Breast Health Global Initiative

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)

BHGlatFredHutch BreastHealthGlobalInitiative

FRED HUTCH CURES START HERE® susan g. komen® BREAST CANCER INITIATIVE 2.5 NCCN National Comprehensive Cancer Network®

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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

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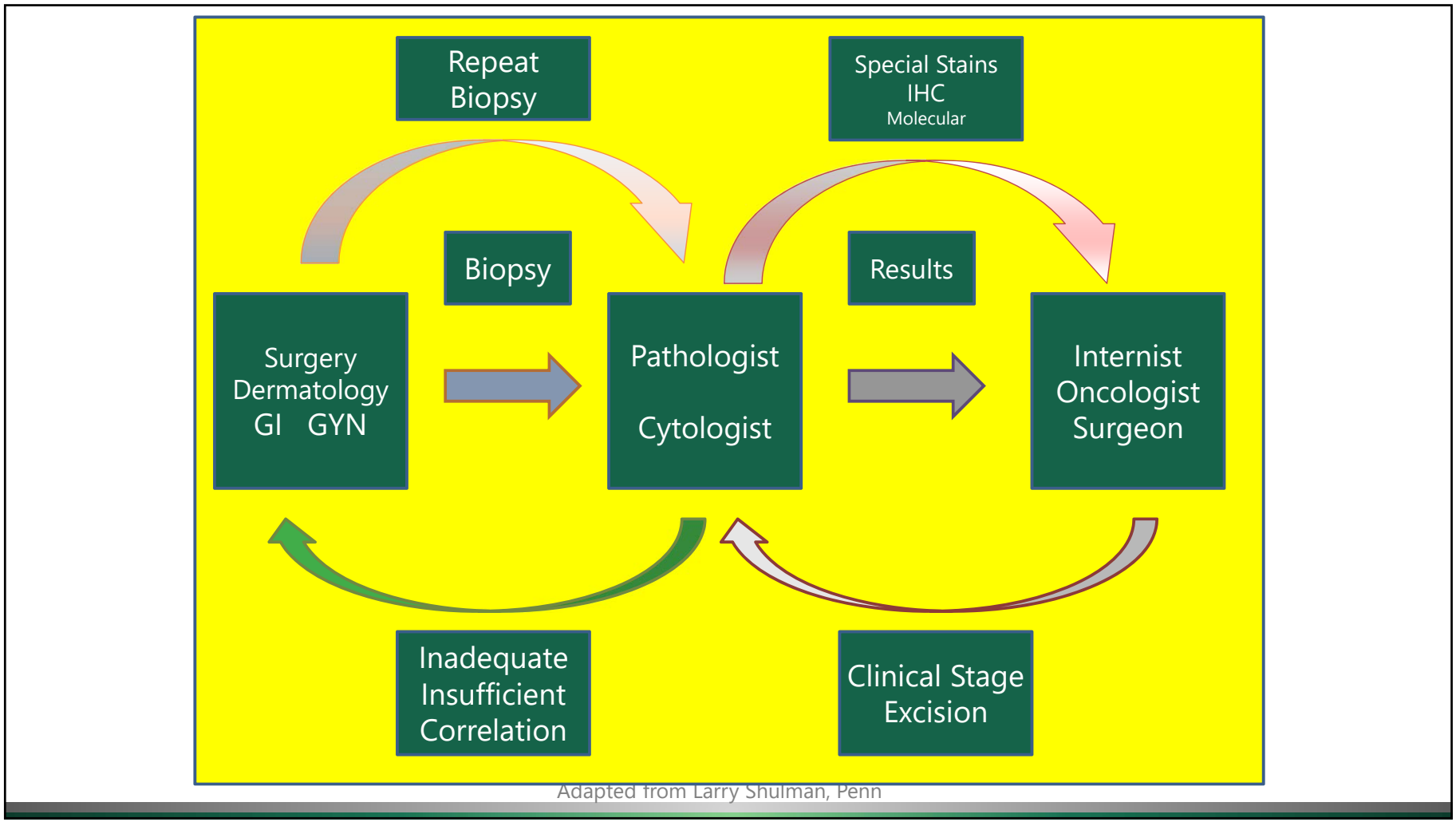

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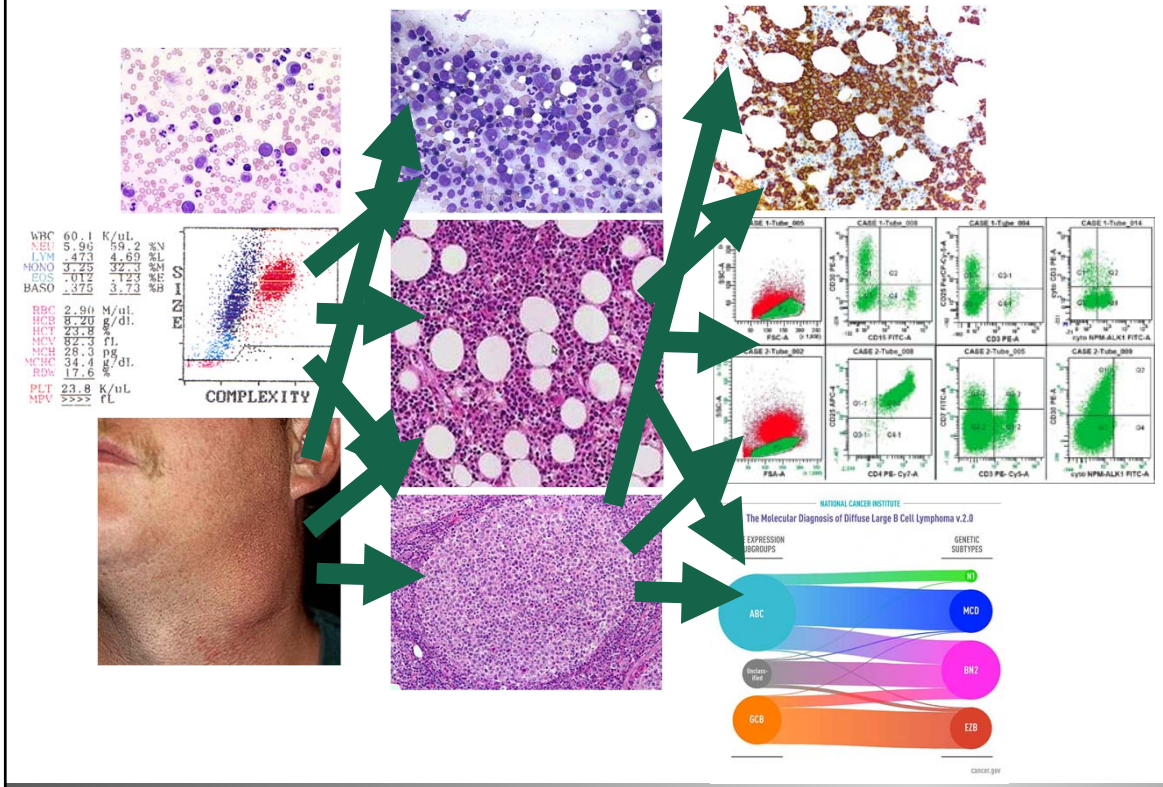
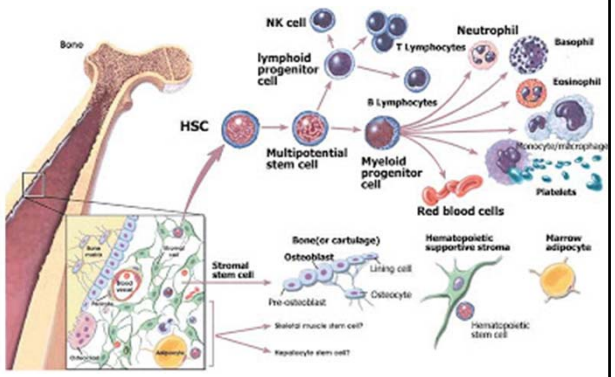
SPD for Hematological Malignancy





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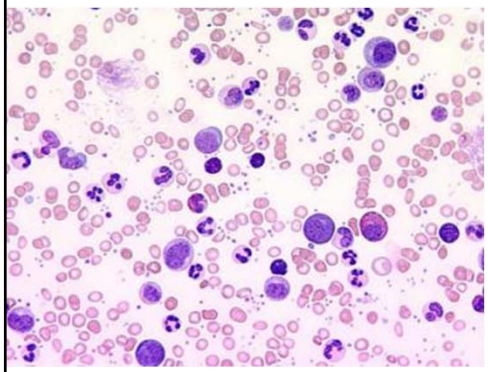
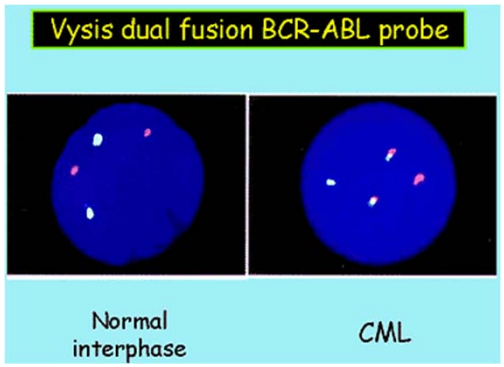
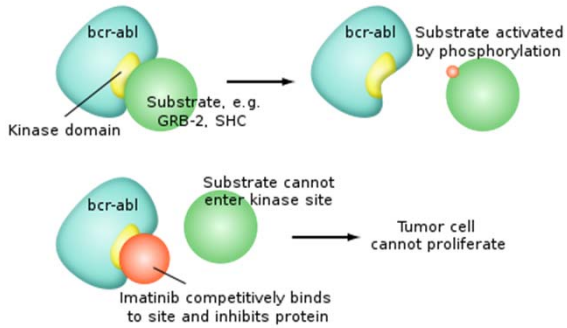
SPD for CML



POSITIVE PERIPHERAL BLOOD SMEAR



bcr-abl Testing



Imatinib Treatment

MAX Foundation – Novartis - Cephe

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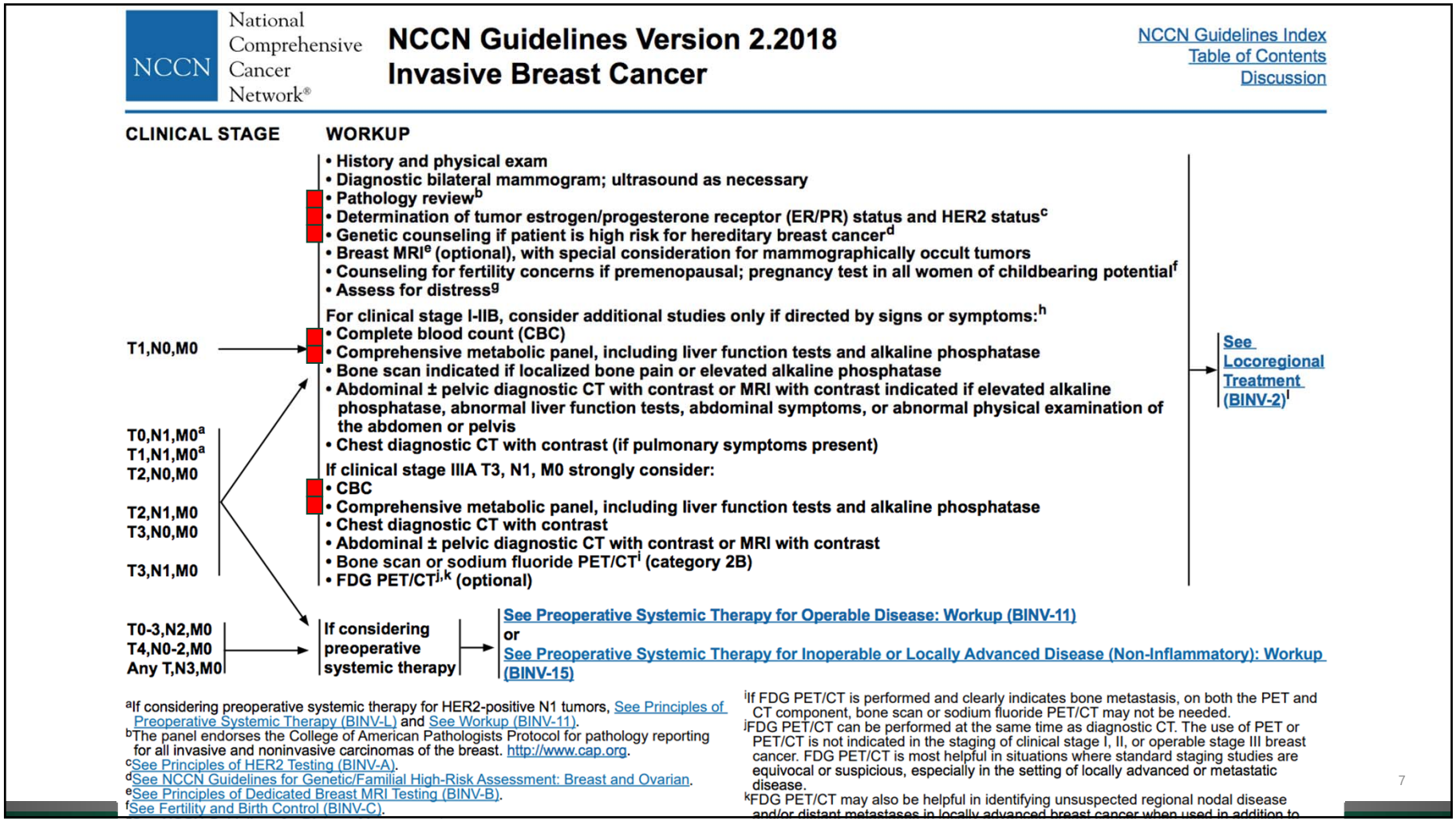

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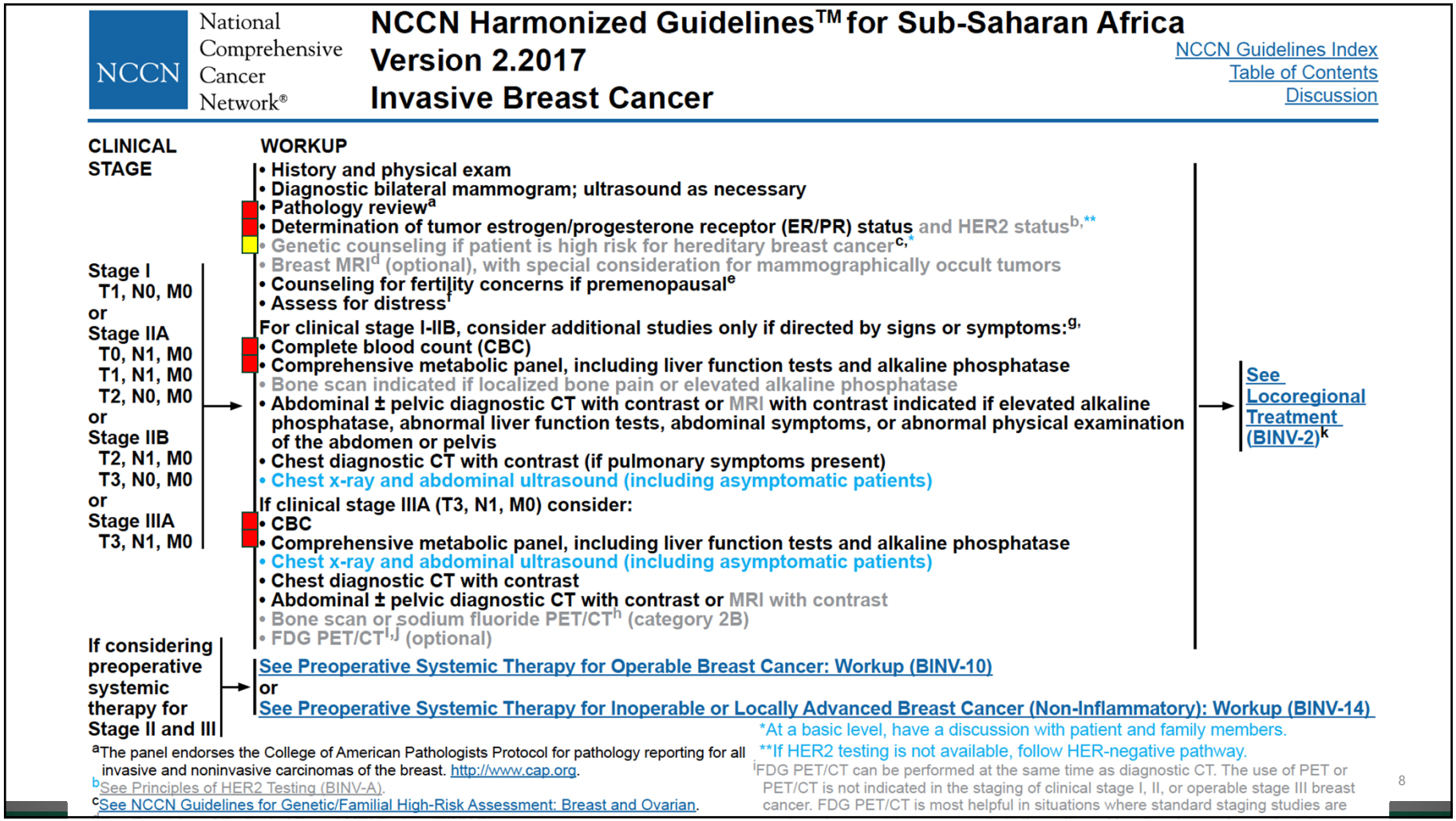

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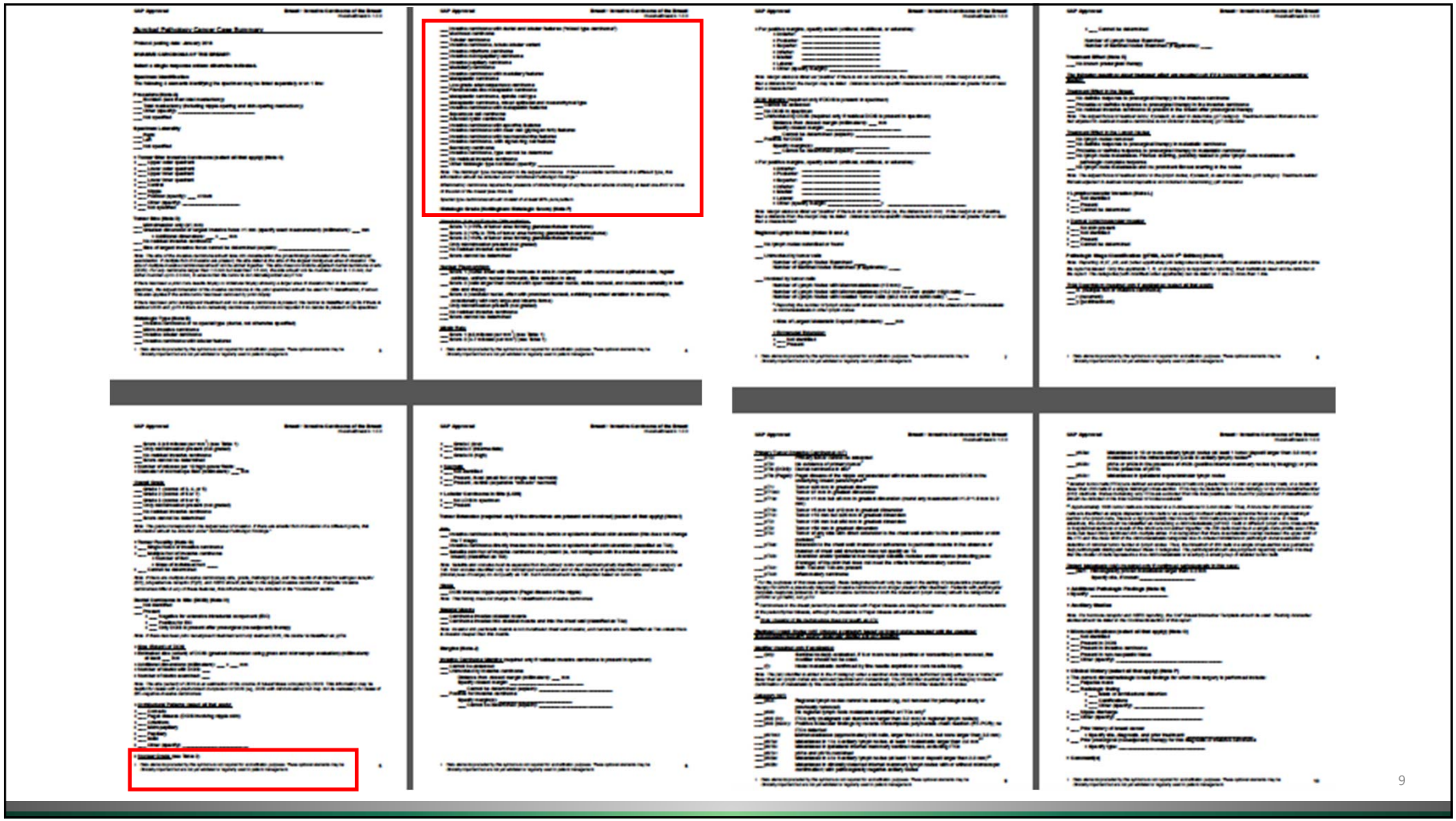

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Histologic Type (Note E)

___ 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.

___ Adenoid cystic carcinoma
___ 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"

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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 Carcin

Microinvasive carcinoma

Invasive carcinoma of no special type (NS

- Pleomorphic carcinoma
- Carcinoma with osteoclast-like st
- Carcinoma with choriocarcinomat
- Carcinoma with melanotic feature

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

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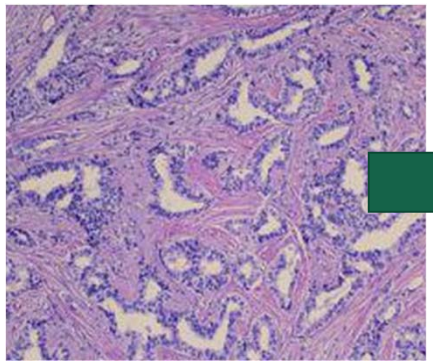
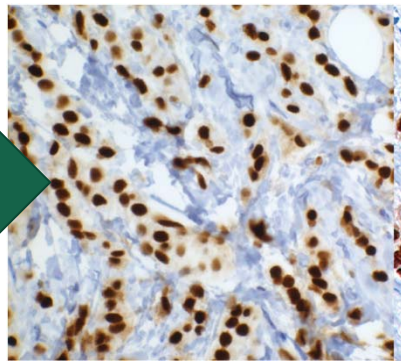
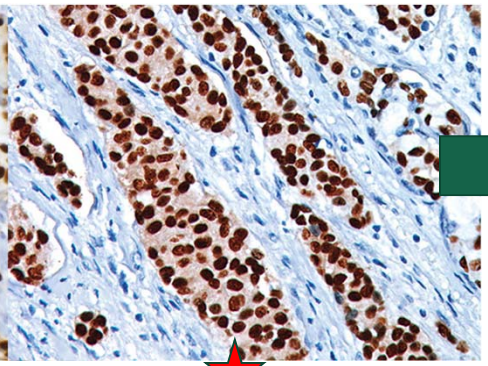
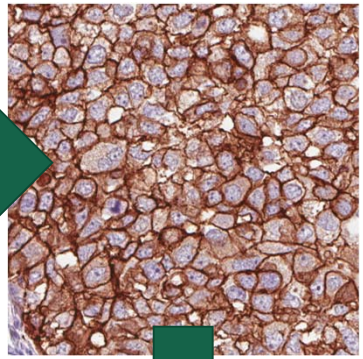
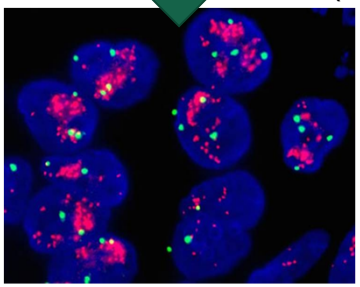
Standard Pathology Diagnostics for Breast CA











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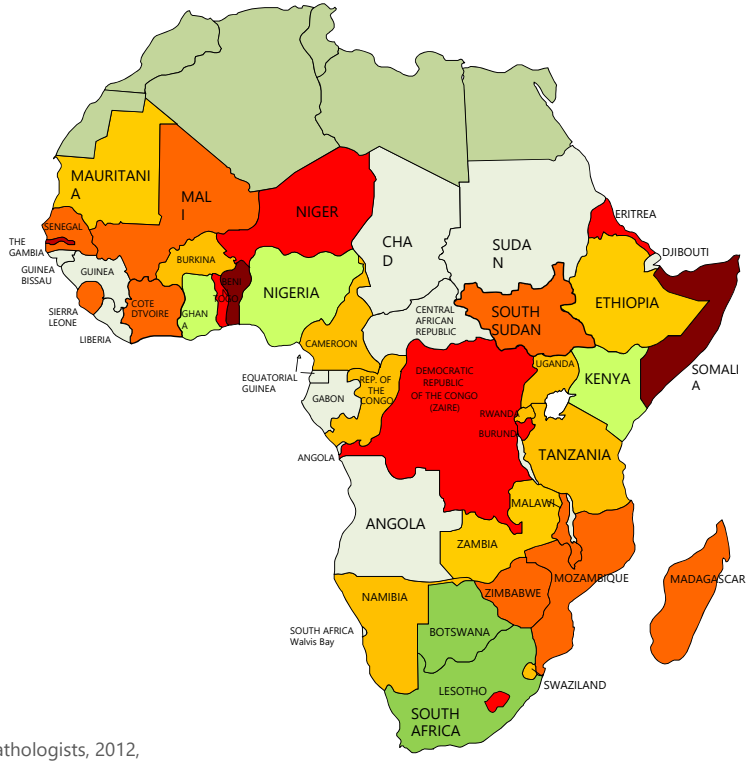
Number of People Served By Each Pathologist in Sub-Saharan Africa

- No Active Pathologist
- >5.0 million
- 2.5-5.0 million
- 1.0-2.5 million
- 500,000-1 million
- 200,000-500,000
- Data Not Available



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

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

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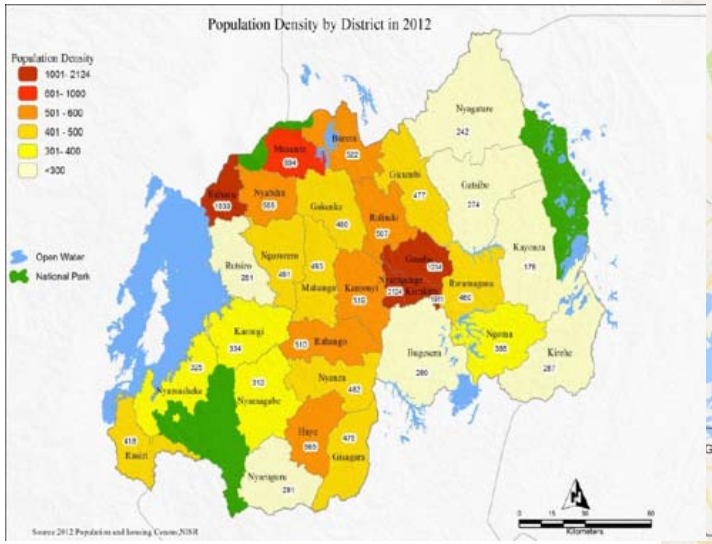
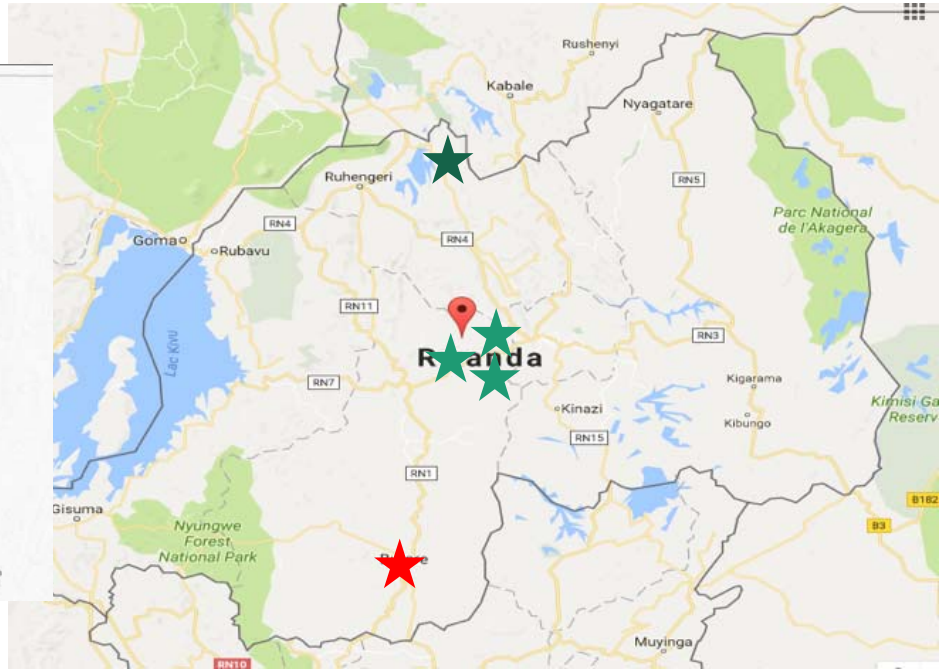
Rwanda – 11.78 M





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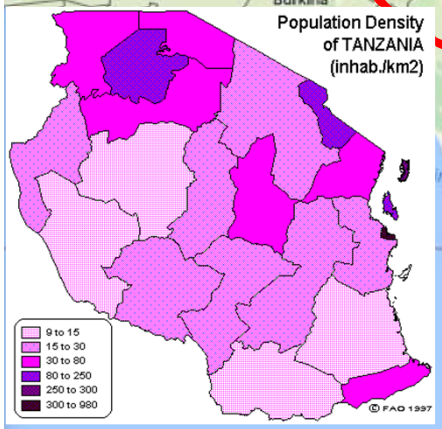
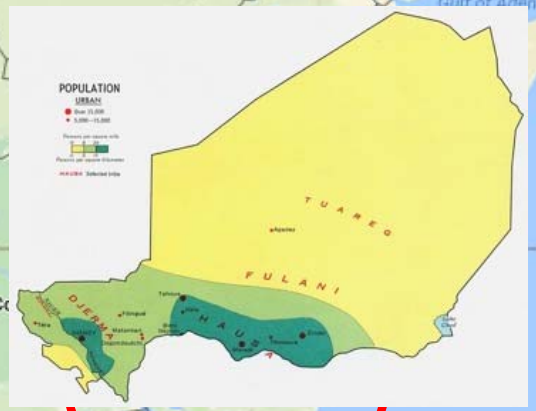
Population-specific Solutions



49.3 M

22.9 M



17.8 M

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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

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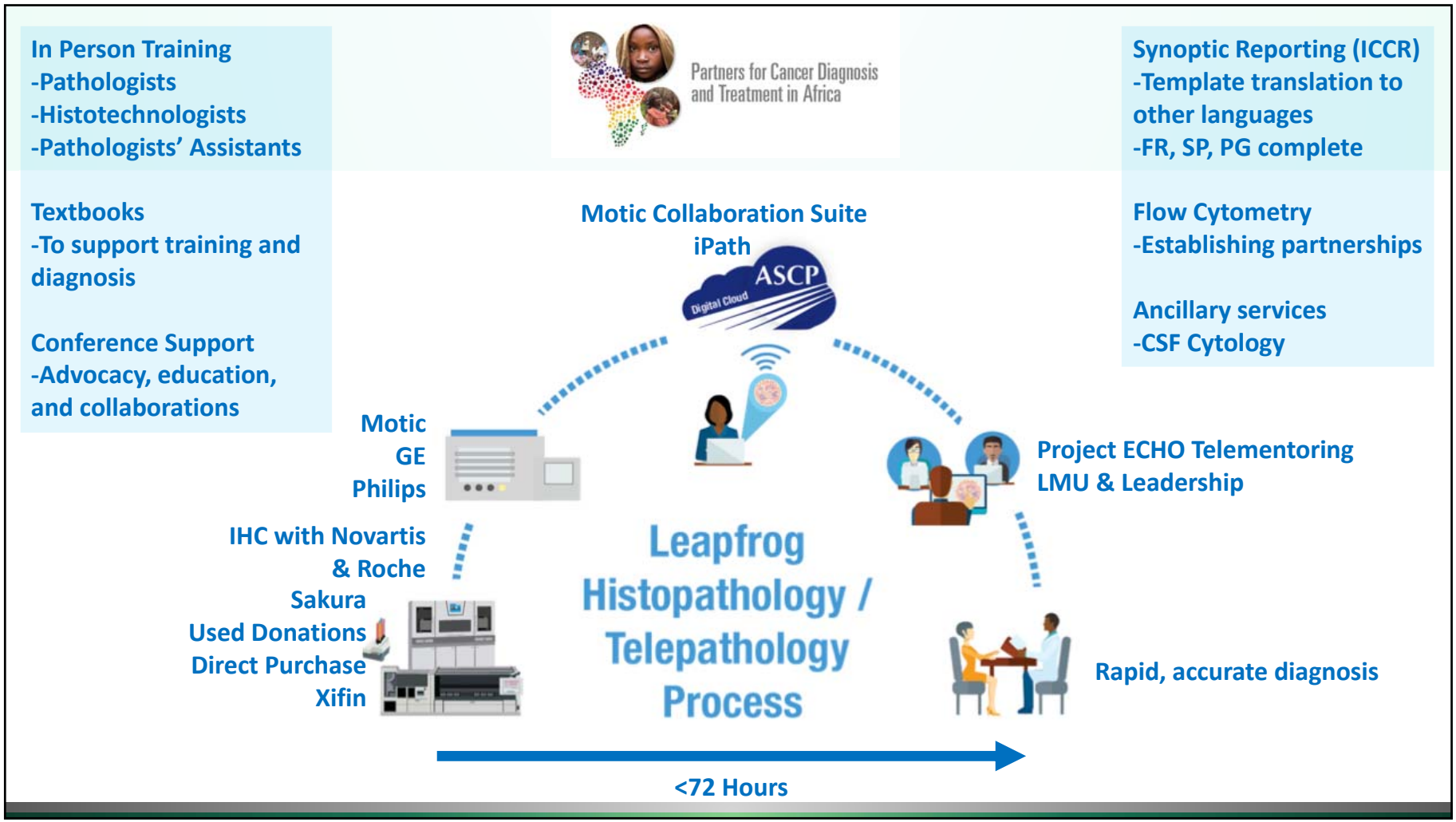

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Crowdsourcing for Pathology Diagnoses

- 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

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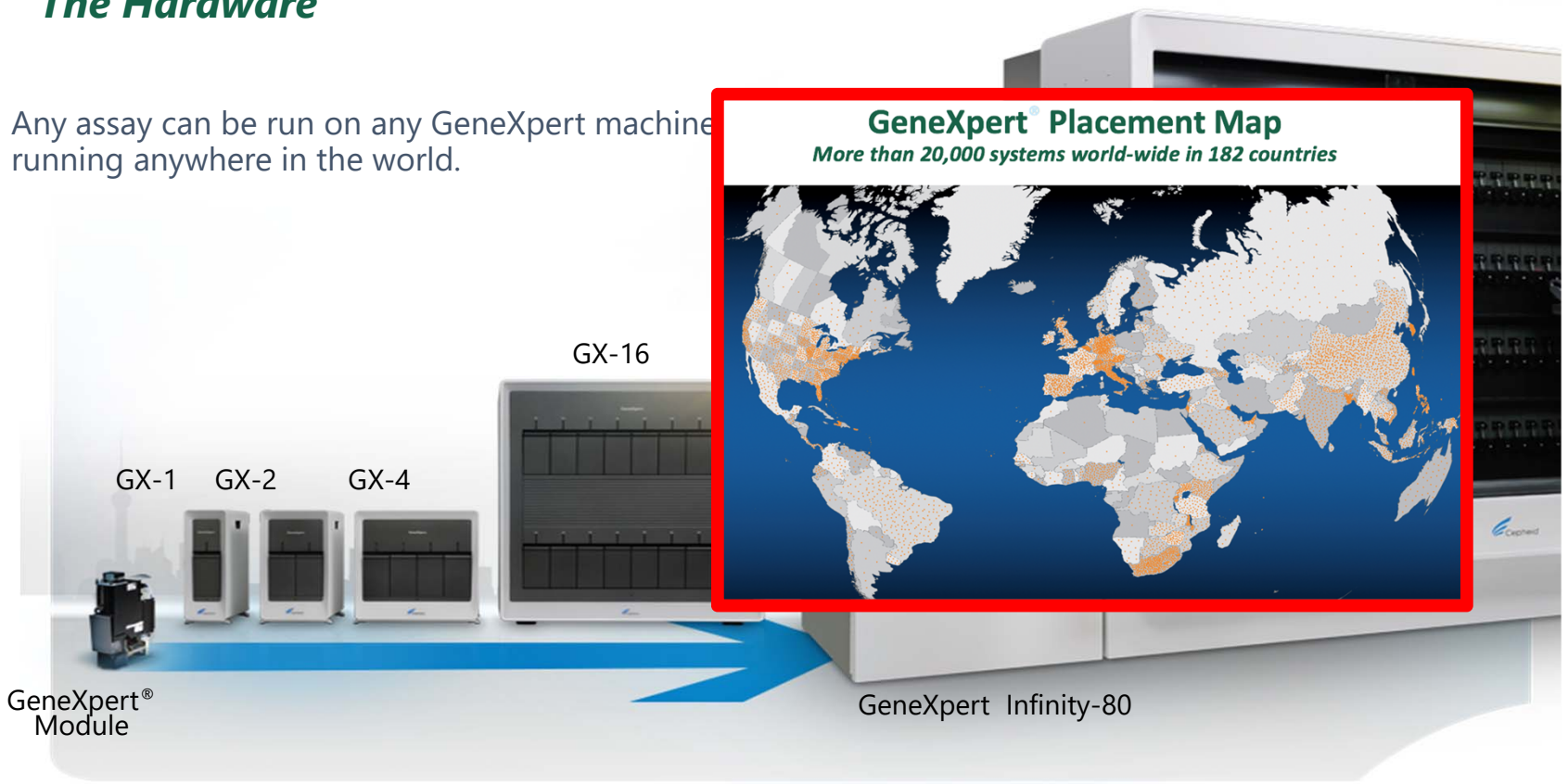
GeneXpert Platform

The Hardware

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



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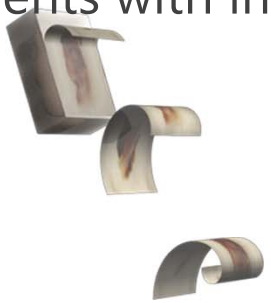
Xpert Breast Cancer STRAT4: Foundational FFPE Assay*

Launched CE-IVD in April 2017

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



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

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

3. Add lysate to GX cartridge.

4. Place cartridge in GeneXpert.

Total assay time-to-result ~ 75 minutes

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

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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

CrossMark

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. Wu[1] · Wendy Wong[1] · Kenneth E. Ho[1] · Victor C. Chu[1] · Annaliza Rizo[1] · Simon Davenport[2] · Devon Kelly[3] · Rosemary Makar[3] · Jacek Jassem[4] · Renata Duchnowska[5] · Wojciech Biernat[4] · Barbara Radecka[6] · Tomoyuki Fujita[7] · Jonathan L. Klein[8] · Mark Stonecypher[8] · Shoichiro Ohta[9] · Hartmut Juhl[10] · Jodi M. Weidler[11] · Michael Bates[11] · Michael F. Press[2]

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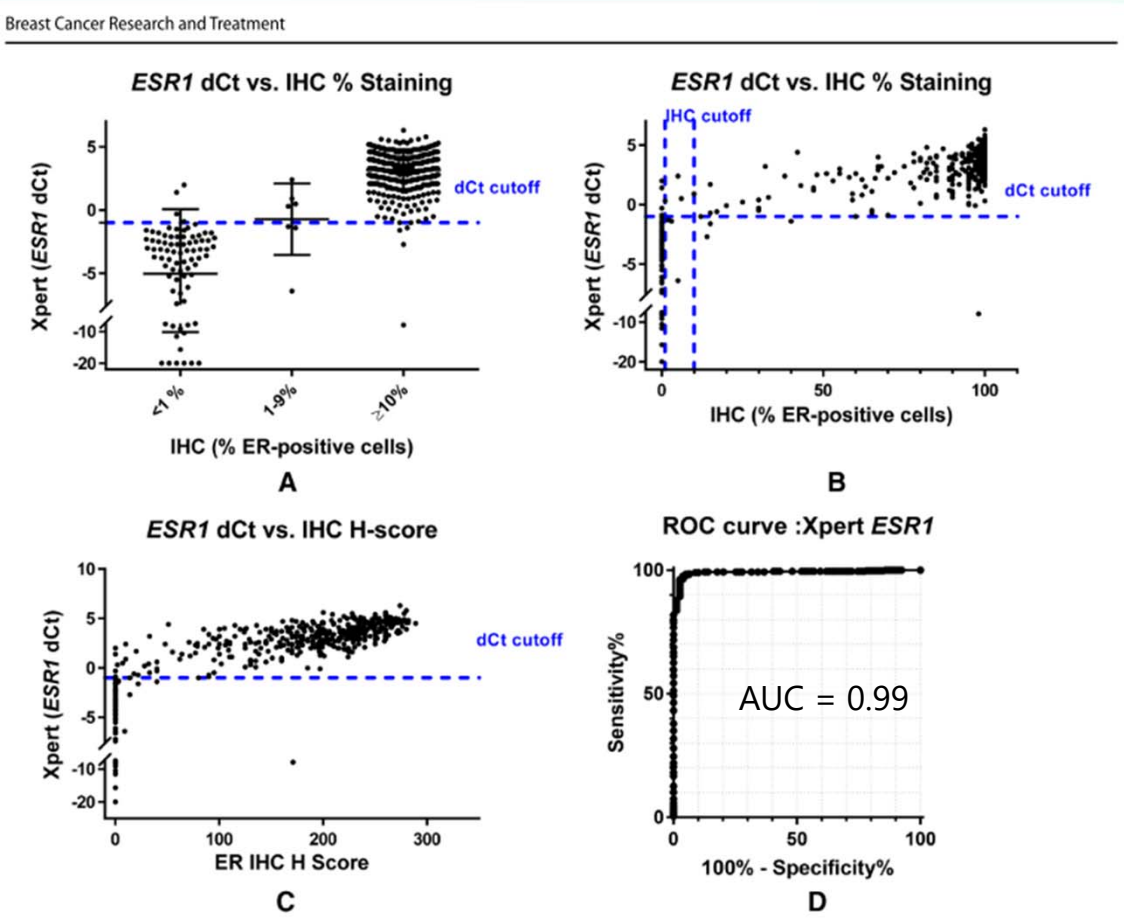
STRAT4 performance:

ER/ESR1 concordance with IHC



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

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Xpert Breast Cancer STRAT4 Collaborations in Africa

US/EU and African Collaborators

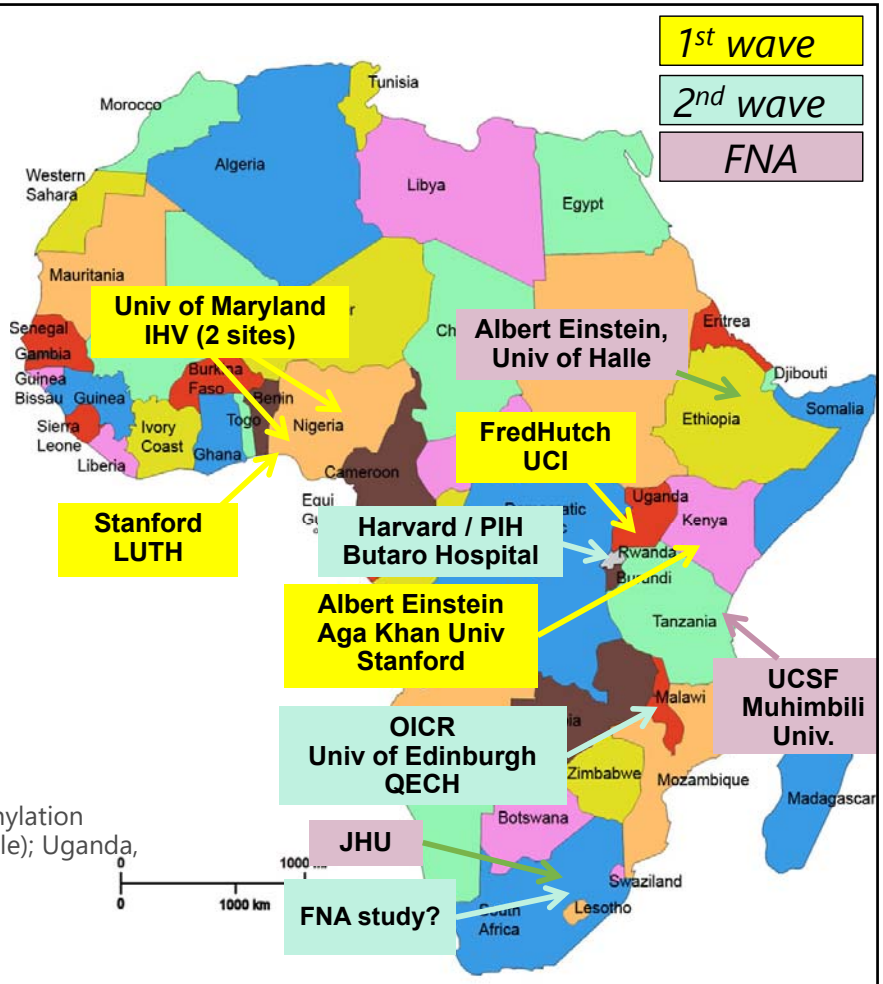
FFPE Studies - Ongoing:

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



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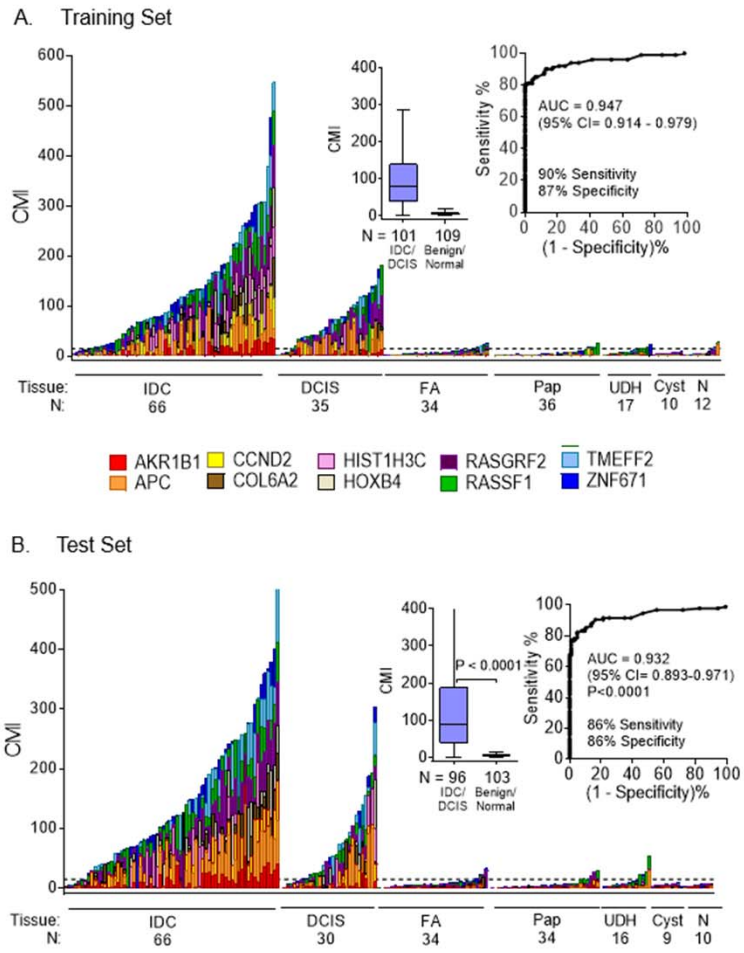
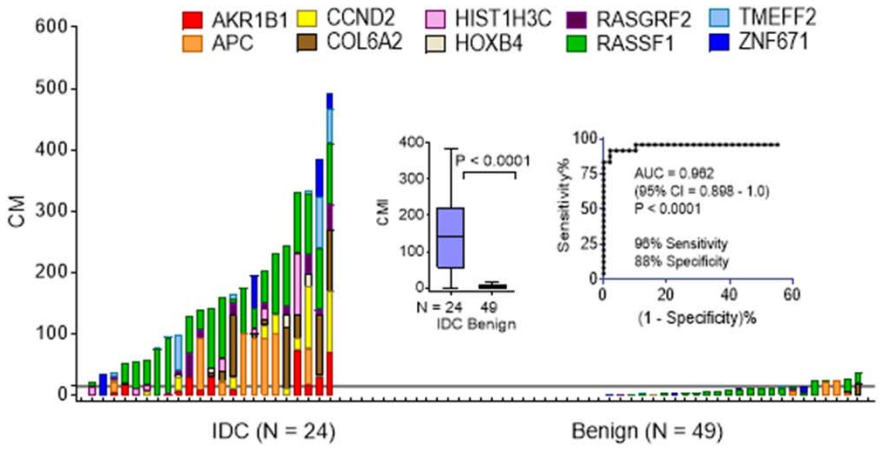


Rapid Diagnosis of Breast Cancer Using a Signature of Methylated DNA Markers and FNA tissue Tested on the GeneXpert Platform

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)



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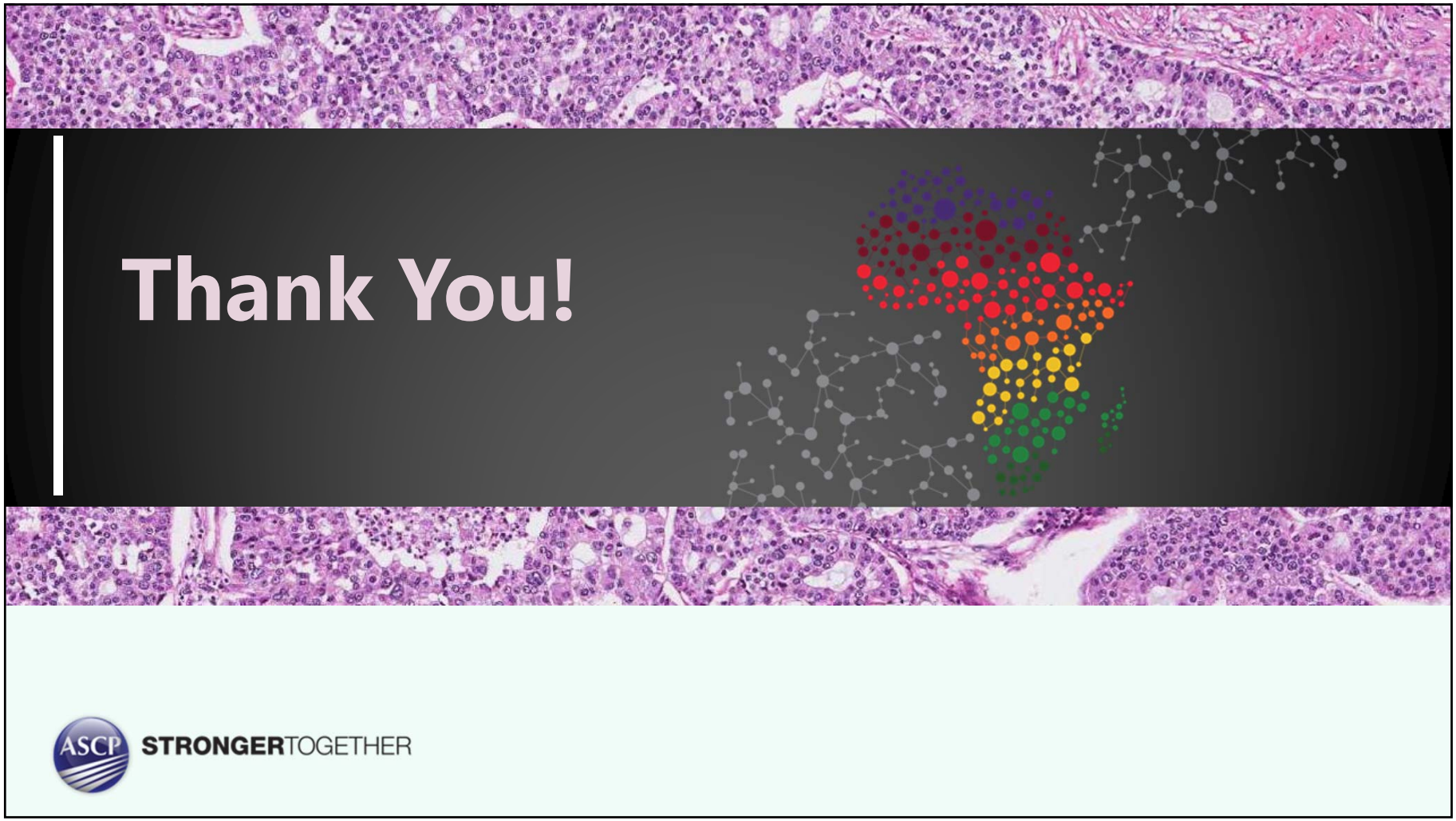

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Additional Slides not presented for review

- These slides provide some additional information about partnerships for solving these challenges as well as the known delays in the pathology value chain and now 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
  - Not aware of cancer as a disease (Education, public awareness)
  - Fear of death, loss of body image (CHW outreach, Survivor Stories)
  - Lack of resources for accessing system (Insurance schemes and donor programs)
- Clinical acumen
  - Not aware of cancer as a disease (National Cancer Control Plans)
  - No guiding documentation (Tiered Training across health sector)
  - Lack of resources for diagnosis (Clinical network procurement plans)

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Delay & (Solutions) In Pathology Value Chain

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

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Delay & (Solutions) In Pathology Value Chain

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

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Delay & (Solutions) In Pathology Value Chain

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

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