Jornada Actualización
Cáncer de Mama y Trabajo

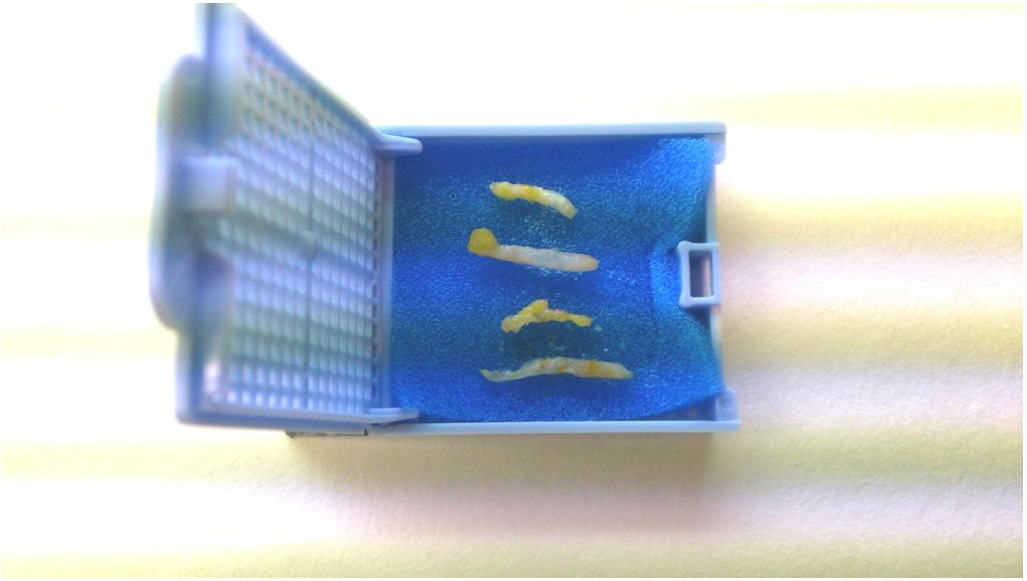
Donostia, 3 junio 2016
Palacio Miramar

Avances diagnósticos Cáncer de Mama

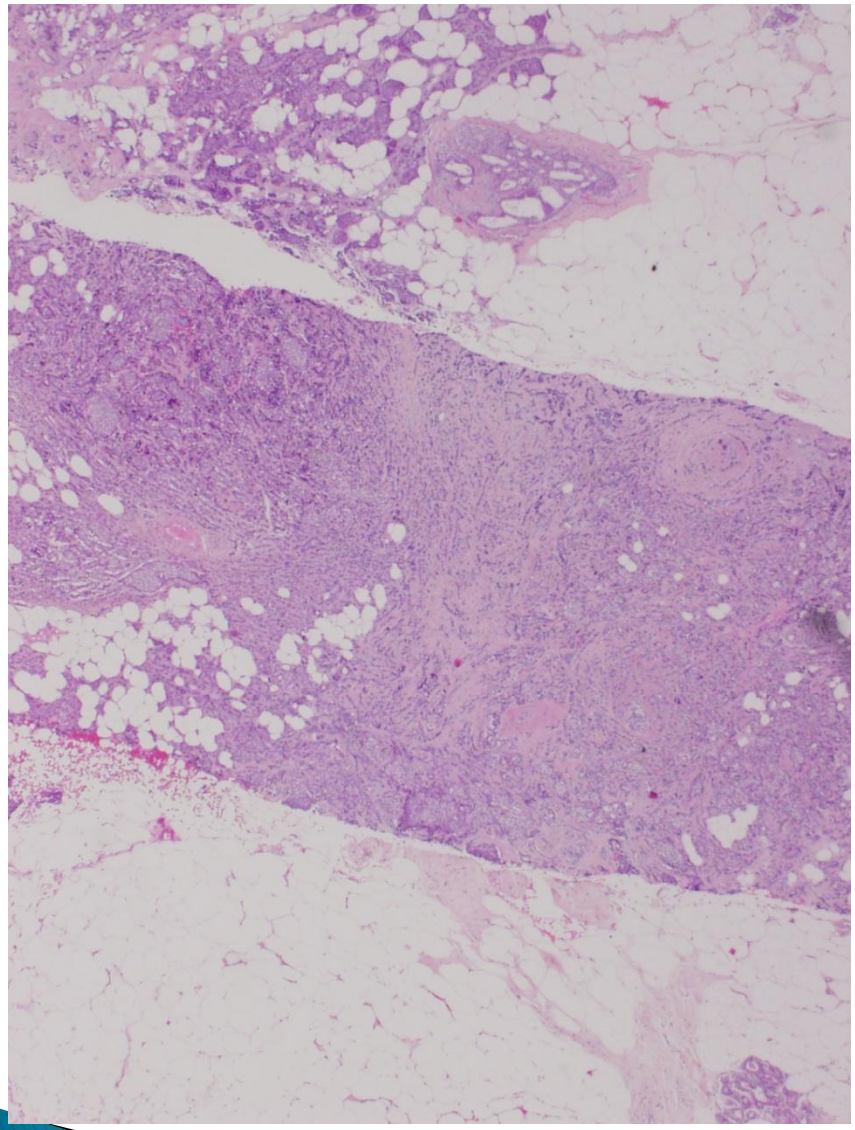
Anatomía Patológica

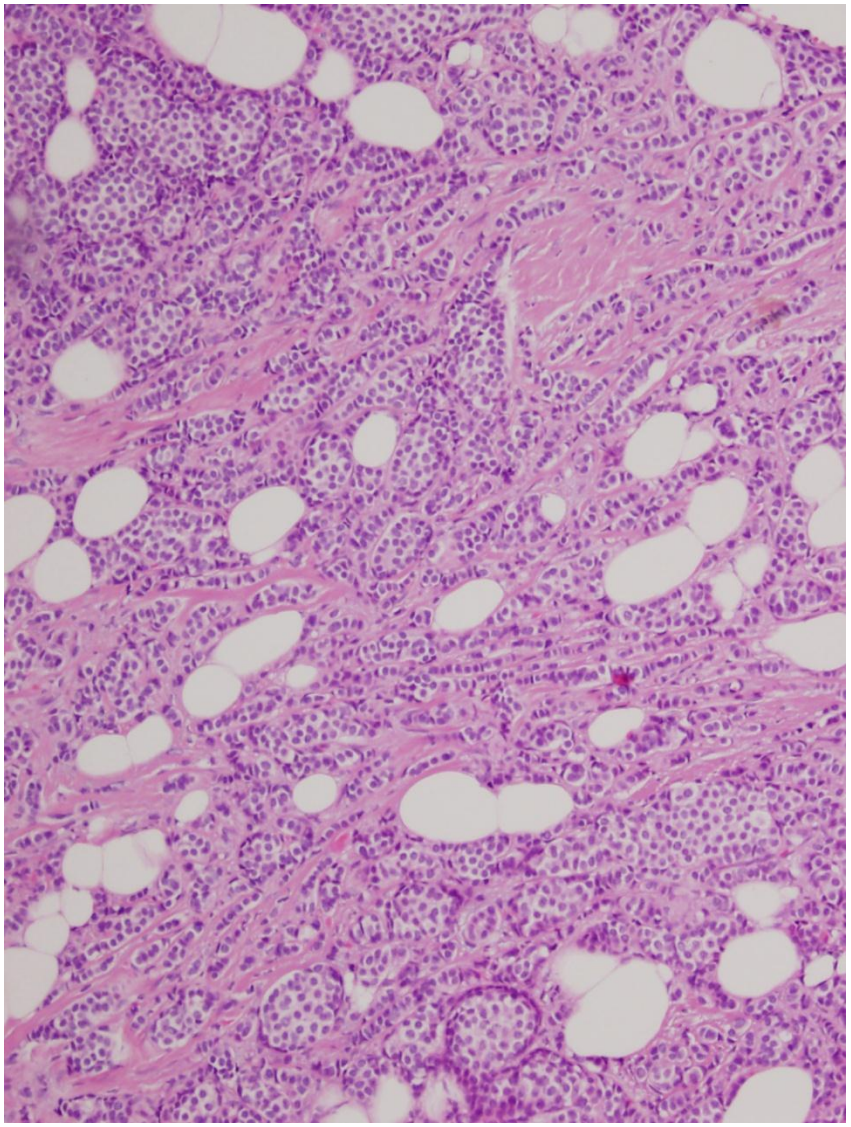
Ricardo Rezola Solaun
Sº Patología

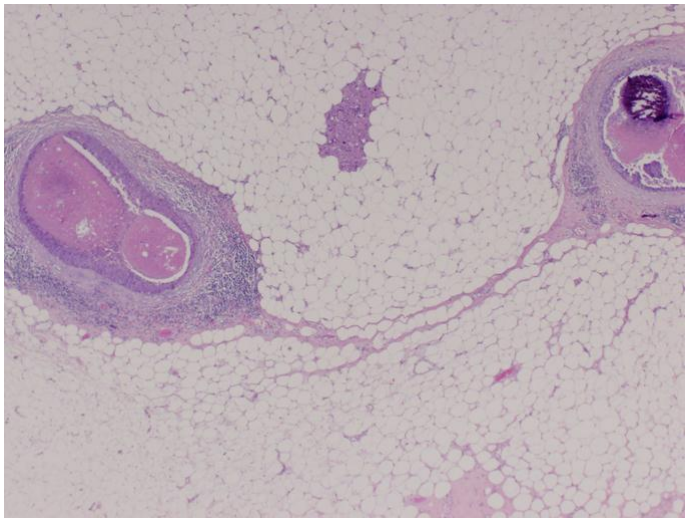
	Década 80-2000	Década 00-2010	Década actual
Diagnóstico	Citología Intraoperatoria Trucut	Trucut	Trucut Biomarcadores Molecular
Cirugía local	MRM Conservador	Conservador MS Biomarcadores	QTNA Conservador MS
Linfadenectomía	Siempre	GC ± VAX	GC VAX ocasional

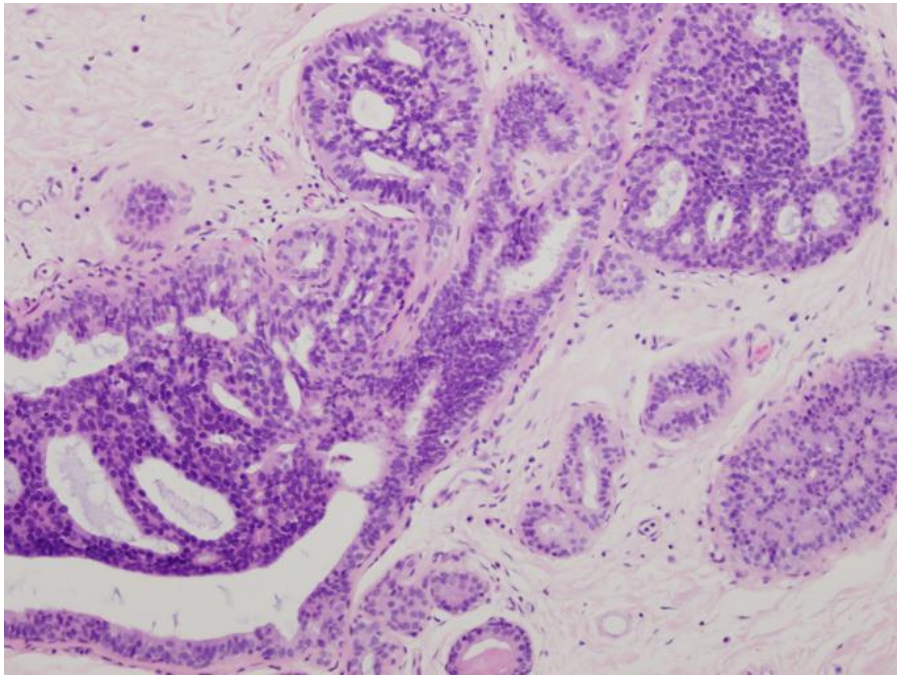


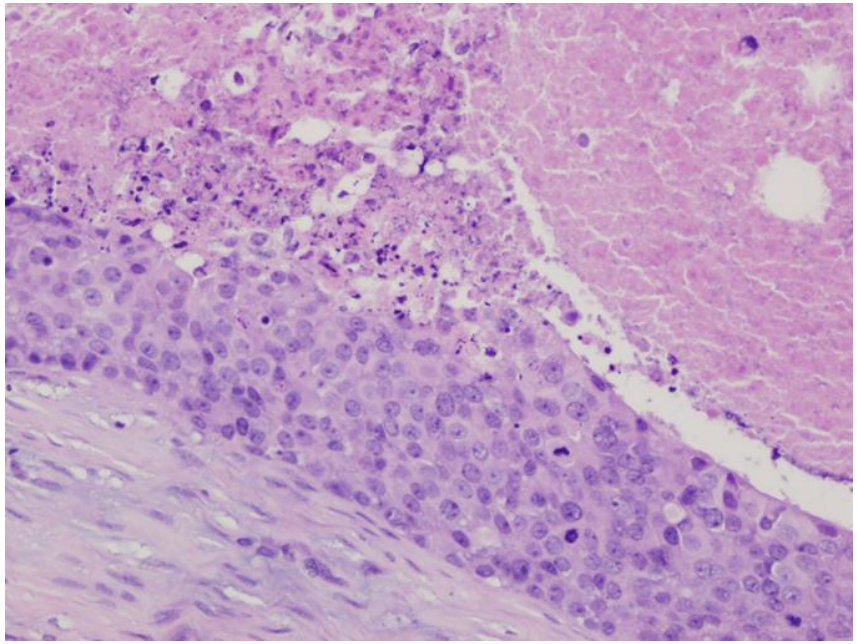
Microbiopsia





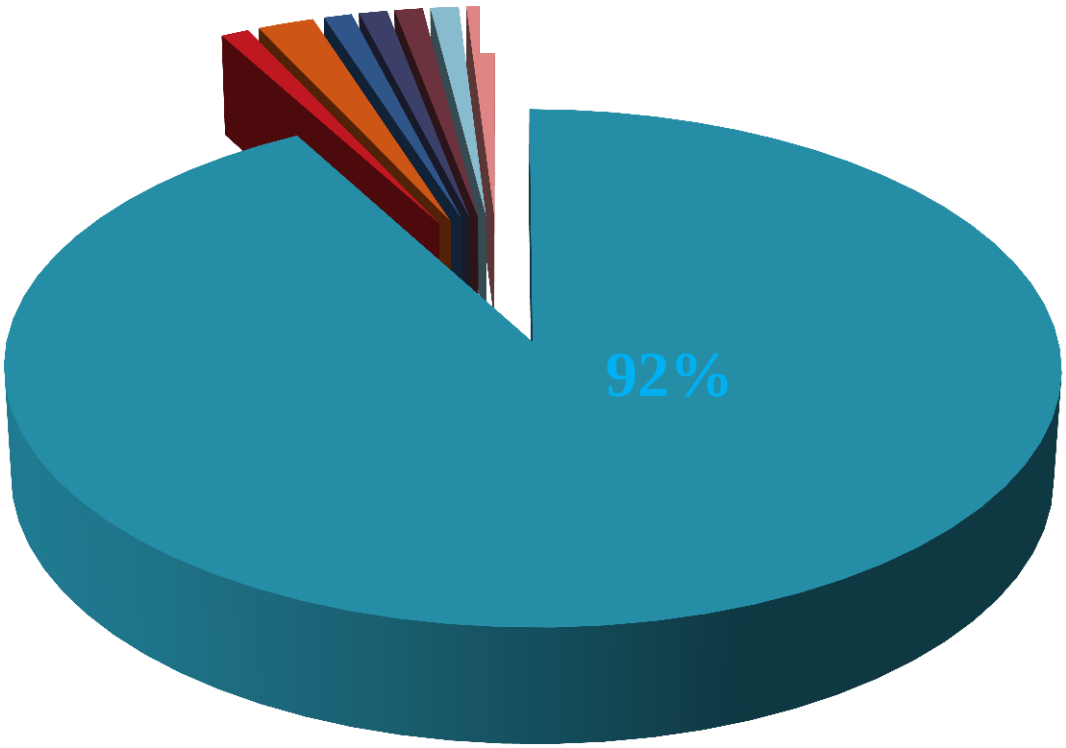




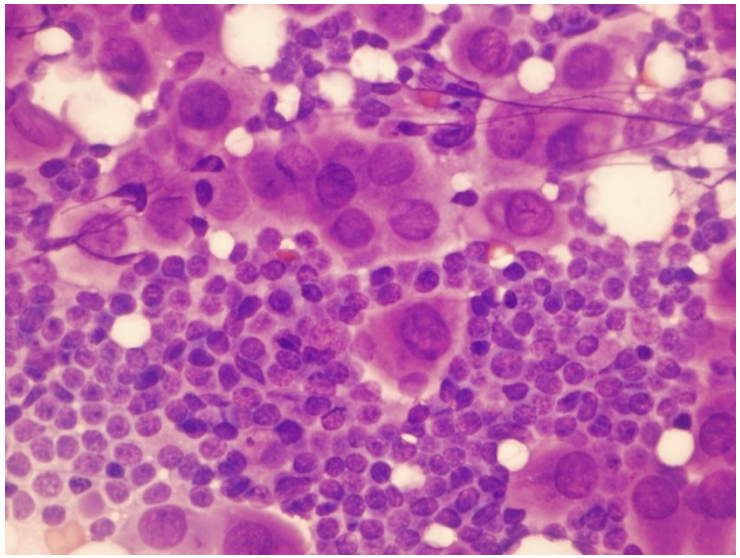


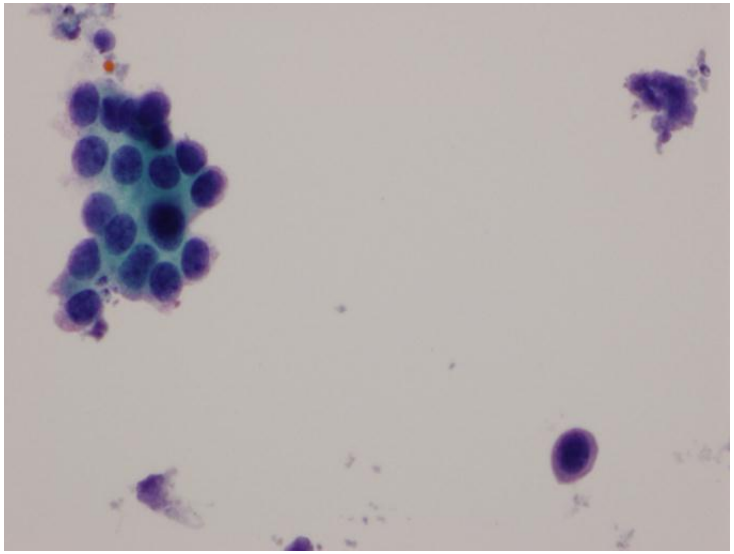
Citología

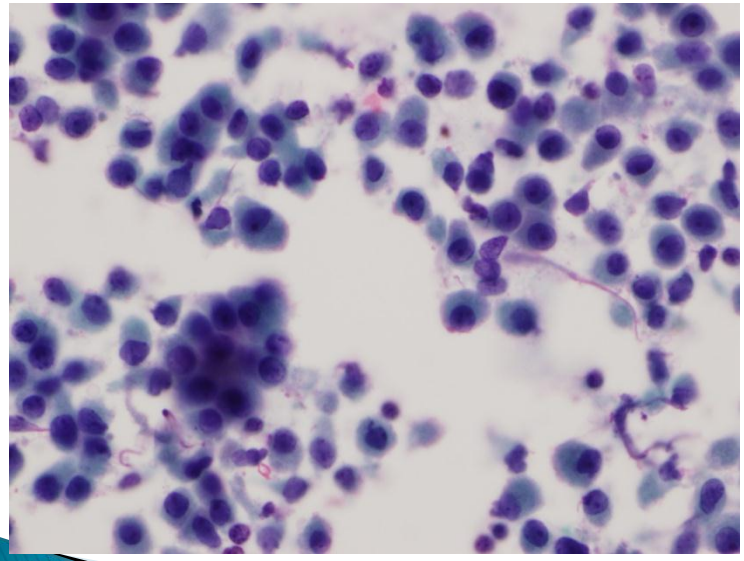
PAAF de axila

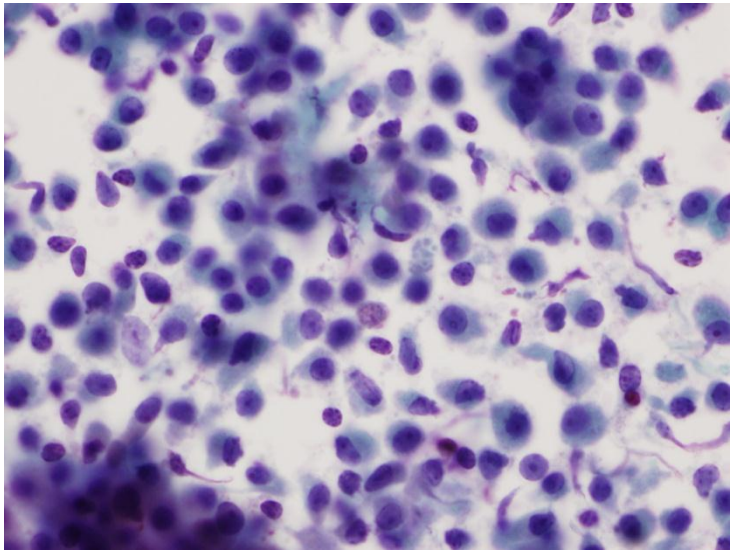


60% malignos
VPP 90%
VPN 70%







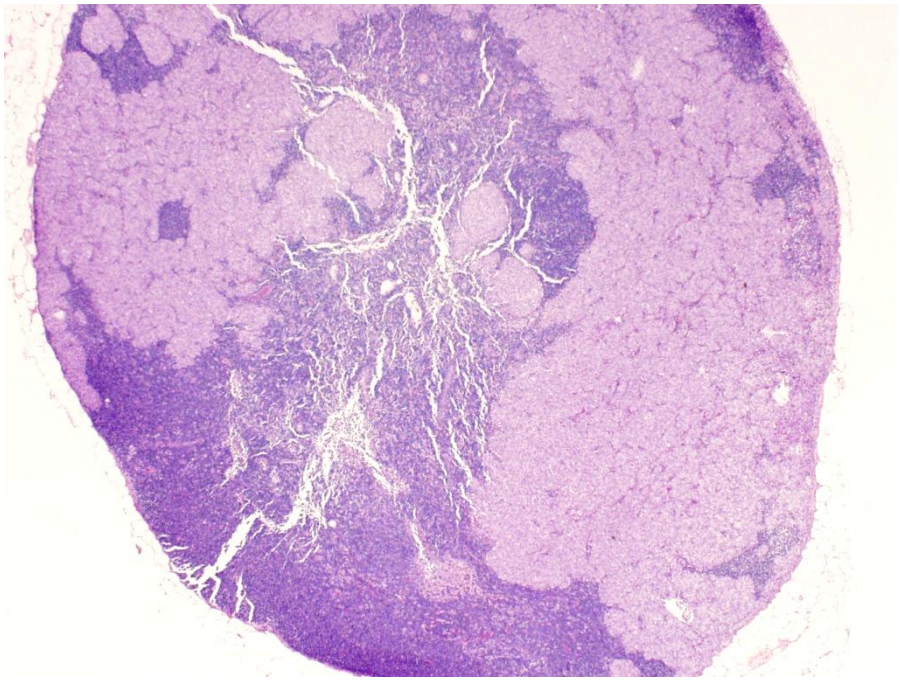


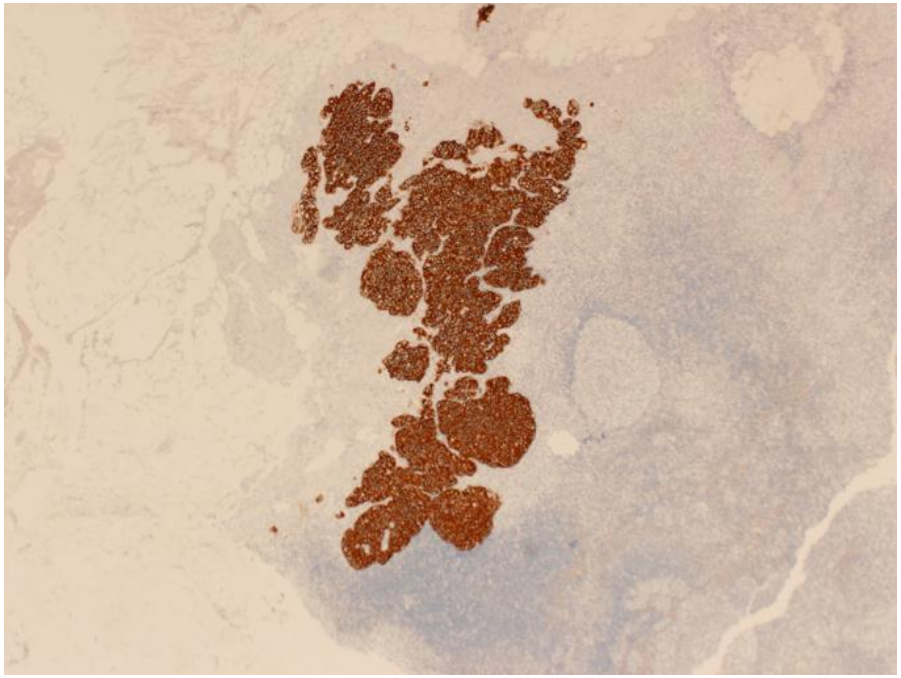
Ganglio centinela - Mama

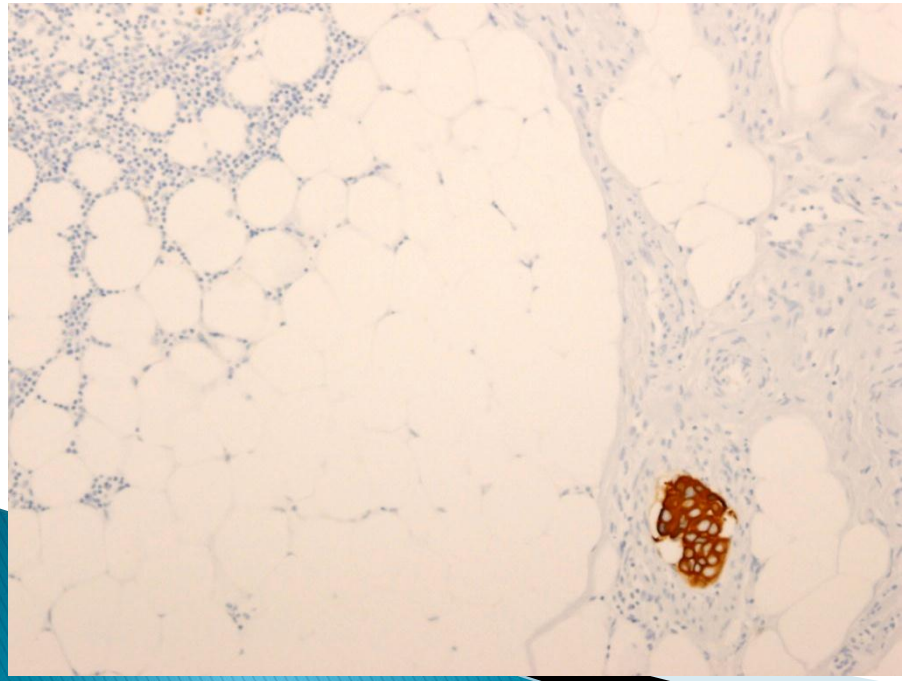
- 1.994 Giuliano en mama (gamma.)
- 1.998 Fase validación: GC y VAX
- Intraoperatoria con improntas citológicas

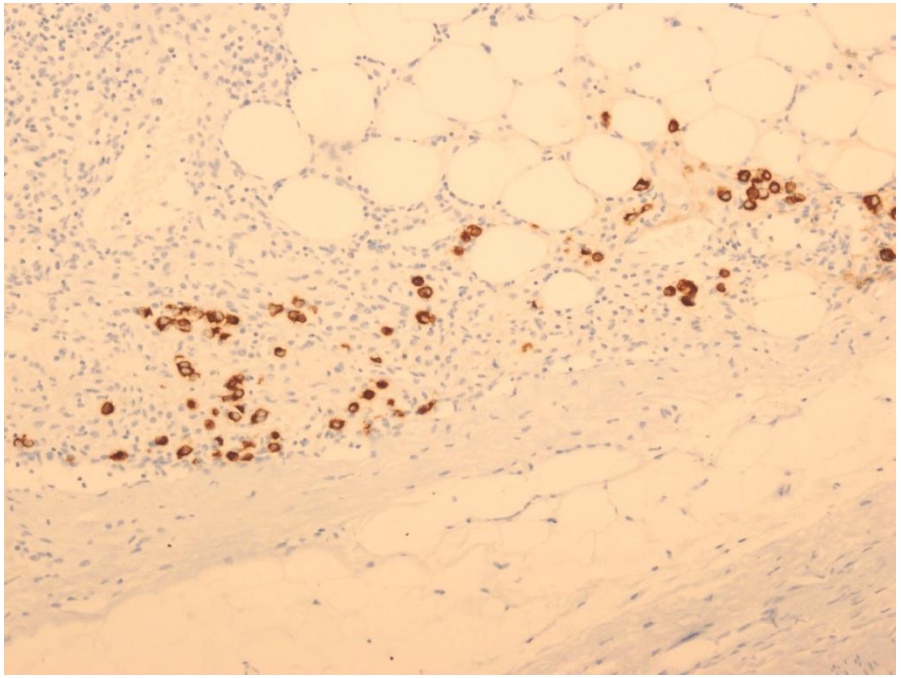
- 2.000 GC negativo NO VAX
- Intraoperatoria OSNA estudio molecular CK19
- Ensayos ACOSOG Z011, AMAROS

- 2.013: GC hasta 2 ganglios metastásicos NO VAX
- No intraoperatoria









DESCUBRIMIENTO DE CLASES

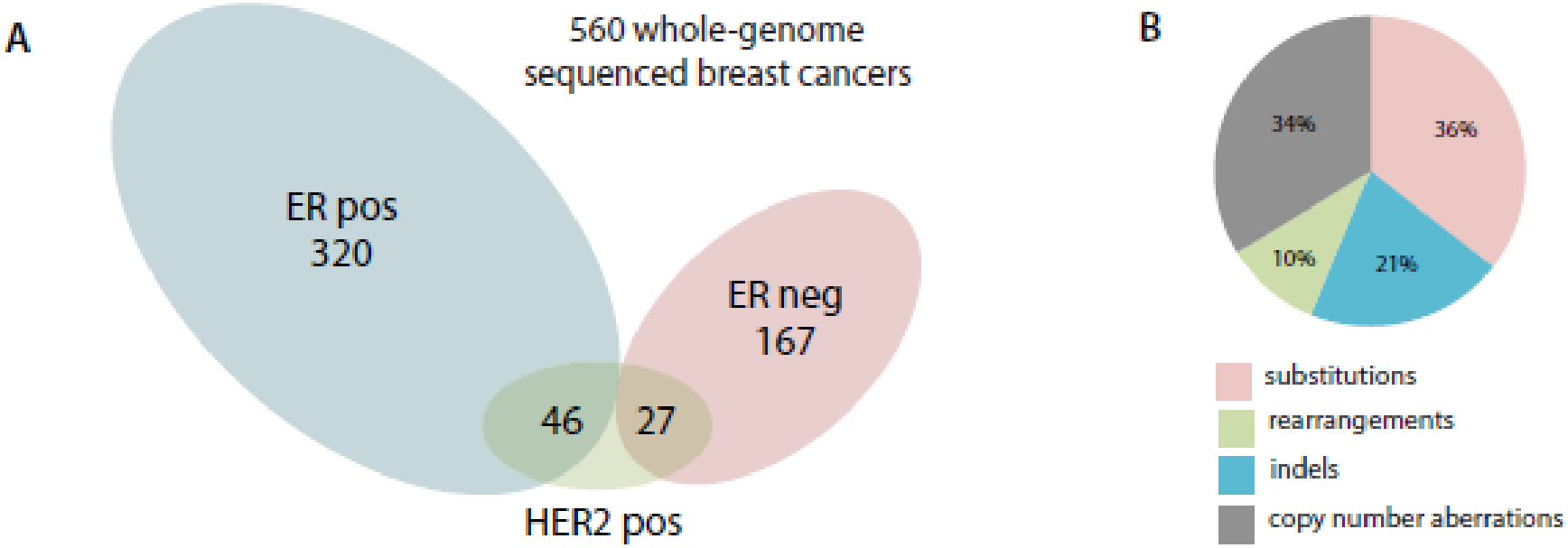
c Ductal, ER+

d ERBB2

e *Basal*

f Normal

Perou et al., Nature 2000


A
560 whole-genome
sequenced breast cancers
ER pos
320
ER neg
167
46
27
HER2 pos
B
34%
36%
10%
21%
substitutions
rearrangements
indels
copy number aberrations

Fenotipos	**REα**	**RP**	**HER2**	**Ki-67**
Luminal A	+	+	-	bajo
Luminal B	+	-	-+	alto
HER2	-	-	+	alto
Basal	-	-	-	alto

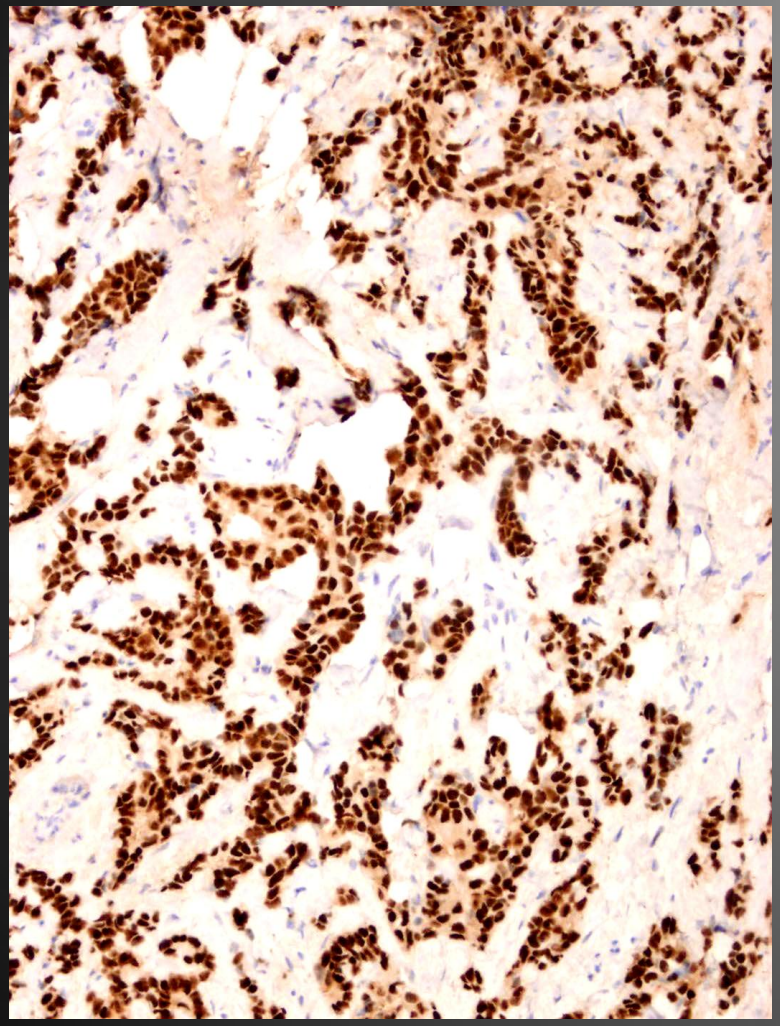
Inmunofenotipo

- Receptores estrógenos
- Receptores de progesterona
- Her2
- Indice de proliferación: Ki67
- E-cadherina

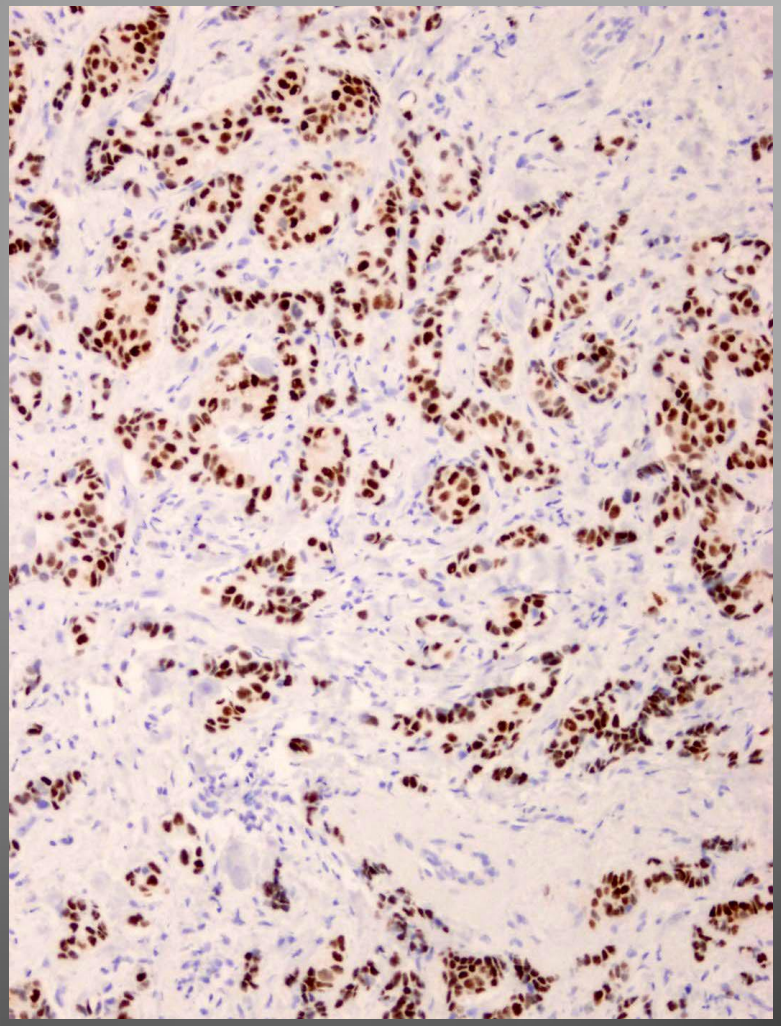
- CK19
- EGFR
- CK 5/6
- Receptores de andrógenos

TILs

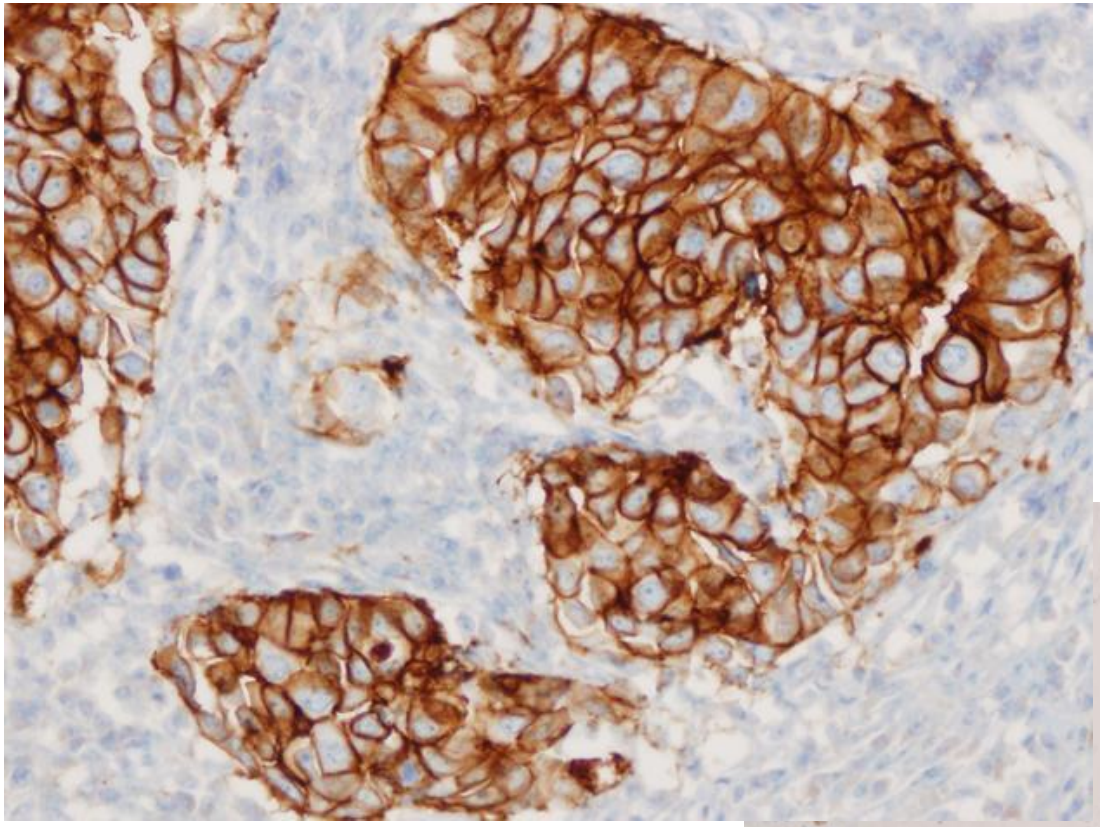
Receptores hormonales



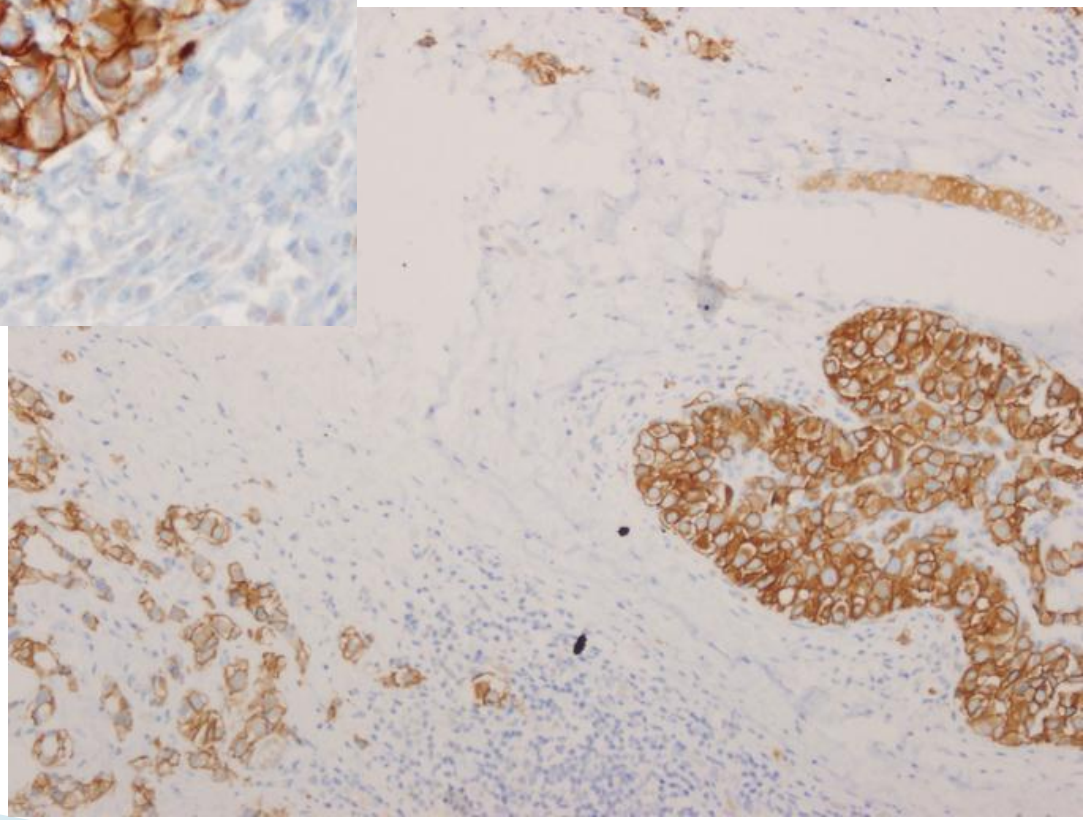
RE



RP

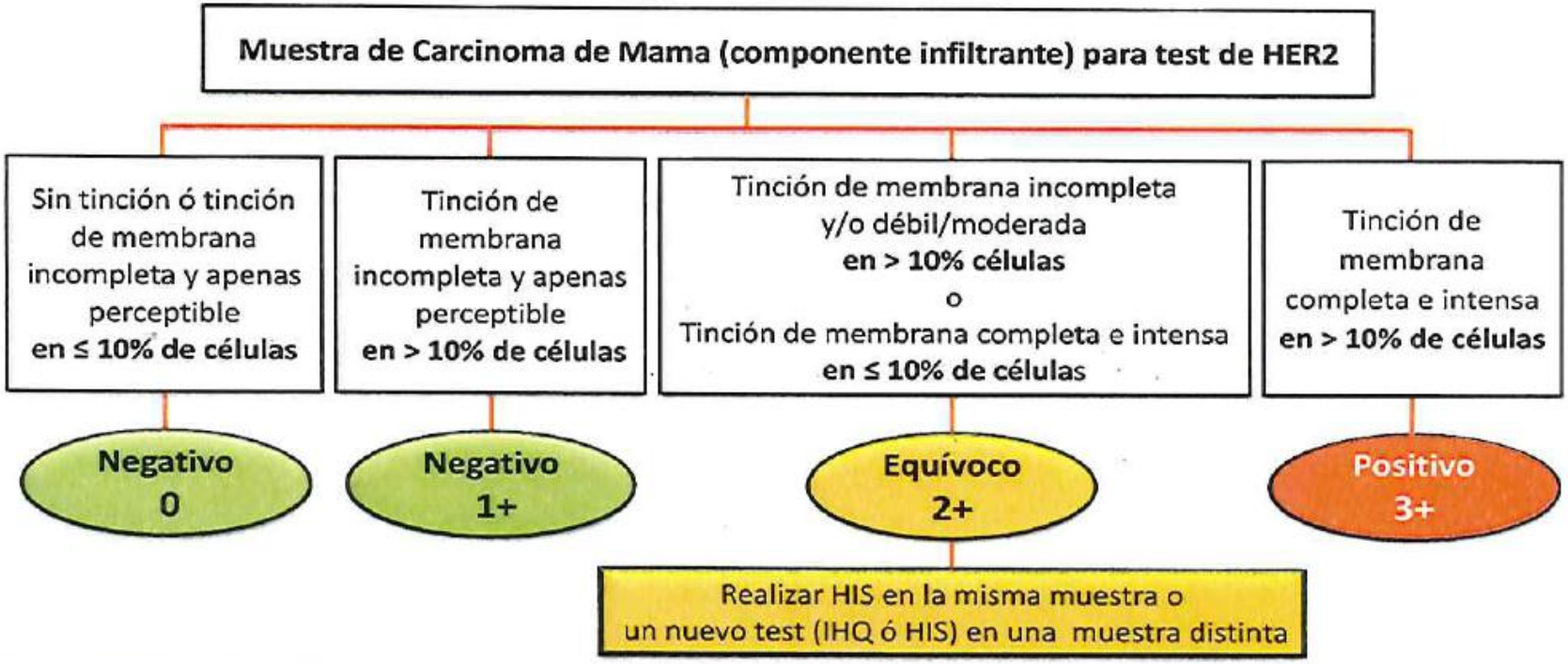


HER2

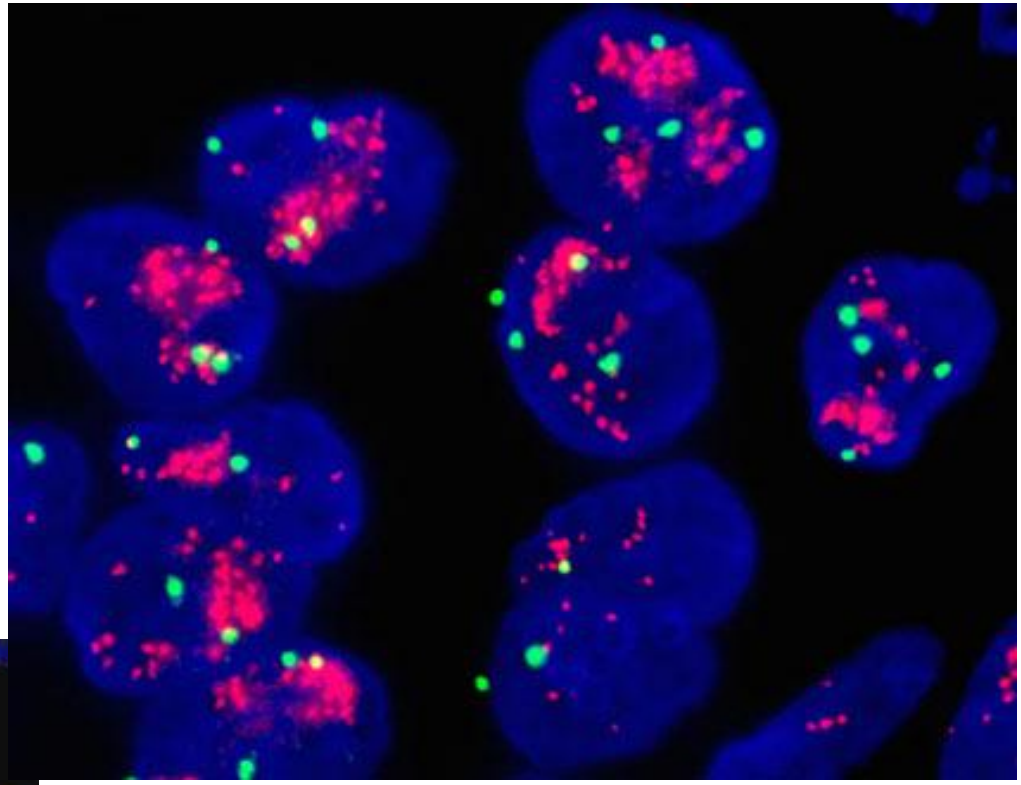


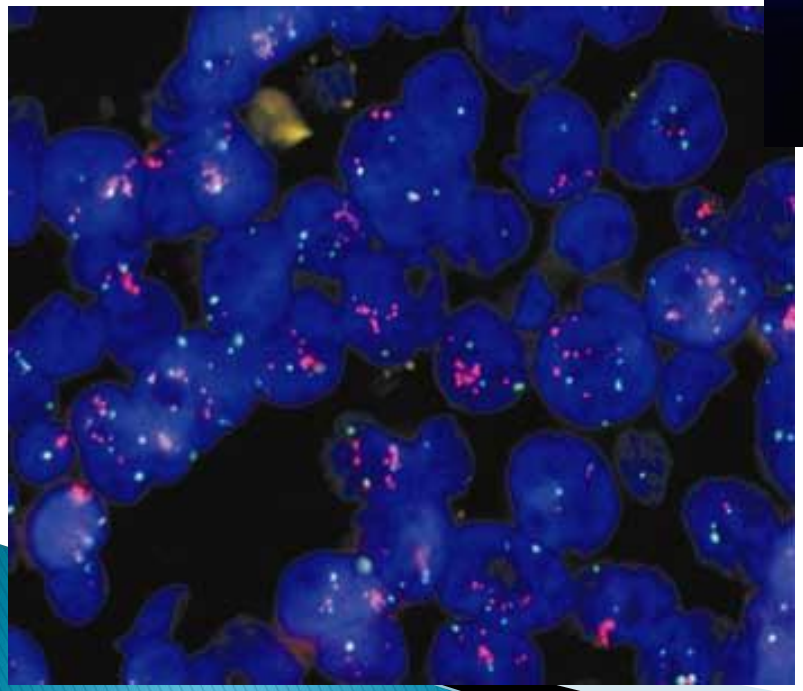
Recommendations for HER2 Testing in Breast Cancer: ASCO/CAP Clinical Practice Guideline Update. *JCO, Wolff et al.*

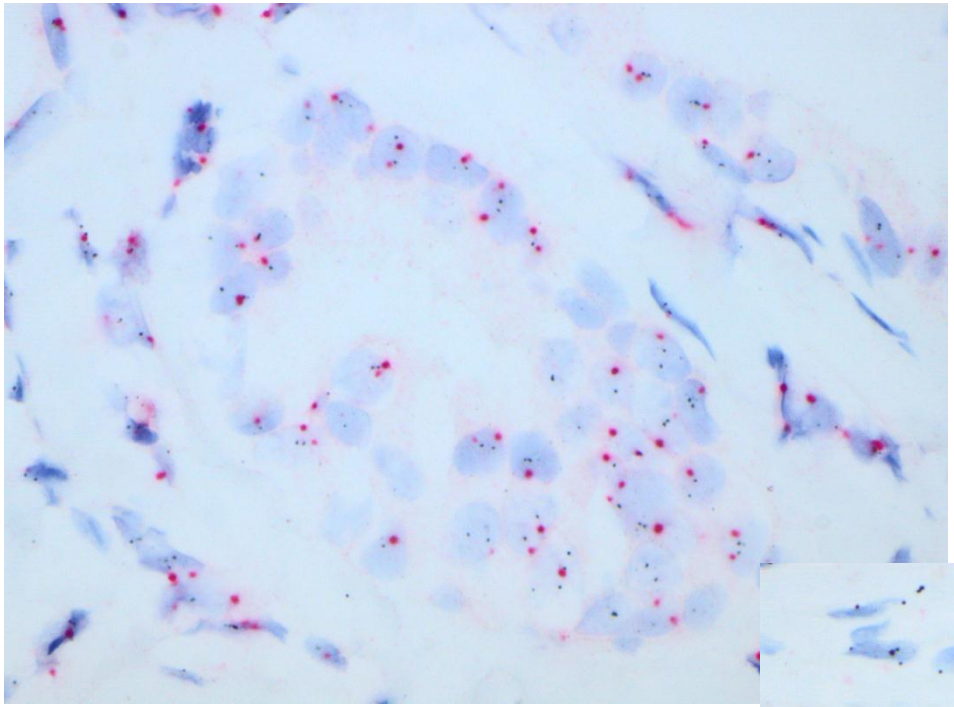
An Agilent Technologies



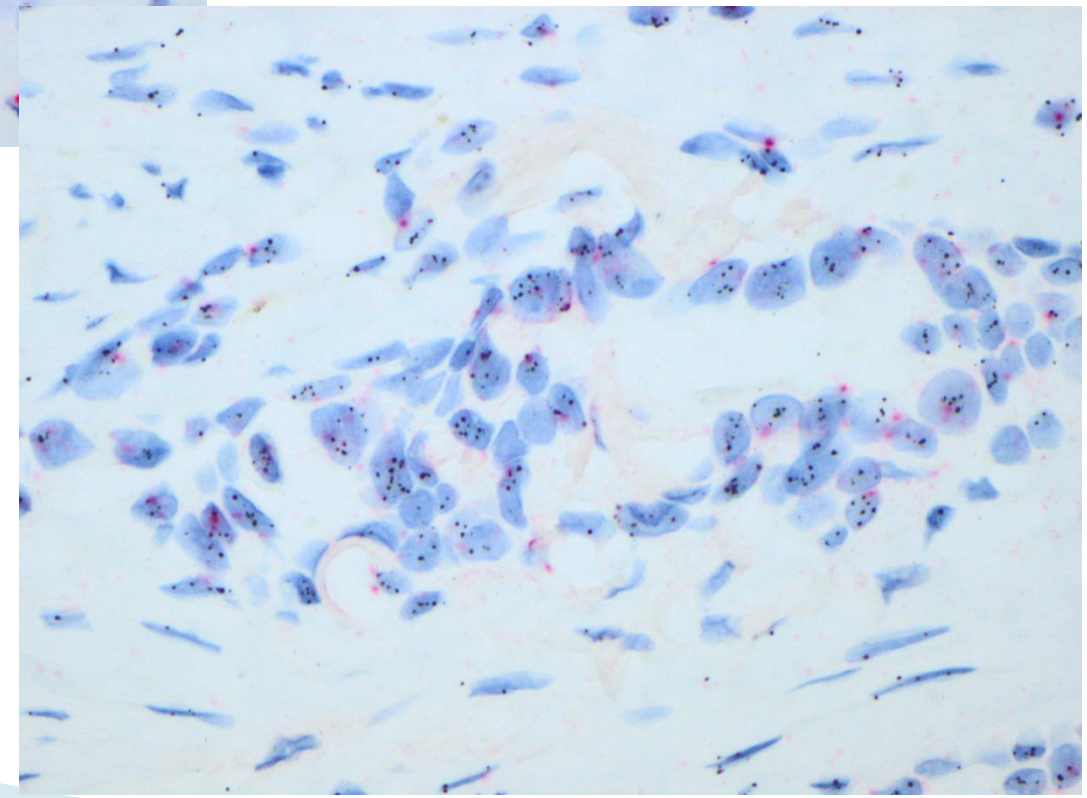
FISH

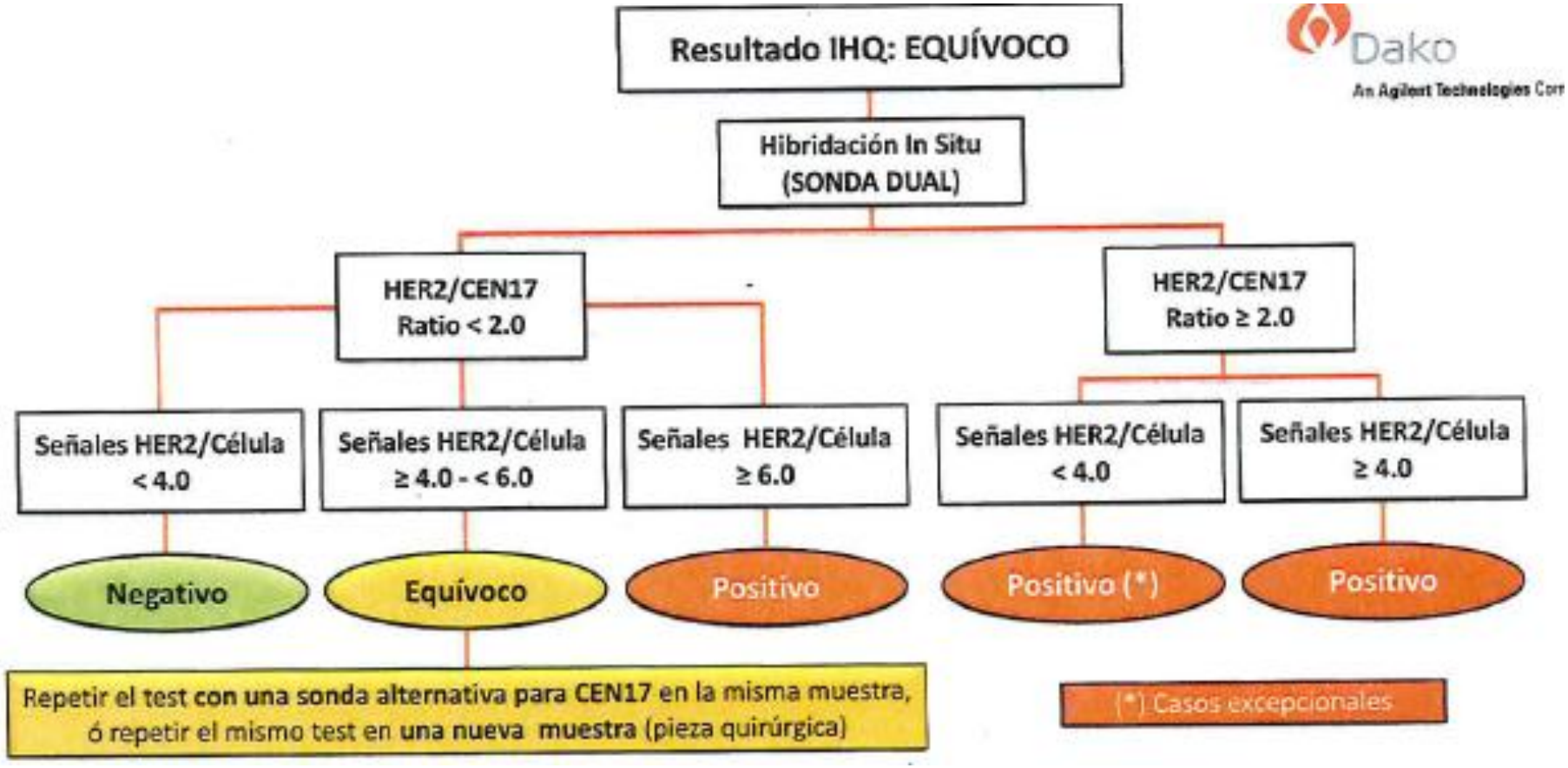




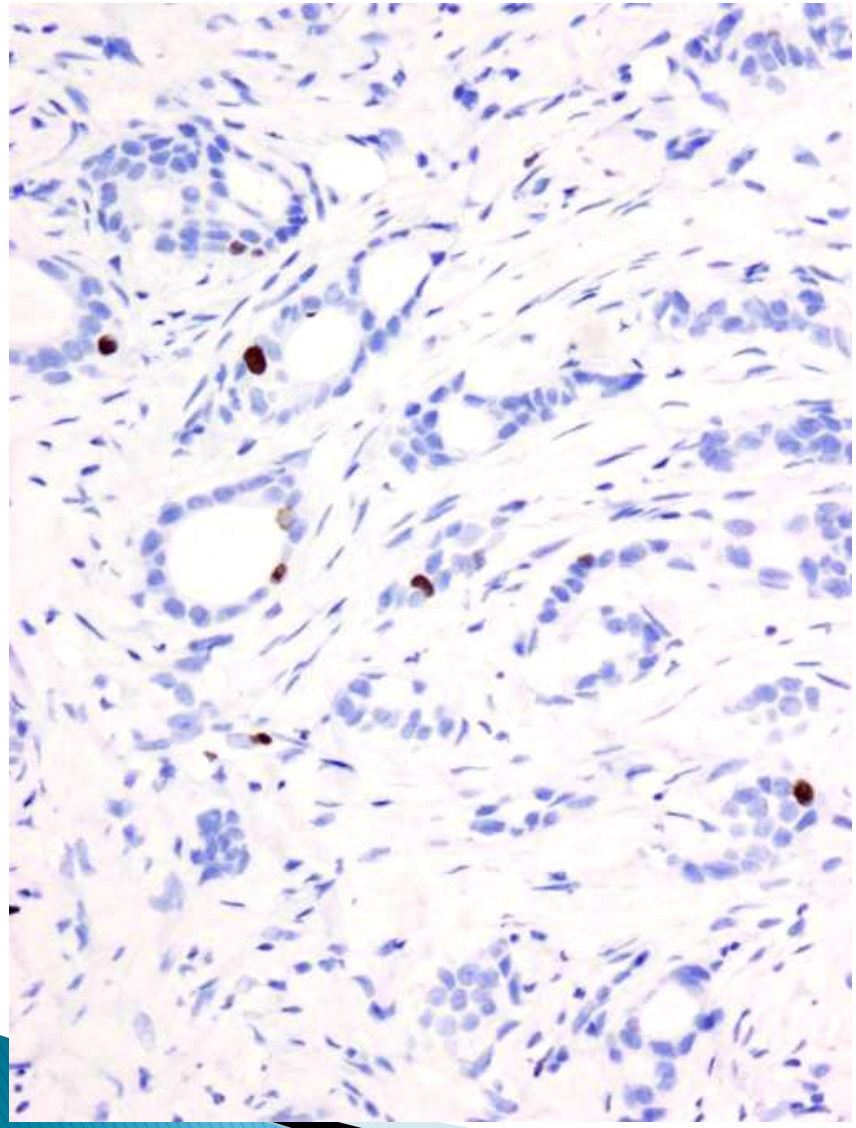


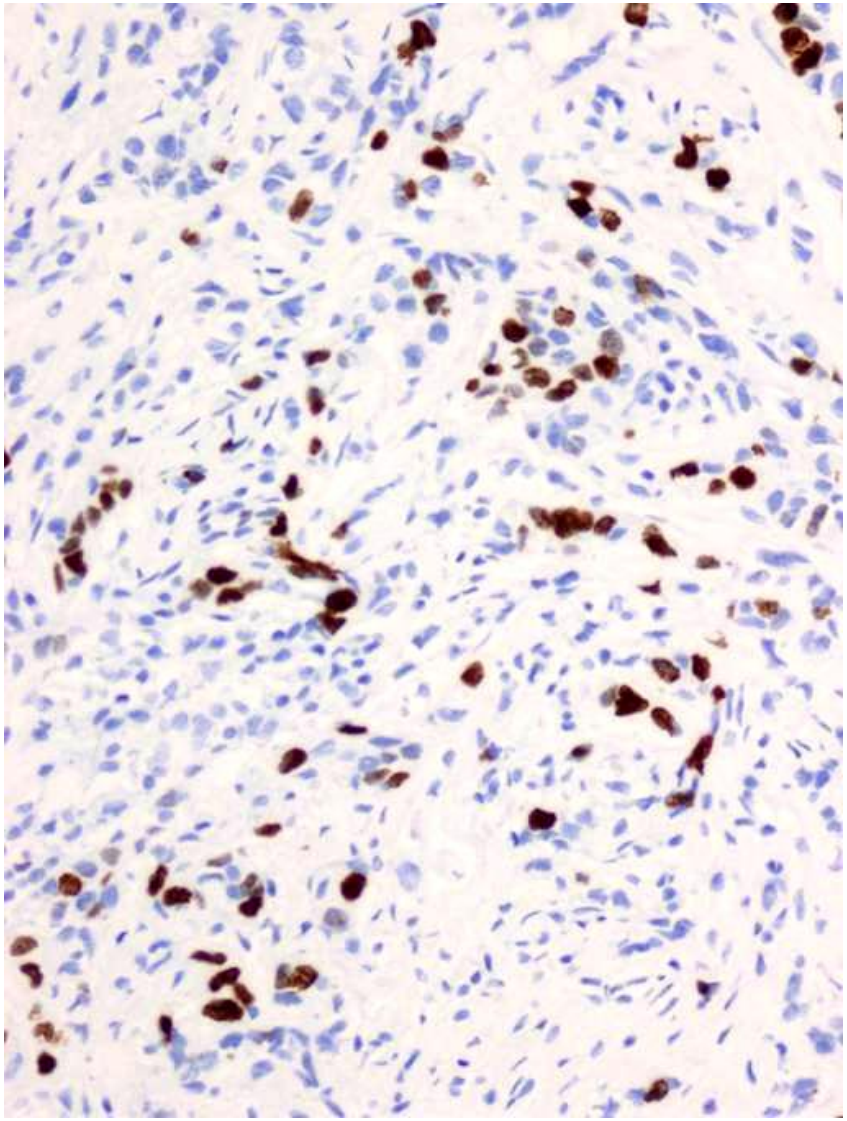
SISH

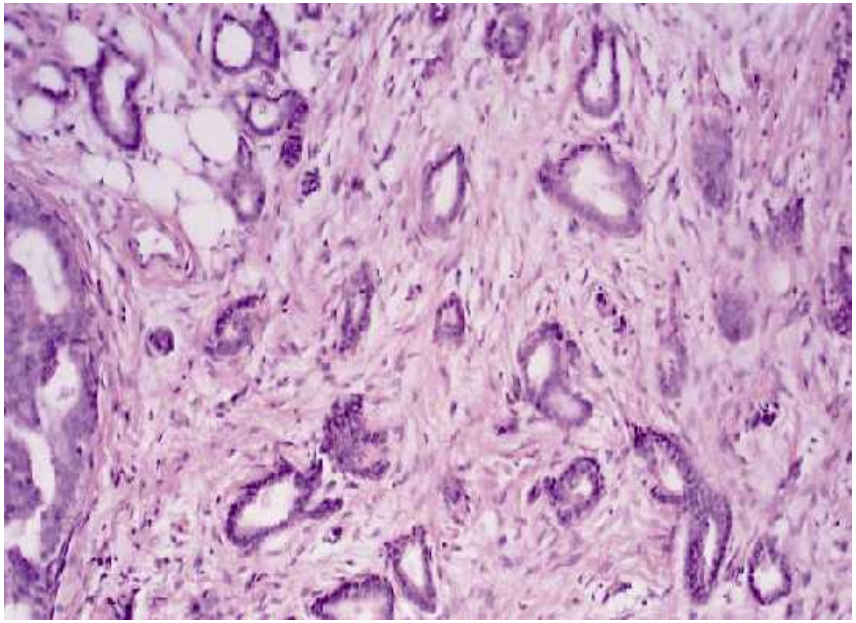



Resultado IHQ: EQUÍVOCO
Dako
An Agilent Technologies Com
Hibridación In Situ
(SONDA DUAL)
HER2/CEN17
Ratio < 2.0
HER2/CEN17
Ratio ≥ 2.0
Señales HER2/Célula
< 4.0
Señales HER2/Célula
≥ 4.0 - < 6.0
Señales HER2/Célula
≥ 6.0
Señales HER2/Célula
< 4.0
Señales HER2/Célula
≥ 4.0
Negativo
Equívoco
Positivo
Positivo (*)
Positivo
Repetir el test con una sonda alternativa para CEN17 en la misma muestra,
ó repetir el mismo test en una nueva muestra (pieza quirúrgica)
(*) Casos excepcionales

Ki67







FENOTIPO LUMINAL (ER+)

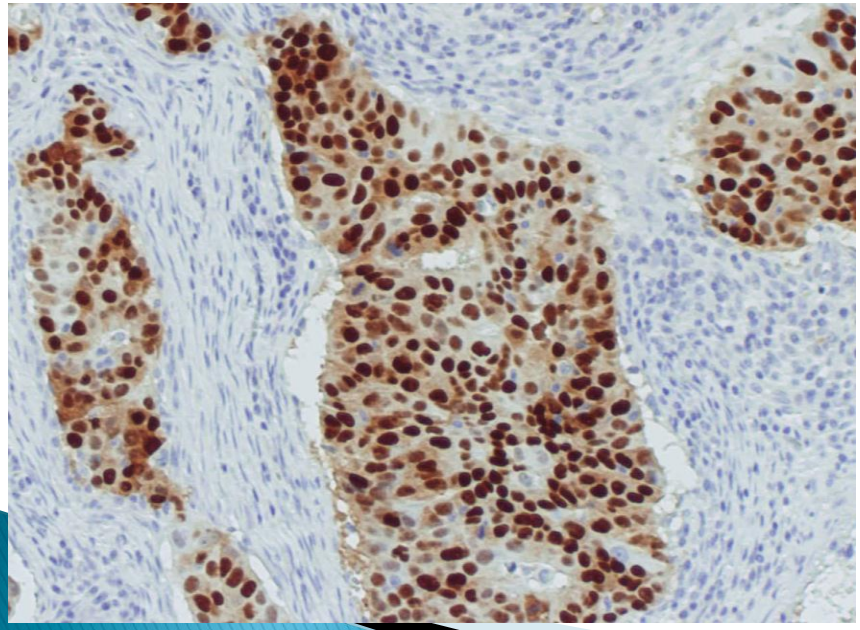
Carcinoma ductal invasivo (grade 1-2/3)

Carcinoma lobular invasivo

Carcinoma tubular

Carcinoma cribiforme invasivo

Carcinoma mucinoso



FENOTIPOS LUMINAL A/B

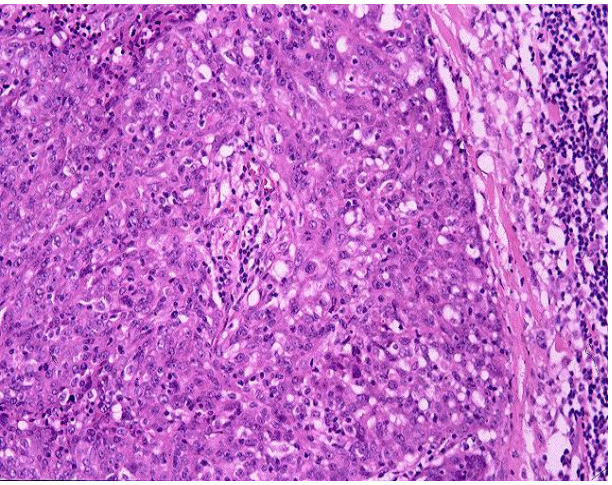
Grado 1-2/3

Niveles RH

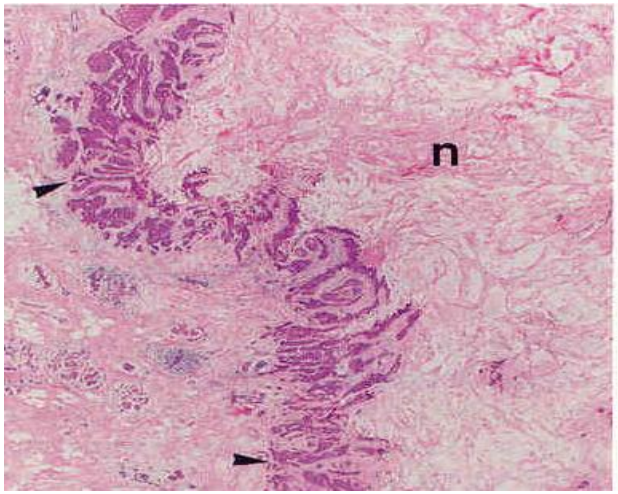
Marcadores proliferación Ki67

Expresión HER2

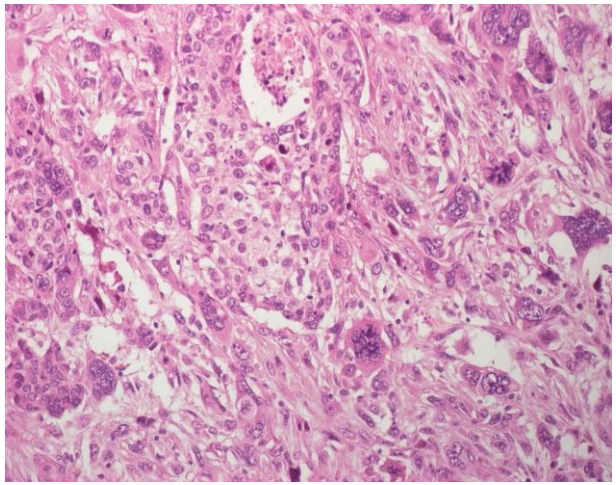
HETEROGENEIDAD MORFOLOGICA E INMUNOHISTOQUIMICA DE DE CARCINOMA DE MAMA CON FENOTIPO BASAL



Carcinoma medular



Carcinoma pobremente diferenciado



Carcinoma metaplasico

VIMENTIN, P-CADHERIN, EGFR, CK5/6, FASCIN

p63, CD10, OSTEONECTIN, SMA, CALPONIN, H-CALDESMON

BRCA1

EGFR

P53

MYC

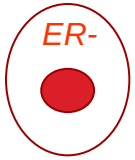
HER2

PIK3CA

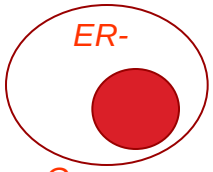
RAS

-16q

CDH1

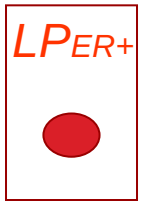


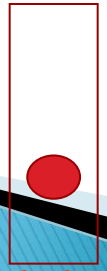
Stem Cell



Common Progenitor

Luminal Progenitors





Luminal cells

BASAL

BASOLUMINAL

HER2

APOCRINO

LUMINAL B

LUMINAL A

SMA

VIMENTIN

C-KIT

EGFR

P-CADHERIN

CK5/6

CK8/18/19

HER2

AR

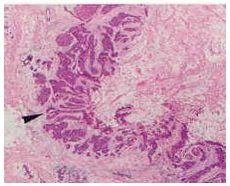
CK8/18/19

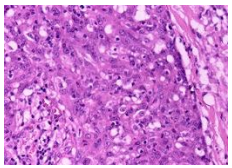
ER

PR

GATA3

CK8/18/19

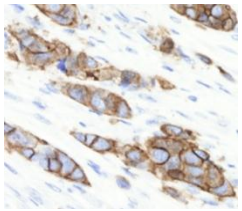




METAPLASICO

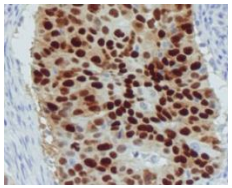
MEDULAR

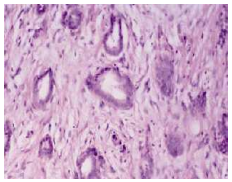
CDI-G3

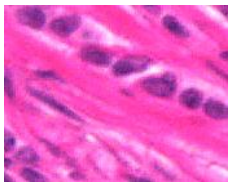


CDI-G2/3

APOCRINO







CDI-G1/2

MUCINOSO

CRIBIFORME

TUBULAR

LOBULAR

Hereditary breast cancer

BRCA1/2: **30%**

BRCA (-): **70%**

	GRADE	ER	PR	BCL2	Ki67	p53	HER2
BRCA1	3	-	-	-	++	++	-
BRCA2	2/3	+	+	+	+	-	-
BRCA(-)	1/2	+	+	+	-	-	+/-

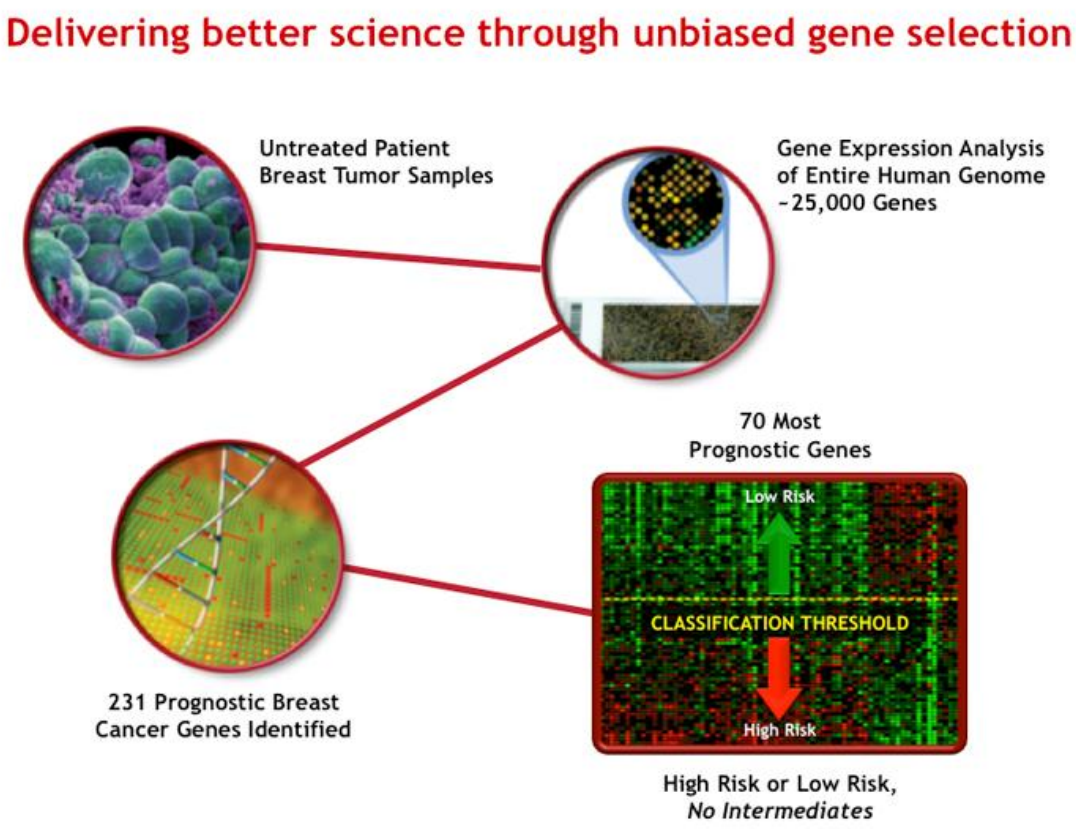
Modelos moleculares

Oncotype: 21 genes
3 grupos de riesgo

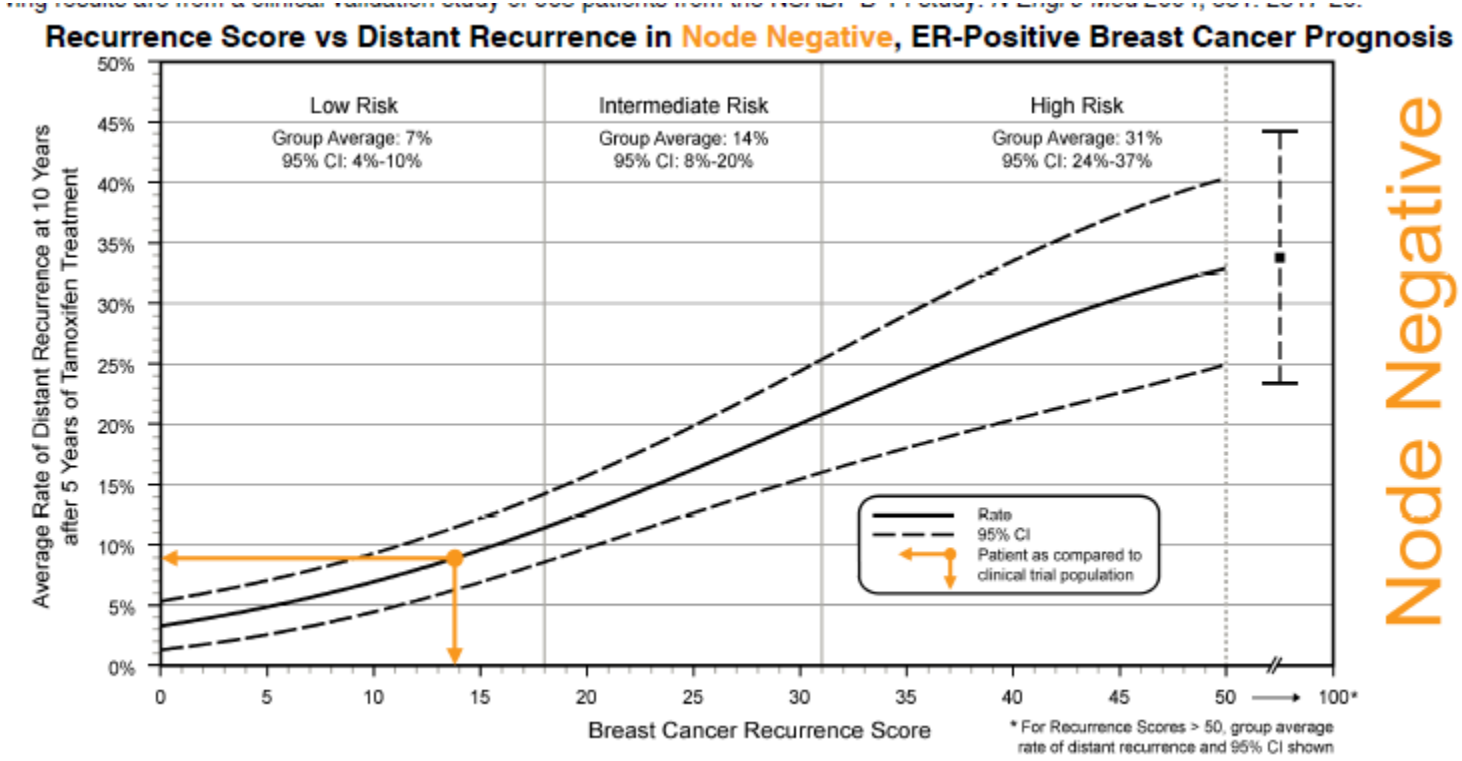
MammaPrint: 70 genes
2 grupos de riesgo

PAM50: 50 genes
3 grupos de riesgo

EndoPredict: 8 genes
2 grupos de riesgo


Delivering better science through unbiased gene selection
Untreated Patient
Breast Tumor Samples
Gene Expression Analysis
of Entire Human Genome
~25,000 Genes
70 Most
Prognostic Genes
Low Risk
CLASSIFICATION THRESHOLD
High Risk
231 Prognostic Breast
Cancer Genes Identified
High Risk or Low Risk,
No Intermediates

Mammaprint



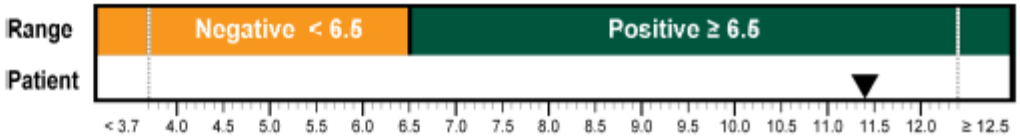
reducción >15% quimioterapia

QUANTITATIVE SINGLE GENE REPORT

The Onco*type* DX assay uses RT-PCR to determine the RNA expression of the genes below. These results may differ from ER, PR, or HER2 results reported using other methods or reported by other laboratories.[1]

The ER, PR, and HER2 Scores are also included in the calculation of the Recurrence Score.

ER Score = **11.4** **Positive**

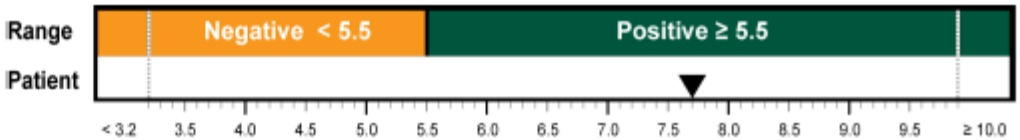


The ER Score positive/negative cut-off of 6.5 units was validated from a study of 761 samples using the 1D5 antibody (immunohistochemistry) and 607 samples using the SP1 antibody (immunohistochemistry). The standard deviation for the ER Score is less than 0.5 units.[2]

Clinical Experience:

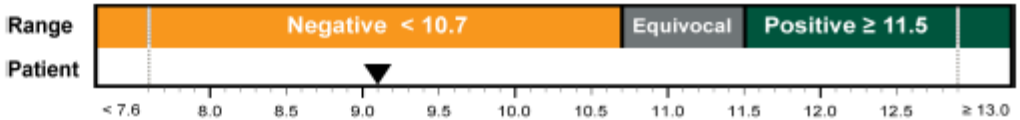
For ER positive breast cancer, the magnitude of tamoxifen benefit increases as the ER Score increases from 6.5 to ≥12.5.[3]
Please note: The Average Rate of Distant Recurrence reported on Page 1 based on the Recurrence Score was determined in patients who received 5 years of tamoxifen treatment and takes into account the magnitude of tamoxifen benefit indicated by the ER Score.

PR Score = **7.7** **Positive**



The PR Score positive/negative cut-off of 5.5 units was validated from a study of 761 samples using the PR636 antibody (immunohistochemistry) and another study of 607 samples using the PR636 antibody (immunohistochemistry). The standard deviation for the PR Score is less than 0.5 units.[2]

HER2 Score = **9.1** **Negative**



The HER2 positive cut-off of ≥ 11.5 units, equivocal range from 10.7 to 11.4 units, and negative cut-off of < 10.7 units were validated from concordance studies of 755 samples using the HercepTest™ assay (immunohistochemistry) and another study of 568 samples using the PathVysion® assay (FISH). The standard deviation for the HER2 score is less than 0.5 units.[4]

Uso clínico

- Ventajas:
  - Reproductibilidad
  - Confianza al oncólogo/paciente
  - Disminución quimioterapia innecesaria

- Desventajas:
  - No generalizado a cualquier tipo tumoral
  - Precio
  - No evidencia clínica

Breast Cancer Molecular Subtypes Respond Differently to Preoperative Chemotherapy

Roman Rouzier,[1,4] Charles M. Perou,[5] W. Fraser Symmans,[2] Nuhad Ibrahim,[1] Massimo Cristofanilli,[1] Keith Anderson,[3] Kenneth R. Hess,[3] James Stec,[6,7] Mark Ayers,[6] Peter Wagner,[1] Paolo Morandi,[1] Chang Fan,[5] Islam Rabiul,[1] Jeffrey S. Ross,[6] Gabriel N. Hortobagyi,[1] and Lajos Pusztai[1]

Table 2. Correlation between molecular classification and pathologic complete response

	Pathologic complete response		
	No	Yes	
Molecular classification	*n* [% (95% CI)]	*n* [% (95% CI)]	
Luminal A/B subtype	28 [93% (78-99)]	2 [7% (1-22)]	
Normal breast like	10 [100% (29-100)]	0 [0% (0-31)]	
erbB 2+	11 [55% (32-77)]	9 [45% (23-68)]	
Basal subtype	12 [55% (32-76)]	10 [45% (24-68)]	$P < 0.001$

Neoadyuvancia

- Quimioterapia / hormonoterapia previa a la cirugía
- Aumento de pCR
- Cada vez mas en tumores mas pequeños
- Ganglio centinela despues del tratamiento neoadyuvante

Valoración respuesta a la quimioterapia neoadyuvante

Grado de respuesta histológica del tumor (Miller y Paine):

Grado 1: no se observa disminución de la densidad celular del tumor en comparación con la biopsia previa al tratamiento.

Grado 2: disminución discreta de la densidad celular del componente infiltrante del tumor, inferior al 30% de la masa tumoral.

Grado 3: disminución significativa del componente infiltrante del tumor entre un 30% y un 90% de la masa tumoral

Grado 4: marcada disminución del componente infiltrante del tumor, detectándose pequeños grupos celulares o células dispersas

Grado 5: ausencia de células tumorales invasivas en una zona previamente invadida por el tumor.

Grado de respuesta en los ganglios linfáticos (Miller y Paine):

Tipo A: ganglios linfáticos negativos, sin cambios atribuibles a quimioterapia.

Tipo B: ganglios linfáticos positivos, sin cambios atribuibles a la quimioterapia

Tipo C: ganglios linfáticos positivos, con evidencia de respuesta parcial a la quimioterapia.

Tipo D: ganglios linfáticos, sin tumor residual, con cambios atribuibles a la quimioterapia.

Residual Cancer Burden Calculator MD Anderson

*Values must be entered into all fields for the calculation results to be accurate.

(1) Primary Tumor Bed

Primary Tumor Bed Area: (mm) X (mm)

Overall Cancer Cellularity (as percentage of area): (%)

Percentage of Cancer That Is *in situ* Disease: (%)

(2) Lymph Nodes

Number of Positive Lymph Nodes:

Diameter of Largest Metastasis: (mm)

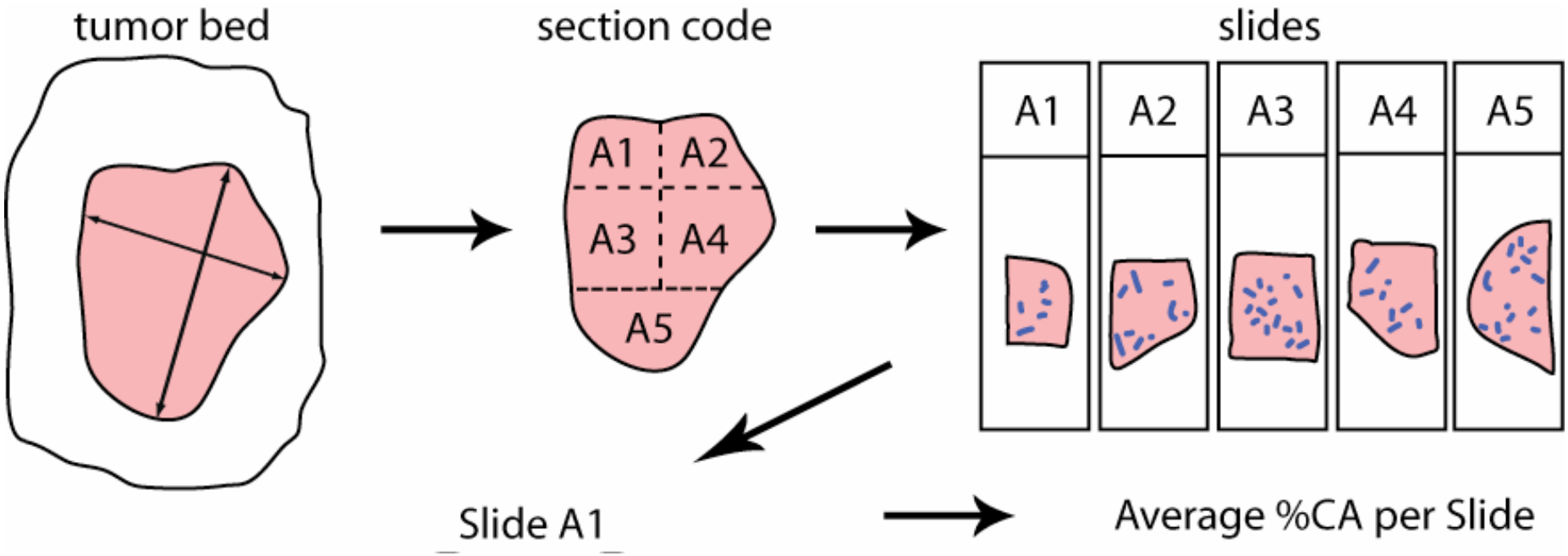
Reset Calculate

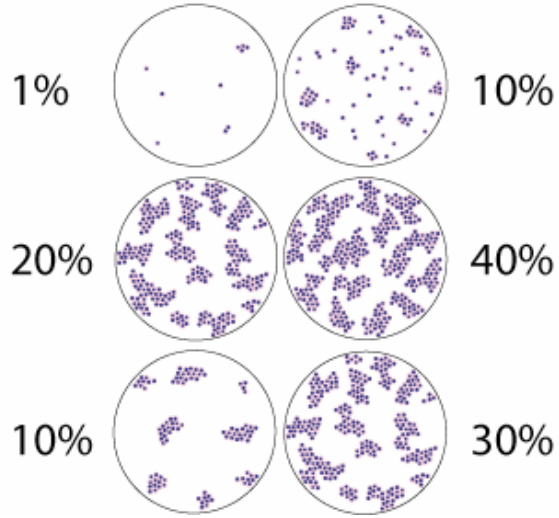
Residual Cancer Burden:

Residual Cancer Burden Class:

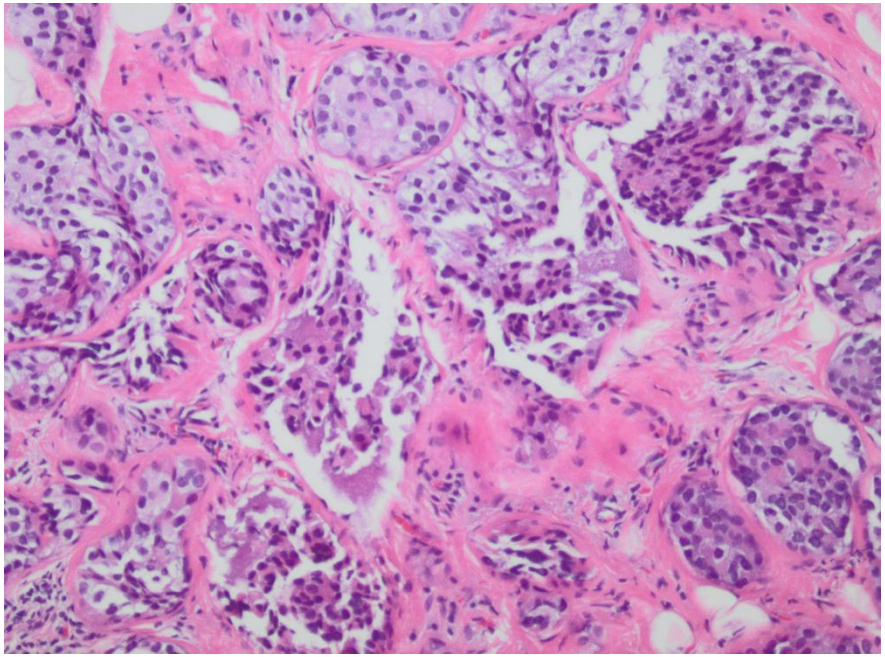
Calculator found online at

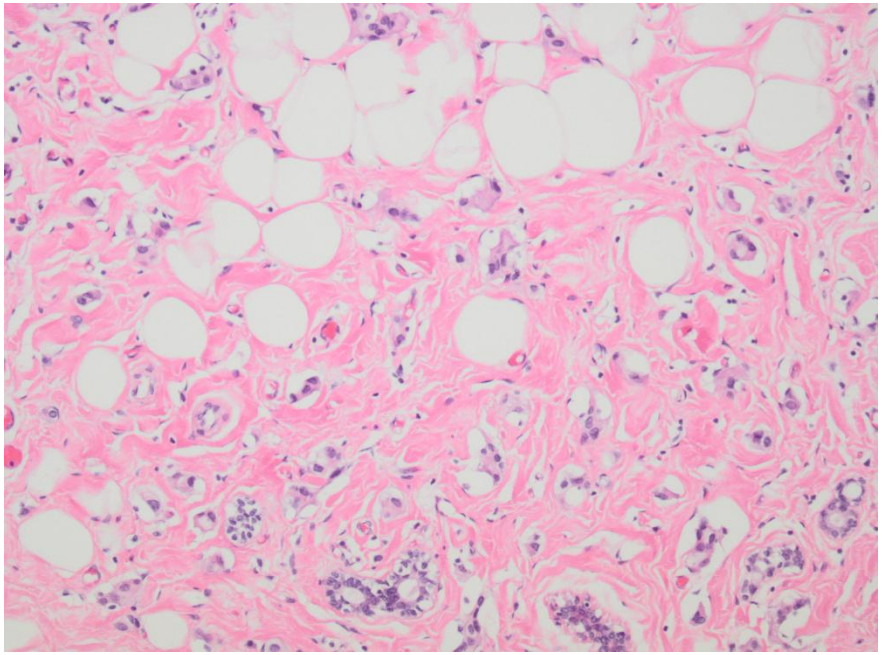
www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3

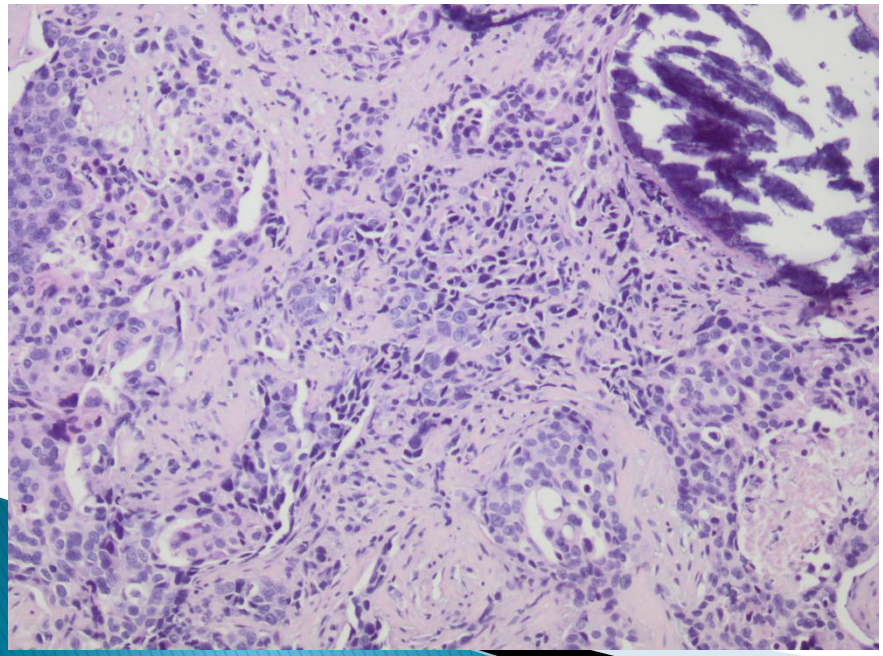


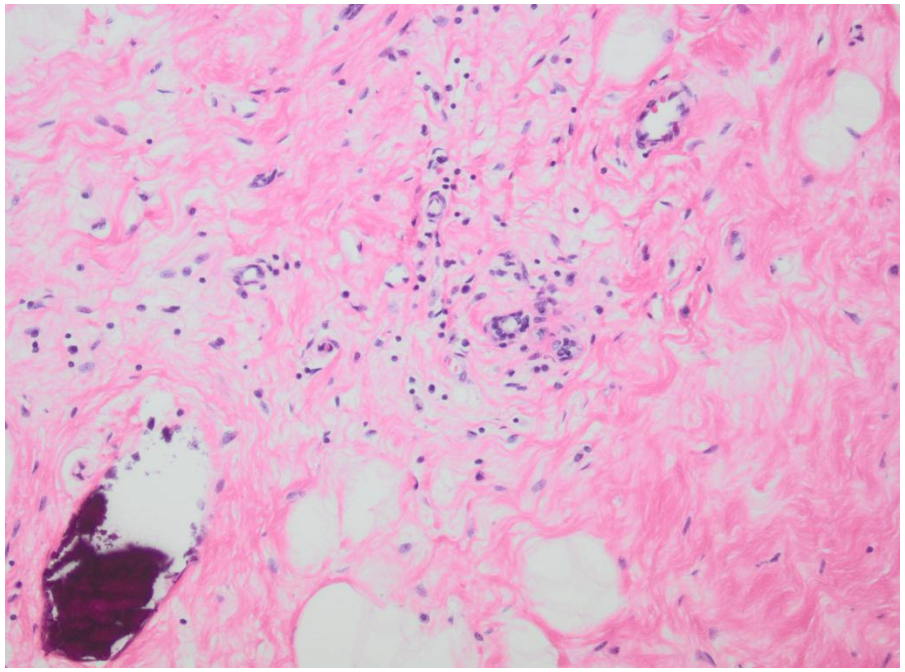


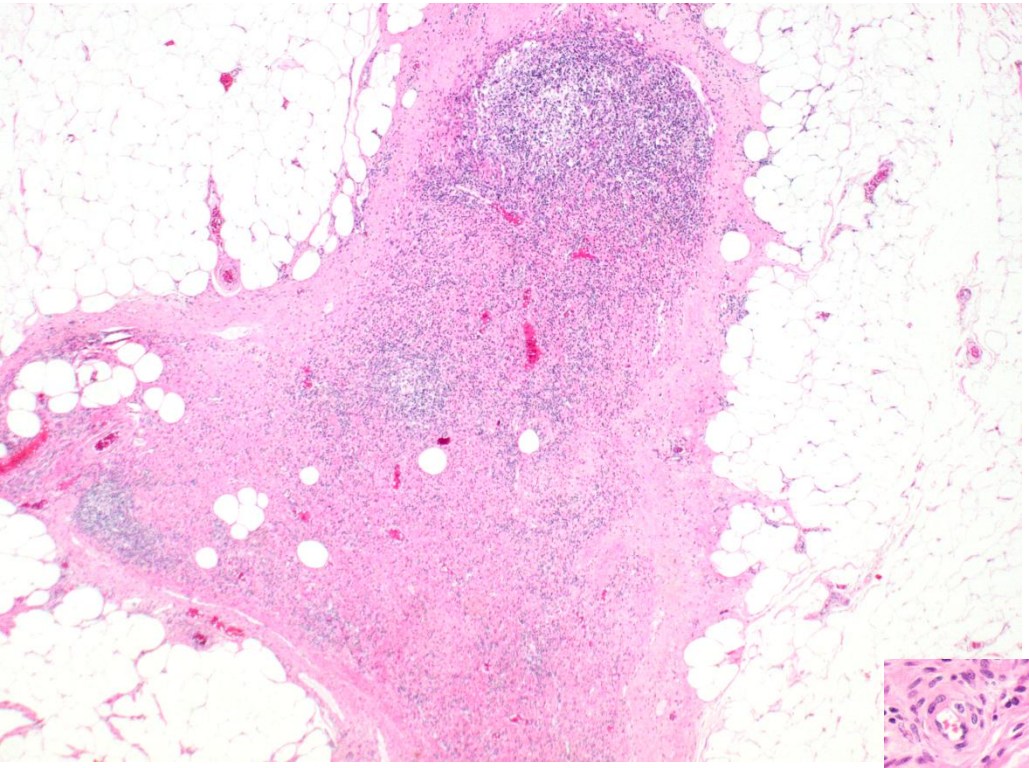
Slide A1	20%
Slide A2	30%
Slide A3	40%
Slide A4	20%
Slide A5	30%
OVERALL	30%
%CIS	1%

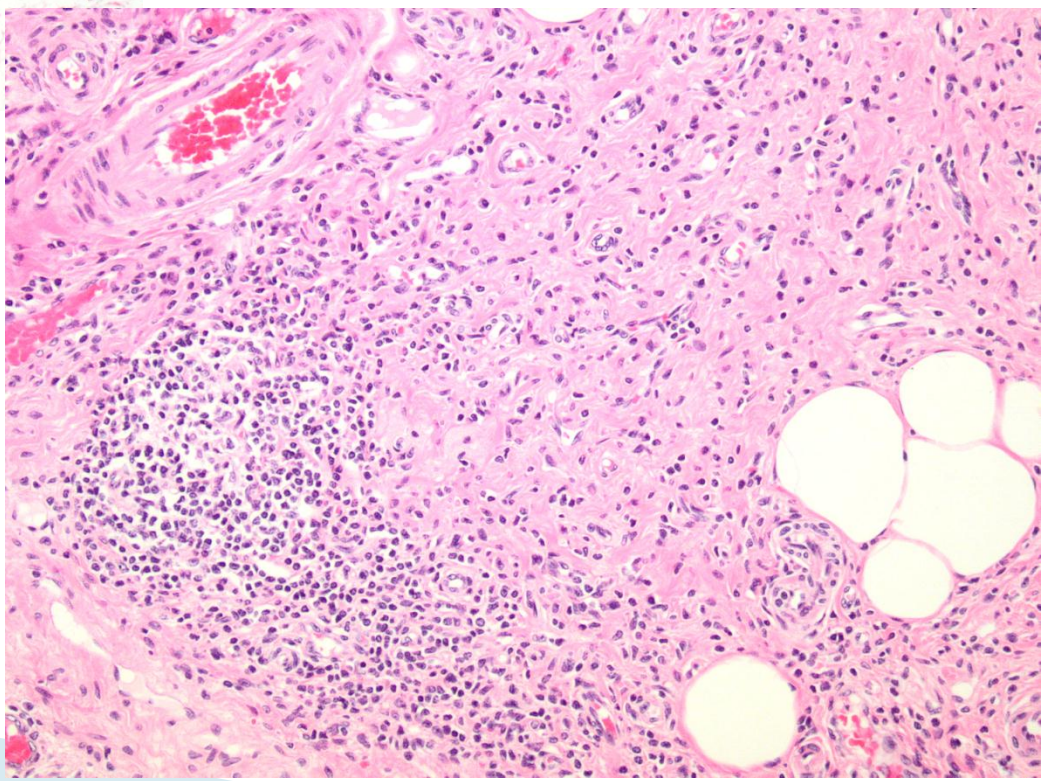




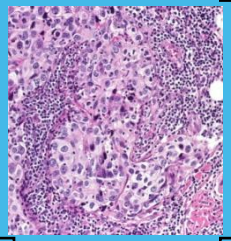


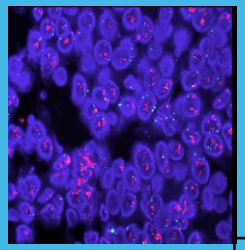


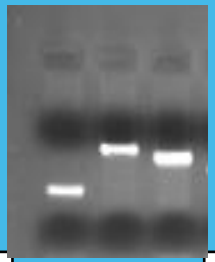


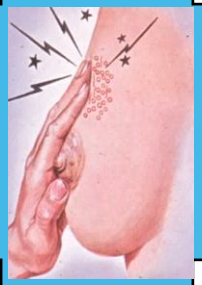


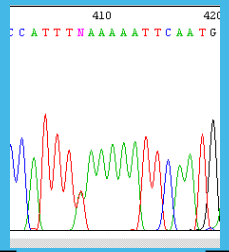
DIAGNÓSTICO INTEGRADO

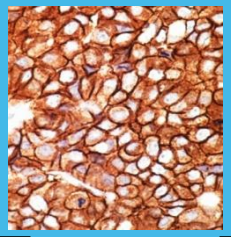


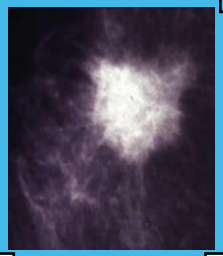


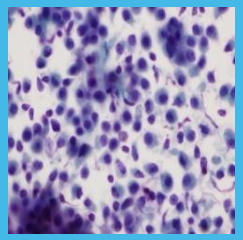












Eskerrik asko