Curriculum Vitae

Dr. dr. Primariadewi R, SpPA(K)

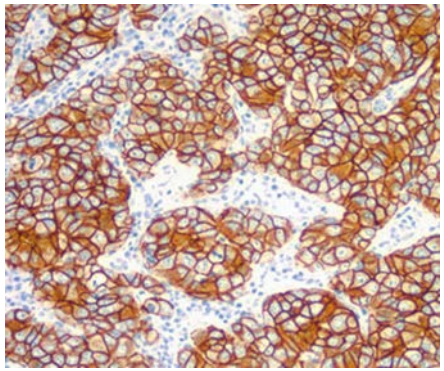
Education :

- Medical Doctor from UKRIDA
- Doctoral Degree from Faculty of Medicine University of Indonesia
- Pathologist Specialist and Consultant from Faculty of Medicine University of Indonesia
- Workshop HER2 Chromogenic In Situ Hybridization
- PathVysion TM HER2-Assay Certification
- Observership in Breast Pathology at Harvard University

Research on Overexpression of HER2 and NM23H1 at ductal invasive carcinoma breast cancer and metastasis at lymph node.

Experience :

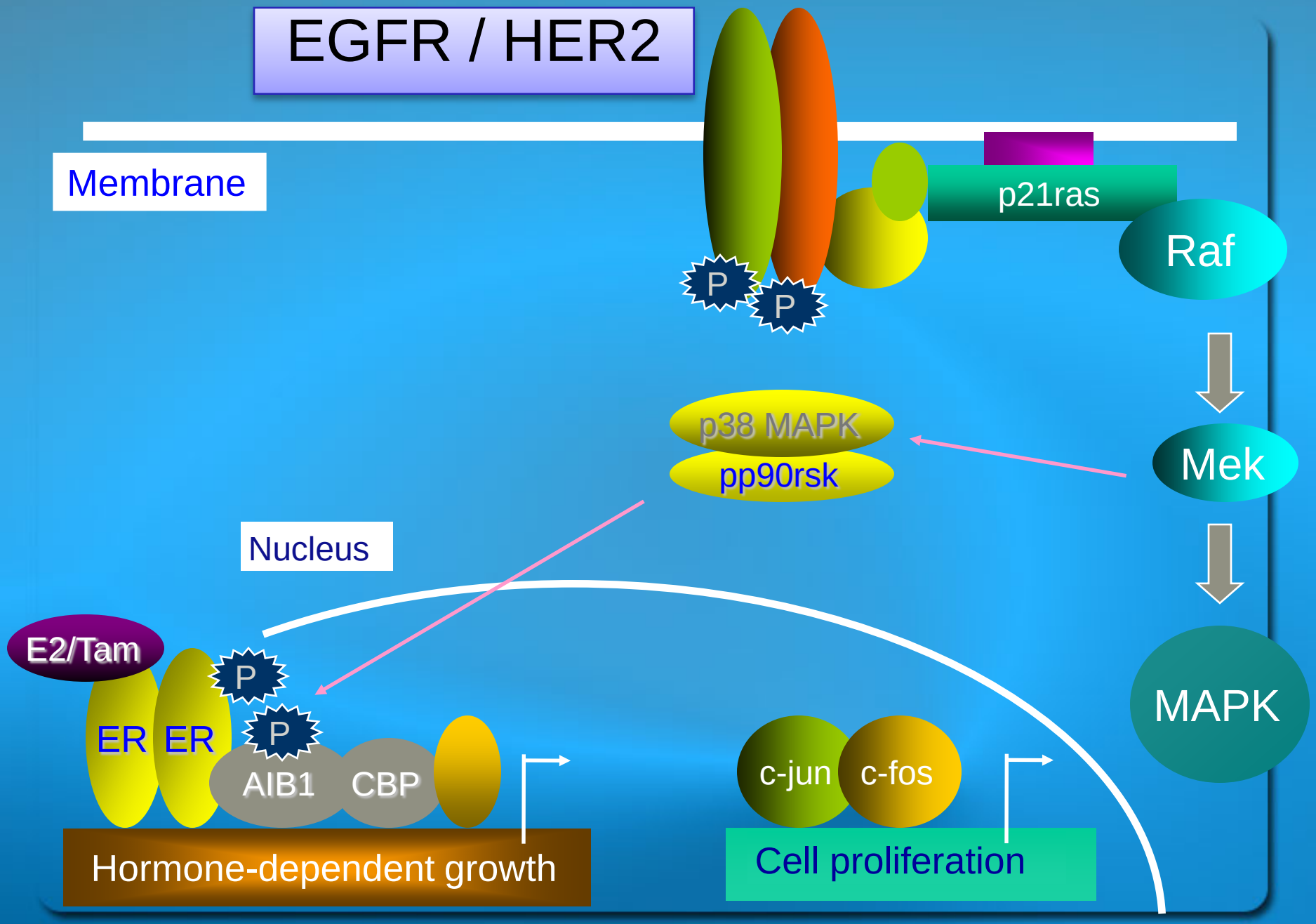
- Pathologist at Medical Department of FKUI-RSCM (since 2000)
- Lecture at FKUI , UIN, UNTAN, University of Palangkaraya, University of Bengkulu



Oncology Testing In Breast Cancer

Topics

1. Breast Cancer Biomarker
2. Guideline Recommendation on Breast Cancer Biomarker
3. HER2 Testing Overview
4. The importance of a multidisciplinary approach to improving care for patients with breast cancer


EGFR / HER2
Membrane
P
P
p21ras
Raf
Mek
p38 MAPK
pp90rsk
MAPK
Nucleus
E2/Tam
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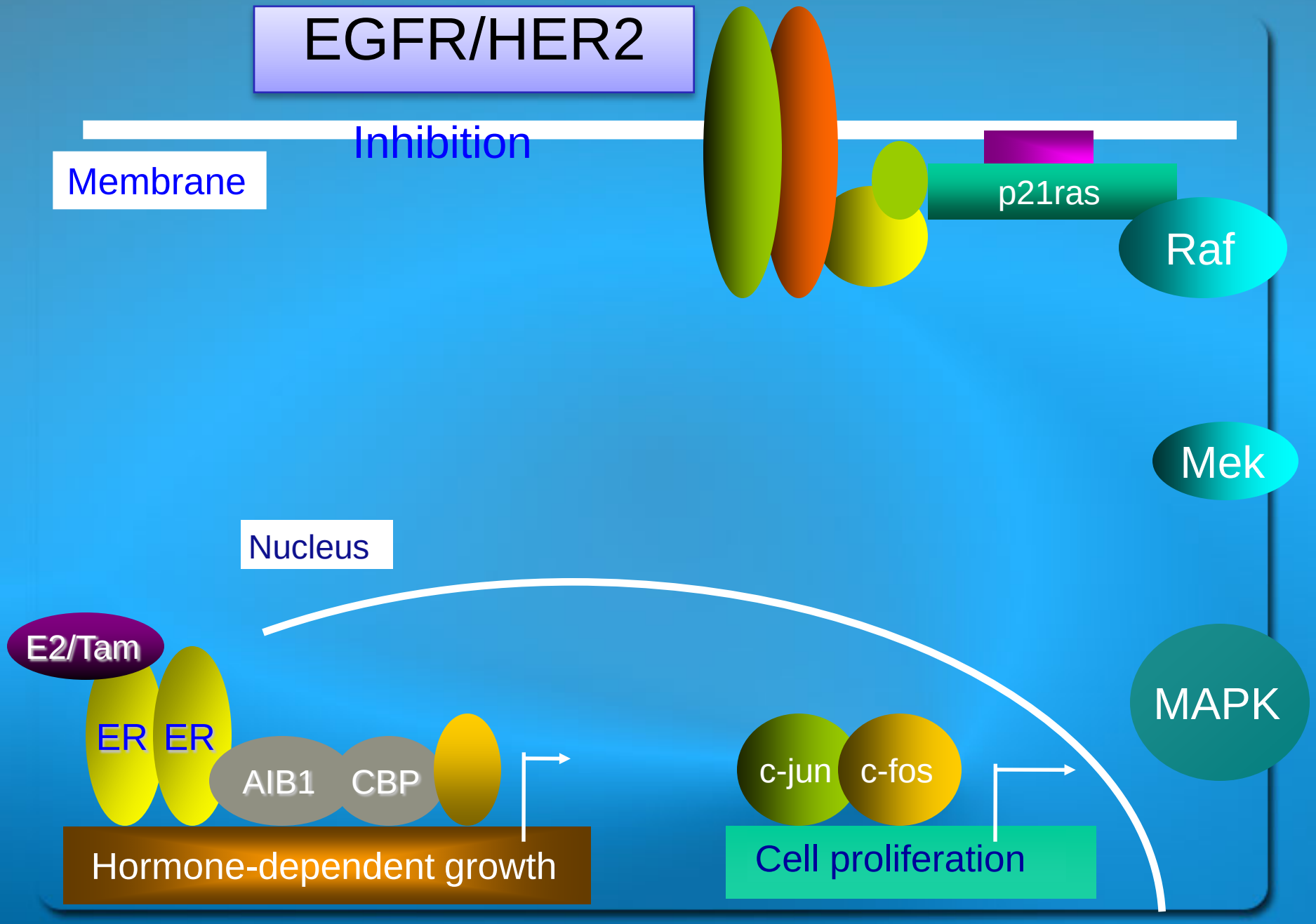
ER
ER
AIB1
CBP
Hormone-dependent growth
c-jun
c-fos
Cell proliferation


EGFR/HER2
Inhibition
Membrane
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Annals of Oncology 23 (Supplement 7): vii11–vii19, 2012
doi:10.1093/annonc/mds232

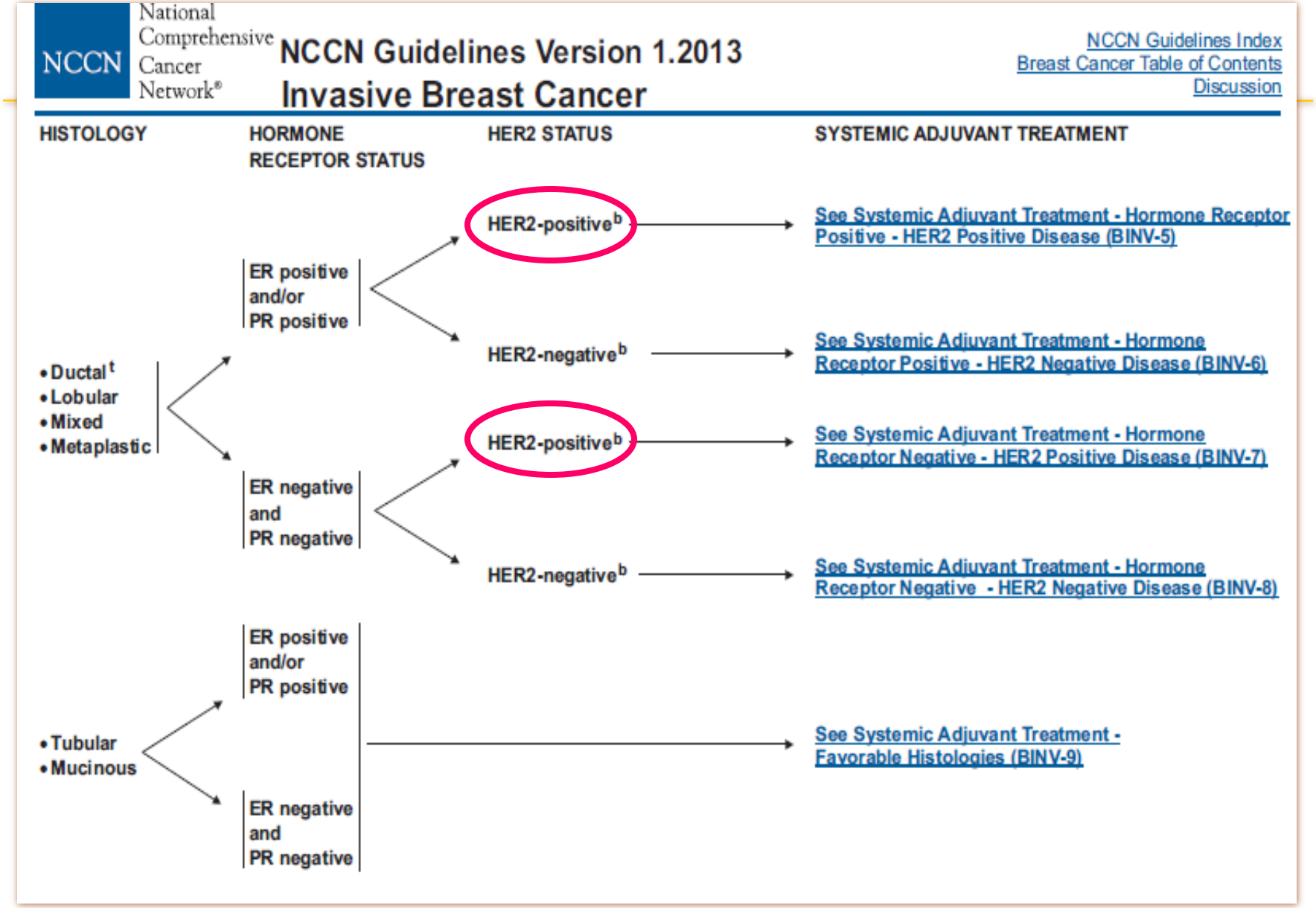
Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

F. Cardoso[1,2], N. Harbeck[3], L. Fallowfield[4], S. Kyriakides[5] & E. Senkus[6], on behalf of the ESMO Guidelines Working Group*

[1]*European School of Oncology, Milan, Italy;* [2]*Breast Cancer Unit, Champalimaud Cancer Center, Lisbon, Portugal;* [3]*Breast Center, Department of Obstetrics and Gynaecology, and Comprehensive Cancer Center (CCC LMU), University of Munich, Germany;* [4]*Brighton and Sussex Medical School, University of Sussex, UK;* [5]*Europa Donna Cyprus, Cyprus;* [6]*Department of Oncology and Radiotherapy, Medical University of Gdańsk, Gdańsk, Poland*

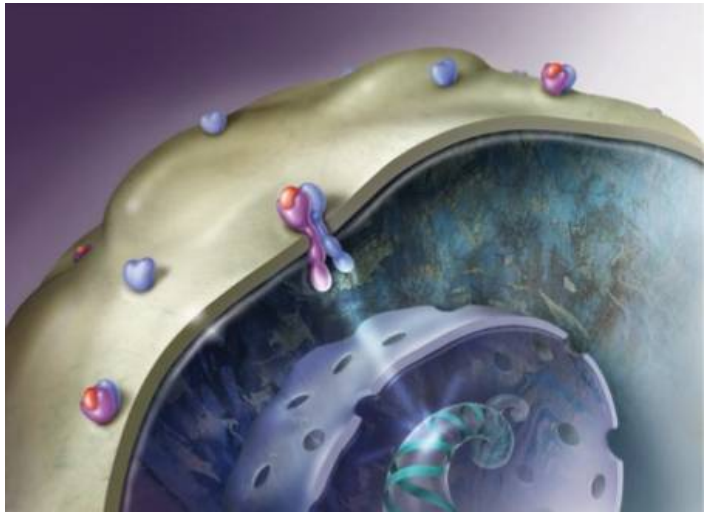
Efforts should be made to obtain histopathological confirmation whenever technically feasible, particularly in the situation of an isolated metastatic lesion. Biological markers important for treatment decisions, such as steroid hormone receptors (ER, PR) and HER-2 status should be re-evaluated, at least once, in a metastatic lesion. Although there are no data to support the choice of therapy in case of discordance in HR/HER-2 status between primary and metastatic tumor, retrospective data suggest inferior outcome in 'discordant' patients (possibly due to inappropriate treatment, not adjusted for biomarker changes). It seems appropriate to recommend that, if at any given biopsy the receptors were positive, targeted therapy (endocrine and/or anti-HER-2 therapy) should be provided.

There is no proven value of routine 'screening' tests for

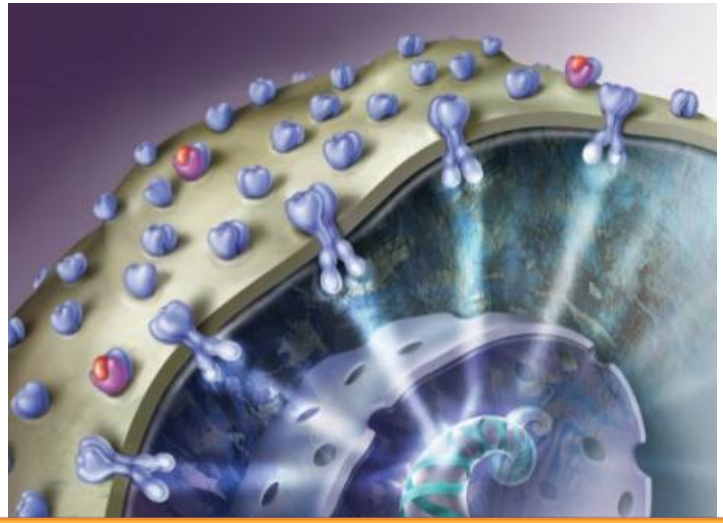

National Comprehensive Cancer Network
NCCN Guidelines Version 1.2013
Invasive Breast Cancer
NCCN Guidelines Index
Breast Cancer Table of Contents
Discussion
HISTOLOGY
HORMONE RECEPTOR STATUS
HER2 STATUS
SYSTEMIC ADJUVANT TREATMENT
• Ductal[t]
• Lobular
• Mixed
• Metaplastic
ER positive and/or PR positive
HER2-positive[b]
See Systemic Adjuvant Treatment - Hormone Receptor Positive - HER2 Positive Disease (BINV-5)
HER2-negative[b]
See Systemic Adjuvant Treatment - Hormone Receptor Positive - HER2 Negative Disease (BINV-6)
ER negative and PR negative
HER2-positive[b]
See Systemic Adjuvant Treatment - Hormone Receptor Negative - HER2 Positive Disease (BINV-7)
HER2-negative[b]
See Systemic Adjuvant Treatment - Hormone Receptor Negative - HER2 Negative Disease (BINV-8)
• Tubular
• Mucinous
ER positive and/or PR positive
ER negative and PR negative
See Systemic Adjuvant Treatment - Favorable Histologies (BINV-9)

HER2 gene amplification induces protein overexpression

- Gene amplification is the cellular process characterised by production of multiple copies of a particular gene or genes to amplify the phenotype that the gene confers on the cell
- Amplification and/or overexpression of HER2 has been reported in numerous cancers including breast, gastric, colon, bladder, ovarian, endometrial, lung, uterine cervix, head and neck, pancreatic, biliary and oesophageal carcinomas[1,2]

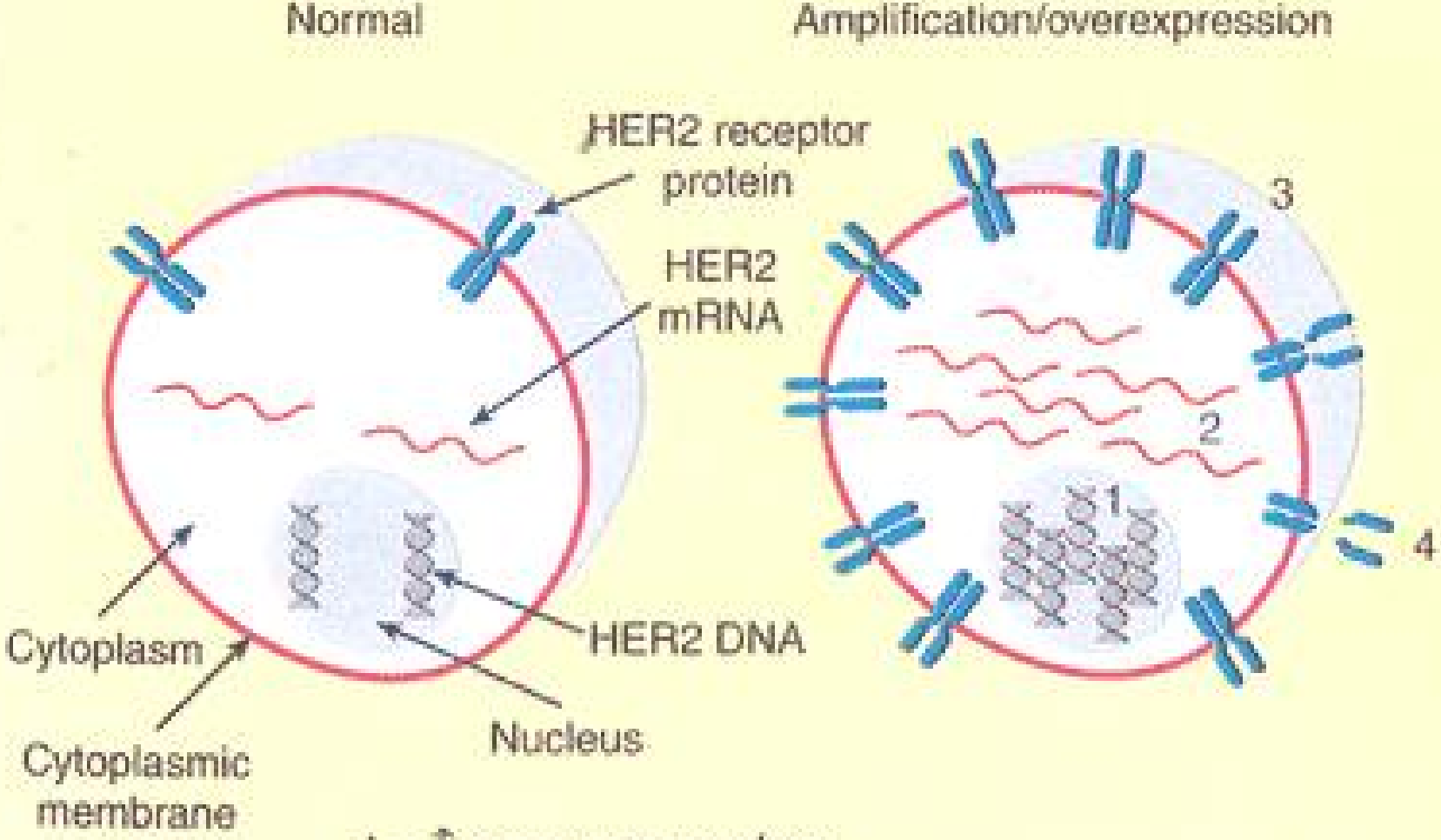


Normal HER2 expression



HER2 overexpression

1. Koeppen HK, et al. Histopathology 2001;38:96–104; 2. Scholl S, et al. Ann Oncol 2001;12:S81–87.



1 = ↑ gene copy number
2 = ↑ mRNA transcription
3 = ↑ cell surface receptor protein expression
4 = ↑ release of receptor extracellular domain

Clinical significance of HER2 status

- Understanding the biology of breast cancer is now of paramount importance
- Clinical, pathological and biological factors can help predict prognosis and guide treatment

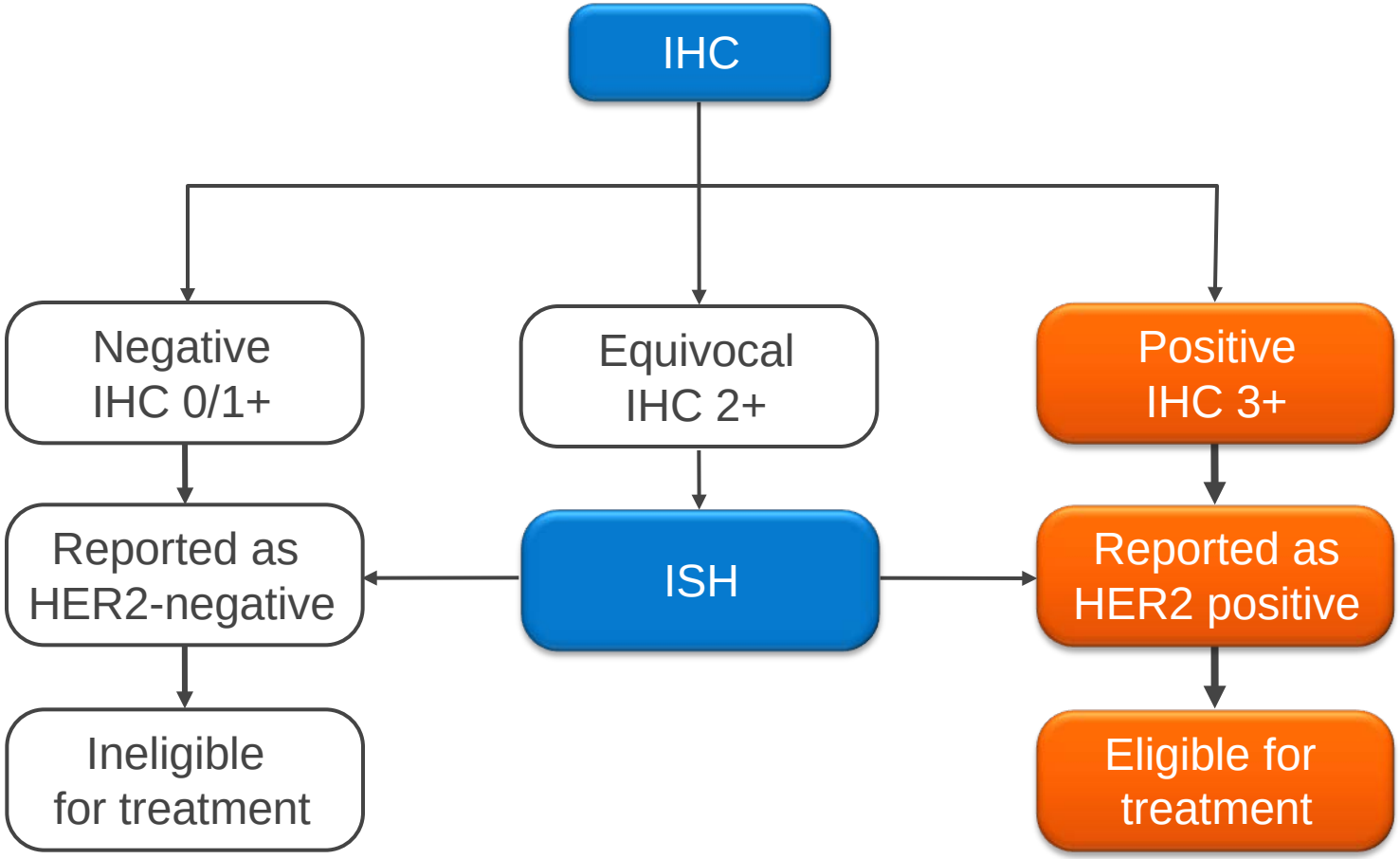
Conventional tumour classification	Biomarkers (such as HER2)
•TNM staging system •Histological grade •Lymph node status	•Provide prognostic and predictive value •Intrinsic subtype •Other genomic signatures

- Assessment of HER2 status is essential to determine patient eligibility for HER2 targeted therapy

1. Carlson RW, et al. JNCCN 2006:4(Suppl 3):S1–S22. 2. Bang YJ, et al. Lancet 2010; 376:687 697.

TNM, tumour, node, metastasis.

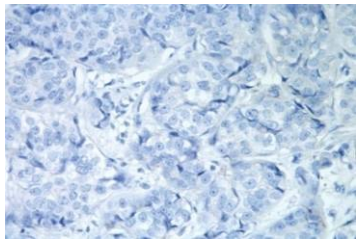
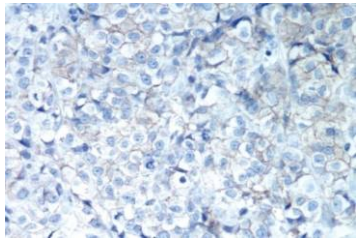
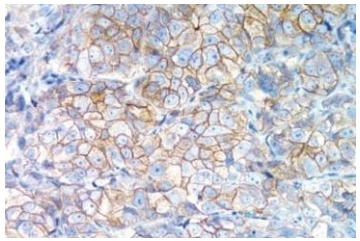
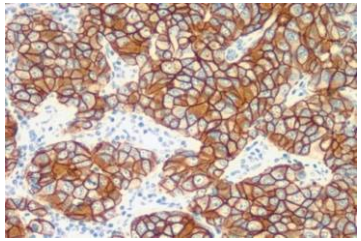
ASCO and CAP guideline recommendations for anti-HER2 targeted therapy eligibility



1. Bilous M, et al. Mod Pathol 2003;16:173–182; 2. Wolff AC, et al. J Clin Oncol 2007;25:118–145; 3. Albarello L, et al. Adv Anat Pathol 2011;18:53–59. Figure adapted by permission from Macmillan Publishers Ltd: Bilous M et al. Mod Pathol 2003;16:173–182. © 2003

ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists

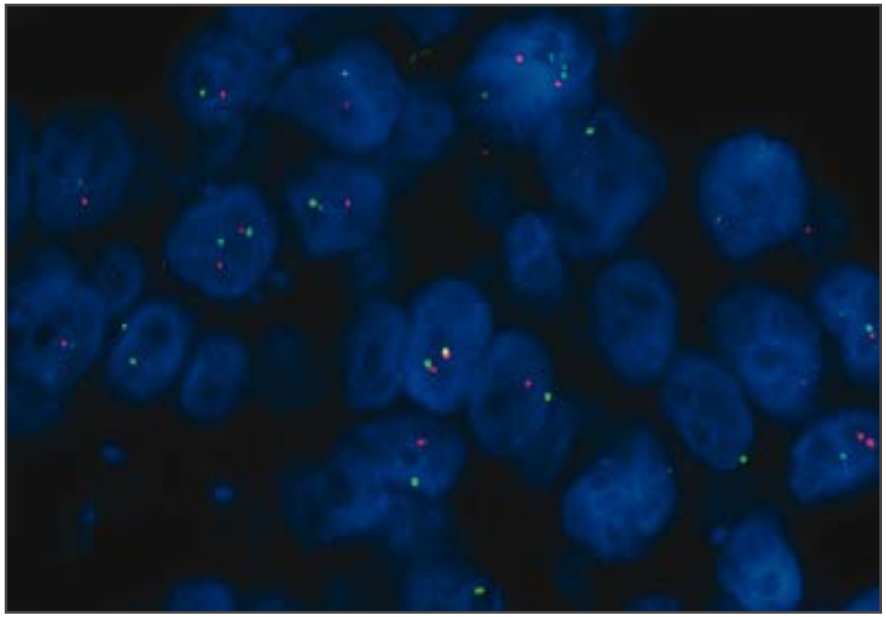
HER2 IHC scoring criteria in breast cancer

	Score	Staining pattern
	IHC 0 (negative)	No reactivity or membrane staining <10% of invasive tumour cells
	IHC 1+ (negative)	Faint/barely perceptible membrane staining in >10% of tumour cells; cells only stained in part of membrane
	IHC 2+ (equivocal)	Weak-to-moderate complete membrane staining in >10% of invasive tumour cells
	IHC 3+ (positive)	Strong complete membrane staining in >10%[1]/30%[2] of invasive tumour cells

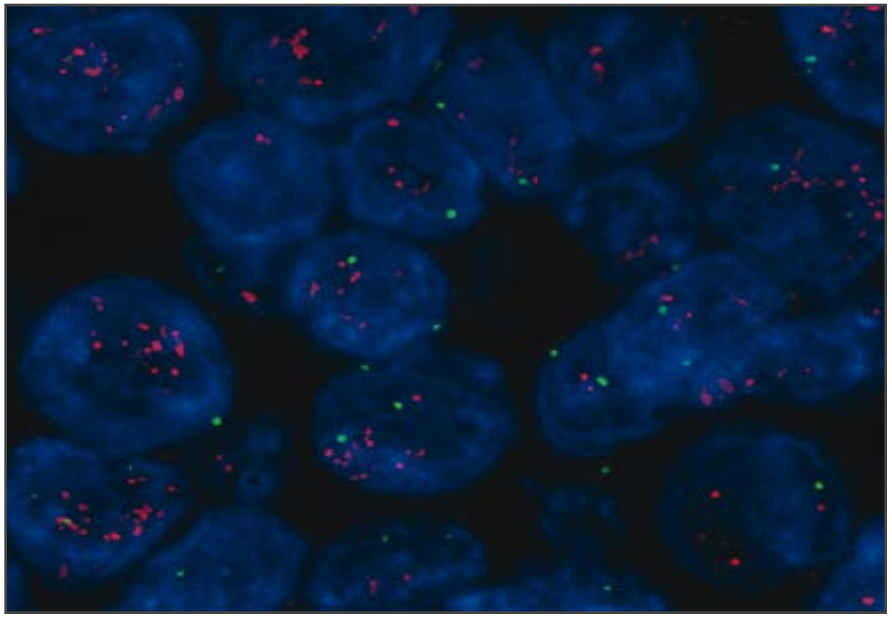
1. Wolff AC et al. J Clin Oncol 2007;25:118–145; 2. Dako. HercepTest™ Interpretation Manual. 2002.

Images courtesy of Dako.

FISH measures HER2 gene amplification (breast cancer)



FISH non-amplified
HER2:CEP17 ratio <1.8



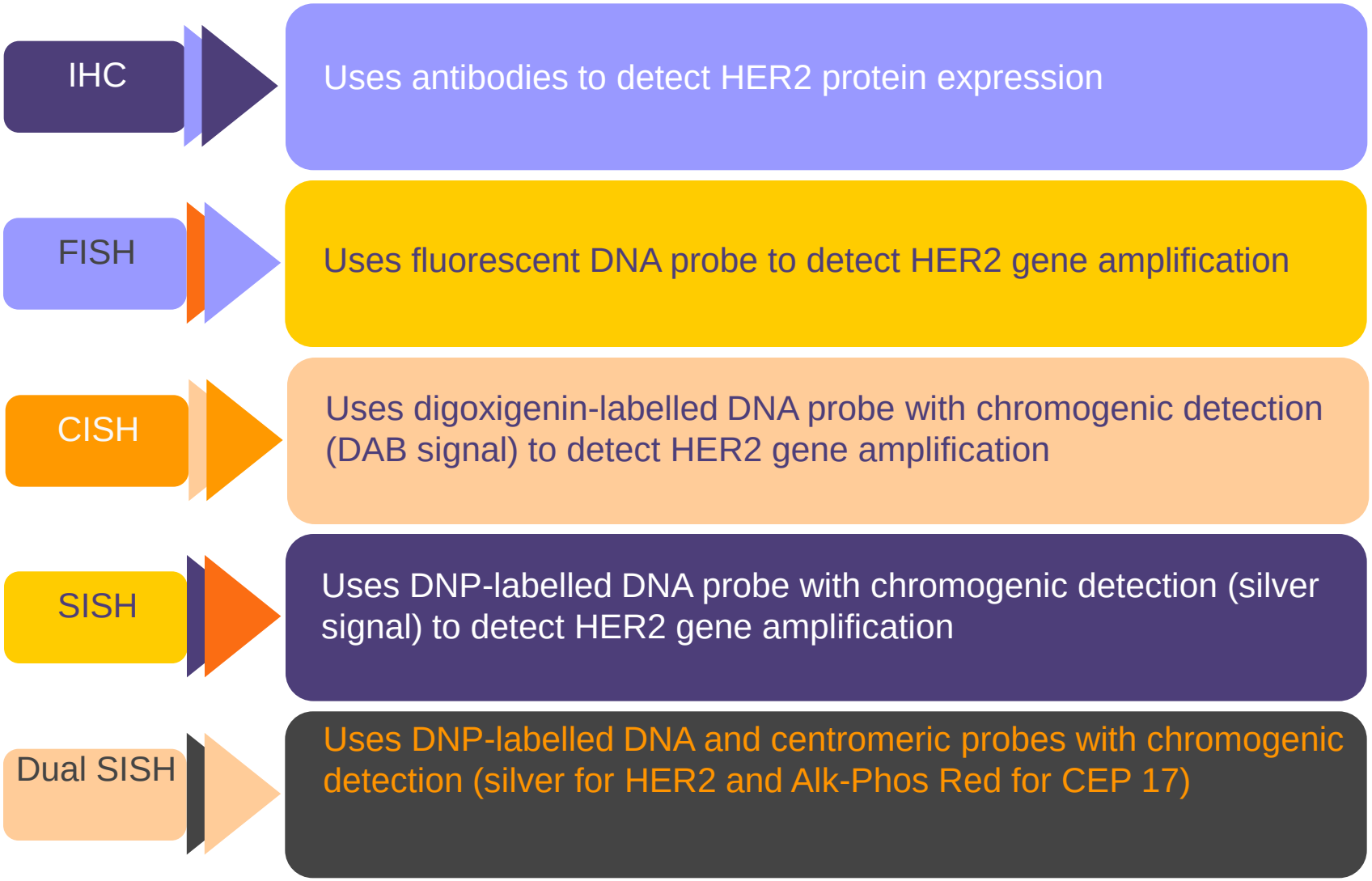
FISH amplified
HER2:CEP17 ratio >2.2

"…patients with a HER2/CEP17 FISH ratio between 2.0 and 2.2 were formerly considered HER2-positive and were eligible for treatment in the adjuvant trastuzumab trials.* Therefore, available efficacy data do not support excluding them from therapy with trastuzumab."

*Based on the adjuvant trastuzumab breast cancer trials, trastuzumab package inserts in some markets recommend a HER2:CEP17 ratio cut-off of 2.0

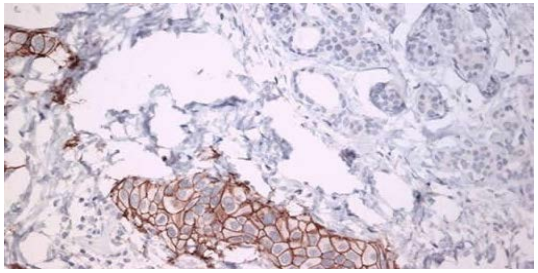
Wolff AC et al. J Clin Oncol 2007;25:118–145.

Summary of HER2 testing methods

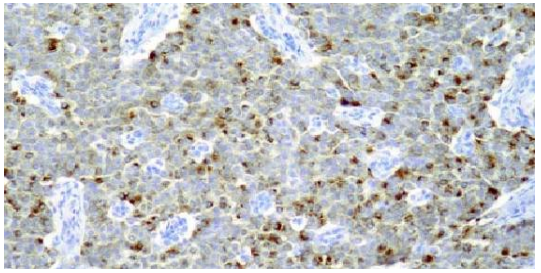


CEP17, chromosome 17 centromere; DNP, dinitro-phenol; DAB, 3,3-diaminobenzidine

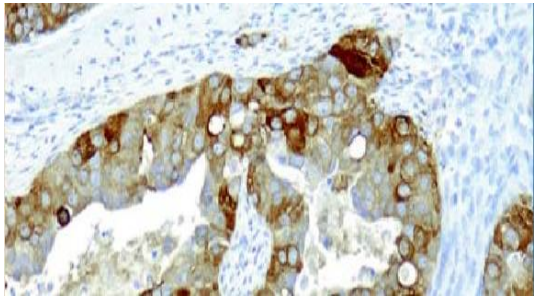
Some of the problems that may arise when interpreting IHC



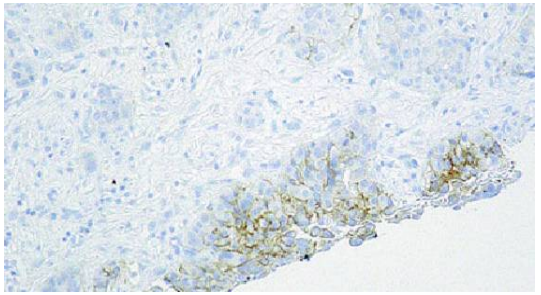
Poor fixation[1]
Heterogeneous staining



Dot artefact[2]
Brown dots represent cytoplasmic staining, not membrane staining



Cytoplasmic staining, IHC[2]
Diffuse homogeneous stain specifically confined to the cytoplasm

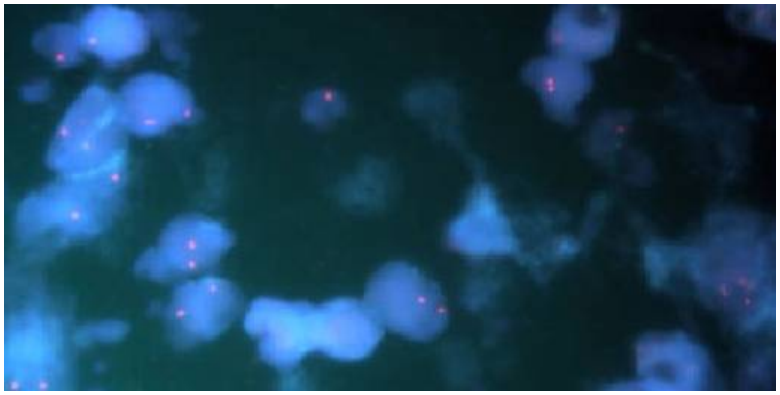


Edge artefact[1]
Staining along edge of tissue while the centrally located tumour is devoid of staining

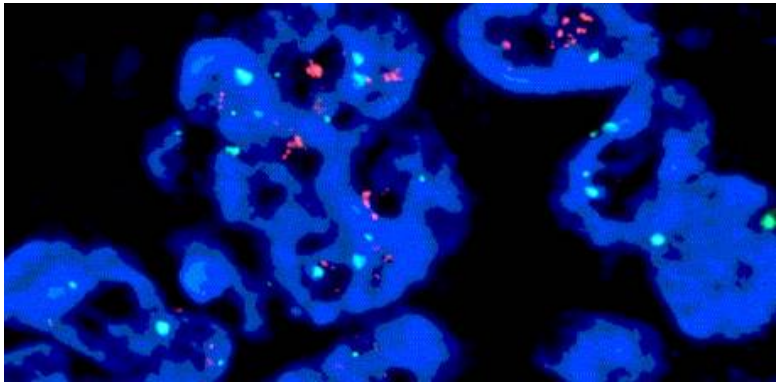
1. Images courtesy of W Hanna; 2. Images from Dako.

Some of the problems that may arise when interpreting FISH

Sample preparation

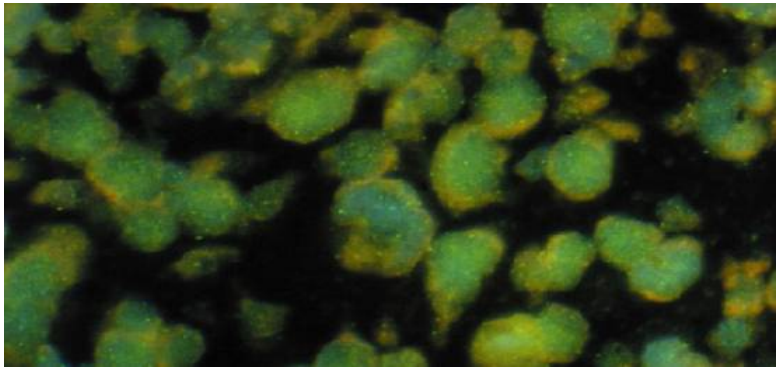


Under-fixation[a]
Patchy staining; weak or missing probe signal



Over-fixation[a]
Continuous spontaneous fluorescence; weak or missing probing signal

Staining procedure



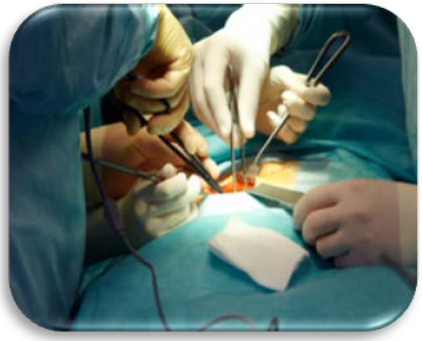
Under-digestion[b]
Strong spontaneous fluorescence; contrast background stain too strong

1. Images courtesy of Abbott
2. Images from Ventana

The principles of the testing flow depend on multidisciplinary collaborations

Understand HER2 assay results and assess best treatment options

Requests HER2 testing



Provides appropriate specimens

Oncologist Surgeon /Surgeon

Technician

Pathologist

Scores and interprets HER2 assay results

Conducts validated HER2 assay

HER2, human epidermal growth receptor 2.

The surgeon's role in the pre-analytic phase

- Remove appropriate tissue sample (excision or biopsy) for HER2 testing
- Ensure surgical staff have been trained on, and adhere to, validated tissue handling protocols
  - Ensure tissue is fixed in only 10% NBF immediately; **no later** than 20 minutes for gastric specimens or **30 minutes for breast specimens**
  - Ensure tissue is submerged in sufficient fixative volume; ideally a volume ratio of 10% NBF to tissue of 10:1
  - Ensure tissue specimens are transported to the laboratory in appropriate containers
- Ensure complete documentation on tissue handling accompanies specimen to the laboratory

HER2, human epidermal growth receptor; NBF, neutral buffered formalin.

The pathologist's role in the pre-analytic phase

- Receives HER2 testing form
- Ensures tissue handling in the surgical theatre is performed according to validated protocols (based on received documentation)
- Examines specimen and marks resection margins
- Ensures tissue handling in the laboratory is performed according to validated protocols
- Slice and fix specimen according to validated protocols:
  - **6–48 hours: breast cancer**
  - 8–48 hours: gastric cancer
- If laboratory is not validated to perform the HER2 test, arrange for transport to a central testing laboratory:
  - < 48 hours: ensure tissue is properly processed and placed in adequate 10% NBF
  - > 48 hours: prepare paraffin block to prevent tissue degradation

HER2, human epidermal growth receptor; NBF, neutral buffered formalin.

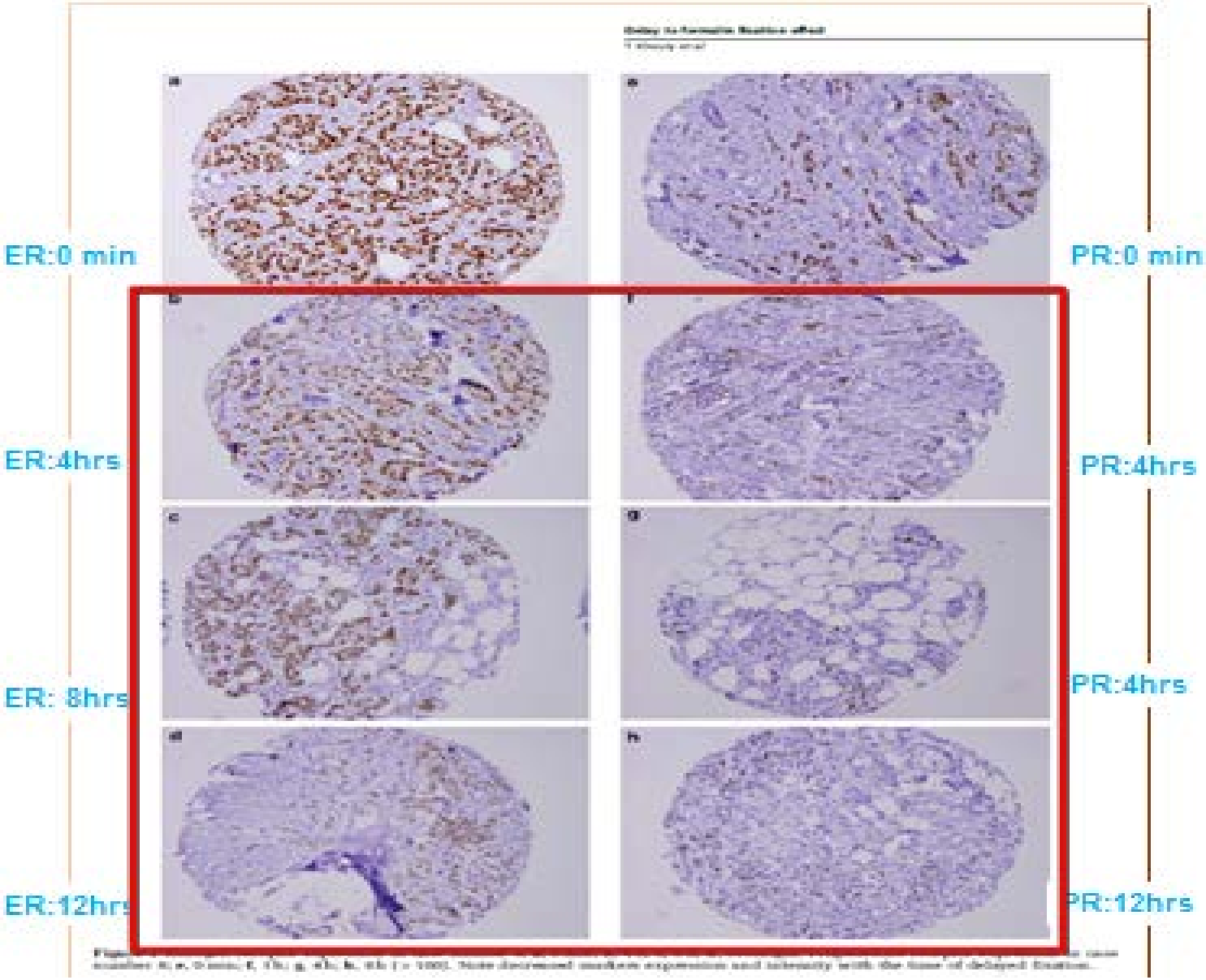
The pathologist's role in the analytic phase

- Ensures testing is performed per validated protocols
- Ensures appropriate controls accompany each specimen tested
- Ensure dedicated staff members are appropriately trained (and reassessed at regular intervals)
  - All processes and reagents are validated; equipment calibrated
  - Validated processes are documented in protocols

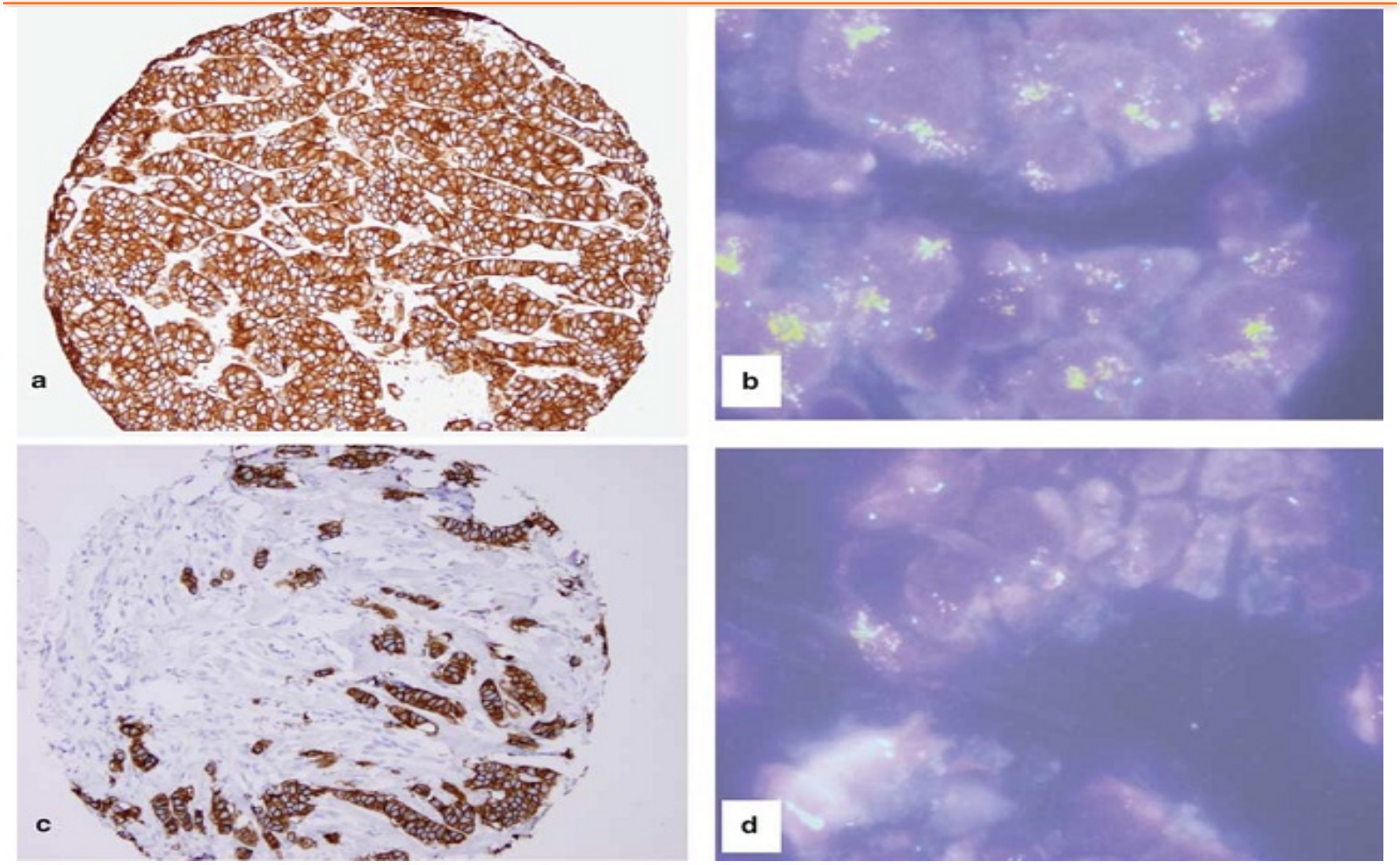
The pathologist's role in the post-analytic phase

- Scores and interprets HER2 test results based on validated algorithms
  - If IHC 2+, immediate retesting with an ISH test is required to confirm HER2 status
  - Treatment cannot be based on an IHC 2+ result
- Diagnoses HER2 status
- Documents findings and recommendations
- Communicates results and implications to oncologist/multidisciplinary team

Delay to Formalin Fixation and Progesterone Receptors Results



Delay to Formalin Fixation and HER2 By Immunohistochemistry and Fluorescence InSitu Hybridization



a,30 min IHC; b,30 min FISH; c,2 h IHC; d,2 h FISH

Check your Hospital Fixative NBF 10%

10% Neutral Buffered Formalin for Human Tissue Fixation of IHC

1 L Volume, consist of :

Mix together (Buffered Phosphate pH 7.4) :

- Na_2HPO_4, anhydrous, 6.5g
- $NaH_2PO_4 \cdot H_2O$, 4g
- Distilled water, 900mL

Adjust pH to 7.4

Then add:

- 40% formaldehyde, 100mL

References
Hassel, J. and Hand, A.R. (1974). J. Histochem. Cytochem. 22 229-239
http://www.ihcworld.com/_protocols/histology/fixatives.htm

Key points

- Oncology testing in Breast Cancer now developing with various biomarker
- Overexpression of HER2 is a key factor in the development of certain cancers
  - HER2 amplification/overexpression occurs in breast cancers
- HER2 positive breast cancer has a poor prognosis
- Reliable and reproducible HER2 testing and accurate interpretation is essential to ensure patients with breast cancer receive appropriate diagnosis and treatment
- A multidisciplinary team involving surgeons, pathologists, technicians and oncologists can help achieve improvements in quality of HER2 testing

All treatment decisions should be made with knowledge of HER2 status

THANKYOU