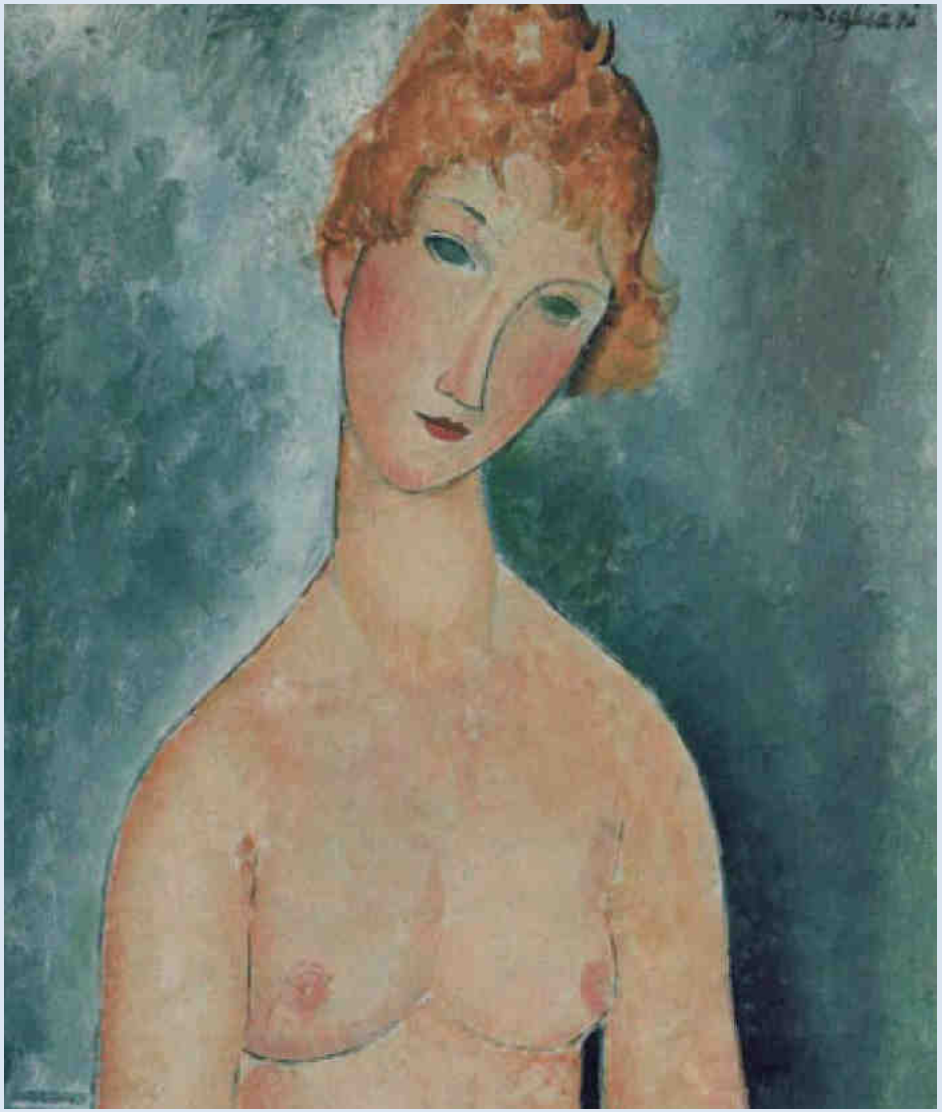


Hacia la personalización en el tratamiento del cáncer de mama

¿Qué aportan los biomarcadores en la actualidad?

Primera Parte

Federico Rojo

XVI Jornada sobre el Cáncer de Mama:
Personalización en el Cáncer de Mama
Barcelona, 22 Febrero 2013

Biomarkers Used in Cancer Management: Questions to be addressed by Cancer Biomarkers

All patients with same diagnosis

Diagnostic

What type of cancer is it?

Prognostic

Will the cancer return?

Predictive

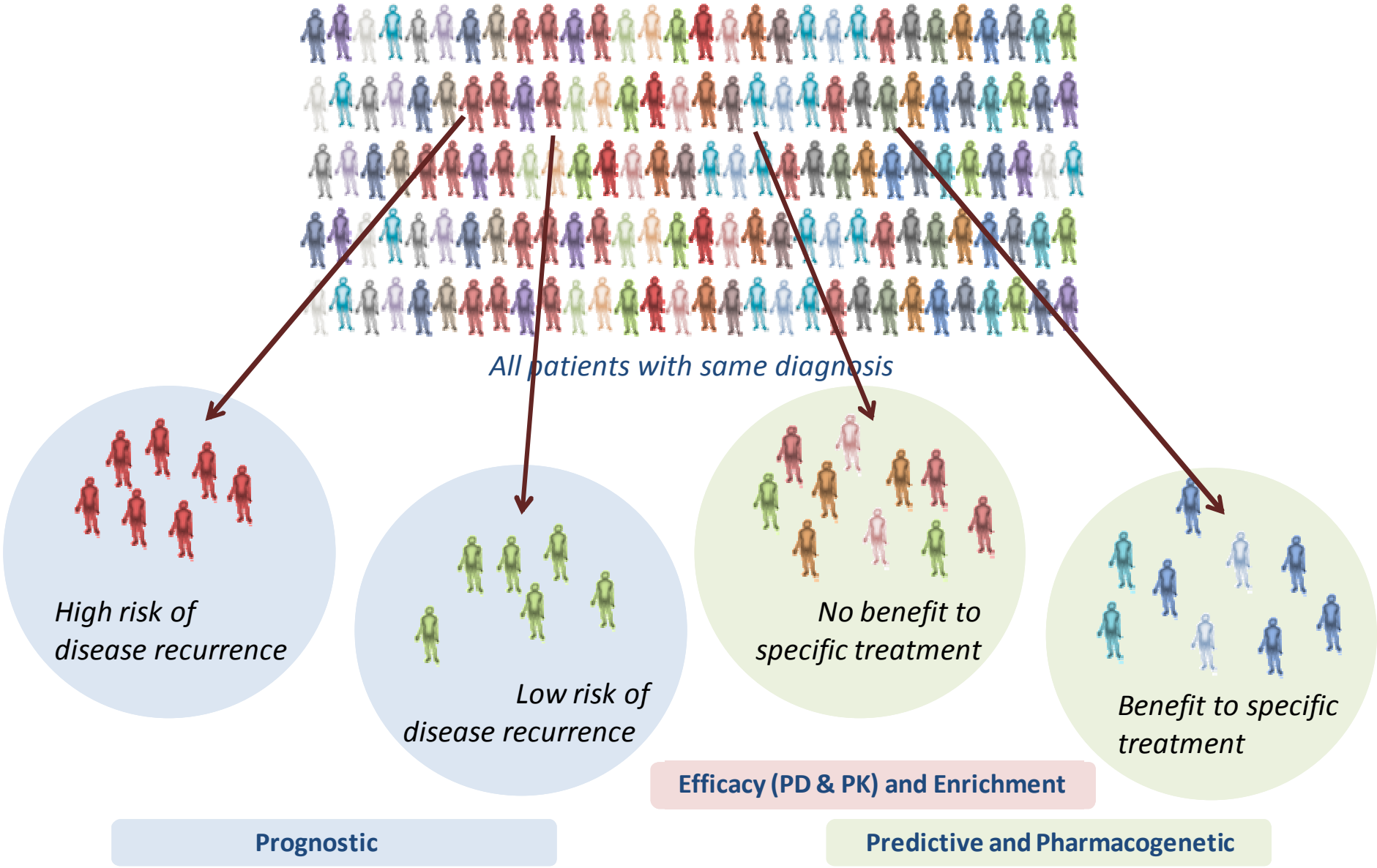
Is this the optimal drug for my cancer?

Pharmacodynamics

What's the optimal dose for my body?

Adapted from McShane, LM. SABCS 2010

Biomarkers Used in Cancer Management

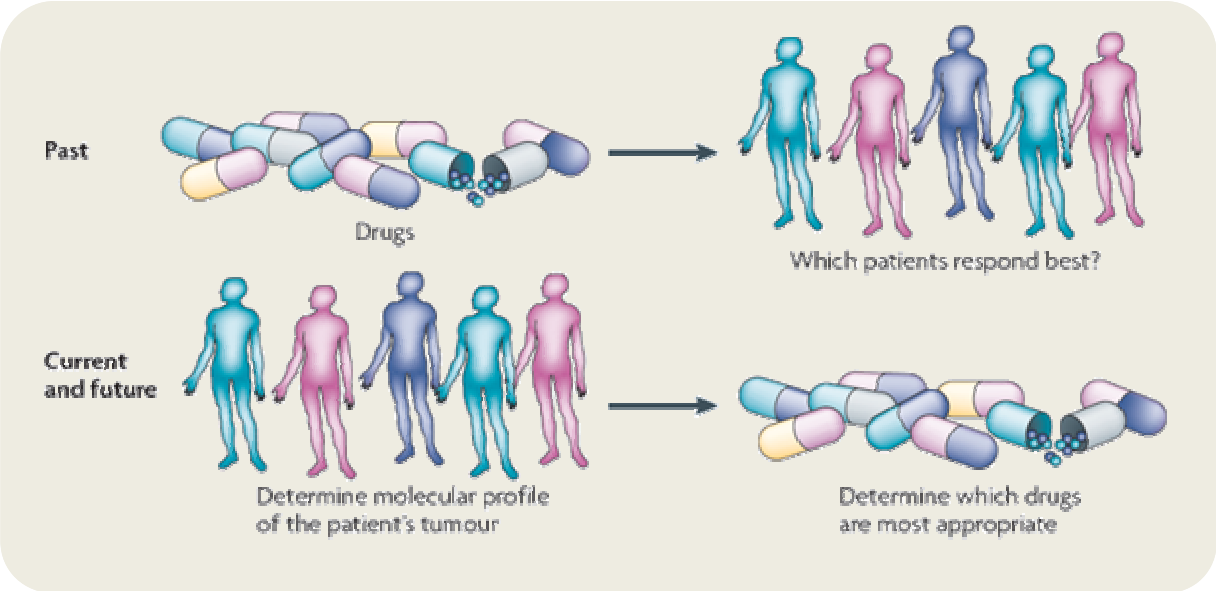


Biomarkers Used in Cancer Management

Type of biomarker	Uses in management and clinical trials	Identification	Validation	Examples
Prognostic biomarker	Treatment choice, patient selection and stratification	Easy, but often flawed or biased	Frequent, but often inadequate because of regression to the mean or flaws in the initial identification study	Poor performance status, elevated hepatic enzymes, multi-site metastases in advanced colorectal cancer. Lymph node status, tumor size, tumor grade, proliferation, cyclin D1 in breast cancer.
Predictive biomarker	Treatment choice, patient selection and stratification	Difficult, requires randomized trial	Uncommon, requires large randomized trial	*KRAS* mutation predictive of lack of activity of cetuximab and panitumumab in colon cancer. Hormone receptor status predictive of effect of tamoxifen and aromatase inhibitors in breast cancer. HER2/*neu* amplification predictive of effect of trastuzumab and lapatinib in breast cancer. *EGFR* mutations predictive of effect of erlotinib and gefitinib in non-small-cell lung cancer.

Buyse M et al. Nature Rev 2010

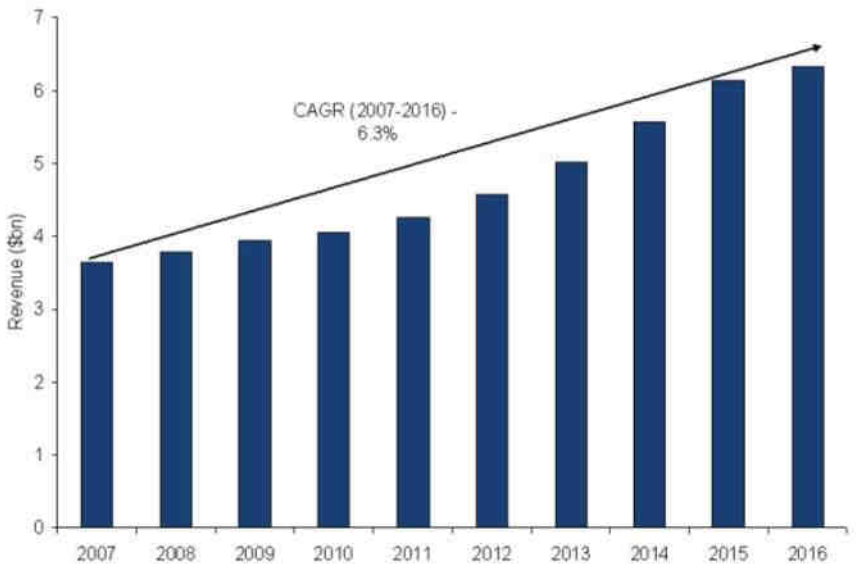
Potential role for biomarker-based diagnostics



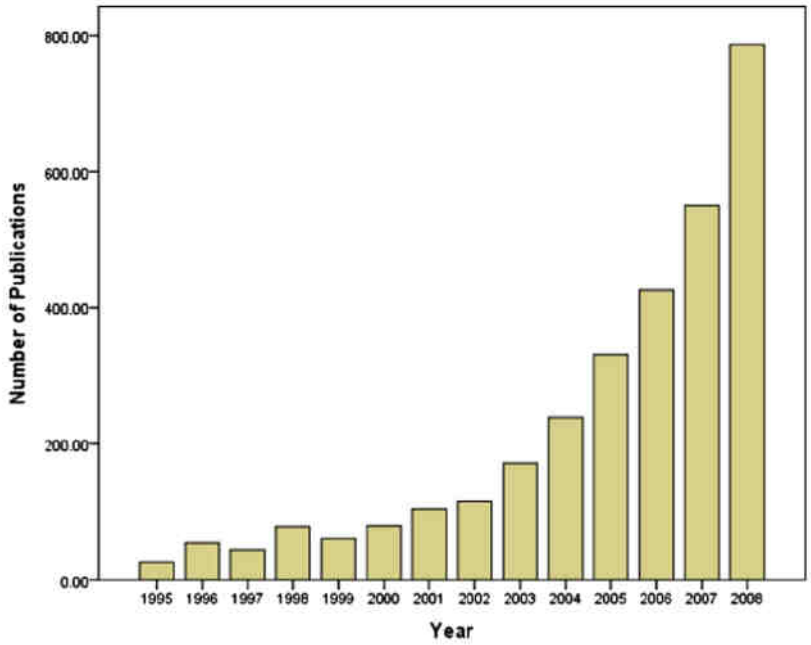
Yap, TA. et al. Nat Rev Cancer 2010

Biomarkers Used in Cancer Management

Biomarkers in cancer research, global.
Cancer Biomarkers Market Revenues ($bn), 2007-16



Cancer predictive biomarkers published literature



Alymani, NA. et al. Eur J Can 2010

Biomarker study deficiencies: Convenience samples

- Retrospective collections
- Biased
- Heterogeneous patient characteristics
- Heterogeneous or unknown treatments and follow up care
- Insufficient sample size
- Uncertain specimen and data quality

McShane, LM. SABCS 2010

Diagnostics and biomarker development: Criteria for determining levels of evidence

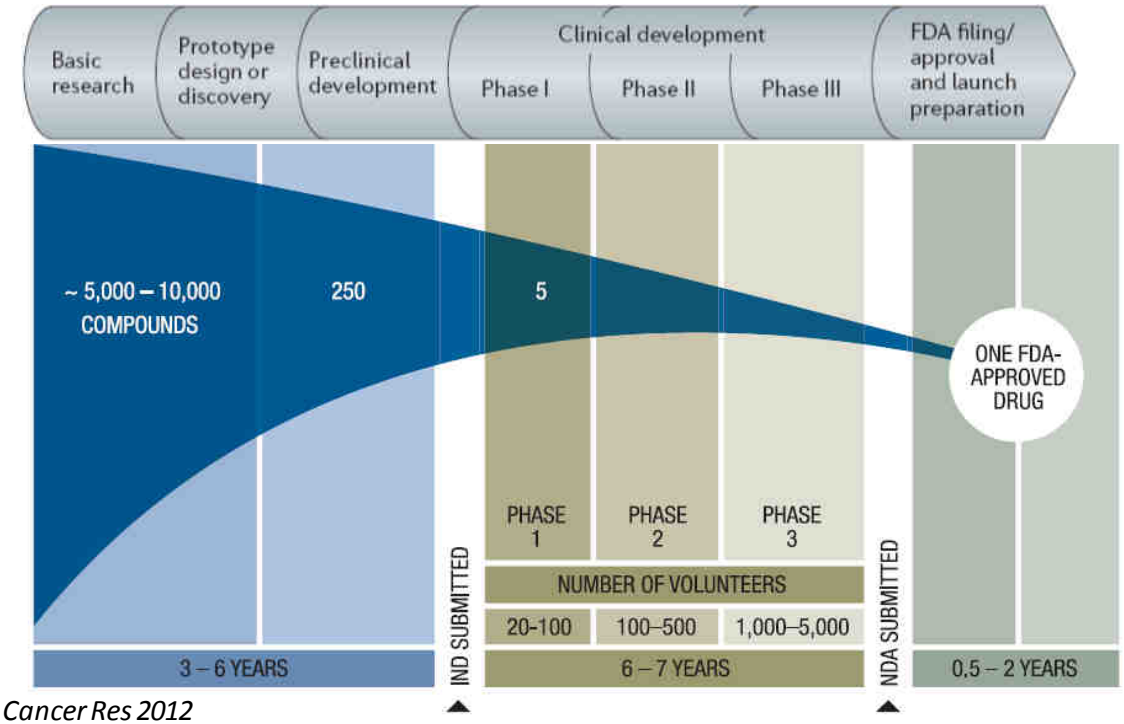
Table 1 | Proposed adaptation* to the criteria for determining levels of evidence for predictive biomarker studies[13,14]

Level	Study design‡	Validation
I-A	Prospective randomized controlled trial specifically designed to assess the utility of the biomarker; samples collected and analysed in real time	Not necessary, but could be useful
I-B	Randomized controlled trial not specifically designed to assess the utility of the biomarker; samples stored during the study and analysed after completion, following a protocol	One or more studies with consistent results
II-B	Randomized controlled trial not specifically designed to assess the utility of the biomarker; samples are stored during the study and analysed after completion, following a protocol	No validation study available or several studies with inconsistent results
II-C1§	Nonrandomized retrospective, matched case–control study aimed to assess the utility of the biomarker using samples that were prospectively collected from patients who were enrolled in a prospective observational registry and who received standard treatment	One or more studies with consistent results
II-C2§	Nonrandomized retrospective, matched case–control study aimed to assess the utility of the biomarker using samples that were retrospectively collected from patients who were enrolled in a prospective observational registry and who received standard treatment	One or more studies with consistent results
III-C1§	Nonrandomized retrospective, matched case–control study aimed to assess the utility of the biomarker using samples that were prospectively collected from patients who were enrolled in a prospective observational registry and who received standard treatment	No validation study available or several studies with inconsistent results
III-C2§	Nonrandomized retrospective, matched case–control study aimed to assess the utility of the biomarker using samples that were retrospectively collected from patients who were enrolled in a prospective observational registry and who received standard treatment	No validation study available or several studies with inconsistent results
IV-D	Nonrandomized retrospective, matched case–control study aimed to assess the utility of the biomarker using samples from a consecutive series of patients who received standard treatment with or without the drug of interest; both clinical data and samples are collected retrospectively	Not applicable as design not satisfactory for determination of utility as a predictive biomarker

*Original criteria outlined by Simon *et al.*[13] ‡Window studies with a truly validated surrogate end point have the same level of evidence as a non-window study. For each level, the following suffixes can be added: –, absence of an underlying molecular mechanism that explains the predictive capacity of the biomarker, or +, presence of an underlying molecular mechanism that explains the predictive capacity of the biomarker. §Proposed new subcategory.

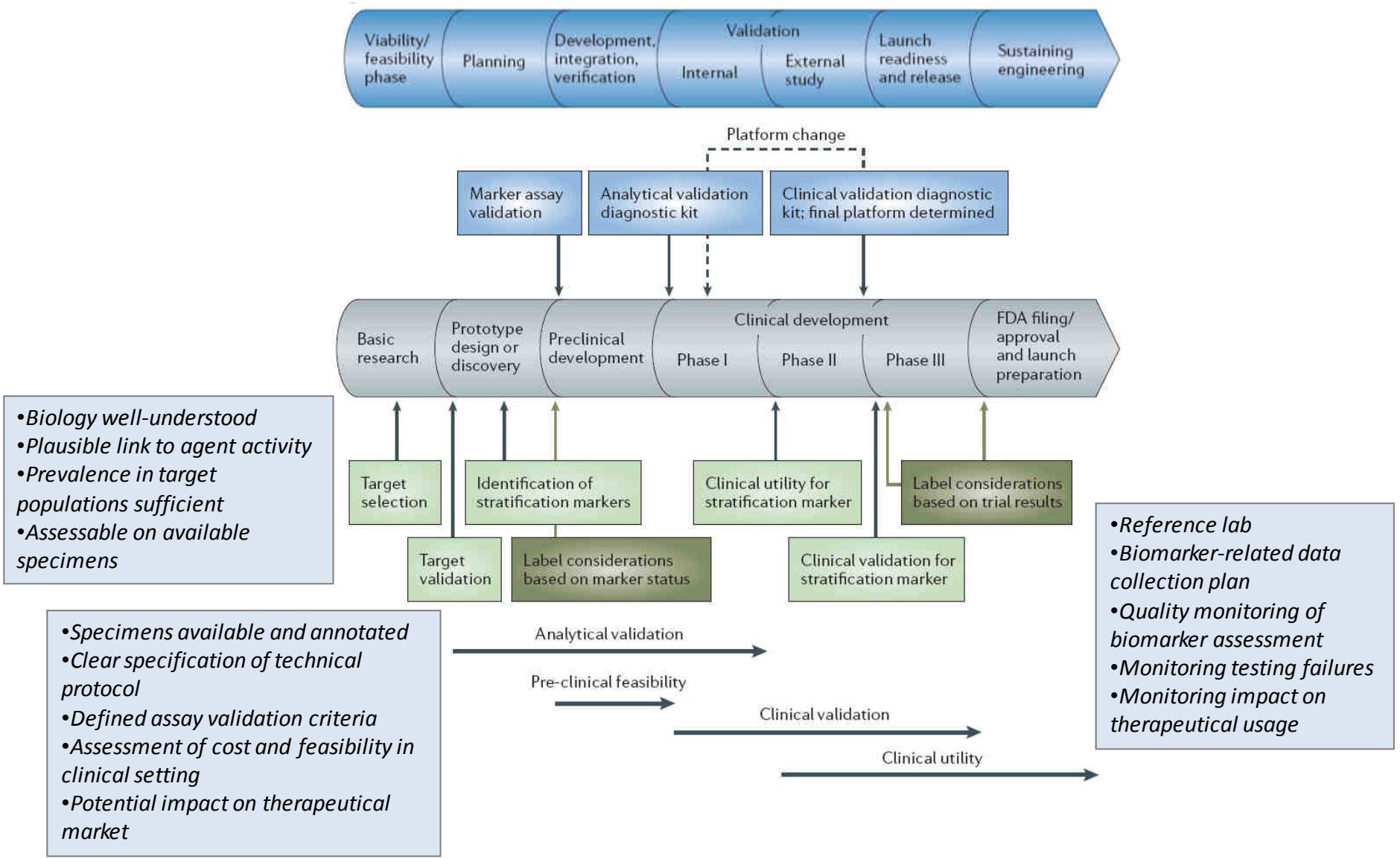
Beelen, K. et al. Nat Rev Clin Oncol 2012

Diagnostics and biomarker development



AACR Cancer Progress Report, Clin Cancer Res 2012
Phillips, KA. Et al. Nat Rev Drug Discov 2006
Taube, SE. Et al. JNCI 2009

Diagnostics and biomarker development



Prognostic and Predictive Markers for Breast Cancer Reported in the Literature

Level of evidence I:

- TNM
- Histological grade
- Histological type
- Estrogen receptors and Progesterone receptors
- HER2
- Multiparameter gene expression analysis

Level of evidence II:

- CA 15-3 , CA 27.29, CEA
- TOP2A
- PI3K, PTEN, AKT
- p53
- Bcl-2
- Cathepsin D
- Urokinase plasminogen activator (uPA) and plasminogen activator inhibitor 1 (PAI-1)
- Lymphatic and vascular invasion
- IHC-based markers of proliferation: Ki67, Cyclin D1 and Cyclin E
- Multiparameter gene expression analysis
- Bone marrow micrometastases, CTCs
- DNA flow cytometry-based proliferation markers

Level of evidence III-IV:

- PCNA, pRb
- mTOR
- Hdm2
- TBX2/3
- Cell cyle: Pokemon, p14, p27, p21, hDMP1
- ARF
- VEGF, angiogenesis
- CYP2D6*4 and XPC gene intron 11 C/A polymorphisms
- BRCA1/2
- EGFR, HER3, HER4
- IGF1R, IR
- TLE3
- TGFa

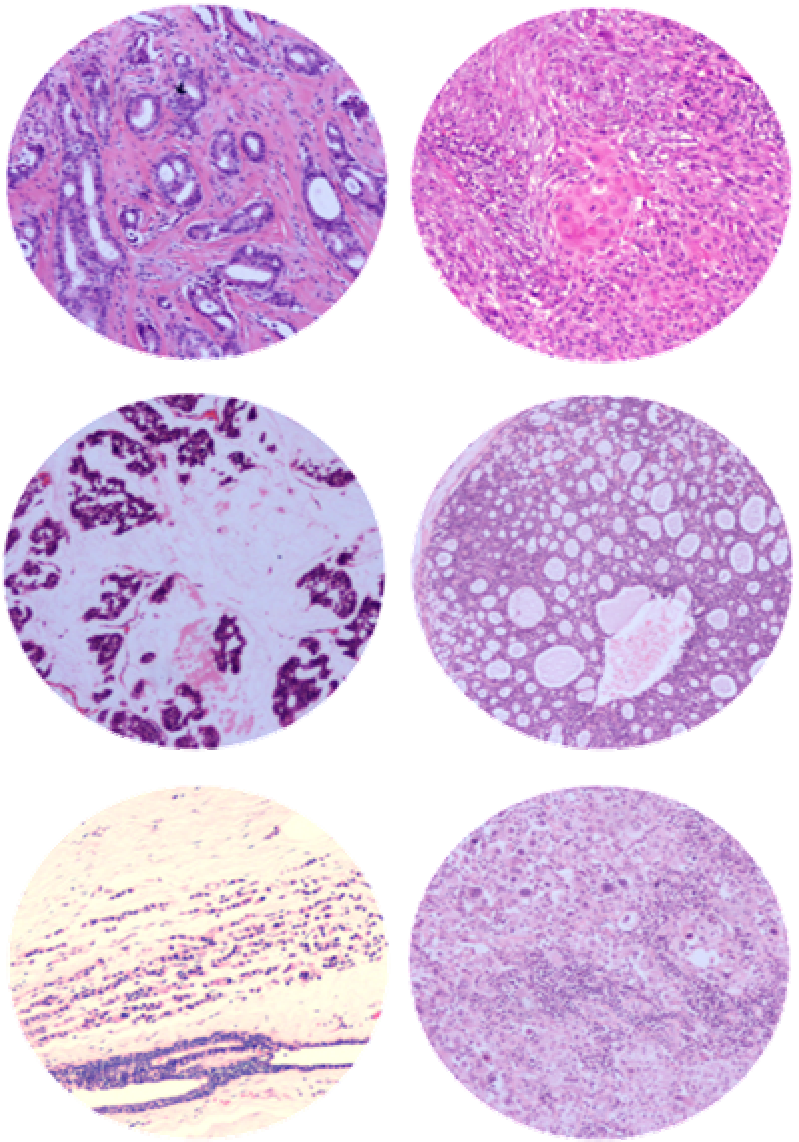
⋮

Several hundreds

Adapted from Harris L et al. J Clin Oncol 2007

Morphological classification of malignant tumors of the breast (WHO): prognostic information

Histopathological type of invasive breast carcinoma	Frequency	10-year survival rate
Invasive ductal carcinoma, not otherwise specified	50–80%	35–50%
Invasive lobular carcinoma	5–15%	35–50%
Mixed type, lobular and ductal features	4–5%	35–50%
Tubular/invasive cribriform carcinoma	1–6%	90–100%
Mucinous carcinoma	<5%	80–100%
Medullary carcinoma	1–7%	50–90%
Invasive papillary carcinoma	<1–2%	Unknown
Invasive micropapillary carcinoma	<3%	Unknown
Metaplastic carcinoma	<5%	Unknown
Acenoid cystic carcinoma	0.1%	Unknown
Invasive aprocrine carcinoma	0.3–4%	Unknown
Neuroendocrine carcinoma	2–5%	Unknown
Secretory carcinoma	0.01–0.15%	Unknown
Lipid-rich carcinoma	<1–6%	Unknown
Acinic cell carcinoma	7 cases	Unknown
Glycogen-rich, clear-cell carcinoma	1–3%	Unknown
Sebaceous carcinoma	4 cases	Unknown



Weigelt, B et al. J Pathology, 2008

Histological grade: prognosis in breast cancer

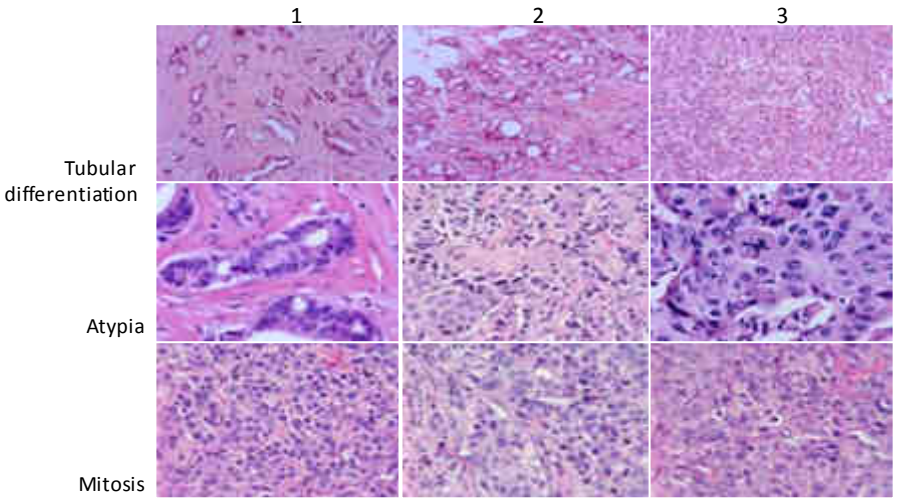
Rakha *et al. Breast Cancer Research* 2010, **12**:207
http://breast-cancer-research.com/content/12/4/207

Breast Cancer RESEARCH

REVIEW

Breast cancer prognostic classification in the molecular era: the role of histological grade

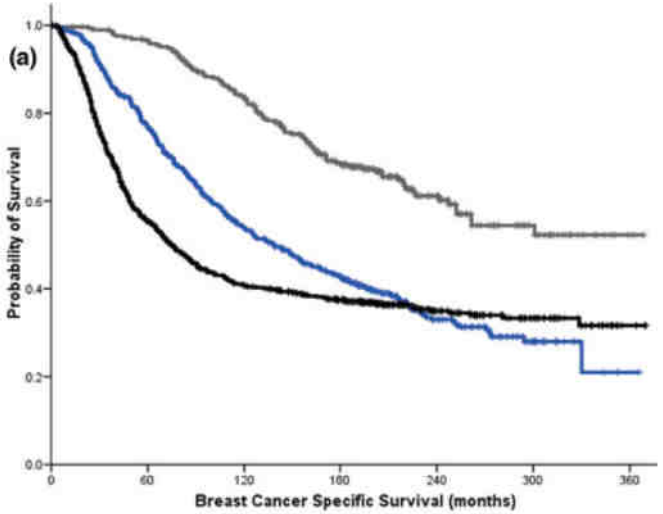
Emad A Rakha[1], Jorge S Reis-Filho[2], Frederick Baehner[3], David J Dabbs[4], Thomas Decker[5], Vincenzo Eusebi[6], Stephen B Fox[7], Shu Ichihara[8], Jocelyne Jacquemier[9], Sunil R Lakhani[10], José Palacios[11], Andrea L Richardson[12], Stuart J Schnitt[13], Fernando C Schmitt[14], Puay-Hoon Tan[15], Gary M Tse[16], Sunil Badve[17] and Ian O Ellis*[1]



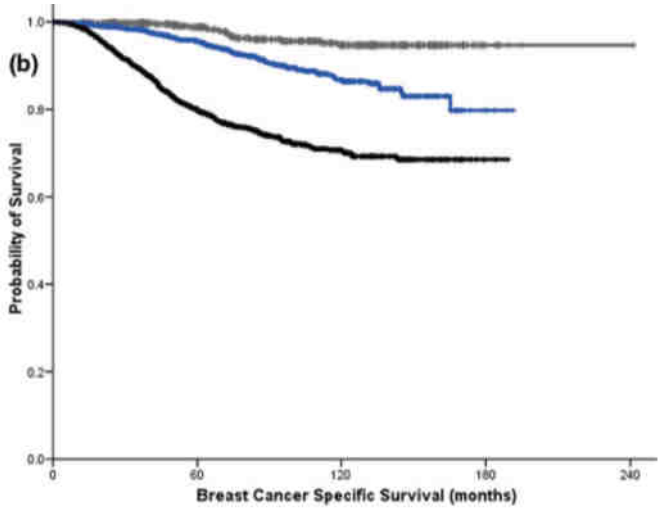
Scarf-Bloom-Richardson (mod. Elston): Low grade 3-5
Intermediate grade 6-7
High grade 8-9

Rakha, EA et al. Breast Can Res 2010

Old Nottingham series (1977-89)



Recent Nottingham series (1990-2002)



Prognostic and Predictive Markers for Breast Cancer Reported in the Literature

VOLUME 25 · NUMBER 33 · NOVEMBER 20 2007

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

American Society of Clinical Oncology 2007 Update of Recommendations for the Use of Tumor Markers in Breast Cancer

Lyndsay Harris, Herbert Fritsche, Robert Mennel, Larry Norton, Peter Ravdin, Sheila Taube, Mark R. Somerfield, Daniel F. Hayes, and Robert C. Bast Jr

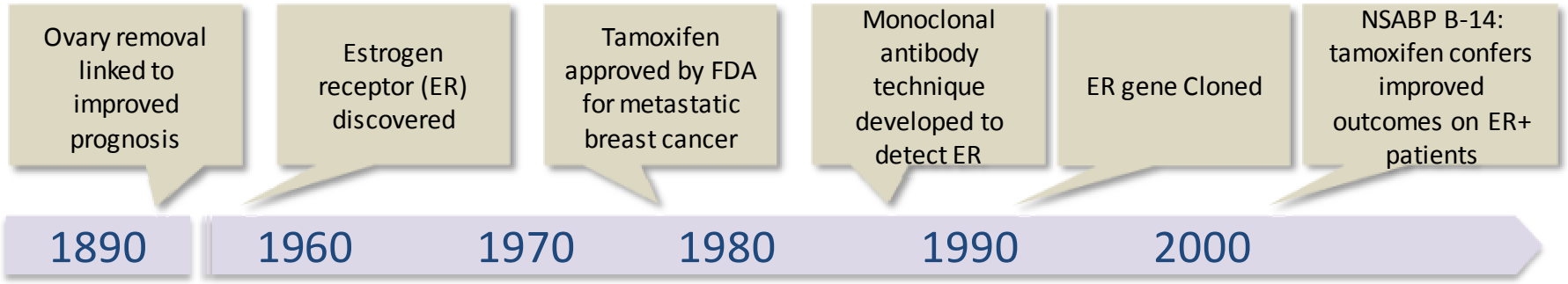
special article

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[†]

Estrogen and progesterone receptors as markers in breast cancer



- Should be measured on every primary invasive breast cancer.
- May be measured on metastatic lesions.
- Use ER and PgR status to identify patients most likely to benefit from endocrine therapy (both early and metastatic disease).
- For patients with DCIS who are candidates for hormonal therapy, data are insufficient to recommend routine measurement of ER and PgR for therapy recommendations.

ASCO

Adapted from Harris L et al. J Clin Oncol 2007

Estrogen and progesterone receptor assays in breast cancer

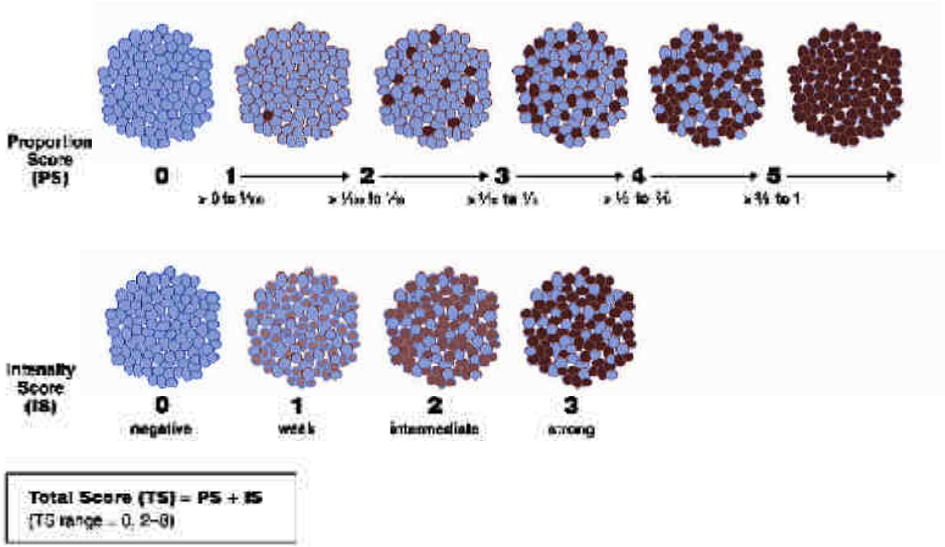
VOLUME 28 · NUMBER 16 · JUNE 1 2010

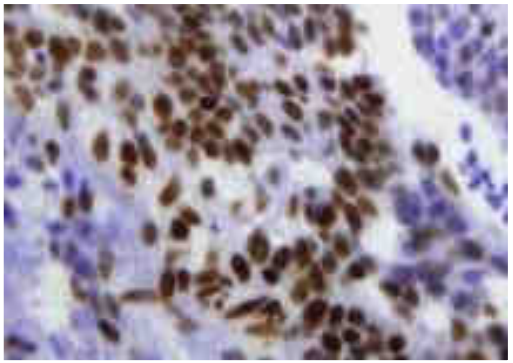
JOURNAL OF CLINICAL ONCOLOGY

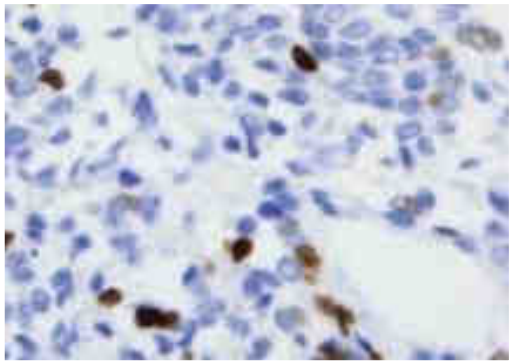
ASCO SPECIAL ARTICLE

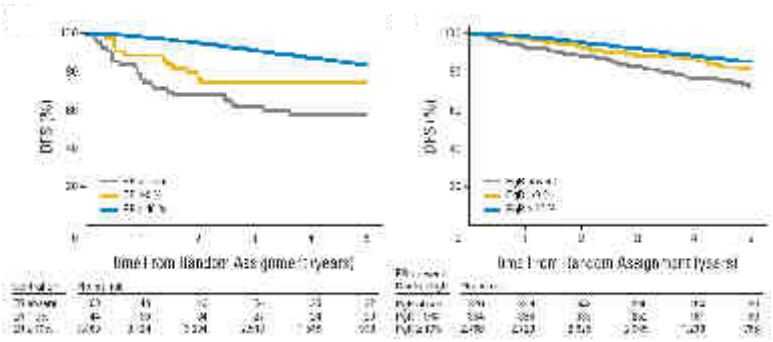
American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer

M. Elizabeth H. Hammond, Daniel F. Hayes, Mitch Dowsett, D. Craig Allred, Karen L. Hagerty, Sunil Badve, Patrick L. Fitzgibbons, Glenn Francis, Neil S. Goldstein, Malcolm Hayes, David G. Hicks, Susan Lester, Richard Love, Pamela B. Mangu, Lisa McShane, Keith Miller, C. Kent Osborne, Soonmyung Paik, Jane Perlmutter, Anthony Rhodes, Hironobu Sasano, Jared N. Schwartz, Fred C.G. Sweep, Sheila Taube, Emina Emilia Torlakovic, Paul Valenstein, Giuseppe Viale, Daniel Visscher, Thomas Wheeler, R. Bruce Williams, James L. Wittliff, and Antonio C. Wolff

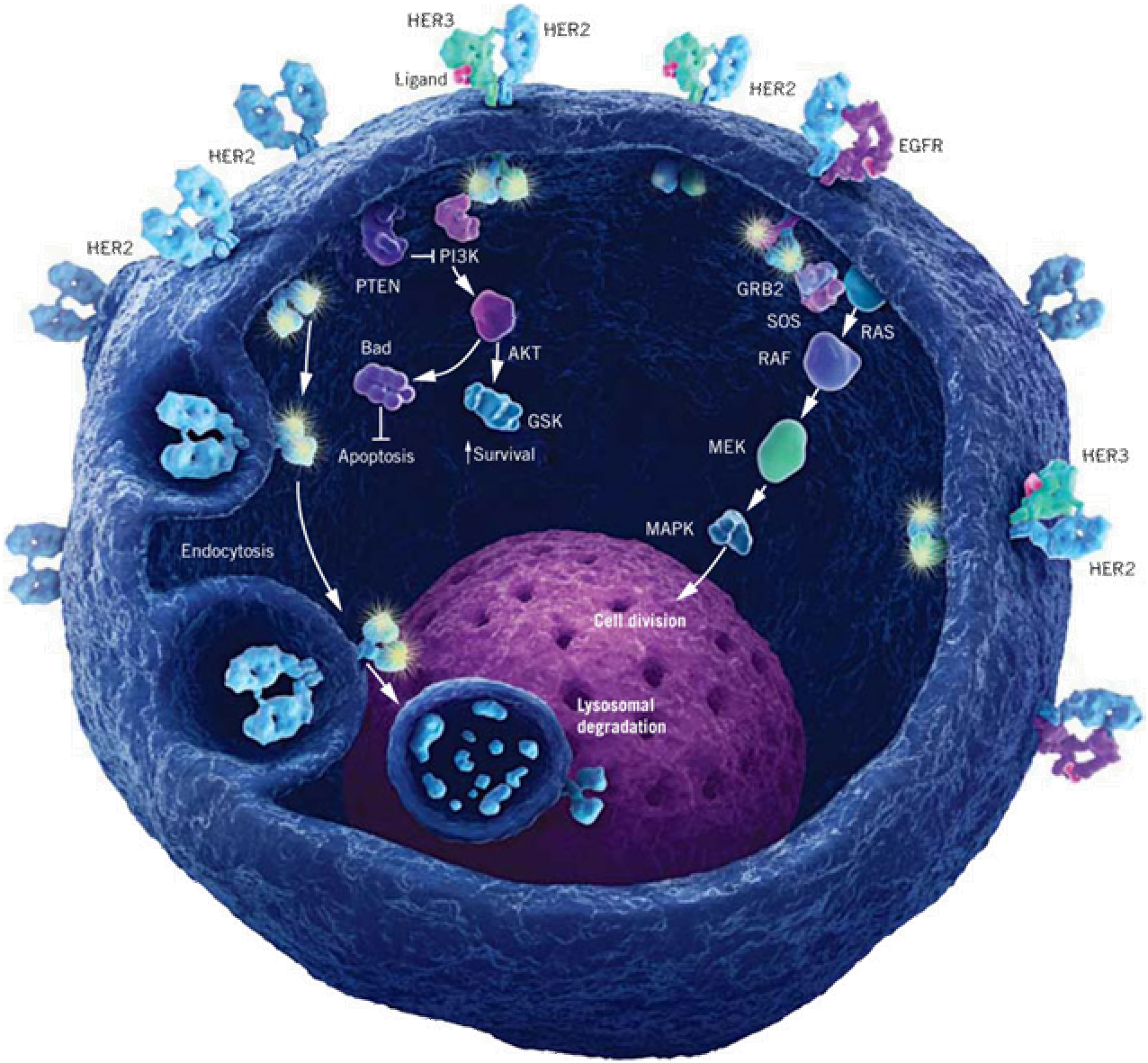




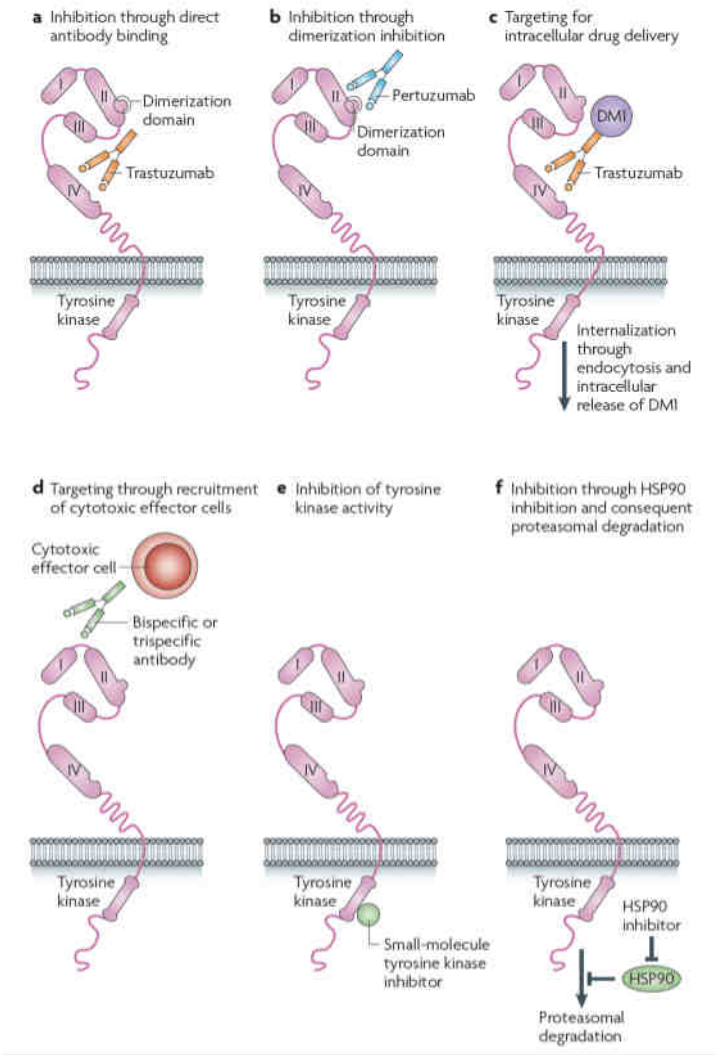




HER2 evaluation as a marker in breast cancer



HER2 inhibitory strategies



Agent	Molecular target	Mechanism of action	Highest development status (protocol number or NCT ID number)	Licensed indications
Antibody-based agents				
Trastuzumab (Herceptin; Genentech)	ERBB2	Suppression of ERBB2 signalling, ERBB2 stabilization, marks cells for immunological attack	• Launched for breast cancer • ERBB2-positive gastric cancer — Phase III (BO18255)	ERBB2-positive metastatic breast cancer, ERBB2-positive early breast cancer
Pertuzumab (Genentech/ Hoffmann-La Roche)	ERBB2	Dimerization inhibitor, marks cells for immunological attack	• Breast cancer — Phase III (NCT00567190) • Ovarian cancer — Phase II (NCT00096993, NCT00058552)	None
Trastuzumab–DM1 (Genentech)	ERBB2	Targeted delivery of a potent anti-microtubule cytotoxic agent	Breast cancer — Phase III (NCT00829166)	None
Ertumaxomab (Fresenius Biotech GmbH)	ERBB2	Bispecific affinity allows recruitment of T cells	Breast cancer — Phase II (NCT00351858, NCT00522457, NCT00452140)	None
AMG 888 or U3-1287 (Amgen)	ERBB3	Not yet defined	Phase I (NCT00730470)	None
TKIs				
Lapatinib (Tykerb; GlaxoSmithKline)	ERBB2	TKI	• Launched for breast cancer • ERBB2-positive gastric cancer — Phase III (NCT00486954, NCT00680901) • NSCLC — Phase II (NCT00528281) • Head and neck cancer — Phase II (NCT00490061, NCT00387127, NCT00424255) • Colorectal adenocarcinoma — Phase II (NCT00574171)	In combination with capecitabine for advanced ERBB2-positive breast cancer previously treated with an anthracycline, a taxane or trastuzumab
HKI-272 (Wyeth)	EGFR, ERBB2	Irreversible TKI	Breast cancer — Phase III (NCT00777101)	None
ARRY-334543 (Array BioPharma)	EGFR, ERBB2, ERBB4	Reversible TKI	Breast cancer — Phase II (NCT00710736)	None
BIBW-2992 (Boehringer Ingelheim)	EGFR, ERBB2	Irreversible TKI	• Breast cancer — Phase II (NCT00425854, NCT00826267, NCT00708214) • NSCLC — Phase III (NCT00425854, NCT00826267, NCT00708214) • Head and neck cancer — Phase II (NCT00514943)	None
Heat-shock protein inhibitors				
17-AAG (Bristol-Myers Squibb)	HSP90	Inhibitory activity reduces the stability of ERBB2, causes abrogation of ERBB2 signalling	• Multiple myeloma — Phase III (NCT00514371) • Breast cancer — Phase II (NCT00817362)	None
IPI-504 (Infinity Pharmaceuticals)	HSP90	Inhibitory activity reduces the stability of ERBB2, causes abrogation of ERBB2 signalling	• Multiple myeloma — Phase II and III (NCT00514371) • Breast cancer— Phase II (NCT00817362) • NSCLC — Phase II (NCT00431015) • Melanoma — Phase II (NCT00087386) • Ovarian cancer — Phase II (NCT00093496)	None

Importance of biomarker assay in cancer: Current molecular assays to select therapy in HER2 breast tumors

Company Location	Name of test Status	Technology
Biogenex San Ramon, California	InSite HER2/neu CB11 FDA approved	Immunohistochemistry assay using a monoclonal antibody directed against the internal domain of HER2/neu available either in automated or manual formats
Dako Glostrup, Denmark	HER2 FISH pharmDx Kit FDA approved	FISH assay to determine HER2 gene amplification in formalin-fixed, paraffin-embedded breast cancer specimens. Gene amplification is determined from the ratio between the number of signals from the hybridization of the HER2 gene probe and the number of signals from the hybridization of the reference chromosome 17 probe (green signals)
Dako	HercepTest FDA approved	Semi-quantitative immunohistochemistry assay for determination of HER2 protein overexpression in breast cancer tissues routinely processed for histological evaluation
Genomic Health	Oncotype DX CLIA validated	RT PCR–based assay analyzes the expression of a panel of 21 genes, among them HER2. Oncotype DX predicts disease recurrence and assesses benefit from certain types of chemotherapy
Invitrogen Carlsbad, California	SPOT-Light HER2 CISH Kit FDA approved	Chromogenic *in situ* hybridization (CISH) using a DNA probe. Quantifiable results are visualized under a standard brightfield microscope.
Monogram Biosciences	HERmark Breast Cancer Assay CLIA-validated	Proximity-based assay, which provides direct quantitative measurements of HER2 total protein and HER2 homodimer levels
Siemens Healthcare Diagnostics Erlangen, Germany	HER2/neu ELISA FDA approved	Sandwich enzyme immunoassay using mouse monoclonal for capture and a different biotinylated mouse monoclonal antibody for the detection of human HER2/neu protein. Detection is by direct chemiluminescence. Protein is quantified by spectrophotometry
Ventana-Roche Tucson	Inform HER2 Silver in situ Hybridization Approved in Europe and elsewhere but not by FDA	Fully automated silver *in situ* hybridization assay for HER2 and chromosome 17 detection. Chromogenic signals are detected through the use of silver deposition technology. Results and morphological significance can be interpreted using conventional brightfield microscopy
Ventana-Roche	Pathway anti-HER2/neu (Clone CB11) FDA approved	Semiquantitative immunohistochemistry assay using a monoclonal antibody for the detection of c-erbB-2 (HER2) antigen using Ventana's family of automated instrument platforms
Vysis (Abbott)	PathVysion HER2 DNA Probe Kit FDA approved	Fluorescence *in situ* hybridization (FISH) assay to determine *HER2* amplification, using LSI HER2 probe, which spans *HER2*, and CEP 17 probe, which hybridizes to the alpha satellite DNA located at the centromere of chromosome

Allison, M. Nature Biotech 2010

Molecular assays to select therapy in HER2 breast tumors

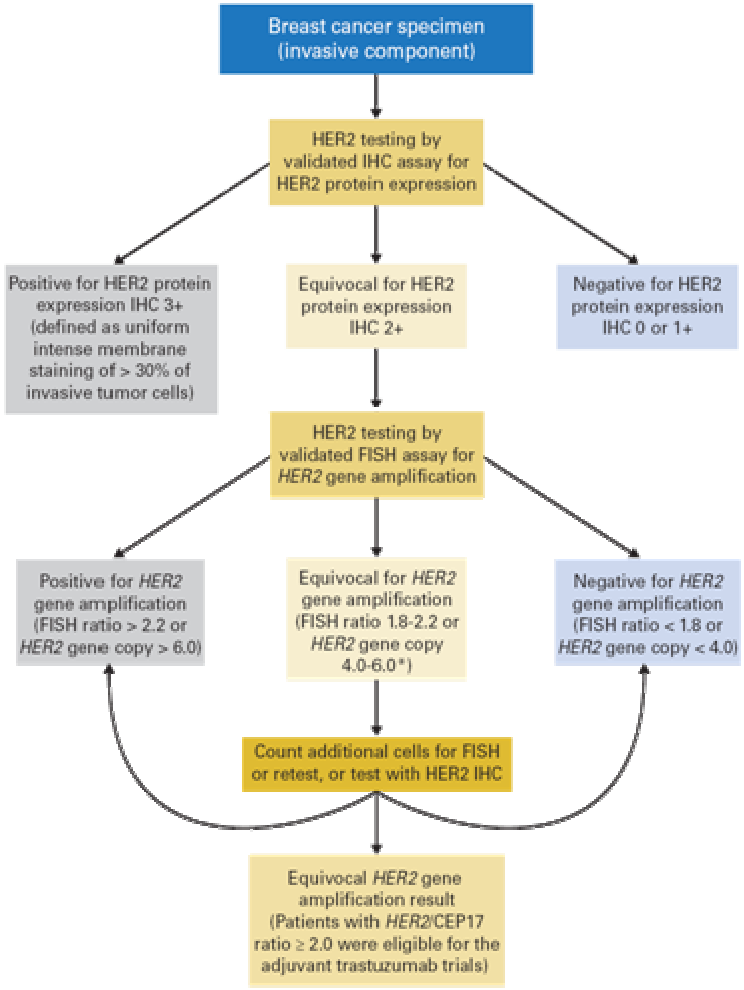
VOLUME 25 · NUMBER 1 · JANUARY 1 2007

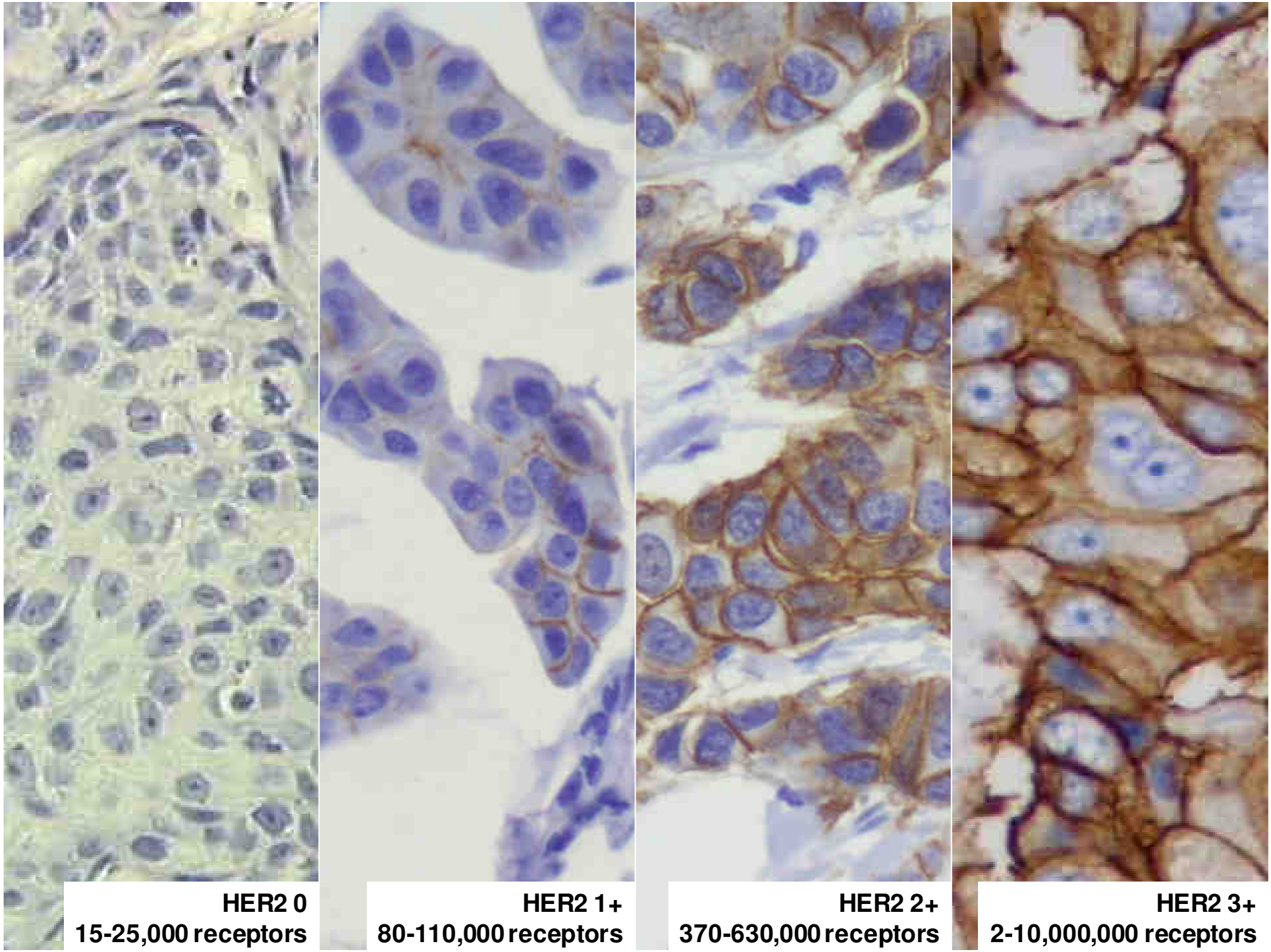
JOURNAL OF CLINICAL ONCOLOGY

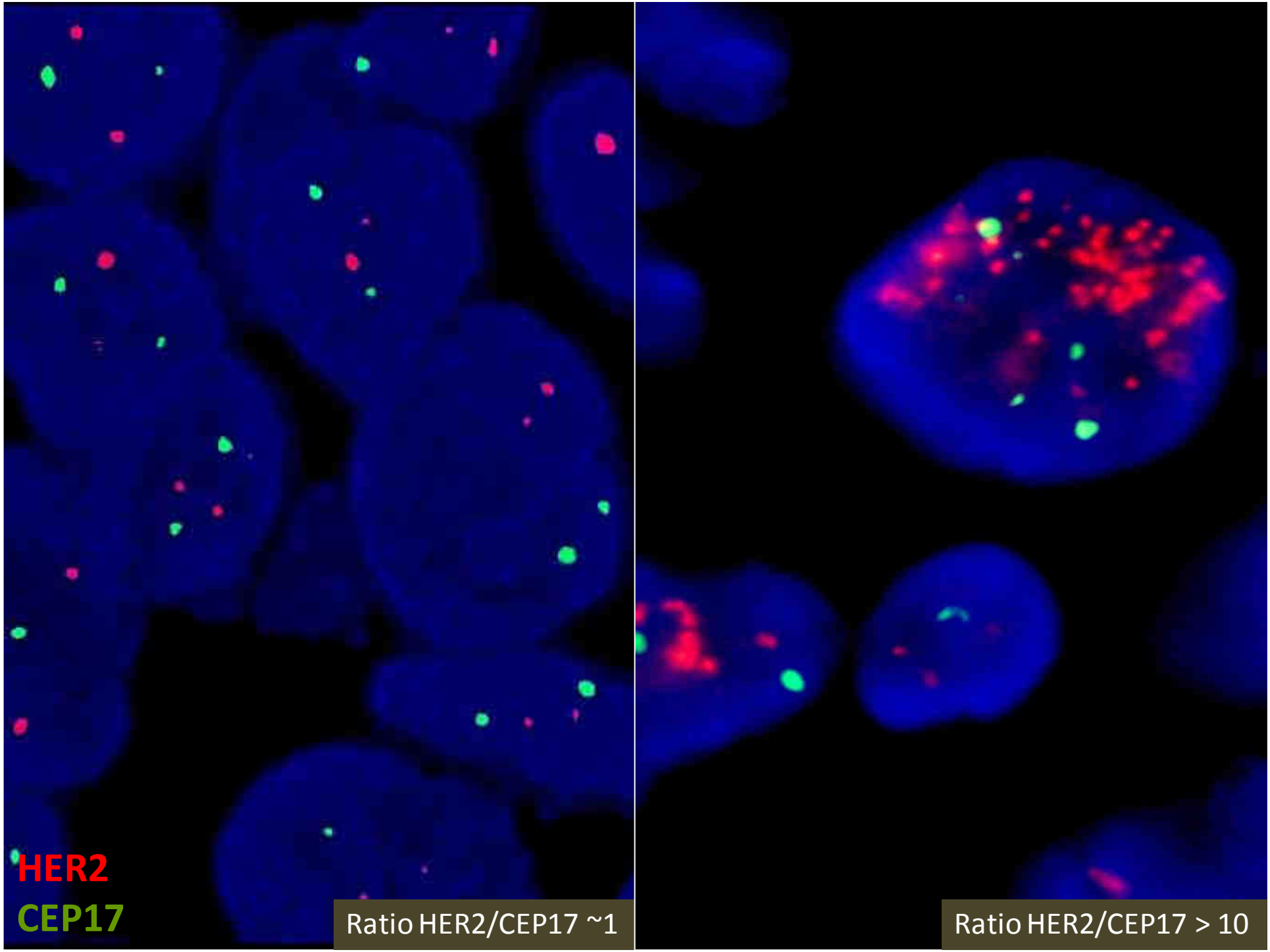
ASCO SPECIAL ARTICLE

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

Antonio C. Wolff, M. Elizabeth H. Hammond, Jared N. Schwartz, Karen L. Hagerty, D. Craig Allred, Richard J. Cote, Mitchell Dowsett, Patrick L. Fitzgibbons, Wedad M. Hanna, Amy Langer, Lisa M. McShane, Soonmyung Paik, Mark D. Pegram, Edith A. Perez, Michael F. Press, Anthony Rhodes, Catharine Sturgeon, Sheila E. Taube, Raymond Tubbs, Gail H. Vance, Marc van de Vijver, Thomas M. Wheeler, and Daniel F. Hayes




HER2 0
15-25,000 receptors
HER2 1+
80-110,000 receptors
HER2 2+
370-630,000 receptors
HER2 3+
2-10,000,000 receptors


HER2
CEP17
Ratio HER2/CEP17 ~1
Ratio HER2/CEP17 > 10

Proliferation in breast cancer: Strong evidence for prognostication?

Vol. 103, Issue 22 | November 16, 2011

COMMENTARY

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

Highlights of the St Gallen International Expert Consensus on early breast cancer 2011: Strategies for subtypes

Intrinsic Subtype (1)	Clinico-pathologic definition	Notes	Type of therapy	Notes on therapy
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.	Endocrine therapy alone	Few require cytotoxics (e.g. high nodal status or other indicator of risk: see text).
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)'.	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)' ER and/or PgR positive Any Ki-67 HER2 over-expressed or amplified	Both endocrine and anti-HER2 therapy may be indicated.	Cytotoxics + anti-HER2 + endocrine therapy	No data are available to support the omission of cytotoxics in this group.
Erb-B2 overexpression	**'HER2 positive (non luminal)'** HER2 over-expressed or amplified ER and PgR absent		Cytotoxics + anti-HER2	Patients at very low risk (e.g. pT1a and node negative) may be observed without systemic adjuvant treatment.
'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.	Cytotoxics	
	Special histological types**		Endocrine therapy	
	A. Endocrine responsive		Cytotoxics	Medullary and adenoid cystic carcinomas may not require any adjuvant cytotoxics (if node negative).
	B. Endocrine nonresponsive			

Goldhirsch, A. et al. Ann Oncol 2011