ER Low Positive Breast Cancer

Grace Callagy
Professor of Pathology NUI Galway
Consultant Pathologist GUH

Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update

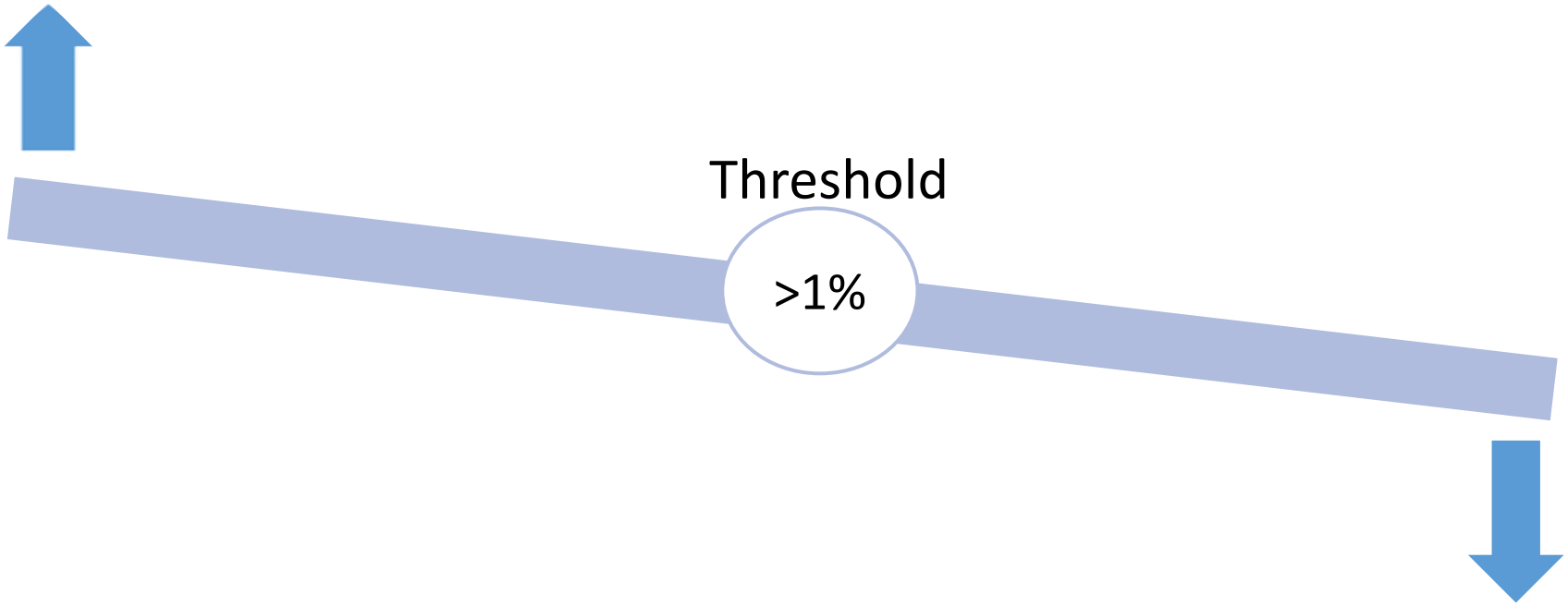
J Clin Oncol 38. © 2020

Results (with validated ER IHC assay)		Interpreted as
0 – < 1% of nuclei positive		ER-negative
1-100% of nuclei positive	1-10% of nuclei positive	ER-Low-Positive
	>10% of nuclei positive	ER-Positive

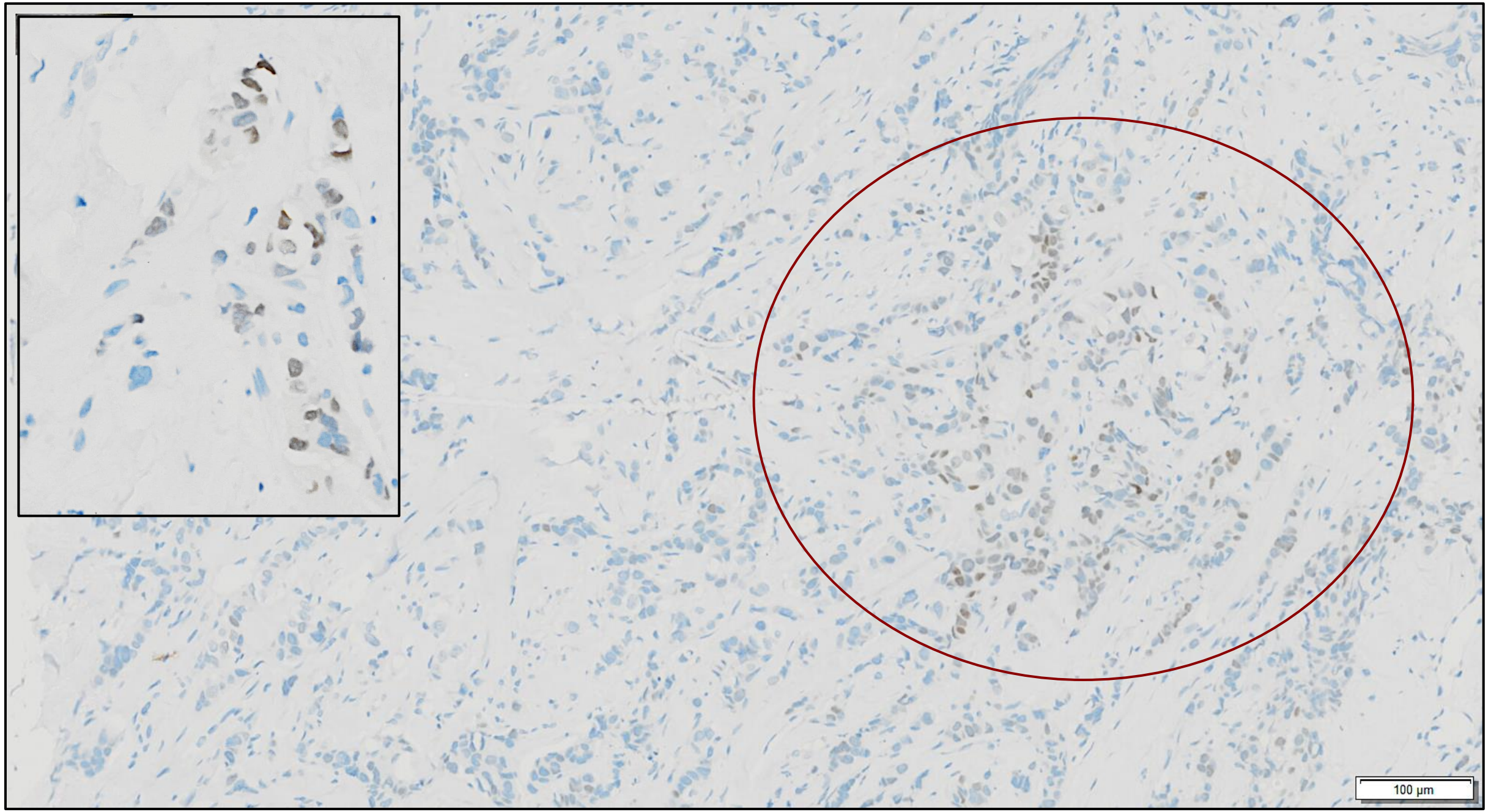
Allison KH, J Clin Oncol 2020

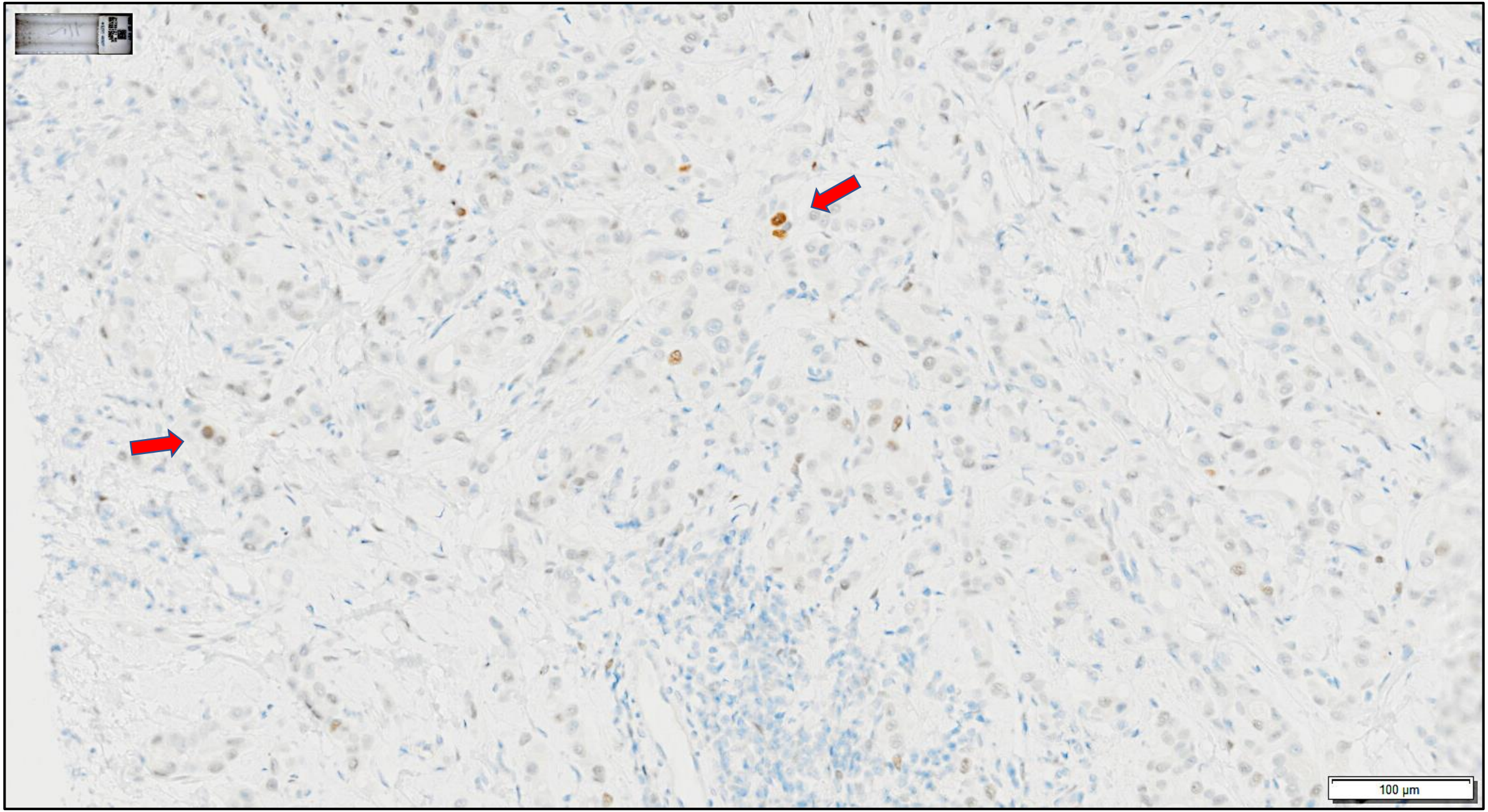
VOLUME 28 · NUMBER 16 · JUNE 1 2010
JOURNAL OF CLINICAL ONCOLOGY
ASCO SPECIAL ARTICLE

Maximises number of patients for endocrine therapy



Underestimates number of patients for ER negative treatment strategies


100 µm

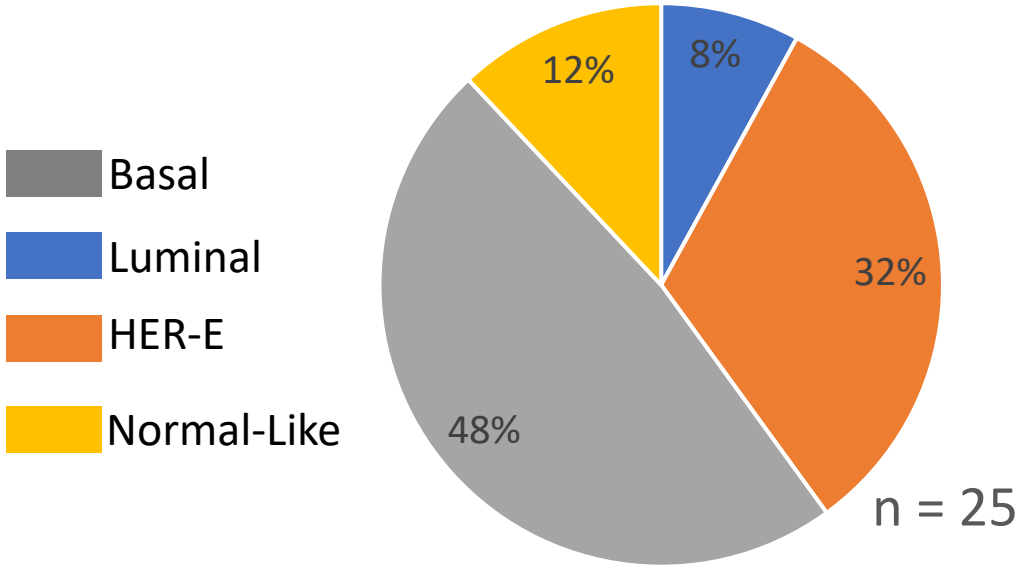

100 µm

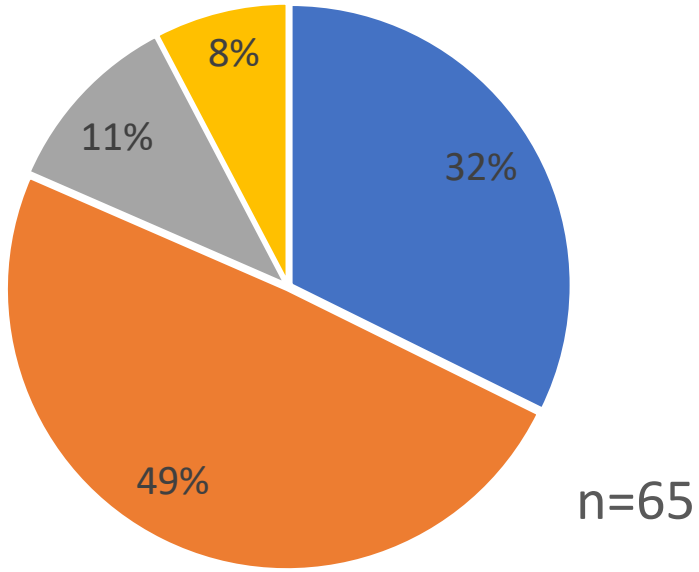
ER Low Positive BC is Molecularly Heterogeneous

- ER mRNA level and the 'ER Gene Signature' comparable to ER negative BC ($p = 0.226, 0.168$) and lower than in ER > 10% ($p < 0.001$)

Iwamoto T, J Clin Oncol 2012

- Encompasses all molecular intrinsic subtypes (PAM50 classifier)





Cheang M Breast Cancer 2015

Clinico-Pathological Features of ER Low Positive BC similar to ER negative BC

	<1% (n=1,625)	p	1-9% (n=250)	≥10% (n=7,764)	p
Young age (mean, yrs)	**52**	ns	**52**	57	<0.0001
Clinical TNM II/III	**68**	0.04	**62**	44%	<0.0001
T size (cm)	**3**	ns	**3**	2	<0.0001
Nodal positive	**33%**	ns	**38%**	28%	0.003
Grade 3	**84%**	ns	**82%**	28%	0.001
HER2 positive	**29%**	ns	**28%**	13%	<0.0001
PR positive (>1%)	15%	<0.0001	**58%**	84%	<0.0001

Yi M, Annals Oncol 2014

How do ER Low Positive BCs Respond to Endocrine Therapy?

Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials *Lancet* 2011; 378: 771–84

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

1/3rd reduction in recurrence at 10 years following 5 years tamoxifen with ER >10 fmol/mg (LBA)

How do ER Low Positive BCs Respond to Endocrine Therapy?

Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials *Lancet* 2011; 378: 771–84

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

→ 1/3rd reduction in recurrence at 10 years following 5 years tamoxifen with ER >10 fmol/mg (LBA)

Estrogen Receptor Status by Immunohistochemistry Is Superior to the Ligand-Binding Assay for Predicting Response to Adjuvant Endocrine Therapy in Breast Cancer

Jennet M. Harvey, Gary M. Clark, C. Kent Osborne, and D. Craig Allred

J Clin Oncol 17:1474-1481. © 1999

→ 10 fmols/mg equivalent to ER Allred score 3, >1% positive cells (IHC)

How do ER Low Positive BCs Respond to Endocrine Therapy?

Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials *Lancet* 2011; 378: 771–84

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

→ 1/3rd reduction in recurrence at 10 years following 5 years tamoxifen with ER >10 fmol/mg (LBA)

Estrogen Receptor Status by Immunohistochemistry Is Superior to the Ligand-Binding Assay for Predicting Response to Adjuvant Endocrine Therapy in Breast Cancer

Jennet M. Harvey, Gary M. Clark, C. Kent Osborne, and D. Craig Allred

J Clin Oncol 17:1474-1481. © 1999

→ 10 fmols/mg equivalent to ER Allred score 3, >1% positive cells (IHC)

Borderline ER-Positive Primary Breast Cancer Gains No Significant Survival Benefit From Endocrine Therapy: A Systematic Review and Meta-Analysis

Tong Chen, *Clinical Breast Cancer,* Vol. 18, No. 1, 1-8 © 2017

→ No significant survival gain for ER LP following ET (IHC)

How does ER Low Positive BC Respond to NACT?

Retrospective study

3,055 HER- negative BC treated with NACT

171 (5.6%) ER Low Positive

Likelihood of pCR for ER Low Positive is similar to ER negative BC

(adj. OR 0.95, 95% CI 0.64-1.40, p=0.792)

and better than for ER >10%

(adj. OR 2.3, 95% CI 1.48-3.47, p<0.001))

Optimal ER cut point to predict pCR was 9.5%

(27% vs 7%; adj. OR 2.17, 95% CI 1.62-2.87, p <0.001)

Fujii T Annal Oncol 2017

How Frequent are Germline Mutations in ER Low Positive BC?

	MD Anderson Genetic Counselling Service *Sanford RA, Cancer 2015*		**Clinical Breast Cancer Care Project** *Lovejoy LA, Genes 2021*	
	ER Low Positive HER2 Negative	TNBC	ER Low Positive HER2 Negative	TNBC
Number of Patients	314	238	56	222
Germline Mutations	36%	40%	16%	17%

Similar Frequency of germline mutations
in ER Low Positive HER2 Negative BC and TNBC

How Reliable is the ER Low Positive Category?

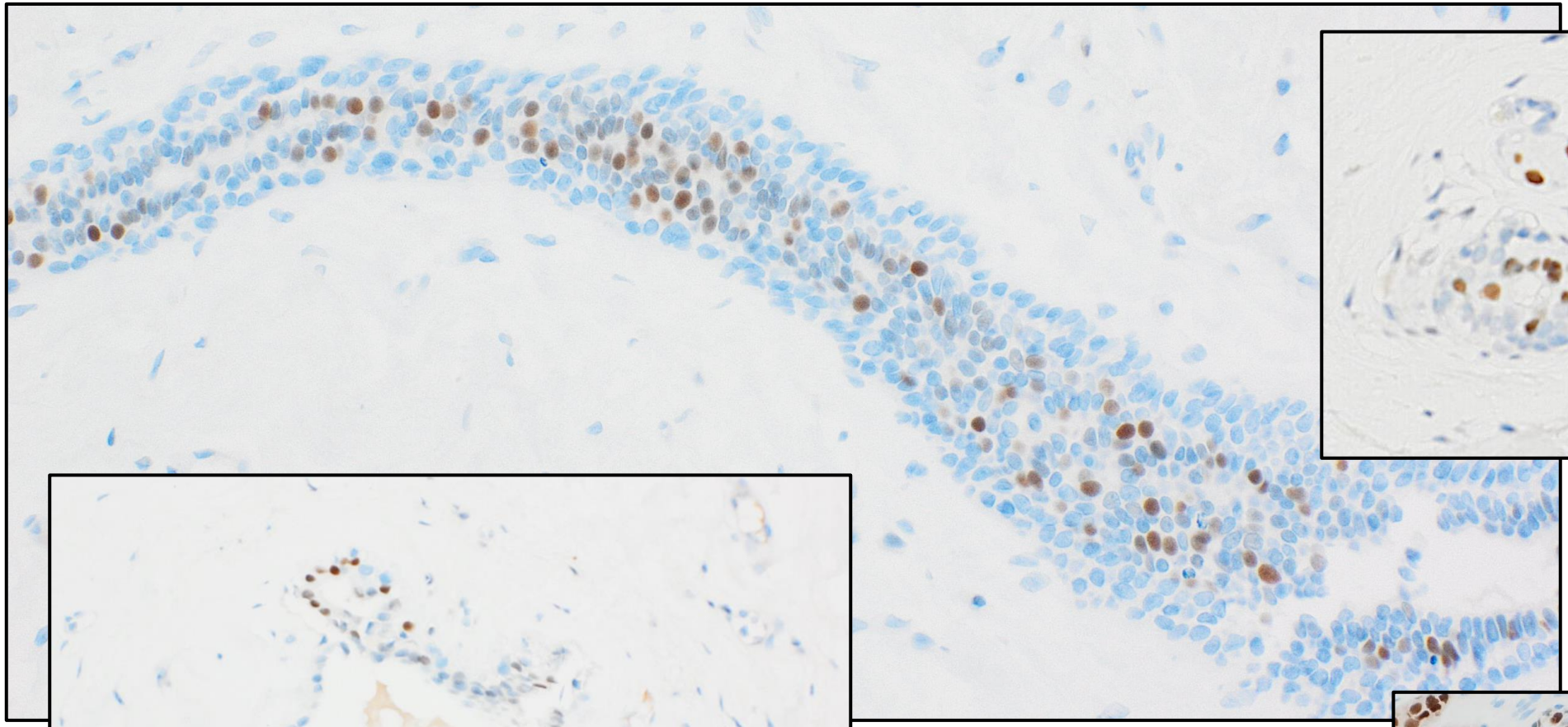
- Almost all discordance in ER reporting in the 1-10% range

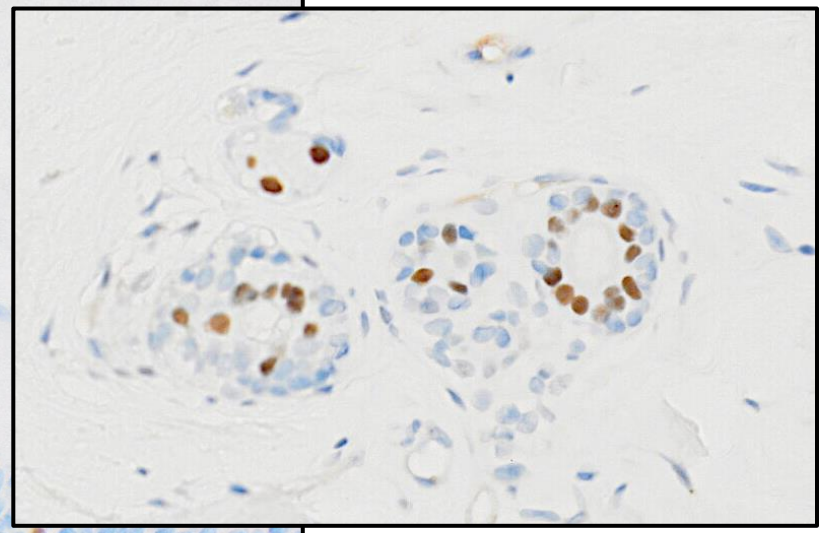
Reisenbichler E, Am J Clin Pathol 2013

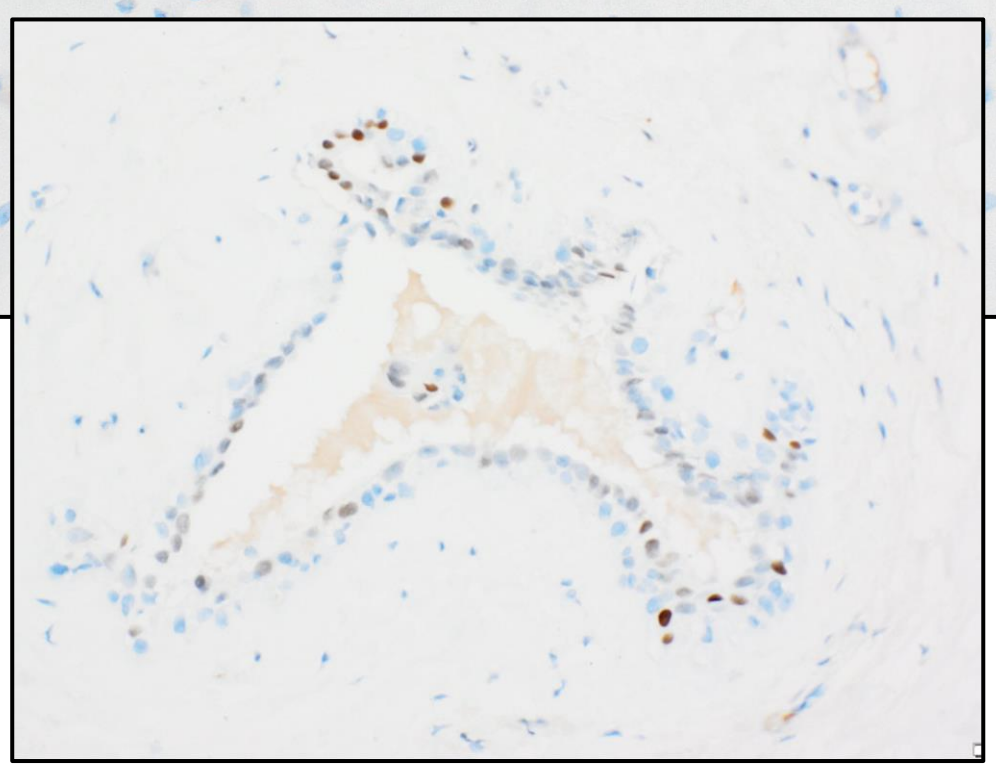
- Sampling is an issue: > 50% (23/39) of ER Low positive cases on NCB are negative on resection

Muftah A, Histopathology 2017

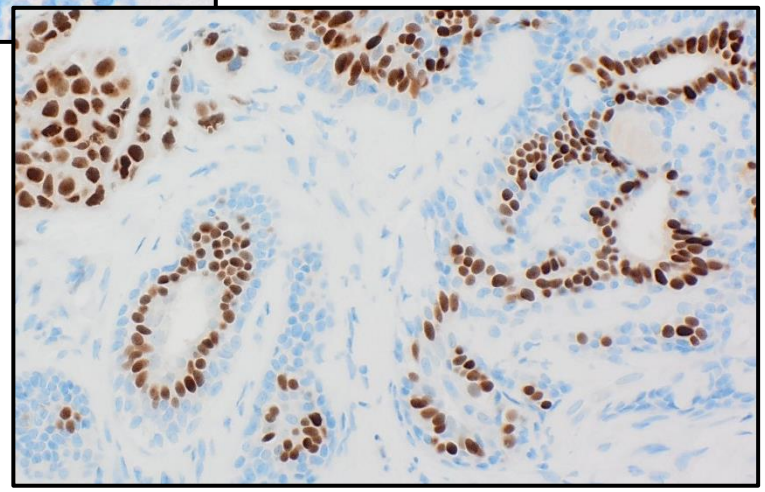
- Inconsistency with pre-analytic and analytic variables can result in weak ER staining







Controls are Critical



QC Considerations for ER Low Positive BC
Attention to controls
Re-testing on same, alternative or resection block
Correlation with tumour type and grade
Comparison with previous pathology
(Image analysis, if validated)

ER Low Positive BC

- Exhibits biological and behavioural differences compared to ER >10% BC and many similarities to ER negative BC
- Response to endocrine therapy is uncertain but remains possible
- Although categorised as ER positive, ER negative treatment options should be considered
- No consensus on the ancillary tests that might aid treatment decisions
- Close attention to QC is important

Thank you for your attention