Putting genomics into clinical practice in early breast cancer

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MD Anderson Cancer Center
Making Cancer History®

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Systems Biology

Vienna, Austria, 10,2012

Outline

- The basics
- Available tests and supporting evidence
- Future applications of new technologies

The basics

Evolution of the concept of breast cancer

Definition of Disease	Treatment strategy
Breast cancer = single disease with variable microscopic appearance	Surgery (+/- chemotherapy)
Breast cancer = single disease, variable microscopic appearance and variable expression of estrogen/progesterone receptors	Anti-estrogen therapy for estrogen receptor-positive cancers
Breast cancer = at least 4 molecularly different diseases of the breast	Various combinations of treatments based on molecular type
Breast cancers = a collection of diseases with various combinations of deregulated molecular pathways	Molecular pathway-directed therapies

Evaluation methods

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative: methods of the EGAPP Working Group

Steven M. Teutsch, MD, MPH[1], Linda A. Bradley, PhD[2], Glenn E. Palomaki, BS[3], James E. Haddow, MD[3], Margaret Piper, PhD[4], Ned Calonge, MD, MPH[5], W. David Dotson, PhD[2,6], Michael P. Douglas, MS[2,6], and Alfred O. Berg, MD, MPH[7], Chair, on behalf of the EGAPP Working Group

Analytical validity

A test's ability to accurately and reliably measure genotype of interest

Clinical validity

A test's ability to accurately and reliably identify or predict a relevant breast cancer survival endpoint

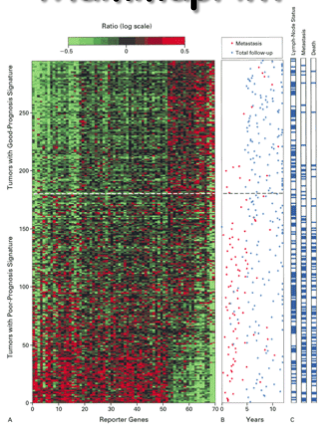
Clinical utility

The evidence that using a test to guide management in patients with early stage breast cancer will significantly improve health-related outcomes

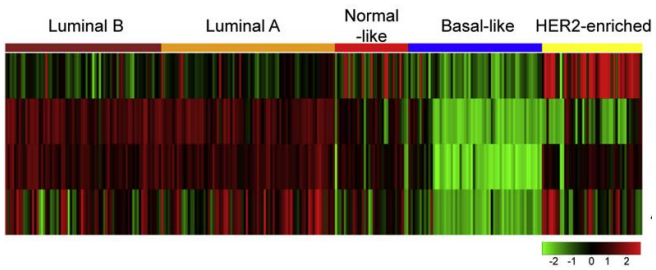
Teutsch et al Genetics Med 2009
Modified from C. Sotiriou 2011

Gene/protein prognostic signatures

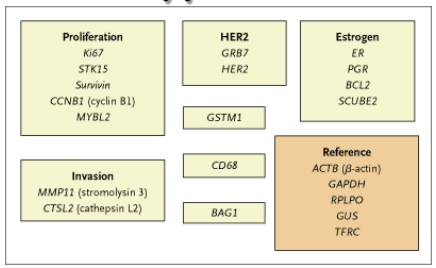
Mammaprint



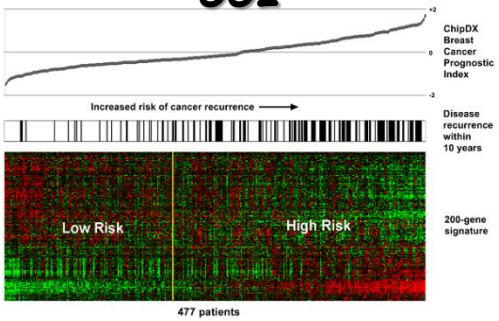
PAM50



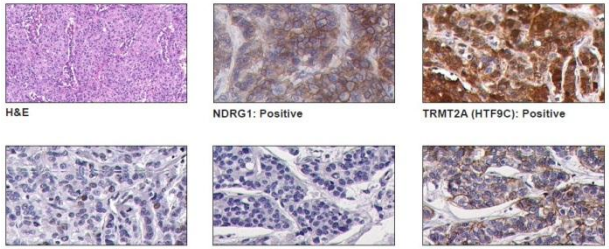
Oncotype DX RS



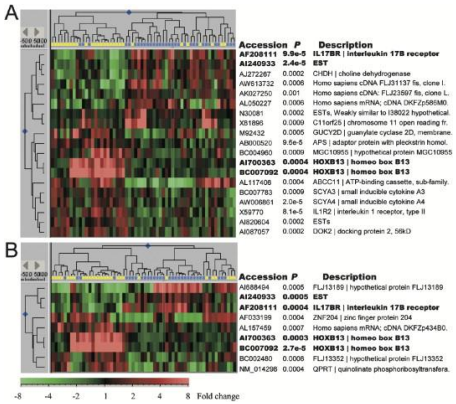
GGI



Mammostrat

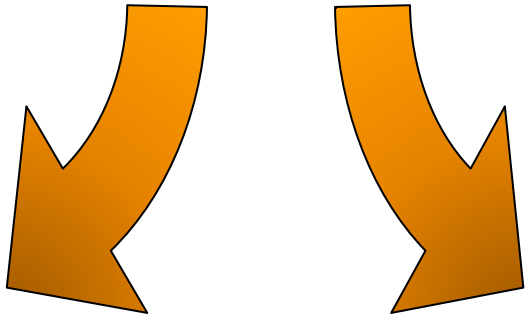


H/I + MGI



Add additional information to current clinico-pathological parameters for decision making for SOME patients

THERAPY DECISION-MAKING FOR EARLY BREAST CANCER



WHO CAN BE SPARED THERAPY?

WHICH THERAPY WILL WORK BEST?

Prognostic markers needed

Predictive markers needed

Modified from M. Piccart 2008

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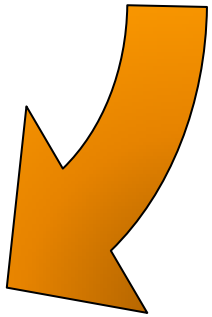
THERAPY DECISION-MAKING FOR EARLY BREAST CANCER



WHO CAN BE SPARED THERAPY?

Identify patients at HIGH risk of recurrence and treat

OR

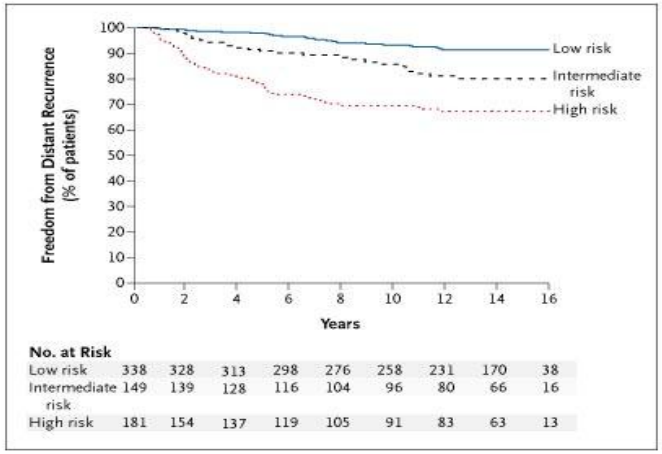
Identify patients at LOW risk of recurrence and avoid the toxicity of adjuvant treatment

Prognostic markers needed

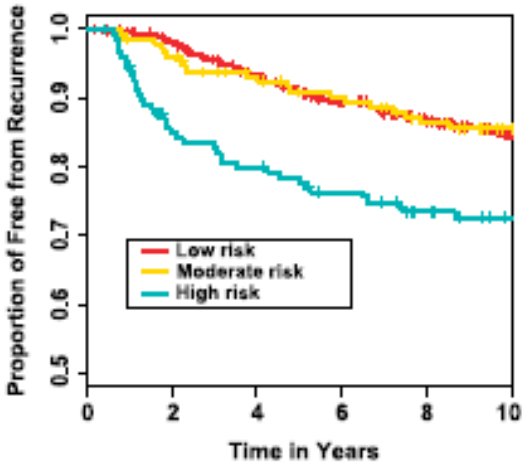
Modified from M. Piccart 2008

Examples of prognosis

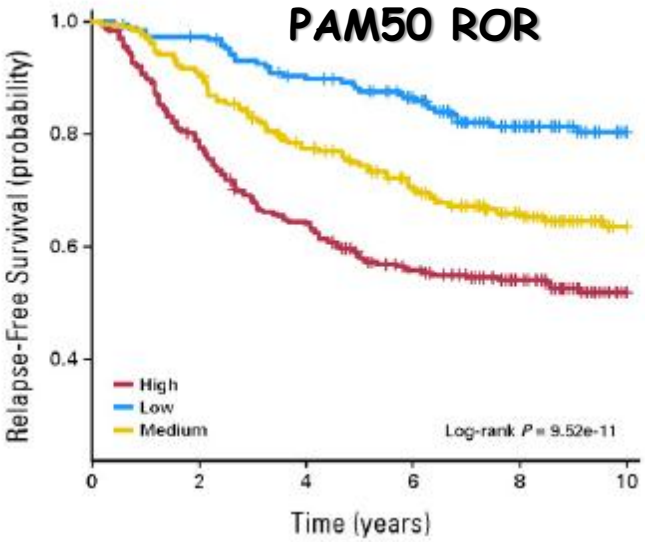
Oncotype DX RS



Mammostrat



PAM50 ROR



Paik et al N Engl J Med 2004 Parker et al J Clin Oncol 2009
Bartlett et al Breast Cancer Res 2010

THERAPY DECISION-MAKING FOR EARLY BREAST CANCER

Identify tumors with HIGH chance to response to an specific therapy

OR

Identify tumors with LOW chance to response to an specific therapy and discover new effective targets to treat them under clinical trials

Identify patients with a HIGH chance to respond to an specific therapy

OR

Identify patients with a LOW chance to respond to an specific therapy and find an alternative

PHARMACOGENOMICS

WHICH THERAPY WILL WORK BEST?

Predictive markers needed

Modified from M. Piccart 2008

THERAPY DECISION-MAKING FOR EARLY BREAST CANCER

Identify tumors with HIGH chance to response to an specific therapy

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Identify tumors with LOW chance to response to an specific therapy and discover new effective targets to treat them under clinical trials

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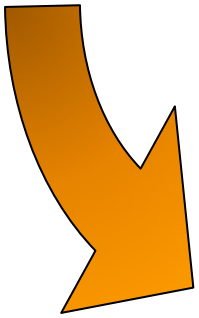


WHICH THERAPY WILL WORK BEST?

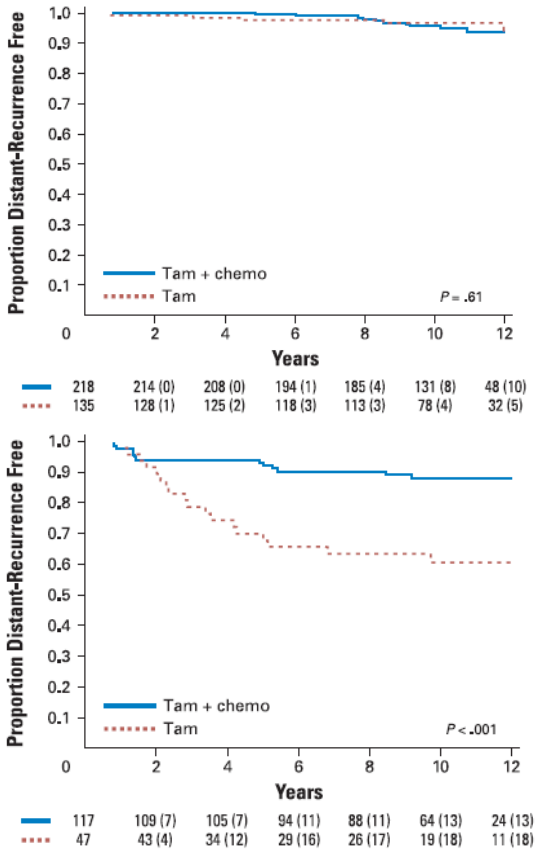
Predictive markers needed

Modified from M. Piccart 2008

Examples of prediction of chemotherapy benefit

Gene Expression and Benefit of Chemotherapy in Women With Node-Negative, Estrogen Receptor–Positive Breast Cancer

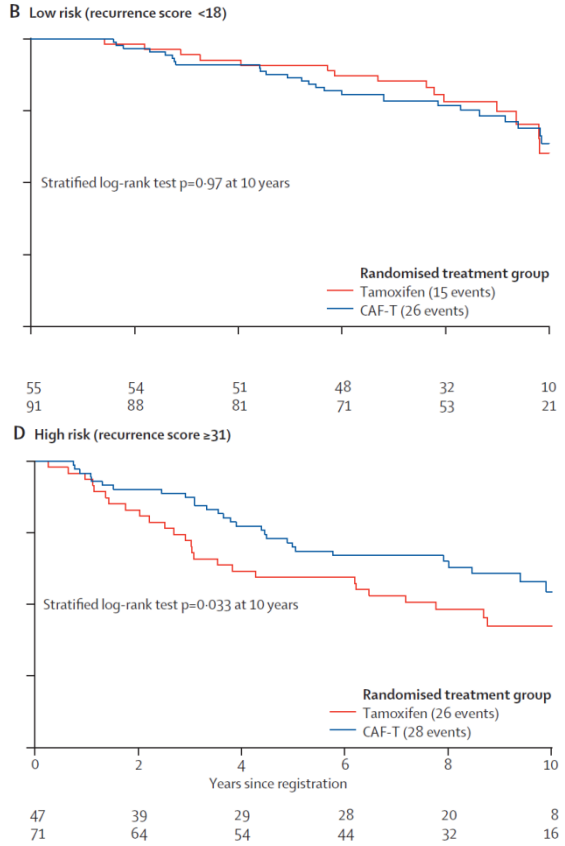
Soonmyung Paik, Gong Tang, Steven Shak, Chungyeul Kim, Joffre Baker, Wanseop Kim, Maureen Cronin, Frederick L. Baehner, Drew Watson, John Bryant, Joseph P. Costantino, Charles E. Geyer Jr, D. Lawrence Wickerham, and Norman Wolmark



Paik et al. J Clin Oncol 2006

Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial

Kathy S Albain, William E Barlow, Steven Shak, Gabriel N Hortobagyi, Robert B Livingston, I-Tien Yeh, Peter Ravdin, Roberto Bugarini, Frederick L Baehner, Nancy E Davidson, George W Sledge, Eric P Winer, Clifford Hudis, James N Ingle, Edith A Perez, Kathleen I Pritchard, Lois Shepherd, Julie R Gralow, Carl Yoshizawa, D Craig Allred, C Kent Osborne, Daniel F Hayes, for The Breast Cancer Intergroup of North America



Albain et al Lancet Oncol 2010

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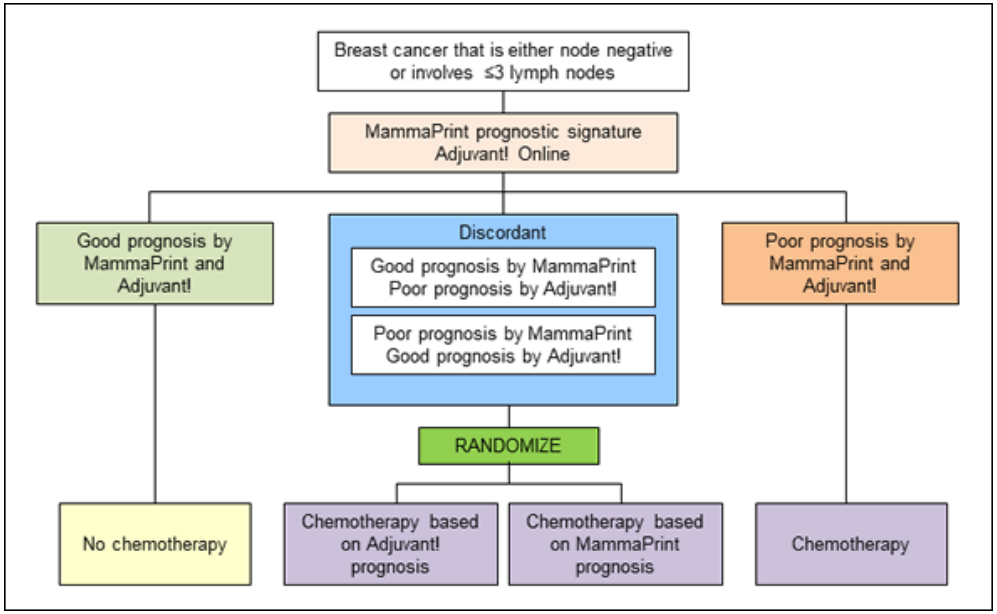
Available tests and supporting evidence

Gene-expression–based profiles used were the 70-gene good vs. poor outcome model (MammaPrint)

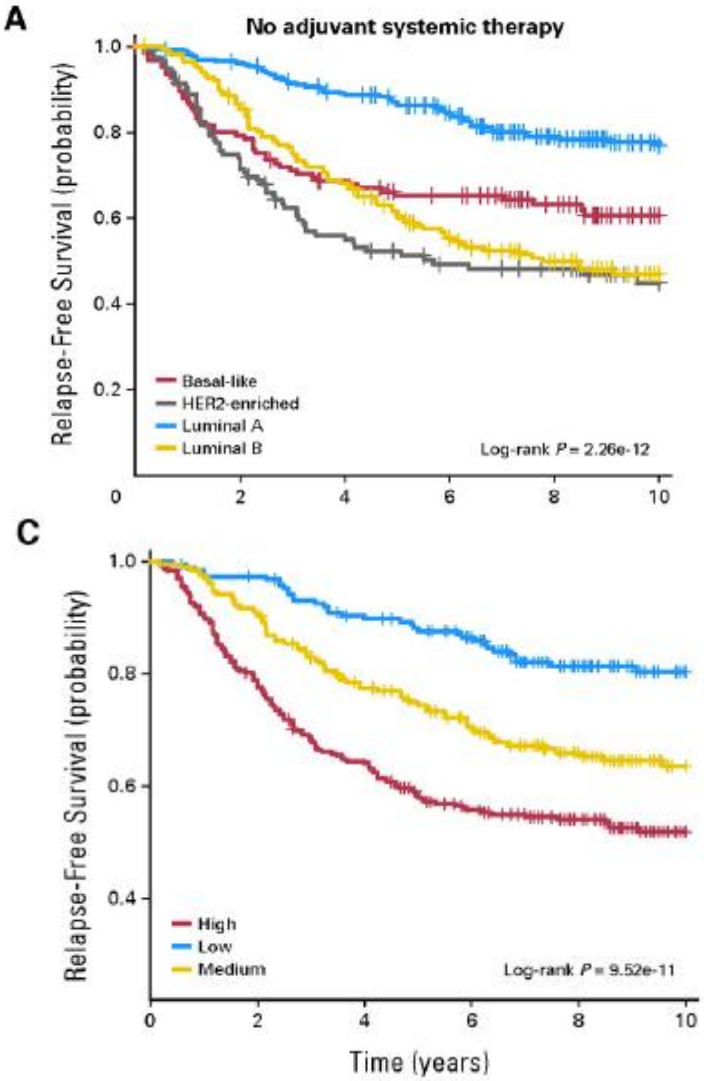
- FDA-approved for prognostication in node-negative <5cm tumors
- Fresh or frozen samples
- Poor/Good prognosis: 5-year recurrence
- Independent prognostic marker
- Provides prognostic information in node+ and HER2+
- Correlates with chemotherapy sensitivity (interaction?)

MINDACT



PAM 50 Risk of Relapse predictor

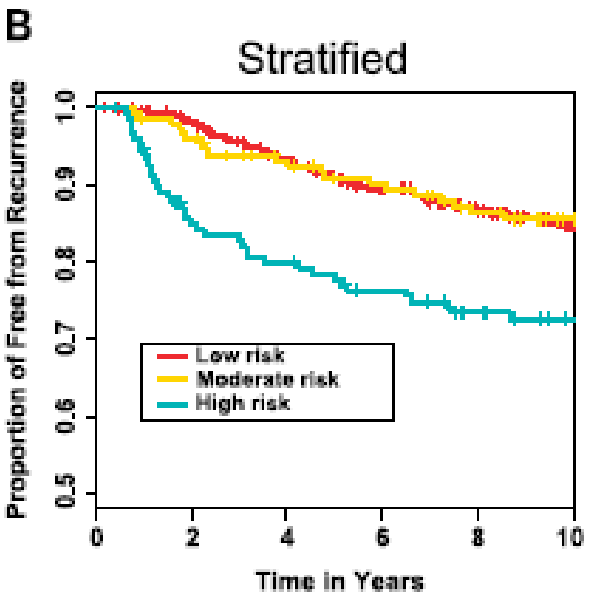
- "Intrinsic" subtypes alone and as part of a ROR predictor in:
  - Patients receiving no adjuvant systemic therapy
  - Patients undergoing (T/FAC) neoadjuvant chemotherapy
- ROR models being tested in ER+, node+ disease and as predictor of chemotherapy response



Parker et al. J Clin Oncol 2009

Mammostrat risk predictor

- Risk predictor in ER+, node- and node+, tamoxifen-treated
- IHC: P53, HTF9C, CEACAM5, IVFRGI, SLC7A5
- Significant association between patients outcome variables (RFI, DRFI, and BCSD)



- Chemo benefit in both high and low risk
- Test for interaction between chemo benefit and risk group (P = 0.13)
- Mammostrat is not predictive of chemotherapy benefit

Ross et al. Clin Cancer Res 2008 Bartlett et al. Breast Cancer Res 2010

21-gene Recurrence Score Oncotype Dx

Level of Evidence

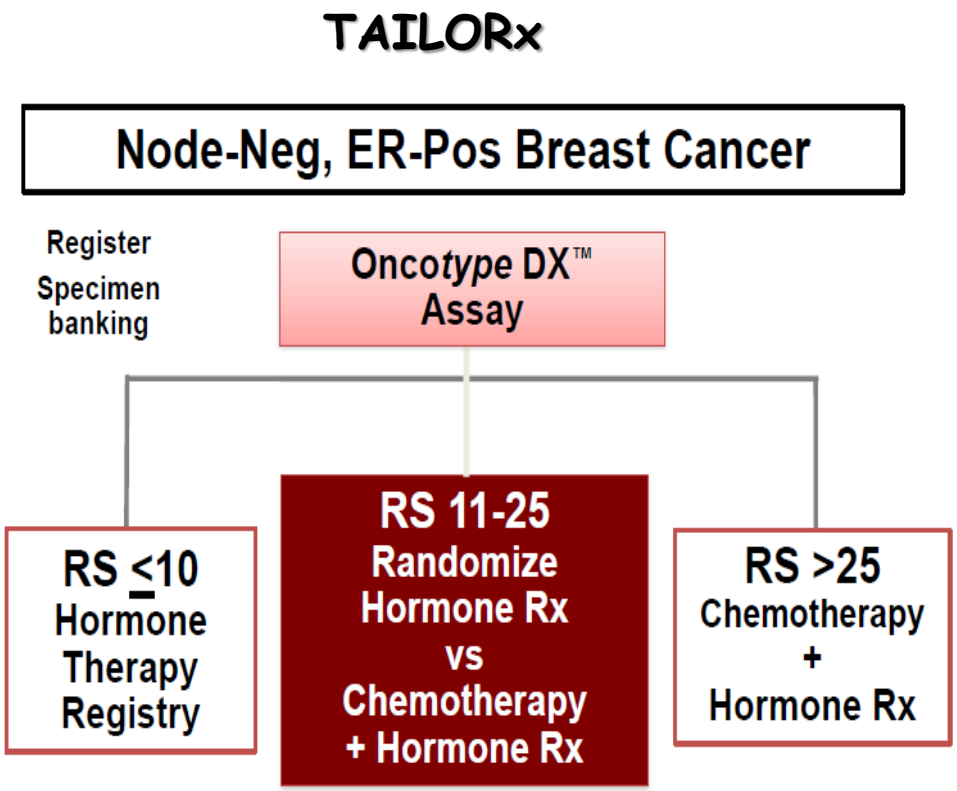
- Validated in tamoxifen treated patients with negative-nodes
- Experience in other populations
- NCCN/ ASCO guidelines

Clinical Utility

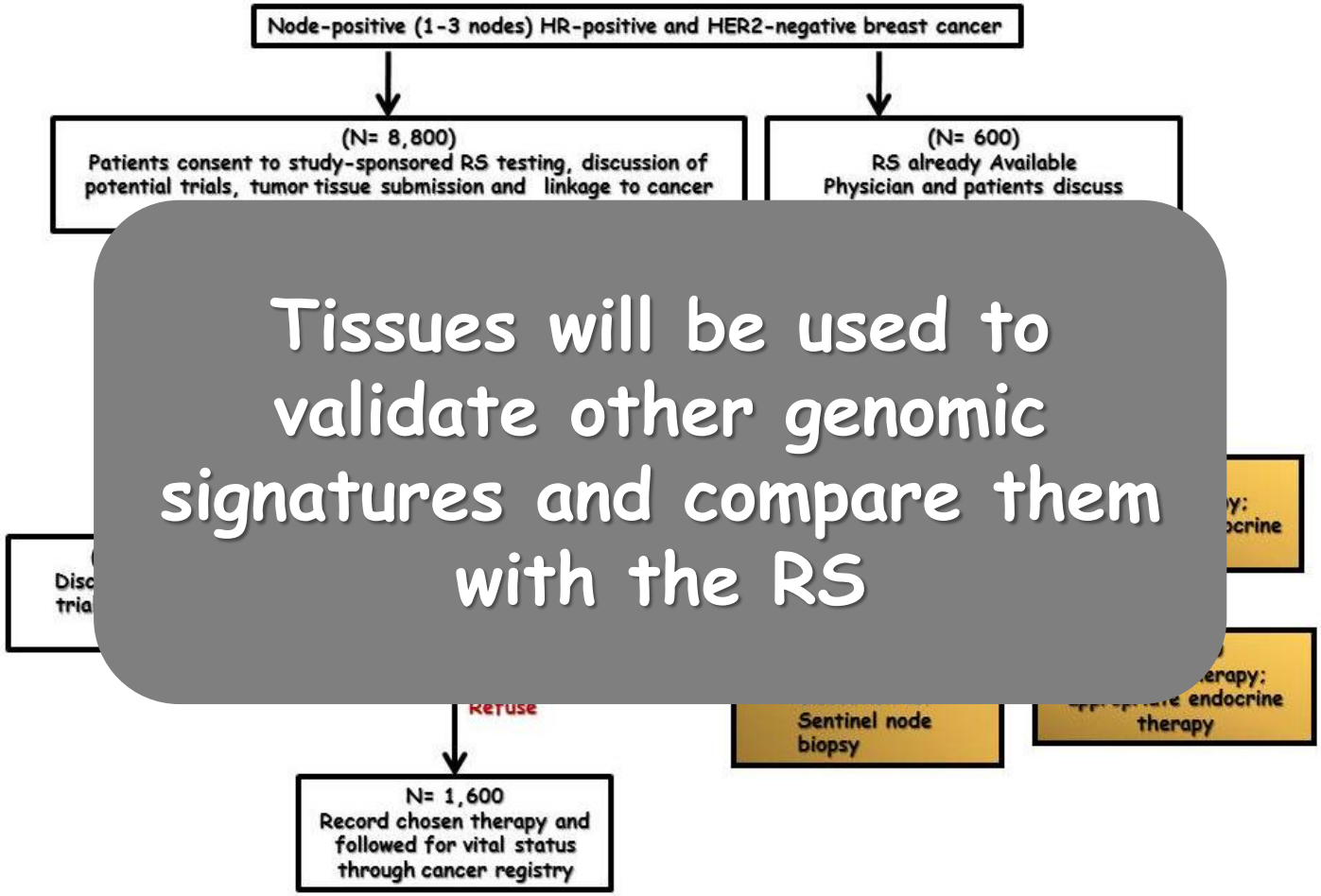
- Common disease type that is commonly overtreated
- Potential for result to influence treatment decisions

Practical Considerations

- CLIA approved, commercially available
- No special processing required
- Extensive post-marketing experience; precedent for reimbursement



Level I evidence for node+ disease is on the works!



Tissues will be used to validate other genomic signatures and compare them with the RS

RxPONDER a clinical trial
Rx for Positive Node, Endocrine Responsive Breast Cancer

PI: AM Gonzalez-Angulo

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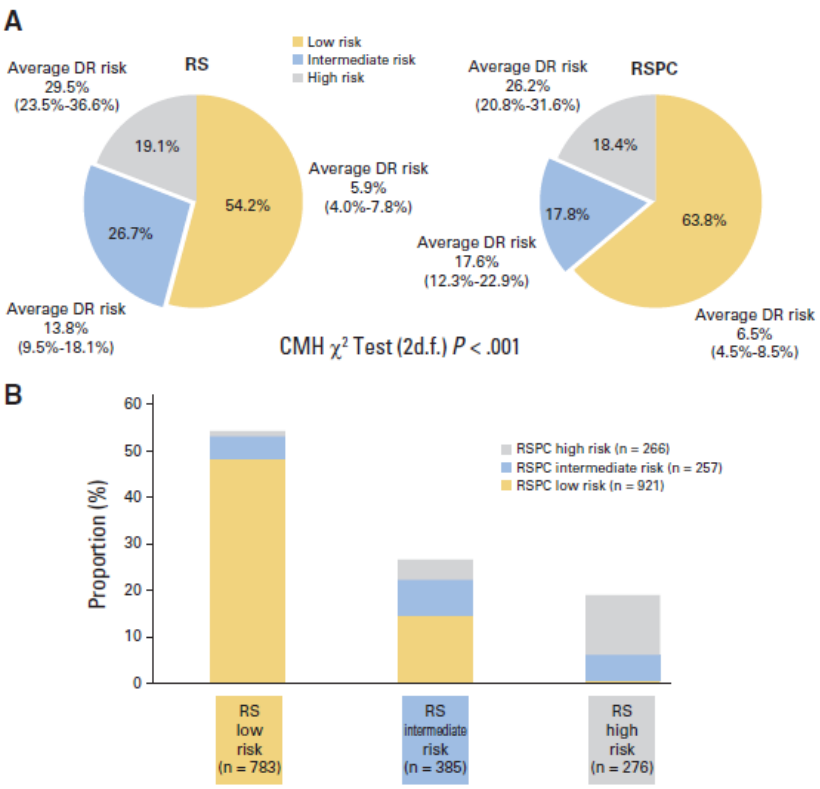
Effect of tumor size on the predictive value of Oncotype DX



Association with Time to Distant Recurrence:

RS: HR: 2.22 (P=0.001)
RSPC: HR: 2.43 (P=0.001)

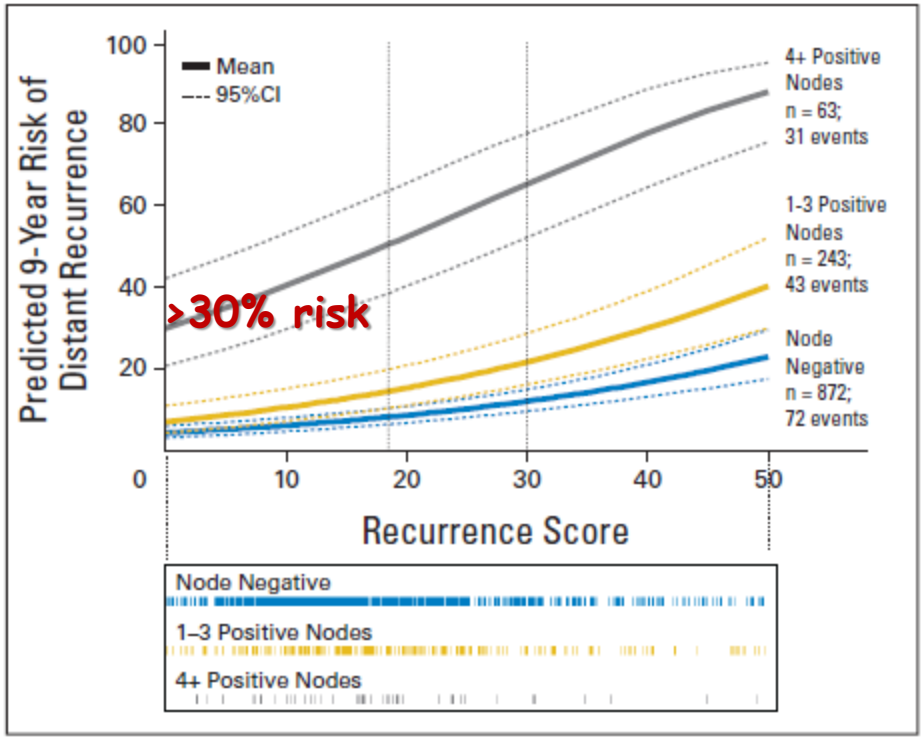
Interaction with chemotherapy treatment:

RS: HR: 0.66 (P=0.037)
RSPC: HR: 0.65 (P=0.1)

Gong et al, J Clin Oncol 2011

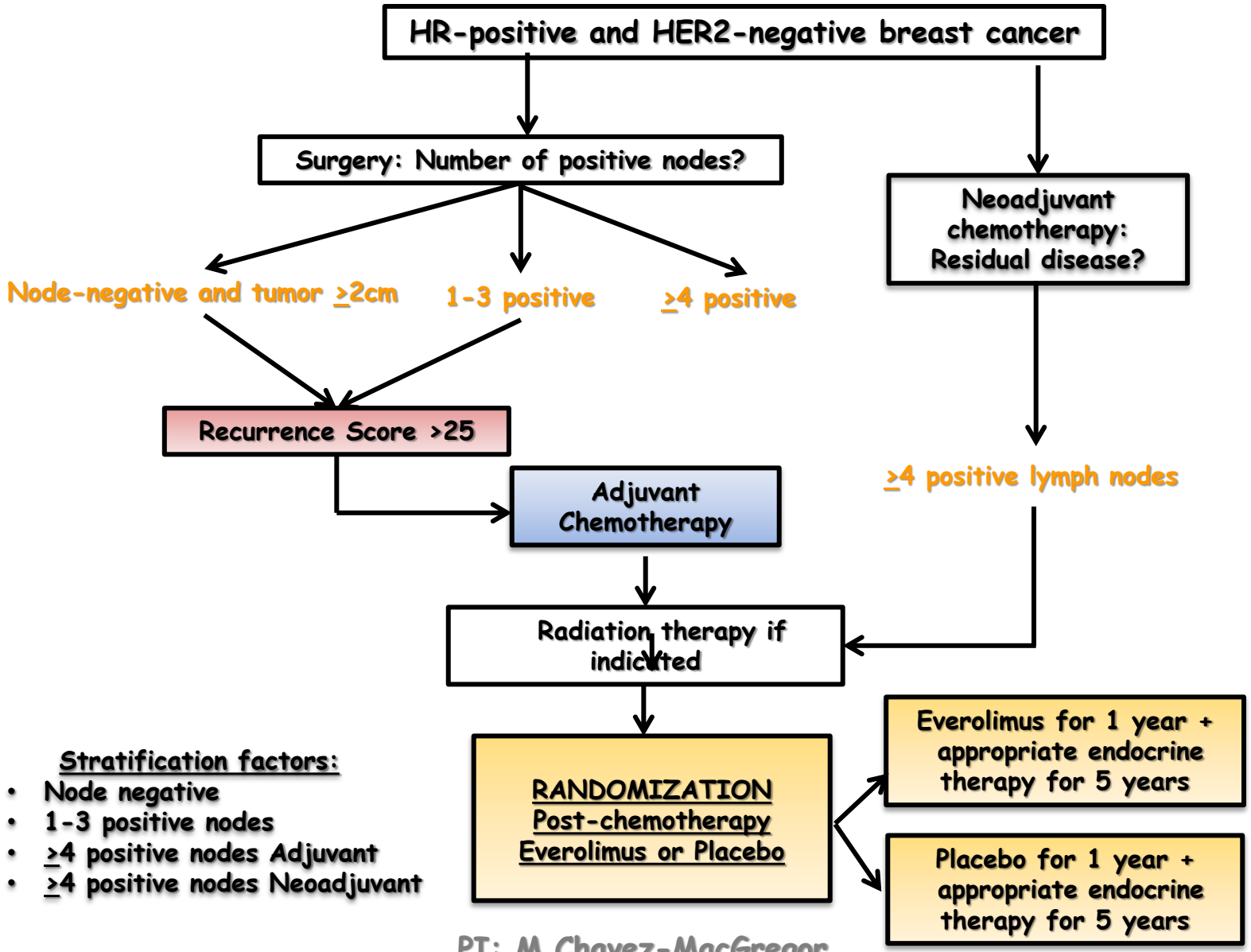
Tumor burden may still matter

- Prognostic signatures may not help!



Dowsett et al. J Clin Oncol 2010

S1207



Stratification factors:

- Node negative
- 1-3 positive nodes
- ≥4 positive nodes Adjuvant
- ≥4 positive nodes Neoadjuvant

PI: M Chavez-MacGregor

UNIRAD trial

Pre and postmenopausal women with HR$^+$ HER2$^-$ breast cancer (≥ 4$^+$ nodes Or N+ post-neoadjuvant)

Relapse-free after 2-3 yrs of adjuvant endocrine therapy

N= 2010

Everolimus 10 mg/d for 2 yrs + AI or Tamoxifen

Placebo for 2 yrs + AI or Tamoxifen

Primary endpoint:
DFS at 2 yr

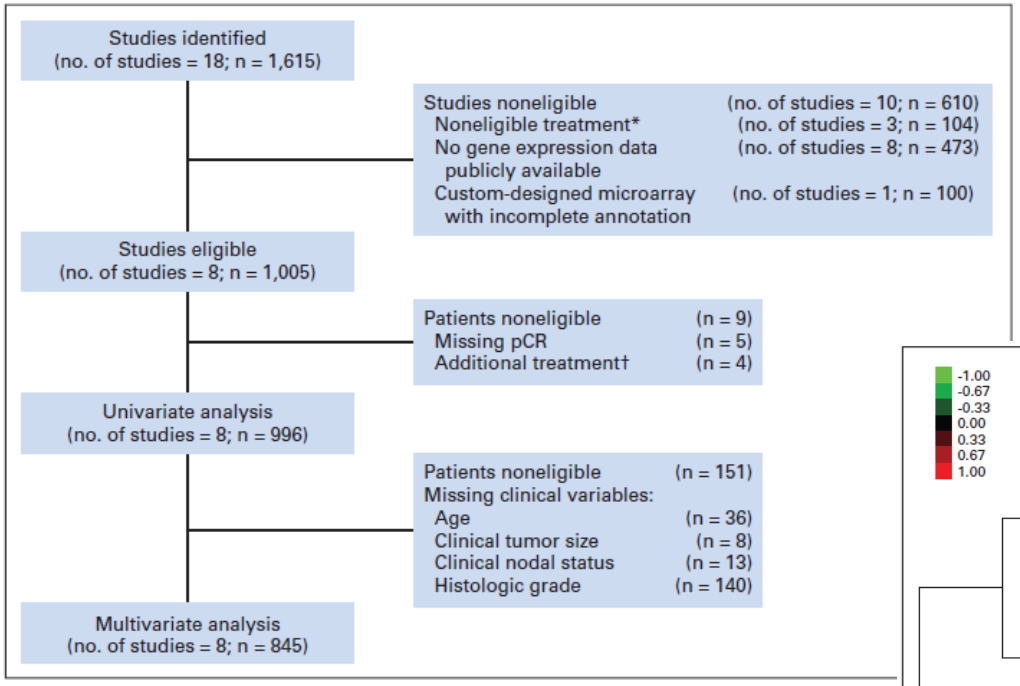
Secondary endpoints:
OS, biomarkers, safety

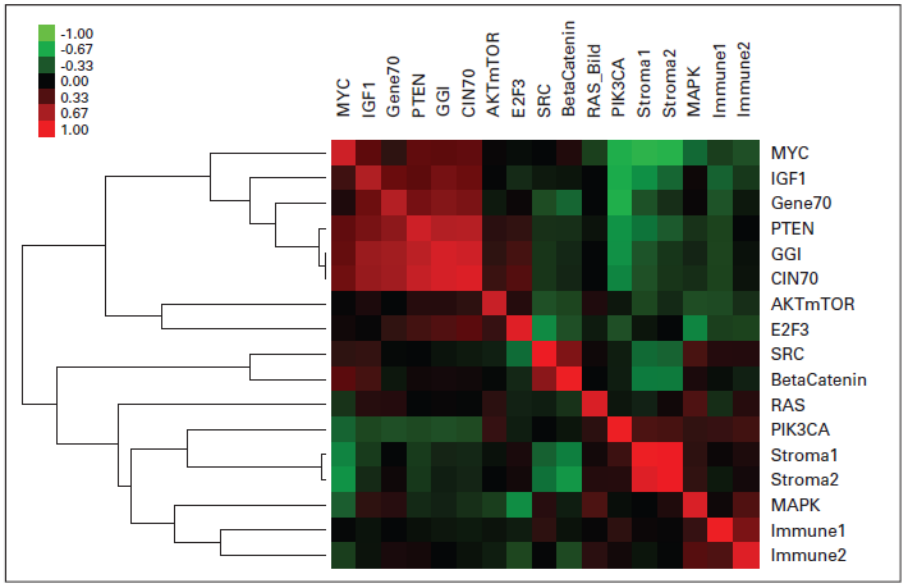
Stratification:

- Endocrine therapy (Tamoxifen vs AIs)
- Adjuvant chemotherapy

PI: F. Andre

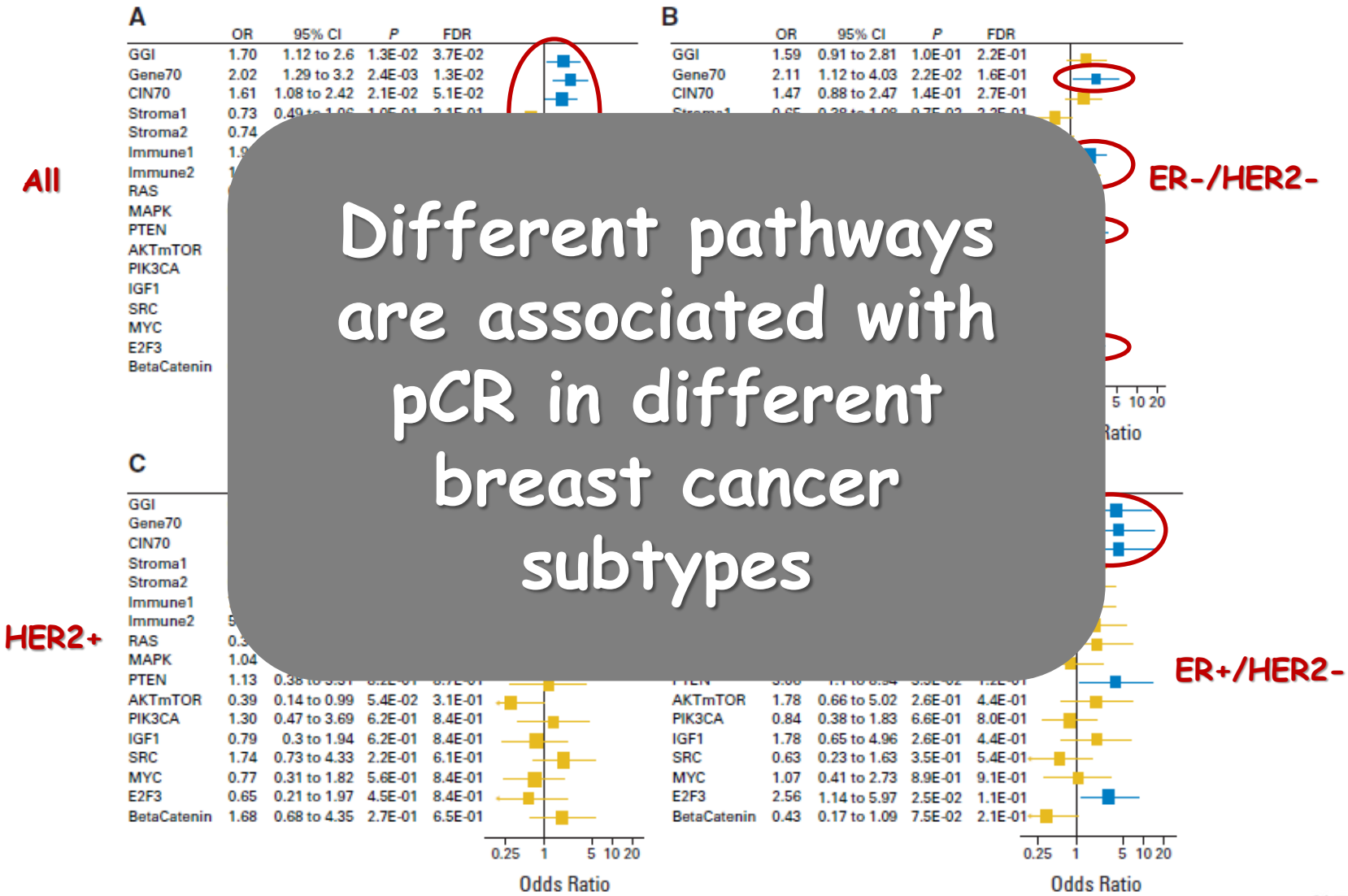
Examples of prediction of chemotherapy response





Ignatiadis et al J Clin Oncol 2012

Examples of prediction of chemotherapy response

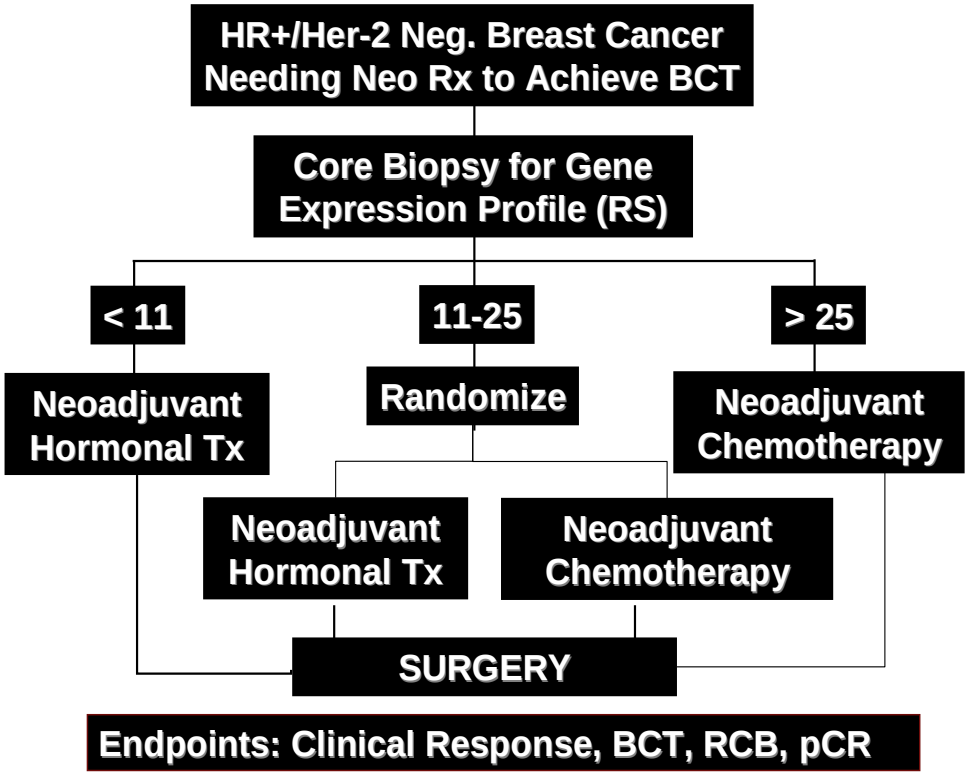


Different pathways are associated with pCR in different breast cancer subtypes

Ignatiadis et al J Clin Oncol 2012

Level I evidence is on the works!

Choosing Neoadjuvant Chemotherapy versus Hormonal Therapy for Breast Cancer Based on Gene Expression Profile



PI: H. Bear

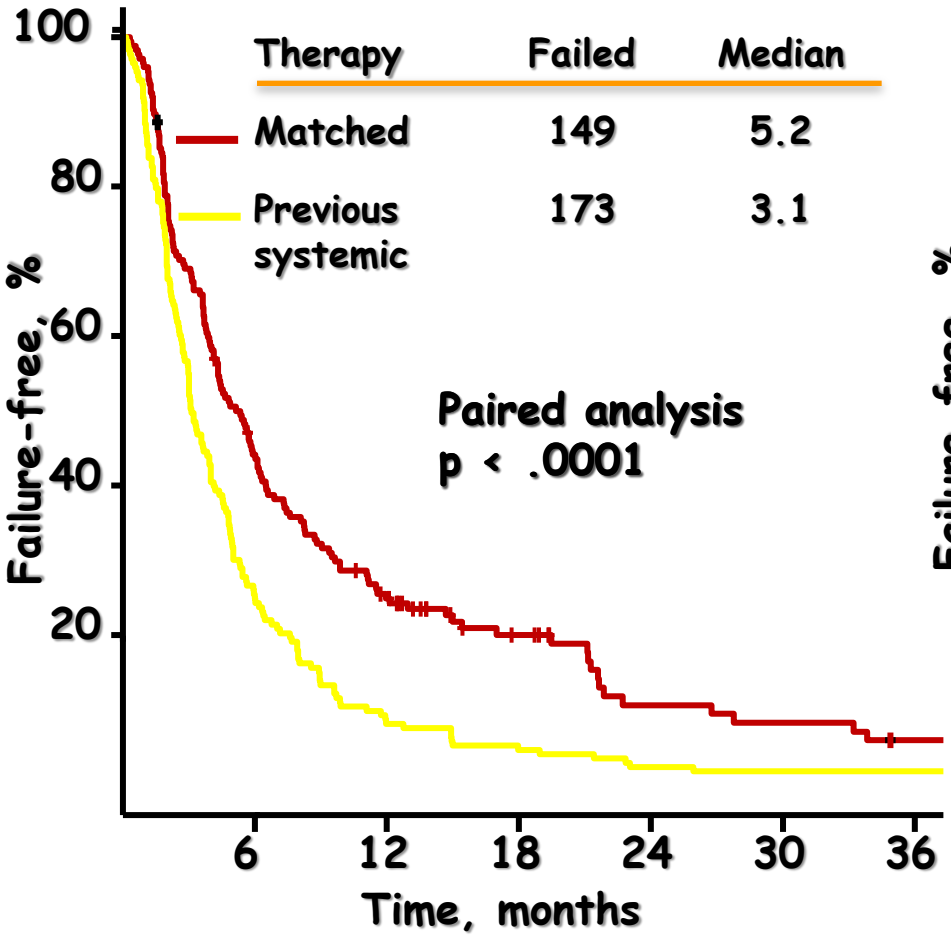
Key differences between assays relevant to whether to add chemotherapy for ER+ breast cancer

	Oncotype DX®	MammaPrint®	PAM 50 ROR®	Mammostrat®
Does the test strongly predict recurrence risk, with low risk group sufficiently low risk?	YES	YES	NO	NO
Was the test externally validated in a suitable population?	YES	NO	YES	YES
What type of tissue does the test use and what is the failure rate?	FFPE (failure < 3%)	Fresh tissue (failure 27%)	FFPE (failure rate unpublished)	FFPE (failure rate unpublished)
What types of samples does the test accept?	Surgical excisions, core biopsies	Surgical excisions, core biopsies	Surgical excisions, core biopsies	Surgical excisions
Does the test supply a result on a continuous scale or a risk category?	Continuous; individualized risk assessment	Group risk assessment (low, high)	Continuous; individualized risk assessment	Group risk assessment (low, intermediate, high)
Does the test predict chemotherapy benefit as defined by a significant test of treatment interaction?	YES	NO	NOT YET	NO
What platform does the test use?	RT-PCR	Microarray	RT-PCR	IHC
What type of regulatory clearance does the test have?	CLIA	CLIA/FDA	CLIA	CLIA
Is the test incorporated in treatment guidelines of ASCO and NCCN?	YES	NO	NO	NO

Future applications of new technologies

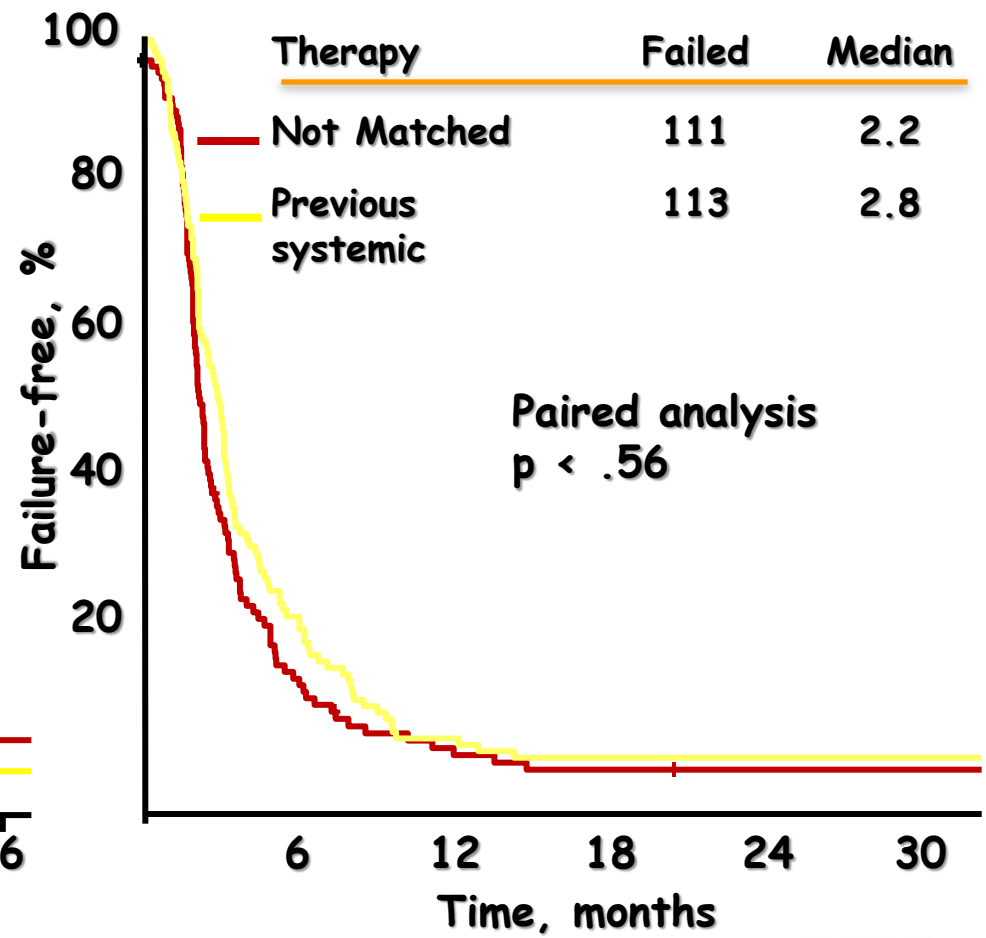
Time-to-Treatment Failure
Comparison with Previous Systemic Therapy

Matched therapy
N=175, 1 aberration



Therapy	Failed	Median
Matched	149	5.2
Previous systemic	173	3.1

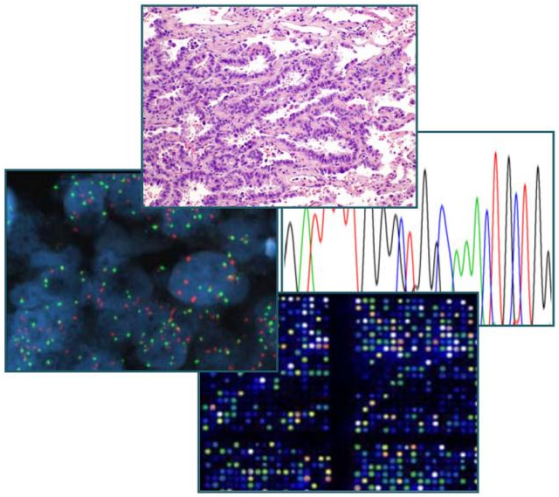
Non-matched therapy
N=116, 1 aberration

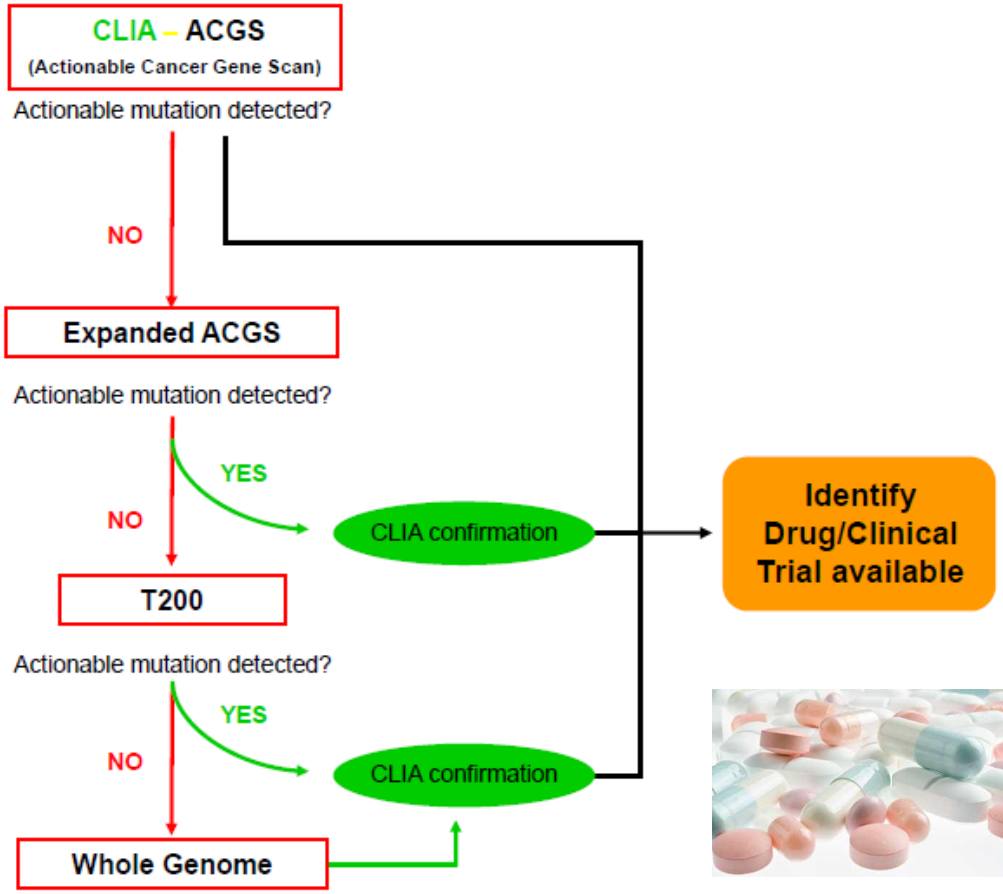


Therapy	Failed	Median
Not Matched	111	2.2
Previous systemic	113	2.8

Courtesy of R. Kurzrock

Clearinghouse and BEAT-IT projects





Sharing Research Data: Cancer Gene Mutation Browser

Overview | **Search** | Administration

Back to Search

Search Results

Sample Id	AKT1	AKT2	AKT3	ALK	BRAF	CDK4	CTNNB1	EGFR	EPHA3	FBWX7	FGFR2	FGFR3	FOXL2	FRAP	GNA11	GNAQ	GNAS	IDH1	IDH2	JAK2	KIT	KRAS	MET	NRAS	PDGFRA	PDPK1	PHLPP2	PIK3CA	PIK3R1	PRKAG1	PRKAG2	RET	TNK2
3496T_Plate172	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Not Available	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Detected	Wild Type	Wild Type	Wild Type	Wild Type
MKN_1_1_Plate172	Inconclusive	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Detected	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type	Wild Type

Detected | Wild Type | Inconclusive | Not Available

FOXL2

☐ Display detected mutation only

Gene Mutation			Replicate 1			Replicate 2		
Gene	Amino acid	Nucleotide	Mutation Status	Percent Mutation	Confidence	Mutation Status	Percent Mutation	Confidence
FOXL2	p.C134W	c.402C>G	WT			WT		

Where are we now?

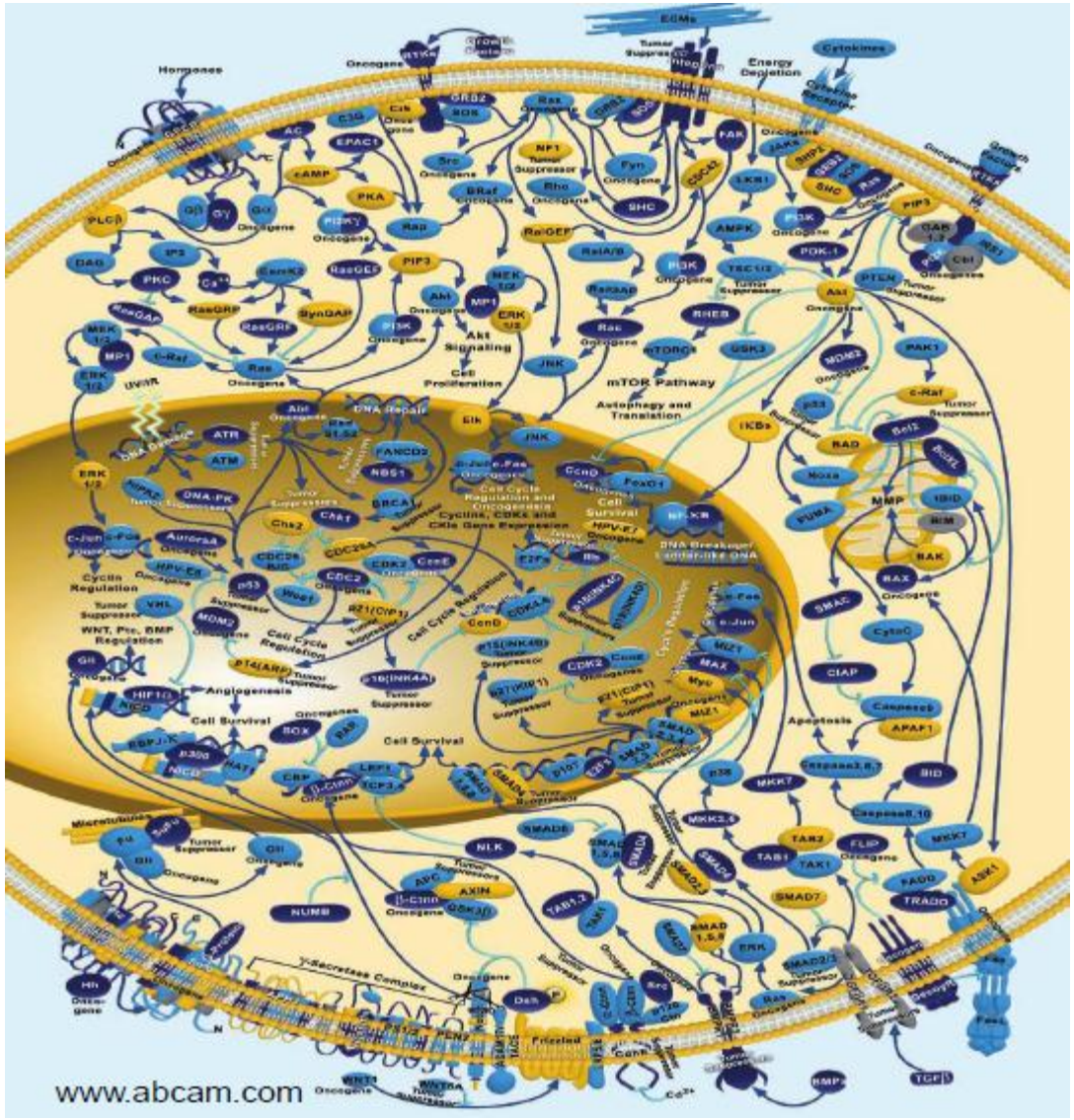
- Our medical practice is based on standards of care (EBM)
  - EBM: best approach for the average populations, not for specific individuals

- Application of systems biology to personalized cancer therapy- Breast cancer as a model
  - Molecular profiling technologies to tailor medical care

- Challenges:
  - Identifying and validating molecular markers
  - Molecular crosstalk and bypass mechanisms
  - High failure rate of molecular targeted therapeutics

- It is critically important to understand the pathways and networks to target as well as of the homeostatic loops induced by the interventions

It is much more complex



Conclusions

- Prognostic and predictive signatures can help in treatment-decision for specific groups of patients
- Some of these assays may be able to identify a group of women with endocrine responsive, disease that may not require chemotherapy thus avoiding the associated toxicities
- Prospective validation trials are completed for node-negative disease and on-going for node-positive disease
- Prospective validation trials are on-going in the neoadjuvant setting
- Until results of such studies are available the current guidelines still endorse the use of adjuvant chemotherapy among all women with node positive disease
- Contribute to clinical trials !!!

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- ACS

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Thank you !!!!

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