Morphological and molecular classification of breast cancer

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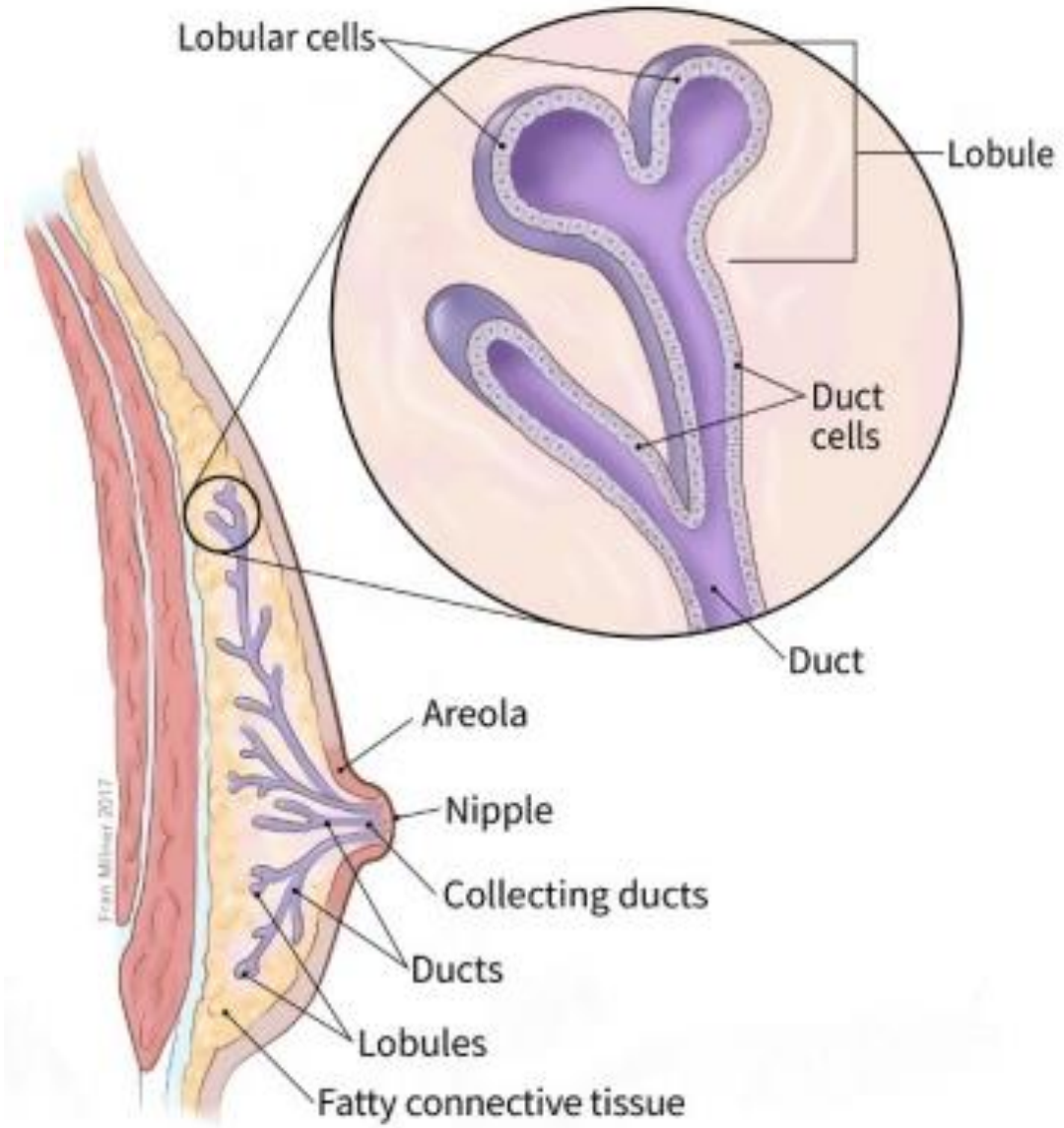
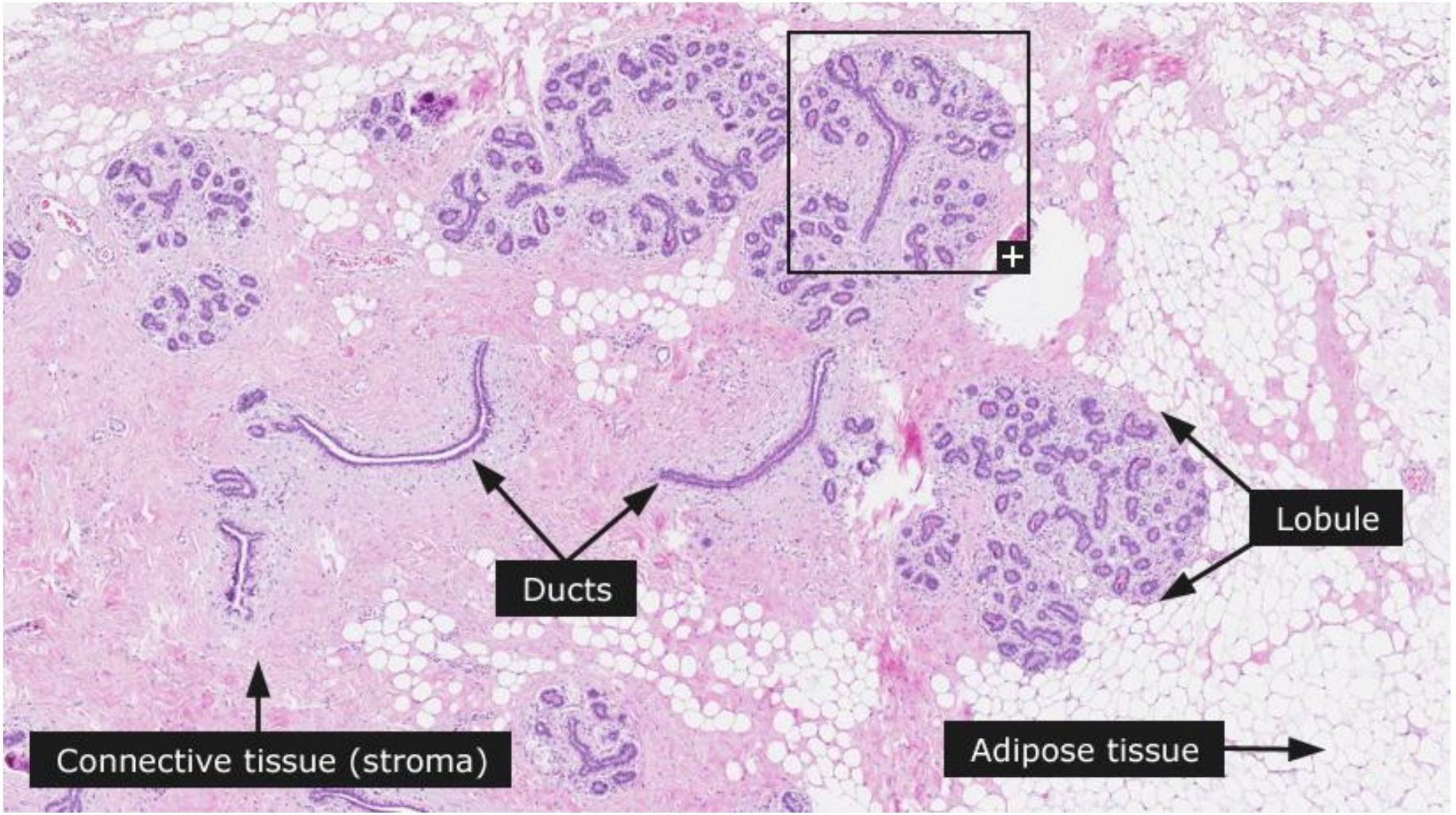
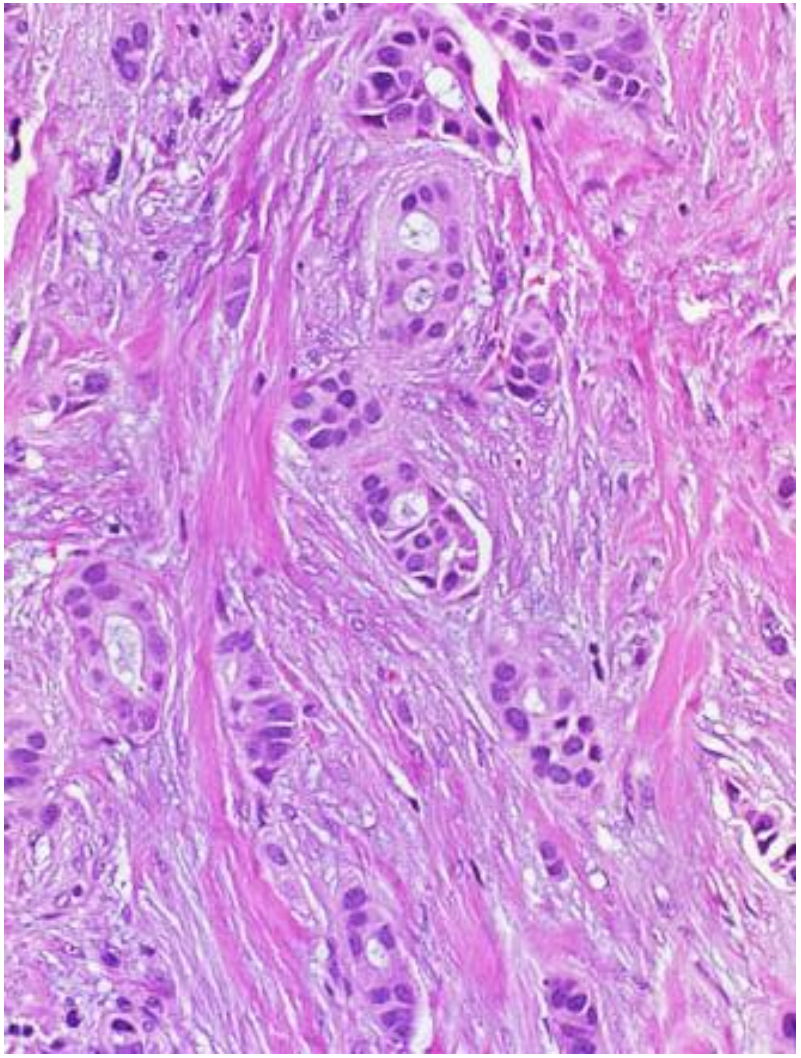
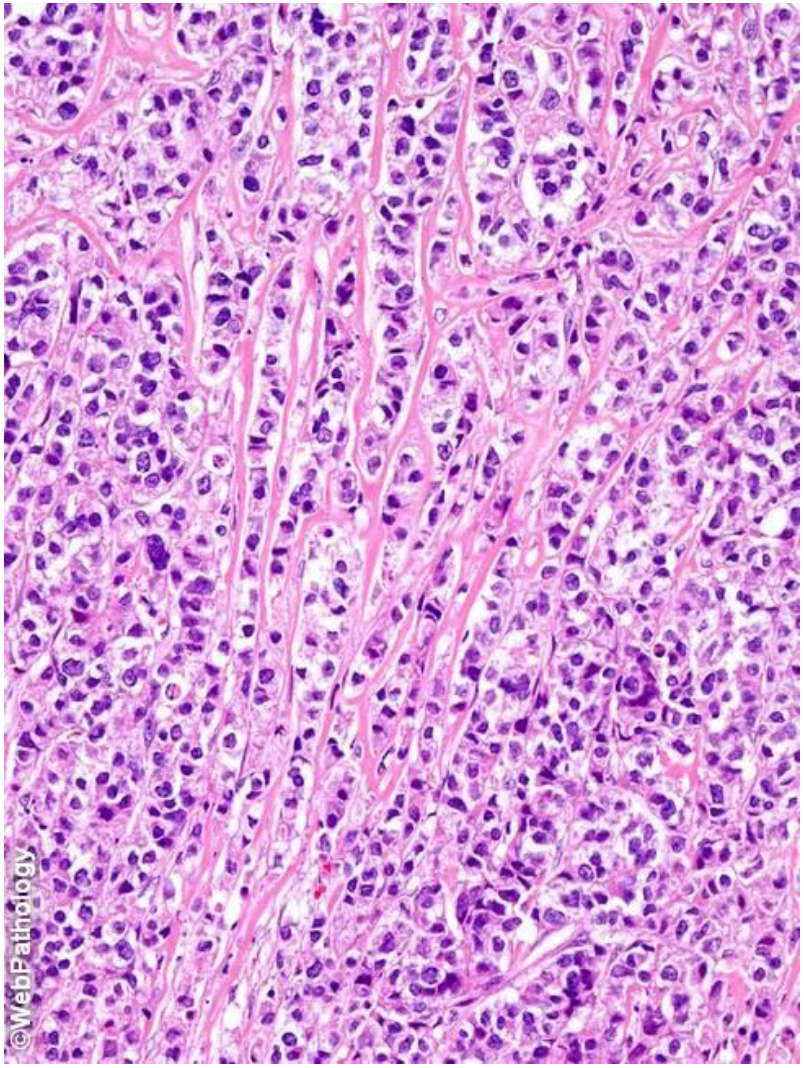

Lobular cells
Lobule
Duct cells
Duct
Areola
Nipple
Collecting ducts
Ducts
Lobules
Fatty connective tissue

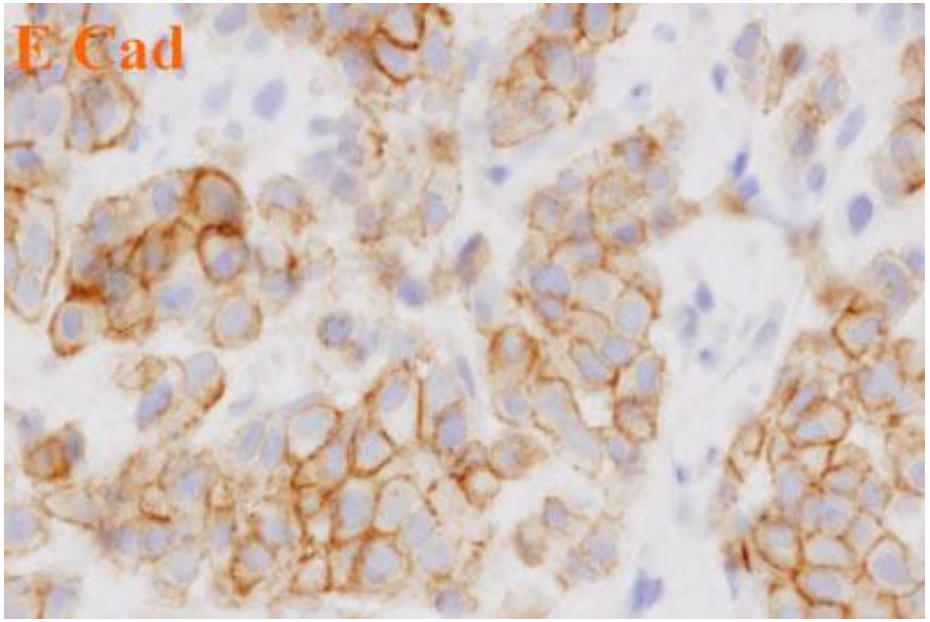

Ducts
Lobule
Connective tissue (stroma)
Adipose tissue



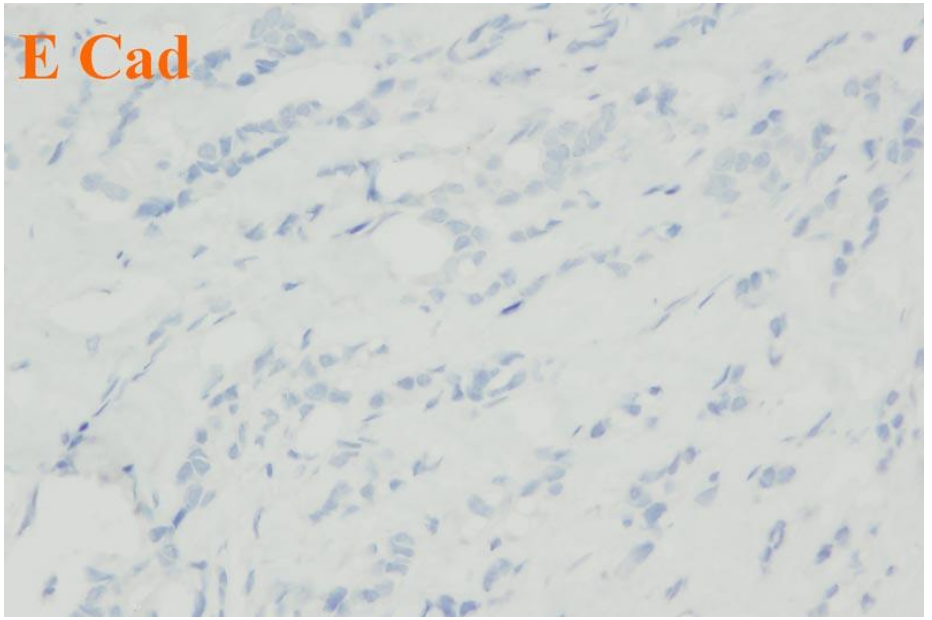
DUCTAL BREAST CARCINOMA



LOBULAR BREAST CARCINOMA



DUCTAL BREAST CARCINOMA

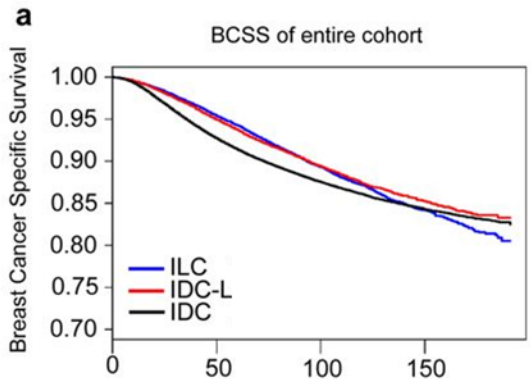


LOBULAR BREAST CARCINOMA

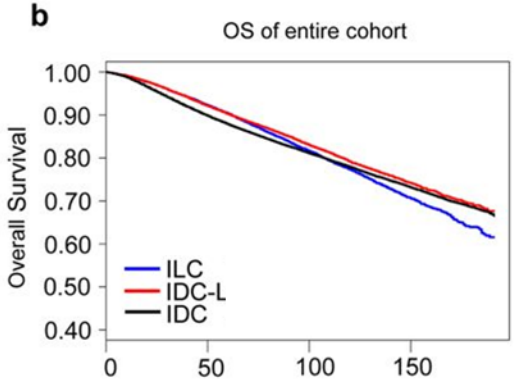
SCIENTIFIC REPORTS

Figure 1

From: Mixed invasive ductal and lobular carcinoma has distinct clinical features and predicts worse prognosis when stratified by estrogen receptor status



No. at risk				
ILC	17503	16010	9782	3019
IDC	172379	153041	94038	28944
IDC-L	19227	17563	11384	3134



No. at risk				
ILC	17503	16010	9782	3019
IDC	172379	153041	94038	28944
IDC-L	19227	17563	11384	3134

Kaplan-Meier curves of breast cancer-specific survival (BCSS) (**a**) and of overall survival (OS) (**b**) according to histological type in all patients. Log-rank tests were compared between IDC-L and IDC or ILC. Abbreviations: IDC-L: invasive ductal carcinoma with lobular features; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; BCSS: breast cancer-specific survival; OS: overall survival.

SCIENTIFIC REPORTS | 7: 10380 | DOI:10.1038/s41598-017-10789-x

NATURE | VOL 406 | 17 AUGUST 2000

letters to nature

Molecular portraits of human breast tumours

Charles M. Perou*†, Therese Sørlie†‡, Michael B. Eisen*, Matt van de Rijn§, Stefanie S. Jeffrey‖, Christian A. Rees*, Jonathan R. Pollack¶, Douglas T. Ross¶, Hilde Johnsen‡, Lars A. Akslen#, Øystein Fluge☆, Alexander Pergamenschikov*, Cheryl Williams*, Shirley X. Zhu§, Per E. Lønning, Anne-Lise Børresen-Dale‡, Patrick O. Brown¶†† & David Botstein***

of every gene in the genome. Here we have characterized variation in gene expression patterns in a set of 65 surgical specimens of human breast tumours from 42 different individuals, using complementary DNA microarrays representing 8,102 human genes. These patterns provided a distinctive molecular portrait

of similarity in their patterns of expression. We focus first on a set of 1,753 genes (about 22% of the 8,102 genes analysed), whose transcripts varied in abundance by at least fourfold from their median abundance in this sample set in at least three of the samples

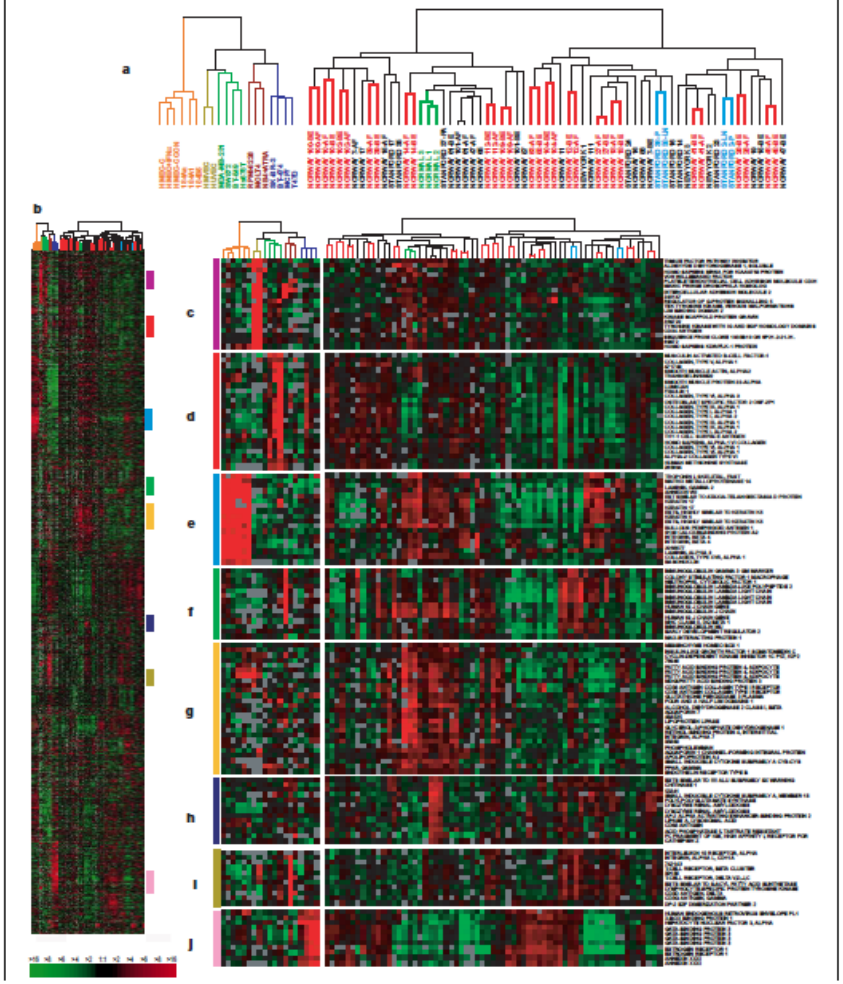
Luminal epithelial/ER gene cluster

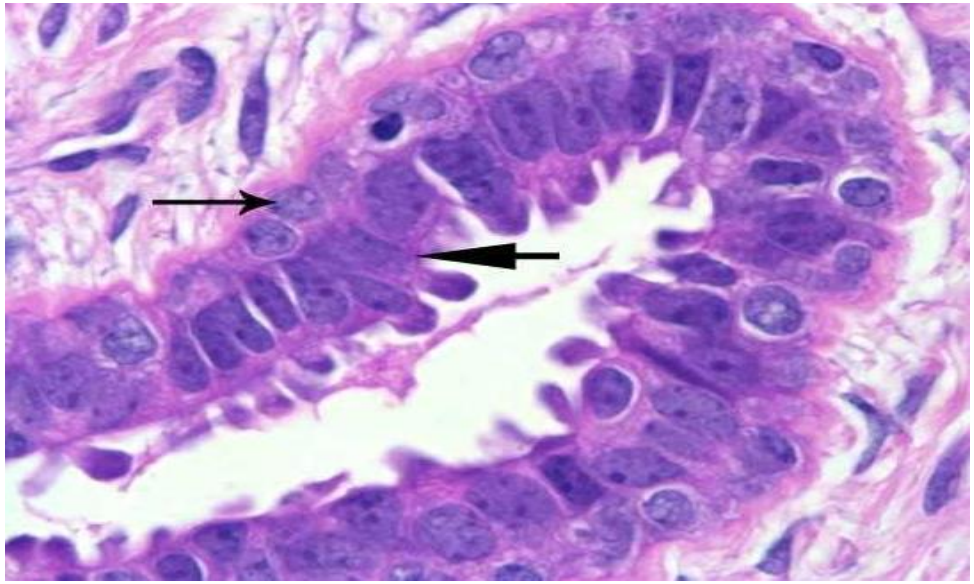
Erb-B2 overexpression cluster

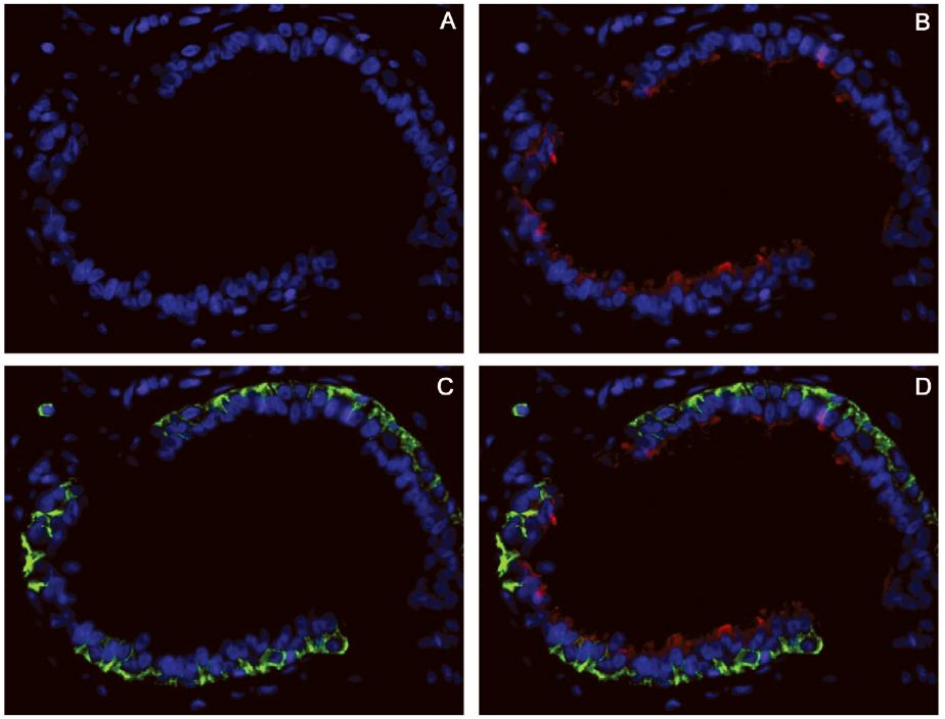
Basal epithelial cell associated cluster

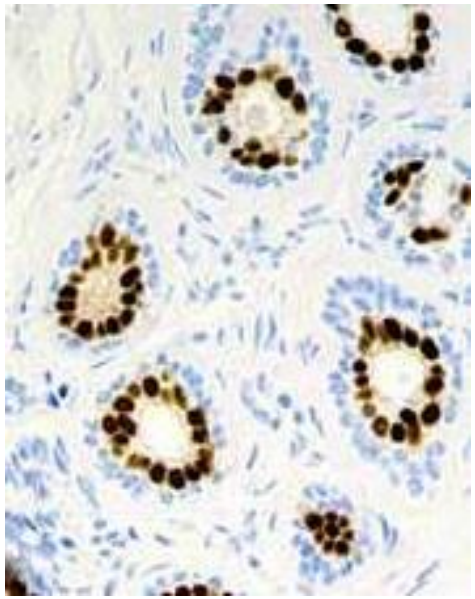
cultured cell lines (see Supplementary Information Table 1); this common 'reference' sample provided an internal standard against which the gene expression of each experimental sample was compared[2,3].

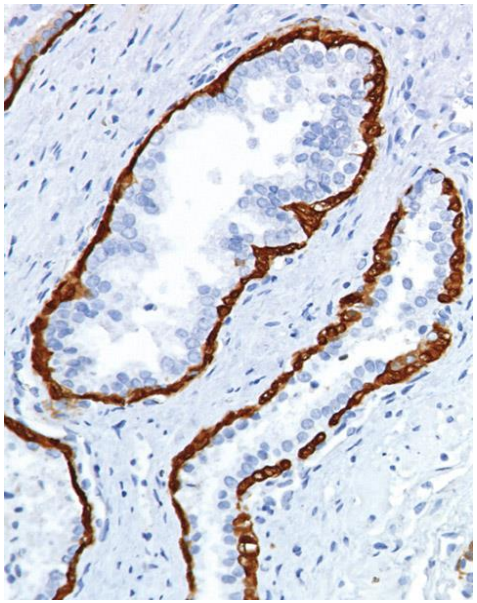
Twenty of the forty breast tumours examined were sampled twice, as part of a larger study on locally advanced breast cancers (T_3/T_4 and/or N_2 tumours; see ref. 4). After an open surgical biopsy to obtain the 'before' sample, each of these patients was treated with doxorubicin for an average of 16 weeks (range 12–23), followed by resection of the remaining tumour. In addition, primary tumours











OPEN ACCESS Freely available online

PLOS ONE

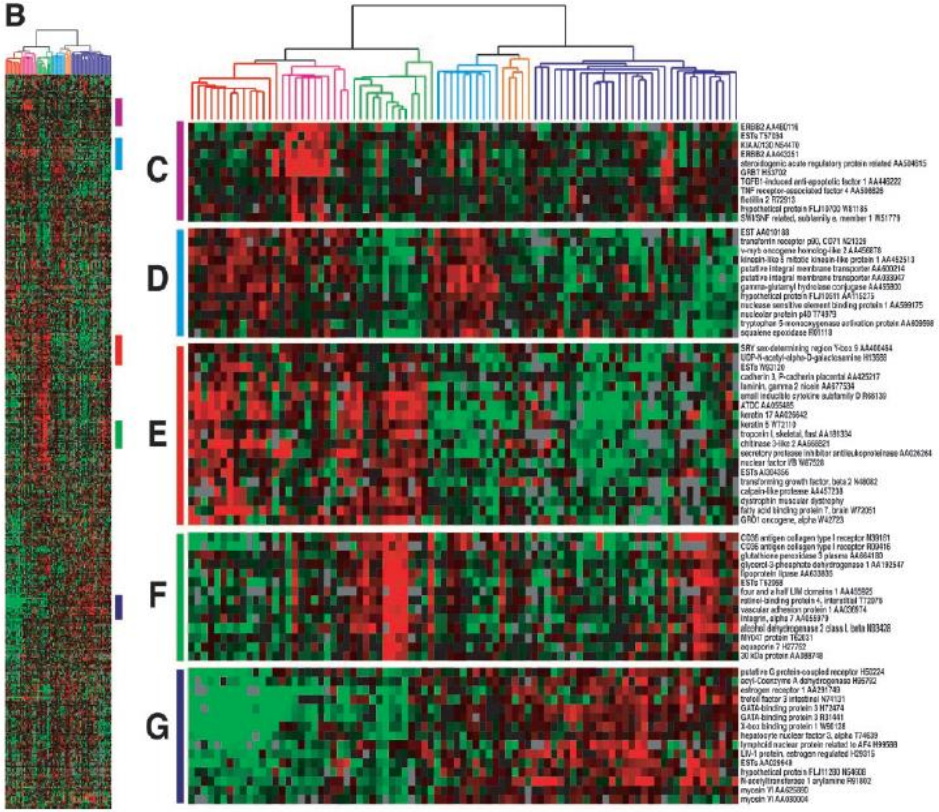
In Situ Identification of CD44+/CD24− Cancer Cells in Primary Human Breast Carcinomas

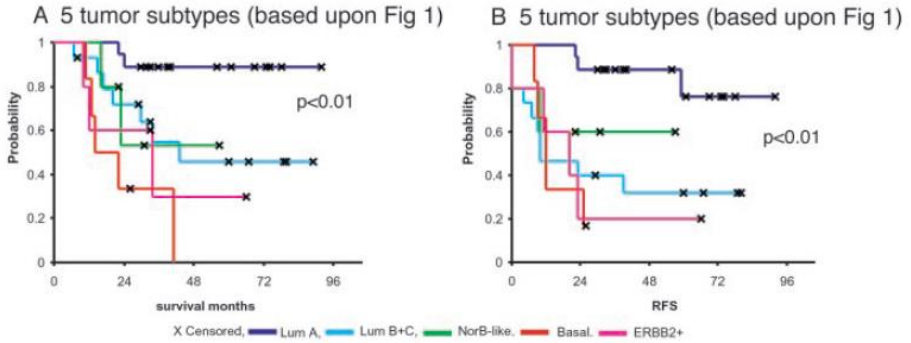
Giuseppe Perrone[1], Laura Maria Gaeta[1], Mariagiovanna Zagami[1,8], Francesca Nasorri[2], Roberto Coppola[3], Domenico Borzomati[3], Francesco Bartolozzi[4], Vittorio Altomare[5], Lucio Trodella[6], Giuseppe Tonini[7], Daniele Santini[7], Andrea Cavani[2], Andrea Onetti Muda[1]*

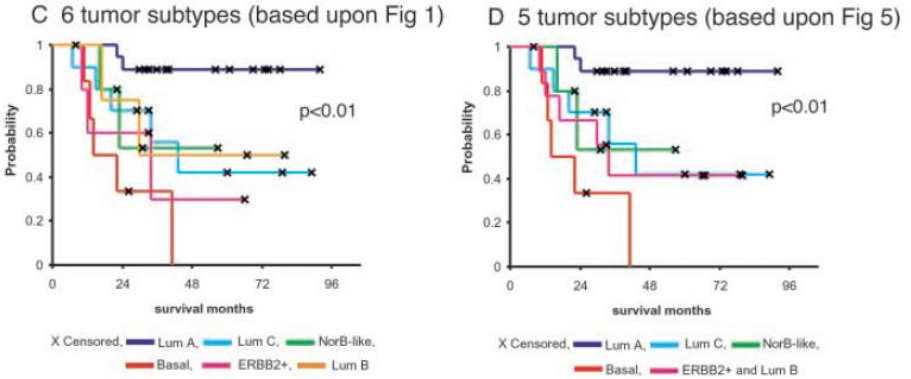
September 2012 | Volume 7 | Issue 9 | e43110

Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications

Therese Sørlie[a,b,c], Charles M. Perou[a,d], Robert Tibshirani[e], Turid Aas[f], Stephanie Geisler[g], Hilde Johnsen[b], Trevor Hastie[e], Michael B. Eisen[h], Matt van de Rijn[i], Stefanie S. Jeffrey[j], Thor Thorsen[k], Hanne Quist[l], John C. Matese[c], Patrick O. Brown[m], David Botstein[c], Per Eystein Lønning[g], and Anne-Lise Børresen-Dale[b,n]







PNAS | September 11, 2001 | vol. 98 | no. 19

VOLUME 27 · NUMBER 8 · MARCH 10 2009

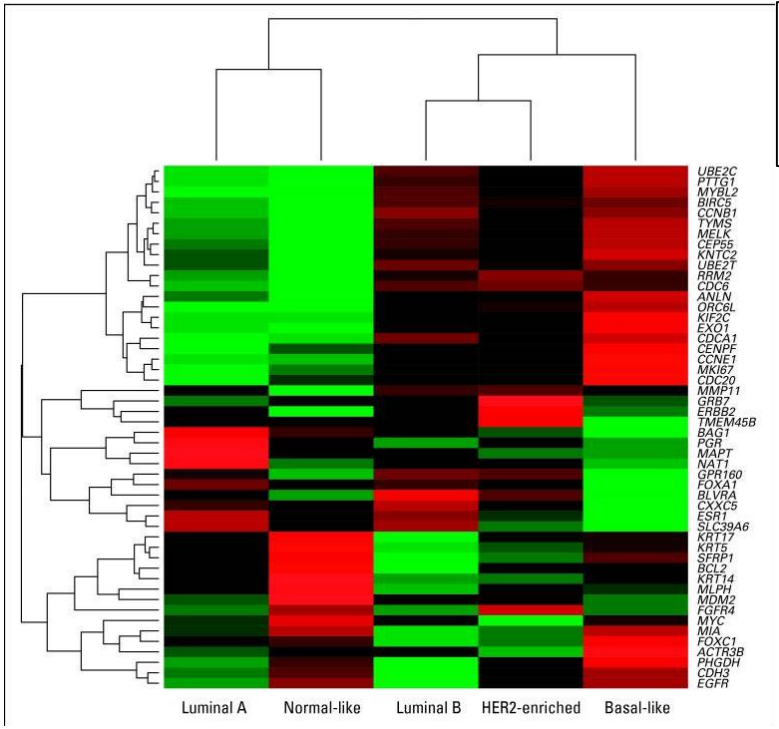
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

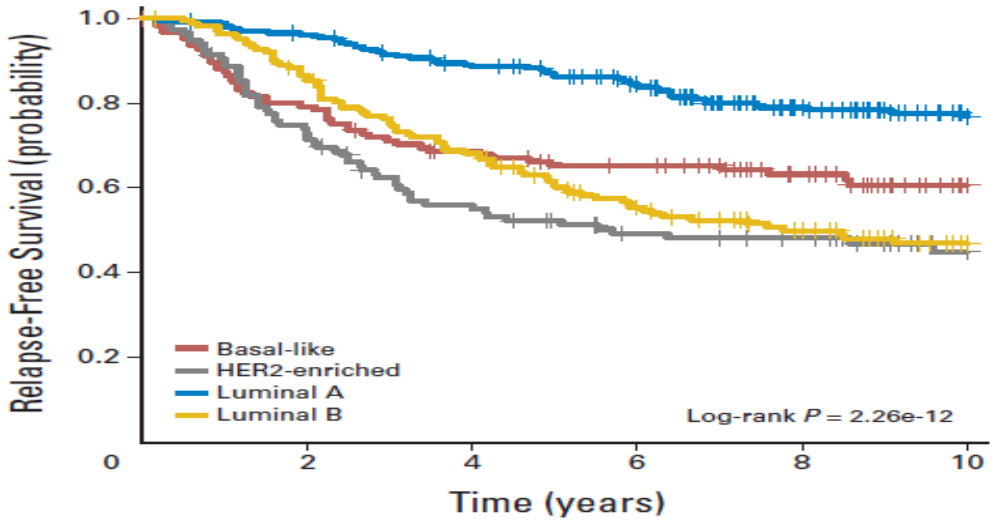
From the Lineberger Comprehensive Cancer Center and Departments of Genetics, Pathology and Laboratory Medicine, and Department of Statistics and Operations Research, Carolina Center for Genome Sciences, University of North Carolina at Chapel Hill, Chapel Hill, NC; Department of Pathology, University of Utah Health Sciences Center; ARUP Institute for Clinical and Experimental Pathology, Salt Lake City, UT; Genetic Pathology Evaluation Centre, Department of Pathology, Vancouver Coastal Health Research

Supervised Risk Predictor of Breast Cancer Based on Intrinsic Subtypes

Joel S. Parker, Michael Mullins, Maggie C.U. Cheang, Samuel Leung, David Voduc, Tammi Vickery, Sherri Davies, Christiane Fauron, Xiaping He, Zhiyuan Hu, John F. Quackenbush, Inge J. Stijleman, Juan Palazzo, J.S. Marron, Andrew B. Nobel, Elaine Mardis, Torsten O. Nielsen, Matthew J. Ellis, Charles M. Perou, and Philip S. Bernard



The 50 gene set was compared for reproducibility of classification across three centroid-based prediction methods: Prediction Analysis of Microarray (PAM),[24] a simple nearest centroid,[6] and Classification of Nearest Centroid.[25]



special article

Annals of Oncology 22: 1736–1747, 2011
doi:10.1093/annonc/mdr304
Published online 27 June 2011

Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011

A. Goldhirsch[1]*, W. C. Wood[2], A. S. Coates[3], R. D. Gelber[4], B. Thürlimann[5], H.-J. Senn[6] & Panel members[†]

[1]International Breast Cancer Study Group, Department of Medicine, European Institute of Oncology, Milan, Italy; [2]Department of Surgery, Emory University School of Medicine, N. E. Atlanta, USA; [3]International Breast Cancer Study Group and University of Sydney, Sydney, Australia; [4]International Breast Cancer Study Group Statistical Center, Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA; [5]Breast Center, Kantonsspital St Gallen, St Gallen; [6]Tumor and Breast Center ZeTuP, St Gallen, Switzerland

Table 2. Surrogate definitions of intrinsic subtypes of breast cancer (4, 7)

Intrinsic Subtype (1)	Clinico-pathologic definition	Notes
Luminal A	**'Luminal A'** ER and/or PgR positive(76) HER2 negative (77) Ki-67 low (<14%)*	This cut-point for Ki-67 labelling index was established by comparison with PAM50 intrinsic subtyping (7). Local quality control of Ki-67 staining is important.
Luminal B**	**'Luminal B (HER2 negative)'** ER and/or PgR positive HER2 negative Ki-67 high	Genes indicative of higher proliferation are markers of poor prognosis in multiple genetic assays (78). If reliable Ki-67 measurement is not available, some alternative assessment of tumor proliferation such as grade may be used to distinguish between 'Luminal A' and 'Luminal B (HER2 negative)'.
	'Luminal B (HER2 positive)' ER and/or PgR positive Any Ki-67 HER2 over-expressed or amplified	Both endocrine and anti-HER2 therapy may be indicated.
Erb-B2 overexpression	**'HER2 positive (non luminal)'** HER2 over-expressed or amplified ER and PgR absent	
'Basal-like'	**'Triple negative (ductal)'** ER and PgR absent HER2 negative	Approximately 80% overlap between 'triple negative' and intrinsic 'basal-like' subtype but 'triple negative' also includes some special histological types such as (typical) medullary and adenoid cystic carcinoma with low risks of distant recurrence. Staining for basal keratins (79) although shown to aid selection of true basal-like tumors, is considered insufficiently reproducible for general use.

*This cut-point is derived from comparison with gene array data as a prognostic factor [7]. Optimal cut-points in Ki-67 labelling index for prediction of efficacy of endocrine or cytotoxic therapy may vary.

**Some cases over-express both luminal and HER2 genes.

Esame Istologico N. 2016-B-00399

Sig.ra [redacted] nata il **30/01/1948**

Regime	Ricoverato	Prelievo del	14/01/2016
Area clinica di provenienza	SENOLOGIA	Accettazione del	15/01/2016
Medico referente	Dott. A. Primavera	Refertazione del	21/01/2016
		Roma, il	28/01/2016

REPERTO MACROSCOPICO

1) Quadrante mammario di cm 7,5 x 6,5 x 4, orientato, sede di neoplasia di cm 1,9 a ridosso del margine profondo.
2) Linfonodo della dimensione massima di cm 1,9, esaminato in sede intraoperatoria ed all'esame istologico definitivo fin ad esaurimento del blocchetto con sezioni ogni 200 micron.
3) Frammento di parenchima mammario di cm 2,5 x 1,5 x 0,5.
Eseguito da: Dott.ssa G. Nicolo'

DIAGNOSI

1) Carcinoma infiltrante NST sec. WHO 2012 (duttale NOS) G2 sec. Nottingham (score 7: 2 tubuli+ 2 pleomorfismo+ 3 mitosi) di 1,9 cm (misura istologica) con microcalcificazioni; scarso l'infiltrato stromale mononucleato. E' presente componente peritumorale di carcinoma duttale in situ di grado intermedio ed alto sec. WHO 2012, talora con necrosi di tipo comedonico, in percentuale pari al 20% della neoplasia.
La noplasia giunge a ridosso del margine di resezione profondo.
Indenni i restanti margini.
Non si documentano angioinvasione ed infiltrazione perineurale peritumorale.
Restante parenchima sede di alterazioni fibrocistiche con focolai di adenosi e metaplasia apocrina.
2) Linfonodo esente da patologia neoplastica e sede di linfadenite reattiva.
3) Parenchima fibroadiposo e frammento di tessuto muscolare esenti da patologia neoplastica

Positiva la determinazione immunoistochimica dei recettori per estrogeni (anticorpo Dako clone EP1) nel 90% delle cellule neoplastiche, e positiva per progesterone (anticorpo Dako clone PgR 636) nel 90% delle cellule neoplastiche.
La frazione proliferante (Ki67) (anticorpo murino Dako clone Mib -1) è pari al 40% (conta effettuata manualmente su tre campi periferici comprendendo uno con più elevato indice di proliferazione).
Determinazione immunoistochimica c-erbB2 (Herceptest DAKO): colorazione di membrana incompleta debole nel 20% delle cellule neoplastiche, score test: 1+ negativo sec. ASCO-CAP 2013.
Il centro partecipa al controllo di qualità interregionale per la determinazione dello stato di Her2.

Age: 68 aa

T: 1,9 cm;
N: 0;
G2

ER: 90%;
PGR: 90%;
Ki67: 40%;
Her2: 1+

special article

Annals of Oncology 22: 1736–1747, 2011
doi:10.1093/annonc/mdr304
Published online 27 June 2011

Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011

A. Goldhirsch[1]*, W. C. Wood[2], A. S. Coates[3], R. D. Gelber[4], B. Thürlimann[5], H.-J. Senn[6] & Panel members[†]

[1]International Breast Cancer Study Group, Department of Medicine, European Institute of Oncology, Milan, Italy; [2]Department of Surgery, Emory University School of Medicine, N. E. Atlanta, USA; [3]International Breast Cancer Study Group and University of Sydney, Sydney, Australia; [4]International Breast Cancer Study Group Statistical Center, Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA; [5]Breast Center, Kantonsspital St Gallen, St Gallen; [6]Tumor and Breast Center ZeTuP, St Gallen, Switzerland

Table 3. Systemic treatment recommendations for subtypes

'Subtype'	Type of therapy	Notes on therapy
'Luminal A'	Endocrine therapy alone	Few require cytotoxics (e.g. high nodal status or other indicator of risk: see text).
'Luminal B (HER2 negative)'	Endocrine ± cytotoxic therapy	Inclusion and type of cytotoxics may depend on level of endocrine receptor expression, perceived risk and patient preference.
'Luminal B (HER2 positive)'	Cytotoxics + anti-HER2 + endocrine therapy	No data are available to support the omission of cytotoxics in this group.
'HER2 positive (non luminal)'	Cytotoxics + anti-HER2	Patients at very low risk (e.g. pT1a and node negative) may be observed without systemic adjuvant treatment.
'Triple negative (ductal)'	Cytotoxics	
'Special histological types'*		
A. Endocrine responsive	Endocrine therapy	
B. Endocrine nonresponsive	Cytotoxics	Medullary and adenoid cystic carcinomas may not require any adjuvant cytotoxics (if node negative).

*Special histological types: Endocrine responsive (cribriform, tubular, and mucinous); Endocrine nonresponsive (apocrine, medullary, adenoid cystic and metaplastic).

Annals of Oncology 26: 1533–1546, 2015
doi:10.1093/annonc/mdv221
Published online 4 May 2015

Tailoring therapies—improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015

A. S. Coates[1], E. P. Winer[2], A. Goldhirsch[3*], R. D. Gelber[4], M. Gnant[5], M. Piccart-Gebhart[6], B. Thürlimann[7], H.-J. Senn[8] & Panel Members[†]

[1]International Breast Cancer Study Group, University of Sydney, Sydney, Australia; [2]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA; [3]International Breast Cancer Study Group, Program of Breast Health (Senology), European Institute of Oncology, Milan, Italy; [4]International Breast Cancer Study Group Statistical Center, Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA; [5]Department of Surgery and Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; [6]Internal Medicine/Oncology, Institut Jules Bordet, Brussels, Belgium; [7]Breast Center, Kantonsspital St Gallen, St Gallen; [8]Tumor and Breast Center ZeTuP, St Gallen, Switzerland

Received 27 April 2015; accepted 28 April 2015

breast cancer subtypes

Extensive genomic analysis of breast cancers discloses four coherent groups [13], similar to the intrinsic subtypes defined by gene expression profiling [14]. Subtypes can be defined by multiparameter molecular tests such as the PAM-50 [15] or MammaPrint/BluePrint [16]. However, in clinical practice, the key question is not the separation of the molecularly defined intrinsic subtypes, but the discrimination between patients who will or will not benefit from particular therapies. Several of the multiparameter molecular markers have been used for this purpose [17, 18]. Because in much of the world, such tests may not be available for logistic or financial reasons, surrogate approaches have been developed using more widely available immunohistochemical (IHC) tests for estrogen receptor, progesterone receptor together with IHC or *in situ* hybridization tests for HER2 overexpression or amplification. Ki-67 is used as an alternative marker of proliferation albeit with lesser analytical validity than molecular testing [19, 20].

What does it mean IHC positive?

%?

Table 2. Treatment-oriented classification of subgroups of breast cancer

Clinical grouping	Notes
Triple-negative	Negative ER, PgR, and HER2
Hormone receptor-negative and HER2-positive	ASCO/CAP guidelines
Hormone receptor-positive and HER2-positive	ASCO/CAP guidelines
Hormone receptor-positive and HER2-negative luminal disease as a spectrum:	ER and/or PgR positive ≥1%[a]
High receptor, low proliferation, low tumor burden (luminal A-like)	Multiparameter molecular marker 'favorable prognosis' if available. High ER/PgR and clearly low Ki-67[b]. Low or absent nodal involvement (N 0–3), smaller T size (T1 T2).
Intermediate	Multiparameter molecular marker 'intermediate' if available[c]. Uncertainty persists about degree of risk and responsiveness to endocrine and cytotoxic therapies.
Low receptor, high proliferation, high tumor burden (luminal B-like)	Multiparameter molecular marker 'unfavorable prognosis' if available. Lower ER/PgR with clearly high Ki-67[b]. More extensive nodal involvement, histological grade 3, extensive lymphovascular invasion, larger T size (T3).

[a]ER values between 1% and 9% were considered equivocal. Thus, endocrine therapy alone cannot be relied upon for patients with these values.
[b]Ki-67 scores should be interpreted in the light of local laboratory values: as an example, if a laboratory has a median Ki-67 score in receptor-positive disease of 20%, values of 30% or above could be considered clearly high; those of 10% or less clearly low.
[c]Not all multiparameter molecular marker tests report an intermediate score.

St. Gallen Consensus Conferences

	ER	PGR	HER2	Ki67
2009	% Any	No data	> 30%	No data
2011	% Any	% Any	> 30%	< 14% (low)
2013	>1%	>20%	> 10%	< 20% (low); >20% (high)
2015	>1% (0-9% ?)	>1%	> 10%	<10% (low); >30% (high); 10-30% ?
2017	>1%	>1%	Sec. ASCO/CAP	Clearly low vs Clearly high
2019	>1% (0-9% ?)	>1%	Sec. ASCO/CAP	?

Luminal A or Luminal B? / Chemotherapy yes or Chemotherapy no?

How IHC is performed?

NordiQC

Assessment Run B27 2019

HER2 IHC

Table 1. Assessment marks for **IHC assays and antibodies run B27, HER2 IHC**

FDA approved HER2 assays	n	Vendor	Optimal	Good	Borderline	Poor	Suff.[1]	Suff. OPS[2]
PATHWAY® rmAb clone **4B5, 790-2991**	191	Ventana/Roche	177	4	2	8	95%	95%
PATHWAY® rmAb clone **4B5, 790-2991**[4]	2	Ventana/Roche	1	-	-	1	-	-
rmAb clone **4B5, 790-4493**	14	Ventana/Roche	12	1	-	1	93%	92%
HercepTest™ **SK001**	24	Dako/Agilent	21	-	1	2	88%	87%
HercepTest™ **SK001**[4]	4	Dako/Agilent	3	1	-	-	-	-
Oracle™ mAb clone **CB11, TA9145**	9	Leica	7	-	-	2	78%	-
Oracle™ mAb clone **CB11, TA9145**[4]	1	Leica	-	-	-	1	-	-
Antibodies[3] for laboratory developed HER2 assays, conc. antibody		Vendor	Optimal	Good	Borderline	Poor	Suff.[1]	Suff. OPS[2]
rmAb clone **BSR44**	1	Nordic Biosite	1	-	-	-	-	-
mAb clone **CB11**	5 1	Leica/Novocastra Biogenex	2	2	-	2	67%	-
mAb clone **C1F7**	1	Celnovte	1	-	-	-	-	-
rmAB clone **EP1045Y**	1	ThermoFisher Scientific	1	-	-	-	-	-
pAb, A0485	44	Dako/Agilent	33	1	2	8	77%	77%
rmAb clone **SP3**	9 6 3 1	ThermoFisher Scientific Cell Marque Zytomed Spring Biosystems	5	-	1	13	26%	50%
rmAb clone **EP3**	3	Cell Marque Diagnostic BioSystems	1	1	-	1	-	-
Antibodies for laboratory developed HER2 assays, RTU		Vendor	Optimal	Good	Borderline	Poor	Suff.[1]	Suff. OPS[2]
mAb clone **CB11, PA0983**	1	Leica	-	-	-	1	-	-
Ab clone **MXR001, RMA-0701**	1	Maixin	1	-	-	-	-	-
rmAb clone **EP3, 237R-17/18**	1	Cell Marque	1	-	-	-	-	-
rmAb clone **SP3, MAD-000308QD**	1	Master Diagnostica	1	-	-	-	-	-
Total	324		268	10	6	40	-	-
Proportion			83%	3%	2%	12%	86%	-

1) Proportion of sufficient stains (optimal or good),
2) Proportion of sufficient stains with optimal protocol settings only, see below.
3) mAb: mouse monoclonal antibody, rmAb: rabbit monoclonal antibody, pAb: polyclonal antibody.
4) RTU system used on a different platform than it was developed for.

NordiQC

Assessment Run B26 2018

Progesteron receptor (PR)

Table 1. **Antibodies and assessment marks for PR, run B26**

Concentrated antibodies	n	Vendor	Optimal	Good	Borderline	Poor	Suff.[1]	Suff. OPS[2]
mAb clone **16**	33 1 1	Leica/Novocastra Biocare Vector	22	6	4	3	82%	82%
mAb clone cocktail **16 + SAN27**	4	Leica/Novocastra	-	4	-	-	-	-
mAb clone **1A6**	1	Leica/Novocastra	-	1	-	-	-	-
mAb clone **PgR 636**	19	Dako Agilent	14	4	1	-	95%	100%
mAb clone **PgR 1294**	10	Dako Agilent	7	2	1	-	90%	89%
rmAb clone **SP2**	3 1	Thermo Scientific Diagnostic BioSystems	2	1	-	1	-	-
rmAb clone **SP42**	2 1 1	Zytomed Spring Biosystems Cell Marque	2	1	1	-	-	-
rmAb clone **Y85**	1	Cell Marque	-	-	1	-	-	-
rmAb clone **P21-S**	1	DB Biotech	-	-	-	1	-	-
Ready-To-Use antibodies								
rmAb clone **Y85**	1	Sakura Finetek	1	-	-	-	-	-
mAb clone **16 PA0312**	11	Leica/Novocastra	9	2	-	-	100%	100%
mAb clone **16 MAD-000670QD**	1	Master Diagnostica	-	-	1	-	-	-
mAb **PgR 636 IR/IS068**	35	Dako Agilent	29	2	1	3	89%	97%
mAb **PgR 1294 GA090**	38	Dako Agilent	23	11	3	1	89%	89%
mAb clone **PgR 1294 K4071/SK310**	1	Dako Agilent	1	-	-	-	-	-
rmAb clone **1E2 790-2223/4296**	180	Ventana	118	31	27	4	83%	83%
rmAb clone **SP2 Kit-0013**	2	Maixin	1	1	-	-	-	-
Total	348		229	66	40	13	-	
Proportion			66%	19%	11%	4%	85%	

1) Proportion of sufficient stains (optimal or good).
2) Proportion of sufficient stains with optimal protocol settings only, see below.

NordiQC

Assessment Run B26 2018

Estrogen receptor (ER)

Table 1. **Antibodies and assessment marks for ER, B26**

Concentrated antibodies	n	Vendor	Optimal	Good	Borderline	Poor	Suff.[1]	Suff. OPS[2]
mAb clone **6F11**	16	Leica/Novocastra	2	5	2	7	44%	100%
rmAb clone **EP1**	12	Dako/Agilent	2	4	4	2	50%	60%
rmAb clone **SP1**	20 6 2 1 1	Thermo Scientific Cell Marque Spring Bioscience Abcam Diagnostic Biosystems	14	7	4	5	70%	95%
rmAb clone **S21-V**	1	DB Biotech	-	-	-	1	-	-
mAb clone **1D5**	1	Biocare Medical	-	-	-	1	-	-
Ready-To-Use antibodies								
mAb clone **1D5 IR/IS657**	1	Dako/Agilent	-	-	-	1	-	-
mAb clones **1D5 + ER-2-123 SK310**	1	Dako/Agilent	-	-	-	1	-	-
mAb clone **6F11 PA0009/PA0151**	11	Leica	1	1	2	7	18%	-
rmAb **EP1 IR/IS084**	32	Dako/Agilent	2	7	13	10	28%	-
rmAb **EP1 IR/IS084**[3]	9	Dako/Agilent	2	-	5	2	22%	-
rmAb **EP1 GA084**	33	Dako/Agilent	4	18	6	5	67%	69%
rmAb **EP1 GA084**[3]	2	Dako/Agilent	1	1	-	-	-	-
rmAb clone **SP1 790-4324/5**	193	Ventana/Roche	75	91	21	6	86%	85%
rmAb clone **SP1 790-4324/5**[3]	1	Ventana/Roche	-	1	-	-	-	-
rmAb clone **SP1 249R-1**	4	Cell Marque	2	1	-	1	-	-
rmAb clone **SP1 KIT-0012**	2	Maixin	1	-	-	1	-	-
rmAb **SP1 M3011**	1	Spring Biosystems	-	-	-	1	-	-
rmAb clone **SP1 MAD-000306QD**	1	Master Diagnostica	-	-	1	-	-	-
rmAb clone **SP1 RM-9101-R7**	3	Thermo Scientific	2	1	-	-	-	-
Total	354		108	137	58	51	-	
Proportion			31%	39%	16%	14%	70%	

1) Proportion of sufficient stains (optimal or good).
2) Proportion of sufficient stains with optimal protocol settings only, see below.
3) RTU system used on a different platform than it was developed for.

Annals of Oncology 26: 1533–1546, 2015
doi:10.1093/annonc/mdv221
Published online 4 May 2015

Tailoring therapies—improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015

A. S. Coates[1], E. P. Winer[2], A. Goldhirsch[3*], R. D. Gelber[4], M. Gnant[5], M. Piccart-Gebhart[6], B. Thürlimann[7], H.-J. Senn[8] & Panel Members[†]

[1]International Breast Cancer Study Group, University of Sydney, Sydney, Australia; [2]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA; [3]International Breast Cancer Study Group, Program of Breast Health (Senology), European Institute of Oncology, Milan, Italy; [4]International Breast Cancer Study Group Statistical Center, Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, USA; [5]Department of Surgery and Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria; [6]Internal Medicine/Oncology, Institut Jules Bordet, Brussels, Belgium; [7]Breast Center, Kantonsspital St Gallen, St Gallen; [8]Tumor and Breast Center ZeTuP, St Gallen, Switzerland

Received 27 April 2015; accepted 28 April 2015

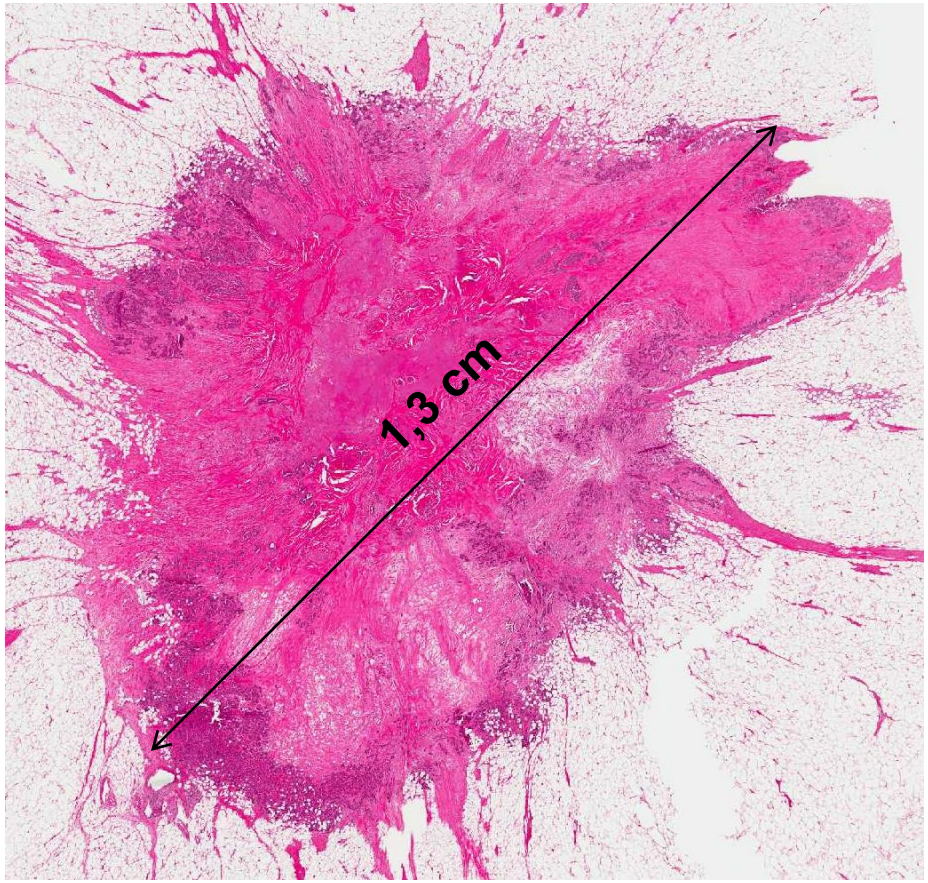
has proved controversial. There can be little doubt that Ki-67 scores carry robust prognostic information [24], and that high values predict the benefit of addition of cytotoxic chemotherapy [25], but definition of a single useful cut point has proved elusive both because Ki-67 displays a continuous distribution [26], and as a result of analytic and preanalytic barriers to standardized assessment [27]. Other news presented at the meeting is summarized in Table 1.

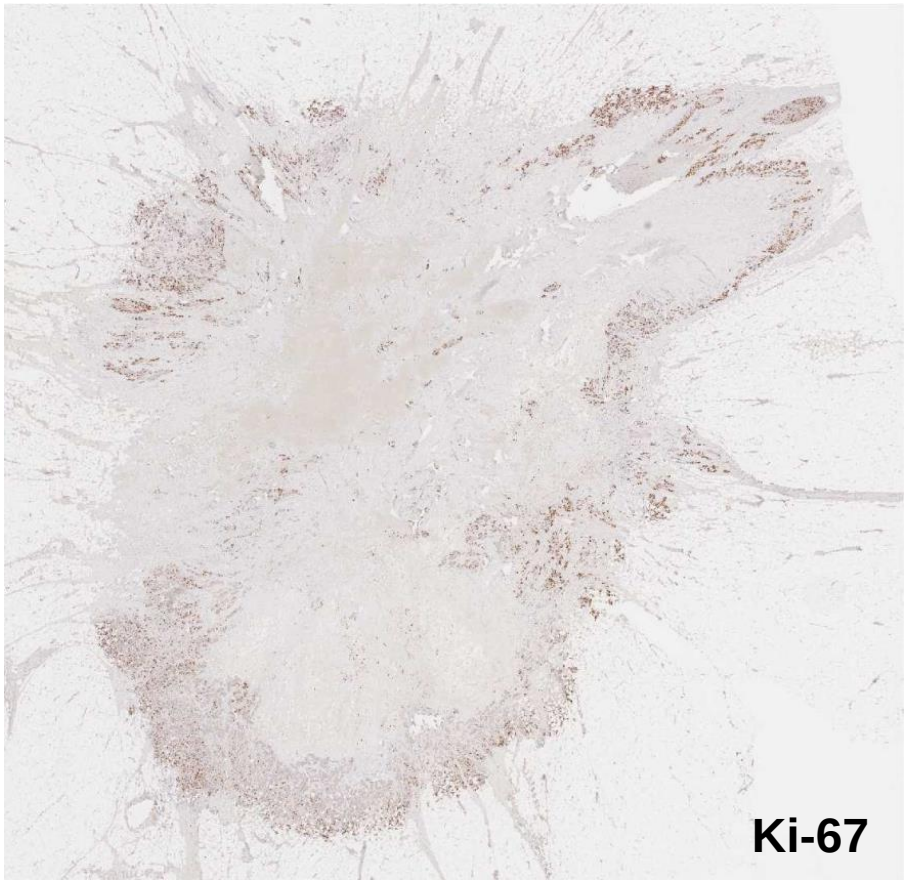
Assessment of Ki67 in Breast Cancer: Recommendations from the International Ki67 in Breast Cancer Working Group

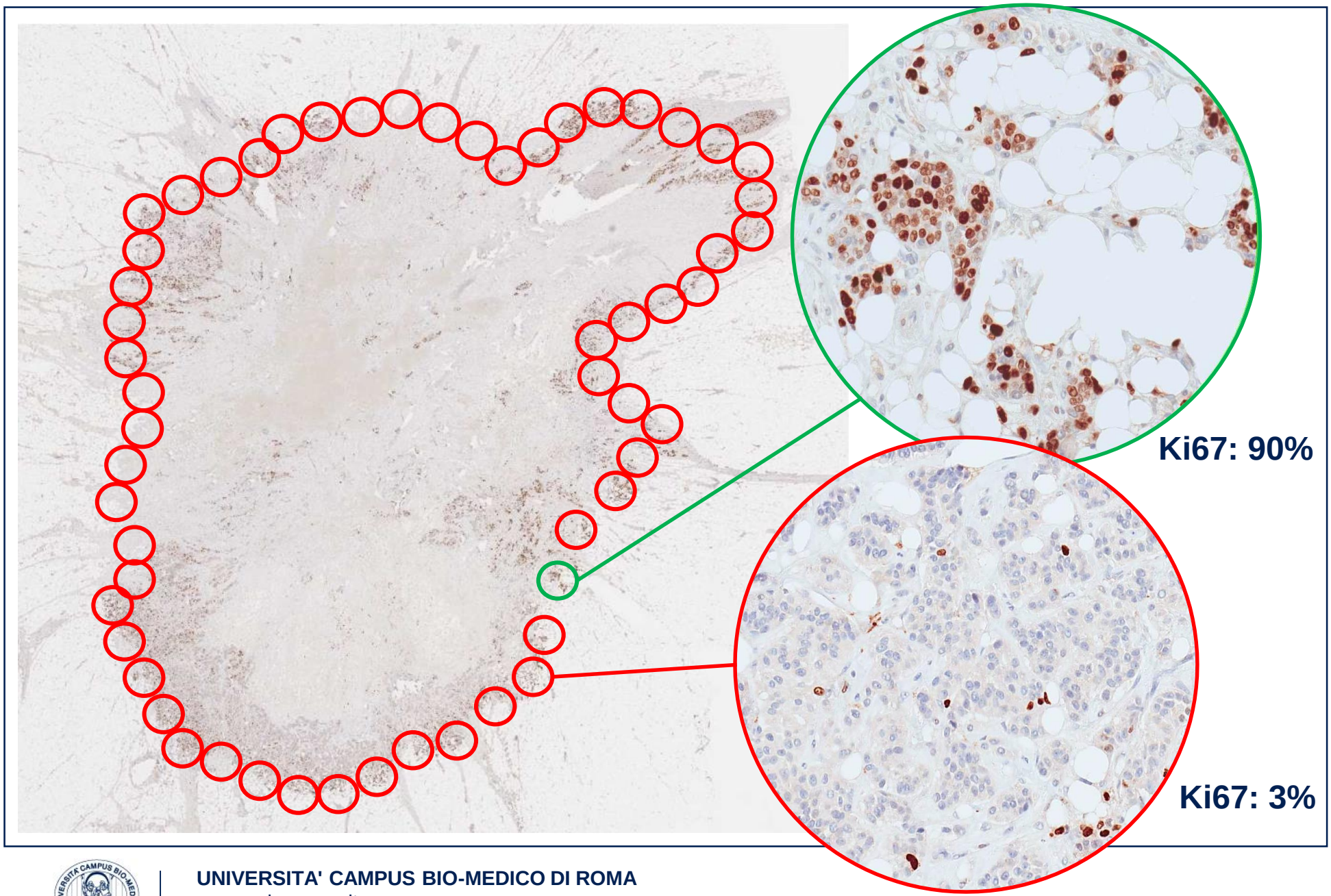
Mitch Dowsett, Torsten O. Nielsen, Roger A'Hern, John Bartlett, R. Charles Coombes, Jack Cuzick, Matthew Ellis, N. Lynn Henry, Judith C. Hugh, Tracy Lively, Lisa McShane, Soon Paik, Frederique Penault-Llorca, Ljudmila Prudkin, Meredith Regan, Janine Salter, Christos Sotiriou, Ian E. Smith, Giuseppe Viale, Jo Anne Zujewski, Daniel F. Hayes

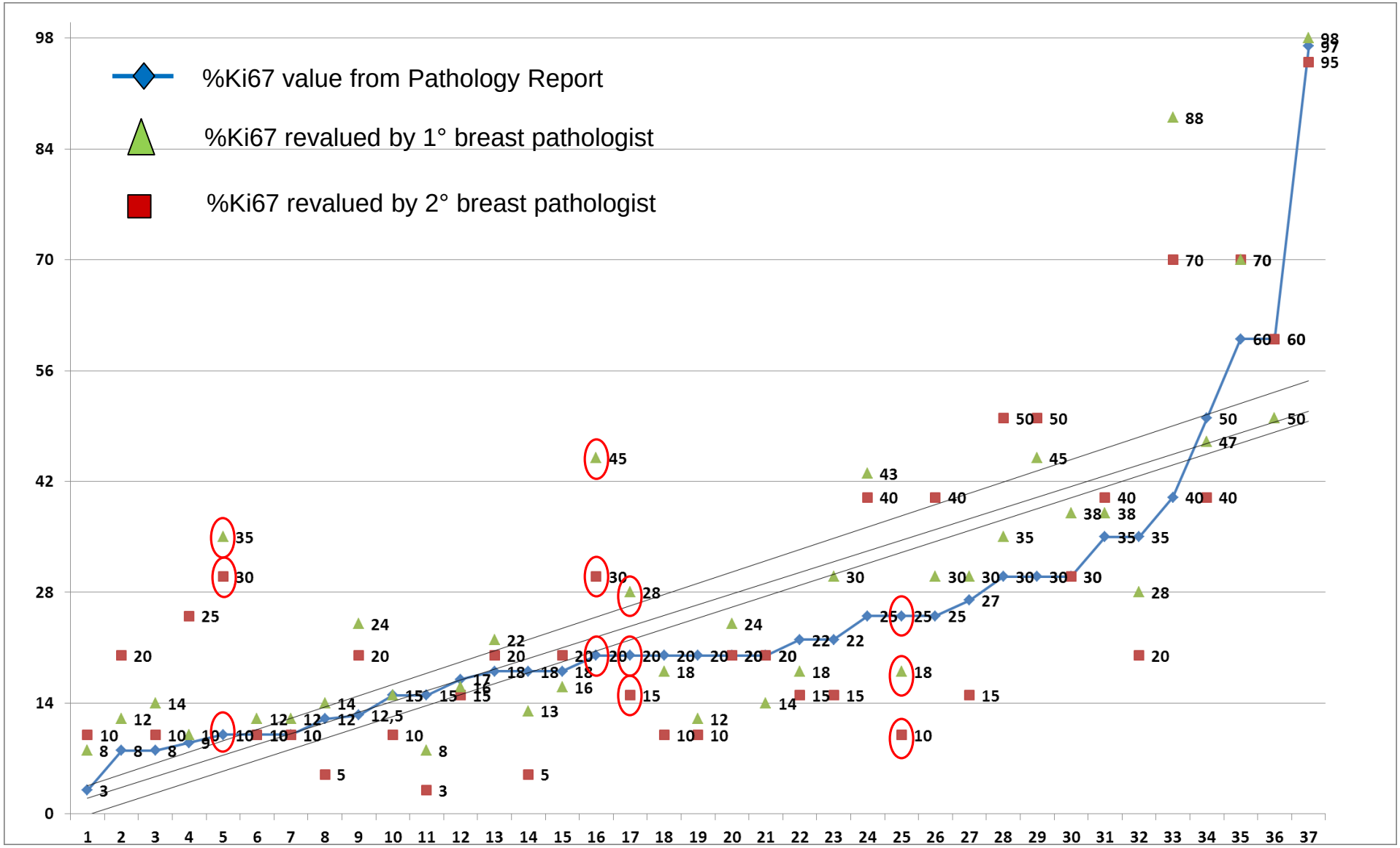
- In full sections, at least three high-power (×40 objective) fields should be selected to represent the spectrum of staining seen on initial overview of the whole section.
- For the purpose of prognostic evaluation, the invasive edge of the tumor should be scored.
- If pharmacodynamic comparisons must be between core cuts and sections from the excision, assessment of the latter should be across the whole tumor.
- If there are clear hot spots, data from these should be included in the overall score.
- Only nuclear staining is considered positive. Staining intensity is not relevant.
- Scoring should involve the counting of at least 500 malignant invasive cells (and preferably at least 1000 cells) unless a protocol clearly states reasons for fewer being acceptable.
- Image analysis methods for Ki67 remain to be proven for use in clinical practice.

J Natl Cancer Inst 2011;103:1656–1664


1,3 cm


Ki-67


Ki67: 90%
Ki67: 3%


%Ki67 value from Pathology Report
%Ki67 revalued by 1° breast pathologist
%Ki67 revalued by 2° breast pathologist
98
84
70
56
42
28
14
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37

J Natl Cancer Inst;2013;105:1897–1906

An International Ki67 Reproducibility Study

Mei-Yin C. Polley, Samuel C. Y. Leung, Lisa M. McShane, Dongxia Gao, Judith C. Hugh, Mauro G. Mastropasqua, Giuseppe Viale, Lila A. Zabaglo, Frédérique Penault-Llorca, John M.S. Bartlett, Allen M. Gown, W. Fraser Symmans, Tammy Piper, Erika Mehl, Rebecca A. Enos, Daniel F. Hayes, Mitch Dowsett, Torsten O. Nielsen, on behalf of the International Ki67 in Breast Cancer Working Group of the Breast International Group and North American Breast Cancer Group

Manuscript received April 2, 2013; revised September 3, 2013; accepted September 16, 2013.

Correspondence to: Torsten Nielsen, MD, PhD, FRCPC, University of British Columbia Pathology and Laboratory Medicine, Anatomical Pathology, JP 1401, Vancouver Hospital & Health Sciences Centre, 855 W 12th Ave, Vancouver, BC V5Z 1M9, Canada (e-mail: torsten@mail.ubc.ca).

Cancer Science | Cancer Sci | November 2013 | vol. 104 | no. 11 | 1539–1543
The official journal of the Japanese Cancer Association

Interobserver concordance of Ki67 labeling index in breast cancer: Japan Breast Cancer Research Group Ki67 Ring Study

Yoshiki Mikami,[1,10] Takayuki Ueno,[2,10] Kenichi Yoshimura,[3] Hitoshi Tsuda,[4] Masafumi Kurosumi,[5] Shinobu Masuda,[6] Rie Horii,[7] Masakazu Toi[2] and Hironobu Sasano[8,9]

Departments of [1]Diagnostic Pathology, [2]Breast Surgery, Kyoto University Hospital, Kyoto; [3]Translational Research Center, Kyoto University Hospital, Kyoto; [4]Diagnostic Pathology Section, Clinical Laboratory Division, National Cancer Center Hospital, Tokyo; [5]Department of Pathology, Saitama Cancer Center, Saitama; [6]Department of Pathology, Nihon University School of Medicine, Tokyo; [7]Department of Pathology, The Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo; [8]Department of Pathology, Tohoku University School of Medicine, Sendai, Japan

PLOS ONE | DOI:10.1371/journal.pone.0125131 May 1, 2015

An Interobserver Reproducibility Analysis of Ki67 Visual Assessment in Breast Cancer

Ruohong Shui[1,2], Baohua Yu[1,2], Rui Bi[1,2], Fei Yang[1,2], Wentao Yang[1,2]*

1 Department of Pathology, Fudan University Shanghai Cancer Center, Fudan University, Shanghai 200032, China, **2** Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China

* yangwt2000@163.com

MODERN PATHOLOGY (2015) 28, 778–786

An international study to increase concordance in Ki67 scoring

Mei-Yin C Polley[1], Samuel CY Leung[2], Dongxia Gao[2], Mauro G Mastropasqua[3], Lila A Zabaglo[4], John MS Bartlett[5], Lisa M McShane[1], Rebecca A Enos[6], Sunil S Badve[7], Anita L Bane[8], Signe Borgquist[9], Susan Fineberg[10], Ming-Gang Lin[11], Allen M Gown[12], Dorthe Grabau[9], Carolina Gutierrez[13], Judith C Hugh[14], Takuya Moriya[15], Yasuyo Ohi[16], C Kent Osborne[13], Frédérique M Penault-Llorca[17], Tammy Piper[18], Peggy L Porter[11], Takashi Sakatani[19], Roberto Salgado[20], Jane Starczynski[21], Anne-Vibeke Lænkholm[22], Giuseppe Viale[23], Mitch Dowsett[24], Daniel F Hayes[25], Torsten O Nielsen[2]
on behalf of the International Ki67 in Breast Cancer Working Group of the Breast International Group and North American Breast Cancer Group (BIG-NABCG)

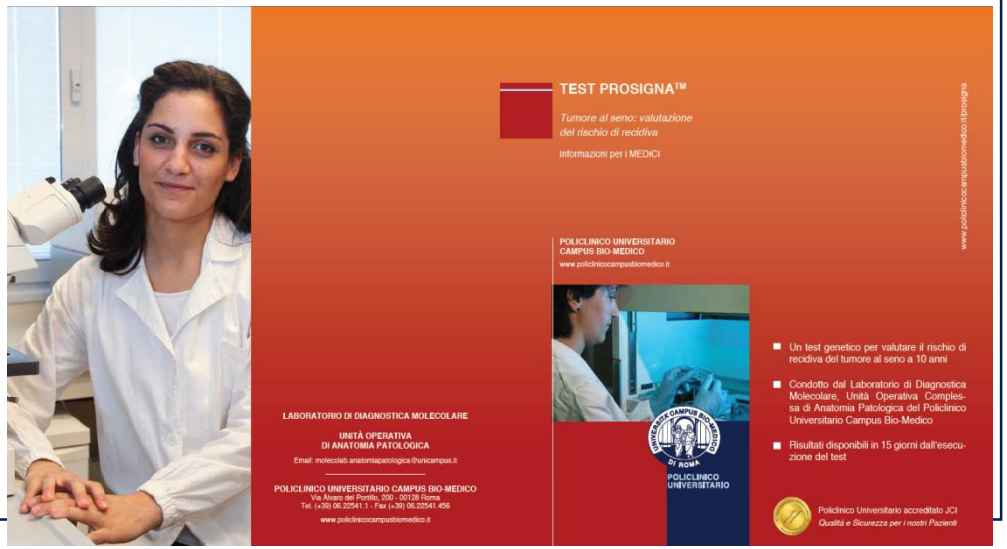
POLICLINICO UNIVERSITARIO CAMPUS BIO-MEDICO

lunedì, 09 giu 2014

Tumore al seno: al Campus Bio-Medico test molecolare per personalizzare la terapia

Una donna su quattro, in post-menopausa e che ha subito un intervento chirurgico di asportazione di tumore al seno, potrebbe evitare la chemioterapia. A prevederlo sarebbe il test Prosigna™, un esame genetico da effettuare sul campione di tessuto asport...

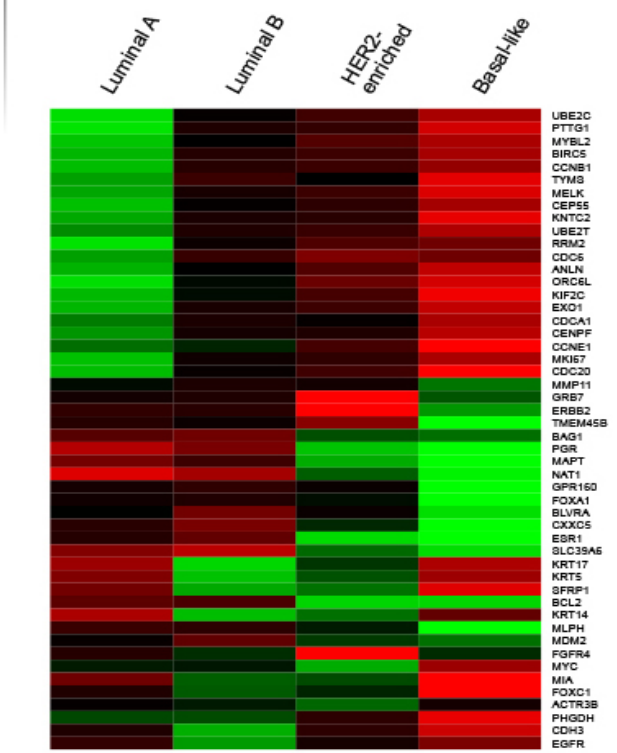
prosigna®
Breast cancer
gene signature assay



- Prosigna was developed based on the PAM50 gene signature, which measures the expression of 50 genes to classify tumors into 1 of 4 intrinsic subtypes[1]
- Intrinsic subtypes provide valuable prognostic information to guide clinical decisions[1,2]
- According to the St. Gallen guidelines, systemic therapy recommendations should follow intrinsic subtype classification[2]

prosigna®
Breast cancer gene signature assay

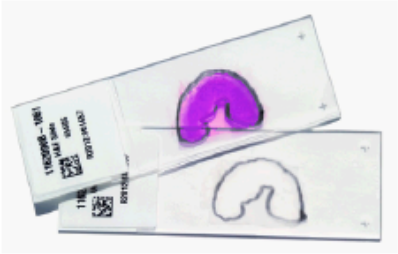
Intrinsic subtypes have distinct gene expression



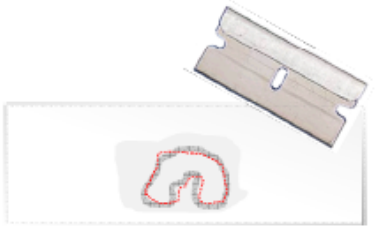
Prosigna™ is Designed to be Used with FFPE Samples

- Tissue Processing:

Select Block



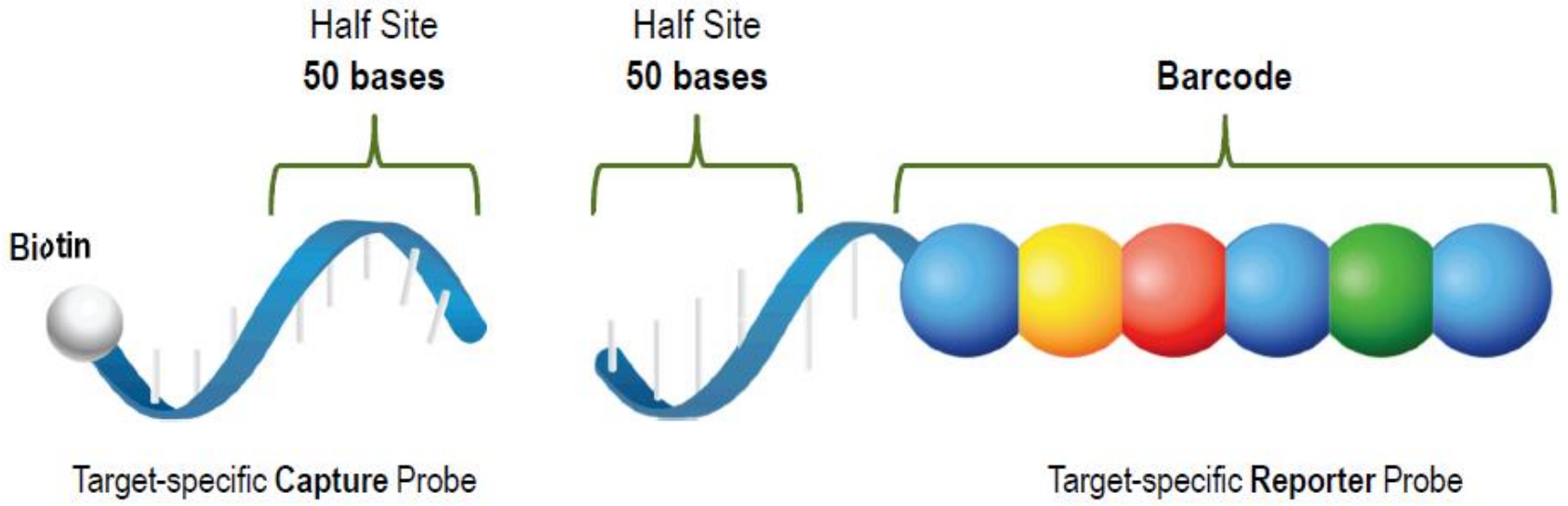
H&E Stain & Transpose



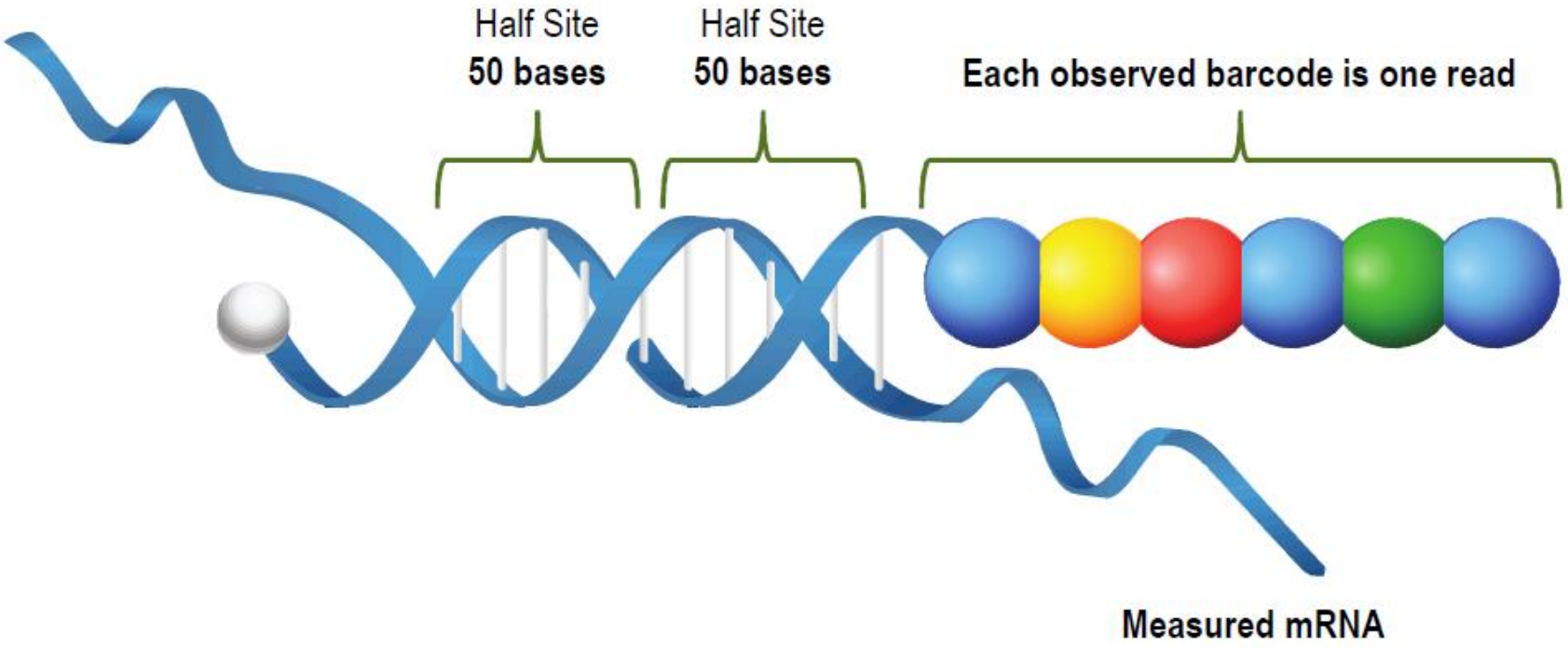
Macrodissect & Digest

Specimen Attribute	Requirement
Tissue input	Viable invasive breast carcinoma (ductal, lobular, mixed, or NOS)
Tissue input format	10-micron-thick slide-mounted tissue sections
Minimum tumor surface area	4 mm^2
Minimum tumor cellularity	10% within tumor area

Digital Counting: How it Works



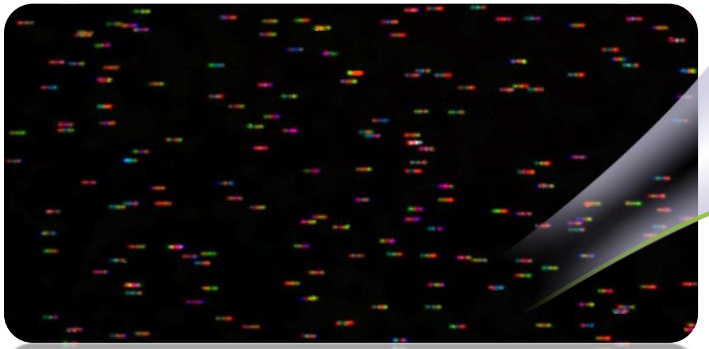
Digital Counting: How it Works

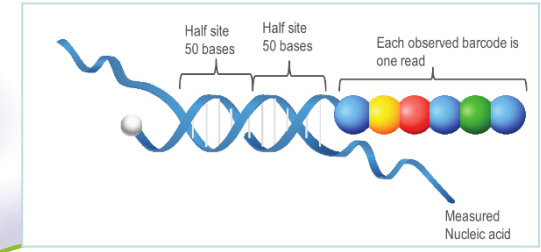


nCounter ® - The only direct, digital, nucleic-acid counting technology

Molecular Barcoding

- Probes up to 800 genes simultaneously
- No amplification
- Digital gene expression applied to biological pathways





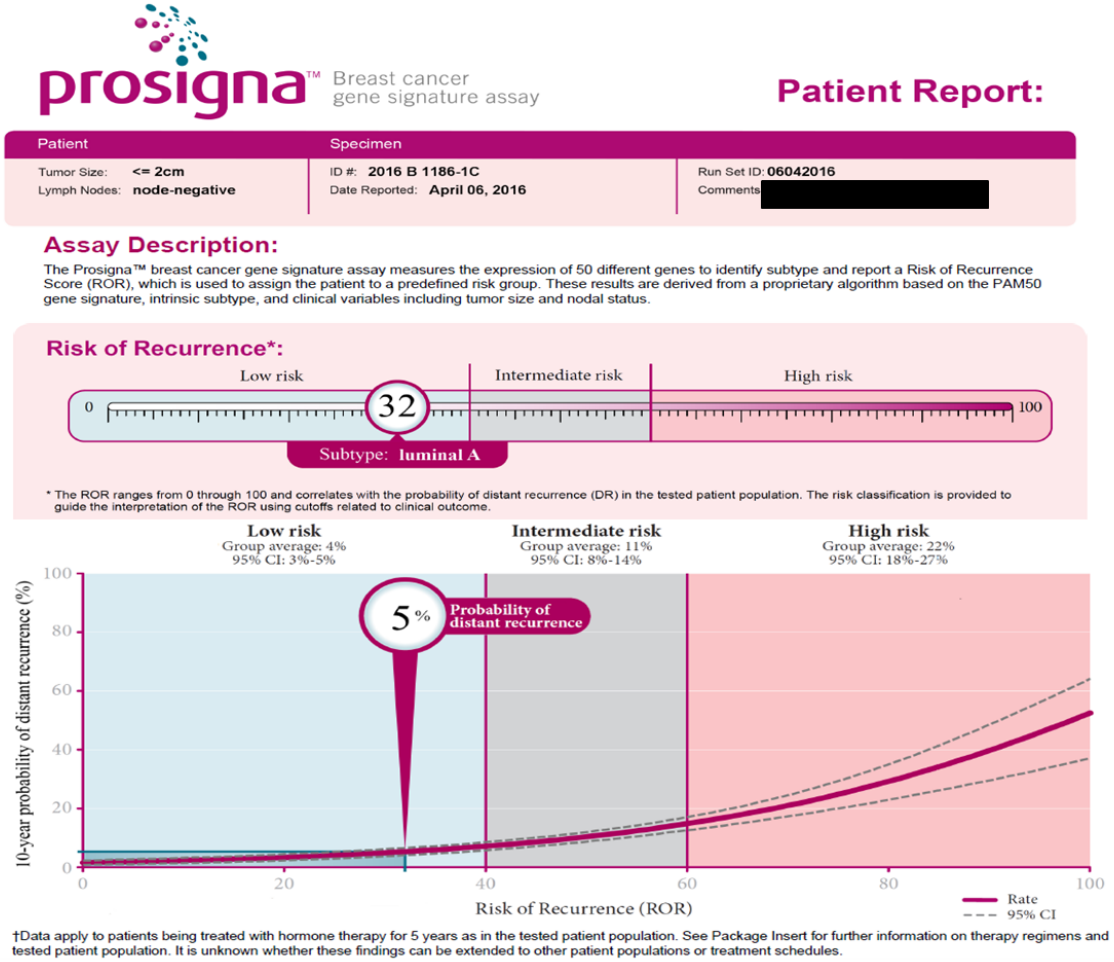
Barcode	Counts	Identity
	3	XLSA
	2	FOX5
	1	INSULIN

Single molecule fluorescent barcodes, each attached to an individual nucleic acid molecule

nCounter Dx Analysis System for use with Prosigna utilizes 58 genes. NanoString research use only products utilize up to 800 genes.

The Prosigna™ Assay – Overview of the Workflow

- Day 1:
  - Identify tumorous tissue on FFPE slides
  - Macrodissect tissue
  - Digest tissue overnight
- Day 2:
  - Isolate RNA
  - Create a Run Set in the web application
  - Hybridize samples with CodeSet
- Day 3:
  - Process samples on nCounter Prep Station
  - Count samples on nCounter Digital Analzyer

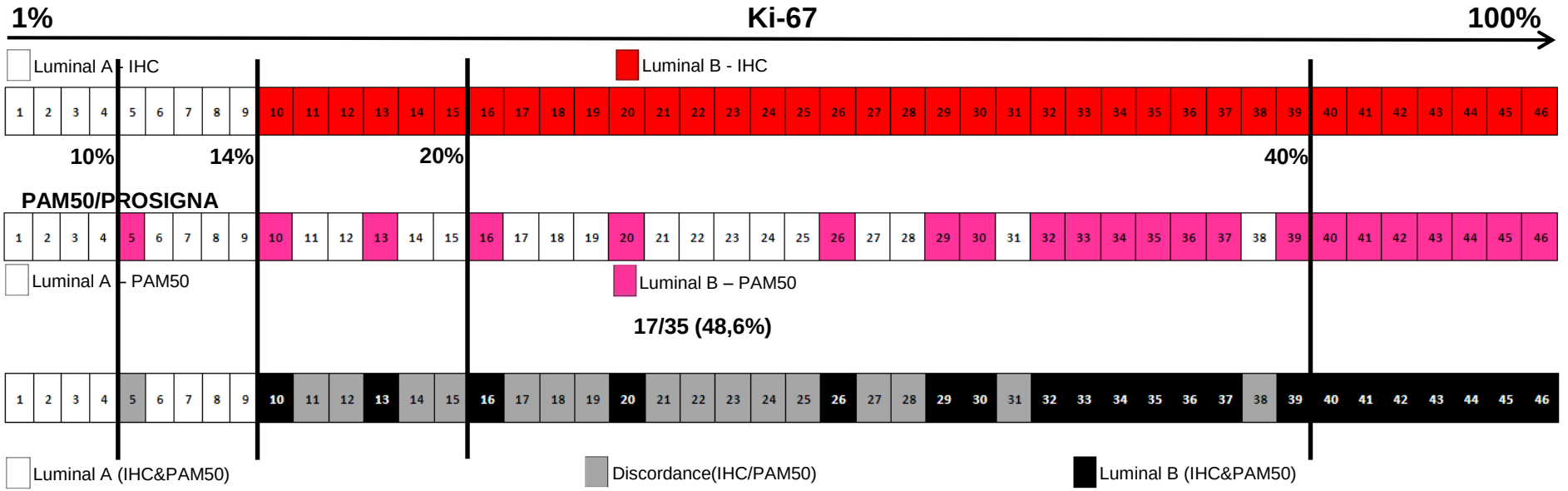


Molecular intrinsic subtype

Risk of recurrence

Figure represents ex-US example Prosigna patient report

Concordance between Ki67 vs PAM50/PROSIGNA





GEICAM 2012-09 (n = 200)

VHIO (n = 148)

CBM-Rome (n = 57)

Assessed for eligibility (n = 405)

Excluded (n = 81)
- Node positive (n = 53)
- ER negative (n = 2)
- HER-2 positive (n = 8)
- No IHC data available (n = 18)

Analyzed (n = 324)

	Lum A	Lum B	HER2-enriched	Basal-like	Total N
VHIO	56 (58.3%)	36 (37.5%)	2 (2.1%)	2 (2.1%)	96
GEICAM 2012-09	127 (66.1%)	61 (31.8%)	2 (1%)	2 (1%)	192
CBM Rome	21 (58.3%)	15 (41.7%)	0	0	36
Chi-square 4.081 p = 0.666					324

Table 1. Distribution of subtypes and ROR groups across Ki67 scores in 324 patients with HR+/HER2-negative node-negative disease.

	Ki67 Group			
	0-10%	11-20%	21-30%	>30%
Intrinsic Subtypes				
Luminal A	139 (81.3%)	36 (56.2%)	17 (38.6%)	8 (20%)
Luminal B	30 (17.5%)	28 (43.8%)	27 (61.4%)	27 (67.5%)
Her-2 Enriched	1 (0.6%)	0	0	2 (5%)
Basal like	1 (0.6%)	0	0	3 (7.5%)
Total	171	64	44	40
ROR and T≤2cm				
ROR-Low	94 (70.7%)	21 (40.4%)	7 (20%)	7 (24.1%)
ROR-Med	37 (27.8%)	24 (46.2%)	20 (57.1%)	7 (24.1%)
ROR High	2 (1.5%)	7 (13.5%)	9 (22.9%)	15 (51.7%)
Total	133	52	35	29
ROR and T>2cm				
ROR-Low	19 (50%)	3 (25%)	1 (11.1%)	0
ROR-Med	10 (26.3%)	5 (41.7%)	2 (22.2%)	0
ROR-High	9 (23.7%)	4 (33.3%)	6 (66.7%)	11 (100%)
Total	38	12	9	11

RegioneLombardia
LA GIUNTA

DELIBERAZIONE N° XI / 1986 Seduta del 23/07/2019

Test di profilazione genica per pazienti affette da carcinoma invasivo della mammella endocrino responsivo di tipo luminale

Criteri di accesso al test.

Le pazienti individuate per questa specifica prestazione sono pazienti con carcinoma invasivo della mammella endocrino responsivo in stadio precoce considerate a rischio intermedio per le quali il clinico potrebbe porre una indicazione a chemioterapia adiuvante. Vengono, pertanto, escluse dalla possibilità di effettuare il test gratuitamente tutte le pazienti a basso rischio, per le quali è indicata la sola ormonoterapia, e ad alto rischio per le quali è indicata l'associazione ormonoterapia-chemioterapia.

Le pazienti a basso e ad alto rischio sono definite in base alle caratteristiche descritte nella tabella seguente:

Basso rischio: almeno 4 delle seguenti caratteristiche	**Alto rischio: almeno 4 delle seguenti caratteristiche**
G1	G3
T1 (a-b)	T3-4
Ki 67<15%	Ki 67>30%
ER>80%	ER<30%
N 0	N positivo

Esame Istologico N. 2016-B-00399

Sig.ra [redacted] nata il **30/01/1948**

Regime	Ricoverato	Prelievo del	14/01/2016
Area clinica di provenienza	SENOLOGIA	Accettazione del	15/01/2016
Medico referente	Dott. A. Primavera	Refertazione del	21/01/2016
		Roma, il	28/01/2016

REPERTO MACROSCOPICO

1) Quadrante mammario di cm 7,5 x 6,5 x 4, orientato, sede di neoplasia di cm 1,9 a ridosso del margine profondo.
2) Linfonodo della dimensione massima di cm 1,9, esaminato in sede intraoperatoria ed all'esame istologico definitivo fin ad esaurimento del blocchetto con sezioni ogni 200 micron.
3) Frammento di parenchima mammario di cm 2,5 x 1,5 x 0,5.
Eseguito da: Dott.ssa G. Nicolo'

DIAGNOSI

1) Carcinoma infiltrante NST sec. WHO 2012 (duttale NOS) G2 sec. Nottingham (score 7: 2 tubuli+ 2 pleomorfismo+ 3 mitosi) di 1,9 cm (misura istologica) con microcalcificazioni; scarso l'infiltrato stromale mononucleato. E' presente componente peritumorale di carcinoma duttale in situ di grado intermedio ed alto sec. WHO 2012, talora con necrosi di tipo comedonico, in percentuale pari al 20% della neoplasia.
La noplasia giunge a ridosso del margine di resezione profondo.
Indenni i restanti margini.
Non si documentano angioinvasione ed infiltrazione perineurale peritumorale.
Restante parenchima sede di alterazioni fibrocistiche con focolai di adenosi e metaplasia apocrina.
2) Linfonodo esente da patologia neoplastica e sede di linfadenite reattiva.
3) Parenchima fibroadiposo e frammento di tessuto muscolare esenti da patologia neoplastica

Positiva la determinazione immunoistochimica dei recettori per estrogeni (anticorpo Dako clone EP1) nel 90% delle cellule neoplastiche, e positiva per progesterone (anticorpo Dako clone PgR 636) nel 90% delle cellule neoplastiche.
La frazione proliferante (Ki67) (anticorpo murino Dako clone Mib -1) è pari al 40% (conta effettuata manualmente su tre campi periferici comprendendo uno con più elevato indice di proliferazione).
Determinazione immunoistochimica c-erbB2 (Herceptest DAKO): colorazione di membrana incompleta debole nel 20% delle cellule neoplastiche, score test: 1+ negativo sec. ASCO-CAP 2013.
Il centro partecipa al controllo di qualità interregionale per la determinazione dello stato di Her2.

Codifica diagnosi
P3-Y5405 T-04000 M-85003
Codifica pTNM
pT 1c pN 0 sn pM x
G2

Age: 68 aa
T: 1,9 cm; N: 0; G2
ER: 90%; PGR: 90%; Ki67: 40%; Her2: neg

prosigna™ Breast cancer gene signature assay

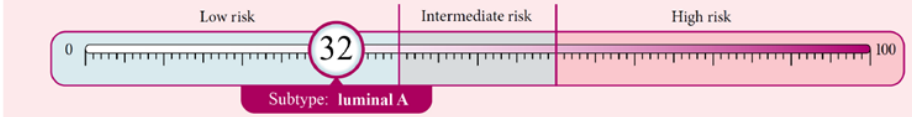
Patient Report:

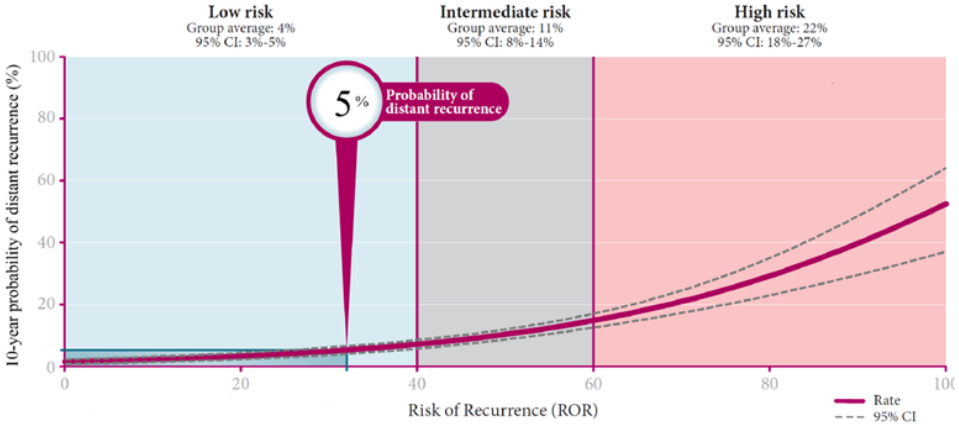
Patient	Specimen	
Tumor Size: <= 2cm	ID #: 2016 B 399-1F	Run Set ID: 16022016
Lymph Nodes: node-negative	Date Reported: February 16, 2016	Comments: [redacted]

Assay Description:

The Prosigna™ breast cancer gene signature assay measures the expression of 50 different genes to identify subtype and report a Risk of Recurrence Score (ROR), which is used to assign the patient to a predefined risk group. These results are derived from a proprietary algorithm based on the PAM50 gene signature, intrinsic subtype, and clinical variables including tumor size and nodal status.

Risk of Recurrence*:





Via XXIV Maggio, 6 00047 - Marino (Roma) Tel. / Fax 06 93 27 30 27

same n° **2015 / 17545** del 29/06/2015

COPIA

[redacted] nato/a il: 07/10/1964

Provenienza: - P.O. ALBANO - CHIR 331203

Ticket:

1) MAMMELLA - QUADRANTECTOMIA O RESEZIONE PARZIALE

MACROSCOPICA:
Quadrante infero-esterno mammella sinistra: tessuto mammario delle dimensioni di cm 6x6x4,5 pervenuto chinato con margini contrassegnati da fili e repere metallico. Al taglio si reperta una neoformazione di consistenza aumentata a margini irregolari del diametro di cm 1,3 . La china prossima alla lesione è quella del margine fascia.

c1 margine areolare
c2 margine infero-esterno
c3 margine fascia
c4 margine cute
c5,6 neoformazione

DIAGNOSI:
Carcinoma duttale infiltrante della mammella, variante n.o.s., a medio grado di differenziazione, con minima componente di carcinoma duttale in situ, di tipo cribriforme, <5% circa, in sede periferica.
Abbondante desmoplasia e lieve infiltrato flogistico linfomonocitario intra e peritumorale.
Si segnala la presenza di infiltrazione perineurale.
Displasia fibrocistica con iperplasia duttale florida nel margine orientato come areolare.
Displasia fibrocistica ed iperplasia fibroadenomatosa nel margine contrassegnato come fascia.
Gli altri due margini sono esenti da alterazioni di rilievo.
pT1c sec. UICC 2009 G2

DIAGNOSI:
La determinazione dei Recettori Ormonali con anticorpo monoclonale ha fornito il seguente esito:
Estrogeno: >90%
Progesterone: 70%
Ki67: <15%
La valutazione immunoistochimica per la determinazione della overespressione di membrana della proteina HER2 , eseguita con controllo interno della metodica , ha fornito il seguente esito:

1+ Positivita di colorazione di membrana in > 10% delle cellule neoplastiche.
Colorazione di membrana discontinua.

Age: 51 aa
T: 1,3 cm; N: 1a; G2
ER: >90%; PGR: 70%; Ki67: <15%; Her2: neg

prosigna™ Breast cancer gene signature assay

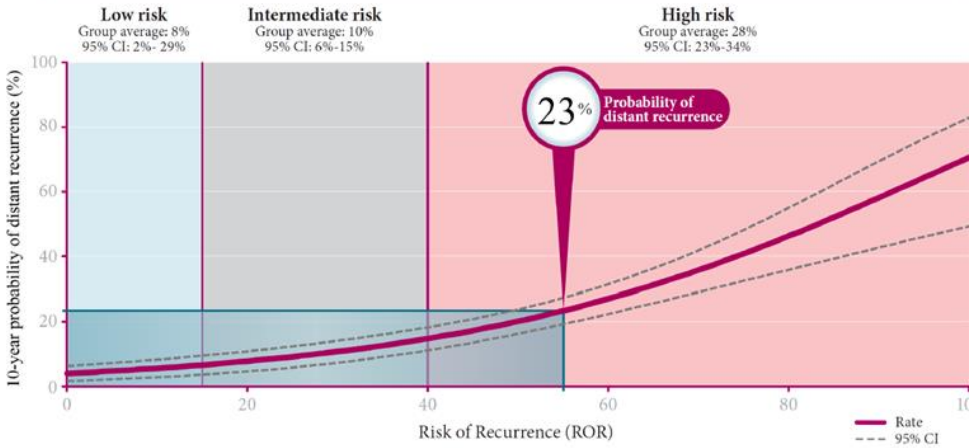
Patient Report:

Patient	Specimen	
Tumor Size: <= 2cm	ID #: 2016 M 143	Run Set ID: 16022016
Lymph Nodes: node-positive (1-3 nodes)	Date Reported: February 16, 2016	Comments: [redacted]

Assay Description:

The Prosigna™ breast cancer gene signature assay measures the expression of 50 different genes to identify subtype and report a Risk of Recurrence Score (ROR), which is used to assign the patient to a predefined risk group. These results are derived from a proprietary algorithm based on the PAM50 gene signature, intrinsic subtype, and clinical variables including tumor size and nodal status.

Risk of Recurrence*:



Esame Istologico N. 2015-B-01963

Sig.ra [redacted] nata il **26/06/1953**

Regime	Ricoverato	Prelievo del	19/02/2015
Area clinica di provenienza	SENOLOGIA	Accettazione del	20/02/2015
Medico referente	Dott. A. Primavera	Refertazione del	25/02/2015
		Roma, il	27/02/2015

REPERTO MACROSCOPICO

1) Quadrante mammario di cm 8 X 7,5 X 4,5. Al taglio è presente lesione di cm 0,9. Losanga cutanea di cm 3 x 0,5.
2) Linfonodo della dimensione massima di cm 0,4, completamente incluso ed esaminato fin ad esaurimento del blocchetto con sezioni ogni 200 micron.
3) Linfonodo della dimensione massima di cm 1,6, in estesa involuzione adiposa, diviso in due, completamente incluso ed esaminato fin ad esaurimento del blocchetto con sezioni ogni 200 micron.

DIAGNOSI

1) Carcinoma infiltrante NST sec. WHO 2012 (duttale NOS) G2 sec. Nottingham (score 6: tubuli 2+pleomorfismo 3+mitosi 1) di cm 0,4 (misura istologica) con componente peritumorale di carcinoma duttale in situ di grado alto con microcalcificazioni sec. WHO 2012 di tipo cribriforme e solido, in percentuale pari al 50% circa della neoplasia. Indenni i margini di resezione chirurgica.
Sono assenti angioinvasione ed infiltrazione perineurale peritumorale.
2,4,6,7) Linfoadenite reattiva.
3) Metastasi di carcinoma (mm 6 di dimensione massima in una sezione) con limitato sconfinamento nel tessuto adiposo peritumorale.
5) Micrometastasi di carcinoma.
8) Tessuto fibroadiposo e vascolare esente da neoplasia.

FATTORI PROGNOSTICI DI RISPOSTA ALLA TERAPIA

Positiva la determinazione immunoistochimica dei recettori per estrogeni (anticorpo Thermoscientific clone SP1) nel 98% delle cellule neoplastiche con colorazione di intensità forte, e negativa per progesterone (anticorpo Thermoscientific clone SP2).
La frazione proliferante (Ki67) (anticorpo murino Dako clone Mib -1) è pari al 18% (conta effettuata manualmente su tre campi periferici comprendendo uno con più elevato indice di proliferazione).
Determinazione immunoistochimica c-erbB2 (anticorpo policlonale rabbit DAKO): colorazione di membrana circonferenziale incompleta, debole-moderata, nell'80% delle cellule neoplastiche, score test: 2+, equivoco sec. ASCO-CAP 2013.
Il centro partecipa al controllo di qualità interregionale per la determinazione dello stato di Her2.

Codifica pTNM
pT 1a pN 1a(sn) pM non dato
G2

Age: 62 aa
T: 0,9 cm; N: 1a; G2
ER: 98%; PGR: 0%; Ki67: 18%; Her2: neg

prosigna™ Breast cancer gene signature assay

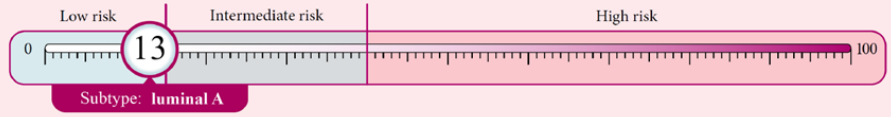
Patient Report:

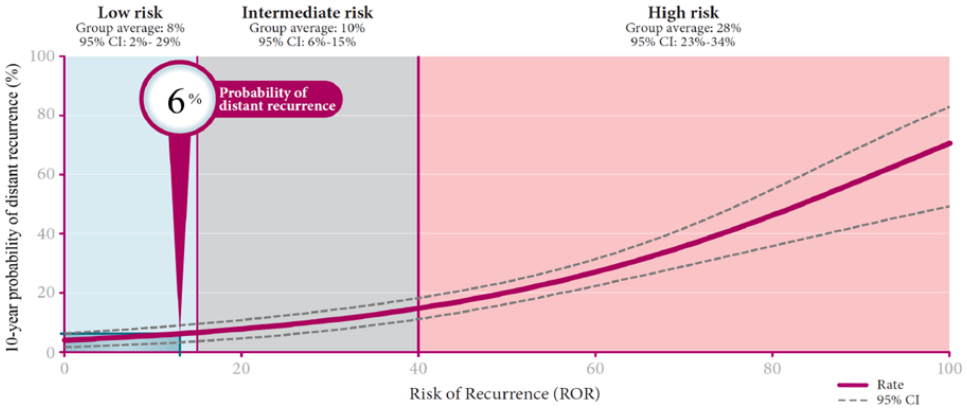
Patient	Specimen	Comments
Tumor Size: <= 2cm Lymph Nodes: node-positive (1-3 nodes)	ID #: 2015 M 416 Date Reported: April 17, 2015	[redacted]

Assay Description:

The Prosigna™ breast cancer gene signature assay measures the expression of 50 different genes to identify subtype and report a Risk of Recurrence Score (ROR), which is used to assign the patient to a predefined risk group. These results are derived from a proprietary algorithm based on the PAM50 gene signature, intrinsic subtype, and clinical variables including tumor size and nodal status.

Risk of Recurrence*:





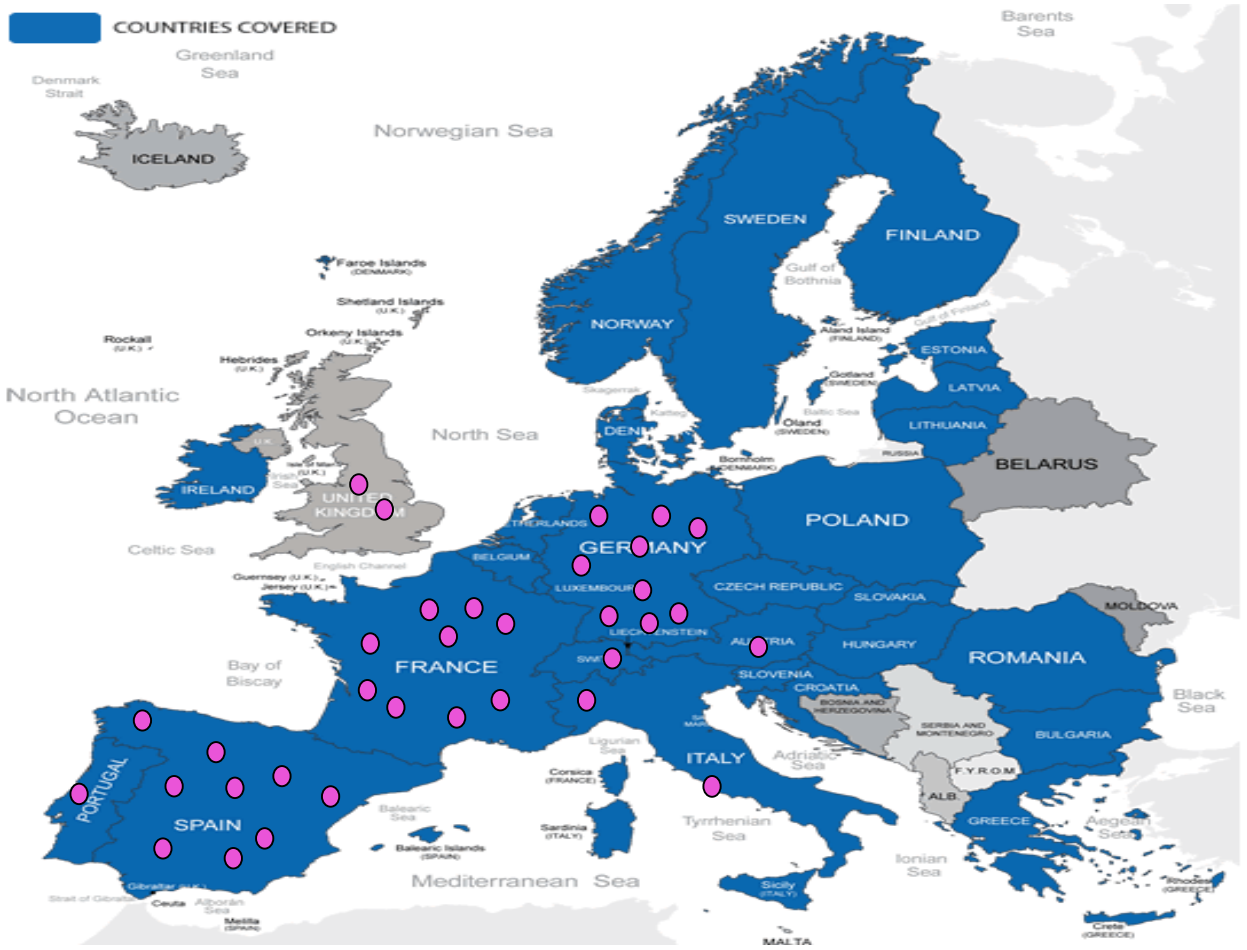
2014

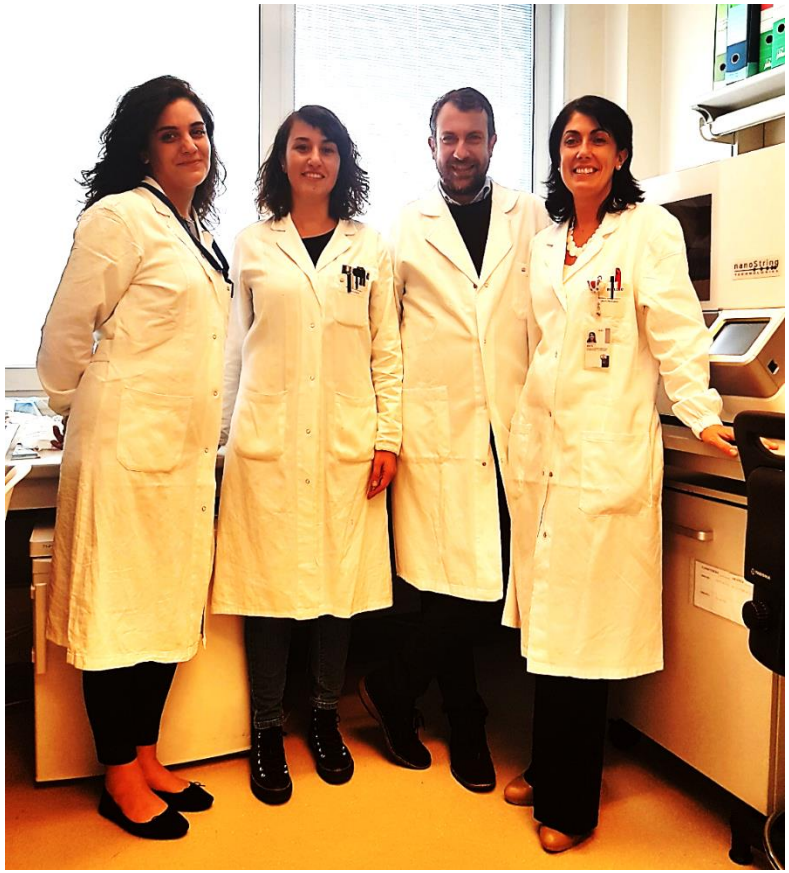

COUNTRIES COVERED
Barents Sea
Greenland Sea
Denmark Strait
ICELAND
Norwegian Sea
SWEDEN
FINLAND
Faroe Islands (DENMARK)
Gulf of Bothnia
Shetland Islands (U.K.)
NORWAY
Orkney Islands (U.K.)
Rockall (U.K.)
Hebrides (U.K.)
Aland Island (FINLAND)
ESTONIA
Gotland (SWEDEN)
LATVIA
North Atlantic Ocean
Skagerrak
Kattegat
Baltic Sea
Oland (SWEDEN)
LITHUANIA
North Sea
DENMARK
RUSSIA
BELARUS
Bornholm (DENMARK)
IRELAND
UNITED KINGDOM
POLAND
NETHERLANDS
GERMANY
Celtic Sea
BELGIUM
English Channel
Guernsey (U.K.)
Jersey (U.K.)
LUXEMBOURG
CZECH REPUBLIC
SLOVAKIA
MOLDOVA
LIECHTENSTEIN
AUSTRIA
HUNGARY
ROMANIA
Bay of Biscay
FRANCE
SWITZ.
SLOVENIA
CROATIA
Black Sea
BOSNIA AND HERZEGOVINA
SERBIA AND MONTENEGRO
BULGARIA
Ligurian Sea
ITALY
Adriatic Sea
F.Y.R.O.M.
PORTUGAL
Corsica (FRANCE)
ALB
SPAIN
Balearic Sea
Tyrrhenian Sea
GREECE
Aegean Sea
Sardinia (ITALY)
Balearic Islands (SPAIN)
Ionian Sea
Mediterranean Sea
Gibraltar
Strait of Gibraltar
Ceuta
Alboran Sea
Sicily (ITALY)
Melilla (SPAIN)
MALTA
Crete (GREECE)

2018

9 France
9 Germany
9 Spain
2 Italy
2 UK
1 Austria
1 Portugal
1 Switzerland

34 Europe





Dr. Maria Francesconi, Dr. Daniela Righi, Prof.ssa Francesca Zalfa

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