Pathology for Treatment Planning – Standard and Novel Techniques

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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
SPD for Hematological Malignancy
SPD for CML

POSITIVE PERIPHERAL BLOOD SMEAR

bcr-abl Testing

Imatinib Treatment

MAX Foundation – Novartis - Ceph
NCCN Guidelines Version 2.2018
Invasive Breast Cancer

CLINICAL STAGE

<table>
<thead>
<tr>
<th>WORKUP</th>
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<tbody>
<tr>
<td>• History and physical exam</td>
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<tr>
<td>• Diagnostic bilateral mammogram; ultrasound as necessary</td>
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</table>
| • Pathology review
g | • Determination of tumor estrogen/progesterone receptor (ER/PR) status and HER2 status
| • Genetic counseling if patient is high risk for hereditary breast cancer
d | • Breast MRI\textsuperscript{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\textsuperscript{g} |

For clinical stage IIB, consider additional studies only if directed by signs or symptoms:\textsuperscript{h}

- 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)

If clinical stage IIIA T3, N1, M0 strongly consider:
- 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/CT\textsuperscript{i} (category 2B)
- FDG PET/CT,\textsuperscript{j} (optional)

If considering preoperative systemic therapy for HER2-positive N1 tumors, See Principles of Preoperative Systemic Therapy (BINV-14) and See Workup (BINV-11).

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.

If 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.

\textsuperscript{a}The panel endorses the College of American Pathologists Protocol for pathology reporting for all invasive and non invasive carcinomas of the breast. http://www.cap.org.

\textsuperscript{b}See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.

\textsuperscript{c}See NCCN Guidelines for Dedicated Breast MRI Testing (BINV-B).

\textsuperscript{d}See Fertility and Birth Control (BINV-C).

\textsuperscript{e}See Principles of HER2 Testing (BINV-A).

\textsuperscript{f}See Principles of HER2 Testing (BINV-A).

\textsuperscript{g}See Principles of HER2 Testing (BINV-A).

\textsuperscript{h}See Principles of HER2 Testing (BINV-A).

\textsuperscript{i}See Principles of HER2 Testing (BINV-A).

\textsuperscript{j}See Principles of HER2 Testing (BINV-A).

\textsuperscript{k}See Principles of HER2 Testing (BINV-A).

\textsuperscript{l}See Principles of HER2 Testing (BINV-A).

\textsuperscript{m}See Principles of HER2 Testing (BINV-A).

\textsuperscript{n}See Principles of HER2 Testing (BINV-A).

\textsuperscript{o}See Principles of HER2 Testing (BINV-A).

\textsuperscript{p}See Principles of HER2 Testing (BINV-A).
NCCN Harmonized Guidelines™ for Sub-Saharan Africa
Version 2.2017
Invasive Breast Cancer

**CLINICAL STAGE**

**WORKUP**
- History and physical exam
- Diagnostic bilateral mammogram; ultrasound as necessary
- Pathology review
- Determination of tumor estrogen/progesterone receptor (ER/PR) status and HER2 status
- Genetic counseling if patient is high risk for hereditary breast cancer
- Breast MRI (optional), with special consideration for mammographically occult tumors
- Counseling for fertility concerns if premenopausal
- Assess for distress

For clinical stage I-IIA, consider additional studies only if directed by signs or symptoms:
- Complete blood count (CBC)
- Comprehenstive 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)

If clinical stage IIIA (T3, N1, M0) consider:
- CBC
- Comprehenstive 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 (category 2B)
- FDG PET/CT (optional)

See Preoperative Systemic Therapy for Operable Breast Cancer: Workup (BINV-10)
Or
See Preoperative Systemic Therapy for Inoperable or Locally Advanced Breast Cancer (Non-Inflammatory): Workup (BINV-14)

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**If HER2 testing is not available, follow HER-negative pathway.

**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 at a basic level, have a discussion with patient and family members.
### 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”
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 stromal giant cells
- Carcinoma with choriocarcinomatous stromal pattern
- Carcinoma with melanotic features

Invasive lobular carcinoma
- Classic lobular carcinoma
- Solid lobular carcinoma
- Alveolar lobular carcinoma
- Pleomorphic lobular carcinoma
- Tubular lobular carcinoma
- Mixed lobular carcinoma
- Tubular carcinoma
- Cribriform carcinoma
- Micropapillary carcinoma
- Carcinoma with medullary features
- Medullary carcinoma
- Atypical medullary carcinoma
- Invasive micropapillary carcinoma
- Invasive micropapillary carcinoma NST with medullary features
- Carcinoma with apocrine differentiation
- Carcinoma with signet ring cell differentiation
- Carcinoma with apocrine differentiation
- Carcinoma with signet ring cell differentiation
- Metaplastic carcinoma of no special type
- Low-grade adenocarcinoma
- Fibromatosis-like metaplastic carcinoma
- Squamous cell carcinoma
- Spindle cell carcinoma
- Metaplastic carcinoma with mesenchymal differentiation
- Chondroid differentiation
- Osteosarcoma differentiation
- Other types of mesenchymal differentiation
- Mixed metaplastic carcinoma
- Myoepithelial carcinoma
- Papillary carcinoma
- Encapsulated papillary carcinoma with invasion
- Solid papillary carcinoma, invasive
- Epithelial-myofibroblastic tumors
- Adenomyofibromatosis 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
- Onocytic 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
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
Rwanda – 11.78 M
Population-specific Solutions

- Tanzania: 49.3 M
- Madagascar: 17.8 M
- Mozambique: 22.9 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
In Person Training
-Pathologists
-Histotechnologists
-Pathologists’ Assistants

Textbooks
-To support training and diagnosis

Conference Support
-Advocacy, education, and collaborations

Motic Collaboration Suite

iPath

Philips

Sakura

Used Donations

Direct Purchase

Xifin

Synoptic Reporting (ICCR)
-Template translation to other languages
-FR, SP, PG complete

Flow Cytometry
-Establishing partnerships

Ancillary services
-CSF Cytology

IHC with Novartis & Roche

Rapid, accurate diagnosis

<72 Hours

Leapfrog Histopathology / Telepathology Process

Project ECHO Telementoring
LMU & Leadership

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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.
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*

*11 posters presented thus far with manuscripts in preparation

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

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

Launched CE-IVD in April 2017

*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 Biernat⁶ · Barbara Radecka⁶ · Tomoyuki Fujita⁷ · Jonathan L. Klein⁸ · Mark Stonelypher⁹ · 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

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

**FFPE Studies - Ongoing:**
- Kenya: Shahin Sayed/P. Castle/Christina Kong
- Nigeria (Lagos): Ami Bhatt/Adekunbiola Banjo
- Nigeria (Abuja/Ibadan): Clement Adebamowo

**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

Performance in FNA Specimens (time-to-result ~4 hours)
Thank You!
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.
# Providing Pathology Services in Resource Restriction or Establishing Equity in Diagnostics for Cancer

<table>
<thead>
<tr>
<th>Type of program</th>
<th>Pros/Cons</th>
</tr>
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<tbody>
<tr>
<td>• Volunteer Programs</td>
<td>• Expertise/Sustainability</td>
</tr>
<tr>
<td>• Donor Funding</td>
<td>• Resources/Sustainability</td>
</tr>
<tr>
<td>• Donor Equipment</td>
<td>• Capacity/Service contracts</td>
</tr>
<tr>
<td>• Public-Private Partnerships</td>
<td>• Many/Complexity</td>
</tr>
<tr>
<td>• Grant Funding</td>
<td>• Resources/Duration &amp; Sustainability</td>
</tr>
<tr>
<td>• Insurance Models</td>
<td>• Many/Political negotiations</td>
</tr>
<tr>
<td>• Coalitions/Initiatives</td>
<td>• Many/Competition</td>
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Delay & (Solutions) In Pathology Value Chain

• Patient presentation
  1. Not aware of cancer as a disease (Education, public awareness)
  2. Fear of death, loss of body image (CHW outreach, Survivor Stories)
  3. Lack of resources for accessing system (Insurance schemes and donor programs)

• Clinical acumen
  1. Not aware of cancer as a disease (National Cancer Control Plans)
  2. No guiding documentation (Tiered Training across health sector)
  3. Lack of resources for diagnosis (Clinical network procurement plans)
Delay & (Solutions) In Pathology Value Chain

• Biopsy tools
  ① No simple tools (FNA) available (Training in FNA/FNB + essential tools)
  ② No biopsy tools (surgical) available (Training in Biopsy + essential tools)

• Specimen Transportation
  ① No formalin available (Defined specimen transport network)
  ② No specimen containers/requisitions (Supplies exchange program)
  ① 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
  1. On paper reporting (APLIS with networking across system)
  2. No laboratory information system (APLIS with networking across system)
  3. No standardize reporting (Synoptic reporting to international standards)
  4. No electronic reporting systems (APLIS with networking across system)

• Communications
  1. Difficult channels between pathology and clinicians
    • (Synoptic reporting)
    • (Interdisciplinary teams)
    • (Standardize requisition forms with rejection rules)