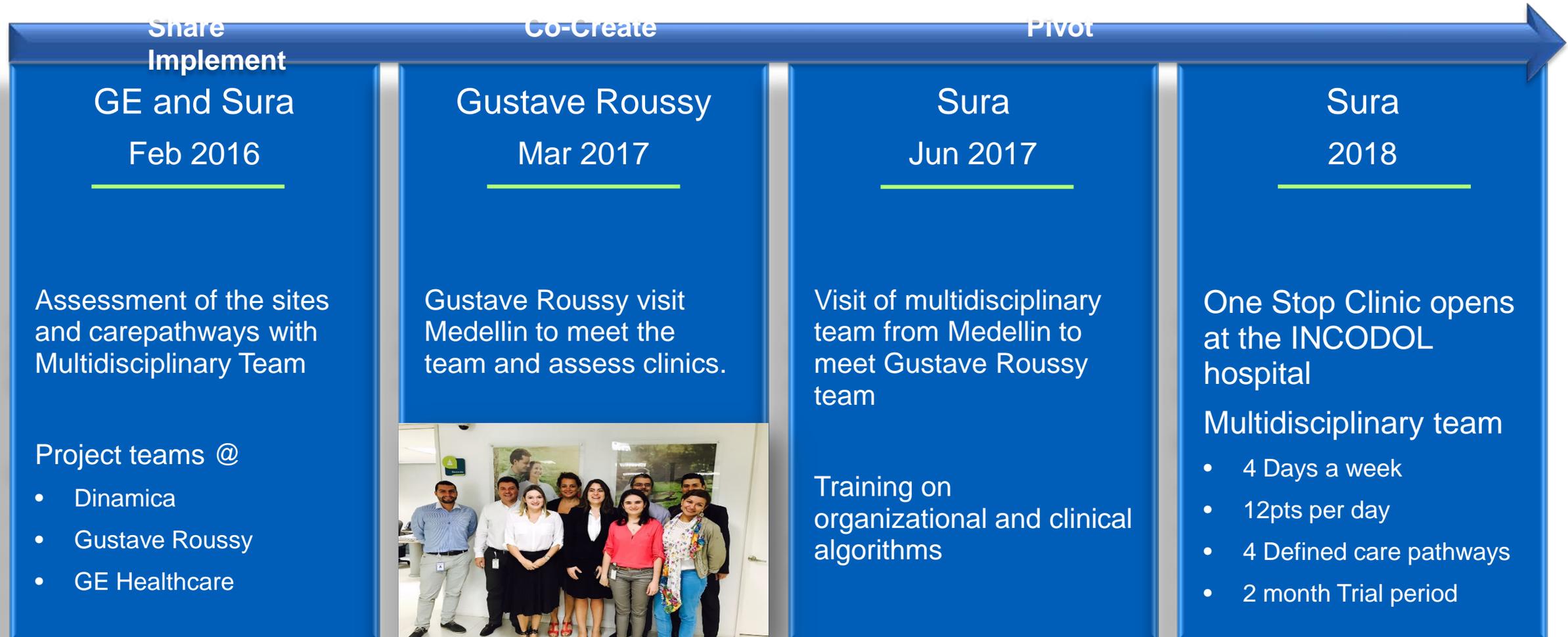
- Screening population of 123,000 women
- Serve 62% of screening population
- Projected 5000 patients with BIRADS 4 & 5



1. The challenge of rapid diagnosis in oncology: Diagnostic accuracy and cost analysis of a large-scale one-stop breast clinic European Journal of Cancer 66 (2016) 131e137



# One Stop Clinic adapted to Medellin, Colombia



# Sura – Tempo Para Ti

« Time For You »

## 4 Carepathways

Asymptomatic

FU BIRADS 3

FU BIRADS  
4&5

Surveillance

- **Patients** 15 per day
- **Staff** Nurse – radiologist – pathologist, mastologist – healthcare personnel
- **Education** GPs training via webex  
Telemarketing to patients  
Dedicated web site
- **Cost** 7-30\$ HMO subsidizes 80% of the co-pay



**SURA HMO** (Health Maintenance Group)  
**Insurance company**



TIEMPO   
PARA TI

*Diagnóstico especializado creado  
para acompañar a las mujeres  
en el cuidado de sus senos*

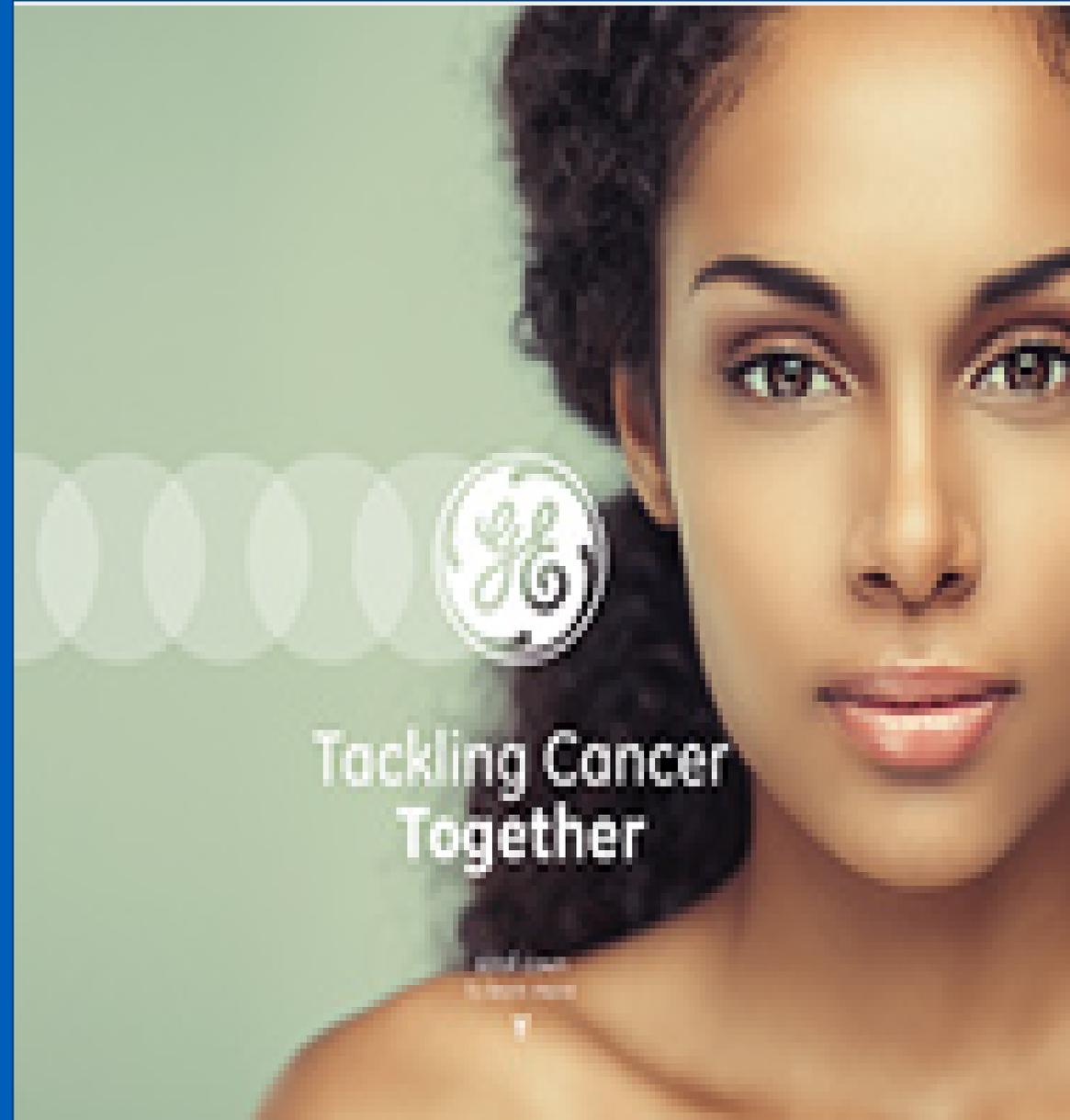
« Time For You »



# Learnings

- Assessment of the pilot sites. **Follow the patient journey**
- Clinical pathways are **reasonable and achievable**
- Training needs - **make everyone feel comfortable**
- Stakeholder buy in and lock down with contracts
- **Small and skilled** project team
- Run the project like a business
- Financial support and governance
- **Be ready to pivot** if you face barriers
- **Embrace diplomacy and empathy**

**Keep the patient at the centre of your goals**



# GE Oncology

Fostering best practices between institutions to improve access to diagnosis and treatment

## New Projects

- Clinic for post-treatment cancer patients & survivors
- Accelerating time to brain cancer diagnosis

# Role of technological advances in breast cancer early detection in limited resource settings

**R. Sankaranarayanan MD**

Senior Visiting Scientist, WHO-IARC, Lyon, France

Senior Medical Advisor, RTI International-India

Former Special Advisor on Cancer Control and Former

Head of Early Detection & Prevention Section, WHO-

IARC, Lyon, France

Conflicts of Interest: None

# Point-of-care testing: what it means?

- *An investigation done at the time of the consultation with instant availability of results to make immediate and informed decisions about patient care*
- *The intention is to perform diagnosis and treatment in the fastest time frame*
- *Done at homes, clinics, doctors offices, primary care settings, hospitals, emergency services, field settings*

# Early detection of cancer: two major strategies

- Screening programs: targets asymptomatic people
- Early diagnosis: targets in symptomatic patients
- Population and health provider awareness as well as adequately developed health systems are critical for both the above approaches

# Early diagnosis

- Targets symptomatic people
- Prompt symptom recognition and physical examination are critical
- Awareness among people and general practitioners and primary care physicians is vital
- Prompt referral and investigations are vital

# The utility of different early detection tests in breast cancer early detection

Early detection test	Screening programs	Early diagnosis
<b>Screen film mammography</b>	Routinely used (screening mammography)	Routinely used (diagnostic mammography)
<b>Digital mammography</b>	Routinely used (screening mammography)	Routinely used (diagnostic mammography)
<b>Digital breast tomosynthesis</b>	No defined role	In selected situations mostly in high income countries
<b>Computer assisted detection</b>	Useful in selected situations	Clinical data absent
<b>Ultrasonography</b>	Not as a primary screening tool, but adjunctive to mammography	Routinely used
<b>Magnetic resonance imaging</b>	No defined role	Useful in selected situations such as high risk women with BRCA mutations, 20% or more lifetime risk
<b>Positron emission tomography</b>	No role	Clinical data absent; not used
<b>Clinical breast examination</b>	Useful adjunctive to mammography/ultrasonography	Routinely used
<b>Breast self- examination</b>	May facilitate participation in screening programs	May facilitate early diagnosis
<b>Breast awareness</b>	May facilitate participation in screening programs	May facilitate early diagnosis

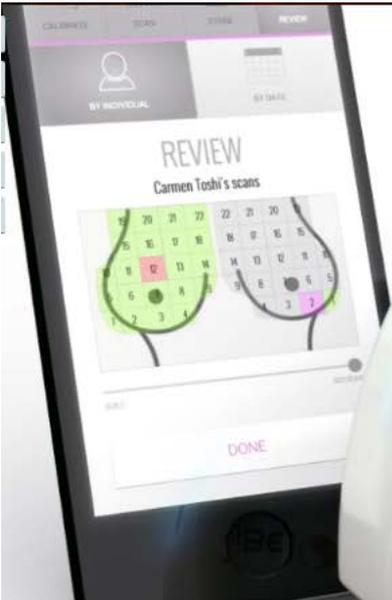
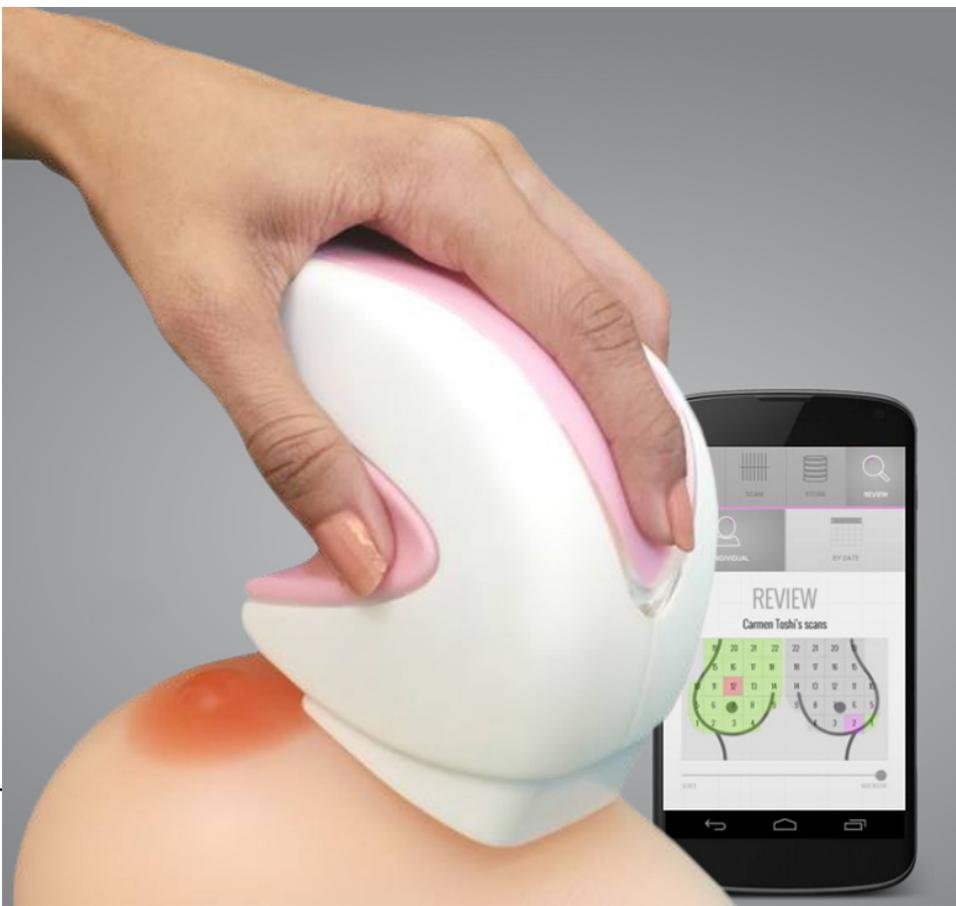
# Point of care testing technologies being evaluated for early detection of breast cancer

- Clinical breast examination
- Handheld, portable, rechargeable battery powered and low cost ultrasound
- Automated ultrasound
- Breast elastography
- Optical imaging technologies using near infrared light
- Fine needle aspiration cytology supported by computer assisted detection using artificial intelligence

# Physical examination of the breast

- Breast cancers  $\leq 2$  cm dimension can be readily detected by physical examination of the breast
- A palpable lump prompts referral for further assessment

# iBreastExam device



# *iBreast examination*

- iBreastExam's sensors assess and identify tissue elasticity differences between hard and stiff breast tumour tissue compared to normal breast tissue.
- The tactile sensor technology using Piezoelectric Sensor Array is a novel, quantitative and low-cost elastic modulus (E) sensor that can measure tissue compression and stiffness by top down touching of the skin surface.
- iBE's ability to apply a gentle force and measure the subtle displacements electrically, all within the sensor, provides 'electronic palpation' sensor for in-vivo breast imaging.

# Portable, handheld ultrasound for breast cancer early detection

- Hardware modifications to improve portability, enhance simplicity of use, and reduce cost have helped promote the use of ultrasound devices in LMICs
- There are now several products in the market that have taken such considerations into account with promising results, demonstrating the feasibility of using compact, portable ultrasound in primary care and can be used by healthcare workers with a range of training levels
- Sensivity: 74-91%; Specificity 72-96%; PPV: 3-32%
- The low-cost ultrasound hardware has prompted the development of pathology-driven, clinically applicable image analysis software such as computer-aided detection and diagnosis (CADD)

# Portable, handheld ultrasound for breast cancer early detection: challenges and limitations

- Handheld screening ultrasound, requires a great deal of resources to screen large numbers of women as the scanning is performed by the technologist.
- The identification of the sonographically detected abnormality is made by the technologist, making it operator dependent.
- The time, required for a bilateral handheld whole breast ultrasound, can range from 15 - 20 min, making it challenging to implement in a clinical practice

*Ref: Thigpen D et al., Diagnostics 2018; 8: 20*

# *Automated ultrasound for breast cancer early detection*

- Automated whole breast ultrasound allows for uncoupling of image acquisition from interpretation.
- The entirety of the breast can be imaged and subsequently the entire data set can be reviewed by the radiologist.
- Allows for more reliable and reproducible imaging of the entirety of the breast
- Allows the radiologist to interpret the entire data set as opposed to representative images obtained by a technologist.
- Image acquisition takes 60 s per view with a total examination time of about 15 minutes. Study interpretation time, performed by the radiologist is around 3 minutes

# Breast elastography

- Breast elastography is a sonographic imaging technique which provides a non-invasive evaluation of the stiffness of a lesion.
- It combines US technology with US elastography which noninvasively assesses tissue deformability by providing information on the elasticity. It is based on the premise that there are significant differences in the mechanical properties of tissues that can be detected by applying an external mechanical force
- Two technical solutions are available for clinical use: strain elastography (real time elastography) and shear wave elastography.
- They may substantially improve differentiating between benign and malignant breast lesions thereby limiting recourse to biopsy and considerably reducing the number of benign breast biopsy diagnoses.

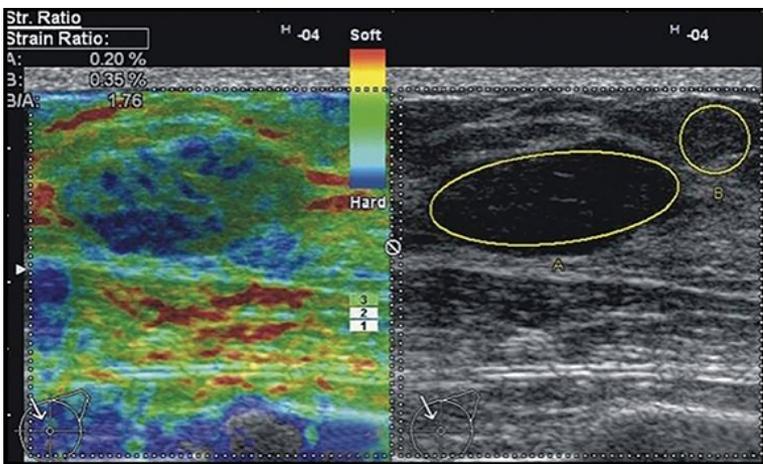
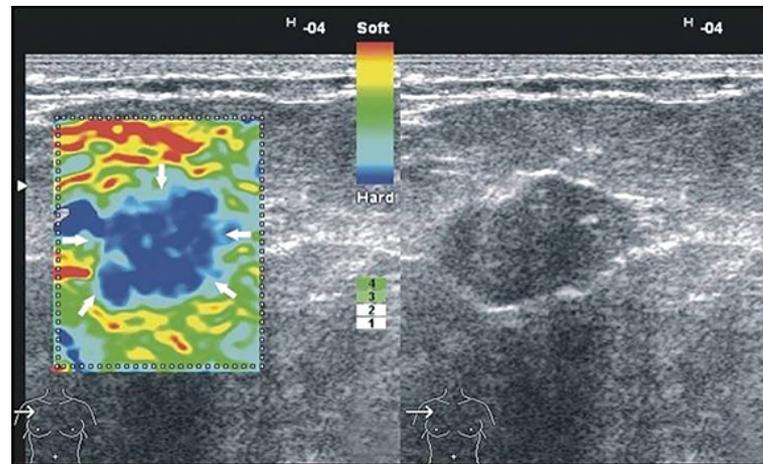
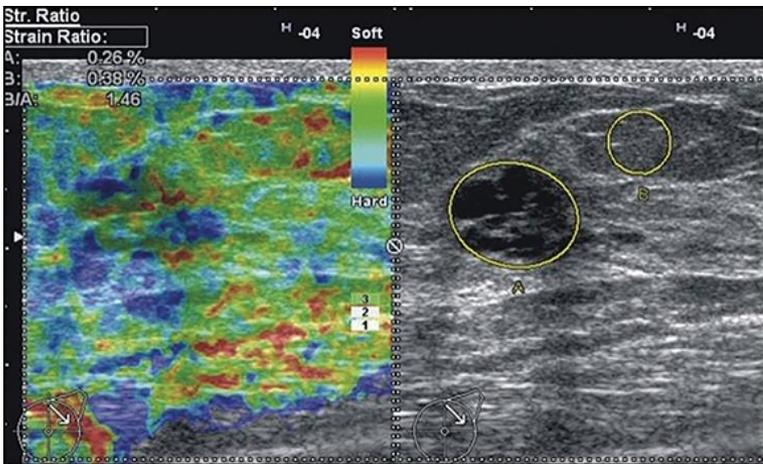
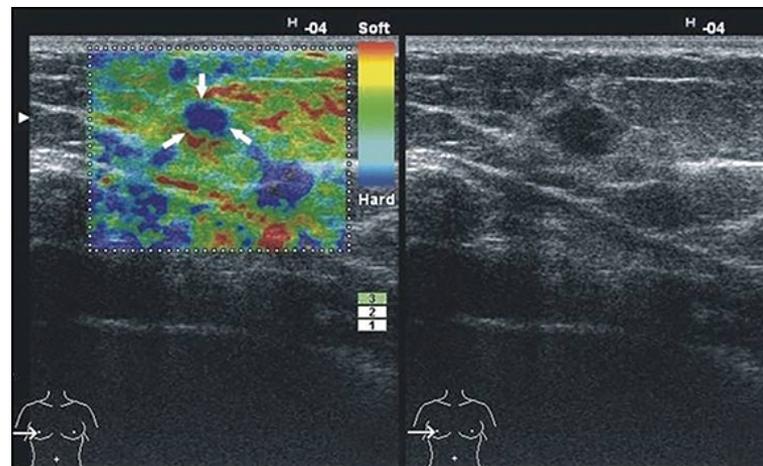
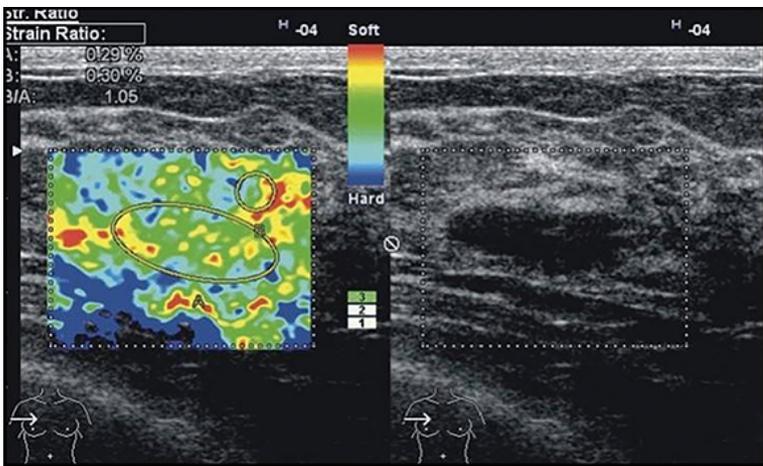
Ref: Goddi et al., Journal of Ultrasound 2012; 15, 192-198

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3558110/pdf/main.pdf>

<https://appliedradiology.com/articles/breast-elastography-a-new-paradigm-in-diagnostic-breast-imaging>

# ***Real time elastography (RTE): Advantages and disadvantages***

- Short examination time required, real-time display, immediate interpretation and limited cost, and the criteria adopted in the image interpretation have proven to be adequate in clinical practice.
- It is an exclusively qualitative method influenced by histotype and lesion size; is an operator dependent technique which requires special training, and the use of semi-quantitative indices does not improve the performance of the method and does not reduce interoperator variability

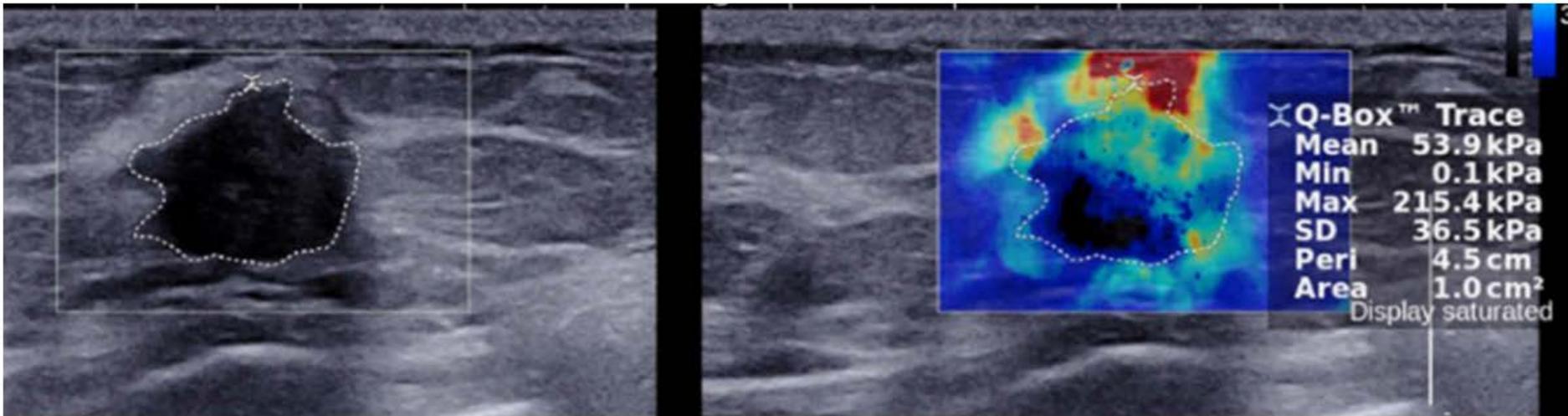


**Breast elastography: A new paradigm in diagnostic breast imaging**

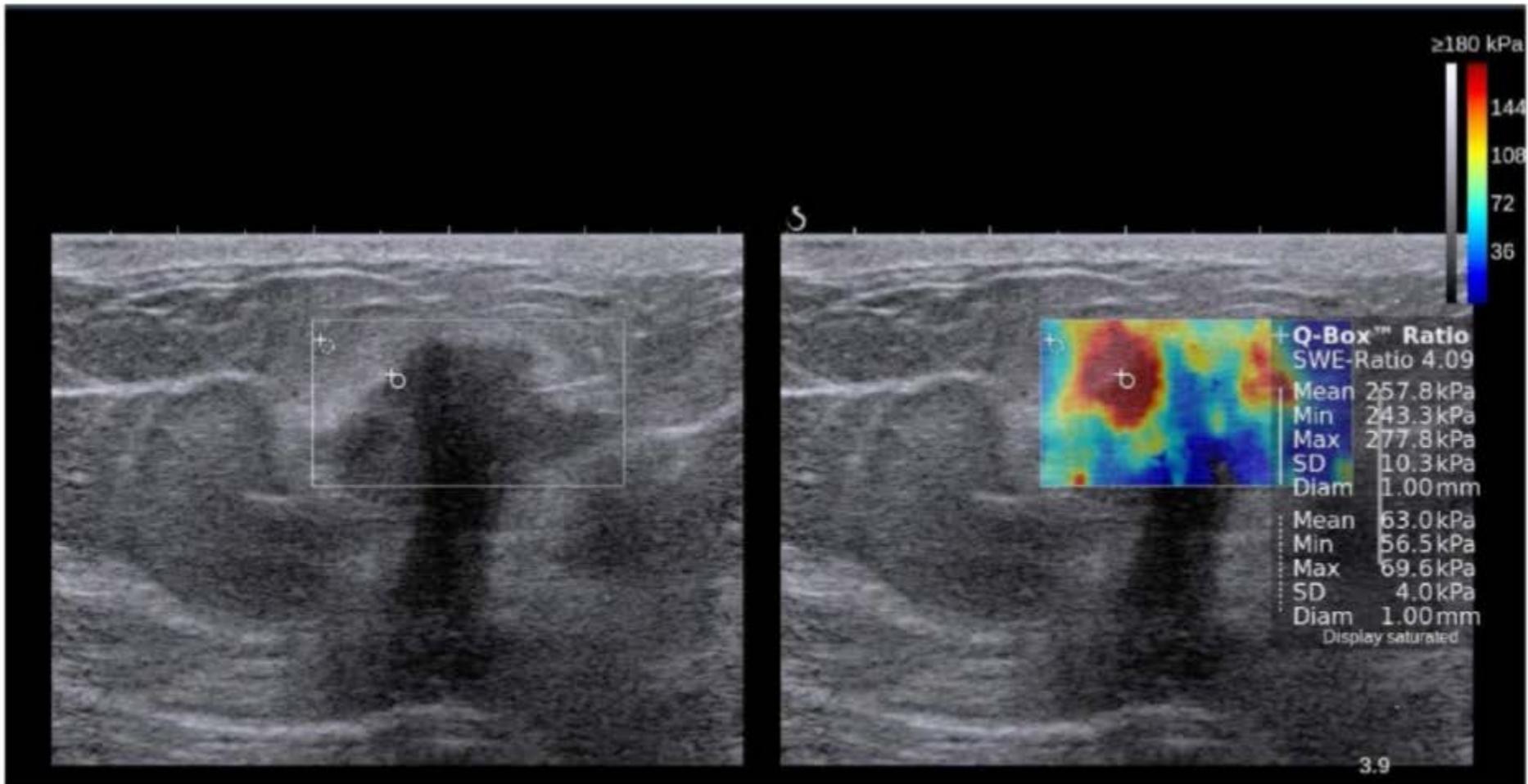
[Source:https://appliedradiology.com/article/s/breast-elastography-a-new-paradigm-in-diagnostic-breast-imaging](https://appliedradiology.com/article/s/breast-elastography-a-new-paradigm-in-diagnostic-breast-imaging)

# Shear Wave Elastography

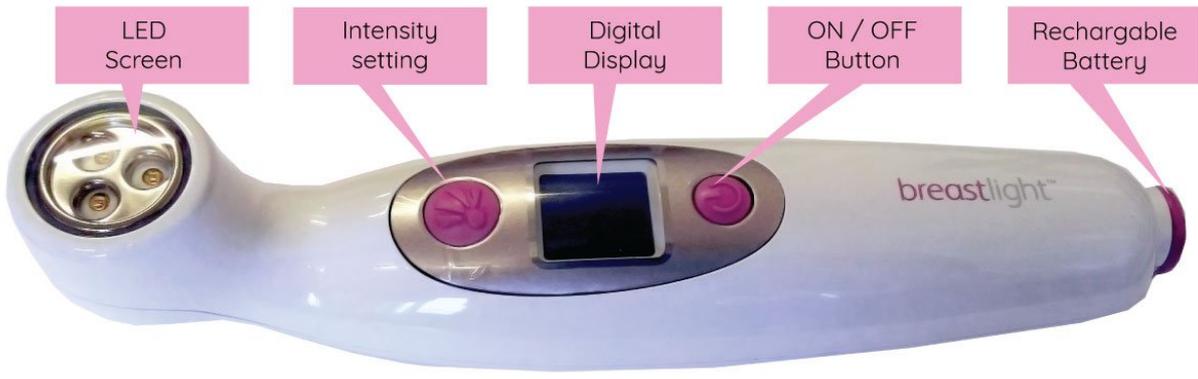
- The limitations of RTE can be compensated by shear wave elastography, which is a quantitative method providing a more accurate assessment of the spatial distribution of tissue stiffness.
- Shear wave elastography has limitations such as the difficulty in measuring shear wave velocity in very stiff breast lesions. In this type of tumors real-time elastography has demonstrated a high sensitivity which can compensate for the limitations of shear wave elastography
- Both RTE and shear wave elastography should be combined to overcome the limitations of both.



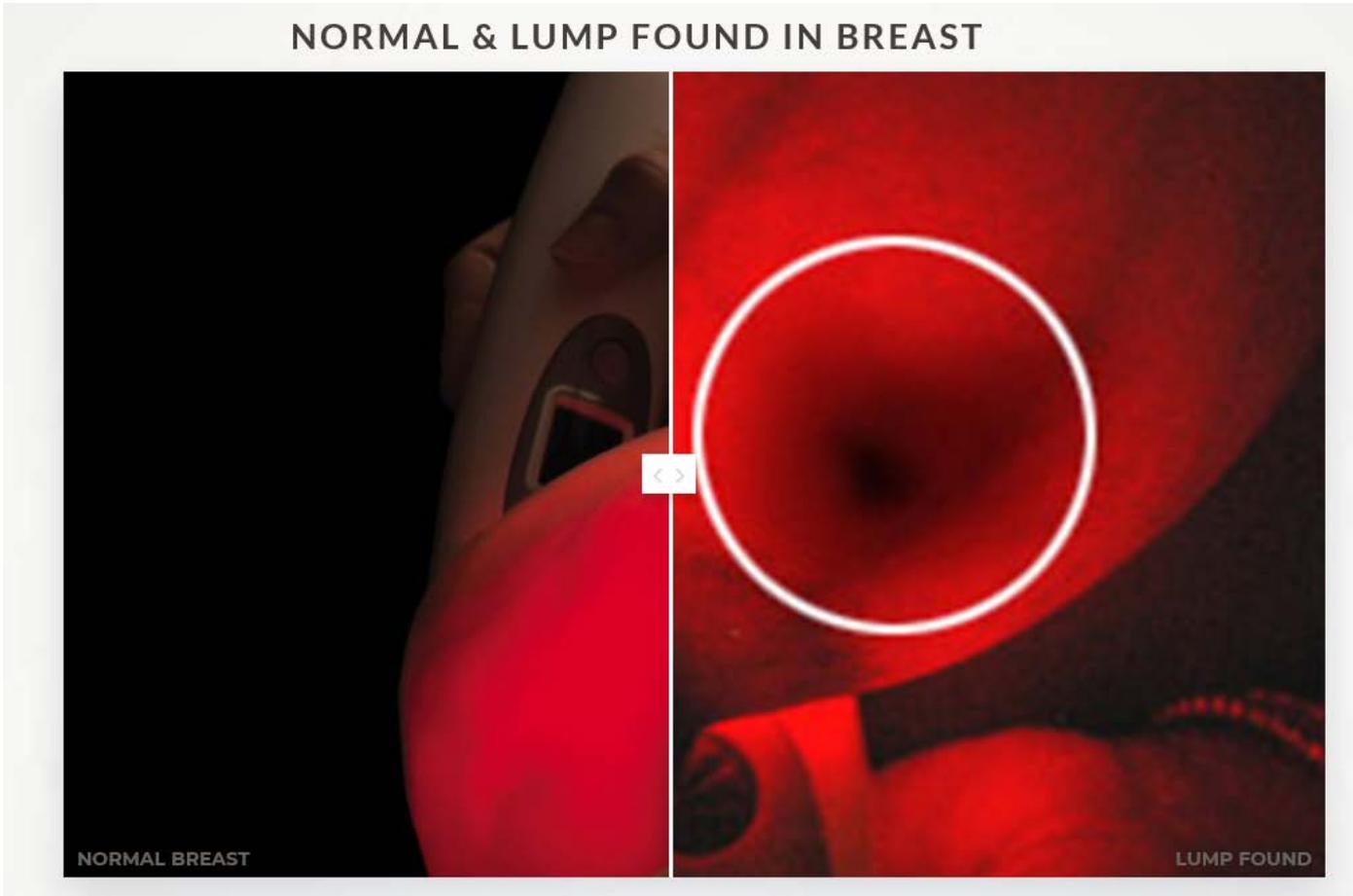
A 42-year-old woman with a pathologically proven invasive ductal carcinoma. A freehand region of interest was drawn manually by tracing the border of the mass using shear-wave elastography to measure lesion elasticity.



Side-by-side display of anatomical B-mode US image (left) and overlaid color map of simultaneous shear wave measurements (right) of a breast lesion obtained with 2D-SWE on a SuperSonic Imagine (SSI) Aixplorer™. In this system, red color represents stiff tissue and blue color reflects soft tissue. The suspicious hypoechoic lesion (shown within rectangle on B-mode image) has an irregular border, angular margins, is slightly wider than tall and shows posterior acoustic shadowing. The elastogram suggested malignant etiology due to increased stiffness (red/yellow/green) and ductal adenocarcinoma was confirmed on subsequent biopsy. Image courtesy by Dr. Osmar Saito.



### NORMAL & LUMP FOUND IN BREAST



# Breast awareness for women

- Each woman knowing what is normal for her
- Being aware of breast cancer symptoms/signs/risk factors
- Being aware of high survival/cure rates and quality of life if detected and treated early
- Undergoing periodic breast inspection and palpation
- Seeking prompt medical attention if any abnormality suspected

# Breast awareness for doctors and nurses

- Knowing about breast cancer!
- Knowing about breast cancer signs and symptoms!
- Knowing about the differential diagnosis of different breast signs and symptoms!
- Knowing the art of clinical suspicious and prompt referral!
- Knowing how to counsel!

# Physician breast awareness: clinical suspicion/differential diagnosis in the case breast signs/symptoms

Clinical presentation	<25 years	25-35 years	35-55 years	>55 years
<b>Mobile lump (single)</b>	Fibroadenoma	Fibroadenoma	Fibroadenoma Phylloides tumour	Phylloides tumour
<b>Ill defined lump/s or lumpy areas or feel-cyclic pain</b>	Uncommon	Fibrocystic disease/ Sclerosing adenosis	Fibrocystic disease	Uncommon
<b>Firm lump/hard lump/fixed lump/skin tethering</b>	Uncommon	Carcinoma	Carcinoma	Carcinoma/Fat necrosis
<b>Nipple ulceration, eczema</b>	Nipple adenoma	Nipple adenoma	Paget's disease/ Nipple adenoma	Paget's disease/ Nipple adenoma
<b>Bloody nipple discharge</b>	Uncommon	Uncommon	Duct papilloma/ In situ carcinoma	Duct papilloma/ In situ carcinoma
<b>Clear discharge/pus</b>	Uncommon	Uncommon	Duct ectasia	Duct ectasia

# Breast sign/symptom and likely differential diagnosis

Lump	Clinical suspicion
Diffuse	Fibroadenosis
Discrete or tethered	Cancer
Mobile	Benign tumour, most likely fibroadenoma
Skin features	
Oedema (peau de orange)/puckering/tethering	Cancer
Erythema	Inflammation/Cancer
Nipple	
Milky discharge	Pregnancy/prolactinoma
White/green discharge	Duct ectasia
Bloody discharge	Duct papilloma/rarely cancer
Retraction/scaling/erythema/eczema	Paget's disease of nipple/carcinoma
Breast Pain	
Cyclical	Fibroadenosis
On palpation	Mastitis
Recent, local, non-cyclical, constant	Cancer

# Early diagnosis of breast cancer: triple diagnosis

- Physical examination (clinical assessment)
- Diagnostic imaging  
(mammography/ultrasonography)
- Tissue sampling (FNAC/core biopsy/excision  
biopsy/frozen section)
- Excellent sensitivity (99%) and specificity (99%)

## 5-year survival from breast cancer in the Cancer Institute (WIA), a tertiary care centre in Chennai, India, during 1967-2006

Stage	Before the introduction of adjuvant treatments		After introduction of adjuvant hormone and chemotherapy treatments	
	1967-76	1977-86	1987-97	1997-2006
I (N=169)	85%	85%	95%	94%
II (N=2624)	62%	78%	75%	86%
III (N=4496)	34%	43%	54%	65%
IV (N=1042)	12%	16%	20%	29%
All stages (N=10 411)	39%	49%	57%	71%