Improving the lives of Breast Cancer Patients in Africa
Impact of Histopathology

Accra, Ghana – March 2016
Roche Pharmaceutical & Diagnostics
Impact of the histopathology in BC management
What is histopathology?
The role of the pathologist

Tissue sample acquired through surgery, biopsy, fine needle aspiration...

... need to be processed to make it compatible for staining and stained...

... such as the pathologist can interpret morphological & biological features for diagnosis and treatment decision
How do we get the tissue sample and how do we process it to make it compatible for anatomo-pathology analysis?
What is histopathology?
The role of the pathologist

Tissue sample acquired through surgery, biopsy, fine needle aspiration ...

... need to be processed to make it compatible for staining and stained...

... such as the pathologist can interpret morphological & biological features for diagnosis and treatment decision
1. Accessioning

Specimens are received in the histology laboratory before gross examination.

- Specimens are given a case number
  - Computer system
  - Logbook
- Request sheet and specimen containers are properly labeled
- Cassettes are made
- Accuracy of all the above is checked.

This process ‘can be’ a MAJOR source of error in the histology laboratory.
2. Gross examination

Tissues must then undergo gross examination and dissection

Gross examination or “grossing” consists of:
- Describing the specimen’s size, shape, color and any apparent abnormalities
- Description of margins and their orientation

Depending on the size and type of specimen, it is either submitted entirely or a 'representative' section is taken. The tissue is placed into small plastic cassette, which will allow fluids to infiltrate the specimens in the processing step.
2. Gross examination
Grossing

- Check fixation status
- Prepare thin slices 2-3 mm
- Avoid specimen trauma
- Avoid cross-contamination
- Avoid overloading cassettes
- Clearly and properly label cassettes
Fixation

Definition:
alters tissue by stabilizing the protein so it is resistant to further changes

A fixative must change the soluble contents of the cell into insoluble substances so that those substances are not lost during subsequent processing steps.
The purpose of tissue processing is to transform the cut tissue into a form hard enough to enable cutting into very thin sections.

This is done by a series of steps to remove water, ultimately infiltrating the tissue with paraffin wax.
1. Fixation: The purpose is to preserve tissues permanently in a state similar that it was taken from the body.

2. Dehydration: Tissue samples are placed in a series of graded alcohols, usually beginning with 70% and ending with 100%.

3. Clearing: An organic solvent (e.g., Xylene) is used as an intermediary step because alcohol and paraffin are not compatible.

4. Infiltration: Tissue samples are then placed into changes of melted paraffin wax.
Embedding

- Tissue samples come off the tissue processor and are manually oriented in embedding molds.
- The bottom of the cassette which contains the accession number is placed then over the mold.
- The mold and cassette are then filled with more molten paraffin.
- The paraffin is then allowed to solidify on a refrigerated surface.
- Once the paraffin is solid the solid block is ready to be cut thin
Microtomy

- A microtome is used to cut very thin precise paraffin sections. (3-6 microns)
- Due to friction, heat is generated on the knife to form a wax ribbon of tissue sections.
- This ribbon is floated on a warm water bath to remove any wrinkles and allows the ribbon to be picked on a slide.
- A positively charged slide should be used for all Immunohistochemical (IHC) procedures.
Sectioning – Slide Drying

The slides are then placed in a oven to evaporate the water on the slide and to properly adhere the section on the slide.

Recommendation:

- 60°C for a maximum of 60 minutes,
- 37°C for a maximum of 24 hours,
- or at ambient temperature for 24 hours or longer
Workflow
Manual Process or Automation

eliminate up to 80% of the labor required for manual and semi-automated staining
Pathology lab flow

Pre-Analytical
- Tissue preparation
- Tracking
- Grossing
- Fixation
- Processing

Primary Staining
- H&E
- SS
- Binary Diagnosis
- Tissue morphology

Advanced Staining
- IHC
- ISH
- Detecting protein and/or molecular target
- Diagnosis
- Predictive / Prognostic

Imaging / Reporting
- Image analysis
- Quantitative
- Report generation
- Tele-pathology
- Archiving

Next Generation Imaging
Anatomo-morphology

What are the main subtype of Breast Cancer according to anatomo-pathology?
The structure of the female breast is complex — including fat and connective tissue, as well as lobes, lobules, ducts and lymph nodes.

Lobes
15 to 20 sections arrange like the petals of daisy
Inside each are many smaller structures
called lobules
At the end of each lobule are tiny sacs (bulbs) that produce milk

Ducts
Lobes, lobules and bulbs are linked by a network of thin tubes (ducts)
Carry milk from bulbs to the areola

Breast has no muscle tissue

Muscles underneath the Breasts separating them from the ribs

lymph nodes & lymph ducts
Drain fluid that carries white blood cells from the breast tissues into lymph nodes that filter harmful bacteria (play a key role in fighting off infection)

http://www.mayoclinic.org
Type of Breast Cancer

About 80%

10 to 20%
Ductal Carcinomas In Situ (DCIS)

Ducts
Lobes, lobules and bulbs are linked by a network of thin tubes (ducts)
Carry milk from bulbs to the areola
Lobes

Lobular Carcinomas In Situ (LCIS)

15 to 20 sections arrange like the petals of daisy. Inside each are many smaller structures called lobules. At the end of each lobule are tiny sacs (bulbs) that produce milk.
What is the molecular subtype?
### Histologic vs. Molecular subtypes

<table>
<thead>
<tr>
<th><strong>Histological subtypes</strong></th>
<th><strong>Ductal</strong></th>
<th><strong>Lobular</strong></th>
<th><strong>Molecular subtypes</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preinvasive cancer</strong></td>
<td>Ductal carcinoma in situ (DCIS) 80% May spread through ducts and distort duct architecture 1% progress to invasive cancer per year Usually unilateral</td>
<td>Lobular carcinoma in situ (LCIS) 20% Does not distort duct architecture Same genetic abnormality as ILC – E-cadherin loss 1% progress per year Can be bilateral</td>
<td><strong>Triple negative</strong> ER−, PR−, HER2−</td>
</tr>
<tr>
<td>25% Cells limited to basement membrane</td>
<td></td>
<td></td>
<td><strong>HER2+</strong></td>
</tr>
<tr>
<td><strong>Invasive cancer</strong></td>
<td>Invasive ductal carcinoma (IDC) 79% Usually from DCIS precursor Cause fibrous response, producing a palpable mass on examination Metastasis through lymphatics and blood</td>
<td>Invasive lobular carcinoma (ILC) 10% Usually from LCIS precursor Minimal fibrous response, presents less often with palpable mass Metastasis through abdominal viscera to GI, ovaries, uterus Almost always ER+</td>
<td><strong>Luminal B</strong></td>
</tr>
<tr>
<td>75% Extension beyond the basement membrane</td>
<td></td>
<td></td>
<td><strong>Luminal A</strong></td>
</tr>
<tr>
<td><strong>Histologic grade</strong></td>
<td>High (grade III)</td>
<td>Low (grade I)</td>
<td></td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Poor</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td><strong>Response to medical therapy</strong></td>
<td>Chemotherapy</td>
<td>Trastuzumab</td>
<td>Endocrine</td>
</tr>
<tr>
<td><strong>% of breast cancers</strong></td>
<td>15-20%</td>
<td>10-15%</td>
<td>20%</td>
</tr>
<tr>
<td><strong>Receptor expression</strong></td>
<td>HER2</td>
<td>ER+/PR+</td>
<td></td>
</tr>
</tbody>
</table>

Breast Cancer: Facts and Numbers
Impact of histopathology in treatment decision
Immunohistology
Explanation text
Why HER2 testing?

The HER2 pathway

**HER family:**
HER1 (EGFR), HER2, HER3, HER4

**Receptor Ligant specific:**
HER1 (EGFR), HER3, HER4, HER2 no ligant

**Dimerization:**
Signaling pathway activation

**Oncogenic process:**
Cell proliferation, survival, mobility, invasiveness
Why HER2 testing?

Prognostic factor

Kaplan–Meier curves for HER2 status. Survival curves showing cumulative survival between patients + or -.

Tovey SM et al, British Journal of Cancer (2009) 100, 680–683
Why HER2 testing?
Predictive factor

Dawood et al., JCO January 1, 2010 vol. 28 no. 1 92-98
How do we test for HER2?

Technical point of view

ImmunoHistoChemistry

Expression level of HER2 protein

In Situ Hybridization

Determination of HER2 gene amplification status
How do we test for HER2?

Guidelines

Pre analytics recommendations
- Ischemia, fixation, best practice...

Scoring guidelines
- Algorithm
- IHC reading rules
- ISH reading rules

Testing guidelines
- FDA approved test

Reporting guidelines
How do we test for HER2?

Testing Algorithm:

1. Patient tumor sample
2. IHC
   - 0
   - 1+
   - 2+
   - 3+
3. ISH
   - -
   - +
How do we test for HER2?

How does the algorithm work?

**Patient tumor sample**

- Controls passed
- No significant staining in normal epithelium

**IHC**

- Weak to moderate
- Incomplete >10%
- Intense ≤10%

- -
- 0
- 1+

- Neg./barely visible
- ≤10% / > 10%

(40x mag., detailed analysis!)

- 2+
- 15-20%
- Intense staining
- Ring shaped>10%

(5x magnification; be aware of artifacts! (edge effect, cytoplasm)

- * in any doubt: score 2+

- 3+
- 10-20%

- +
- 15-25%

Eligible for Herceptin

- -
- 

- +

- overestimate?
How do we test for HER2?

HER2 IHC interpretation

HER2 testing (invasive component) by validated IHC assay

Batch controls and on-slide controls show appropriate staining

Circumferential membrane staining that is complete, intense, and within > 10% of tumor cells*  

IHC 3+ positive

Circumferential membrane staining that is incomplete and/or weak/moderate and within > 10% of tumor cells*

IHC 2+ equivocal

Incomplete membrane staining that is faint/barely perceptible and within > 10% of tumor cells*

IHC 1+ negative

No staining is observed* or Membrane staining that is incomplete and is faint/barely perceptible and within ≤ 10% of tumor cells

IHC 0 negative

Must order reflex test (same specimen using ISH) or order a new test (new specimen if available, using IHC or ISH)
Are all IHC tests the same?
How do we test for HER2?

HER2 IHC quality

High Specificity

High Sensitivity

Pre-dilute

EQA

High ISH concordance$^{1,2,3}$

How do we test for HER2?
HER2 IHC quality

Suff. OPS 2 = with optimal protocol

<table>
<thead>
<tr>
<th>Competition Ab (Herceptest)</th>
<th>Ventana Ab (HER2 4B5)</th>
<th>Concentrated Ab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor</td>
<td>Good</td>
<td>Optimal</td>
</tr>
<tr>
<td>83%</td>
<td>56%</td>
<td>15%</td>
</tr>
<tr>
<td>15%</td>
<td>5%</td>
<td>24%</td>
</tr>
<tr>
<td>4%</td>
<td>2%</td>
<td>7%</td>
</tr>
<tr>
<td>23%</td>
<td>13%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Run

Pass rate

Competition Ab (Herceptest)
Ventana Ab (HER2 4B5)
Concentrated Ab
In Situ Hybridization (ISH)
How do we test for HER2?

HER2 gene alteration

**DNA**

- HER2 gene copy # alterations (amplification or polysomy)
- HER2 gene mutations

**RNA**

- HER2 RNA overexpression

**PROTEIN**

- HER2 protein overexpression
- HER2 post-translational modifications (e.g., phosphorylation)

How do we test for HER2?

HER2 gene alteration

Non amplified $\rightarrow$ Non overexpressed

Amplified $\rightarrow$ Overexpressed
How do we test for HER2?

HER2 ISH

- Historical « Gold Standard » is FISH
- ISH method with non-fluorescent detection for detection of HER2 status
How do we test for HER2?

**HER2 ISH interpretation**

1. **Patient tumor sample**
   - **IHC**
     - 0
     - 1+
     - 2+
     - 3+
   - **ISH**
     - -
     - +

2. **HER2 testing (invasive component)** by validated dual-probe ISH assay
   - Batch controls and on-slide controls show appropriate hybridization

3. **HER2/CEP17 ratio** ≥ 2.0*
   - Average HER2 copy number ≥ 4.0 signals/cell*
     - **ISH positive**
   - Average HER2 copy number < 4.0 signals/cell*
     - **ISH positive**

4. **HER2/CEP17 ratio** < 2.0
   - Average HER2 copy number ≥ 4.0 and < 6.0 signals/cell*
     - **ISH positive**
   - Average HER2 copy number < 4.0 signals/cell
     - **ISH negative**

*Must order a reflex test (same specimen using IHC), test with alternative ISH chromosome 17 probe, or order a new test (new specimen if available, ISH or IHC).*
How do we test for HER2?
Technical point of view

**Dual ISH (brightfield ISH)**
- Fully automated
- Brightfield microscopy
- Morphological context
- Archivable
- High sensitivity (detection of single gene copy)

**FISH (Fluorescent ISH)**
- Manual Assay
- Does not fit into a pathologist's workflow (i.e. fluorescent microscope necessary)
- Poor morphology
- Non-archiviable: signal quenches over time
How do we test for HER2?
Morphological context

A
B

A
B

A
B
How do we test for HER2?

Technical point of view

Bright-field In Situ Hybridization for HER2 Gene Amplification in Breast Cancer Using Chromogenic (ISH) Methods

Correlation Between Chromogenic (ISH) and Silver-enhanced (SISH) Methods

Jung Bik Jang, Eun Jeong Jang and Ji-Young
Department of Pathology, Kyungpook National University Hospital

Dual-color silver-enhanced hybridization for assessing amplification in breast cancer

Young Wha Koh, Ho Jin Lee, Jong Won Lee, Jung Ok Sung

Comparison of automated silver enhanced in situ hybridisation (SISH) and fluorescence ISH (FISH) for the validation of HER2 gene status in breast carcinoma according to the guidelines of the American Society of Clinical Oncology and the College of American Pathologists

M. Dietel, I. O. Ellis, H. Höfle, H. Kreipe, H. Moch, A. Dankof, K. Köhlé, G. Kristiansen

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© Springer-Verlag 2007

Kirsten Gadgaard Jensen, HT, and Vibeke Jensen, MD, PhD
How do we test for HER2?
Interpretation support

Interpretation Guide
Ventana INFORM HER2 Dual ISH
DNA Probe Cocktail Assay

**Scoring algorithm flow diagram**

1. **Start**
2. HER2/CHR17 Stained Slide
   - Slide Adequate?
     - No → Inadequate
     - Yes → Identify and Select Target Area
3. Count HER2 and Chromosome 17 Signals in 20 nuclei
4. Calculate HER2/Chr17 ratio by dividing the total number of HER2 signals from Target Area 1 by total number of Chr17 signals from Target Area 1
5. Is $1.8 \leq \frac{\text{HER2}}{\text{Chr17}} \leq 2.2$?
   - Yes → Count additional 20 nuclei
   - No → Calculate HER2/Chr17 ratio by dividing the total number of HER2 signals from Target Areas 1 and 2 by the total number of Chr17 signals from Target Areas 1 and 2
6. Report Results
   - Non-Amplified: HER2/Chr17 < 2.0
   - Positive: HER2/Chr17 ≥ 2.0
Who should be tested for HER2

Patient with newly diagnosed breast cancer

- HER2-negative
  - Not eligible for HER2-targeted therapy
    - No disease progression
    - Disease progression
      - Patient presenting with metastatic disease
        - HER2 retesting
          - HER2-negative
            - Not eligible for HER2-targeted therapy
          - HER2-positive
            - Eligible for HER2-targeted therapy
        - HER2-positive
          - Eligible for HER2-targeted therapy

- HER2-positive
  - Eligible for HER2-targeted therapy
    - No disease progression
    - Disease progression
      - Patient presenting with metastatic disease
        - HER2 retesting
          - HER2-negative
            - Not eligible for HER2-targeted therapy
          - HER2-positive
            - Eligible for HER2-targeted therapy
        - HER2-negative
          - Re-consider treatment options including HER2-targeted therapy
          - Eligible for HER2-targeted therapy

Recommendation:
ALL patients presenting with metastatic disease who were HER2-negative in the eBC setting should be retested

HER2 test performed in a metastatic site, if tissue sample is available; especially considered for a patient who previously tested HER2-negative in a primary tumour and presents with disease recurrence with clinical behaviour suggestive of HER2-positive or triple-negative disease.

How will the pre-analytics processing impact the diagnosis and the patient management?
Guidelines for pre – analytics?

1. Preheat oven to 325 degrees F (165 degrees C). …

2. Cream 1/2 cup plus 2 tablespoons butter and 1 1/2 cups sugar …. Add eggs one at a time beating after each addition. Blend in the lemon peel.

3. In a separate bowl, mix flour, salt, soda and baking powder. Add flour mixture alternately with buttermilk to creamed butter mixture. Add lemon extract and raisins.

4. Bake at 325 degrees F (165 degrees C) for 50 minutes cool 5 minutes, then turn out onto serving plate. Prick hot cake with skewer or fork and pour on lemon topping.

5. Combine 1/3 cup sugar, 1/3 cup butter and water in a saucepan and heat until butter melts. Add lemon juice . Spoon over hot cake
Anatomic pathology tissue specimen workflow
Pre analytics is not so simple

- Time to fixation
- Type of fixation
- Quality of fixative
- Duration of fixation
- Temperature of fixation
- Quantity of fixative
- Tissue to fixative ratio

Reception - Fixation

- Transfer Duration
- Transfer Temperature
- Transfer conditions
- Sample Size
- Fresh vs. fixed
- Tissue type
- Type of container

Microscopy to slide

- Spreading Temperature
- Spreading medium
- Spreading technique
- Type of slide
- Storage of slides
- Microtome temperature
- Section thickness

Dehydration - Embedding

- Processor / Protocols
- Bath duration / Week end
- Reagent turn over / Quality of reagent
- Temperature of reagents
- Temperature & melting point of wax

Drying

- Duration
- Method
- Temperature

Archive

- Duration
- Temperature
- Hygrometry
- Type of support
Targeting the Pre analytical 

1. Cold Ischemia time 
2. Fixation 
3. Tissue processing
What is cold ischemia time

Definition:
Time from the removal of the tissue from the patient to the initiation of tissue fixation

- tissue ischemia,
- acidosis,
- enzymatic degradation

Pekmezci 2012
But what can be the impact to the patient management?

Effect of Cold Ischemia time

For long ischemia time Estrogen Receptor Status might be interpreted as negative (False Negative)

Impact for patient management

No Hormonal Therapy

Higher Risk of Recurrence

Qiu 2009
But what can be the impact to the patient management?
Effect of Cold Ischemia time

For 2hrs ischemia time HER2 status is highly impacted (false negative or non interpretable)

Impact for patient management
No HER2 targeted therapies
Worse outcome for the patient

Khoury 2009
What is tissue fixation

Kills the tissue so that no post-mortem activities can occur:

- decay,
- putrification (bacterial attack)
- autolysis (enzyme attack)

must change the soluble contents of the cell into insoluble substances so that those substances are not lost during subsequent processing steps
But what can be the impact to the patient management?

Effect of Fixative type

- NBF 10% Formalin
- Alcoholic formalin
- Zn formalin
- AFA
- Bouin

Babic 2010
But what can be the impact to the patient management?

Effect of Fixative type

Use of different type of fixative will impact result (poor IHC quality, non interpretable results)

Impact for patient management
- False negative / False Positive
- Worse outcome for the patient

10% Neutral Buffered Formalin

Babic 2010
Some basic rules to keep in mind

There are 2 effects ongoing in parallel during fixation with formalin:
- Penetration of fixative
- Diffusion
- Cross-linking proteins
- \(-\text{CH}_2\text{-}\) linkage

10 min 16 hrs 5 days
Some basic rules to keep in mind

• 10% Neutral Buffered Formalin NBF: Buffer pH 7.2-7.4
• Penetration: Formalin penetrates fast, but continues to cross link proteins for a long time after penetration is complete
• Volume 10:1 in a container.
• Cut Thickness 3-5 mm
• Temperature 22°C – 37°C
But what can be the impact to the patient management?

**Effect of Fixative time**

Extended fixation time might generate weak staining

Impact for patient management

False negative

Under/no treatment / missclassification

- Epitope can be hidden through fixation
- Pretreatment will open access to the epitope

Bogen 2009
What is tissue processing

The purpose of tissue processing is to transform the cut tissue into a form hard enough to enable cutting into very thin sections.

This is done by a series of steps to remove water, ultimately infiltrating the tissue with paraffin wax.
But what can be the impact to the patient management?
Effect of Fixative processing

Avoid contamination
- Lead to false diagnosis by mixing patients

Avoid excessive heat
- Poor quality of H&E and IHC staining

Slicing quality
- Poor morphology and artifacts
Impact of the pre analytics
Impact of the pre analytics
Impact of the pre analytics
Impact of the pre analytics
Impact of the pre analytics
Quality impact not only the patient
Breast Cancer: Facts and Numbers
Diagnosis is a key element

Quality
EQA example
HER2 IHC quality (NordiQC)

Suff. OPS 2 = with optimal protocol
Socioeconomic Impact of Inaccuracy

Vyberg et al. BMC Health Services Research (2015) 15:352
DOI 10.1186/s12913-015-1018-6

RESEARCH ARTICLE

Immunohistochemical expression of HER2 in breast cancer: socioeconomic impact of inaccurate tests

Mogens Vyberg¹*, Søren Nielsen¹, Rasmus Røge¹, Beth Sheppard², Jim Ranger-Moore², Eric Walk², Juliane Gartemann³, Ulrich-Peter Rohr³ and Volker Teichgräber³
Methodology

Possible consequences of

• False Positive
• False Negative

were considered in relation to:

• direct medical costs,
• life expectancy,
• quality of life
• loss of productivity in

• early stage breast cancer (EBC; stage II and III disease) receiving systemic treatment,
• metastatic breast cancer (MBC; stage IV disease)
EQA example
HER2 IHC quality

Run
Pass rate
Suff.
OPS
2 = with optimal protocol

Competition Ab
(Herceptest)
Ventana Ab (HER2 4B5)
Concentrated Ab

FDA / CE-IVD

LD

poor
borderline
good
optimal

Suff. OPS 2 = with optimal protocol
False Positive

1 slide, 5 tissue samples:
1. Ductal carcinoma (IHC 0/1+; FISH unamplified)
2. Ductal carcinoma (IHC 0/1+; FISH unamplified)
3. Lobular carcinoma (IHC 1+; FISH unamplified)
4. Ductal carcinoma (IHC 2/3+; FISH amplified)
5. Ductal carcinoma (IHC 3+; FISH amplified)

Cores validated to have same HER2 expression and gene status; obtained from different patients

Stain and return slides for NordiQC to interpret

Staining assessed as:
- Optimal
- Good
- Borderline (low signal-to-noise ratio)
- Poor (false negative or false positive staining)

Results pooled and published every 6 months

0% For approved IVD

5% For Lab Dev IVD
False Negative

- 1 slide, 5 tissue samples:
  1. Ductal carcinoma (IHC 0/1+; FISH unamplified)
  2. Ductal carcinoma (IHC 0/1+; FISH amplified)
  3. Lobular carcinoma (IHC 1-2+; FISH unamplified)
  4. Ductal carcinoma (IHC 2+; FISH amplified)
  5. Ductal carcinoma (IHC 3+; FISH amplified)

- Cores validated to have same HER2 expression and gene status; obtained from different patients
- Stain and return slides for NordiQC to interpret
  - Staining assessed as:
    - Optimal
    - Good
    - Borderline (low signal-to-noise ratio)
    - Poor (false negative or false positive staining)
- Results pooled and published every 6 months

11% For approved IVD

25% For Lab Dev IVD
Results
Medical Cost

40,9 M$
Difference in Total direct cost for EBC (App IVD vs. LD IVD)

5,1 M$
Difference in Total direct cost for MBC (App IVD vs. LD IVD)

were considered in relation to:
• direct medical costs,
• life expectancy,
• quality of life
• loss of productivity in
  • early stage breast cancer (EBC; stage II and III disease) receiving systemic treatment,
  • metastatic breast cancer (MBC; stage IV disease)

False Negative
App. IVD = 11% vs. LD IVD = 25%

National Surgical Adjuvant Breast & Bowel Project B31
North Central Ca Treatment Group trial N9831
Phase III H0648g
Interaction between QALYs & productivity
US healthcare system
Results
Cost of lost productivity

4,2M$
Difference in Total cost of lost prod for EBC (App IVD vs. LD IVD)

0,3M$
Difference in Total cost of lost prod for MBC (App IVD vs. LD IVD)

were considered in relation to:
- direct medical costs,
- life expectancy,
- quality of life
- **loss of productivity** in
  - early stage breast cancer (EBC; stage II and III disease) receiving systemic treatment,
  - metastatic breast cancer (MBC; stage IV disease)

False Negative
App. IVD = 11% vs. LD IVD = 25%

National Surgical Adjuvant Breast & Bowel Project B31
North Central Ca Treatment Group trial N9831
Phase III H0648g
US healthcare system

interaction between QALYs & productivity

Difference in Total cost of lost prod for EBC (App IVD vs. LD IVD)

0,3M$

Results
Global impact on cost

FDA CE-IVD approved test

10M$

Laboratory Develop. test

2.5M$
Results
Global impact on cost

FDA CE-IVD approved test + FN & FP additional costs = 25,0M$

Laboratory Develop. test + FN & FP additional costs = 62,5M$
Doing now what patients need next