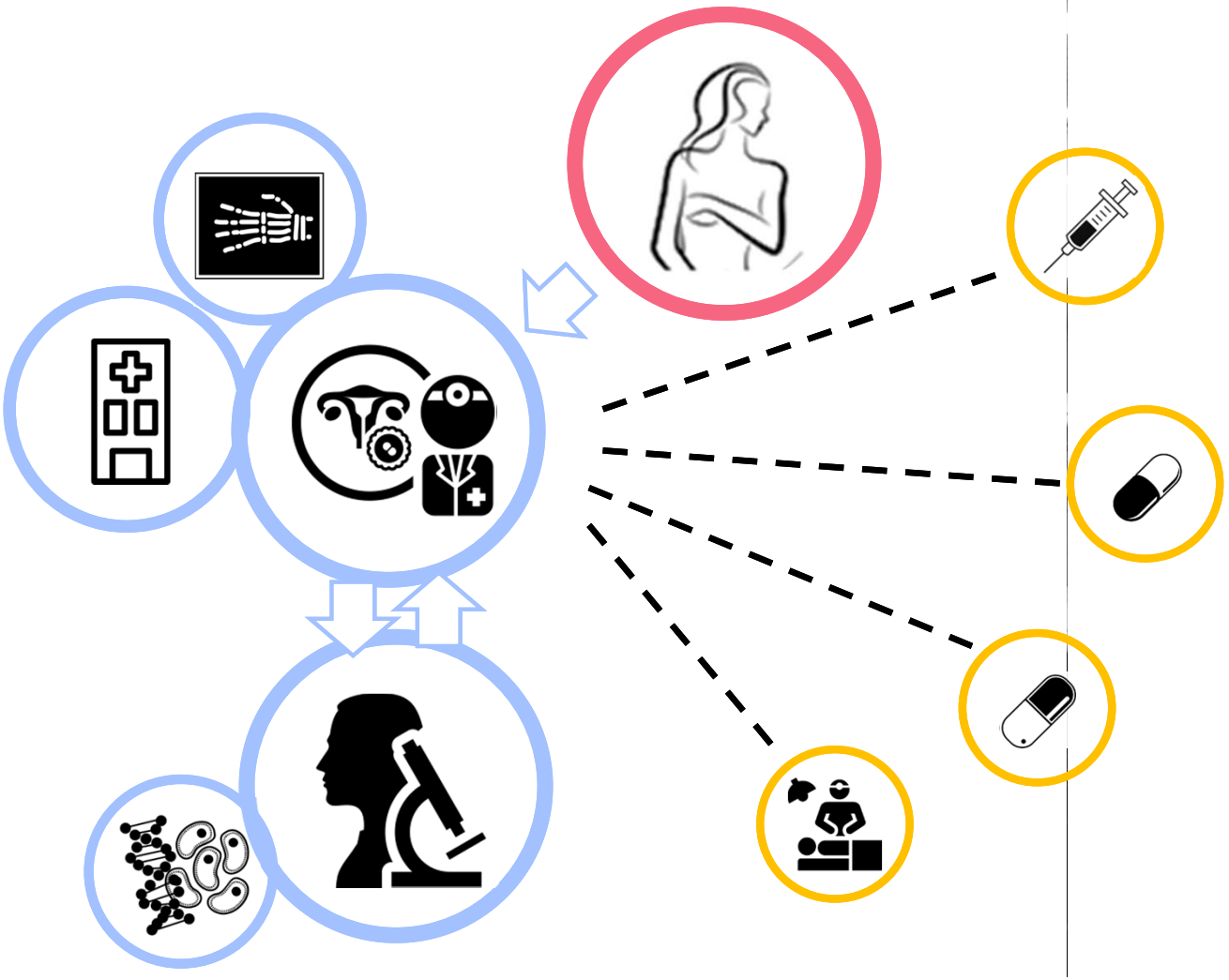
Improving the lives of Breast Cancer Patients in Africa

Impact of Histopathology

Accra, Ghana – March 2016

Roche Pharmaceutical & Diagnotics

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

Pre-Analytics

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

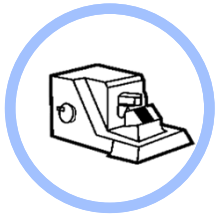
Anatomic pathology tissue specimen workflow

Accessioning / Grossing

Tissue Processing

Embedding

Sectioning



Staining

Reporting

Archive

1. Accessioning

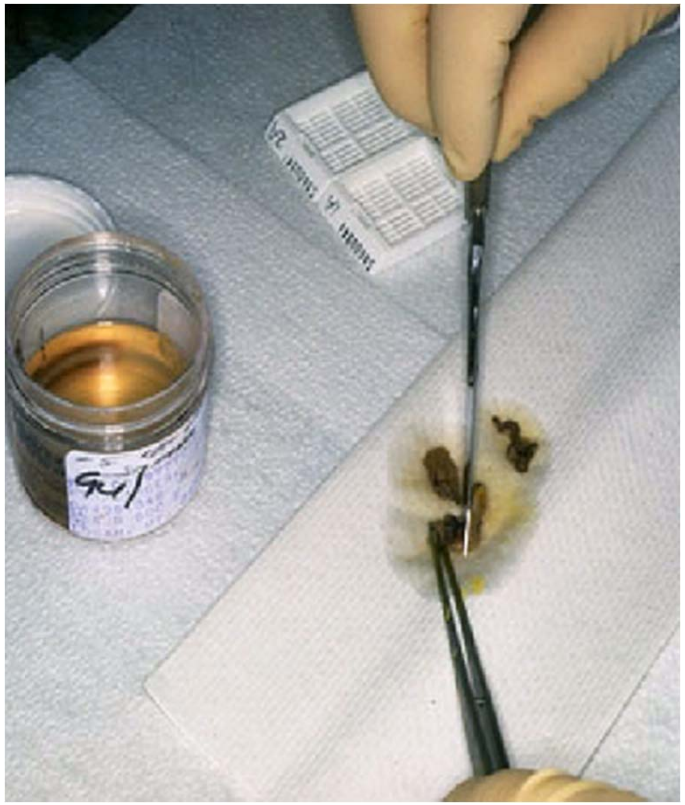
Specimens are received in the histology laboratory

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

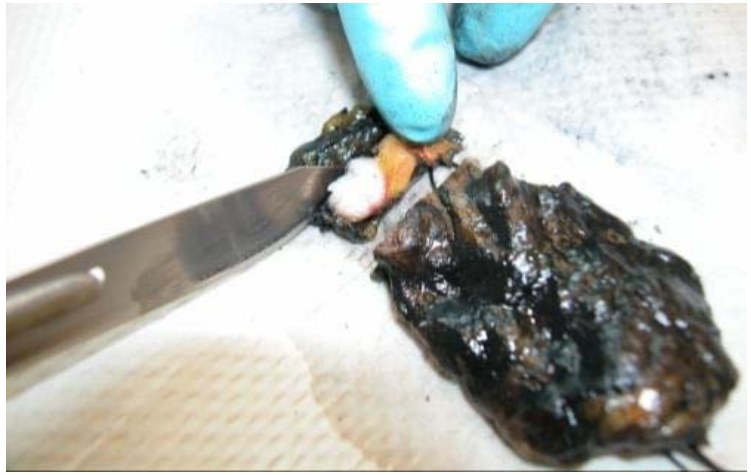
Gross examination or “grossing” consists of:

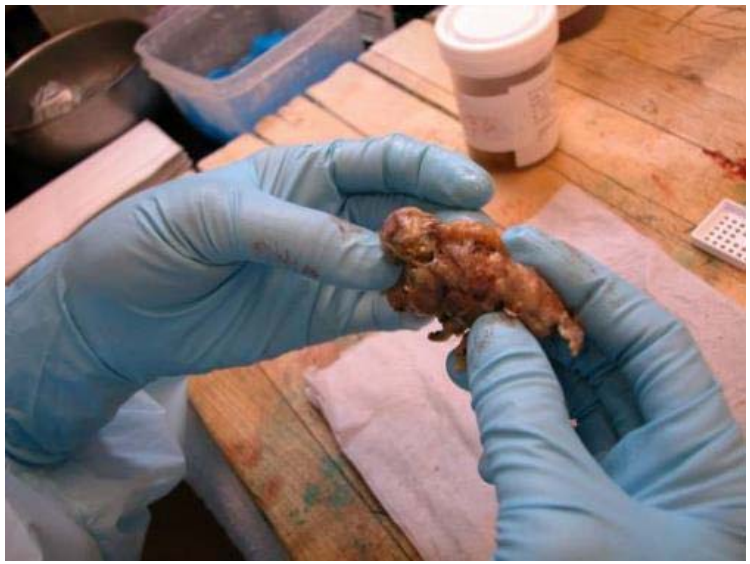
- **Describing the specimen’s size, shape, color and any apparent abnormalities**
- **Description of margins and their orientation**

Depending on the size and type of specimen, it is either submitted entirely Or a 'representative' section is taken

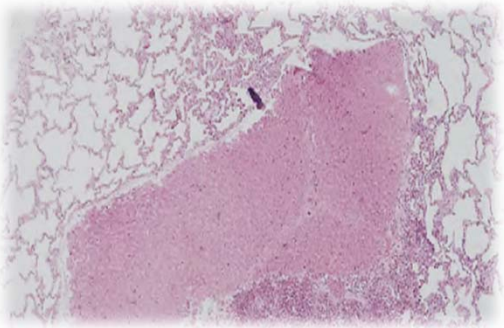
The tissue is placed into small plastic cassette, which will allow fluids to infiltrate the specimens in the processing step

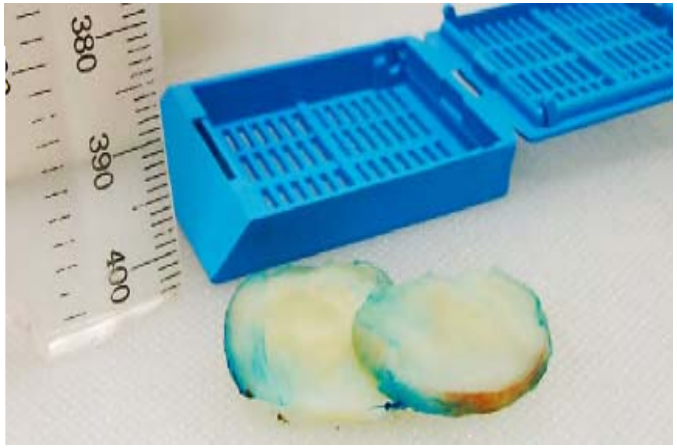
2. Gross examination

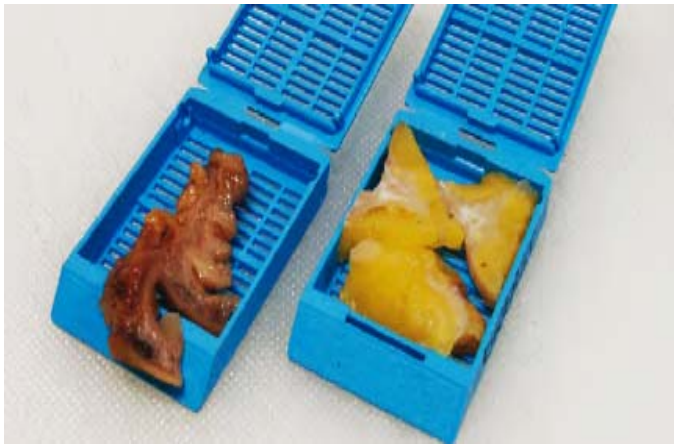




Grossing







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

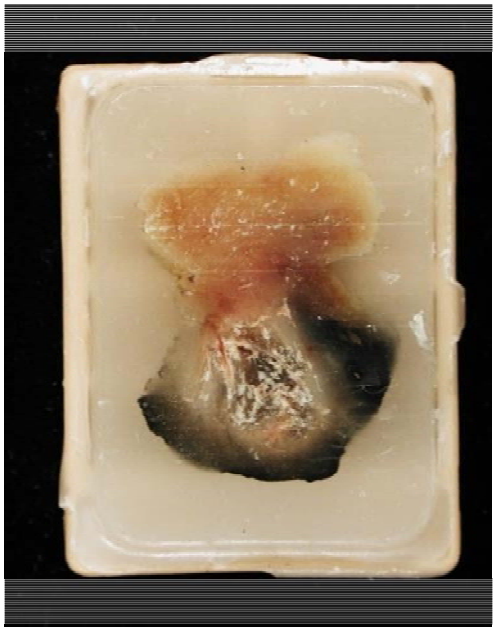
Fixation

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

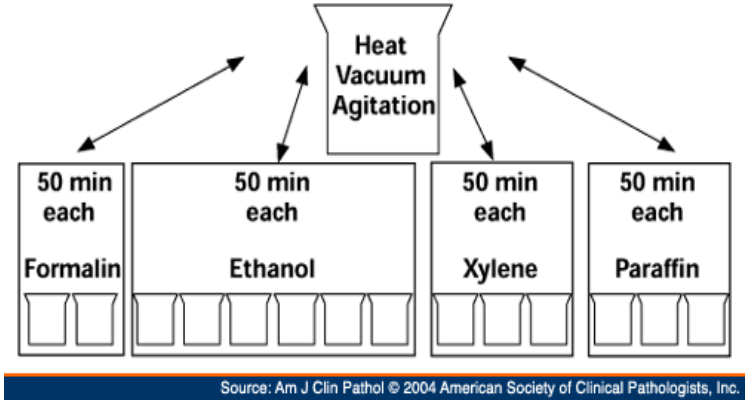
3. Tissue Processing



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

Processing Steps



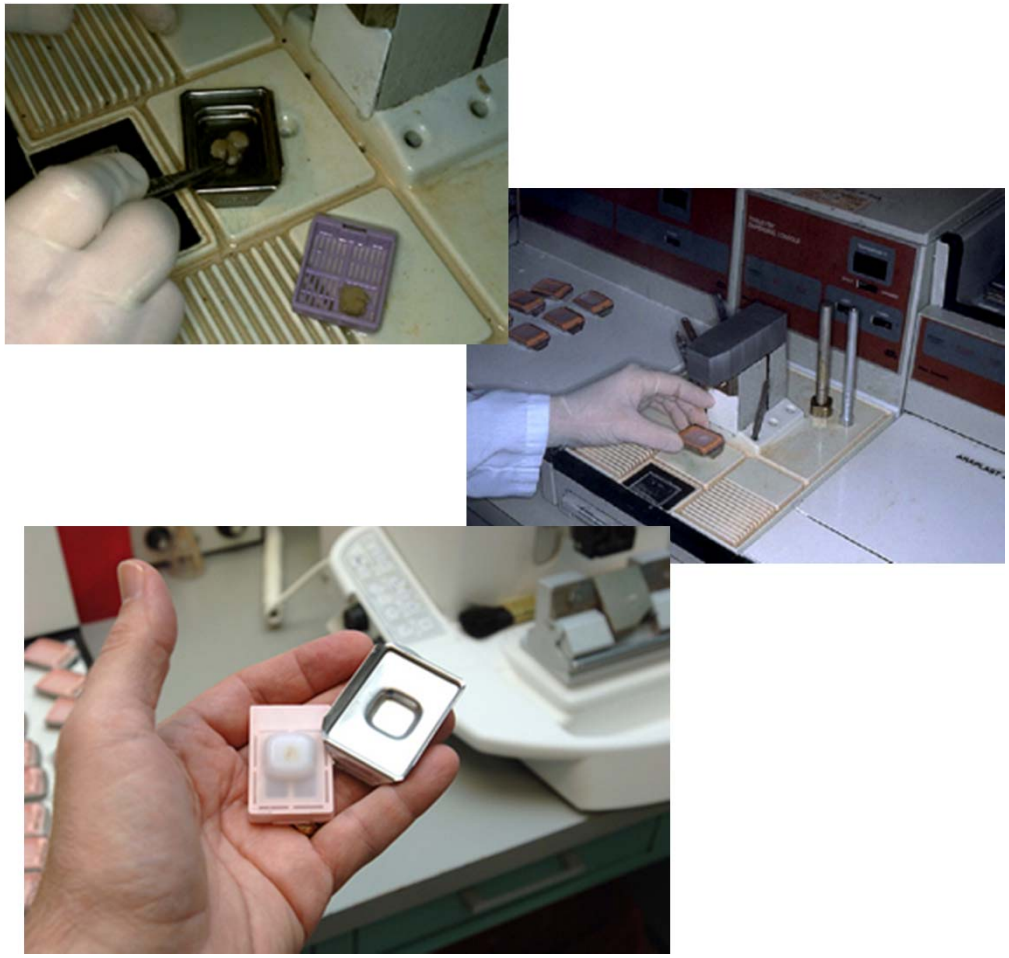
1. Fixation: The purpose is to preserve tissues permanently in a state similar that it was taken form the body

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.

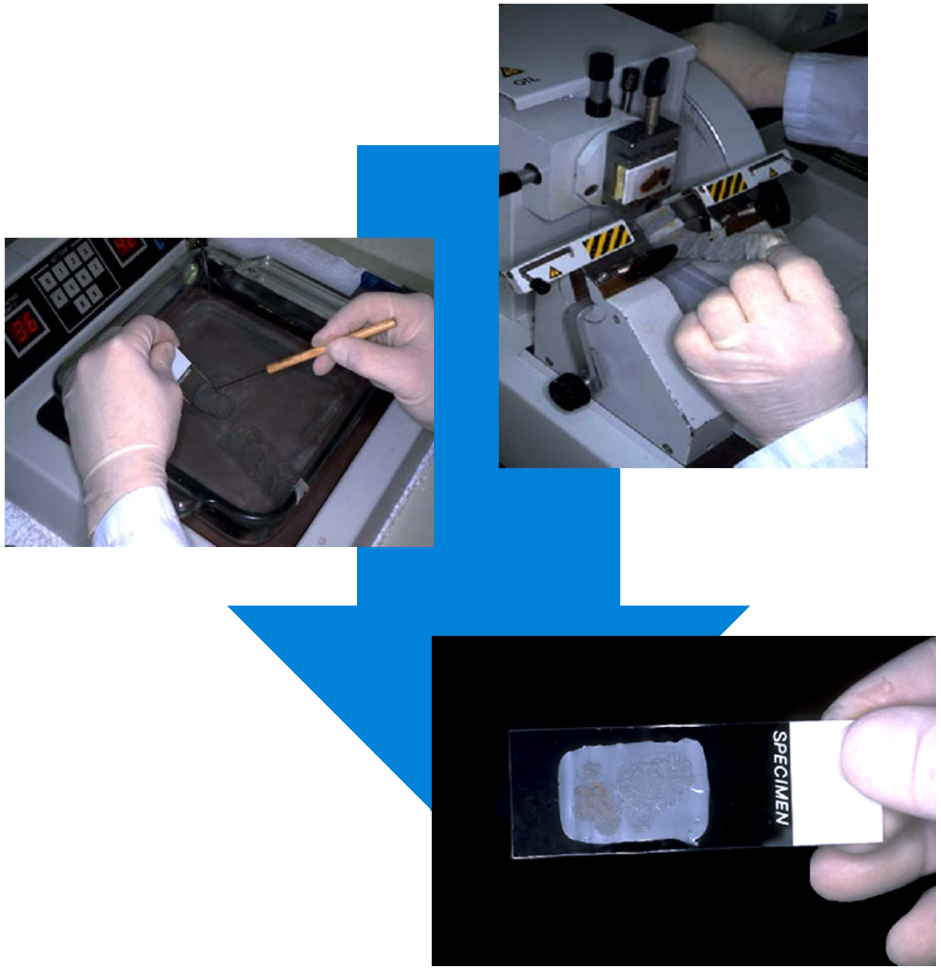
4. Infiltration : Tissue samples are then placed into changes of melted paraffin wax.

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

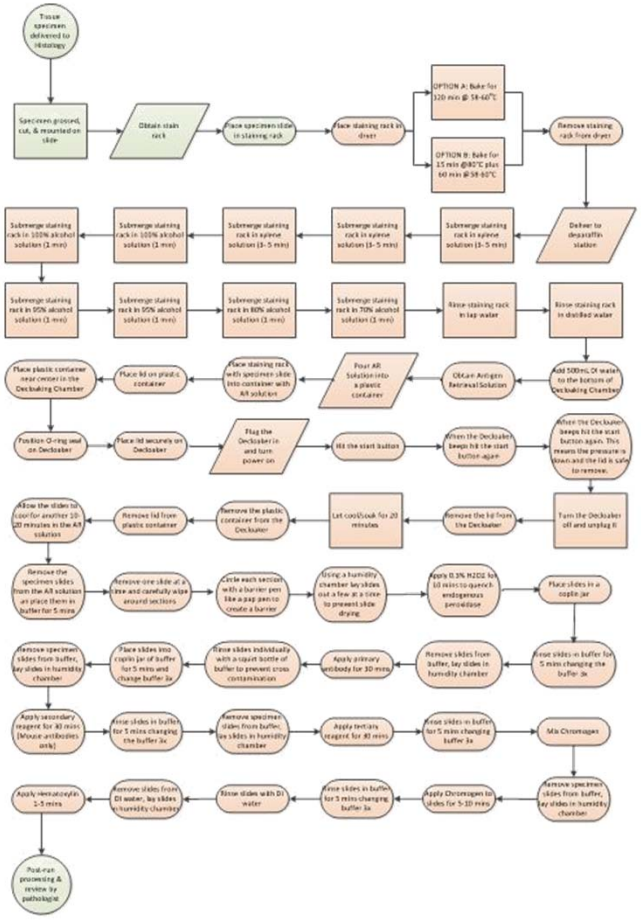
Sectioning – Slide Drying

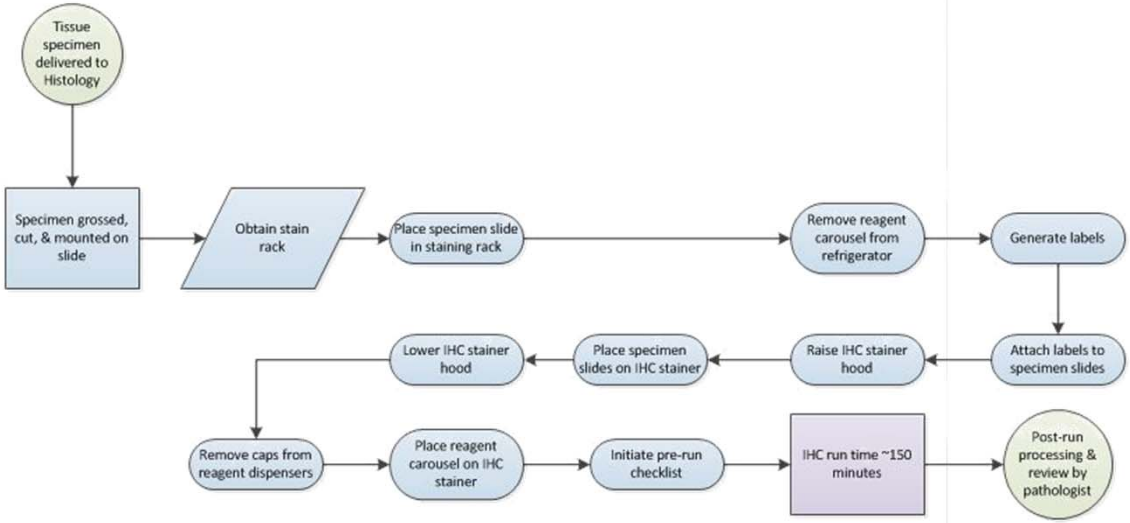
The slides are then placed in a oven to evaporate the water on the slide and to properly adhere the section on the slide.

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**

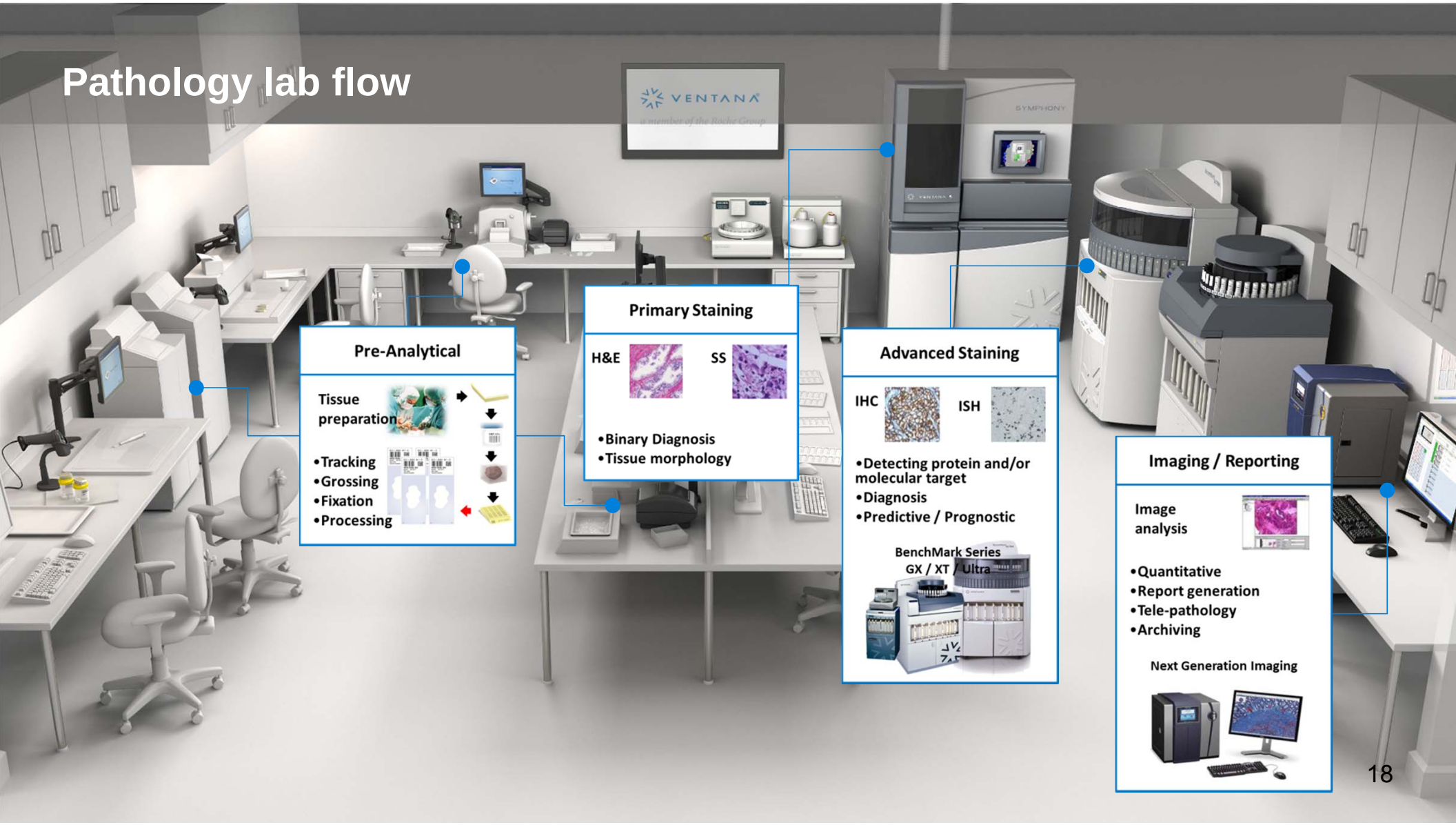
Workflow
Manual Process or Automation





Eliminate up to 80% of the labor required for manual and semi-automated staining

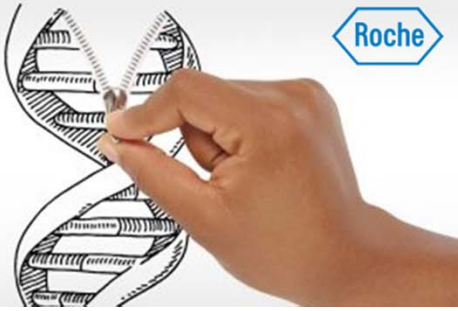
Pathology lab flow



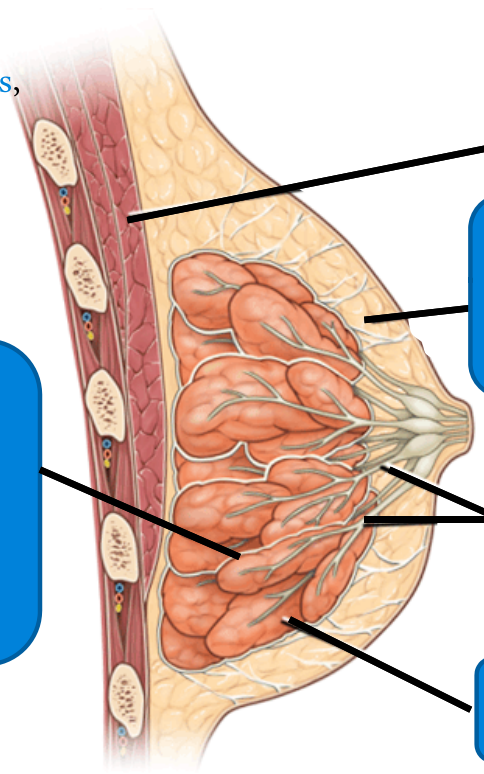
Anatomo-morphology

What are the main subtype of Breast Cancer according to anatomo-pathology ?

Femal Breast Anatomy



The structure of the female breast is complex — including fat and connective tissue, as well as lobes, lobules, ducts and lymph nodes.



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)

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

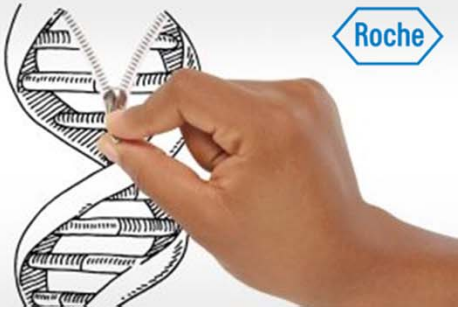
Ducts

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

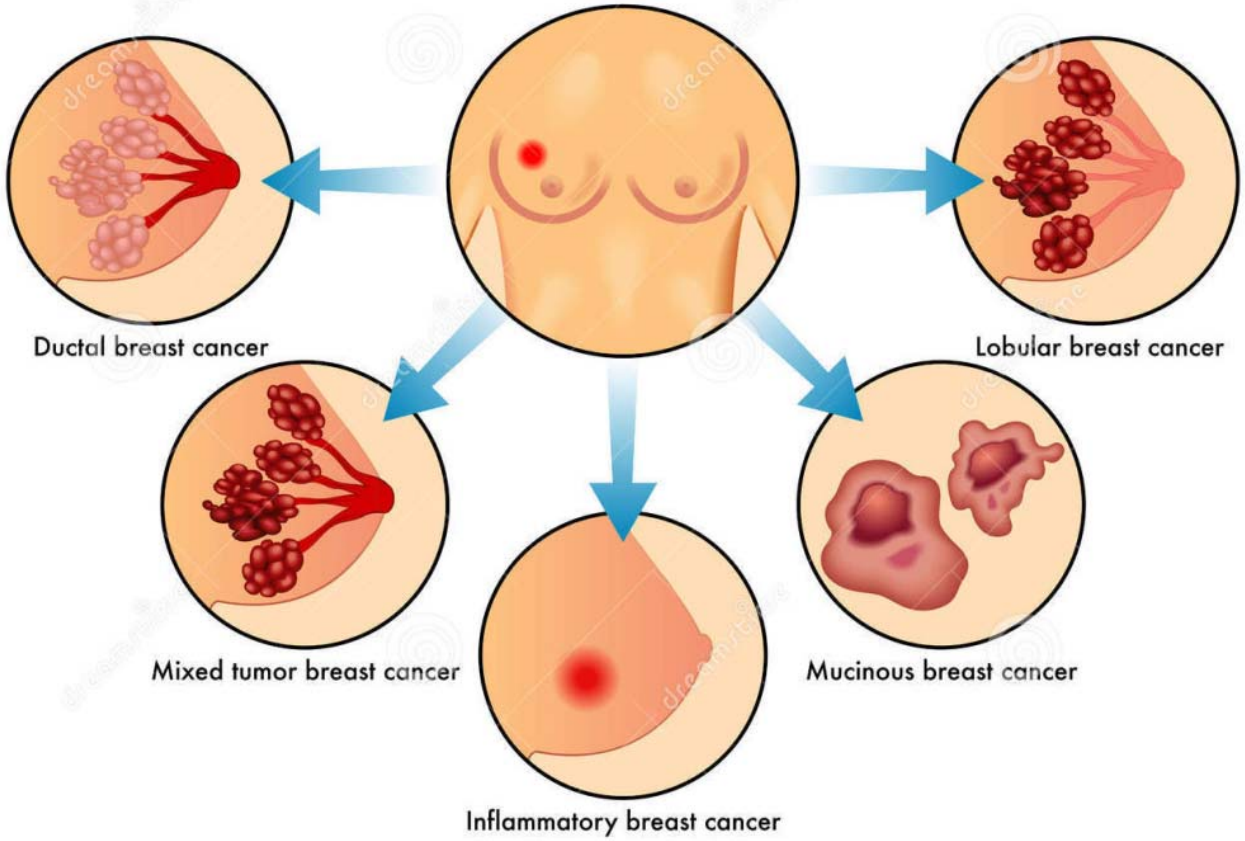
Breast has no muscle tissue

http://www.mayoclinic.org

Type of Breast Cancer



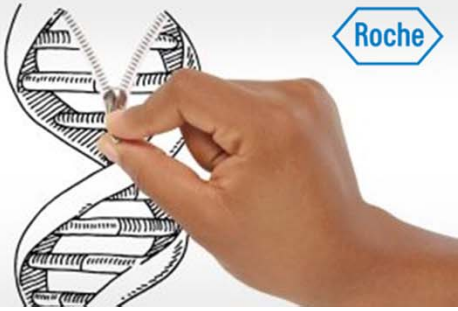
About 80%

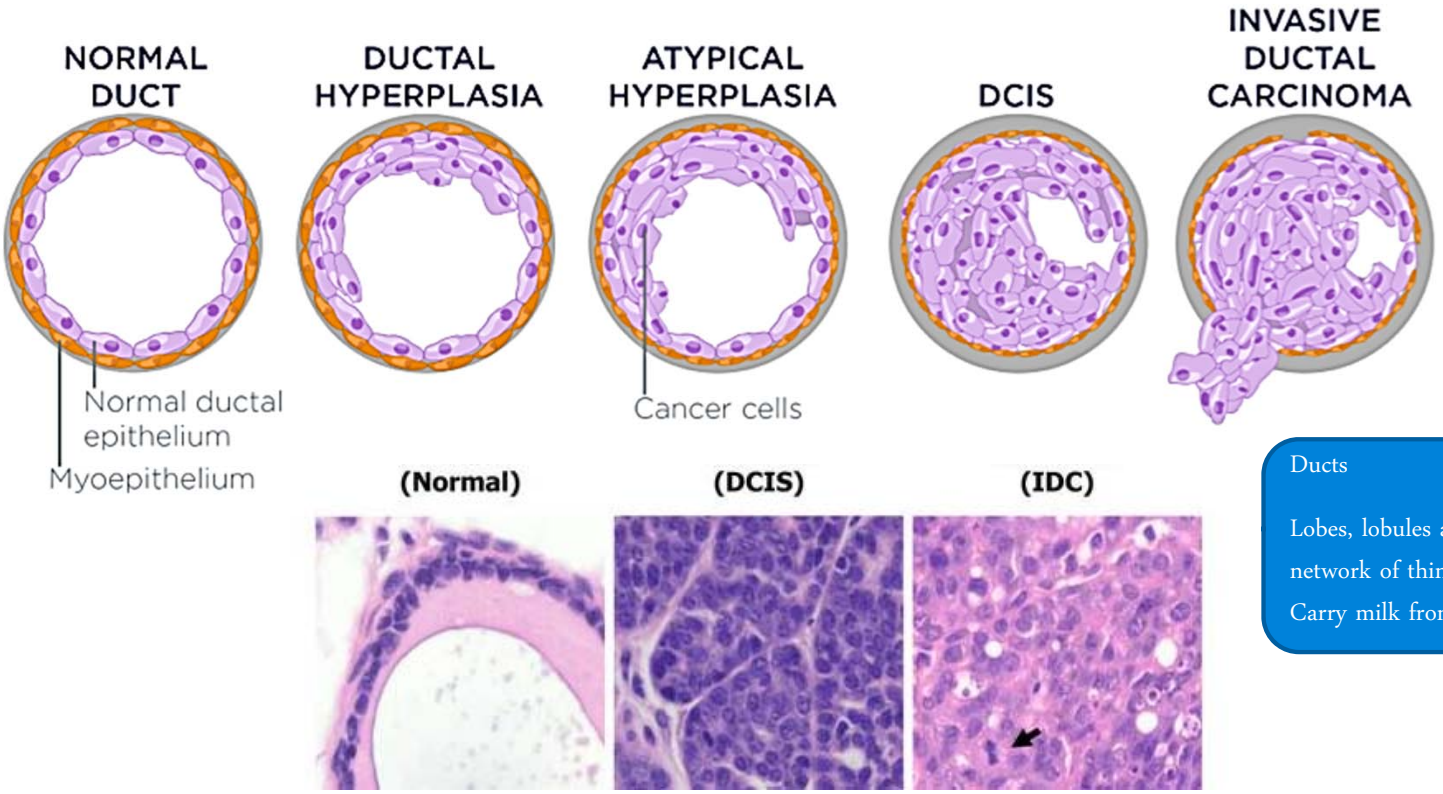


10 to 20%

Curr Treat options Oncol. 2000 Aug: 1(3): 199-209
Clin Transl Oncol. 2008 Dec; 10(12):777-85
Nat Clin Prat Oncol. 2007 Sep;4(9):516-25

Ductal Carcinomas In Situ (DCIS)



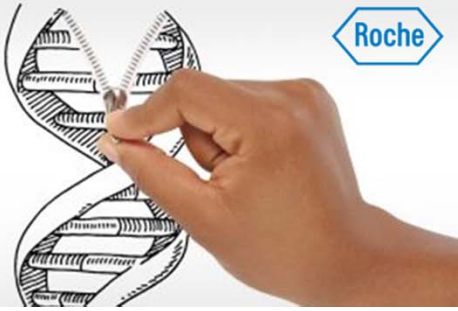


Ducts

Lobes, lobules and bulbs are linked by a network of thin tubes (ducts)

Carry milk from bulbs to the areola

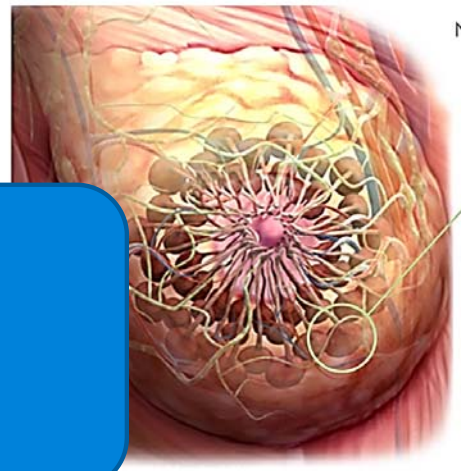
Lobular Carcinomas In Situ (LCIS)

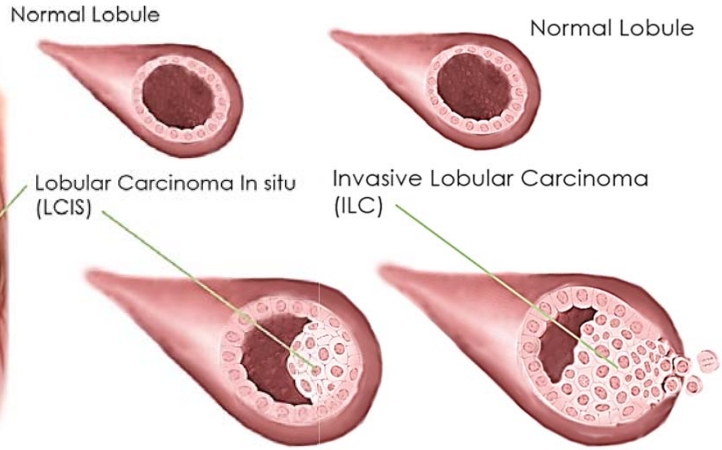


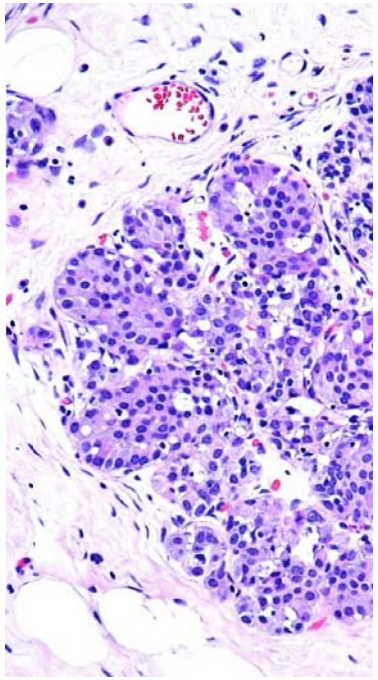
Lobes

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



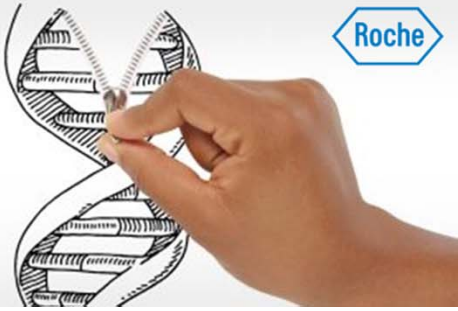




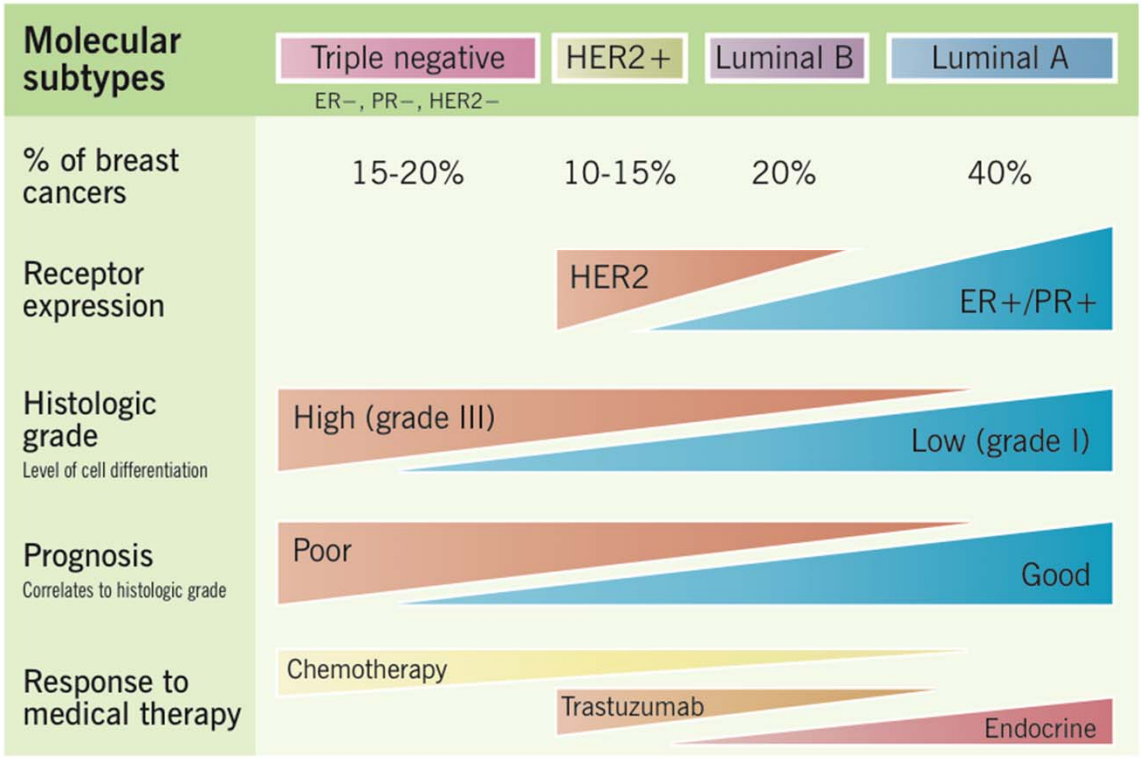
What is the molecular subtype?

Explanation text

Histologic vs. Molecular subtypes

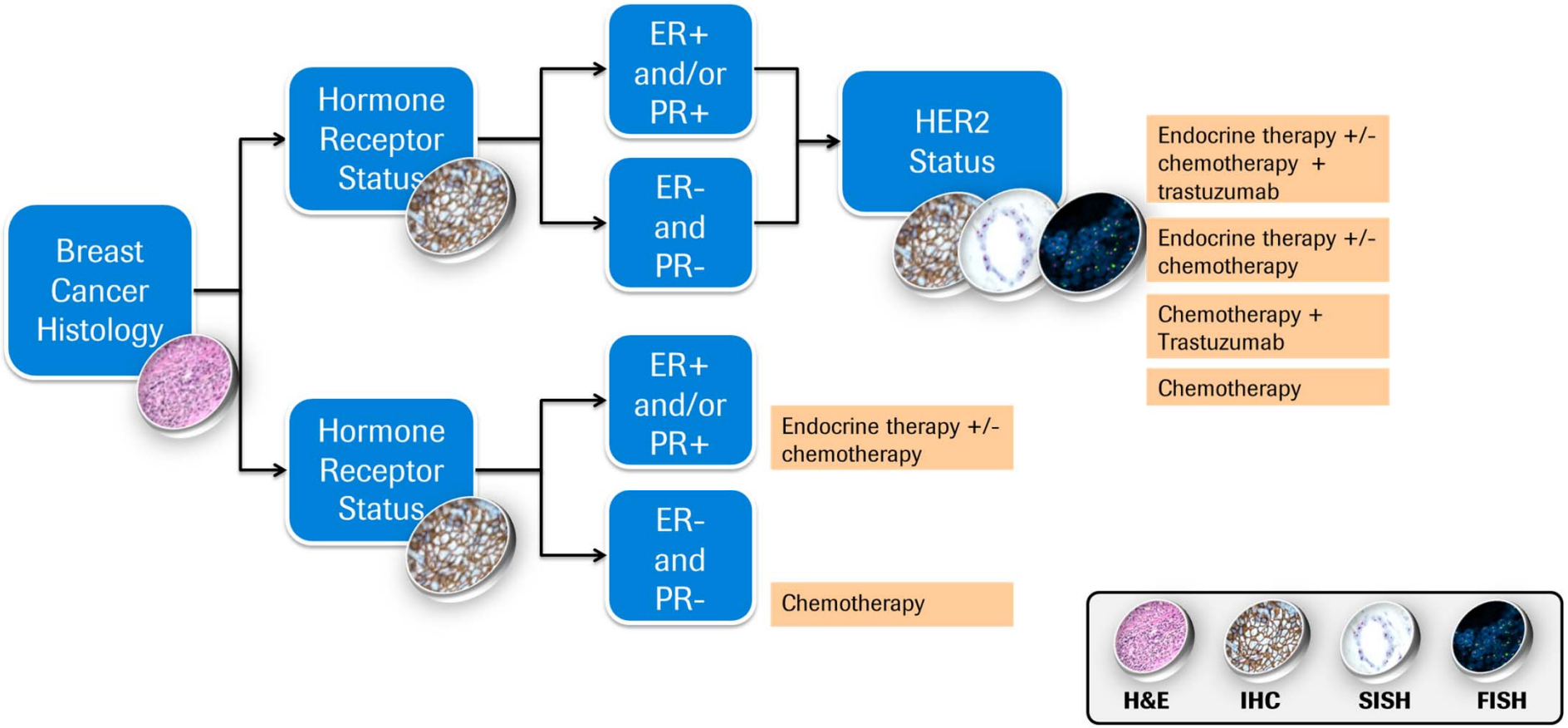


Histological subtypes	Ductal	Lobular
Preinvasive cancer 25% Cells limited to basement membrane	Ductal carcinoma in situ (DCIS) 80% May spread through ducts and distort duct architecture 1% progress to invasive cancer per year Usually unilateral	Lobular carcinoma in situ (LCIS) 20% Does not distort duct architecture Same genetic abnormality as ILC – E-cahderin loss 1% progress per year Can be bilateral
Invasive cancer 75% Extension beyond the basement membrane	Invasive ductal carcinoma (IDC) 79% Usually from DCIS precursor Cause fibrous response, producing a palpable mass on examination Metastasis through lymphatics and blood	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+



Curr Treat options Oncol. 2000 Aug: 1(3): 199-209 / Clin Transl Oncol. 2008 Dec; 10(12):777-85 / Nat Clin Prat Oncol. 2007 Sep;4(9):516-25

Breast Cancer : Facts and Numbers
Impact of histopathology in treatment decision



Immunohistochemistry IHC

Explanation text

Why HER2 testing?

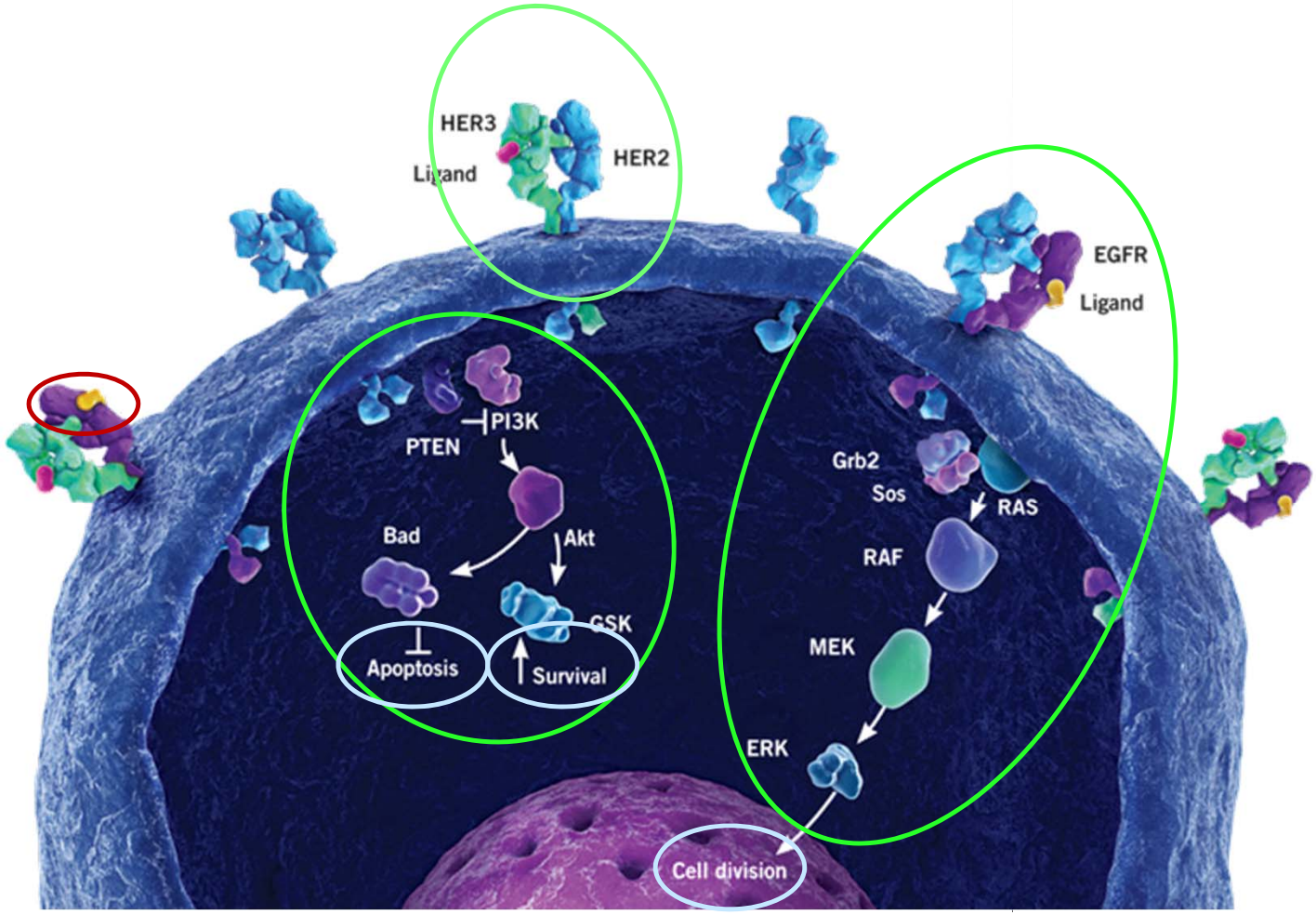
The HER2 pathway

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

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

Dimerization :
Signaling pathway activation

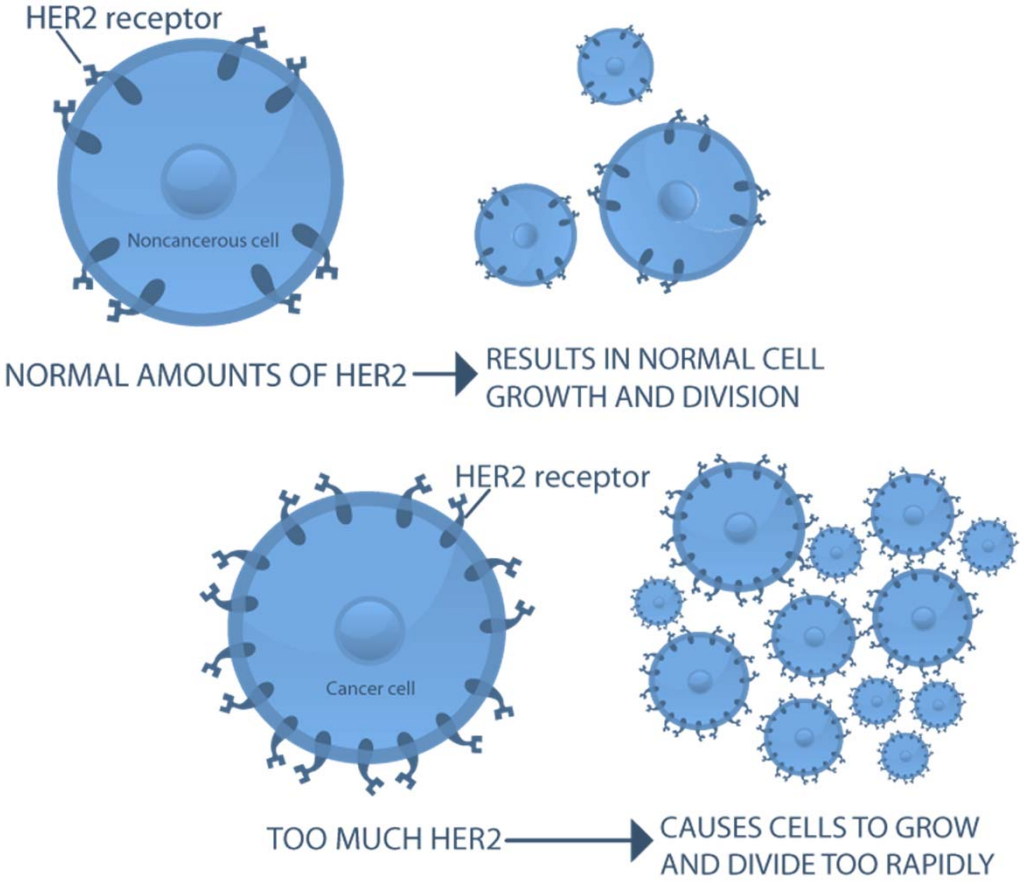
Oncogenic process :
Cell proliferation, survival, mobility, invasivness



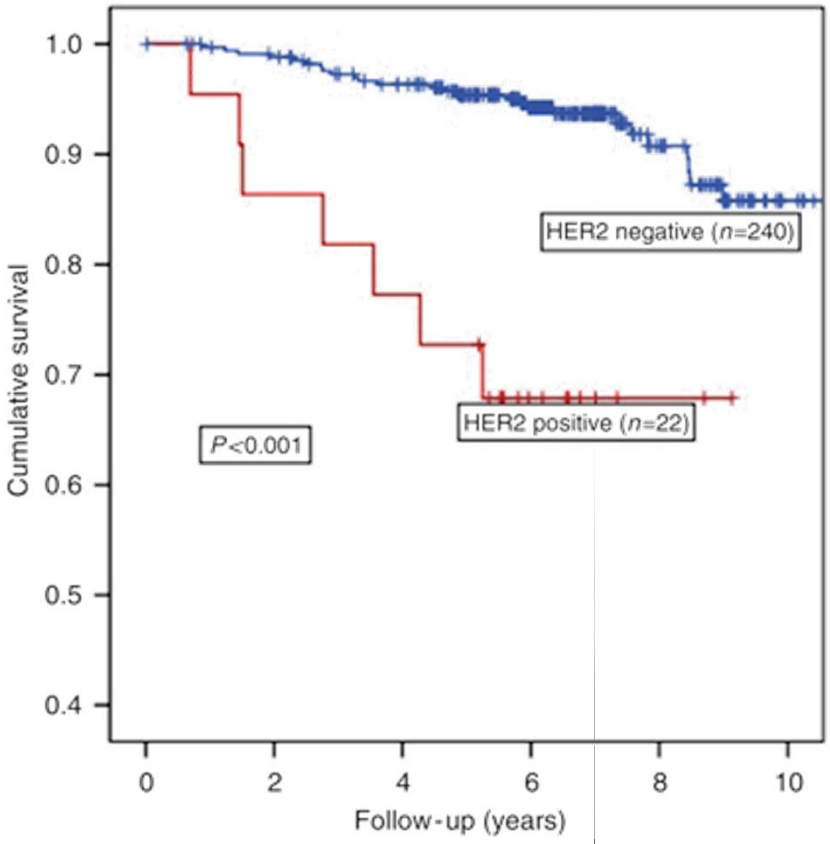
Ross JS et al, The Oncologists 2009. 14. 320-368

Why HER2 testing?

Prognostic factor



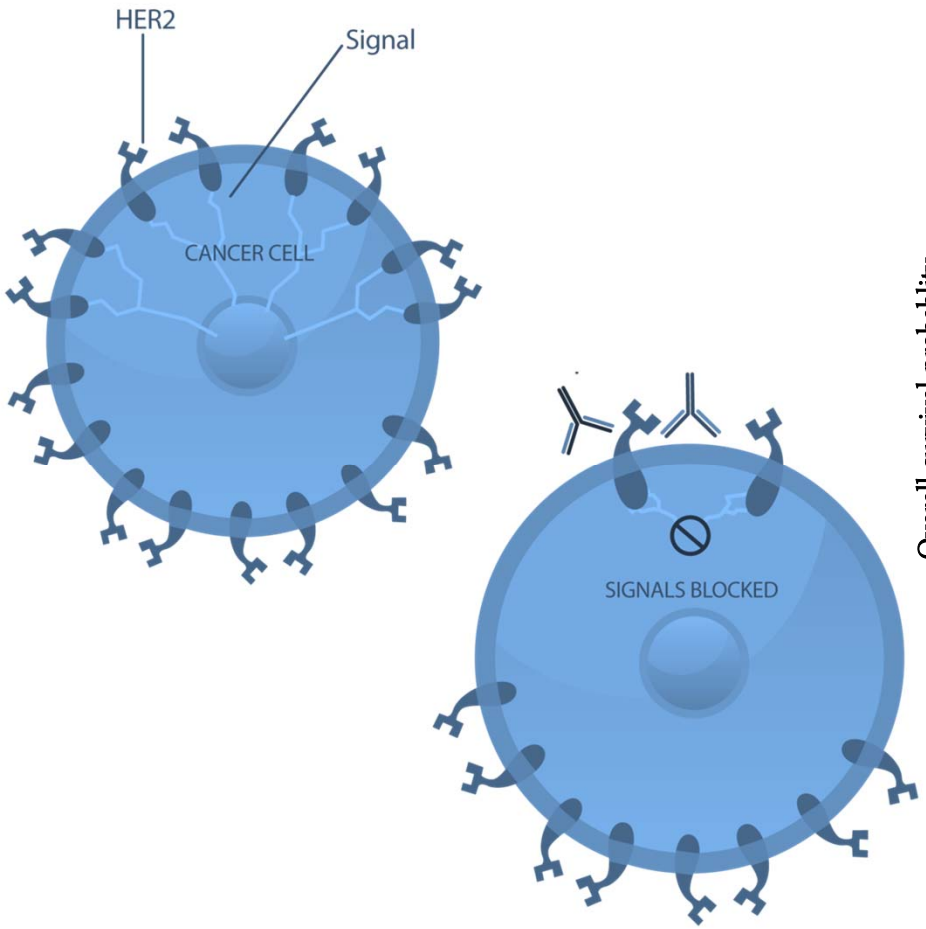
Kaplan–Meier curves for HER2 status. Survival curves showing cumulative survival between patients + or -.

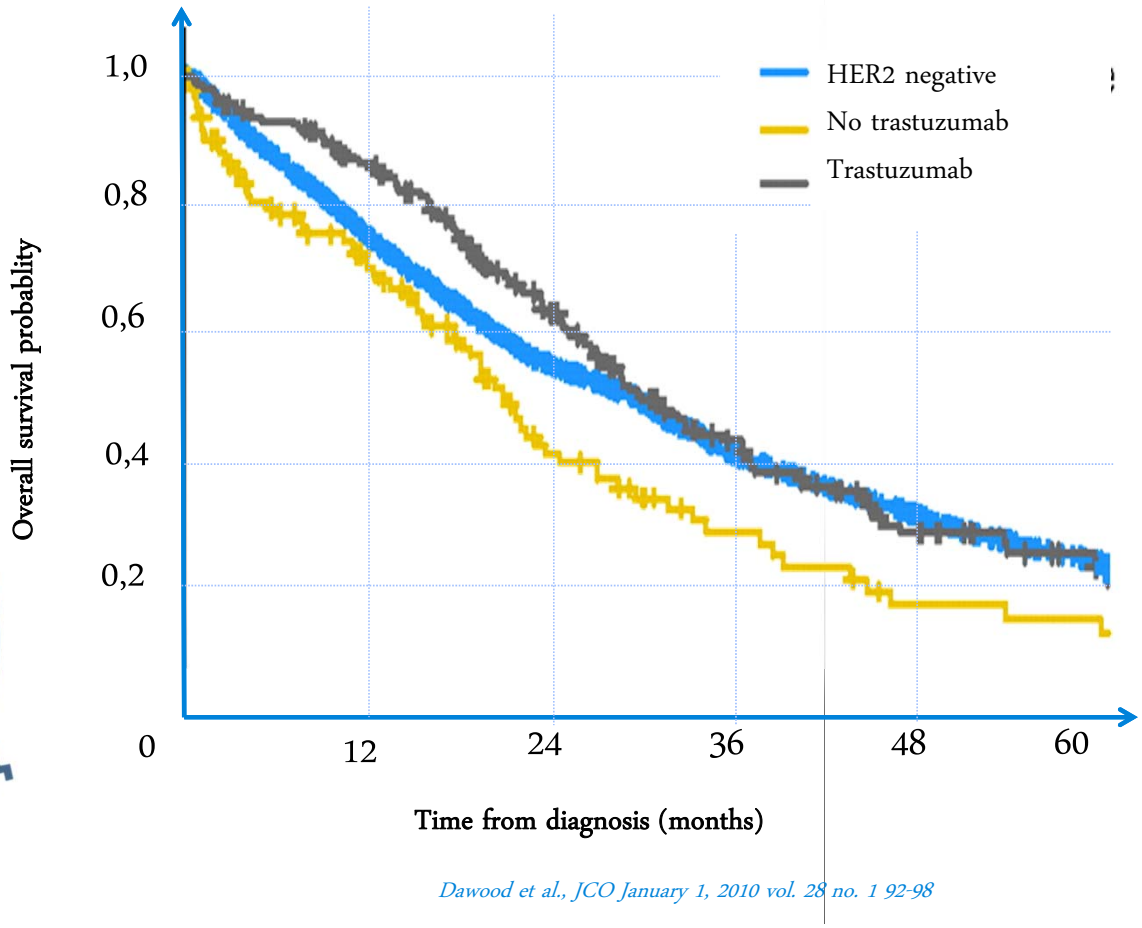


Tovey SM et al, British Journal of Cancer (2009) 100, 680–683

Why HER2 testing?

Predictive factor





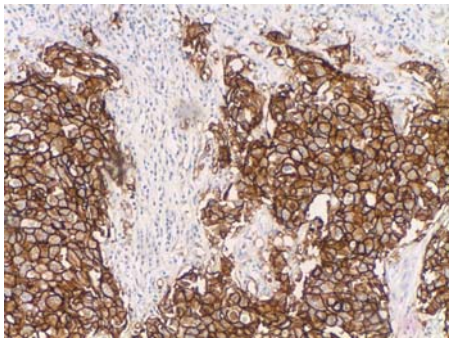
Dawood et al., JCO January 1, 2010 vol. 28 no. 1 92-98

How do we test for HER2 ?

Technical point of view

IHC

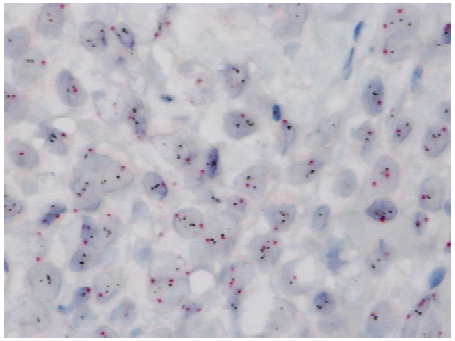
ImmunoHistoChemistry



Expression level of HER2 protein

ISH

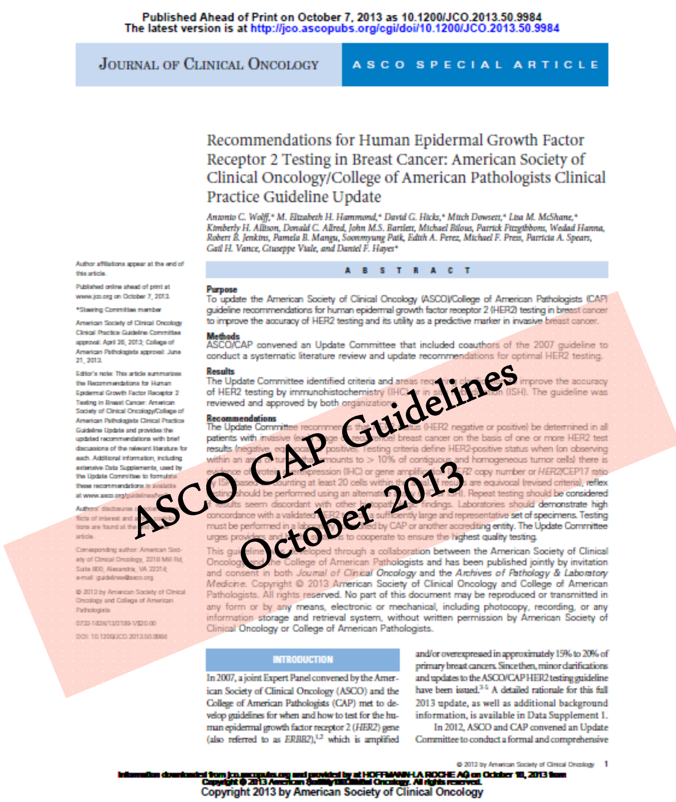
In Situ Hybridization



Determination of HER2 gene amplification status

How do we test for HER2 ?

Guidelines



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JOURNAL OF CLINICAL ONCOLOGY — ASCO SPECIAL ARTICLE

Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update

Antonio C. Wolff,* M. Elizabeth H. Hammond,* David G. Hicks,* Mitch Dowsett,* Lisa M. McShane,* Kimberly H. Allison, Donald C. Allred, John M.S. Bartlett, Michael Bilous, Patrick Fitzgibbons, Wedad Hanna, Robert B. Jenkins, Pamela B. Mangu, Soonmyung Paik, Edith A. Perez, Michael F. Press, Patricia A. Spears, Gail H. Vance, Giuseppe Viale, and Daniel F. Hayes*

Author affiliations appear at the end of this article.

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*Steering Committee member

American Society of Clinical Oncology Clinical Practice Guideline Committee approval: April 26, 2013; College of American Pathologists approval: June 21, 2013.

Editor's note: This article summarizes the Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update and provides the updated recommendations with brief discussions of the relevant literature for each. Additional information, including extensive Data Supplements, used by the Update Committee to formulate these recommendations is available at www.asco.org/guidelines/her2.

Corresponding author: American Society of Clinical Oncology, 2318 Mill Rd, Suite 800, Alexandria, VA 22314; e-mail: guidelines@asco.org.

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0732-183X/13/3199-1/$20.00

DOI: 10.1200/JCO.2013.50.9984

ABSTRACT

Purpose
To update the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guideline recommendations for human epidermal growth factor receptor 2 (HER2) testing in breast cancer to improve the accuracy of HER2 testing and its utility as a predictive marker in invasive breast cancer.

Methods
ASCO/CAP convened an Update Committee that included coauthors of the 2007 guideline to conduct a systematic literature review and update recommendations for optimal HER2 testing.

Results
The Update Committee identified criteria and areas requiring clarification to improve the accuracy of HER2 testing by immunohistochemistry (IHC) or in situ hybridization (ISH). The guideline was reviewed and approved by both organizations.

Recommendations
The Update Committee recommends that HER2 status (HER2 negative or positive) be determined in all patients with invasive (early stage or recurrence) breast cancer on the basis of one or more HER2 test results (negative, equivocal, or positive). Testing criteria define HER2-positive status when (on observing within an area of tumor that amounts to > 10% of contiguous and homogeneous tumor cells) there is evidence of protein overexpression (IHC) or gene amplification (HER2 copy number or HER2/CEP17 ratio by ISH based on counting at least 20 cells within the area). If results are equivocal (revised criteria), reflex testing should be performed using an alternative assay (IHC or ISH). Repeat testing should be considered if results seem discordant with other histopathologic findings. Laboratories should demonstrate high concordance with a validated HER2 test on a sufficiently large and representative set of specimens. Testing must be performed in a laboratory accredited by CAP or another accrediting entity. The Update Committee urges providers and health systems to cooperate to ensure the highest quality testing.

This guideline was developed through a collaboration between the American Society of Clinical Oncology and the College of American Pathologists and has been published jointly by invitation and consent in both *Journal of Clinical Oncology* and the *Archives of Pathology & Laboratory Medicine*. Copyright © 2013 American Society of Clinical Oncology and College of American Pathologists. All rights reserved. No part of this document may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without written permission by American Society of Clinical Oncology or College of American Pathologists.

INTRODUCTION

In 2007, a joint Expert Panel convened by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) met to develop guidelines for when and how to test for the human epidermal growth factor receptor 2 (*HER2*) gene (also referred to as *ERBB2*),[1,2] which is amplified and/or overexpressed in approximately 15% to 20% of primary breast cancers. Since then, minor clarifications and updates to the ASCO/CAP HER2 testing guideline have been issued.[3-5] A detailed rationale for this full 2013 update, as well as additional background information, is available in Data Supplement 1.

In 2012, ASCO and CAP convened an Update Committee to conduct a formal and comprehensive

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Pre analytics recommandations

- Ischemia, fixation, best practice…

Scoring guidelines

- Algorithm
- IHC reading rules
- ISH reading rules

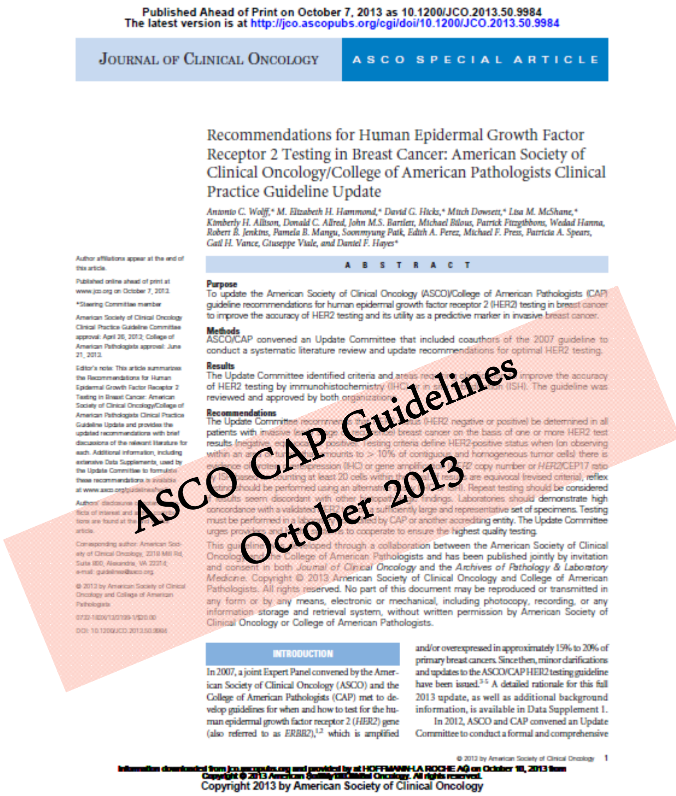
Testing guidelines

- FDA approved test

Reporting guidelines

How do we test for HER2 ?

Testing Algorithm



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JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update

Antonio C. Wolff, M. Elizabeth H. Hammond,* David G. Hicks,* Mitch Dowsett,* Lisa M. McShane,* Kimberly H. Allison, Donald C. Allred, John M.S. Bartlett, Michael Bilous, Patrick Fitzgibbons, Wedad Hanna, Robert B. Jenkins, Pamela B. Mangu, Soonmyung Paik, Edith A. Perez, Michael F. Press, Patricia A. Spears, Gail H. Vance, Giuseppe Viale, and Daniel F. Hayes**

Author affiliations appear at the end of this article.

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*Steering Committee member

American Society of Clinical Oncology Clinical Practice Guideline Committee approval: April 26, 2013; College of American Pathologists approval: June 21, 2013.

Editor's note: This article summarizes the Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update and provides the updated recommendations with brief discussions of the relevant literature for each. Additional information, including extensive Data Supplements, used by the Update Committee to formulate these recommendations is available at www.asco.org/guidelines/her2.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: American Society of Clinical Oncology, 2318 Mill Rd, Suite 800, Alexandria, VA 22314; e-mail: guidelines@asco.org.

0732-183X/13/3199-1/$20.00

DOI: 10.1200/JCO.2013.50.9984

A B S T R A C T

Purpose
To update the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guideline recommendations for human epidermal growth factor receptor 2 (HER2) testing in breast cancer to improve the accuracy of HER2 testing and its utility as a predictive marker in invasive breast cancer.

Methods
ASCO/CAP convened an Update Committee that included coauthors of the 2007 guideline to conduct a systematic literature review and update recommendations for optimal HER2 testing.

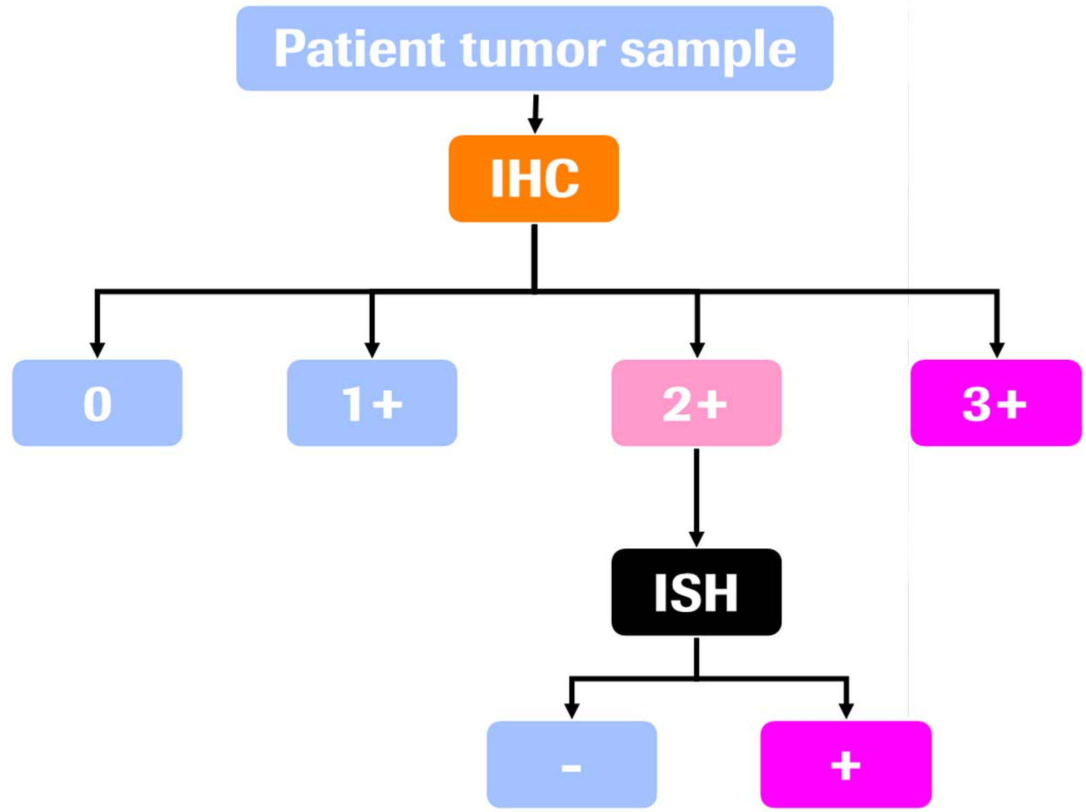
Results
The Update Committee identified criteria and areas requiring clarification to improve the accuracy of HER2 testing by immunohistochemistry (IHC) or in situ hybridization (ISH). The guideline was reviewed and approved by both organizations.

Recommendations
The Update Committee recommends that HER2 status (HER2 negative or positive) be determined in all patients with invasive (early stage or recurrence) breast cancer on the basis of one or more HER2 test results (negative, equivocal, or positive). Testing criteria define HER2-positive status when (on observing within an area of tumor that amounts to > 10% of contiguous and homogeneous tumor cells) there is evidence of protein overexpression (IHC) or gene amplification (*HER2* copy number or *HER2*/CEP17 ratio by ISH based on counting at least 20 cells within the area). If results are equivocal (revised criteria), reflex testing should be performed using an alternative assay (IHC or ISH). Repeat testing should be considered if results seem discordant with other histopathologic findings. Laboratories should demonstrate high concordance with a validated HER2 test on a sufficiently large and representative set of specimens. Testing must be performed in a laboratory accredited by CAP or another accrediting entity. The Update Committee urges providers and health systems to cooperate to ensure the highest quality testing.

INTRODUCTION

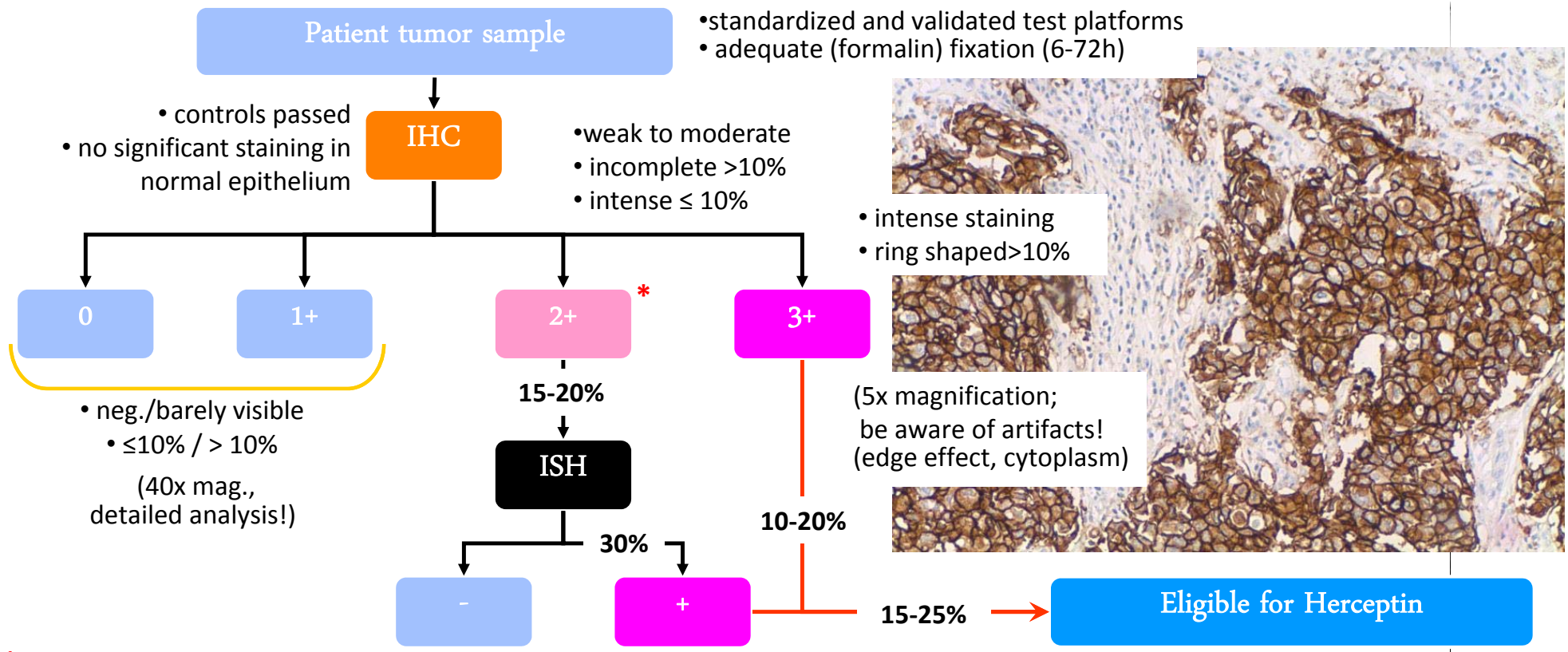
In 2007, a joint Expert Panel convened by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) met to develop guidelines for when and how to test for the human epidermal growth factor receptor 2 (*HER2*) gene (also referred to as *ERBB2*),[1,2] which is amplified and/or overexpressed in approximately 15% to 20% of primary breast cancers. Since then, minor clarifications and updates to the ASCO/CAP HER2 testing guideline have been issued.[3-5] A detailed rationale for this full 2013 update, as well as additional background information, is available in Data Supplement 1.

In 2012, ASCO and CAP convened an Update Committee to conduct a formal and comprehensive



How do we test for HER2 ?

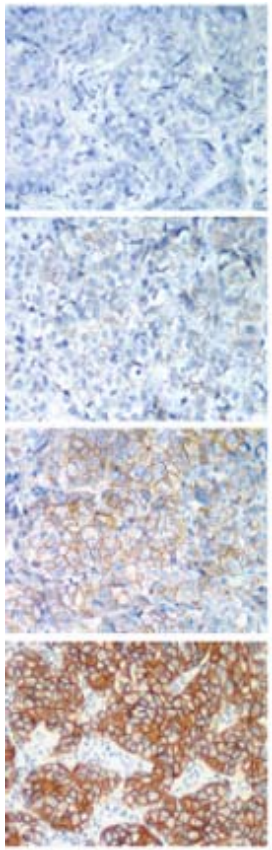
How does the algorithm work ?

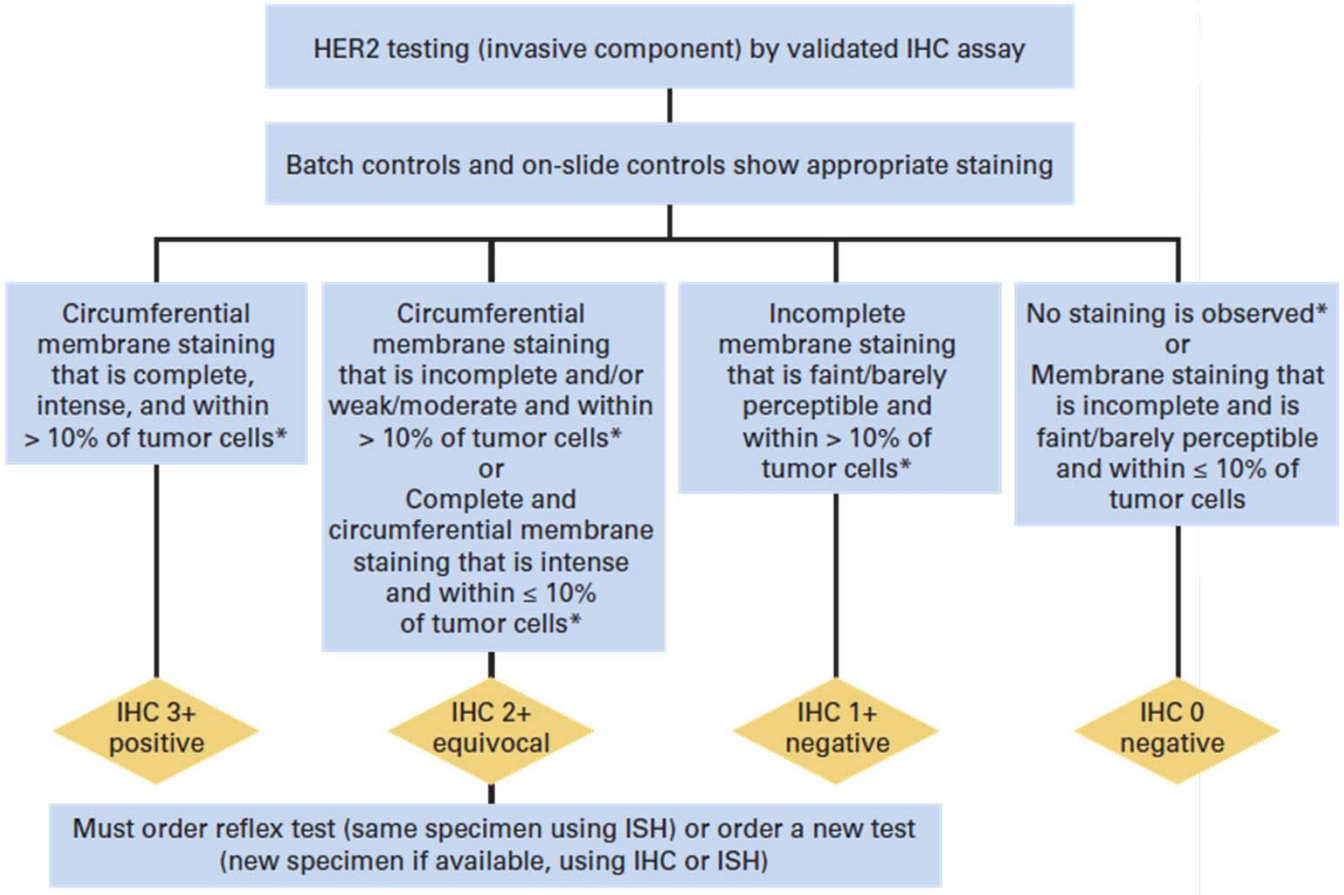


*in any doubt: score 2+

How do we test for HER2 ?

HER2 IHC interpretation





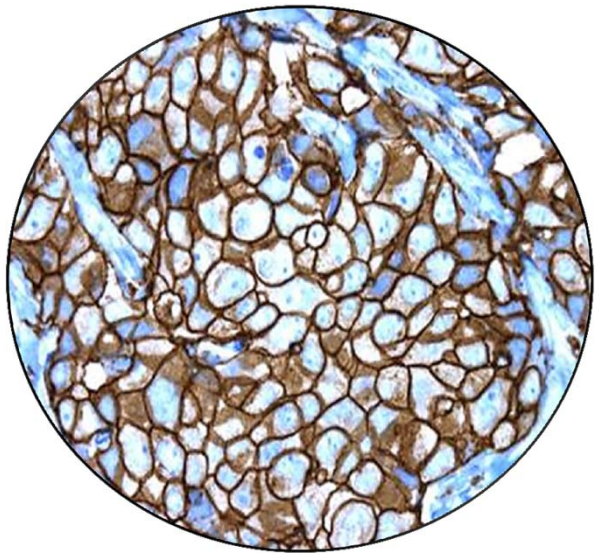
Are all IHC tests the same?

Explanation text

How do we test for HER2 ?

HER2 IHC quality

High Specificity



High Sensitivity

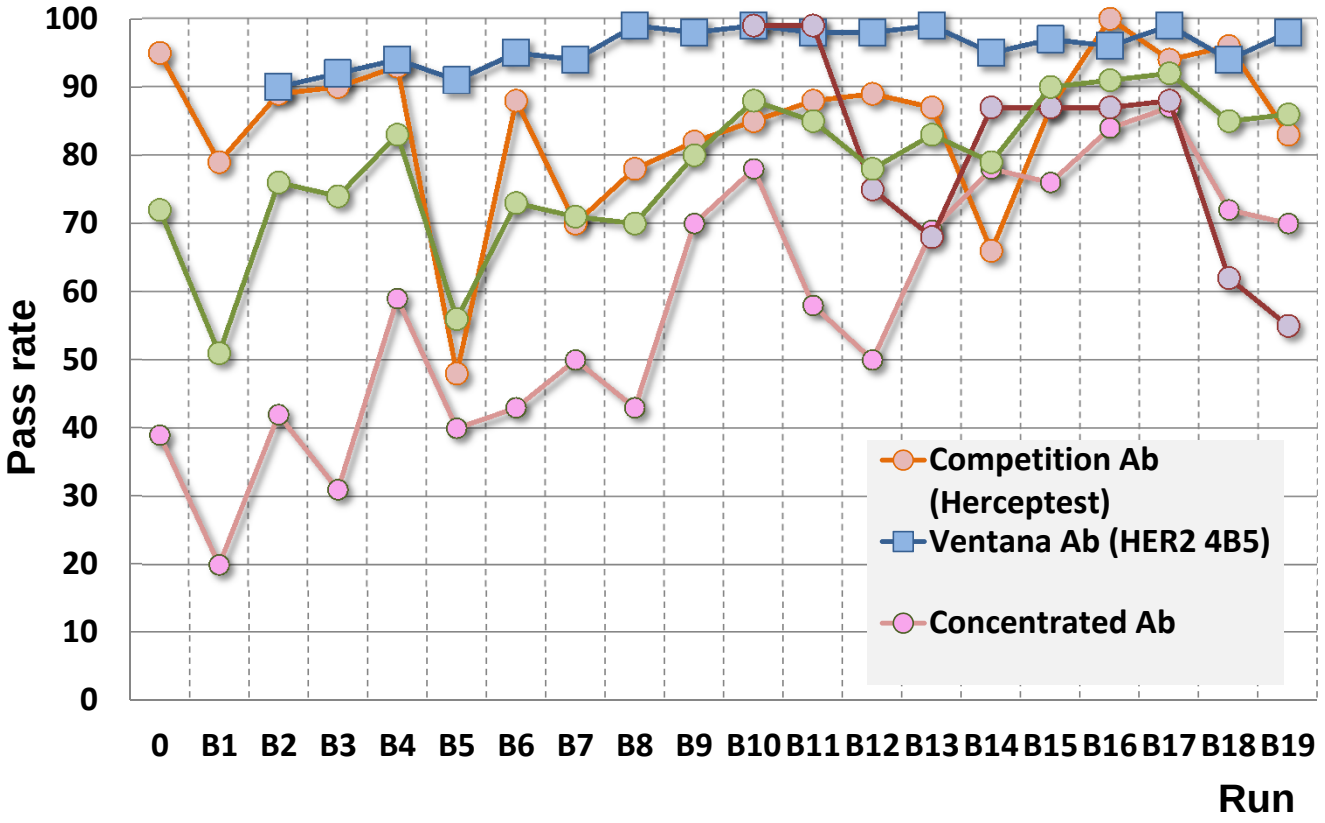
Pre-dilute

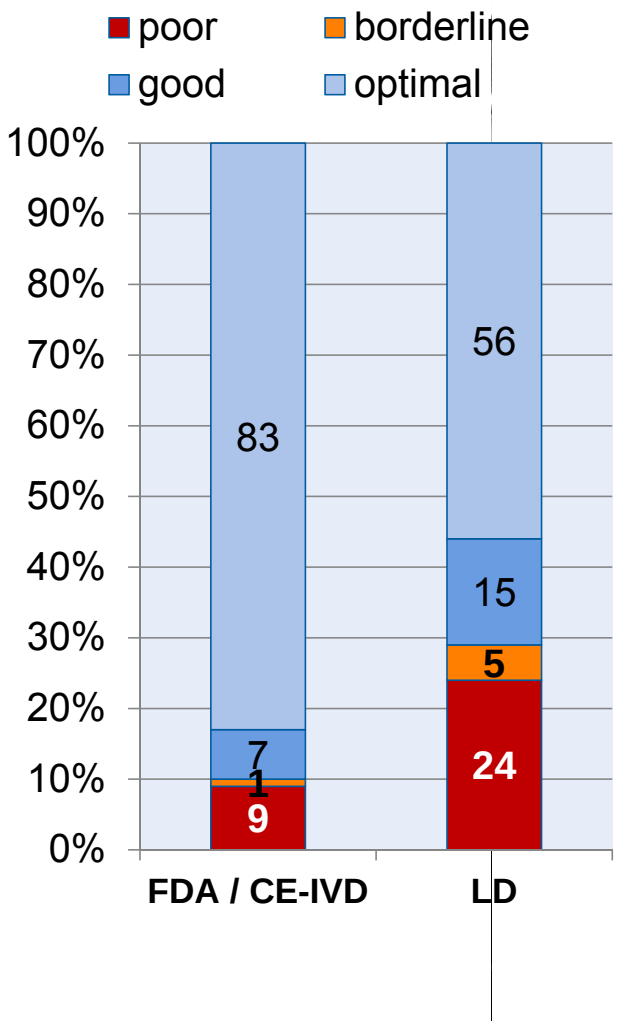
EQA

High ISH concordance[1,2,3]

1. Powell et al. A. Appl. Immunohistochem. Mol. Morphol. 2007;15(1): 94-102.
2. Starczynski et al. National Cancer Research Institute (UK) conference poster. October 2006.
3. Mayr D., et al. Virchows Archiv Mar 2009 (epub: 24 Jan 2009), vol. 454, no. 3, p. 241-8

How do we test for HER2 ?
HER2 IHC quality





Suff. OPS 2 = with optimal protocol

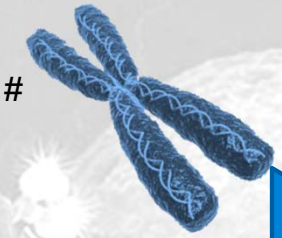
In Situ Hybridization

ISH

Explanation text

How do we test for HER2 ?
HER2 gene alteration

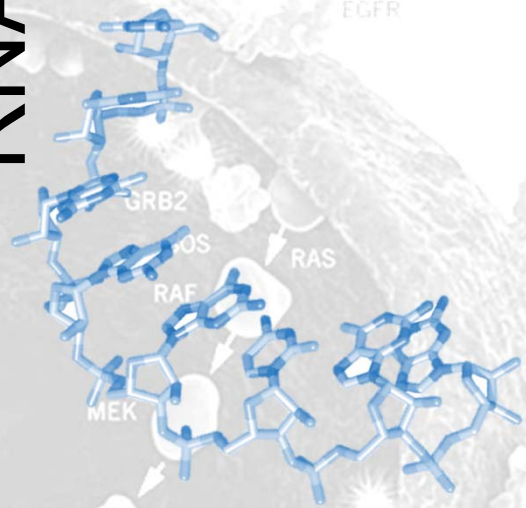
DNA



HER2 **gene copy # alterations (amplification or polysomy)**

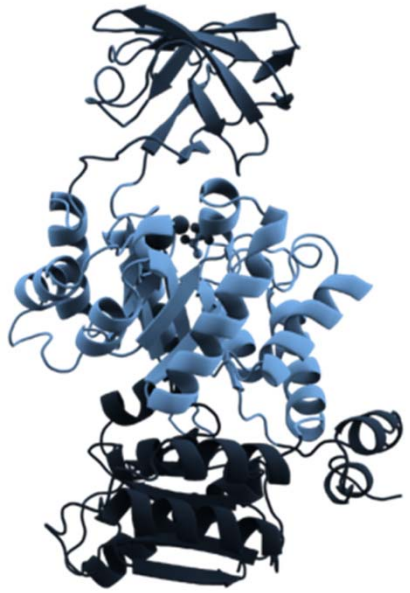
HER2 **gene mutations**

RNA



HER2 **RNA over expression**

PROTEIN

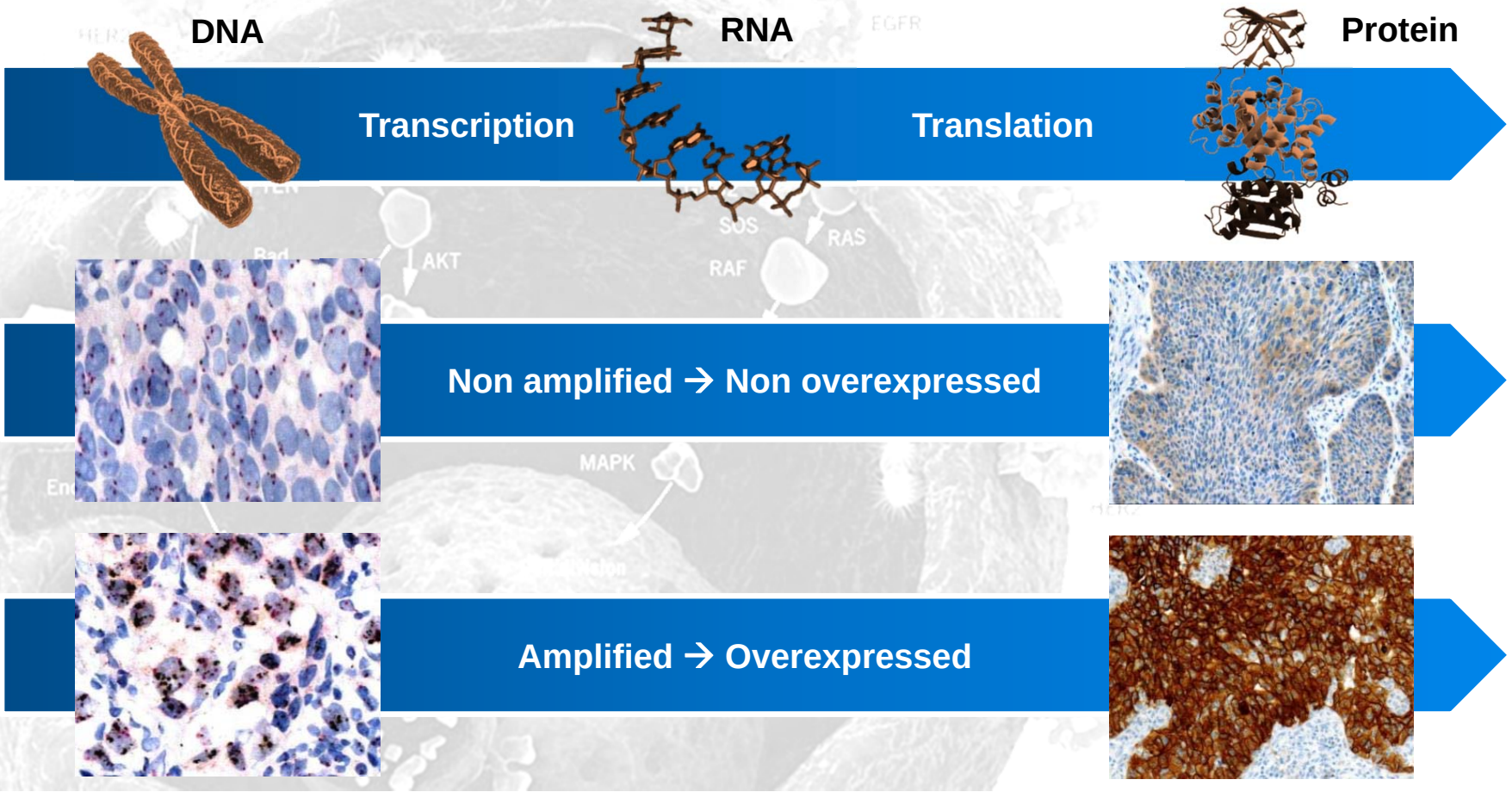


HER2 protein overexpression

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

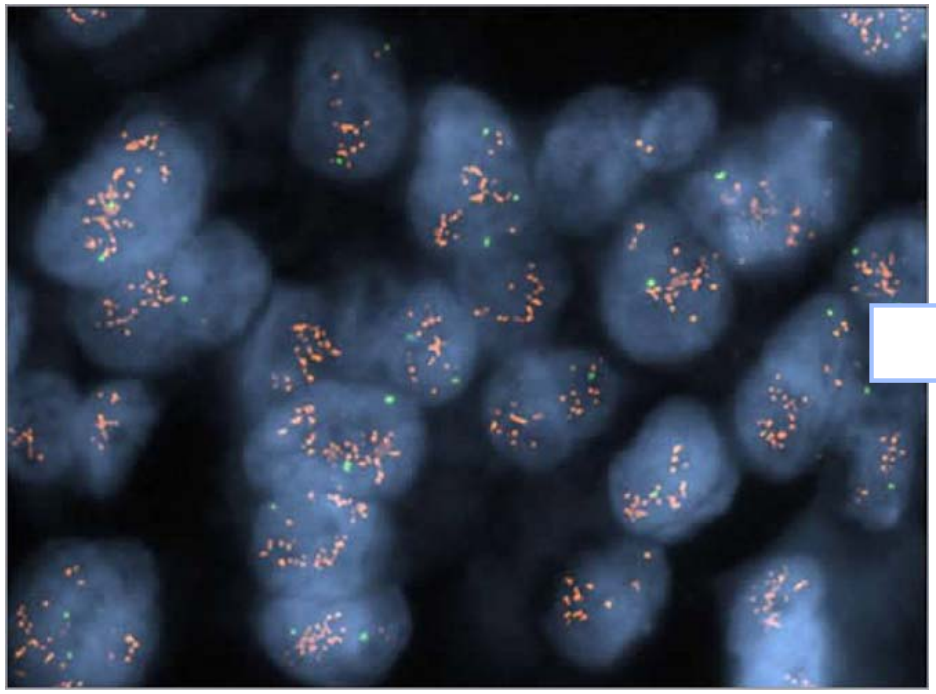
Gherardi E, *et al. Nature Rev Cancer* 2012; **12**:89–103; Christensen J, *et al. Cancer Lett* 2005; **225**:1–26; Liu X, *et al. Trends in Mol Med* 2010; **16**:37–45; Cecchi F, *et al. Eur J Cancer* 2010; **46**:1260–1270; Lai A, *et al. Trends Cell Biol* 2009; **19**:542–551.

How do we test for HER2 ?
HER2 gene alteration

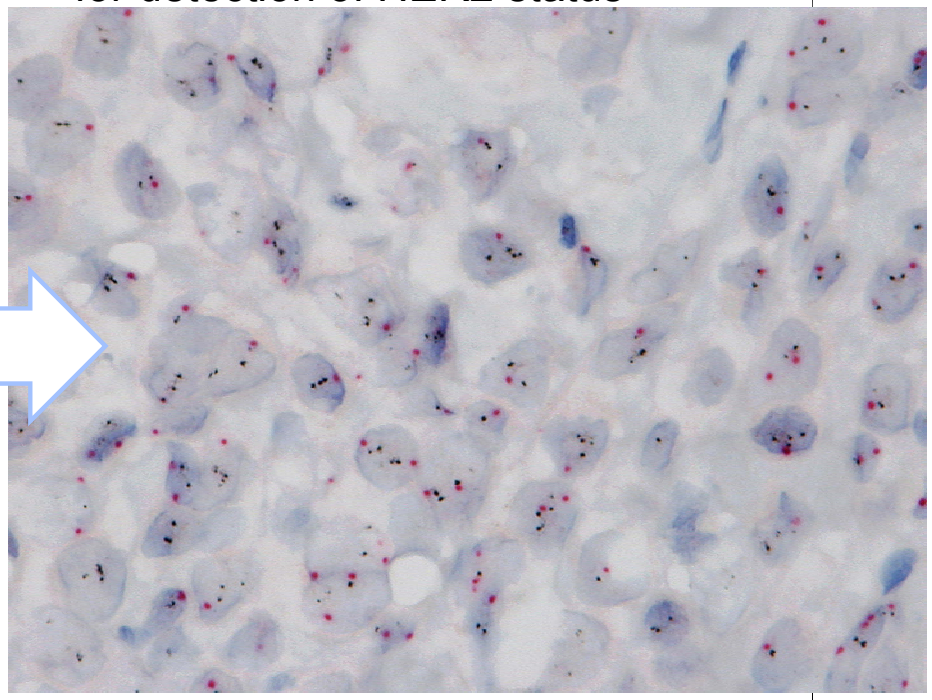


How do we test for HER2 ?
HER2 ISH

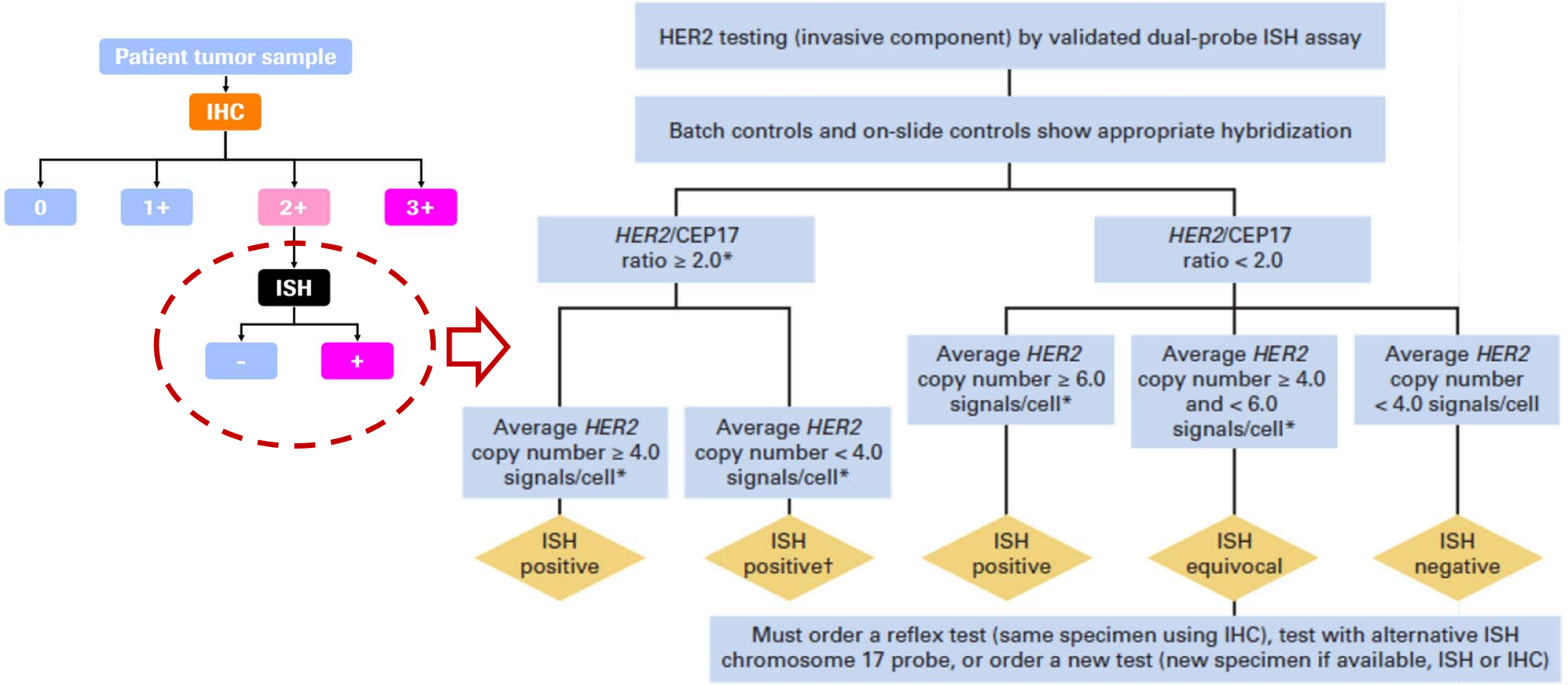
- Historical « Gold Standard » is FISH



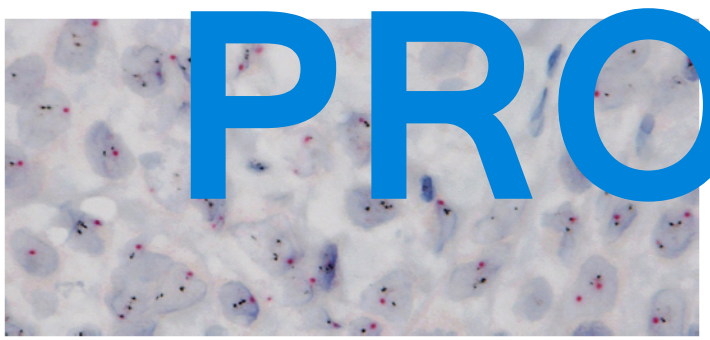
- ISH method with non-fluorscent detection for detection of HER2 status



How do we test for HER2 ?
HER2 ISH interpretation

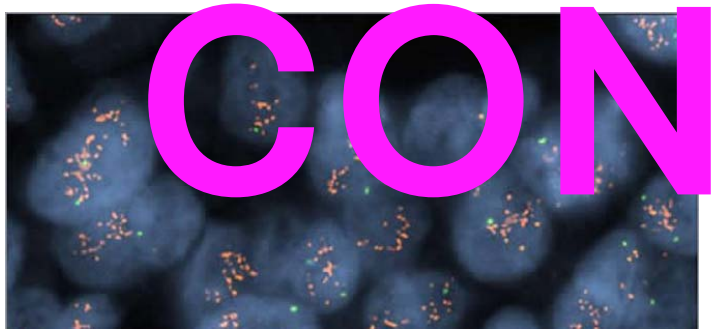


How do we test for HER2 ?
Technical point of view



Dual ISH (brighfield ISH)

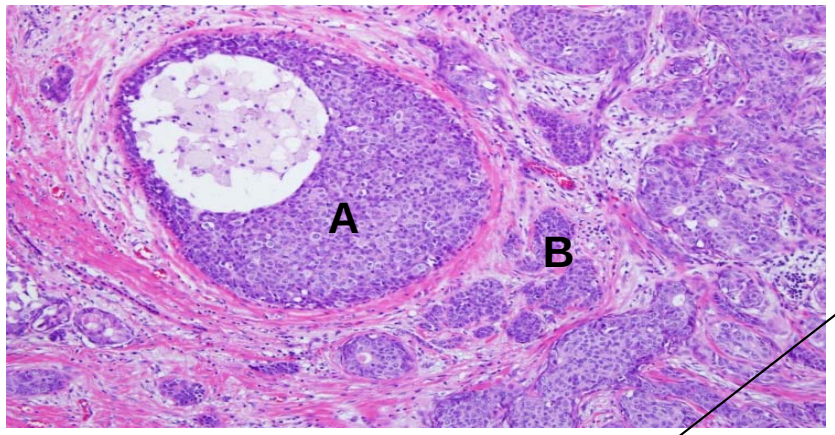
- Fully automated
- Brightfield microscopy
- Morphological context
- Archivable
- High sensitivity (detection of single gene copy)

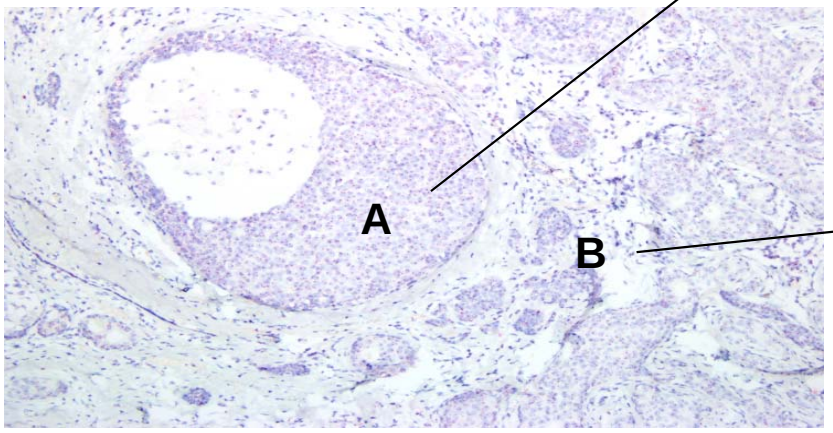


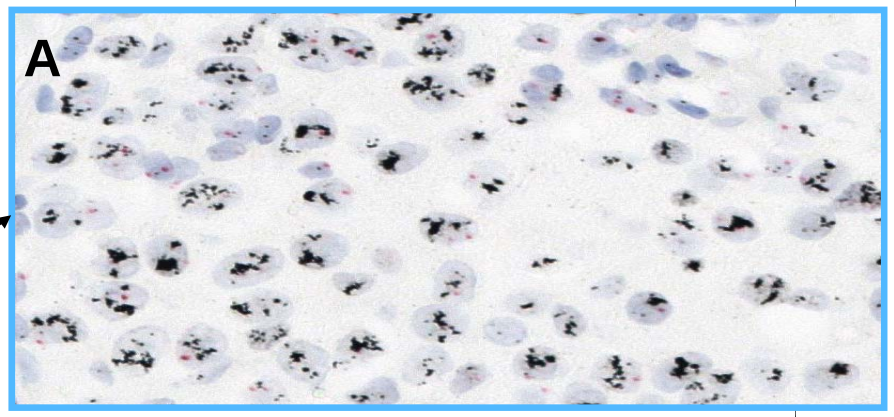
FISH (Fluorescent ISH)

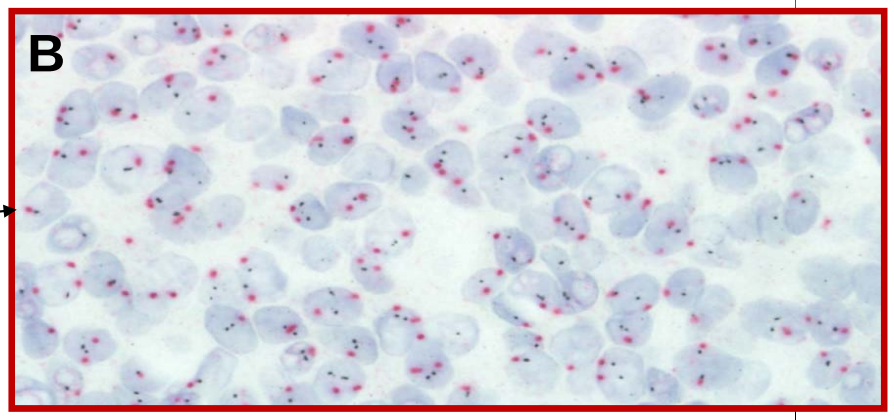
- Manual Assay
- Does not fit into a pathologist's workflow (i.e. fluorescent microscope necessary)
- Poor morphology
- Non-archivable : signal quenches over time

How do we test for HER2 ?
Morphological context









How do we test for HER2 ?
Technical point of view

ORIGINAL ARTICLE

Bright-field In Situ Hybridization for *HER2* Gene Amplification in Breast Cancer Using Tissue Microarrays

Correlation Between Chromogenic (C Silver-enhanced (SISH) Methods W

Glenn D. Francis, MBBS, FRCPA, MBA, Mark Geoffrey F. Beadle, MBBS, FRACP, FRACR,‡ and Sa*

using monoclonal antibody and pol

Jung Sik Jang, Eun Jeong Jang and Ji-Young

Department of Pathology, Kyungpook National University Hospi

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

Young Wha Koh[1,*], Hee Jin Lee[1,*], Jong Won Lee[2], Juu

[1]*Department of Pathology, University of Ulsan College of Medicine, Asan*
[2]*Department of Surgery, University of Ulsan College of Medicine, Asan Medica*
[3]*Department of Pathology, Military Manpower Administration, Government of Re*

"97% C SIS

"96% concordance"

Modern Pathology (2012) 25, 675–682

RTICLE ion

ance of SH"

Virchows Arch (2007) 451:19–25
DOI 10.1007/s00428-007-0424-5

ORIGINAL ARTICLE

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. Höfler · H. Kreipe · H. Moch · A. Dankof · K. Kölble · G. Kristiansen

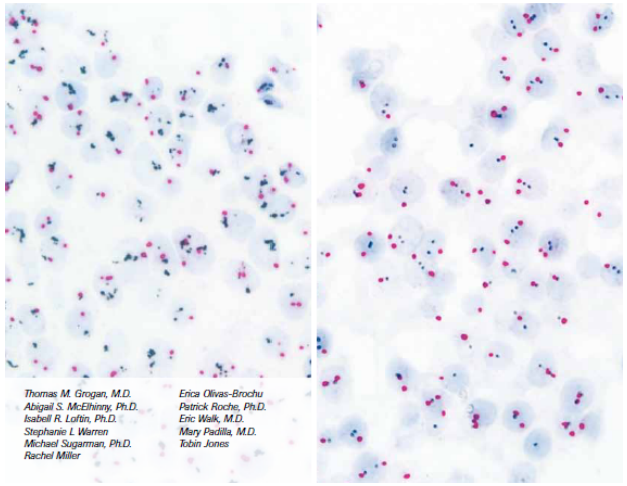
"96% concordance"

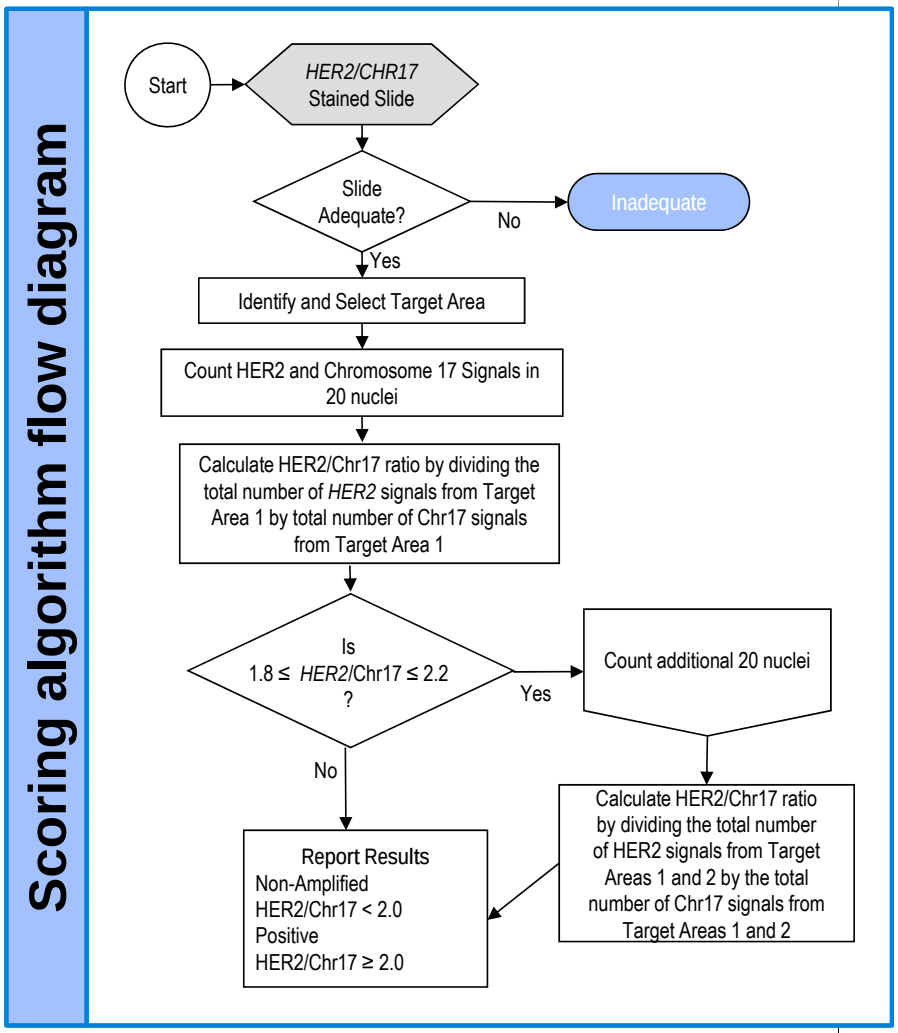
Received: 24 April 2007 / Accepted: 24 April 2007 / Published online: 12 June 2007

Kirsten Gadgaard Jensen, HT, and Vibeke Jensen, MD, PhD†*

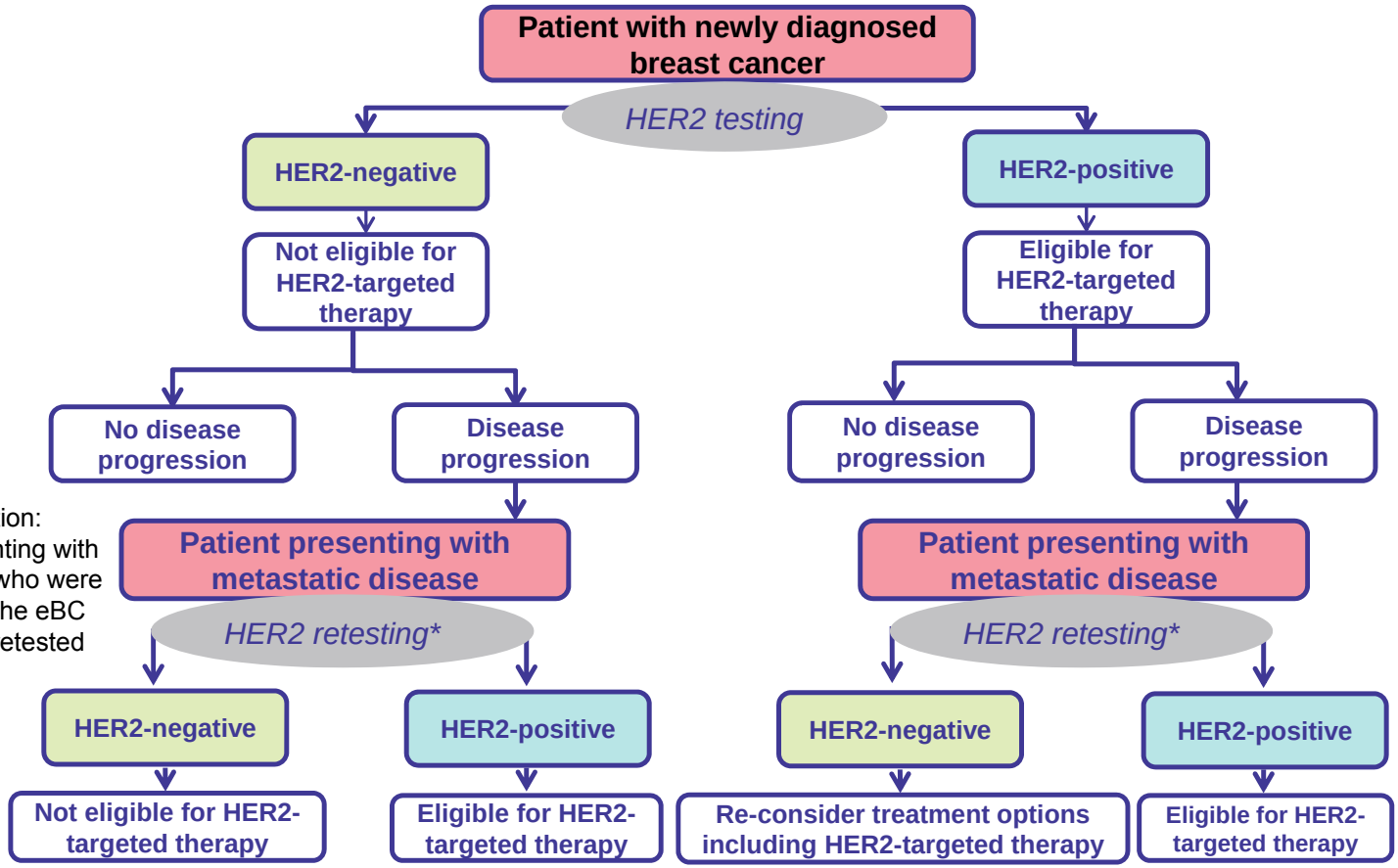
How do we test for HER2 ?
Interpretation support

Interpretation Guide
Ventana INFORM HER2 Dual ISH
DNA Probe Cocktail Assay





Who should be tested for HER2



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

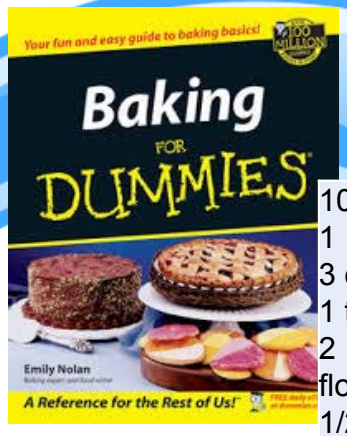
*HER2 test performed in a metastatic site, if tissue sample is available; especially considered for a patient who previously tested HER2-negative in a primary tumour and presents with disease recurrence with clinical behaviour suggestive of HER2-positive or triple-negative disease.

Wolff AC, *et al*. *J Clin Oncol* 2013; **31**:3997–4013; Penault-Llorca F, *et al. Breast* 2013; **22**:200–202.

Pre Analytics consideration

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

Guidelines for pre – analytics?

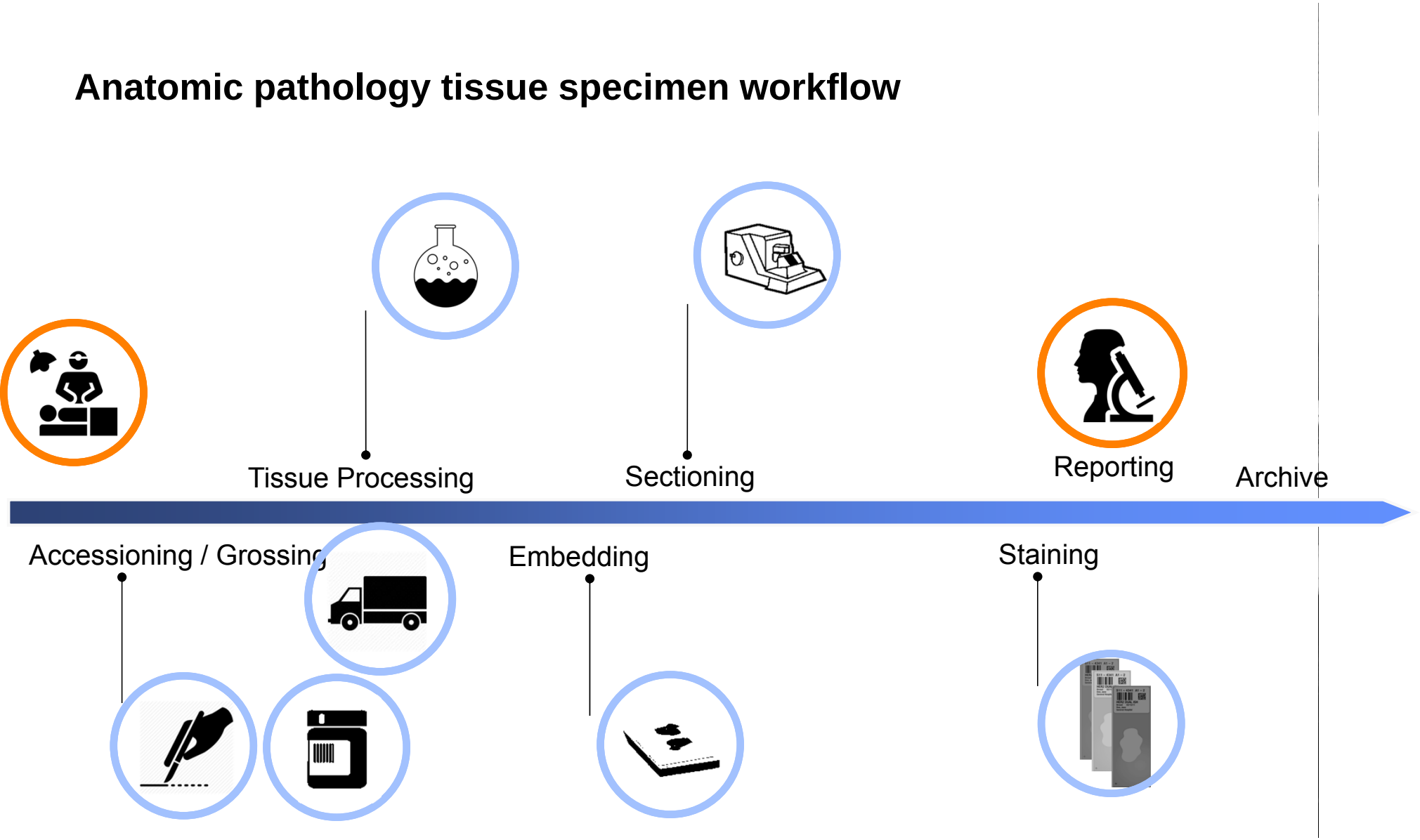


10 tablespoons butter
1 1/2 cups white sugar
3 eggs
1 tablespoon grated lemon zest
2 1/2 cups sifted all-purpose flour
1/2 teaspoon salt
1/2 teaspoon baking soda
1 teaspoon baking powder
1 cup buttermilk
3/4 teaspoon lemon extract
1/2 cup golden raisins

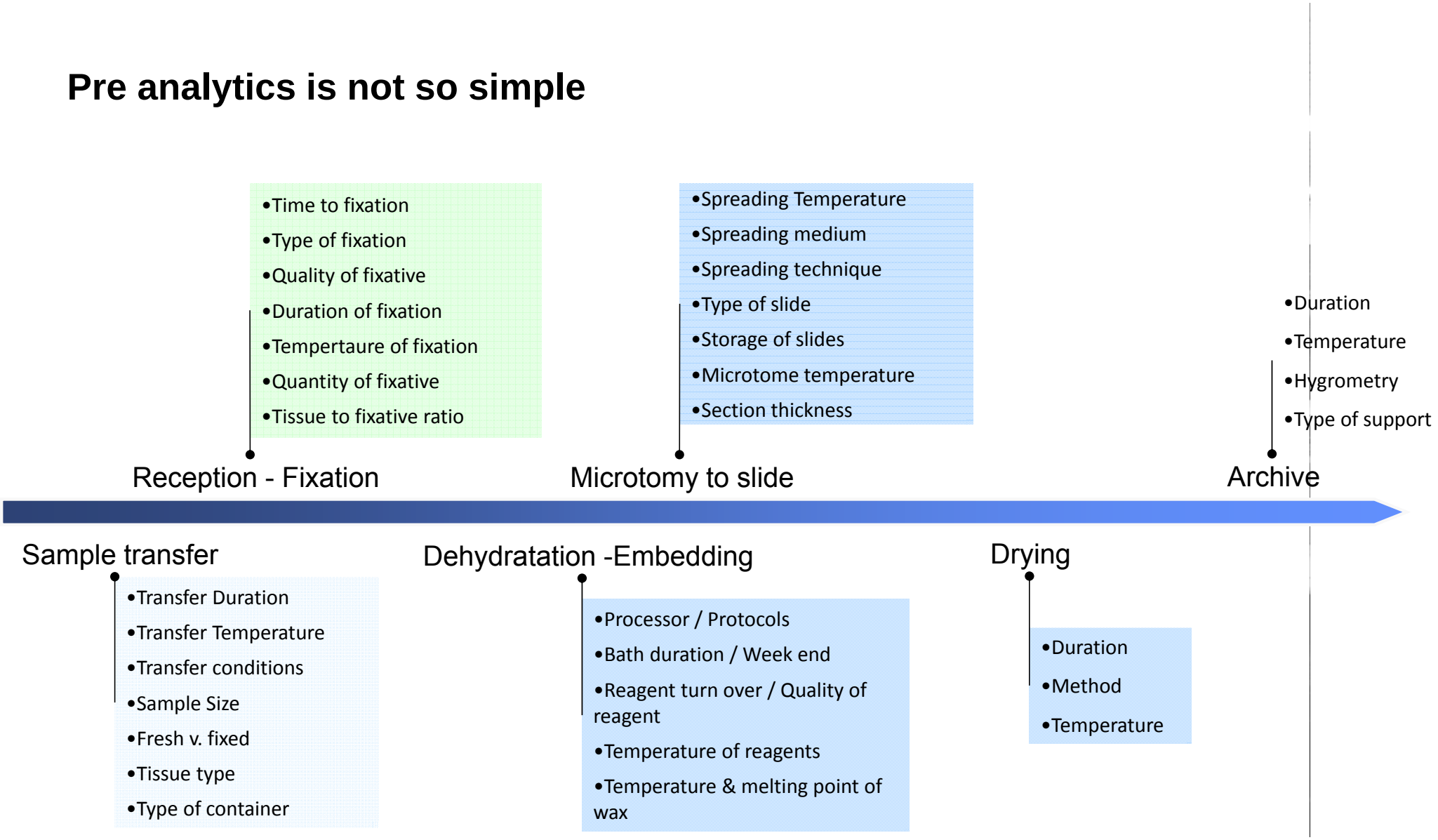
1/3 cup white sugar
1/3 cup butter
1 1/2 tablespoons water
2 tablespoons fresh lemon juice

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



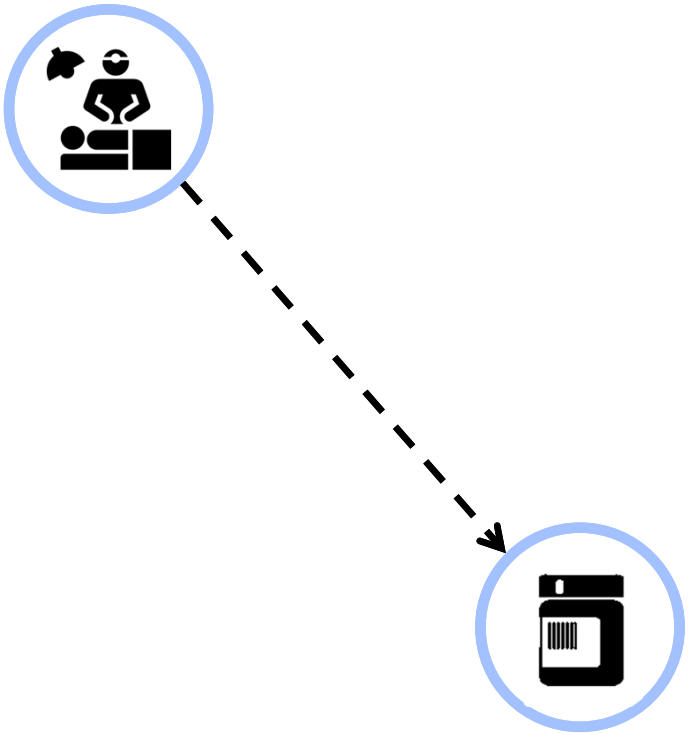
Targeting the Pre analytical

1 Cold Ischemia time

2 Fixation

3 Tissue processing parameters

What is cold ischemia time



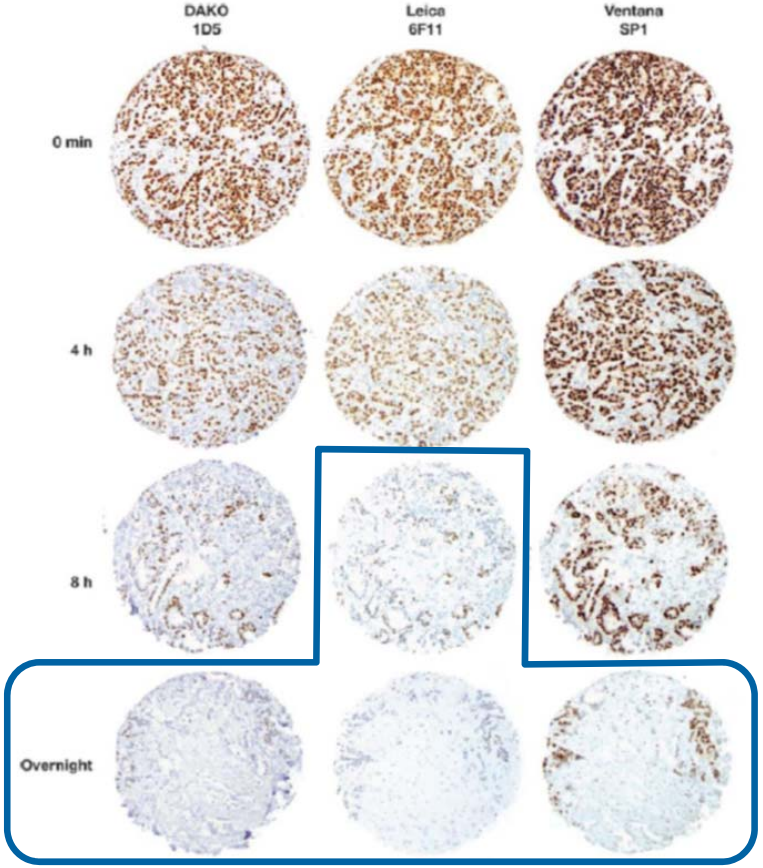
Definition :

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 interpret as negative (False Negative)

Impact for patient management

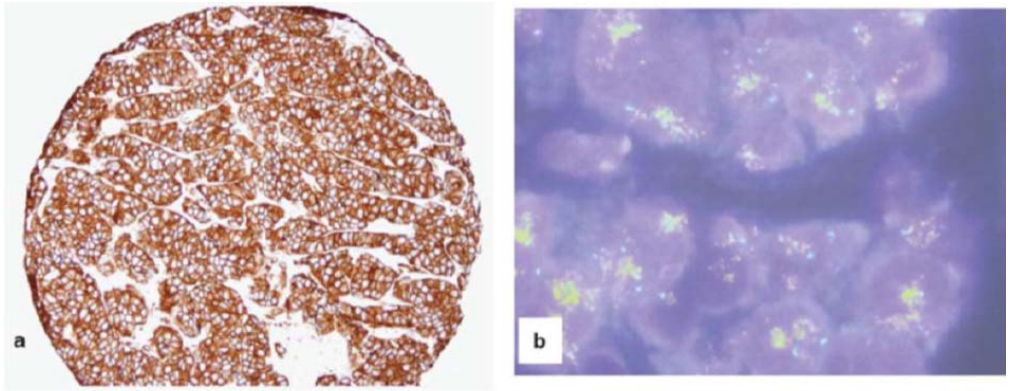
No Hormonal Therapy

Higher Risk of Recurrence

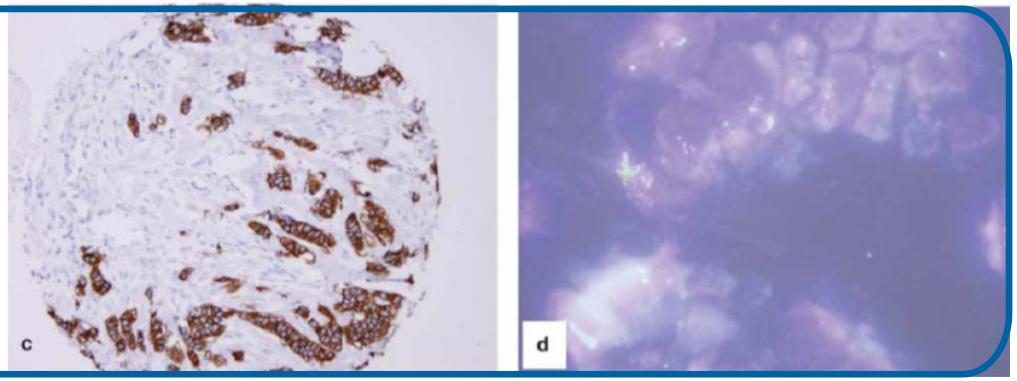
Qiu 2009

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

0,5h (30min)



2h (120min)



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

Impact for patient management

↓

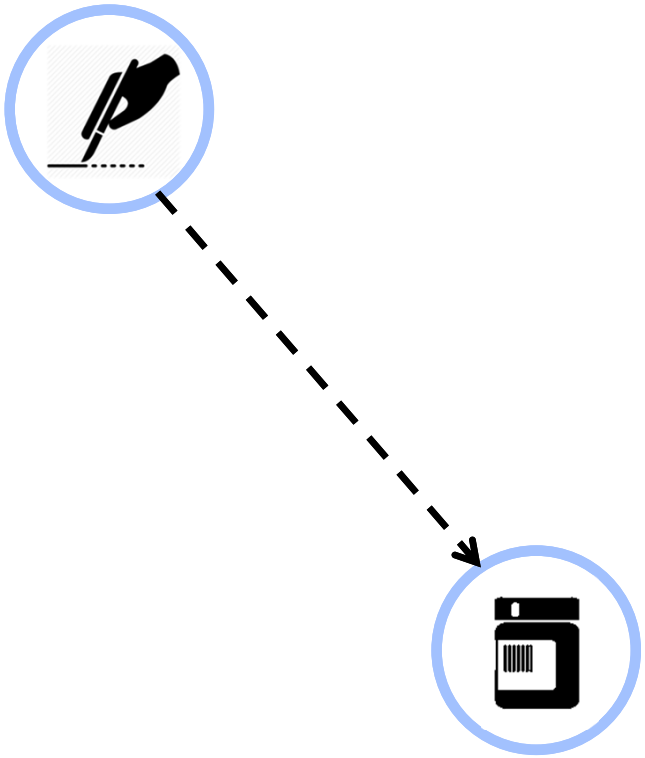
No HER2 targeted therapies

↓

Worse outcome for the patient

Khoury 2009

What is tissue fixation

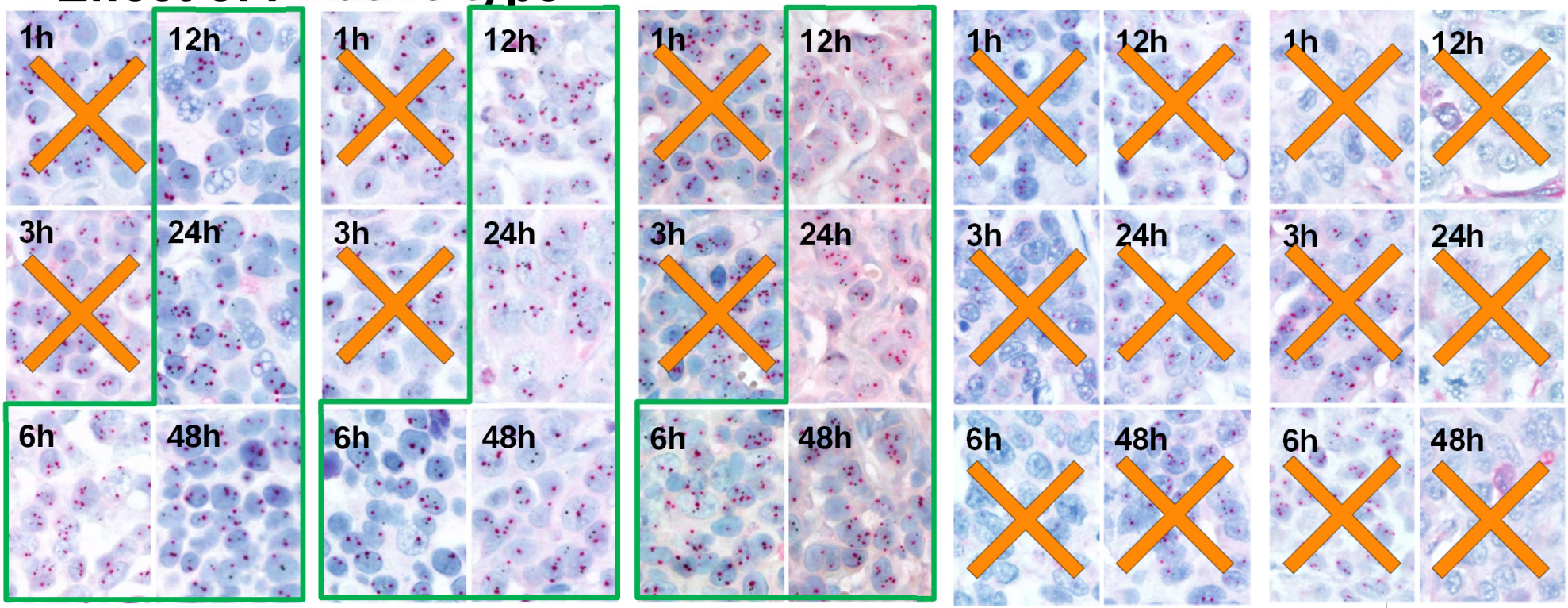


Kills the tissue so that no post-mortem activities can occur :

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

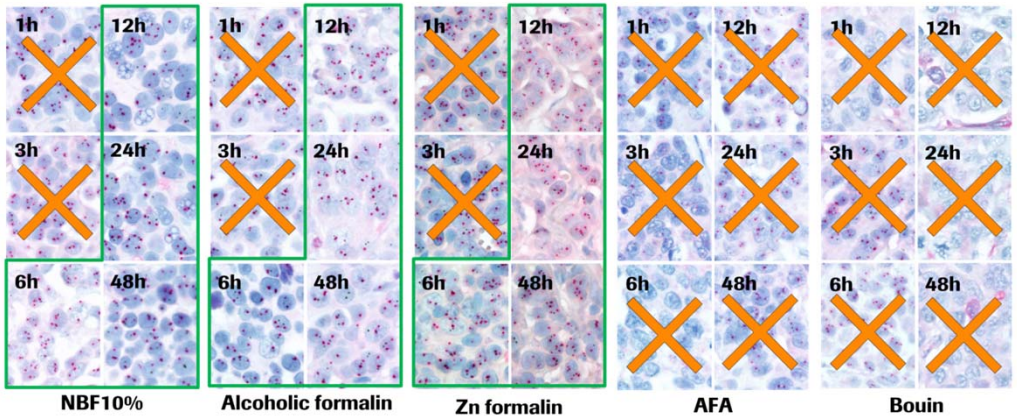
must change the soluble contents of the cell into insoluble substances so that those substances are not lost during subsequent processing steps

But what can be the impact to the patient management?
Effect of Fixative type



Babic 2010

But what can be the impact to the patient management?
Effect of Fixative type



10% Neutral Buffered Formalin

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

Impact for patient management

↓

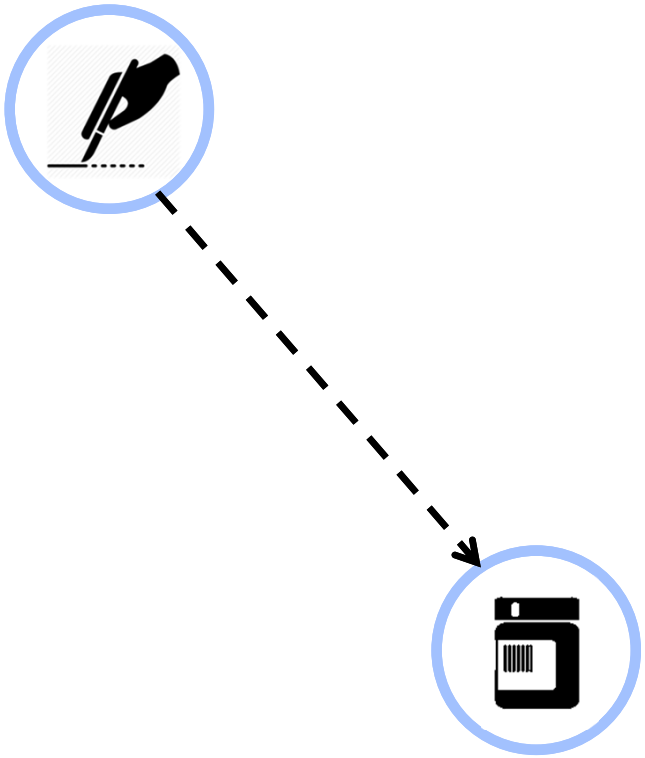
False negative / False Positive

↓

Worse outcome for the patient

Babic 2010

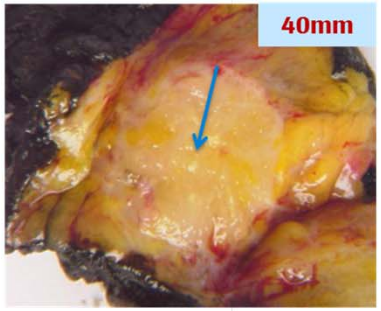
Some basic rules to keep in mind



There are 2 effects ongoing in parallel during fixation with formalin

Penetration of fixative
Diffusion

cross-linking proteins
-CH2- linkage

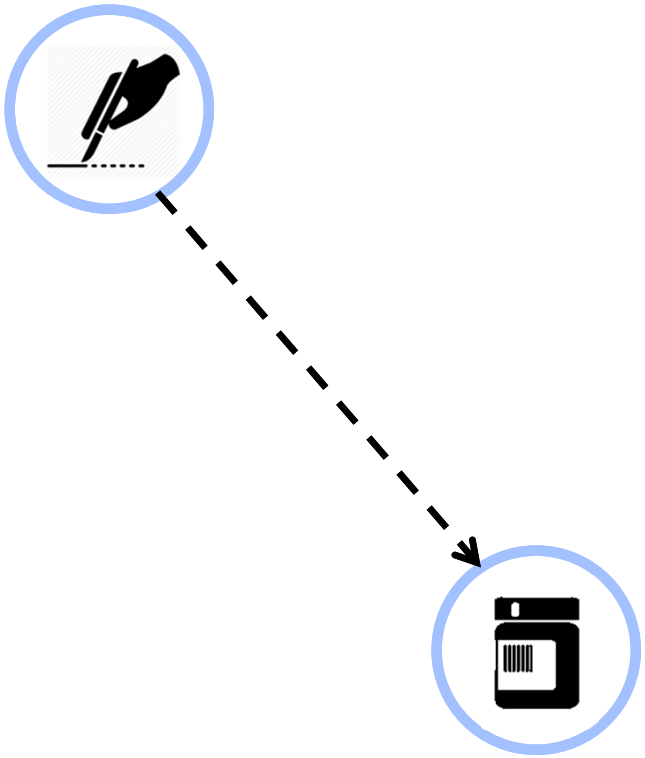


10 min

16hrs

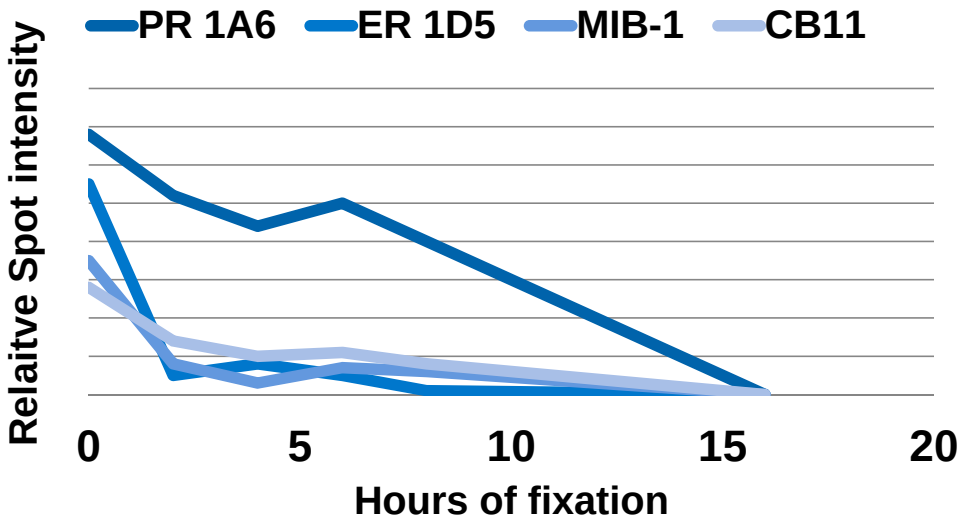
5 days

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



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

Extended fixation time might generate weak staining

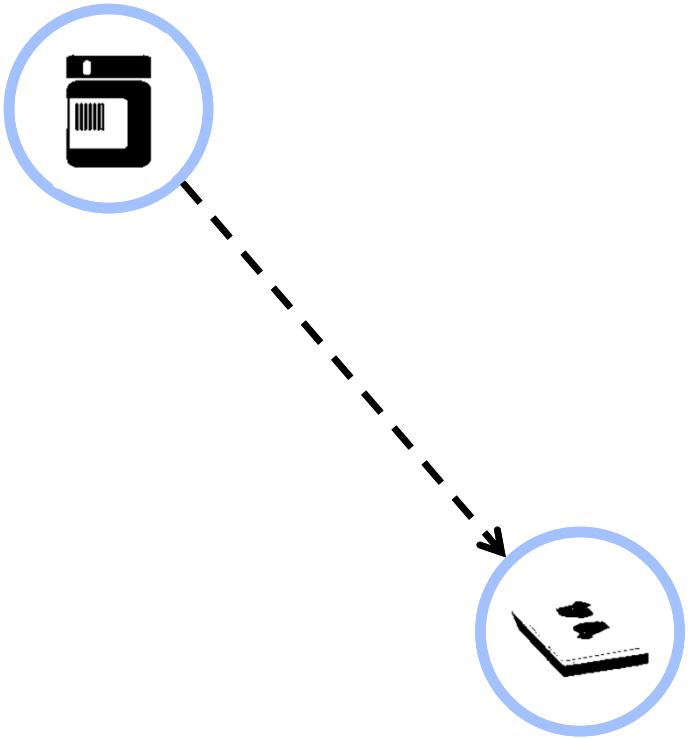
Impact for patient management

False negative

Under/no treatment / missclassification

Bogen 2009

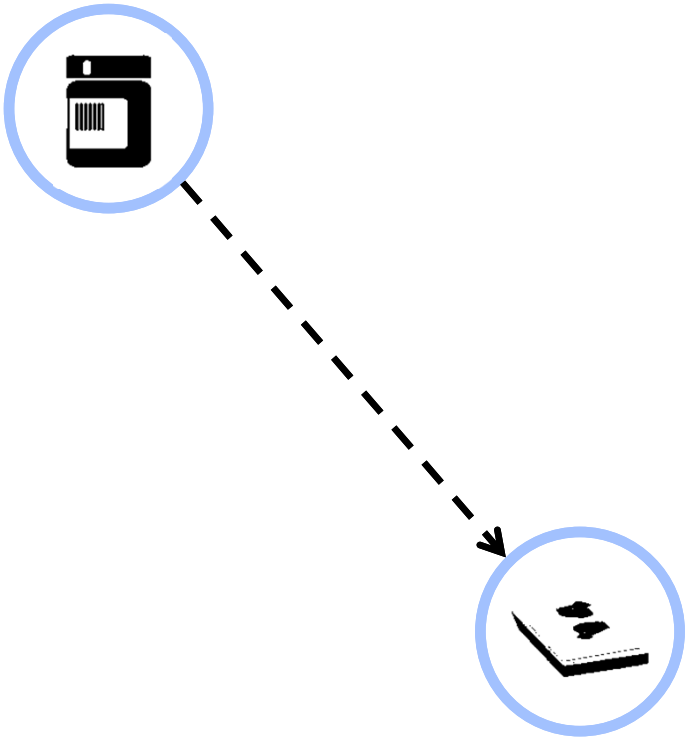
What is tissue processing



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

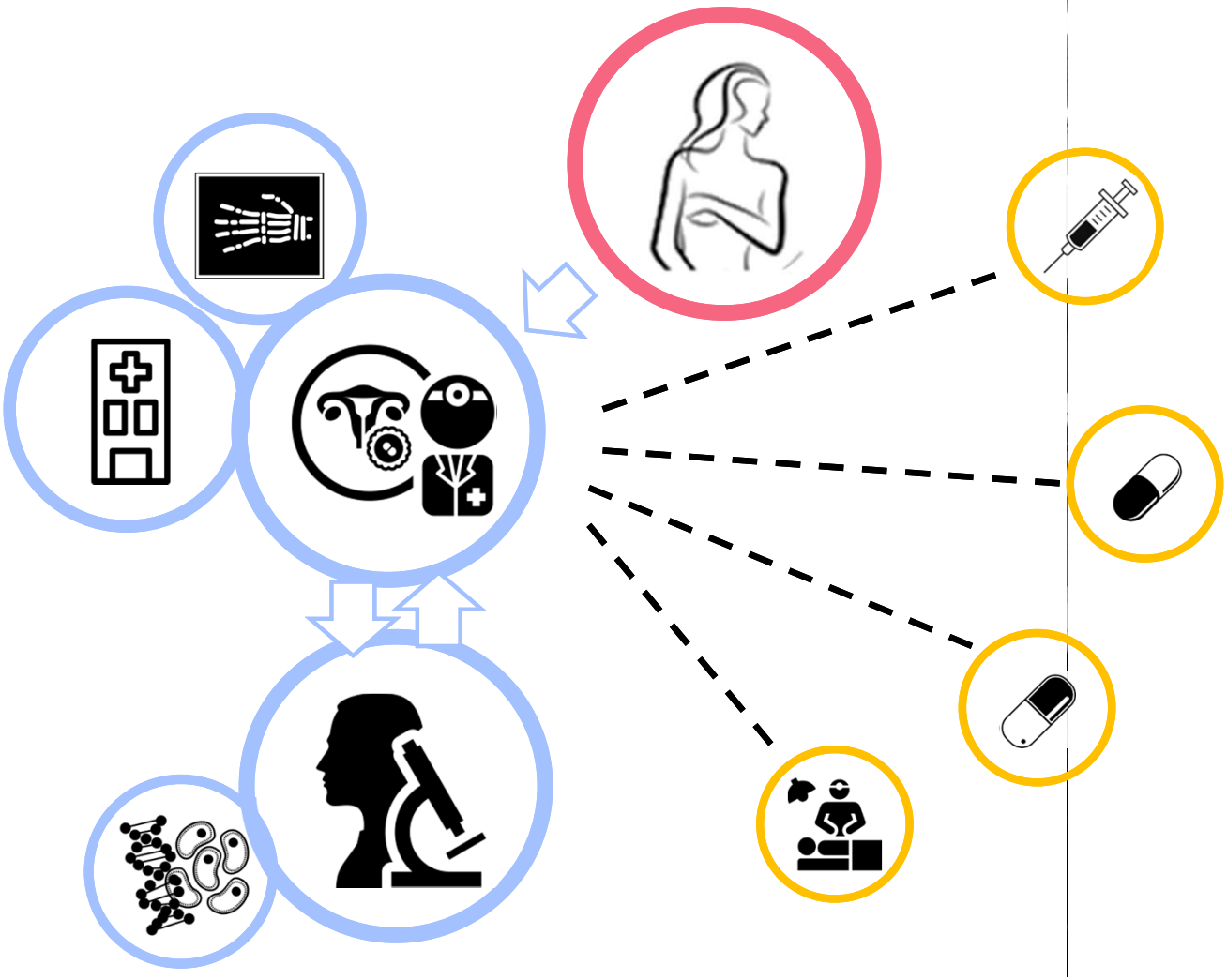
Avoid excessive heat

Poor quality of H&E and IHC staining

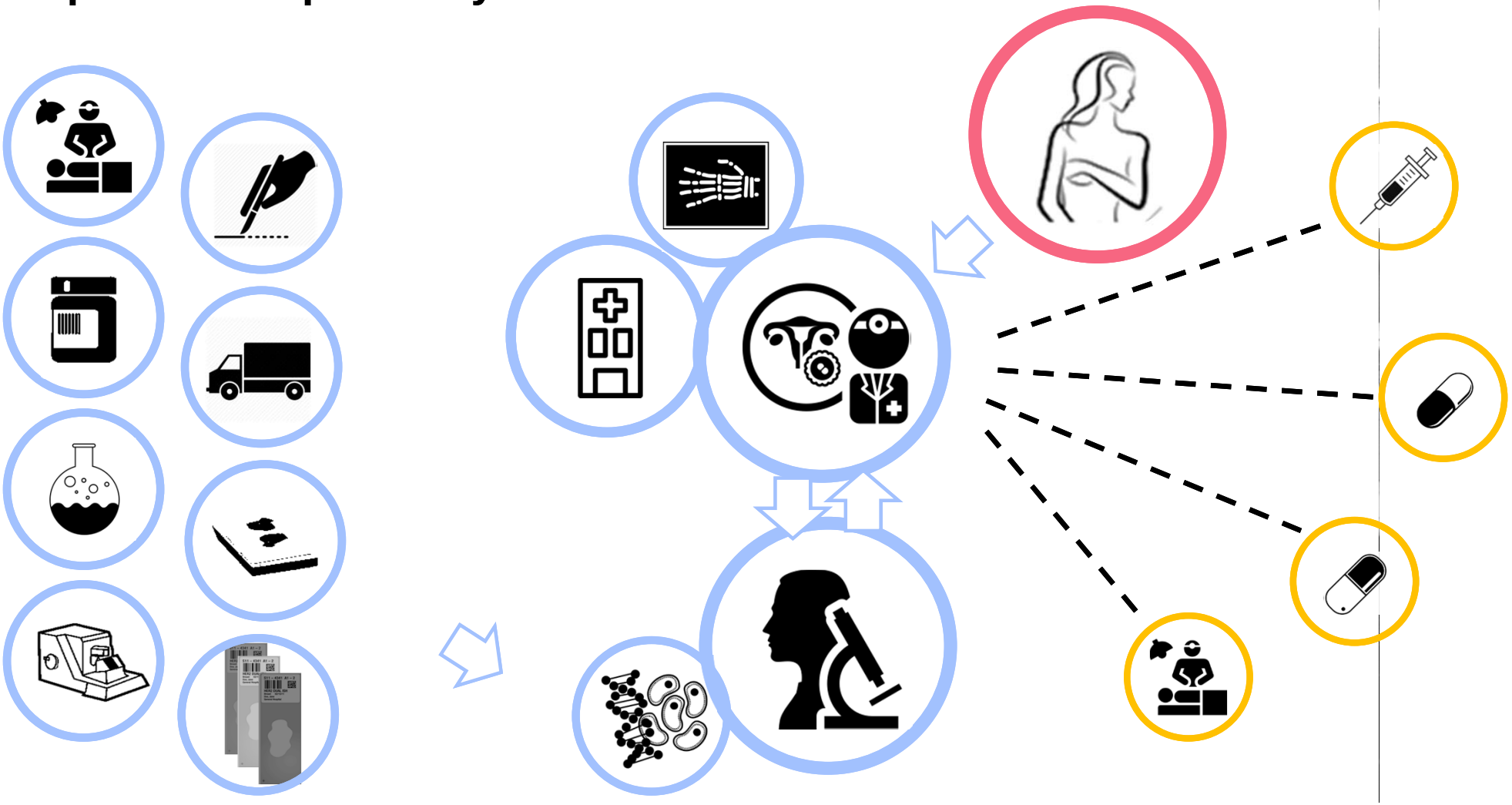
Slicing quality

Poor morphology and artifacts

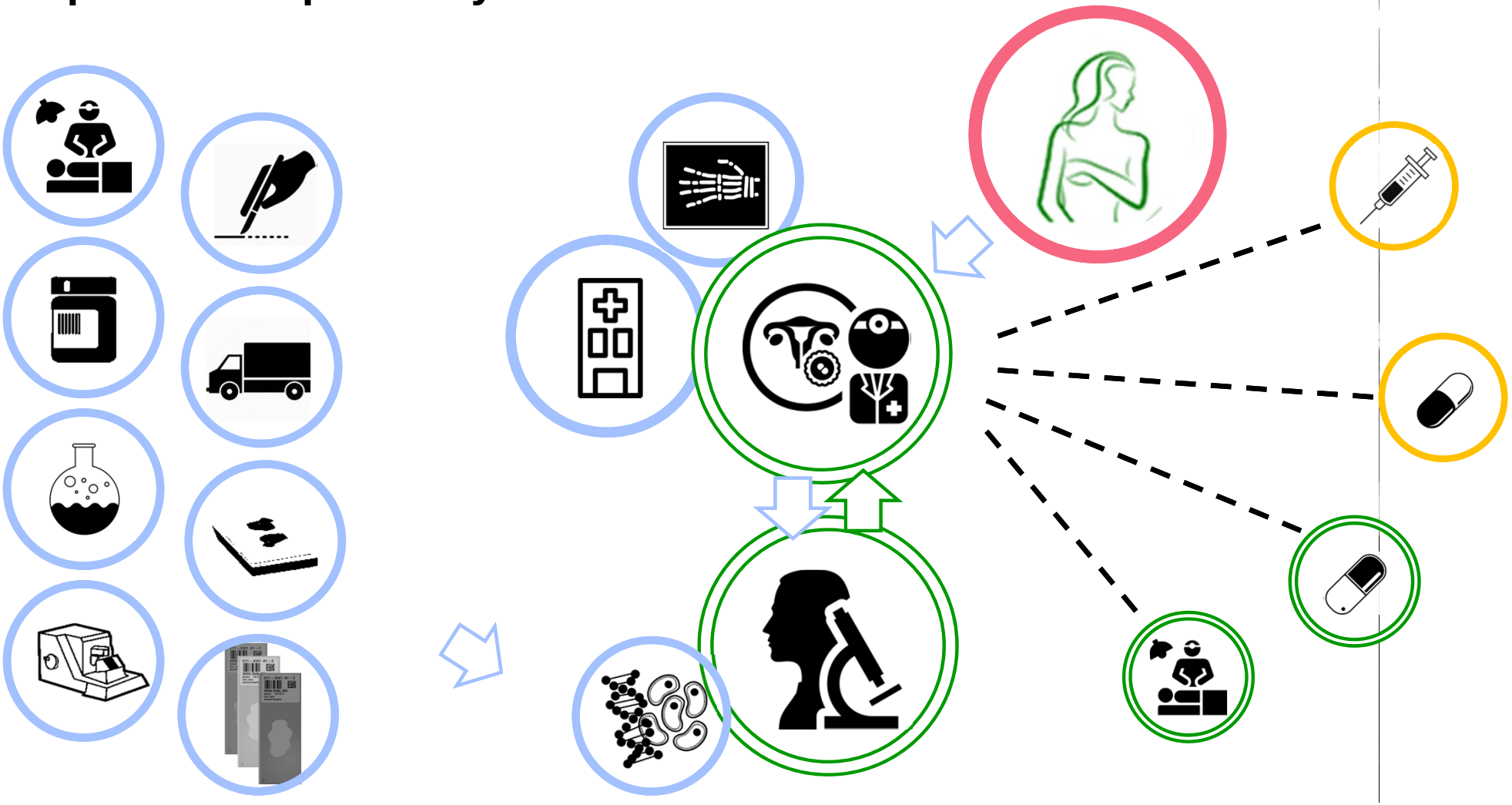
Impact of the pre analytics



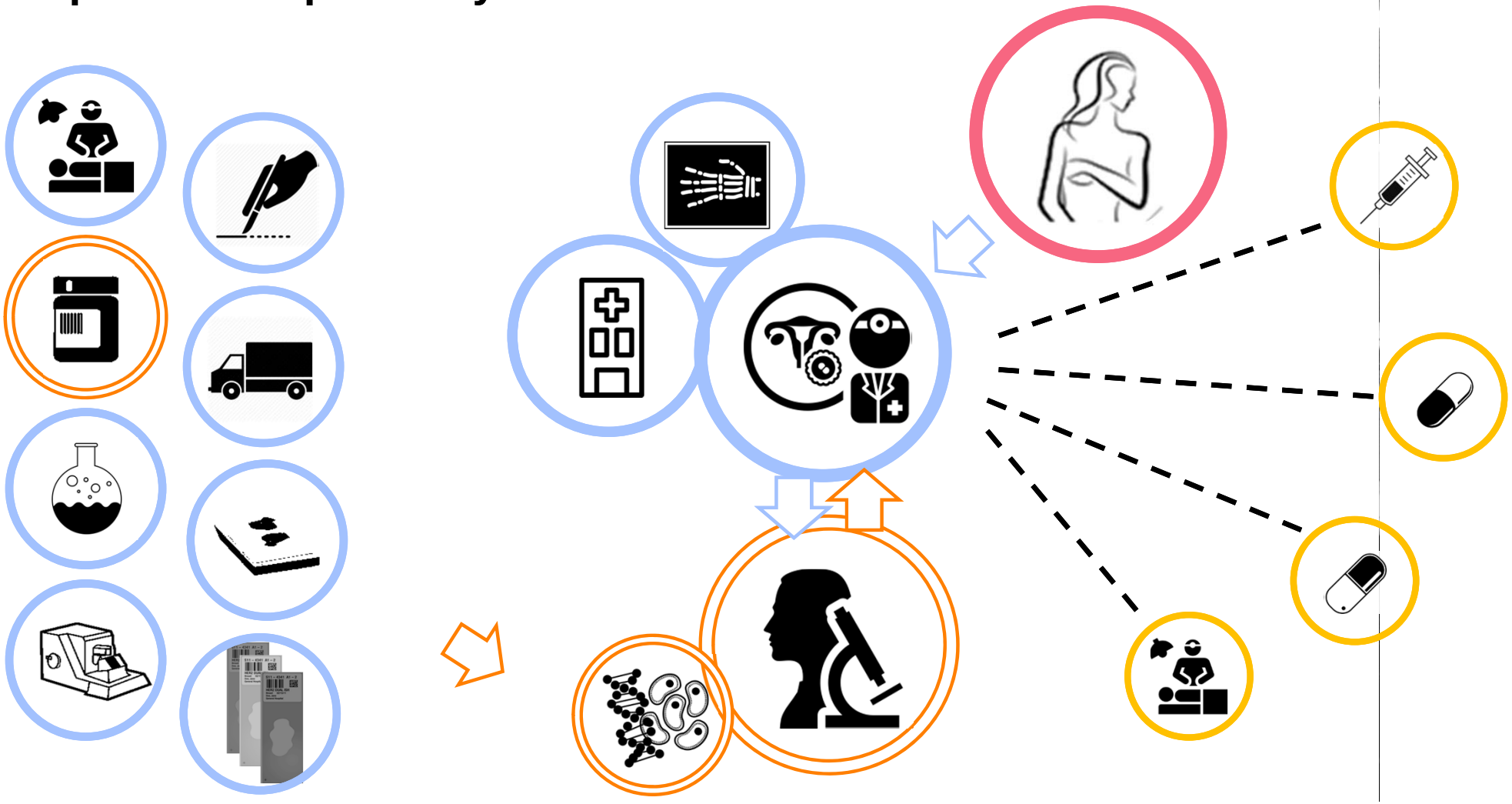
Impact of the pre analytics



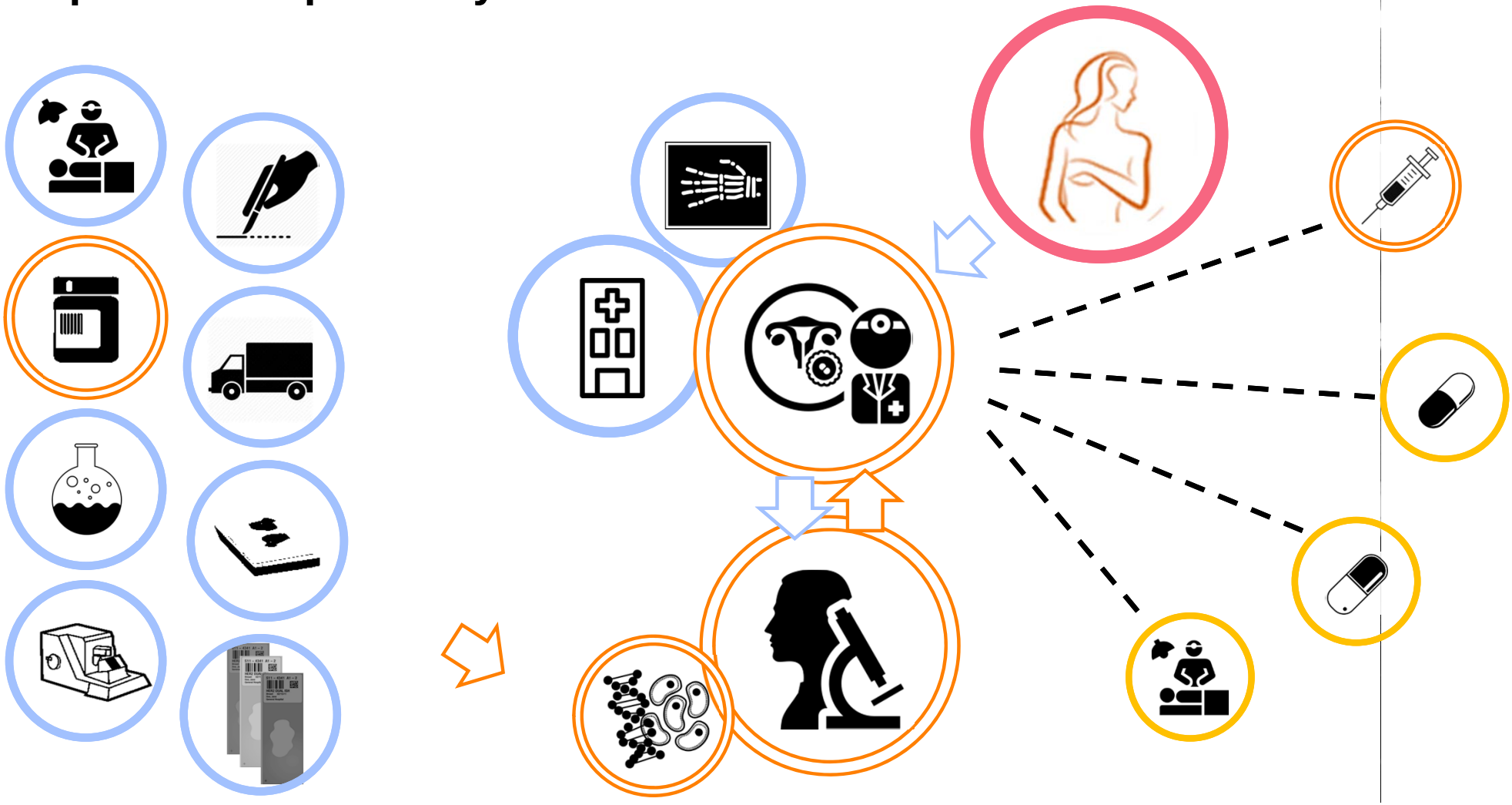
Impact of the pre analytics



Impact of the pre analytics



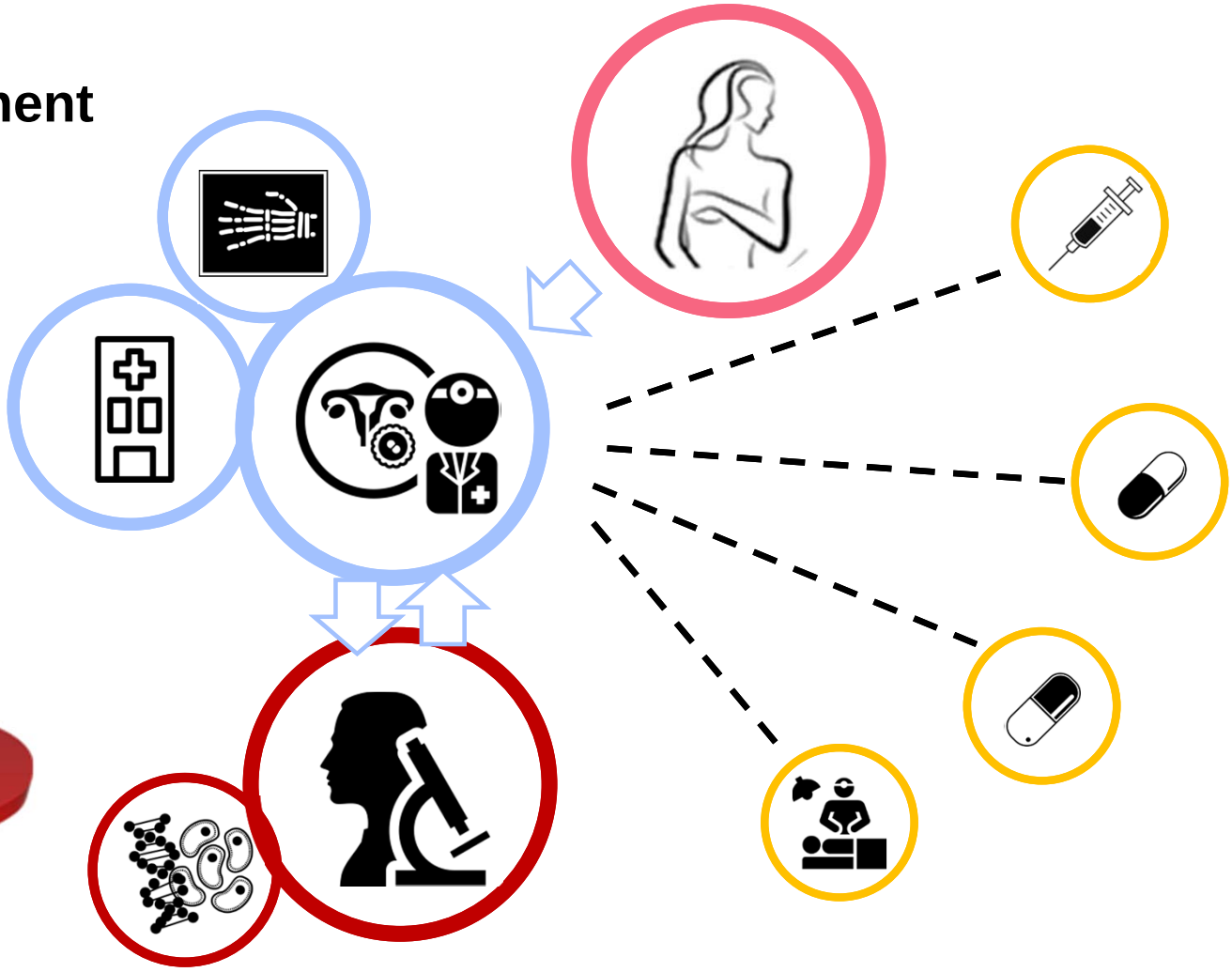
Impact of the pre analytics



Quality impact not only the patient

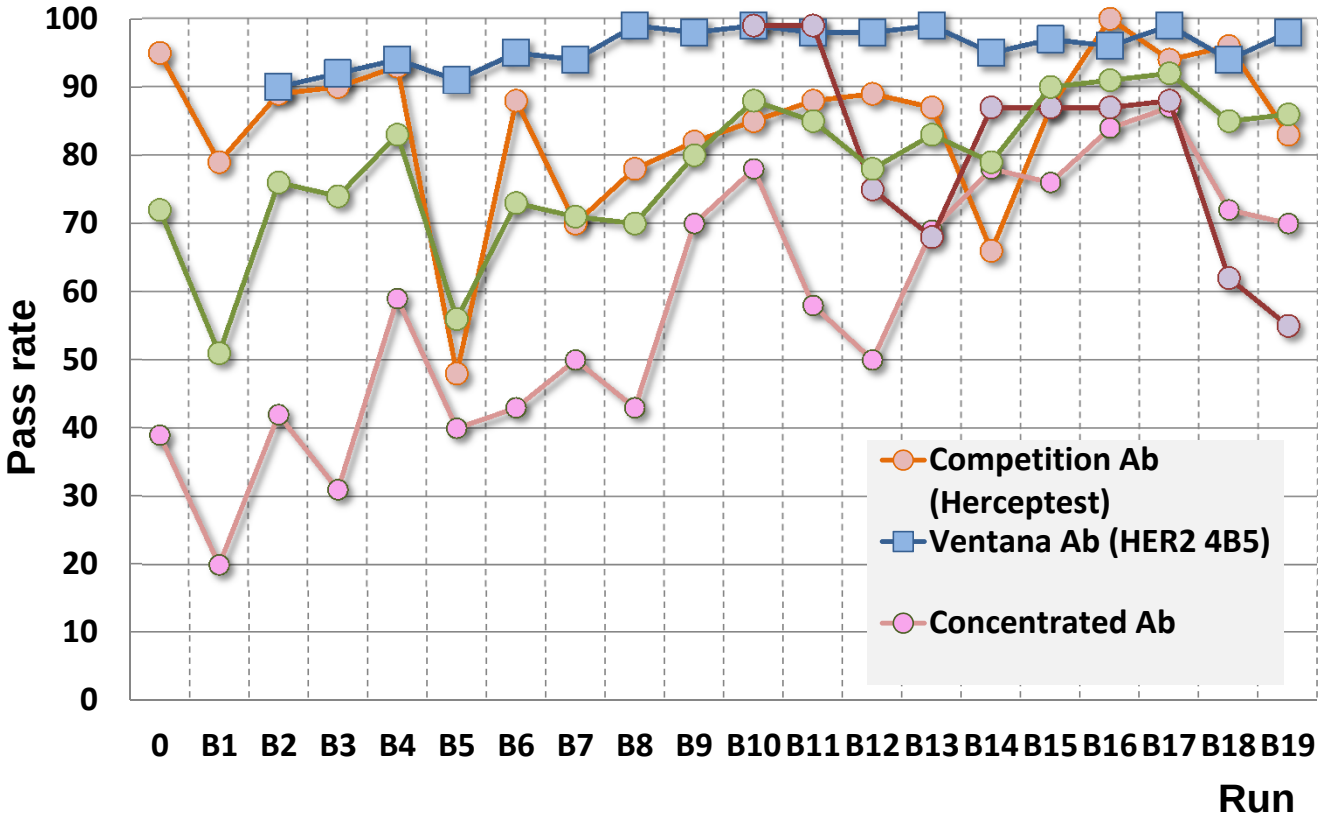
Explanation text

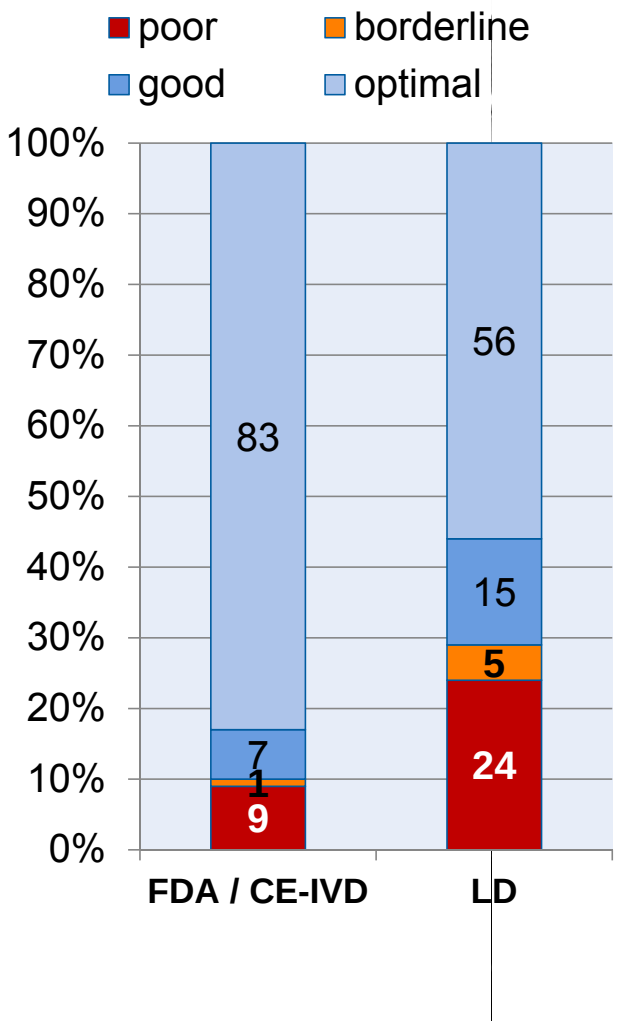
Breast Cancer : Facts and Numbers
Diagnosis is a key element



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

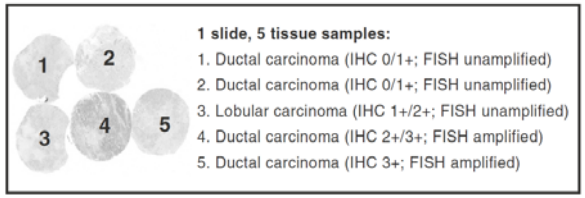
BMC
Health Services Research

RESEARCH ARTICLE Open Access

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

Mogens Vyberg[1*], Søren Nielsen[1], Rasmus Røge[1], Beth Sheppard[2], Jim Ranger-Moore[2], Eric Walk[2], Juliane Gartemann[3], Ulrich-Peter Rohr[3] and Volker Teichgräber[3]

Methodology



1 slide, 5 tissue samples:

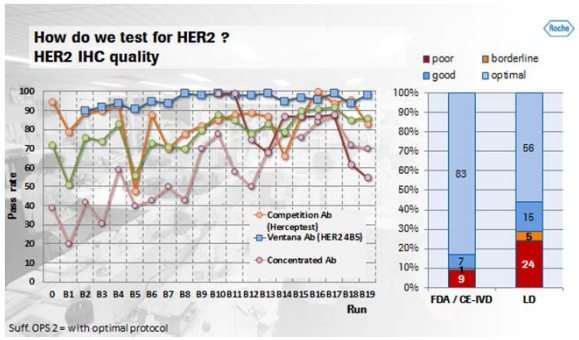
1. Ductal carcinoma (IHC 0/1+; FISH unamplified)
2. Ductal carcinoma (IHC 0/1+; FISH unamplified)
3. Lobular carcinoma (IHC 1+/2+; FISH unamplified)
4. Ductal carcinoma (IHC 2+/3+; FISH amplified)
5. Ductal carcinoma (IHC 3+; FISH amplified)

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



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)

National Surgical Adjuvant Breast & Bowel Project B31[1]

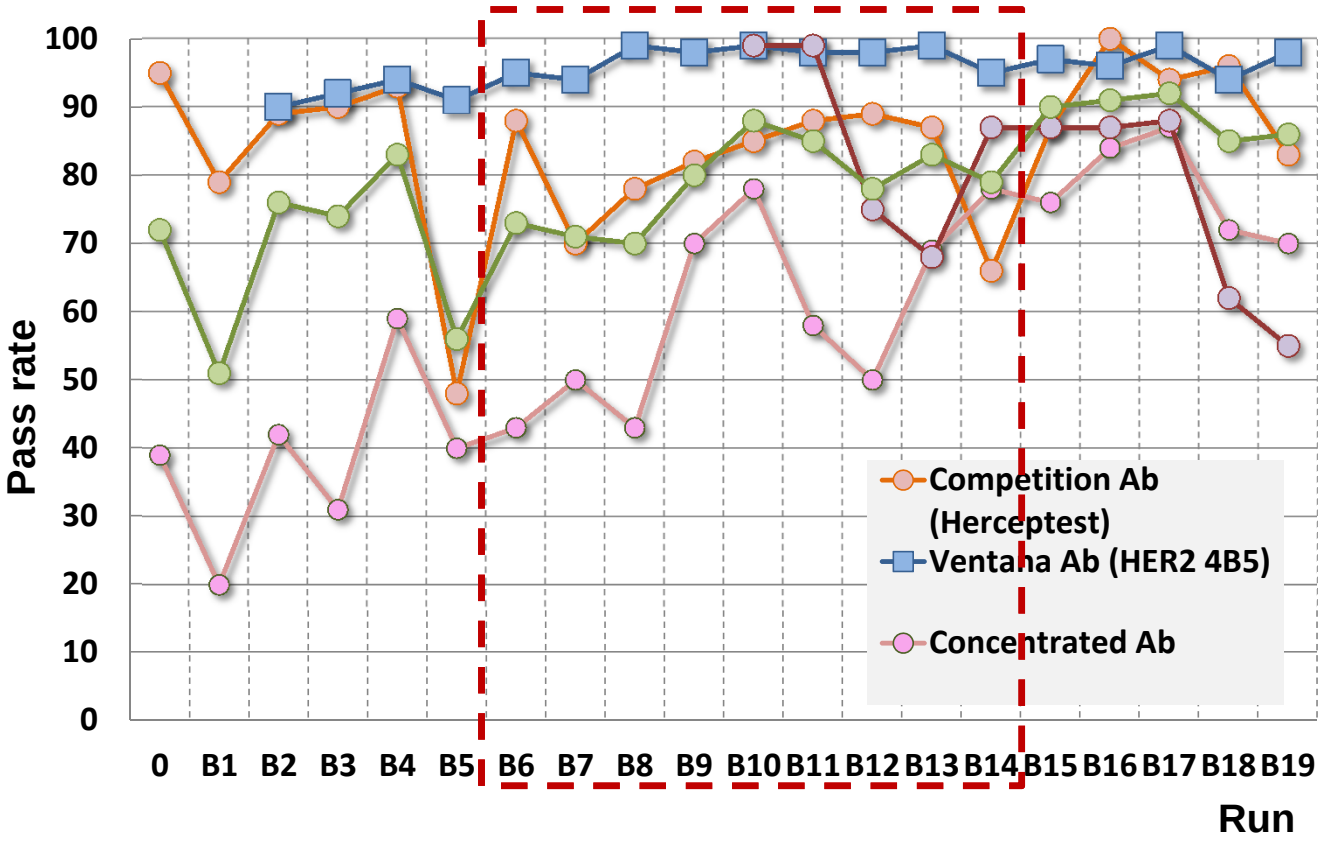
North Central Ca Treatment Group trial N9831[1]

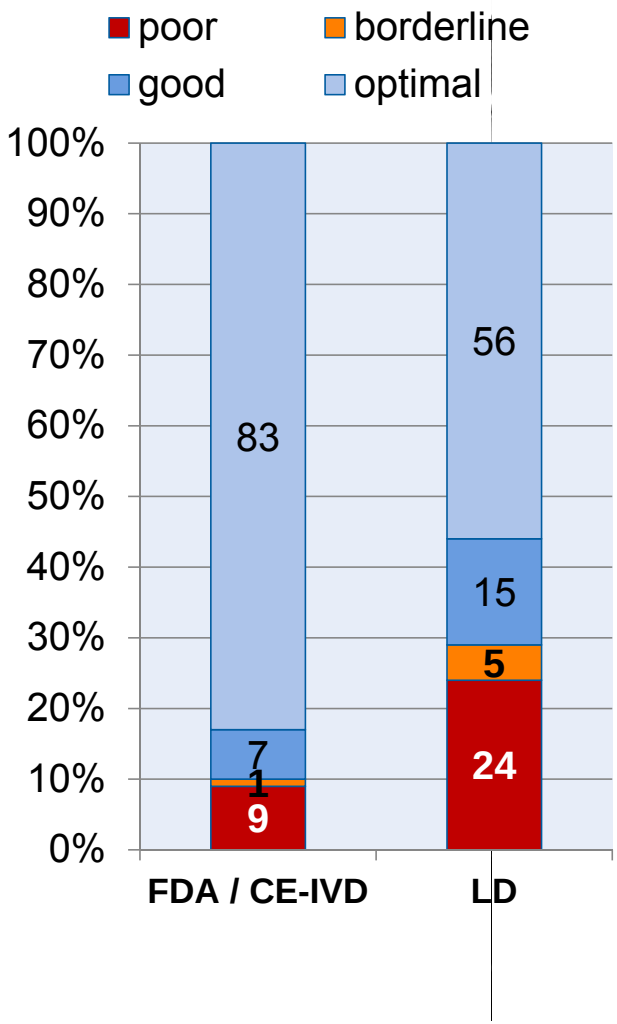
Phase III H0648g[2]

interaction between QALYs & productivity[3]

US healthcare system

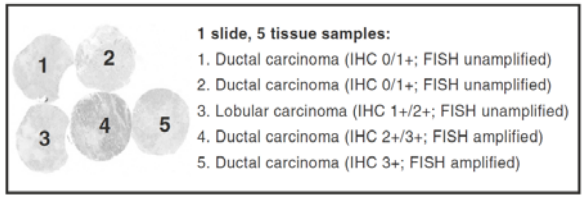
EQA example
HER2 IHC quality





Suff. OPS 2 = with optimal protocol

False Positive



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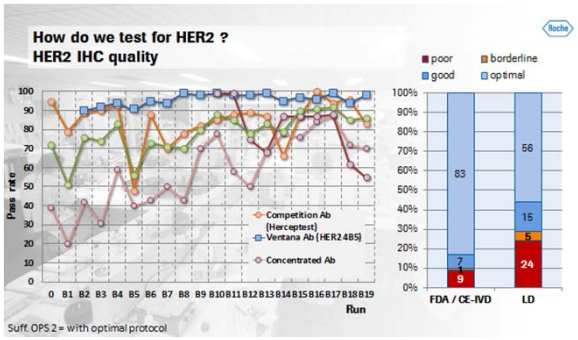
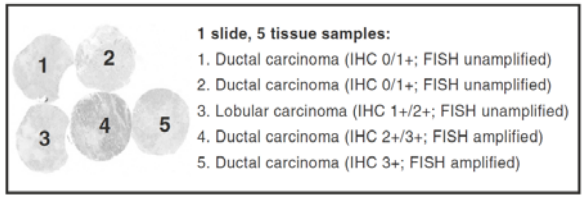


0% For approved IVD

5% For Lab Dev IVD

False Negative



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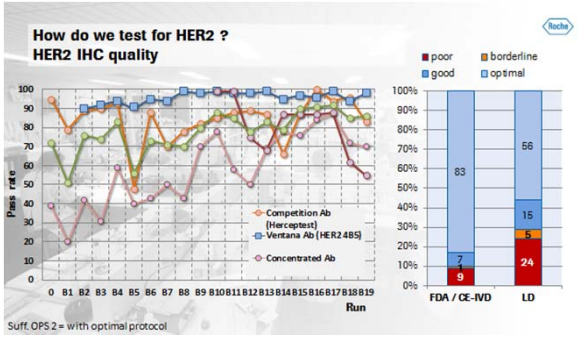

11% For approved IVD

25% For Lab Dev IVD

Results

Medical Cost

40,9M$

Difference in Total direct cost for EBC (App IVD vs. LD IVD)

5,1M$

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[1]

North Central Ca Treatment Group trial N9831[1]

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interaction between QALYs & productivity[3]

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

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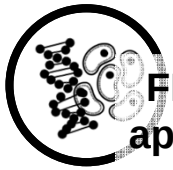
US healthcare system

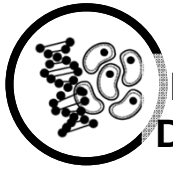
Results

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

10M$

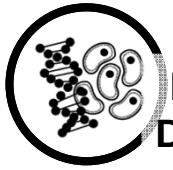
+

FN & FP additional costs

15M$

=

25,0M$



Laboratory Develop. test

2,5M$

+

FN & FP additional costs

60M$

=

62,5M$

Doing now what patients need next