Molecular Characterization of Breast Cancer: The Clinical Significance

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The Plan

- To present an overview of molecular characterization of breast cancer and its impact on clinical care and patient outcome

Molecular Characterization of Breast Cancer

The Way We Were

- Pathology diagnosis was based on
  - Gross examination
  - Light microscopy
- The most common diagnosis was:
  - Undifferentiated malignant neoplasm

Molecular Characterization of Breast Cancer

Recent Advances

- The emergence of new technologies
- Molecular characterization of tumors
- Stratification of patients for therapy based on tumor characteristics
- A paradigm shift in patient care

Integration of Breast Health Services

Survivorship

Nurse Navigator
Breast Care
Coordinator

Radiology

Patient and
Physician
Education

Pathology

Surgery

Data Management

Medical Oncology

Research

Radiation
Therapy

Psychosocial
Support

Genetic
Counseling

Plastic and
Reconstructive
Surgery

Molecular Characterization of Breast Cancer

Changing Role of Pathologists

- Establish a diagnosis
- Classify a neoplasm
- Differentiate between a primary versus a metastatic tumor
- Predict a response to therapy
- Provide a prognosis

Molecular Characterization of Breast Cancer

Prognosis: Treatment Planning

- Tumor size/type
- Histologic grading
- Lympho-vascular invasion
- Lymph node status
- Status of surgical margins
- Presence or absence of ductal carcinoma in situ
- Multicentricity/multifocality
- Presence or absence of nipple involvement and ulceration

Molecular Characterization of Breast Cancer

Prediction of Response to Therapy

- Assessment of the status of expression of estrogen and progesterone receptors
  - Endocrine therapy
- Assessment of the pattern of expression/gene amplification of Her-2/neu oncogene
  - Herceptin therapy
- Assessment of new genetic molecular pathways
  - Molecular/adjuvant chemotherapy

Molecular Characterization of Breast Cancer

The Significance of Accurate Prognostic/Predictive Testing

- Selection of those patients who will most likely benefit from systemic therapy
- Offering personalized medicine with greater safety and effectiveness
- Providing affordable and cost-effective care

Molecular Characterization of Breast Cancer

The Issue

- Up to 30 % of women with node negative breast caner die of the disease regardless of adjuvant therapy
- Up to 70% survive without adjuvant therapy
- Heterogeneity in breast cancer can not be captured by traditional prognostic factors

Molecular Characterization of Breast Cancer

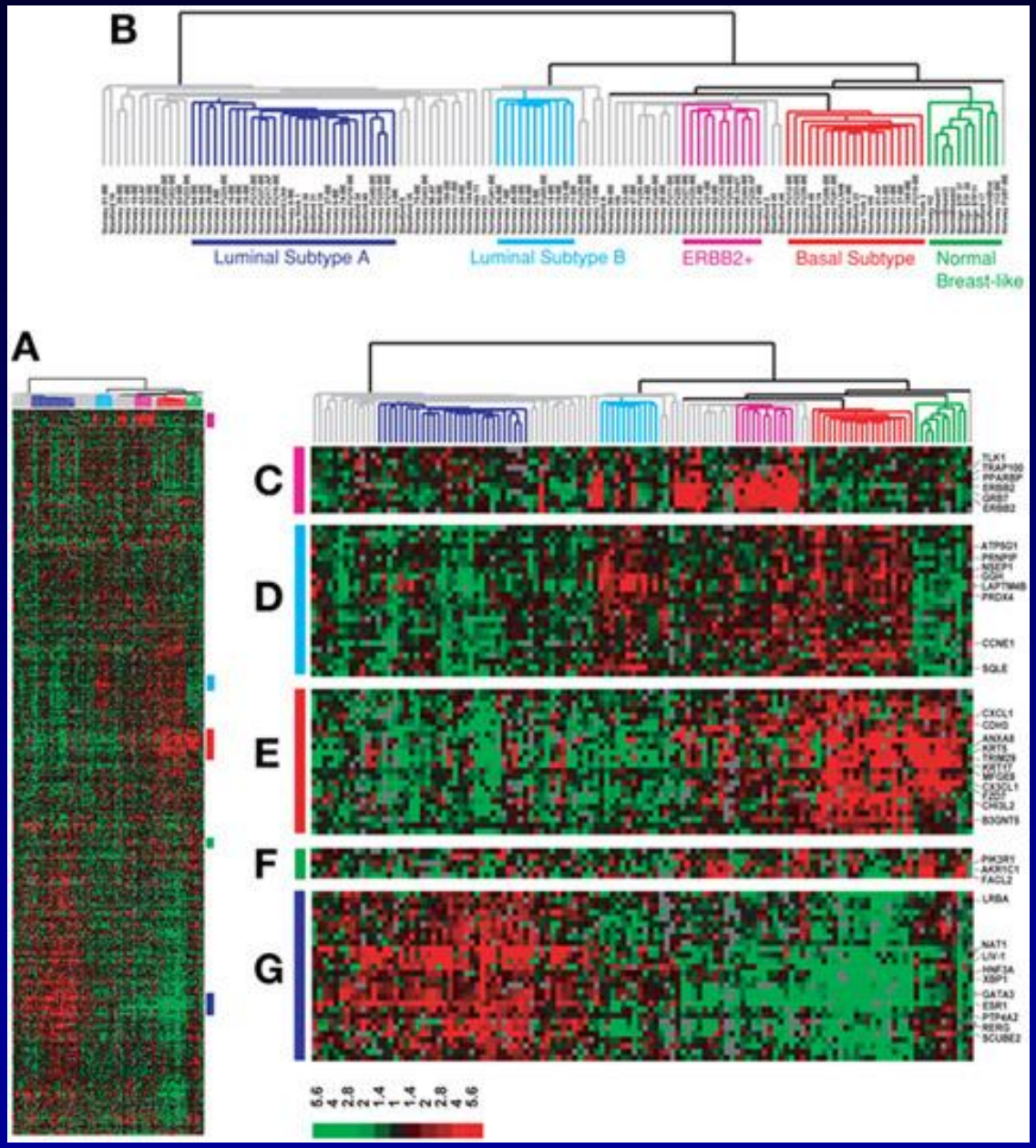
The Rationale

- Better definition of the biological complexity of breast cancer
- Development of more sophisticated and sensitive testing to better stratify patients for systemic therapy

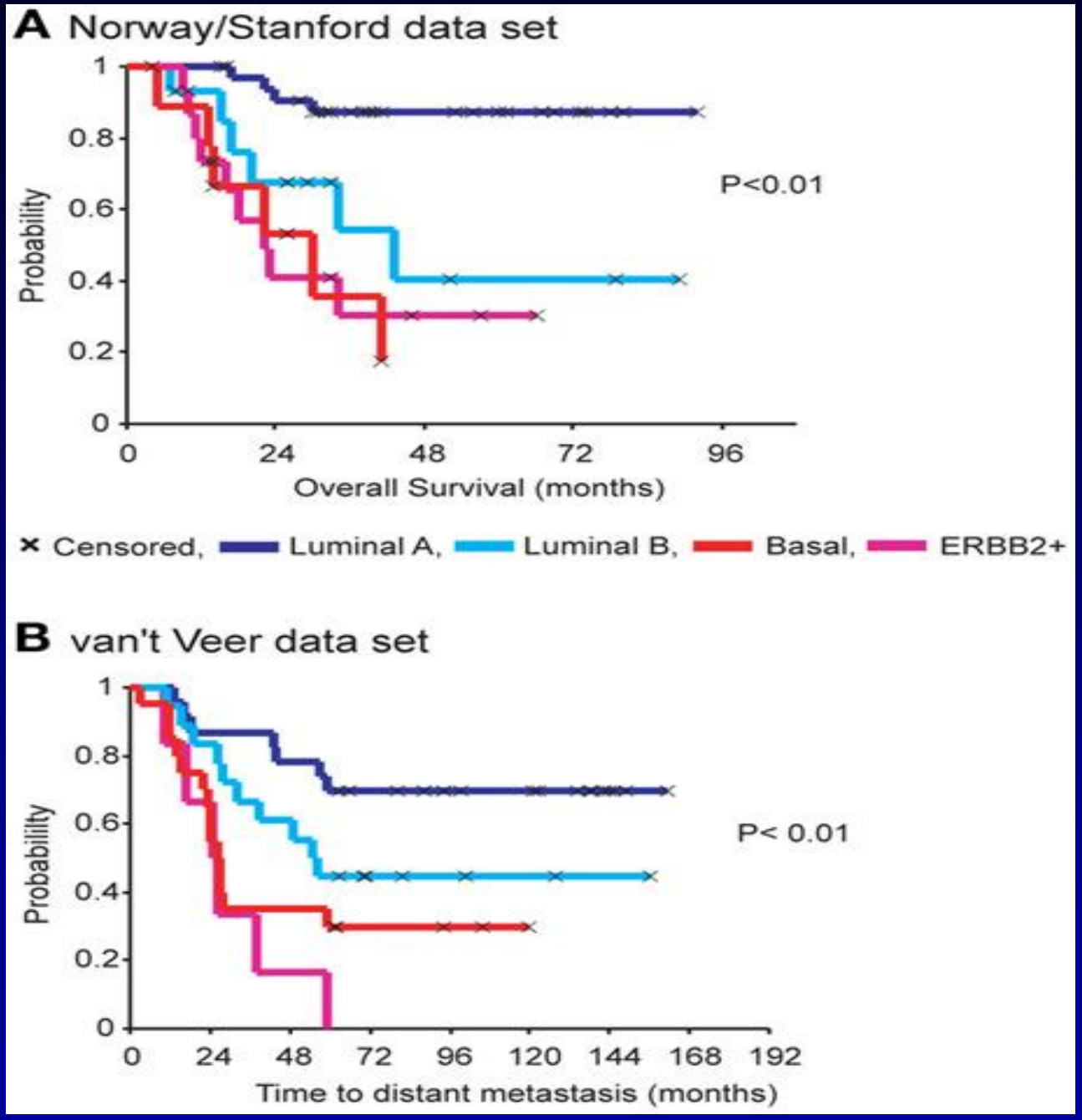
Molecular Characterization of Breast Cancer

The Process

- Gene expression profiling provided an opportunity to classify tumors at a genomic level into subclasses of potential prognostic and predictive significance



Sorlie T: Molecular Classification of Breast Tumors. Methods in Molecular Biology 2007;360:91-114



Kaplan-Meier analysis of disease outcome in two patient cohorts

(A) Overall survival for 72 patients with locally advanced breast cancer in the Norway cohort. The normal-like tumor subgroups were omitted from both data sets in this analysis.

(B) Time for development of distant metastasis in 97 sporadic cases.

Sorlie T: Molecular Classification of Breast Tumors. Methods in Molecular Biology 2007;360:91-114

Molecular Characterization of Breast Cancer

Breast Cancer is a Family of Diseases

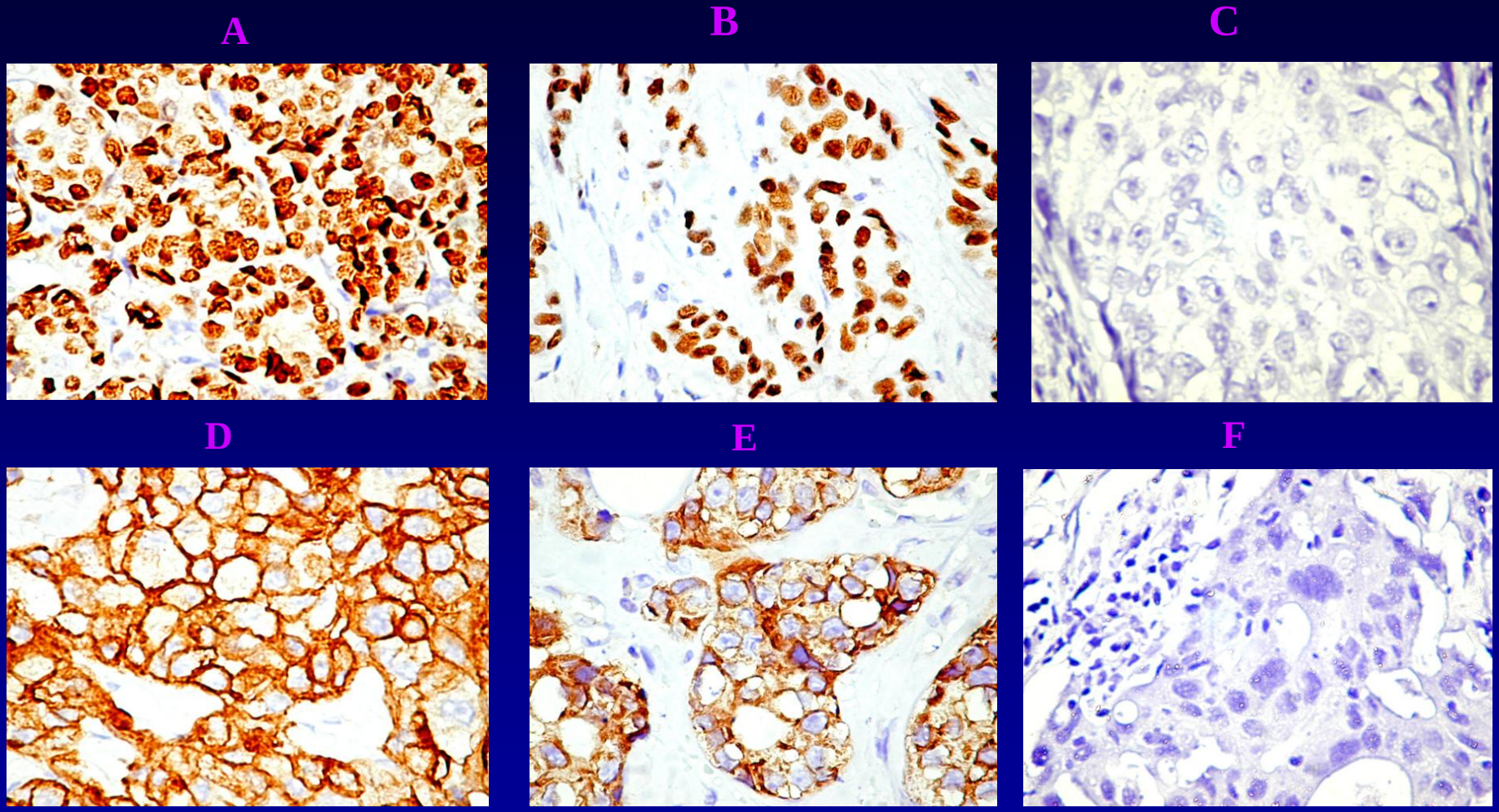
- ER+ (Luminal A) (56%-61%)
- ER+ (Luminal B) (9%-16%)
- Her-2/neu + (8%-16%)
- Basal-like/Triple negative (8%-20%)
- Unclassified/normal breast-like (6%-10%)

Molecular Characterization of Breast Cancer

Luminal Subtypes

- Luminal A/B – generally carry a good prognosis and show a favorable response to endocrine therapy
- Luminal A – better prognosis than type B
- Luminal B – show a moderate expression of gene expressed by the breast luminal cells, higher proliferation rate and lower progesterone receptor

ER+ Luminal Type



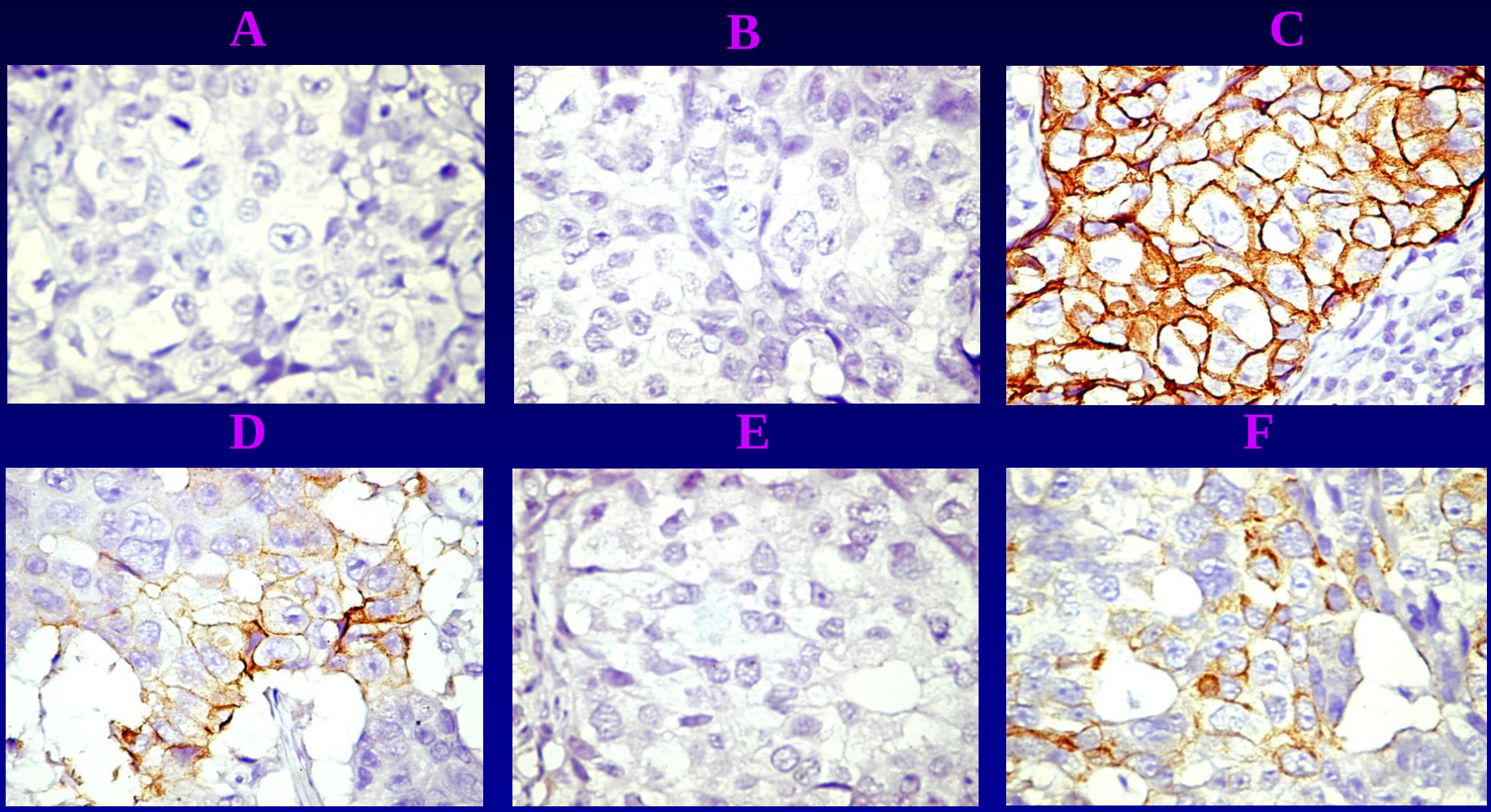
Immunohistochemical profile of luminal A subtype. ER positive (A), PR positive (B), HER2 negative ©, CK8/18 positive (D), Bcl-2 positive (E), and EGFR negative (F)

Molecular Characterization of Breast Cancer

Her-2/neu + Type

- Presents as two distinct forms
  - ER-
  - ER+
- Frequently associated with DCIS
- Associated with poor prognosis

Her-2/neu + Type



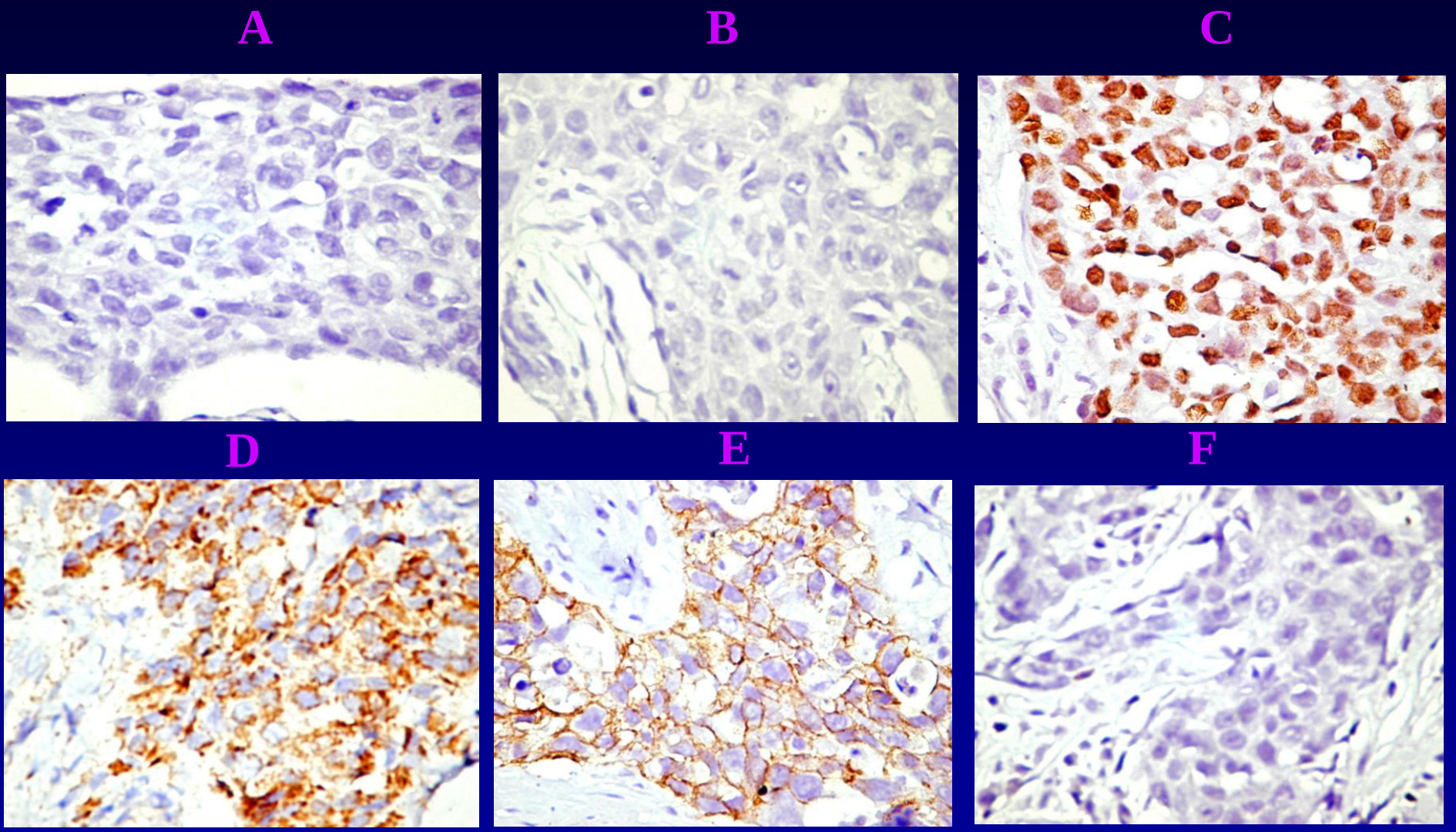
Immunohistochemical profile of HER2 subtype. ER negative (A), PR negative (B), HER 2 positive +3 ©, EGFR focal positive (D), CK5 negative (E), CK8/18 heterogeneous and moderate positive (F)

Molecular Characterization of Breast Cancer

Basal-Like Breast Cancers

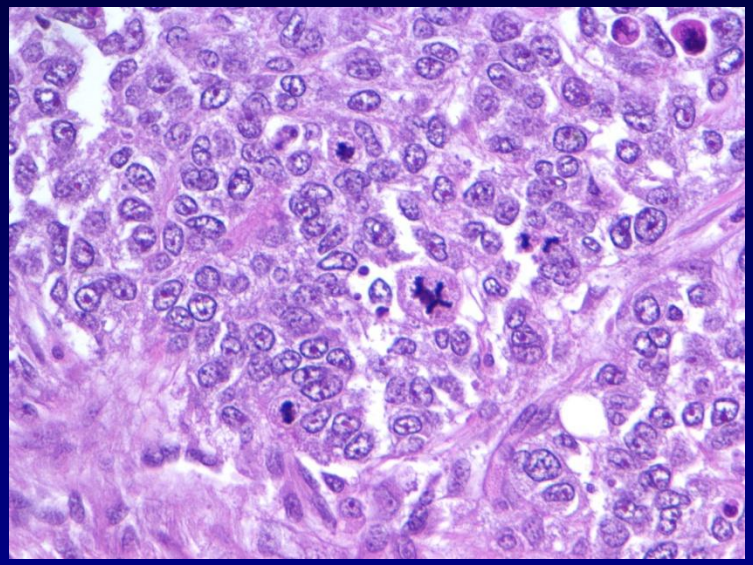
- No internationally accepted definition
- Triple negative phenotype (ER-, PR-, and HER2-/neu-)
- Expression of high molecular weight cytokeratin (CK 5/6, CK 14, CK 17), EGFR, CKIT, P63, E-Cadherin, SMA

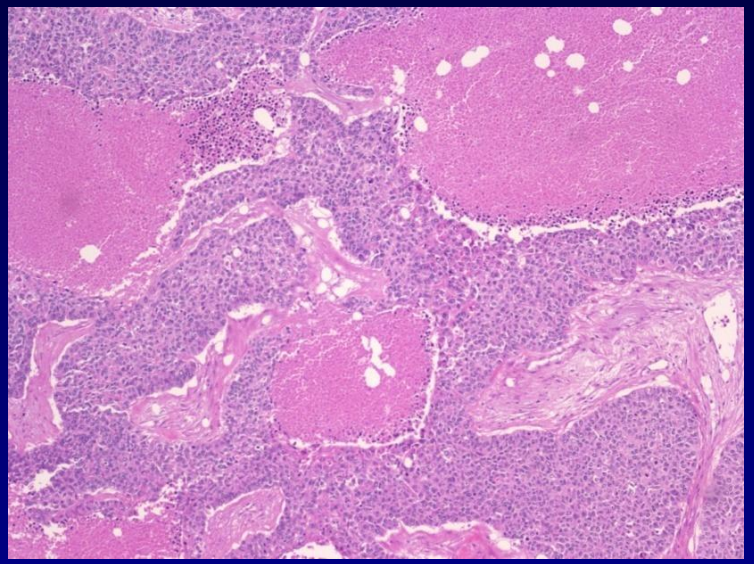
Molecular Characterization of Breast Cancer



Immunohistochemical profile of basal-like breast carcinoma. ER negative (A), HER2 negative (B), p53 positive (C), CK5 positive (D), EGFR positive (E), and Bcl-2 negative (F)

Basal-Like Breast Cancers Morphologic Features





- High mitotic rate
- Geographic, central necrosis
- Lymphoplasmacytic infiltrate with the medullary carcinoma - like features

Molecular Characterization of Breast Cancer

Biology of Basal-Like Breast Carcinoma

- Account for 10%-20% of all breast cancer
- More frequently affects younger patients
- More prevalent in African American women
- More prevalent in those with germline BRCA-1 mutation carriers
- Are biologically more aggressive
- Have a unique metastatic pattern
- Majority of death occurs in the first 5 years after primary treatment

Molecular Characterization of Breast Cancer

Triple Negative Breast Cancer

- Triple-negative tumors represent the majority of cancers within the basal-like subtype
- Not all triple negative breast cancers display the basal-like phenotype and vice versa
- Currently no specific targeted approach is available for triple negative tumors

Molecular Characterization of Breast Cancer

Possible Molecular Targeted Therapies for the Treatment of Triple Negative Breast Cancer

Molecular Targets	Agents tested in clinical phase trials
EGFR	Anti-EGFR antibody: cetuximab EGFR tyrosine kinase inhibitor: erlotinib
c-kit	Multiple tyrosine kinase inhibitors: imatinib, sunitinib
Src	Multiple tyrosine kinase inhibitors: dasatinib
mTOR	mTOR inhibitor: everolimus

Kurebayashi J: Possible treatment strategies for triple-negative breast cancer on the basis of molecular characteristics. Breast Cancer 16:275-280, 2009.

Molecular Characterization of Breast Cancer

Current Status

- Patients with hormone receptor positive, Her-2/neu oncogene negative tumors benefit from adjuvant hormone therapy
- Patients with Her-2/neu positive tumors, any ER/PR or menopausal status derive major benefits from the administration of Herceptin ® therapy in combination with chemotherapy

Molecular Characterization of Breast Cancer

Current Status

- There is a need to develop additional forms of systemic therapy for those tumors that fail to express hormone receptors and/or Her-2/neu oncogene
- It is essential to search for factors that can better stratify patients for systemic therapy

Molecular Characterization of Breast Cancer

Assessment of New Genetic Pathways

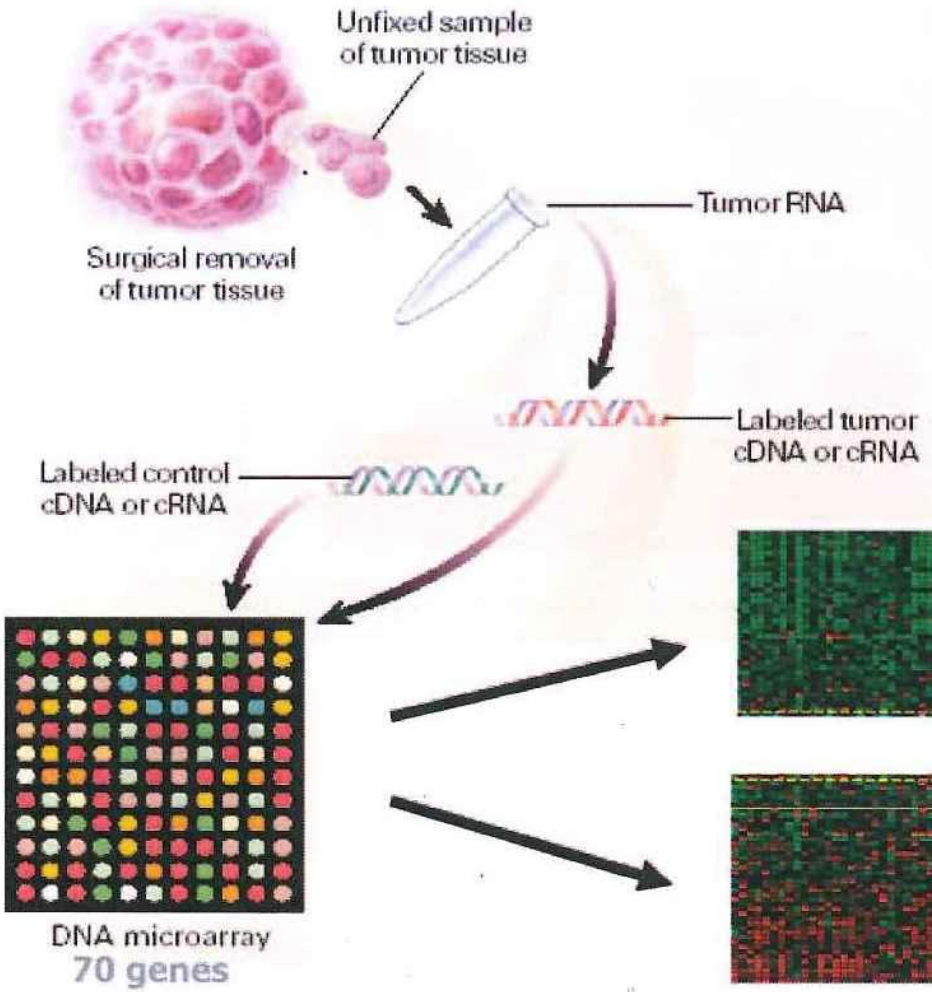
- MammaPrint 70-gene assay (Agendia BV, Amsterdam, the Netherlands)
- Onco*type* DX 21-gene assay (Genomic Health, Redwood City, California)
- H/I (AvariaDX, Carlsbad, California)
- Others…….

MammaPrint

Biological Function	MammaPrint Gene Count
Metabolism	7
Cell cycle and DNA replication	12
Extracellular matrix adhesion and remodeling	5
Growth, proliferation, transformation and cell death	17
General signal transduction and intracellular transport	3
Growth factor	7
Motility or actin filament related	5
Intracellular hydrolase	1
Immune response	1
Neuropeptide	1
Predicted transmembrane protein with unknown function	2
Predicted transcriptional control or DNA binding proteins	5
Unknown function	4
Total Gene Count	70

Dutch Health Care Insurance Board (CVZ)/ NKI

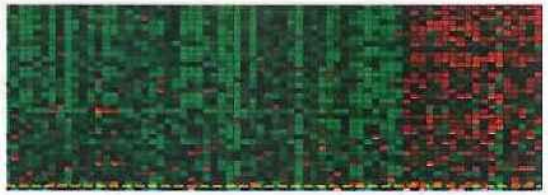
'Raster trial'



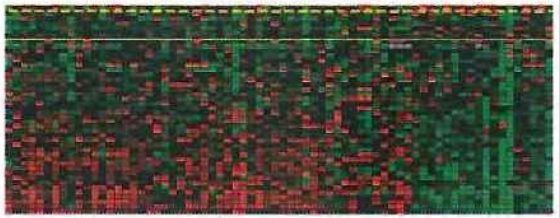
RASTER

- ≤ 60 yrs, lymph node-negative
- Constructive Technology Assessment
- 2004-2006: ~650 patients, 17 Dutch hospitals

Preliminary: ~50% low, ~50% high risk

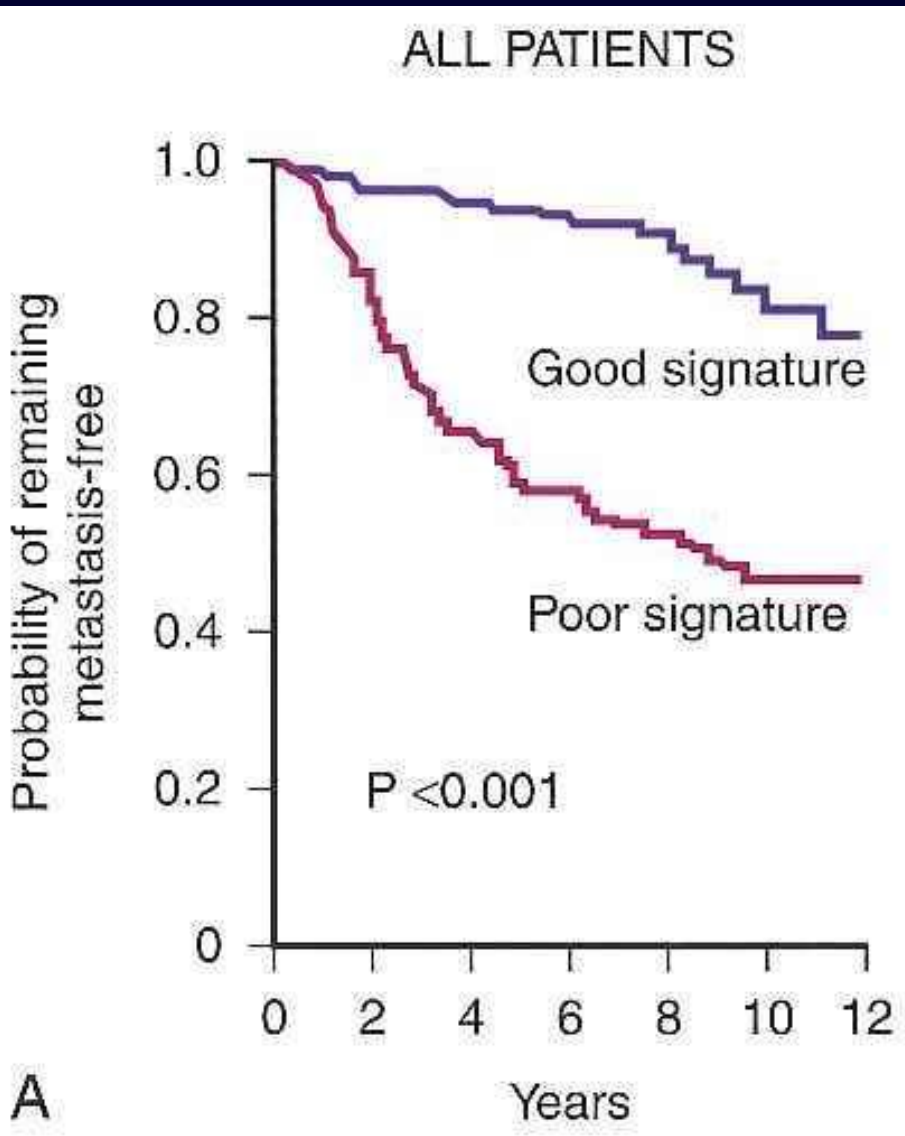


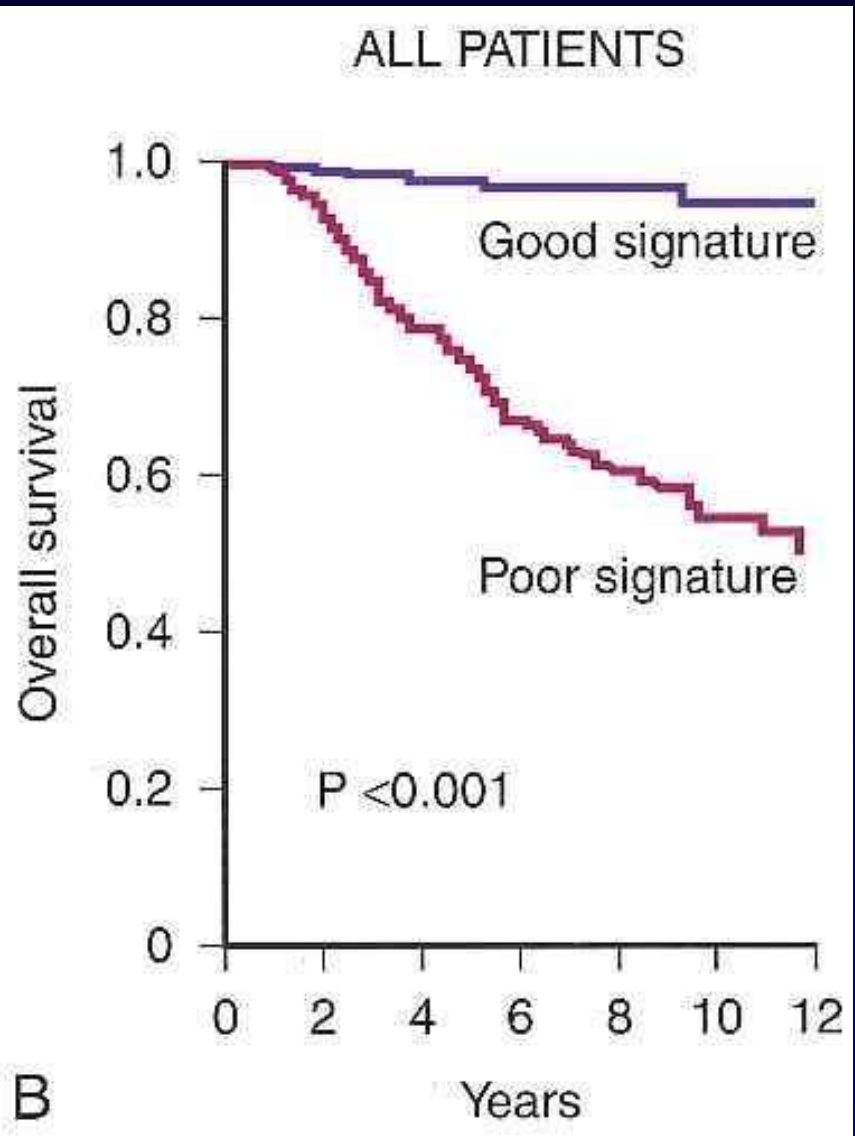
Good signature
Low risk



Poor signature
High risk

Figure 1. *RASTER study design. From Sauter G and Simon R. Predictive Molecular Pathology. N Engl J Med 347(25): 1995-1996, 2002. Copyright © 2002 Massachusetts Medical Society. All rights reserved. Adapted with permission, 2007.*





Validation of the 70-gene classifier. A and B, kaplan-Meier analysis of the probability that a patient would remain free of distant metastases and the probability of overall survival among all patients.

Oncotype DX® 21-Gene Recurrence Score (RS) Assay

16 Cancer and 5 Reference Genes From 3 Studies

PROLIFERATION
Ki-67
STK15
Survivin
Cyclin B1
MYBL2

ESTROGEN
ER
PR
Bcl2
SCUBE2

GSTM1

BAG1

INVASION
Stromelysin 3
Cathepsin L2

CD68

Her2
GRB7
Her2

REFERENCE
Beta-actin
GAPDH
RPLPO
GUS
TFRC

RS =
+ 0.47 x Her2 Group Score
- 0.34 x ER Group Score
+ 1.04 x Proliferation Group Score
+ 0.10 x Invasion Group Score
+ 0.05 x CD68
- 0.08 x GSTM1
- 0.07 x BAG1

Category	RS (0 -100)
Low risk	**RS <18**
Int risk	**RS 18 - 30**
High risk	**RS ≥ 31**

Paik et al. N Engl J Med. 2004;351:2817-2826.

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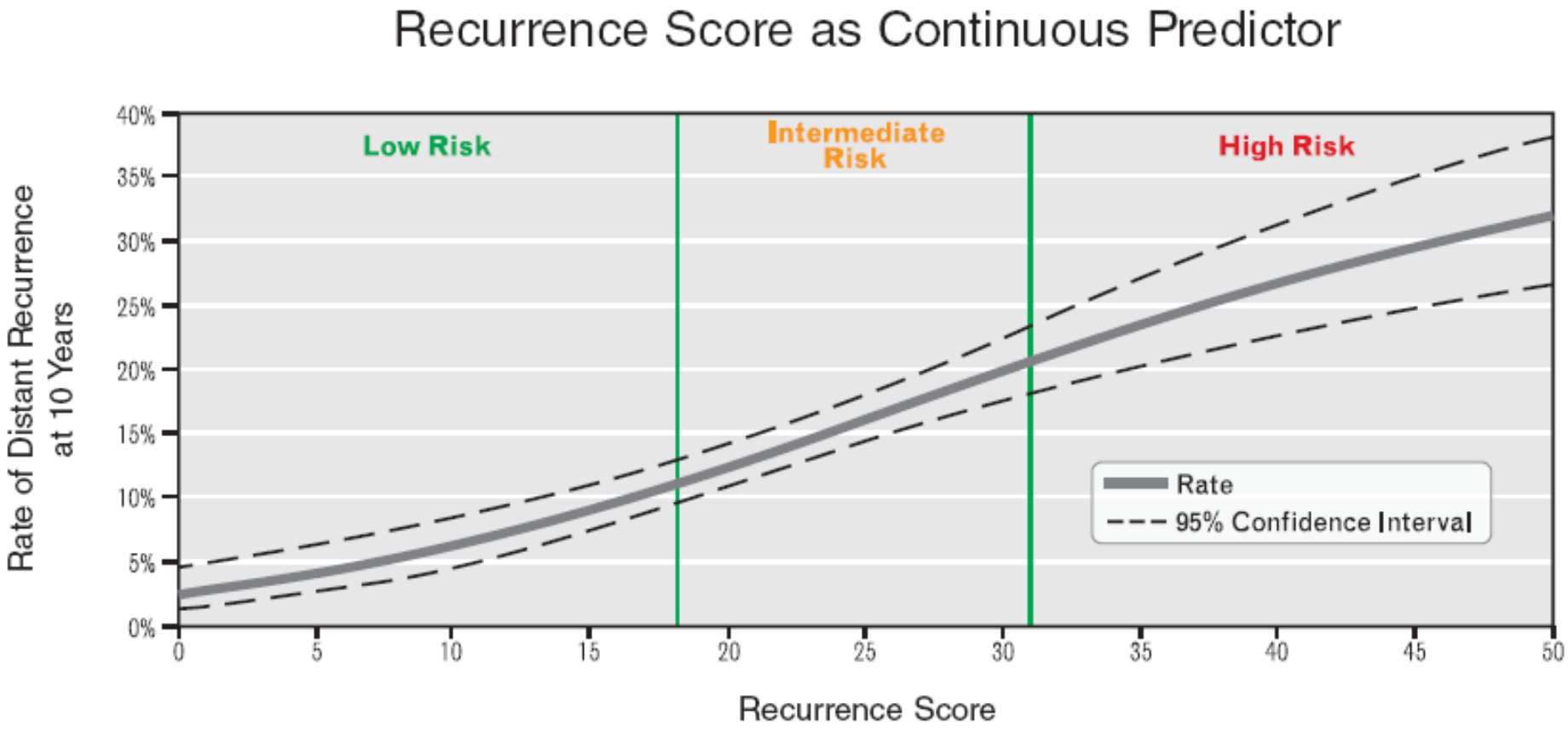
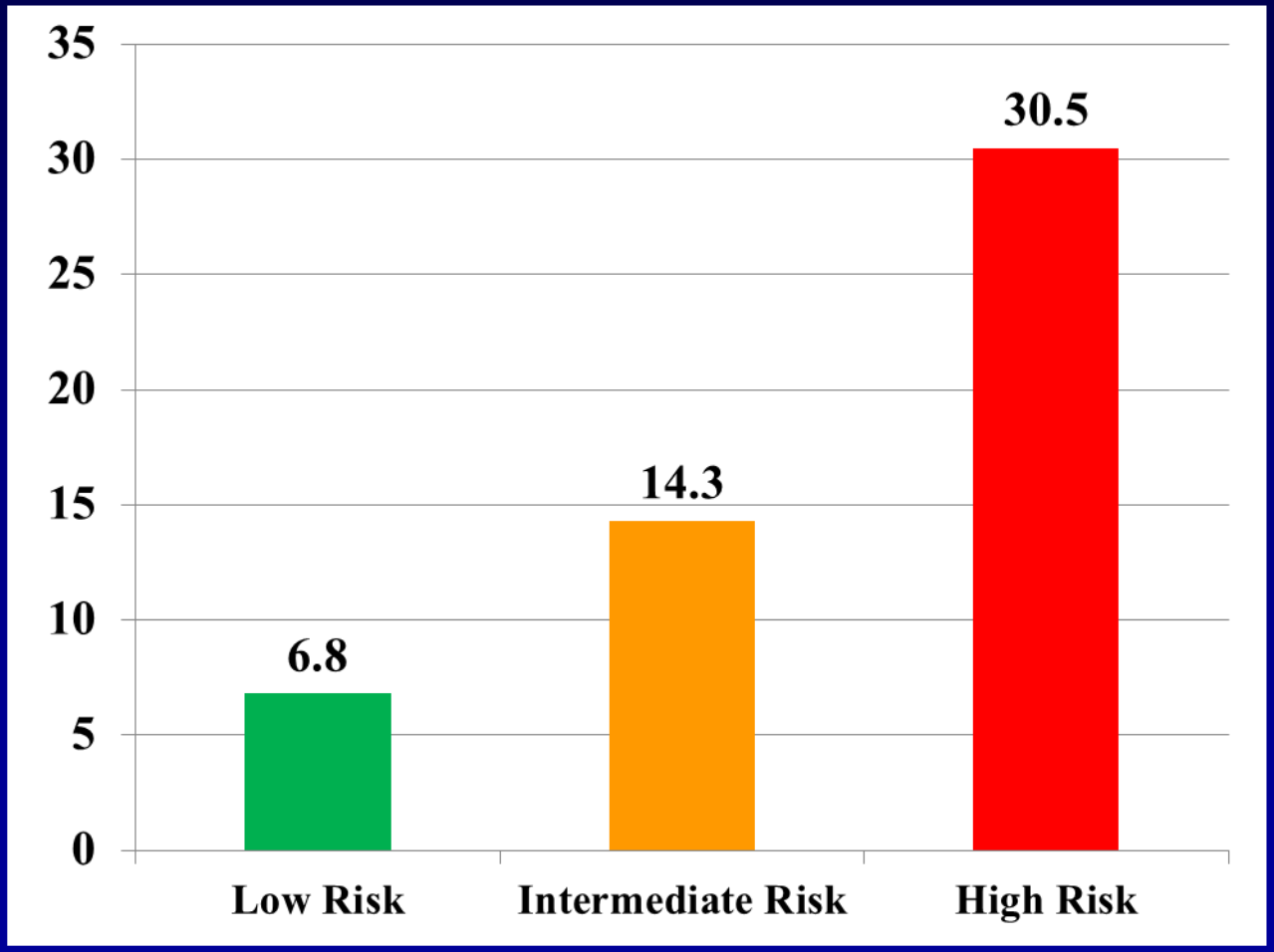
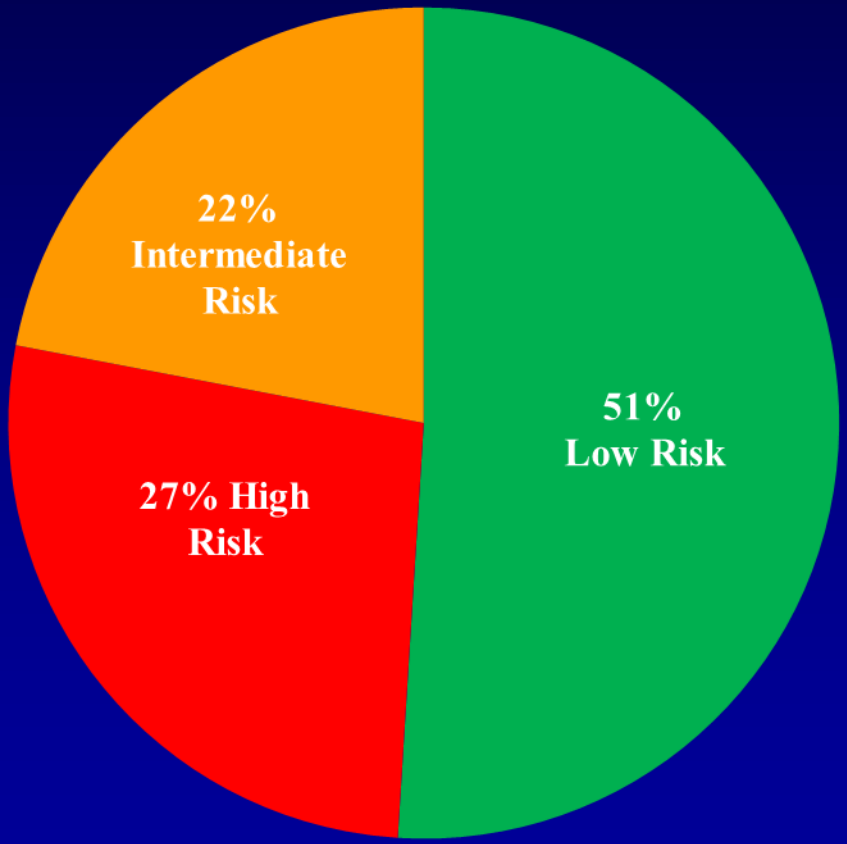


Rate of Distant Recurrence at 10 Years by Oncotype *DX* Risk Group in the Clinical Validation Study



Population Distribution by Onco*type* DX Risk Group in the Clinical Validation Study

Rate of Distant Recurrence at 10 Years



Molecular Characterization of Breast Cancer

Current Clinical Trails

- TAILORx
  - Trail Assigning Individualized Options for Treatment
- MINDACT
  - Microarray In Node-Negative Disease May Avoid Chemotherapy Trial
- Rx PONDER
  - Rx for Positive Node Endocrine Response Breast Cancer

Comparison of the TAILORx, MINDACT, and RxPONDER trials

Trial/Characteristic	TAILORx	MINDACT	RxPONDER
Coordinating group	ECOG	EORTC	SWOG
Design	Prospective, randomized, open-label trial	Prospective, randomized, open label trial	Prospective, randomized, open-label trial
No, of patients registered/randomized	10,263/6908	6000/1920	8800/4400
Biomarker	Onco*type* DX	MammaPrint	Onco*type* DX
Key eligibility criteria	ER+, HER2-, LN-	LN- or 1~3 LN+	ER+, HER2-, 1~3 LN+
Randomize group	RS 11~25	Discrepant risk between MammaPrint and Adjuvant! Online	RS <25
Randomized treatment	Endocrine vs endocrine + chemotherapy	Treatment by clinical criteria (Adjuvant! Online) or gene expression (MammaPrint)	Endocrine vs endocrine + chemotherapy
Primary end point	Disease-free survival	Distant metastasis-free survival	Disease-free survival
Status	Completed accrual	Completed accrual	Accruing

Tissue banking is a common feature for all 3 trials.

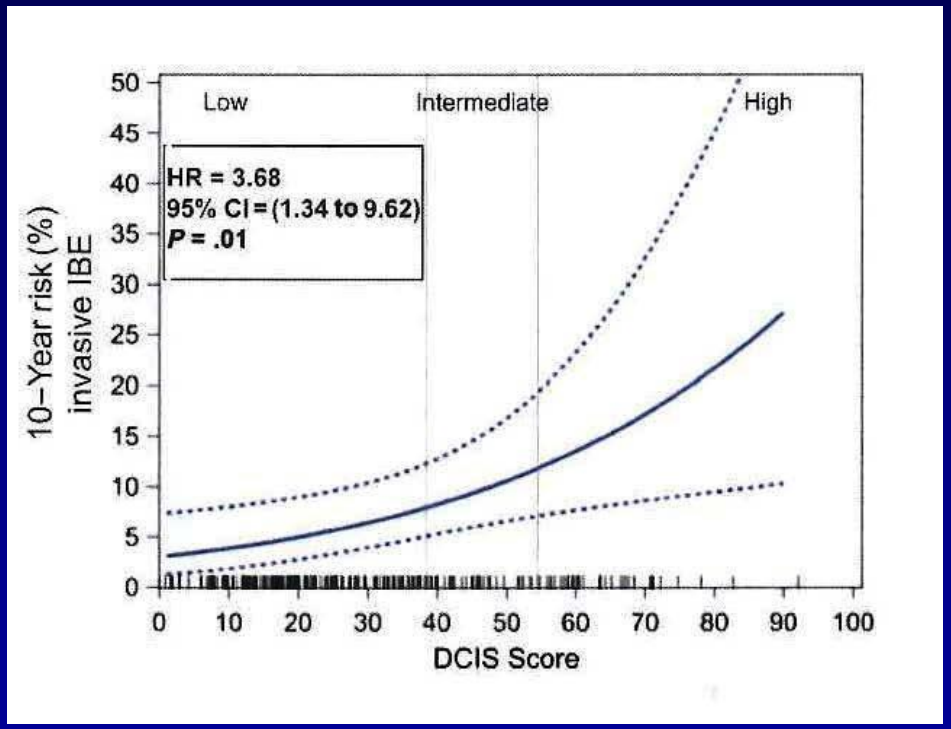
ECOG indicates Eastern Cooperative Oncology Group; EORTC, European Organization of Research and Treatment of Cancer; ER, estrogen receptor; LN, lymph node; RS, recurrence score; SWOG, Southwest Oncology Group

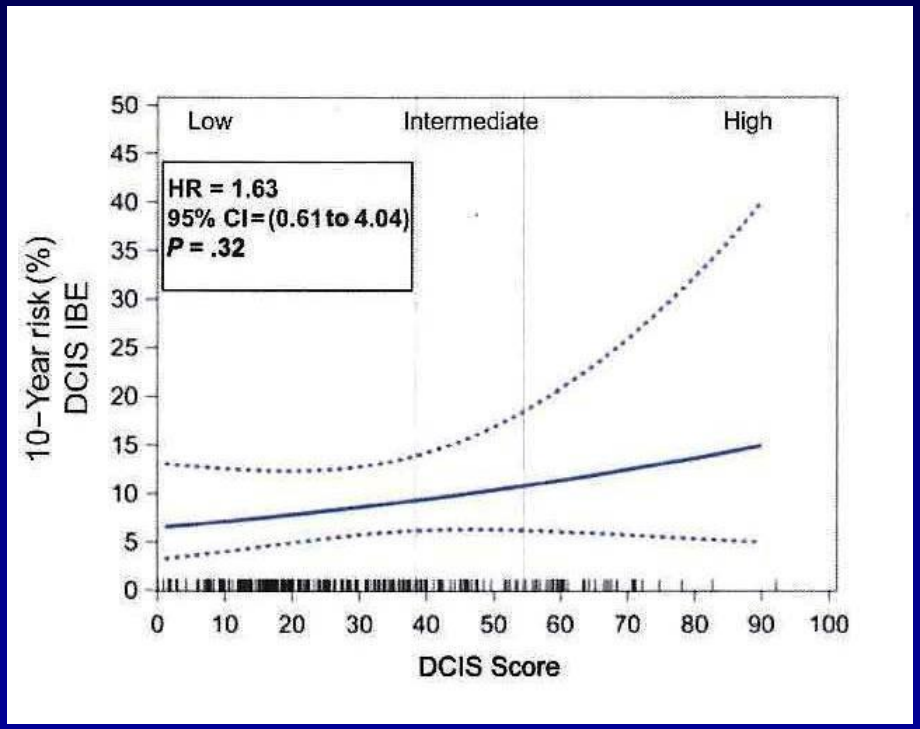
A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast

- The Onco*type* DX breast cancer assay was performed for 327 patients with DCIS treated without radiation in the (ECOG) E5194 study
- A DCIS score was established for each case

Solin L J, et al. J Nat Cancer Institute 2013;105:701-710.

A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast





Solin L J, et al. J Nat Cancer Institute 2013;105:701-710

A multigene expression assay to predict local recurrence risk for ductal carcinoma in situ of the breast

- DCIS score predicts the risk of local recurrence and invasive local recurrence and provides information that complements traditional clinical and pathologic factors

Solin L J, et al. J Nat Cancer Institute 2013;105:701-710.

Molecular Characterization of Breast Cancer

Future Directions

- Emerging classification system with clinical relevance based on
  - Morphology
  - Phenotype
  - Molecular genetics
- Routine provision of prognostic and predictive information
- Identification of key therapeutic targets

Molecular Characterization of Breast Cancer

Future Directions

- Translation of research technology into routine clinical practice
- Robust validated and standardized routine methods
- Establishment of quality control measures assuring the accuracy of pathology reporting

Molecular Characterization of Breast Cancer

Summary

- Breast cancer includes at least five discrete, molecularly defined subgroups with distinct natural histories, drug sensitivities and specific molecular therapeutic targets.
- Systemic treatments are estimated to reduce annual odds of recurrence by 50%-60% and annual odds of death by about 40%-50%
- Combined modality therapy is the therapeutic approach of choice for management of early breast cancer

Molecular Characterization of Breast Cancer

Summary

- As more advances are made in molecular genetics and more molecular targeted therapies become available, the responsibility of pathologists to find the right answers for the right patients will become greater
- This approach will form the foundation of the delivery of quality, personalized breast health care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