



Global Summit on International Breast Health and Cancer Control:

Improving Breast Health Care through Resource-Stratified Phased Implementation

Pathology for Treatment Planning – Standard and Novel Techniques

Dan Milner, MD

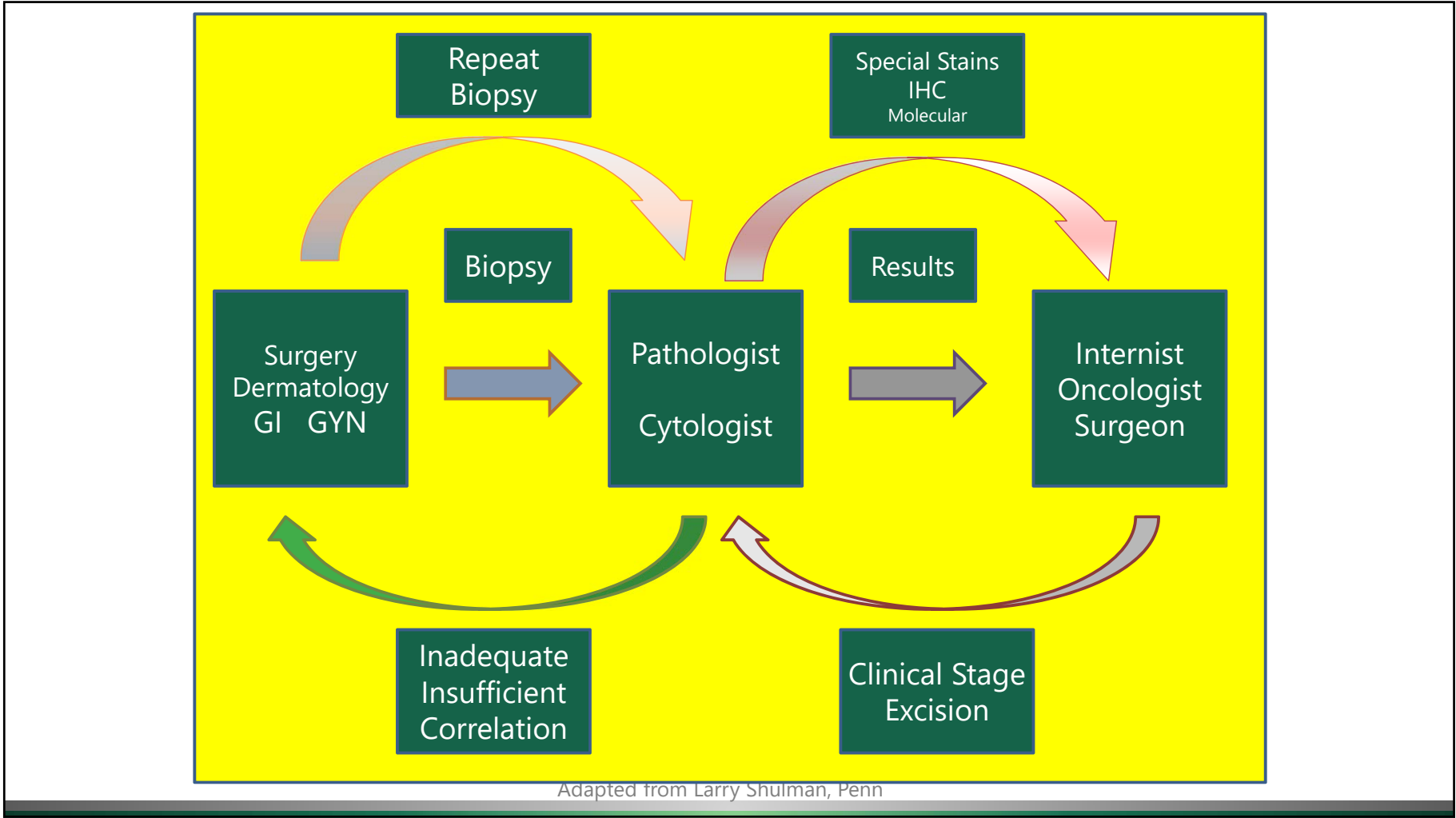
American Society of Clinical Pathology (USA)



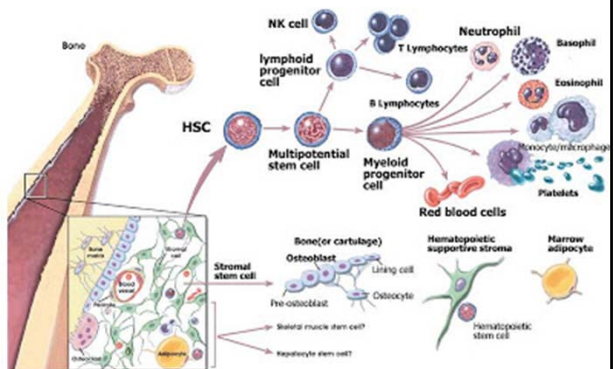
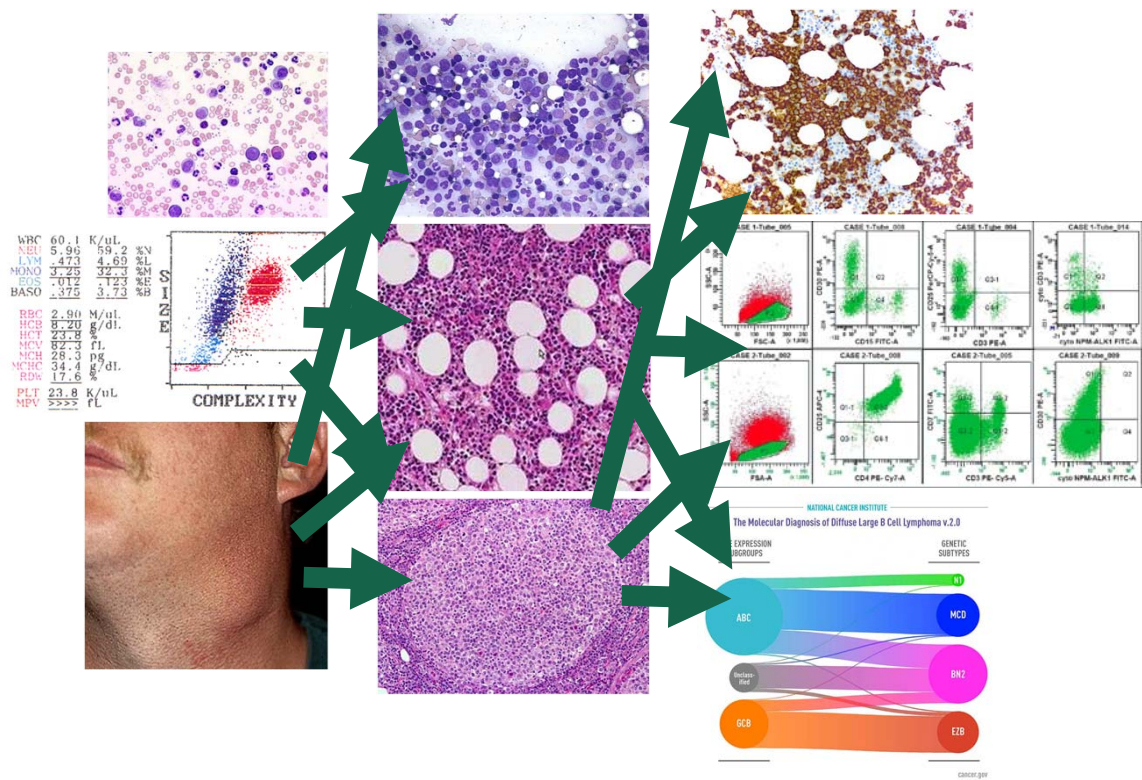
Disclosures

- I have no personal financial disclosures
- I will be presenting data on specific technologies used in global health cancer diagnostic work from specific manufacturers; however, these should be regarded as examples and not promoted products.
- ASCP has received grants (Novartis) and donations (Pfizer, GE) to support our global health implementation work
- Companies to be mentioned are:
 - Sakura-Finetek
 - Motic
 - GE
 - Philips
 - Cepheid
 - Merck
 - Novartis
 - Roche
 - Xifin
 - Pfizer

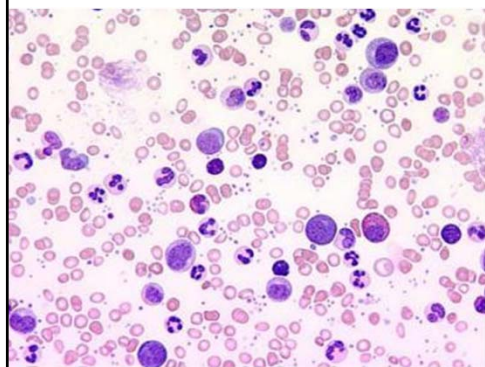
3



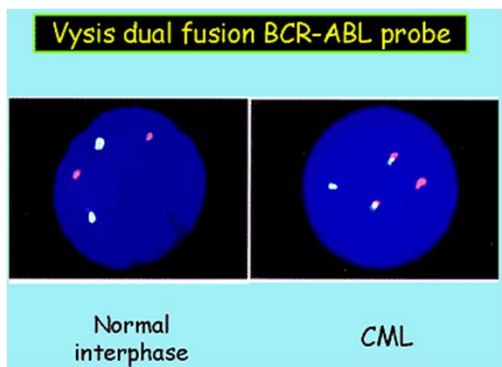
SPD for Hematological Malignancy



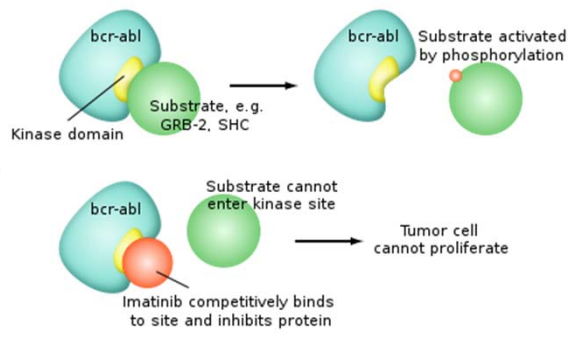
SPD for CML



POSITIVE PERIPHERAL
BLOOD SMEAR




bcr-abl Testing



Imatinib Treatment

MAX Foundation – Novartis - Cephe

 National Comprehensive Cancer Network®		NCCN Guidelines Version 2.2018 Invasive Breast Cancer		NCCN Guidelines Index Table of Contents Discussion
CLINICAL STAGE	WORKUP			
	<ul style="list-style-type: none">• History and physical exam• Diagnostic bilateral mammogram; ultrasound as necessary• Pathology review^b• Determination of tumor estrogen/progesterone receptor (ER/PR) status and HER2 status^c• Genetic counseling if patient is high risk for hereditary breast cancer^d• Breast MRI^e (optional), with special consideration for mammographically occult tumors• Counseling for fertility concerns if premenopausal; pregnancy test in all women of childbearing potential^f• Assess for distress^g			
	For clinical stage I-IIIB, consider additional studies only if directed by signs or symptoms: ^h			
T1,N0,M0	<ul style="list-style-type: none">• Complete blood count (CBC)• Comprehensive metabolic panel, including liver function tests and alkaline phosphatase• Bone scan indicated if localized bone pain or elevated alkaline phosphatase• Abdominal ± pelvic diagnostic CT with contrast or MRI with contrast indicated if elevated alkaline phosphatase, abnormal liver function tests, abdominal symptoms, or abnormal physical examination of the abdomen or pelvis• Chest diagnostic CT with contrast (if pulmonary symptoms present)			
T0,N1,M0 ^a T1,N1,M0 ^a T2,N0,M0	<ul style="list-style-type: none">• CBC• Comprehensive metabolic panel, including liver function tests and alkaline phosphatase• Chest diagnostic CT with contrast• Abdominal ± pelvic diagnostic CT with contrast or MRI with contrast• Bone scan or sodium fluoride PET/CTⁱ (category 2B)• FDG PET/CT^{j,k} (optional)			
T2,N1,M0 T3,N0,M0				
T3,N1,M0				
T0-3,N2,M0 T4,N0-2,M0 Any T,N3,M0	If considering preoperative systemic therapy	See Preoperative Systemic Therapy for Operable Disease: Workup (BINV-11) or See Preoperative Systemic Therapy for Inoperable or Locally Advanced Disease (Non-Inflammatory): Workup (BINV-15)		
		See Locoregional Treatment (BINV-2)^l		
^a If considering preoperative systemic therapy for HER2-positive N1 tumors, See Principles of Preoperative Systemic Therapy (BINV-L) and See Workup (BINV-11) .				
^b The panel endorses the College of American Pathologists Protocol for pathology reporting for all invasive and noninvasive carcinomas of the breast. http://www.cap.org .				
^c See Principles of HER2 Testing (BINV-A) .				
^d See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian .				
^e See Principles of Dedicated Breast MRI Testing (BINV-B) .				
^f See Fertility and Birth Control (BINV-C) .				
		^h If FDG PET/CT is performed and clearly indicates bone metastasis, on both the PET and CT component, bone scan or sodium fluoride PET/CT may not be needed.		
		ⁱ FDG PET/CT can be performed at the same time as diagnostic CT. The use of PET or PET/CT is not indicated in the staging of clinical stage I, II, or operable stage III breast cancer. FDG PET/CT is most helpful in situations where standard staging studies are equivocal or suspicious, especially in the setting of locally advanced or metastatic disease.		
		^k FDG PET/CT may also be helpful in identifying unsuspected regional nodal disease and/or distant metastases in locally advanced breast cancer when used in addition to		

<div><div><div>NCCN</div><div>National Comprehensive Cancer Network®</div></div><div><div>NCCN Harmonized Guidelines™ for Sub-Saharan Africa</div><div>Version 2.2017</div><div>Invasive Breast Cancer</div></div></div>		<div>NCCN Guidelines Index Table of Contents Discussion</div>
CLINICAL STAGE	WORKUP	
Stage I T1, N0, M0 or Stage IIA T0, N1, M0 T1, N1, M0 T2, N0, M0 or Stage IIB T2, N1, M0 T3, N0, M0 or Stage IIIA T3, N1, M0	<ul style="list-style-type: none">• History and physical exam• Diagnostic bilateral mammogram; ultrasound as necessary• Pathology review^a• Determination of tumor estrogen/progesterone receptor (ER/PR) status and HER2 status^{b,**}• Genetic counseling if patient is high risk for hereditary breast cancer^{c,*}• Breast MRI^d (optional), with special consideration for mammographically occult tumors• Counseling for fertility concerns if premenopausal^e• Assess for distress^f <p>For clinical stage I-IIIB, consider additional studies only if directed by signs or symptoms:^g</p> <ul style="list-style-type: none">• Complete blood count (CBC)• Comprehensive metabolic panel, including liver function tests and alkaline phosphatase• Bone scan indicated if localized bone pain or elevated alkaline phosphatase• Abdominal ± pelvic diagnostic CT with contrast or MRI with contrast indicated if elevated alkaline phosphatase, abnormal liver function tests, abdominal symptoms, or abnormal physical examination of the abdomen or pelvis• Chest diagnostic CT with contrast (if pulmonary symptoms present)• Chest x-ray and abdominal ultrasound (including asymptomatic patients) <p>If clinical stage IIIA (T3, N1, M0) consider:</p> <ul style="list-style-type: none">• CBC• Comprehensive metabolic panel, including liver function tests and alkaline phosphatase• Chest x-ray and abdominal ultrasound (including asymptomatic patients)• Chest diagnostic CT with contrast• Abdominal ± pelvic diagnostic CT with contrast or MRI with contrast• Bone scan or sodium fluoride PET/CT^h (category 2B)• FDG PET/CT^{i,j} (optional)	<div>See Locoregional Treatment (BINV-2)^k</div>
If considering preoperative systemic therapy for Stage II and III	<div>See Preoperative Systemic Therapy for Operable Breast Cancer: Workup (BINV-10)</div> <div>or</div> <div>See Preoperative Systemic Therapy for Inoperable or Locally Advanced Breast Cancer (Non-Inflammatory): Workup (BINV-14)</div>	
<div><div><div>^aThe panel endorses the College of American Pathologists Protocol for pathology reporting for all invasive and noninvasive carcinomas of the breast. http://www.cap.org.</div><div>^bSee Principles of HER2 Testing (BINV-A).</div><div>^cSee NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.</div></div><div><div>[*]At a basic level, have a discussion with patient and family members.</div><div>^{**}If HER2 testing is not available, follow HER-negative pathway.</div><div>ⁱFDG PET/CT can be performed at the same time as diagnostic CT. The use of PET or PET/CT is not indicated in the staging of clinical stage I, II, or operable stage III breast cancer. FDG PET/CT is most helpful in situations where standard staging studies are</div></div></div>		

C

Histologic Type (Note E)

- ☐ Invasive carcinoma of no special type (ductal, not otherwise specified)
- ☐ Micro-invasive carcinoma
- ☐ Invasive lobular carcinoma
- ☐ Invasive carcinoma with lobular features
- ☐ Invasive carcinoma with ductal and lobular features ("mixed type carcinoma")
- ☐ Mucinous carcinoma
- ☐ Tubular carcinoma
- ☐ Invasive carcinoma, tubulo-lobular variant
- ☐ Invasive cribriform carcinoma
- ☐ Invasive micropapillary carcinoma
- ☐ Invasive papillary carcinoma
- ☐ Medullary carcinoma
- ☐ Invasive carcinoma with medullary features

Note: The histologic type corresponds to the largest carcinoma. If there are smaller carcinomas of a different type, this information should be included under "Additional Pathologic Findings."

Inflammatory carcinoma requires the presence of clinical findings of erythema and edema involving at least one-third or more of the skin of the breast (see Note M).

Special type carcinomas should consist of at least 90% pure pattern.

- ☐ Invasive carcinoma with apocrine features
- ☐ Invasive carcinoma with clear cell (glycogen rich) features
- ☐ Invasive carcinoma with neuroendocrine features
- ☐ Invasive carcinoma, with signet-ring cell features
- ☐ Secretory carcinoma
- ☐ Invasive carcinoma, type cannot be determined
- ☐ No residual invasive carcinoma
- ☐ Other histologic type not listed (specify): _____

"See Note E"

E. Histologic Type

This protocol applies to all invasive carcinomas of the breast. The World Health Organization (WHO) classification of breast carcinoma is presented below, although the protocol does not preclude the use of other classifications or histologic types. Carcinomas may be classified based on the H&E appearance without the use of immunohistochemical studies.

A modified list is presented in the protocol, based on the most frequent types of invasive carcinomas and terminology that is in widespread usage. The modified list is intended to capture the majority of tumors and reduce the classification of tumors being reported as “other.” The WHO classification is presented for completeness.

WHO Classification of Invasive Carcinoma

Microinvasive carcinoma

Invasive carcinoma of no special type (NST)

 Pleomorphic carcinoma

 Carcinoma with osteoclast-like stroma

 Carcinoma with choriocarcinomatous areas

 Carcinoma with melanotic features

Invasive lobular carcinoma

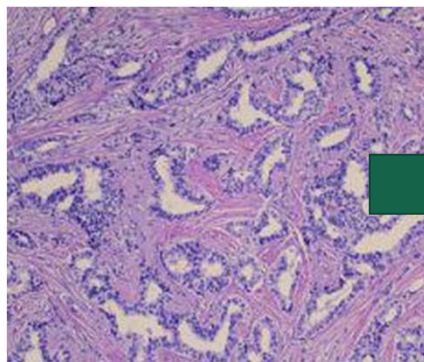
Classic lobular carcinoma
Solid lobular carcinoma
Alveolar lobular carcinoma
Pleomorphic lobular carcinoma
Tubulolobular carcinoma
Mixed lobular carcinoma
Tubular carcinoma
Cribriform carcinoma
Mucinous carcinoma
Carcinoma with medullary features
 Medullary carcinoma
 Atypical medullary carcinoma
Invasive carcinoma NST with medullary features
Carcinoma with apocrine differentiation
Carcinoma with signet-ring-cell differentiation
Invasive micropapillary carcinoma
Metaplastic carcinoma of no special type
 Low-grade adenosquamous carcinoma
 Fibromatosis-like metaplastic carcinoma
 Squamous cell carcinoma
 Spindle cell carcinoma
 Metaplastic carcinoma with mesenchymal differentiation
 Chondroid differentiation
 Osseous differentiation
 Other types of mesenchymal differentiation
 Mixed metaplastic carcinoma
 Myoepithelial carcinoma
Papillary carcinoma
 Encapsulated papillary carcinoma with invasion
 Solid papillary carcinoma, invasive

Epithelial-myoepithelial tumors
Adenomyoepithelioma with carcinoma
Adenoid cystic carcinoma

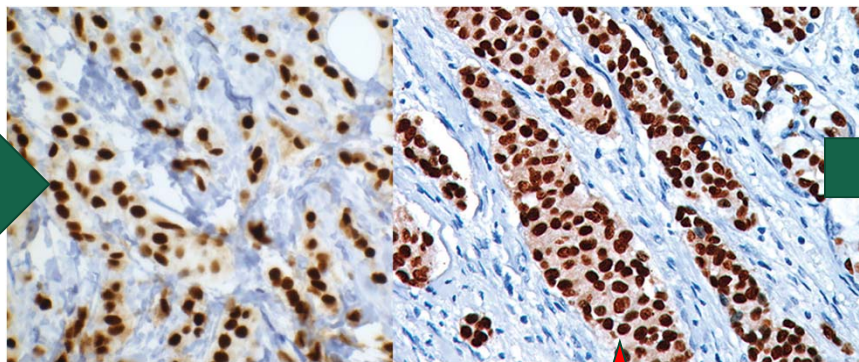
Rare types
Carcinoma with neuroendocrine features
 Neuroendocrine tumor, well-differentiated
 Neuroendocrine carcinoma poorly differentiated (small cell carcinoma)
 Carcinoma with neuroendocrine differentiation

Secretory carcinoma
Invasive papillary carcinoma
Acinic cell carcinoma
Mucoepidermoid carcinoma
Polymorphous carcinoma
Oncocytic carcinoma
Lipid-rich carcinoma
Glycogen-rich clear cell carcinoma
Sebaceous carcinoma

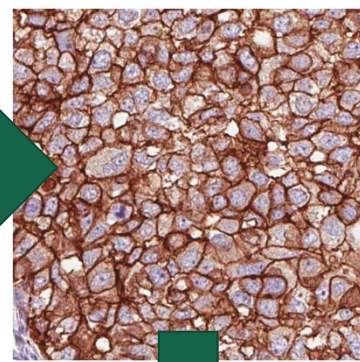
Standard Pathology Diagnostics for Breast CA



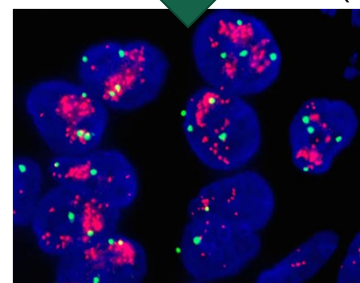
- Gross Description (size)
- Histological type
- Histological Grade
- Lymph node status
- Ki-67/mitotic rate★



- Estrogen Receptor Status★
- Progesterone Receptor Status★
- Other IHC markers for challenging histology



- Her2 (IHC)★
- Her2 (FISH)

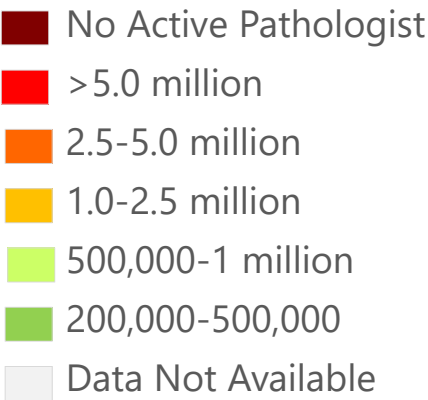


Advanced Testing:

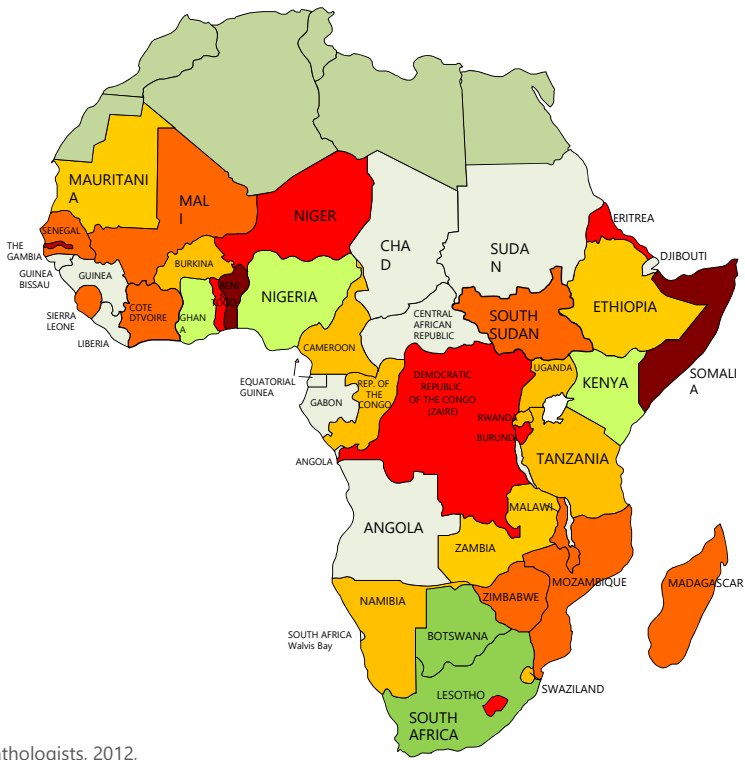
- BRCA1/2 Panel★
- Homologous recombination deficiency phenotype★
- Aromatase inhibitor resistance testing★

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Number of People Served By Each Pathologist in Sub-Saharan Africa

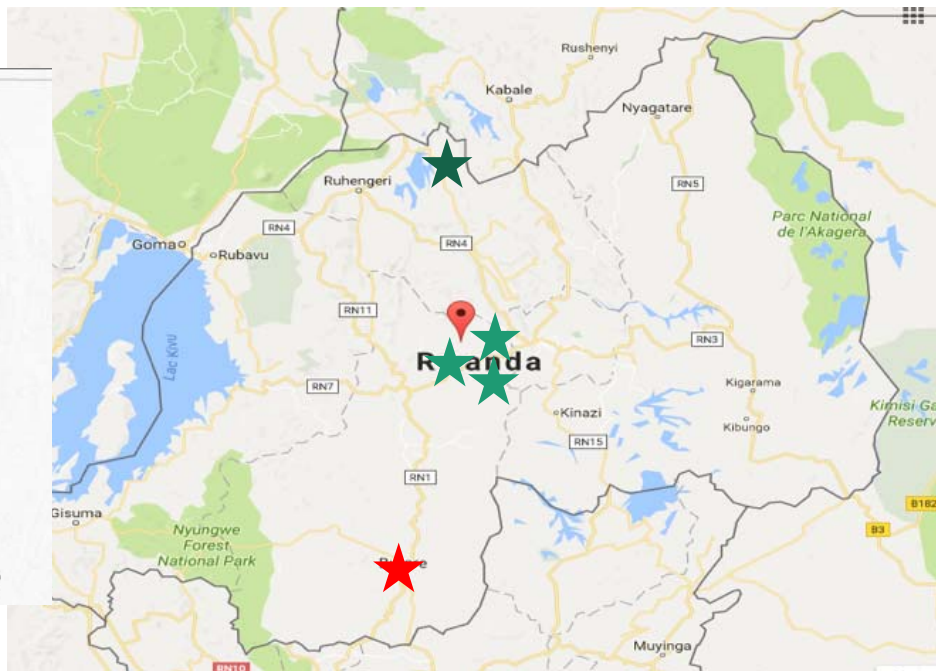
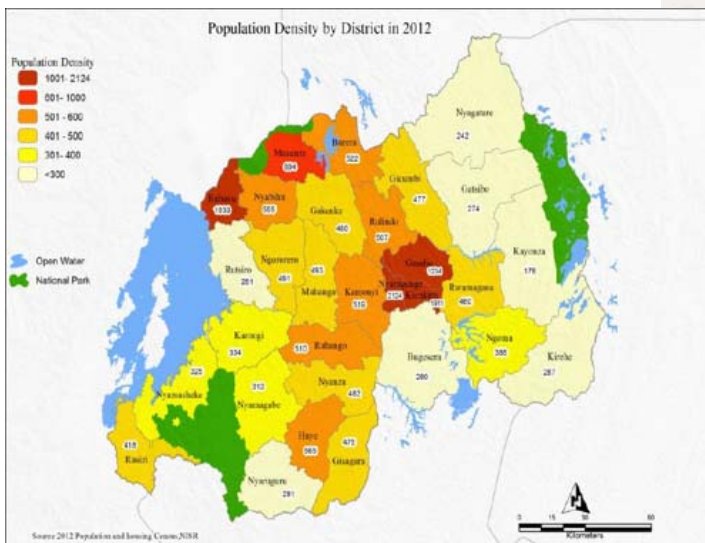


Number of People Per
Pathologist:
UK*: 15,108 US**:
19,232



*Royal College of Pathologists, 2012,
**Anatomic and Clinical Pathologists, AAMC, 2007

Rwanda – 11.78 M



Telepathology as a solution...

Static image

Transfer of still images from MD to MD

Dynamic image

Transfer of live images from slide to MD

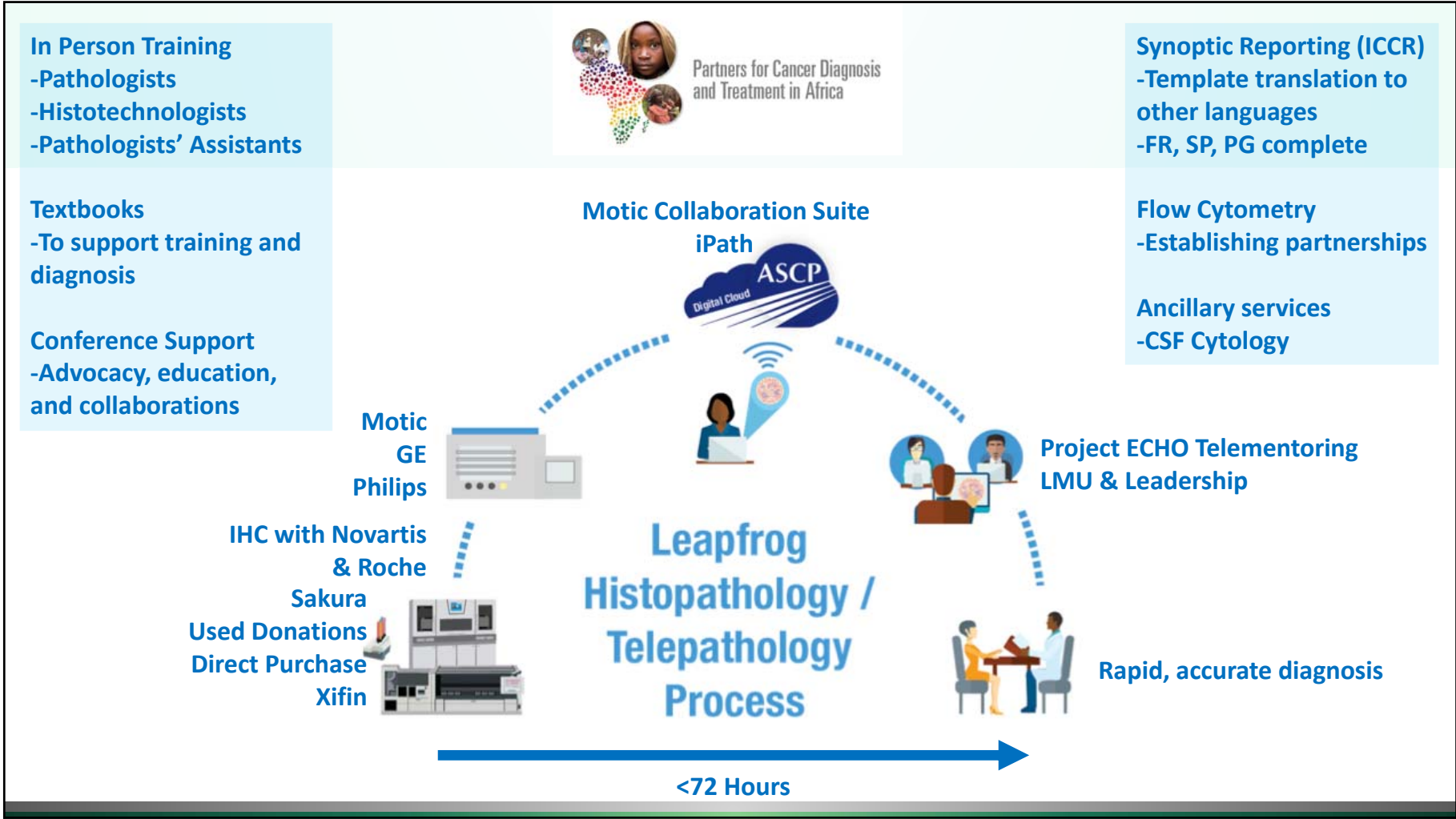
Whole Slide image

Transfer of whole image from server to MD

Automated Histology

Computer-assisted/directed slide review





Crowdsourcing for Pathology Diagnoses

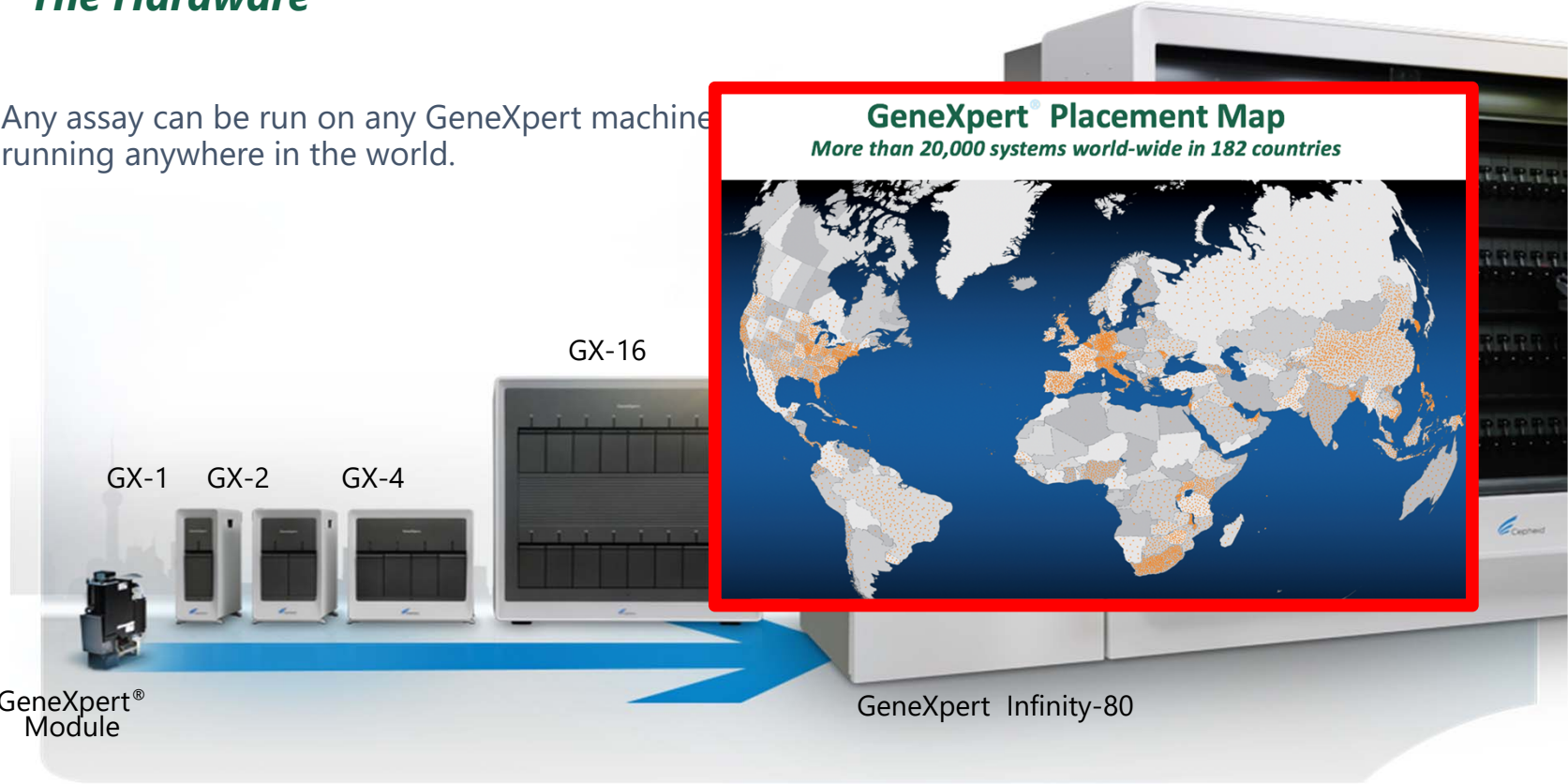
- ASCP members provide *pro bono* diagnostic and training services.
- Volunteers are recruited via meetings, email and social media
- Focused searches for collaborating academic centers for virtual pathologist teams
 - Duke/UCSF – Tanzania
 - UW/MGH – Uganda
 - UNC – Malawi
 - OSU - Ethiopia
- Teams of up to 15 pathologists members (licensed) per country with range of specialties across AP
- Laboratory professionals access process for improvements



GeneXpert Platform

The Hardware

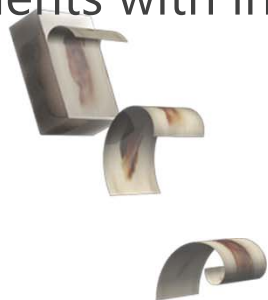
Any assay can be run on any GeneXpert machine running anywhere in the world.



Xpert Breast Cancer STRAT4: Foundational FFPE Assay*

Launched CE-IVD in April 2017

- Determination of *ESR*, *PGR*, *ERBB2*, and *MKi67* RNA expression in patients with invasive breast cancer



Using 4uM FFPE section, Pathologist performs H&E stain and macrodissects invasive tumor tissue.

1



Add FFPE lysis reagents and heat. Add ethanol and vortex.

2



Add lysate to GX cartridge.

3



Place cartridge in GeneXpert.

4

Total assay time-to-result ~ 75 minutes

****11 posters presented thus far with manuscripts in preparation***

STRAT4 – recently published clinical validation manuscript Concordance with a world-class central lab in > 500 FFPE specimens

Breast Cancer Research and Treatment
<https://doi.org/10.1007/s10549-018-4889-5>

PRECLINICAL STUDY



Comparison of central laboratory assessments of ER, PR, HER2, and Ki67 by IHC/FISH and the corresponding mRNAs (*ESR1*, *PGR*, *ERBB2*, and *MKi67*) by RT-qPCR on an automated, broadly deployed diagnostic platform

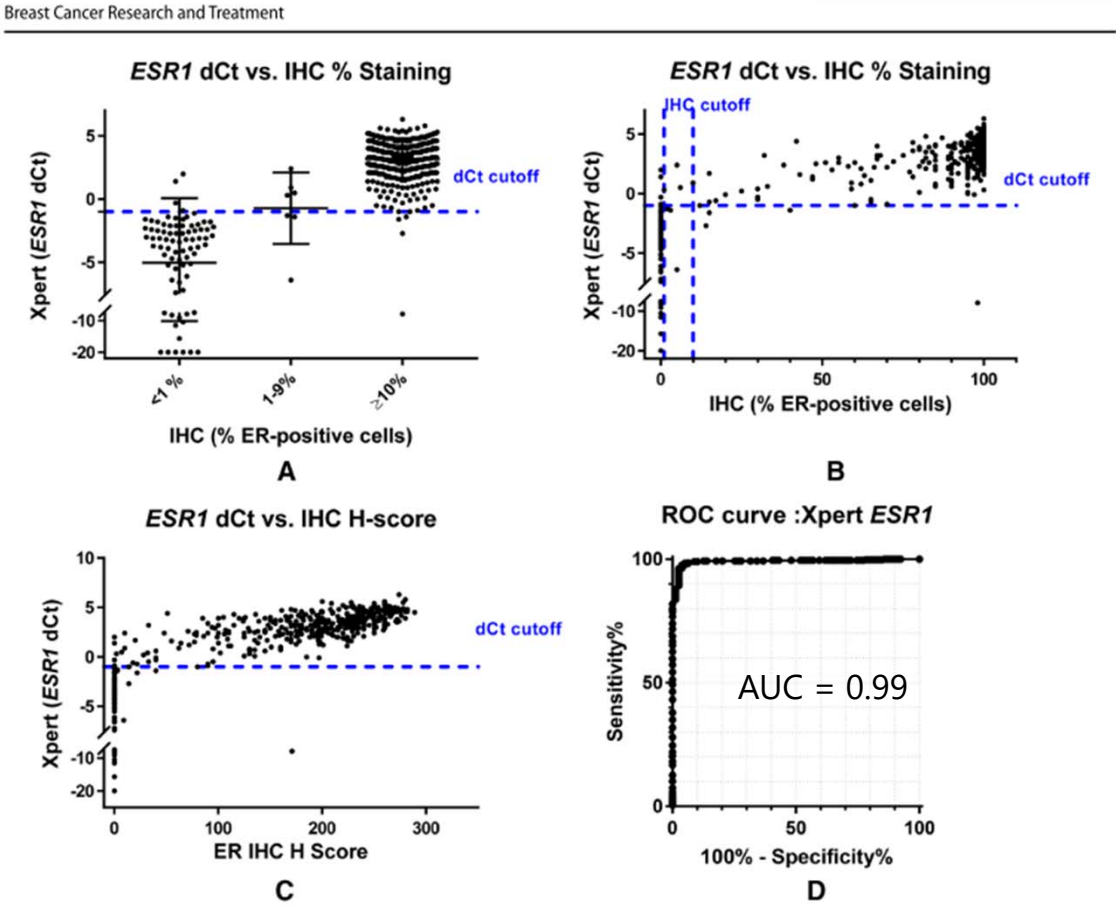
Natalie C. Wu¹ · Wendy Wong¹ · Kenneth E. Ho¹ · Victor C. Chu¹ · Annaliza Rizo¹ · Simon Davenport² · Devon Kelly³ · Rosemary Makar³ · Jacek Jassem⁴ · Renata Duchnowska⁵ · Wojciech Biernat⁴ · Barbara Radecka⁶ · Tomoyuki Fujita⁷ · Jonathan L. Klein⁸ · Mark Stonecypher⁸ · Shoichiro Ohta⁹ · Hartmut Juhl¹⁰ · Jodi M. Weidler¹¹ · Michael Bates¹¹ · Michael F. Press²

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STRAT4
performance:

ER/ESR1
concordance with
IHC

Wu, et al.
Breast Cancer Research and Treatment
published online, July 2018



Xpert Breast Cancer STRAT4 Collaborations in Africa

US/EU and African Collaborators

FFPE Studies - Ongoing:

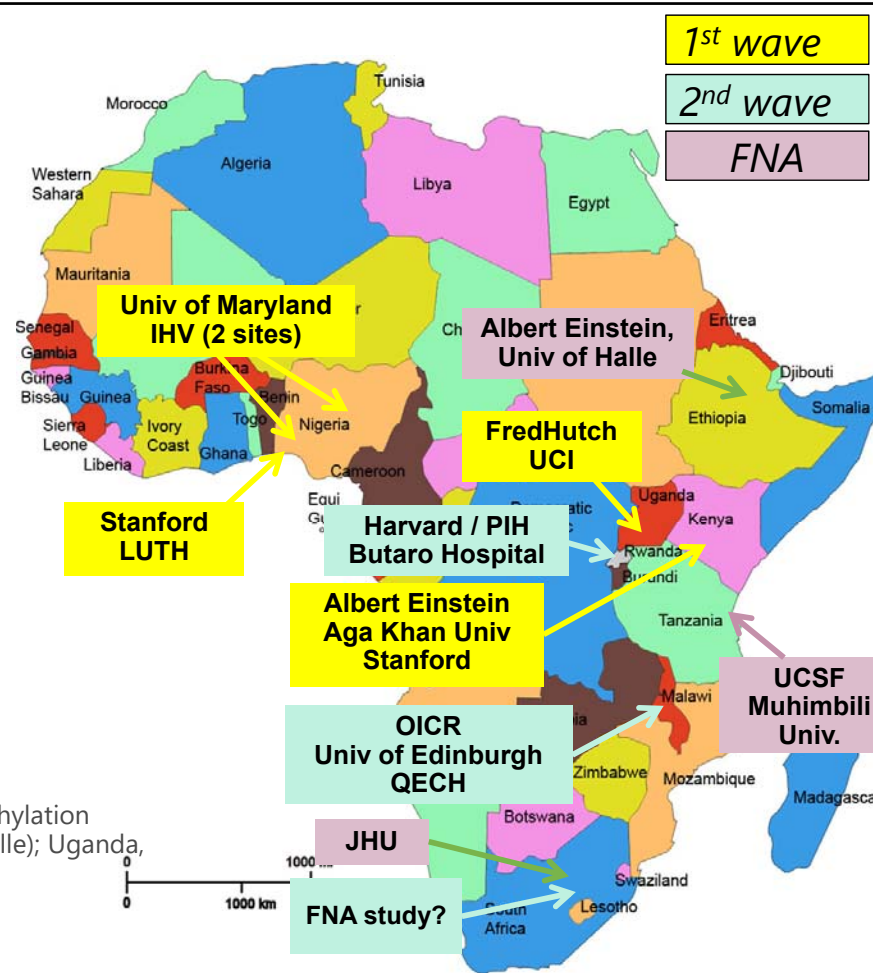
1. Kenya: Shahin Sayed/P. Castle/Christina Kong
2. Nigeria (Lagos): Ami Bhatt/Adekunbiola Banjo
3. Nigeria (Abuja/Ibadan): Clement Adebamowo

FFPE Studies - pending:

1. Uganda: Manoj Manon/Jackson Orem
2. Malawi: John Bartlett/Leo Masamba/Ewan Brown
3. Rwanda: Deo Ruhangaza, Jane Brock (BWH)

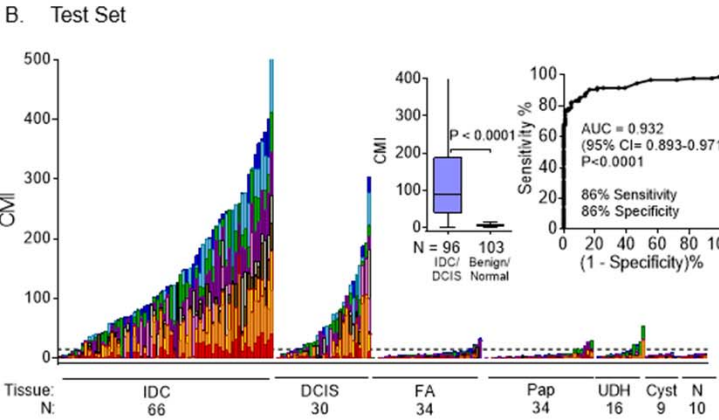
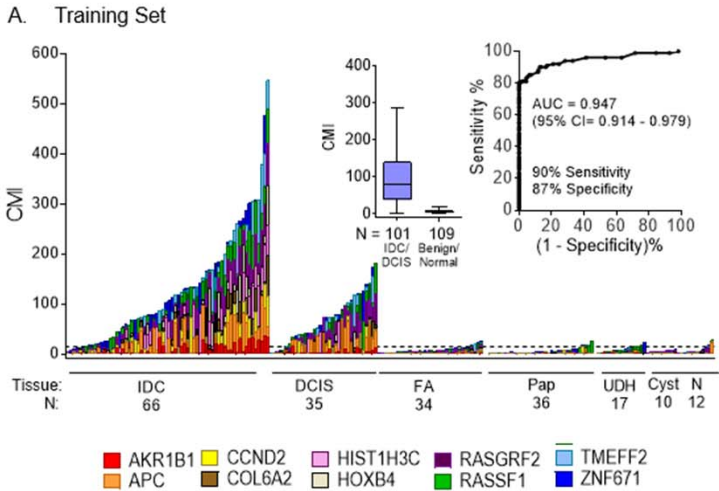
FNA studies

- PoC: UCSF-Tanzania: Britt-Marie Ljung, Dianna Ng
- Other FNA studies after lysis procedure finalized incl
 - South Africa (+China): Sara Sukumar (JHU) (reflex test to BrCa methylation triage) ; Ethiopia (Carol Harris-Einstein, Eva Kantelhardt-Univ of Halle); Uganda, Kenya, Abuja/Ibadan Nigeria
- **NEW: S. Africa FNA opportunity**

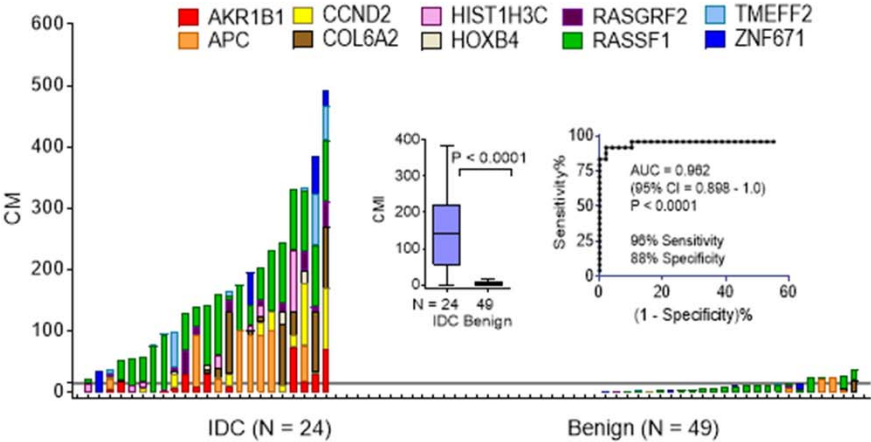


Rapid Diagnosis of Breast Cancer Using a Signature of Methylated DNA Markers and FNA tissue Tested on the GeneXpert Platform

Downs, BM, et al. “DNA Methylation Markers for Breast Cancer Detection in the Developing World: Marker Training, Assay Validation, Automation and Pilot Testing”
Manuscript submitted to Clinical Cancer Research



Performance in FNA Specimens (time-to-result ~4 hours)





Thank You!



STRONGERTOGETHER



Breast Health
Global Initiative

Global Summit on International Breast Health and Cancer Control:

Improving Breast Health Care through Resource-Stratified Phased Implementation

INTERNET ACCESS: Marriott_CONFERENCE
ACCESS CODE: BHGI2018



BHGIatFredHutch



BreastHealthGlobalInitiative



FRED HUTCH
CURES START HERE®



susan g.
komen.



BREAST
CANCER
INITIATIVE 25



NCCN
National
Comprehensive
Cancer
Network®

Additional Slides not presented for review

- These slides provide some additional information about partnerships for solving these challenges as well as the known delays in the pathology value chain and how to overcome that delay with known solutions.

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Providing Pathology Services in Resource Restriction or Establishing Equity in Diagnostics for Cancer

Type of program

- Volunteer Programs
- Donor Funding
- Donor Equipment
- Public-Private Partnerships
- Grant Funding
- Insurance Models
- Coalitions/Initiatives

Pros/Cons

- Expertise/Sustainability
- Resources/Sustainability
- Capacity/Service contracts
- Many/Complexity
- Resources/Duration & Sustainability
- Many/Political negotiations
- Many/Competition

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Delay & (Solutions) In Pathology Value Chain

- Patient presentation
 - ⑩ Not aware of cancer as a disease (Education, public awareness)
 - ⑩ Fear of death, loss of body image (CHW outreach, Survivor Stories)
 - ⑩ Lack of resources for accessing system (Insurance schemes and donor programs)
- Clinical acumen
 - ⑩ Not aware of cancer as a disease (National Cancer Control Plans)
 - ⑩ No guiding documentation (Tiered Training across health sector)
 - ⑩ Lack of resources for diagnosis (Clinical network procurement plans)

Delay & (Solutions) In Pathology Value Chain

- Biopsy tools
 - ⑩ No simple tools (FNA) available (Training in FNA/FNB + essential tools)
 - ⑩ No biopsy tools (surgical) available (Training in Biopsy + essential tools)
- Specimen Transportation
 - ⑩ No formalin available (Defined specimen transport network)
 - ⑩ No specimen containers/requisitions (Supplies exchange program)
 - ⑩ Unclear referral network (Public-private partnerships)

Delay & (Solutions) In Pathology Value Chain

- Personnel
 - ⑩ No pathologist (Telepathology, visiting pathologists, training)
 - ⑩ No trained or poorly trained technical staff (On site and remedial training with support)
 - ⑩ Management issues (Laboratory management training)
- Reagents and Supplies
 - ⑩ No reliable supply of standard reagents (Defined role of laboratory in network)
 - ⑩ No supply of special reagents (Central support for recurring procurement)
 - ⑩ Delays in procurement (Public-private partnerships)

Delay & (Solutions) In Pathology Value Chain

- Reporting Process
 - ⑩ On paper reporting (APLIS with networking across system)
 - ⑩ No laboratory information system (APLIS with networking across system)
 - ⑩ No standardize reporting (Synoptic reporting to international standards)
 - ⑩ No electronic reporting systems (APLIS with networking across system)
- Communications
 - ⑩ Difficult channels between pathology and clinicians
 - (Synoptic reporting)
 - (Interdisciplinary teams)
 - (Standardize requisition forms with rejection rules)

