Gene Panels: Promise, Progress, and Limitations

JoAnne Zujewski [zujewskj@mail.nih.gov]
Musa Mayer [musa@echonyc.com]
Jane Perlmutter [janep@gemini-grp.com]

NBCC
May, 2005

Gene Panels in Breast Cancer: Topics

Promise

Progress

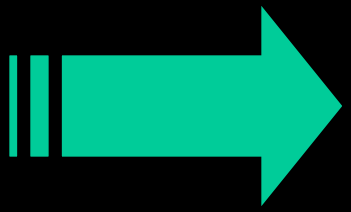
Limitations

Discussion


Promise

Clinical Relevance

- Screening
- Detection
- Diagnosis
- Prognosis
- Treatment Selection
- Monitoring Therapy
  Early Relapse



- Prolonged survival, or disease-free survival
- Improved QOL
- Avoidance of ineffective and/or toxic treatment
- Reduction in cost

Definitions

- Prognostic:
  - Discriminates between patients who will do well in the absence of treatment
  - Positive correlation between gene panel and selected end-point
- Predictive:
  - Distinguishes between patients for whom a treatment is or is not likely to be useful (sensitive or resistant)
  - Interaction between treatment and gene panel

Levels of Evidence Summary

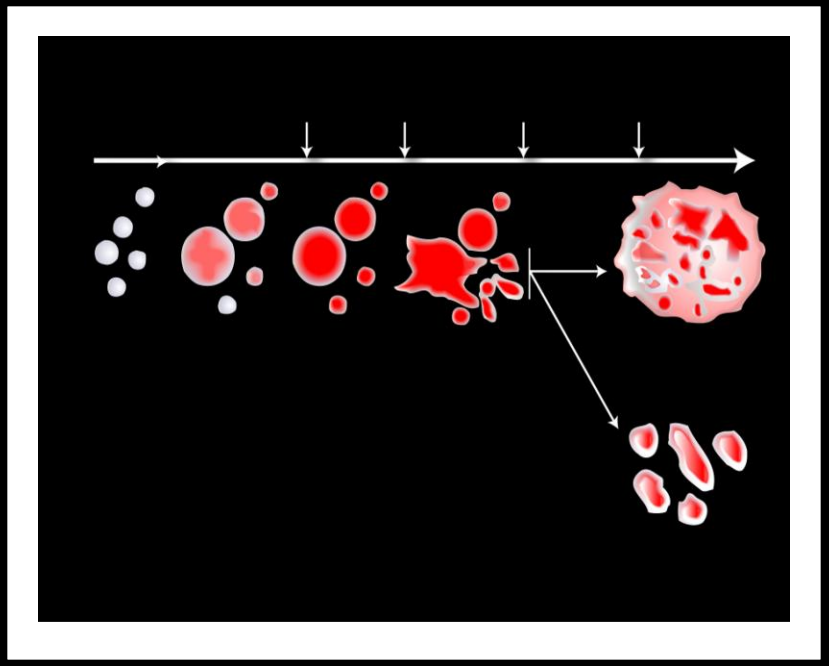
Level	Definition
Level 1	Larger randomized clinical trials or meta-analyses of multiple randomized clinical trials
Level 2	Smaller randomized clinical trials
Level 3	Prospective, controlled, non-randomized, cohort studies
Level 4	Historic, non-randomized, cohort or case-control studies
Level 5	Case series: patients compiled in serial fashion, lacking a control group
Level 6	Animal studies or mechanical model studies
Level 7	Extrapolations from existing data collected for other purposes, theoretical analyses
Level 8	Rational conjecture (common sense); common practices accepted before evidence-based guidelines

The Promise

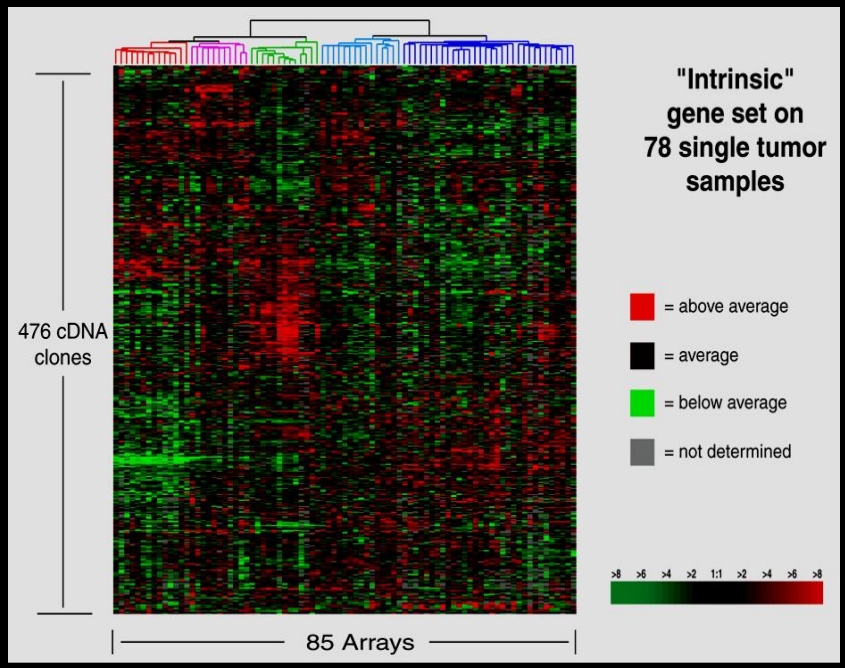
- Targeted therapy based on biology of tumor
  - Low toxicity
  - High probability of cure

Progress

Paradigm shift in breast cancer

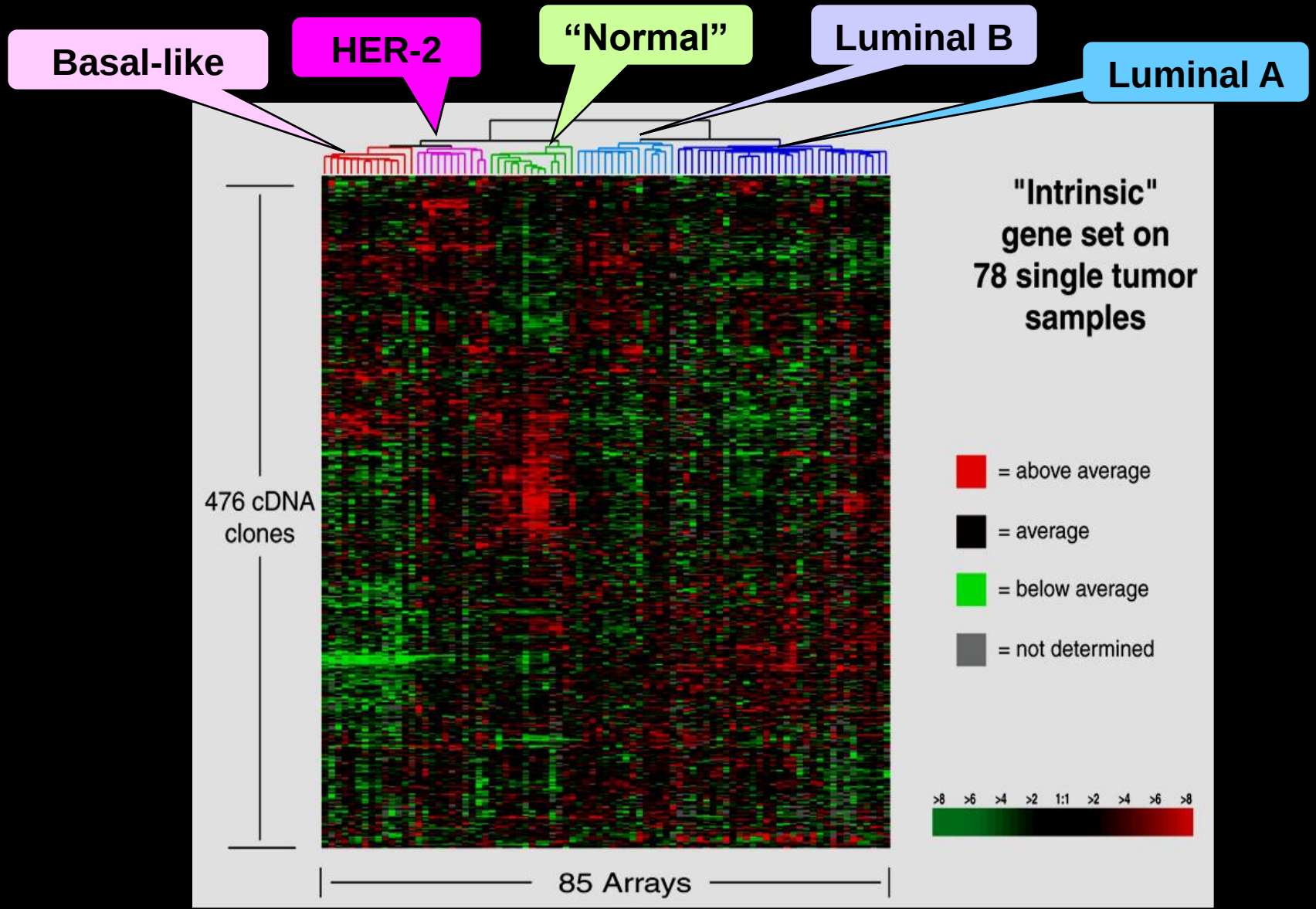


Progression



Molecular characterization

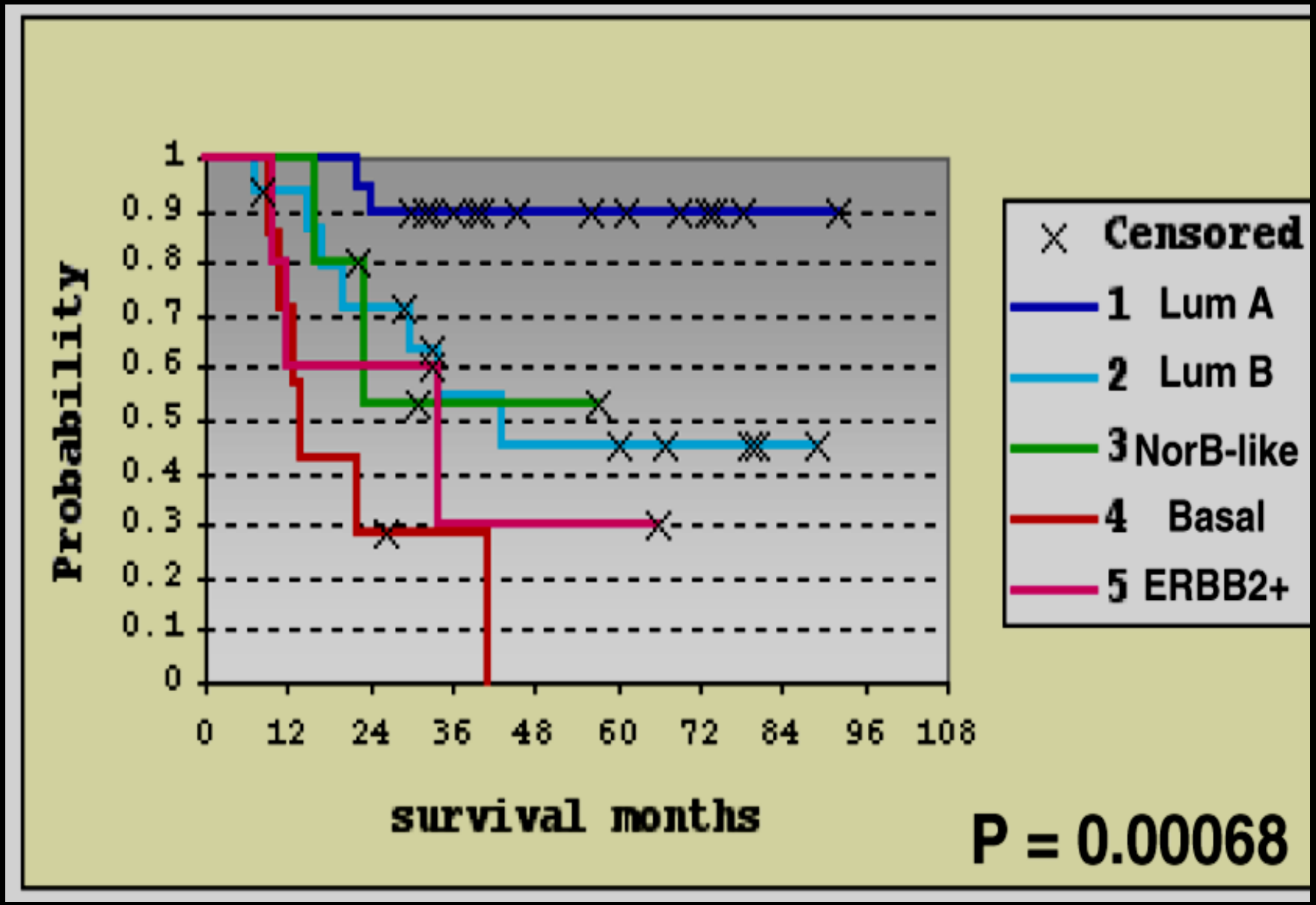
Molecular Portrait of Breast Cancers



Sorlie T et al, PNAS 2001

Slide courtesy of L. Carey

Subtypes and Prognosis



Sorlie T et al, PNAS 2001

Slide courtesy of L. Carey

Subtyping in 2005

- **Array results**
  - **“signatures” are here**
  - **Subtypes are not (yet)**
- **“Proxies”:**

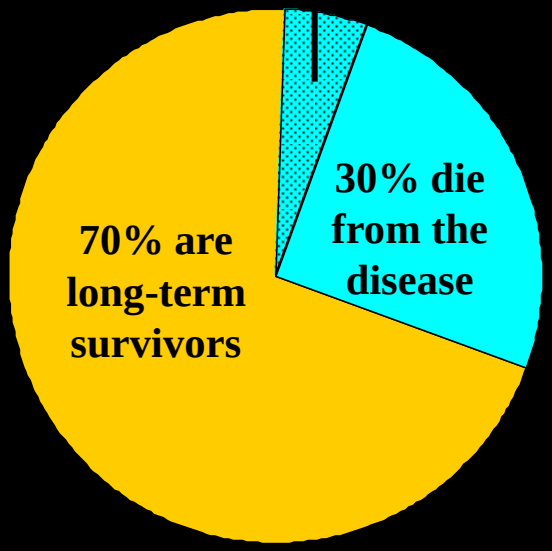
	Triple Negative	ER/PR+	HER2+ ER/PR-
Basal-like	75%	9%	0%
Luminal	12%	76%	14%
“HER2”	9%	5%	85%

Courtesy of L Carey

Genomics Studies: Questions?

- **Class Discovery**
  - Clustering specimens (e.g. are there different types of breast cancer?)
- **Class Prediction**
  - Assessing if an individual specimen fits in a class (e.g. does Ms. Jones have the "basal subtype" of breast cancer?)
- **Class Comparison**
  - Gene sets to predict specific endpoint (e.g. are there gene expression patterns that predict response to tamoxifen?
  - Examples: Oncotype Dx, Amsterdam 70-gene prognosticator

NODE NEGATIVE BREAST CANCER POPULATION



Medical treatment reduces BC mortality

Shown by large clinical trials

Modest gains with increasingly more effective and more expensive drugs

…but

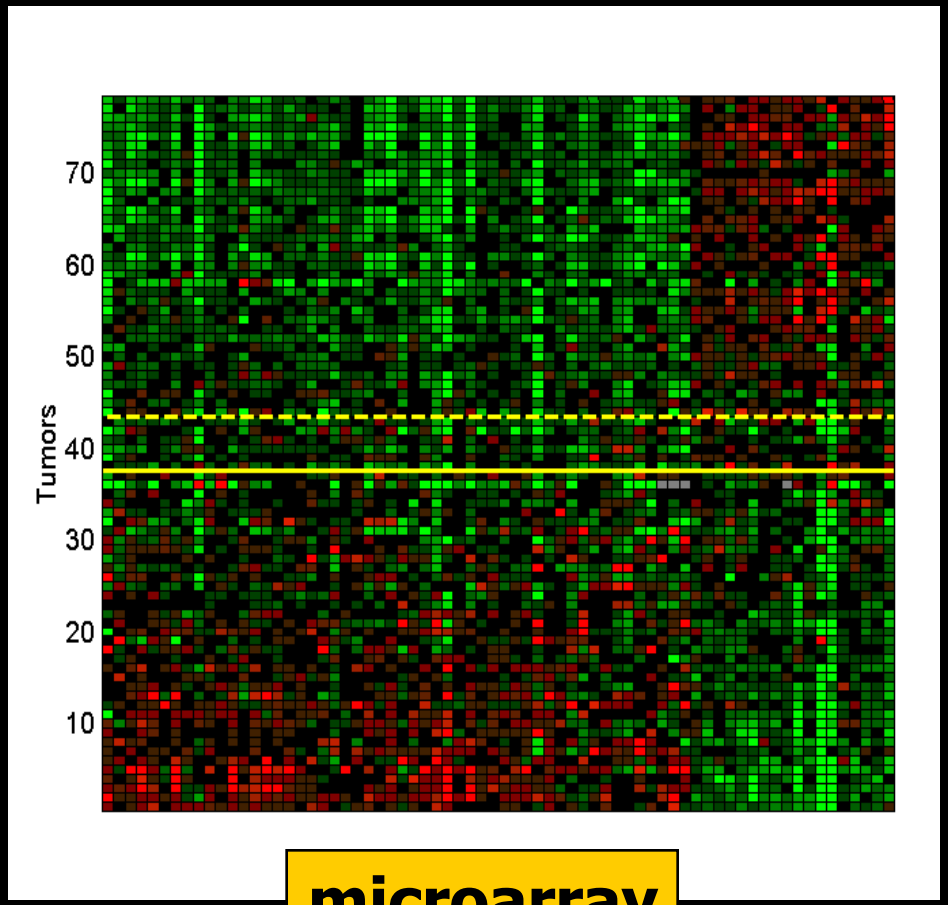
WHO NEEDS TREATMENT ?

Today's medicine leads to overtreatment !

WHICH TREATMENT WORKS BEST FOR WHOM ?

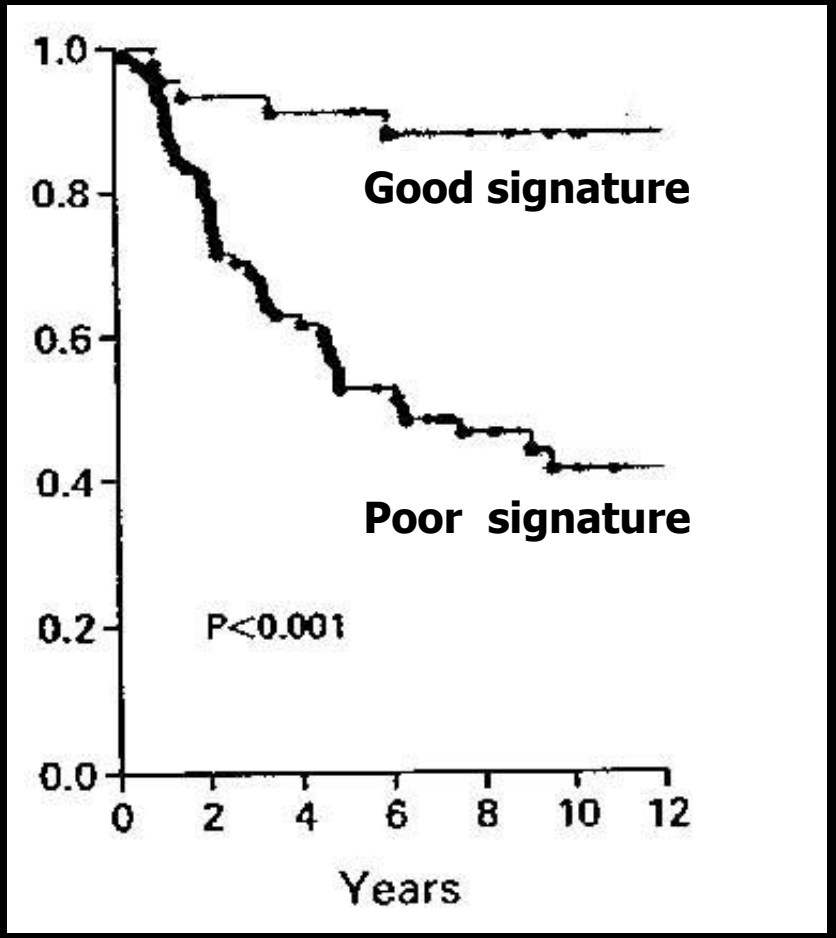
- **Today's medicine may select ineffective treatment !**

IMPROVED RISK ASSESSMENT OF EARLY BREAST CANCER THROUGH GENE EXPRESSION PROFILING



microarray

Gene-expression profile



N Engl J Med, Vol 347 (25), Dec. 2002

MINDACT:

Microarray for **N**ode Negative **D**isease may **A**void **C**hemo **T**herapy

CLINICAL APPLICATION OF GENOMICS FOR IMPROVED TREATMENT TAILORING

BENEFITS:

Only women who NEED chemotherapy RECEIVE it!

Reduce toxicity & side effects

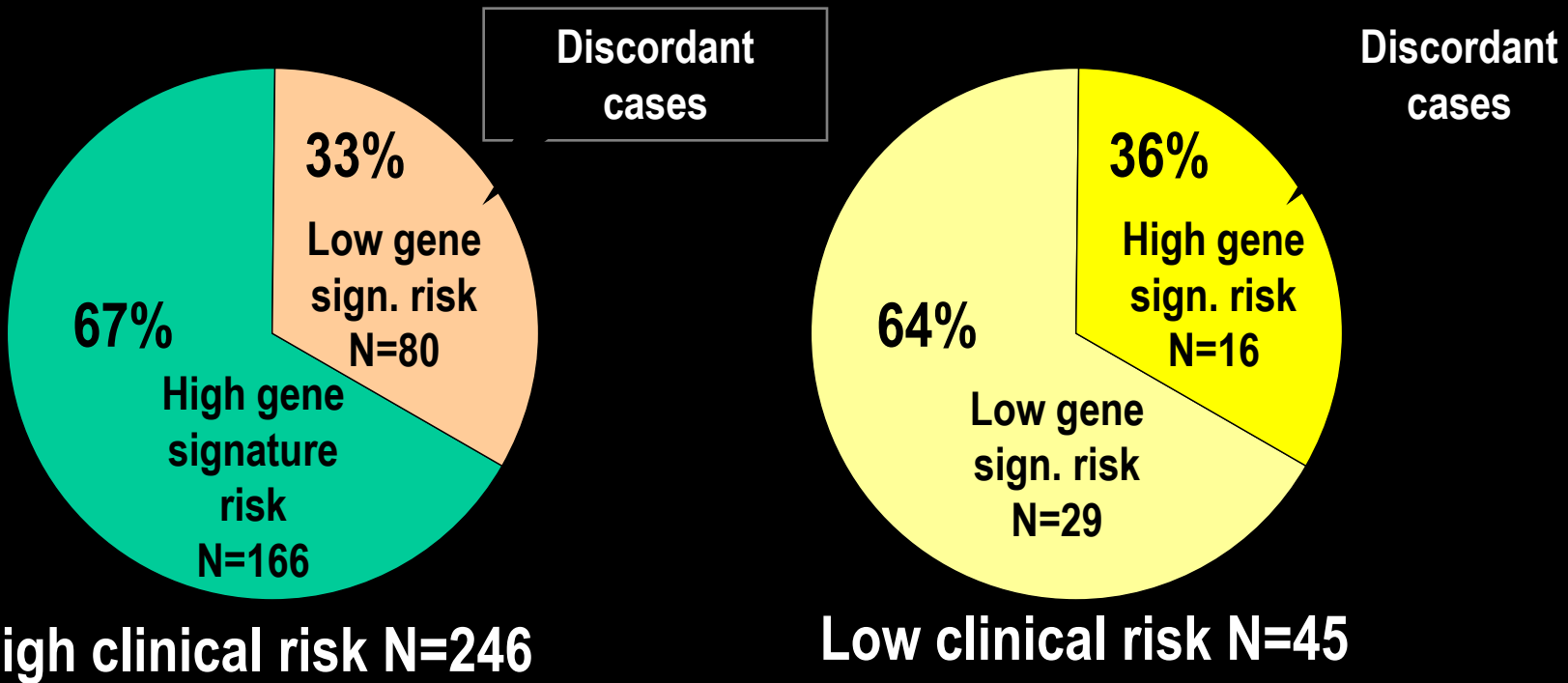
Reduce cancer care costs

Reduce burden on health care systems

CONCORDANCE BETWEEN CLINICAL AND GENE SIGNATURE RISK CLASSIFICATIONS

VALIDATION SERIES

Threshold for low clinical risk defined as predicted 10-year O.S. > 90%



Discordant cases with other clinical risk classifications

St-Gallen = 35%
NPI = 36%

St-Gallen = 43%
NPI = 54%

CONSIDERATIONS

- **Key question for use of 70-gene to decide on chemotherapy: evaluate the risk of undertreating patients who would otherwise get chemotherapy (per clinical-pathological criteria)**

- **Chemo effect in N0 is well-documented**

- **Prove that the key group has a good prognosis that will unlikely be significantly altered by chemotherapy**

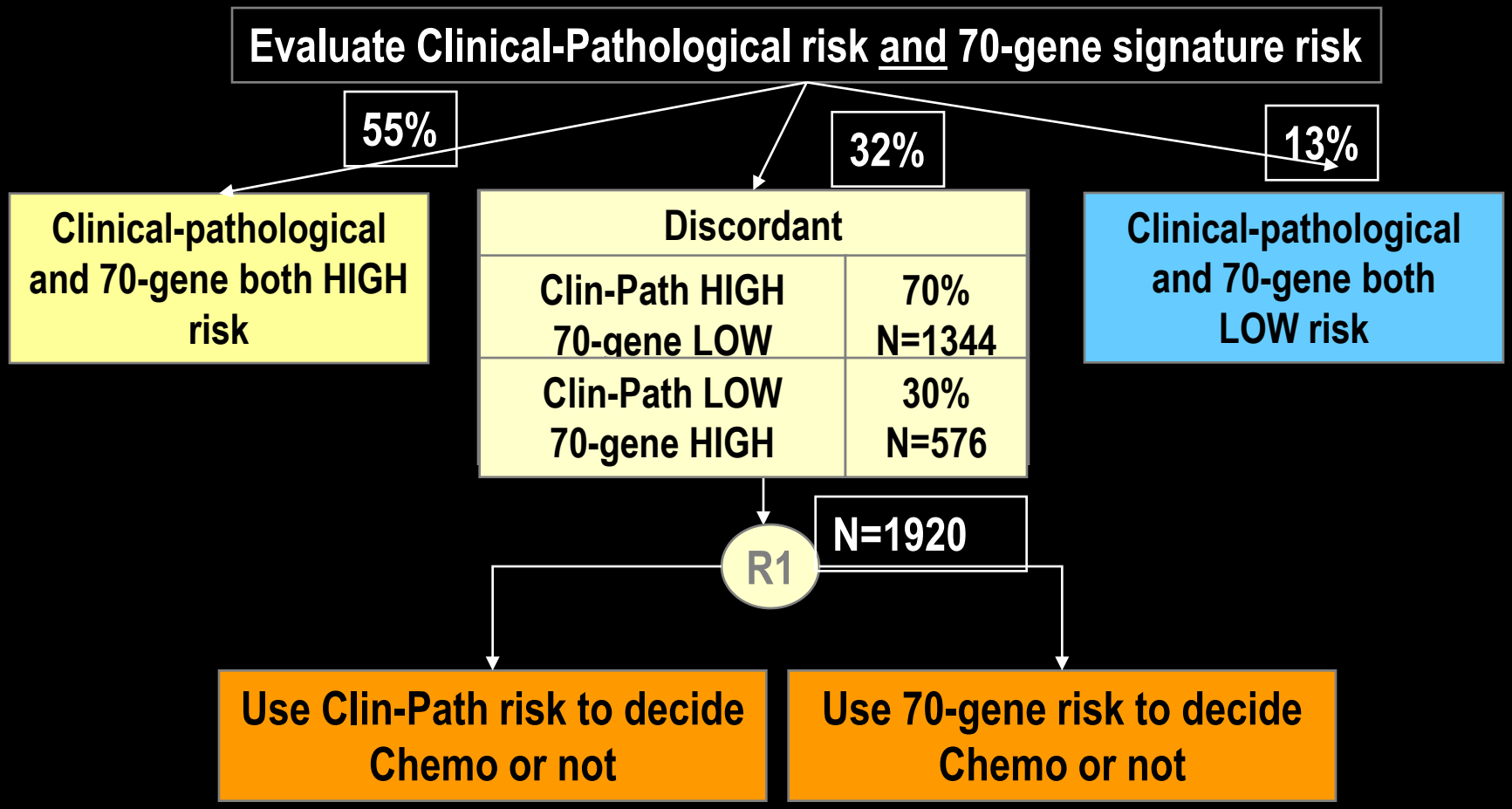
CONSIDERATIONS (CONT.)

- Concentrate on the discordant cases
  - Those that have a different risk for clinical/pathological and 70-gene
  - Concordant cases do not affect the evaluation, but will go into secondary questions (chemotherapy, endocrine)
  - Need microarrays and central pathology on all patients
  - Ability to evaluate translational questions (chemotherapy predictive/resistance, endocrine predictive/resistance)

MINDACT DESIGN

- **The numbers are estimated from the validation study**
- **Clinical-pathological high risk = Adjuvant! Online 10-year Breast Cancer Survival prognosis of 88% for ER-positive and 92% for ER-negative patients**
- **Will need to evaluate the estimates of percentages expected in each category after first 800 patients enrolled**

EORTC-BIG MINDACT TRIAL DESIGN
6,000 Node negative women



Potential CT sparing in 10-15% pts

PRIMARY TEST

- **Dataset: the patients who have a low risk gene prognosis signature and high risk clinical-pathologic criteria, and who were randomized to receive no chemotherapy. Expected size: 672**

- **Null hypothesis: 5-year DMFS = 92% will be tested**
- **Assuming:**
  - **3 years accrual**
  - **6 years total duration (3 to 6 years follow up per patient)**
  - **two-sided test at 95% confidence level**
  - **true 5-year DMFS = 95%**
- **This test has 80% power**

SECONDARY TESTS/ESTIMATES

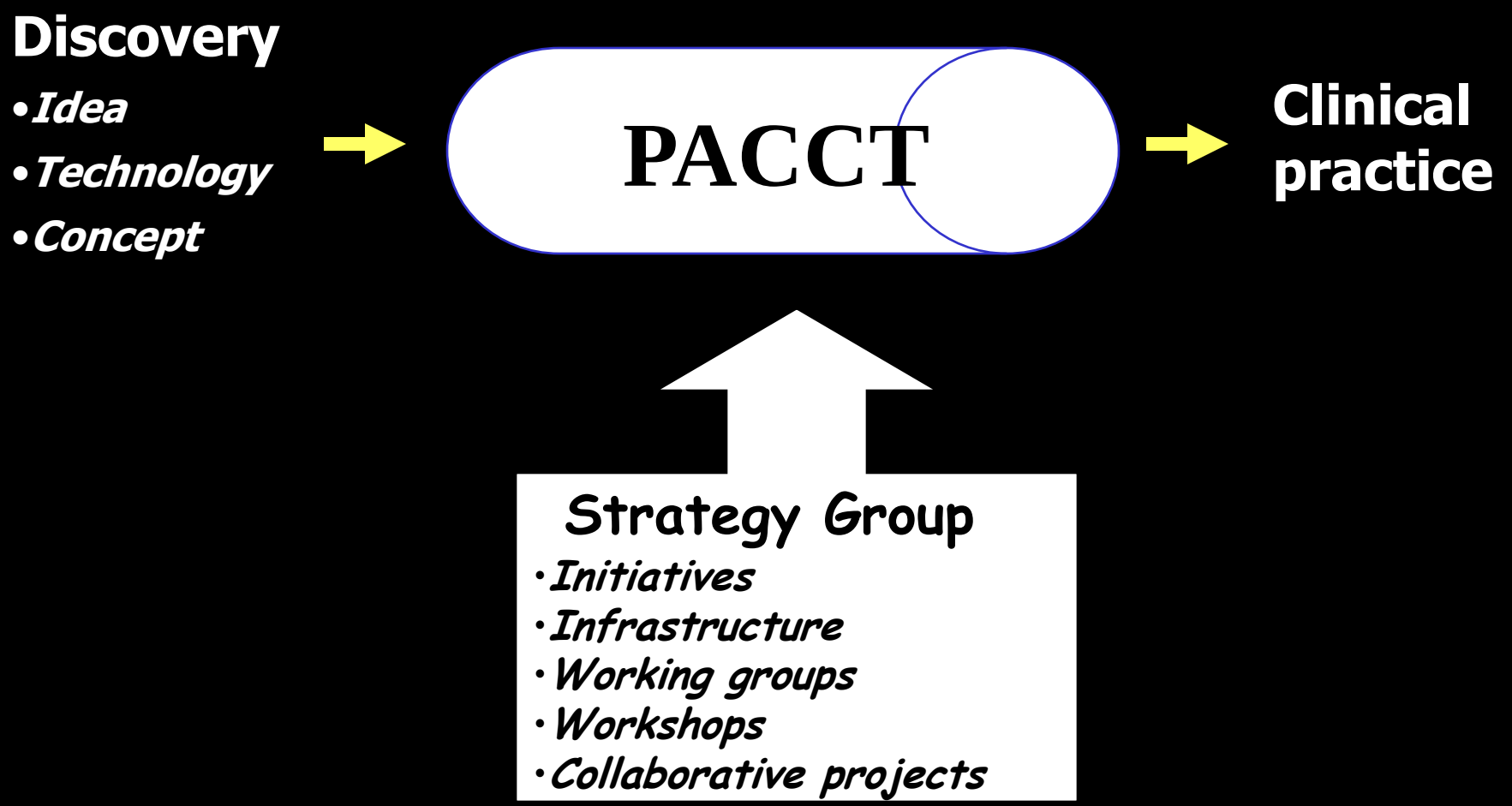
- **Subgroup of clinical/pathological high risk and 70-gene low risk (size 1344)**
  - **Compare DMFS between chemo and no chemo**
  - **80% power for HR=0.5 (ie. 5-year DMFS of 93% vs. 96.5%)**
  - **After 5.5 years follow-up (8.5 years overall), there is 80% power for HR=0.6 (ie. 5-year DMFS of 93% vs. 96.1%)**
- **Subgroup of clinical/pathological low risk and 70-gene high risk (size 576)**
  - **Compare DMFS between chemo and no chemo**
  - **Low power**
  - **After 5.5 years follow-up (8.5 years overall), there is 80% power for HR=0.48 (84% vs. 91.2% 5 yr. DMFS)**
- **Make overall estimates of efficacy endpoints (DFS, DMFS, OS) for the two treatment strategies according to clinical-pathological criteria and the 70-gene signature**
- **Estimate the percentages of patients receiving chemotherapy according to the two strategies**

POTENTIAL IMPACT OF MINDACT IN BREAST CANCER MANAGEMENT

MINDACT: **Microarray for Node-Negative Disease May Avoid ChemoTherapy !**

- Reduction of the proportion of women receiving unnecessary chemotherapy
- Conversion of microarray test into a cheaper, more user-friendly prognostic tool
- Discovery of gene signatures predicting for greater efficacy of endocrine therapy and/or chemotherapy
- Discovery of new drug targets
- Refinement in prognosis / prediction of treatment efficacy through proteomics

Program for the Assessment of Clinical Cancer Tests



The NEW ENGLAND JOURNAL of MEDICINE

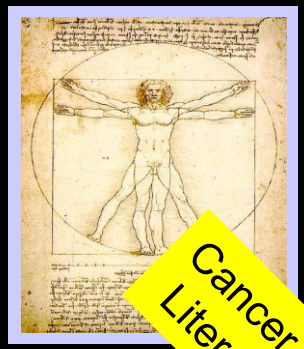
Volume 351:2817-2826 December 30, 2004 Number 27

A Multigene Assay to Predict Recurrence of Tamoxifen-Treated, Node-Negative Breast Cancer

Soonmyung Paik, M.D., Steven Shak, M.D., Gong Tang, Ph.D., Chungyeul Kim, M.D., Joffre Baker, Ph.D., Maureen Cronin, Ph.D., Frederick L. Baehner, M.D., Michael G. Walker, Ph.D., Drew Watson, Ph.D., Taesung Park, Ph.D., William Hiller, H.T., Edwin R. Fisher, M.D., D. Lawrence Wickerham, M.D., John Bryant, Ph.D., and Norman Wolmark, M.D.

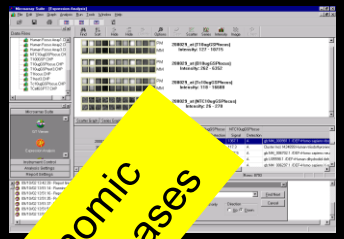
Candidate Gene Selection

From ~40,000 genes

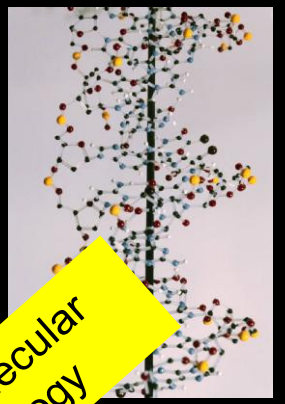


Cancer Literature

Microarray Data*



Genomic Databases



Molecular Biology

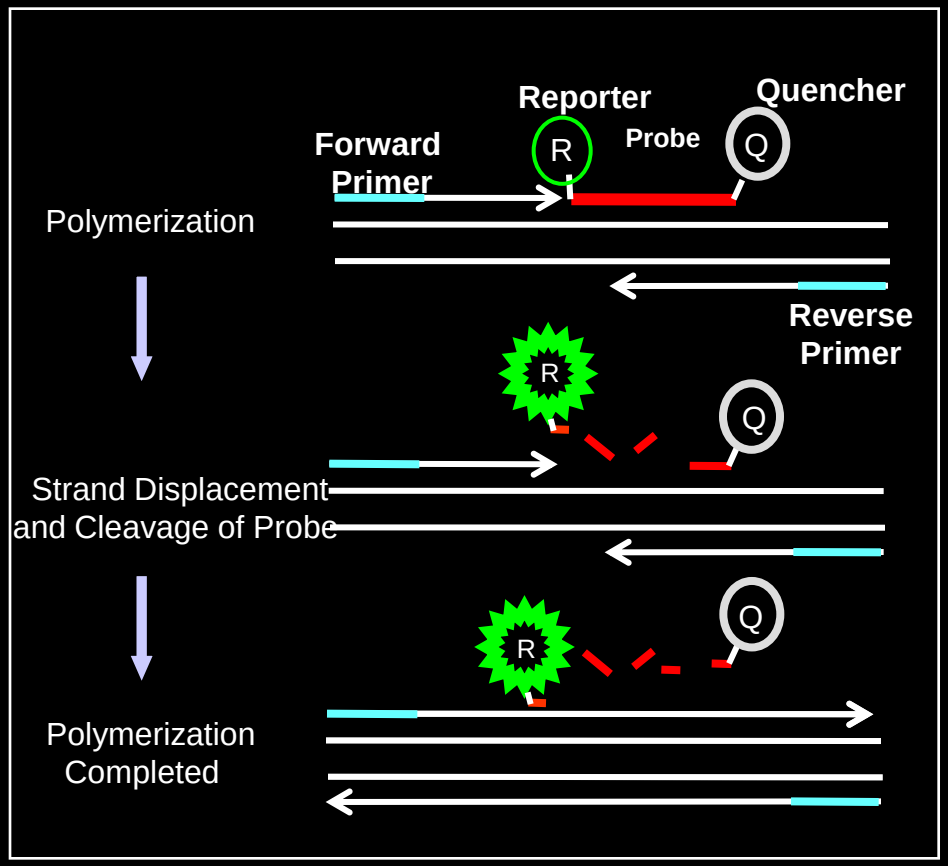
250 cancer-related candidate genes

***Sources include:**

1) Van 't Veer et al, Nature 415:530, 2002
2) Sorlie et al, Proc. Natl. Acad. Sci. USA 98:10869, 2001
3) Ramaswamy et al, Nature Genetics 33:4, 2003
4) Gruvberger et al, Cancer Res. 61:5979, 2001

RT-PCR Assay is Especially Suited to Quantify Small RNA Fragments in FPET

- Sensitive
- Specific
- Wide dynamic range
- Reproducible
- Up to 400 genes from three 10 micron sections of paraffin embedded tissue
- Mature technology—used for clinical assays for viral infections



Oncotype DX (ODX) Recurrence Score (RS)

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
Stromolysin 3
Cathepsin L2

CD68

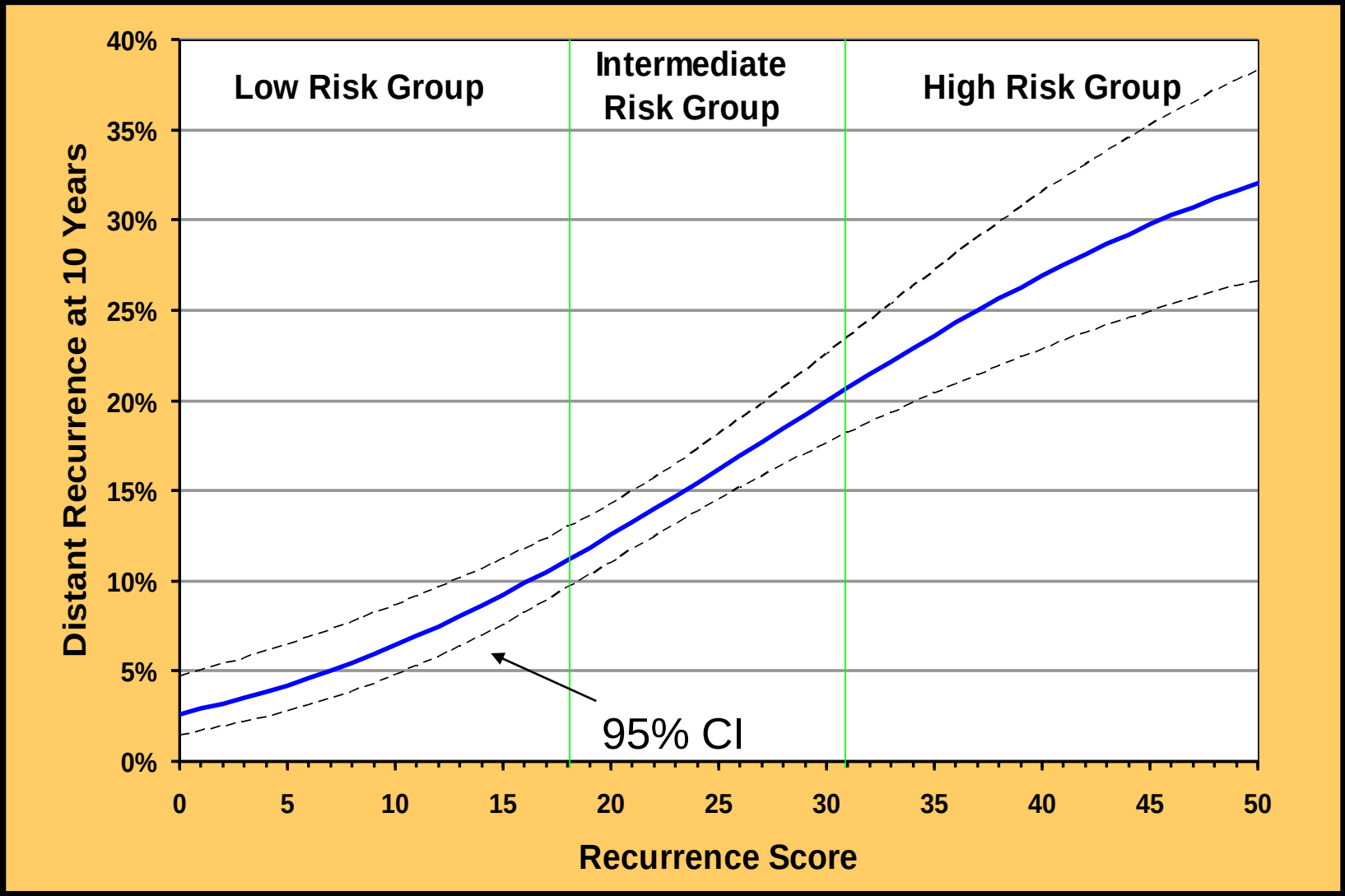
HER2
GRB7
HER2

REFERENCE
Beta-actin
GAPDH
RPLPO
GUS
TFRC

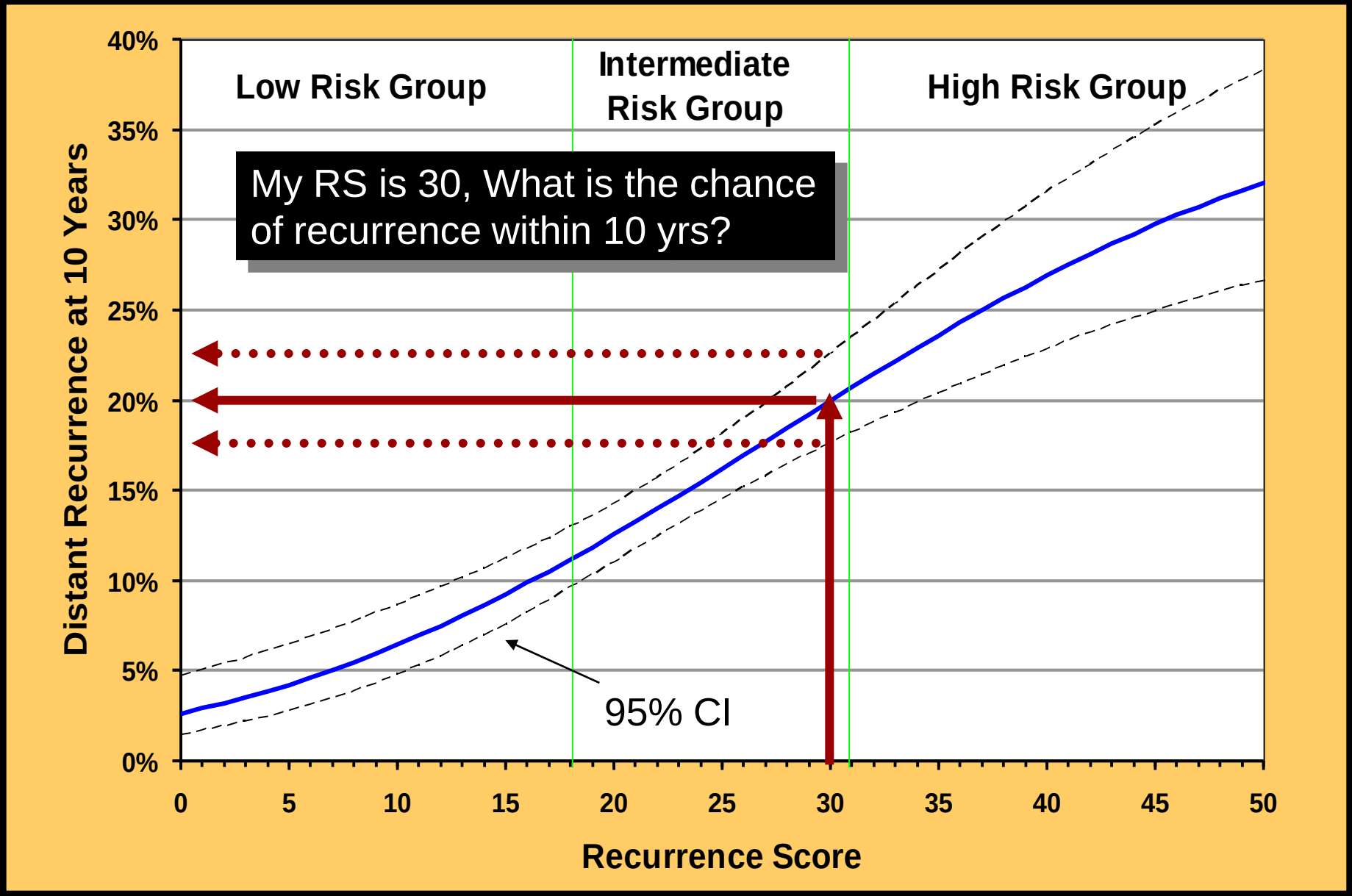
RS = + 0.47 x HER2 Group Score
- 0.34 x ER Group Score
+ 1.04 x Proliferation Group Score
+ 0.10 x Invasion Group Score
+ 0.05 x CD68
- 0.08 x GSTM1
- 0.07 x BAG1

Category	RS (0 – 100)
Low risk	RS < 18
Int risk	RS ≥ 18 and < 31
High risk	RS ≥ 31

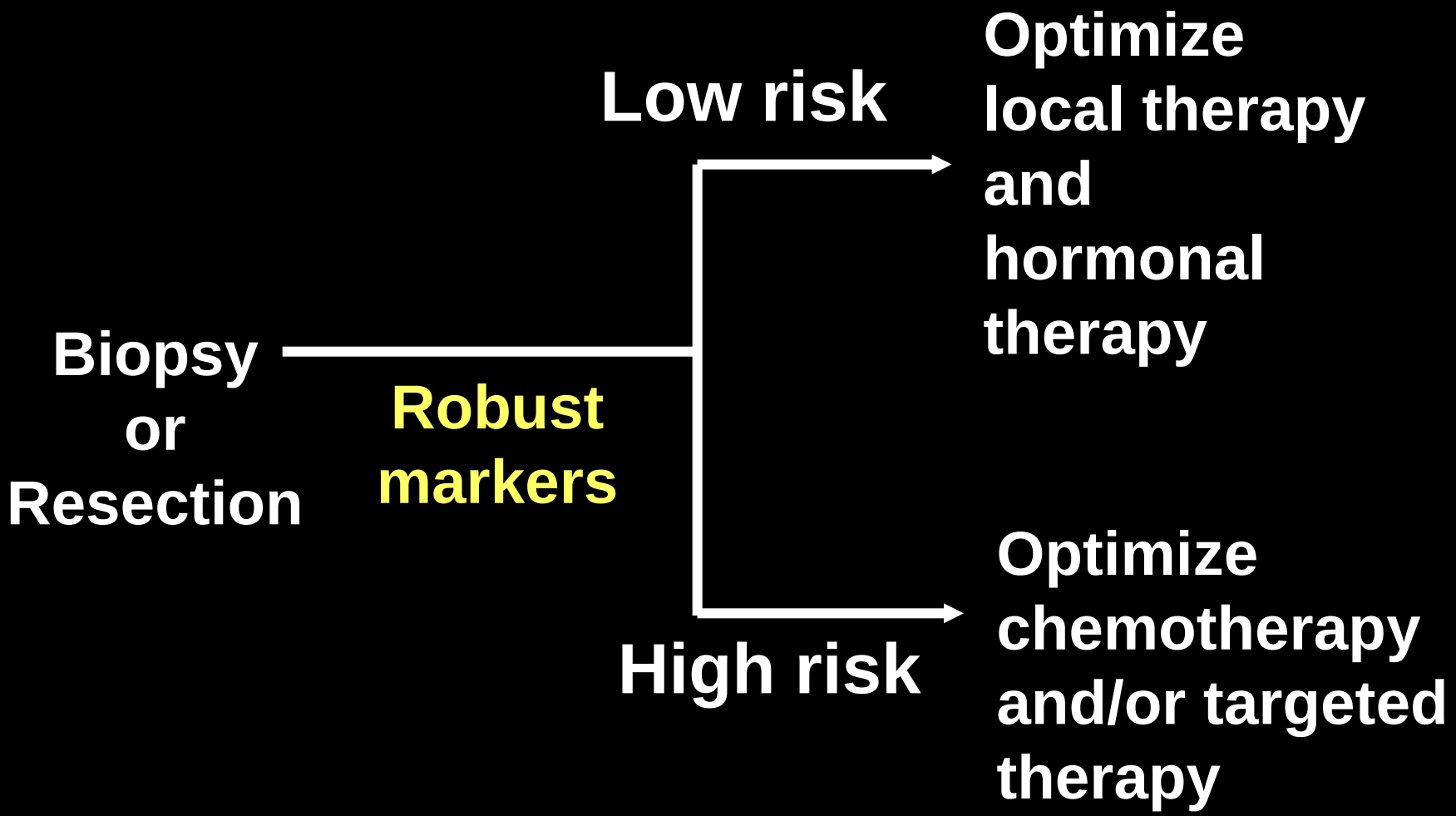
NSABP B-14 Recurrence Score as a Continuous Predictor



Recurrence Score as a Continuous Predictor



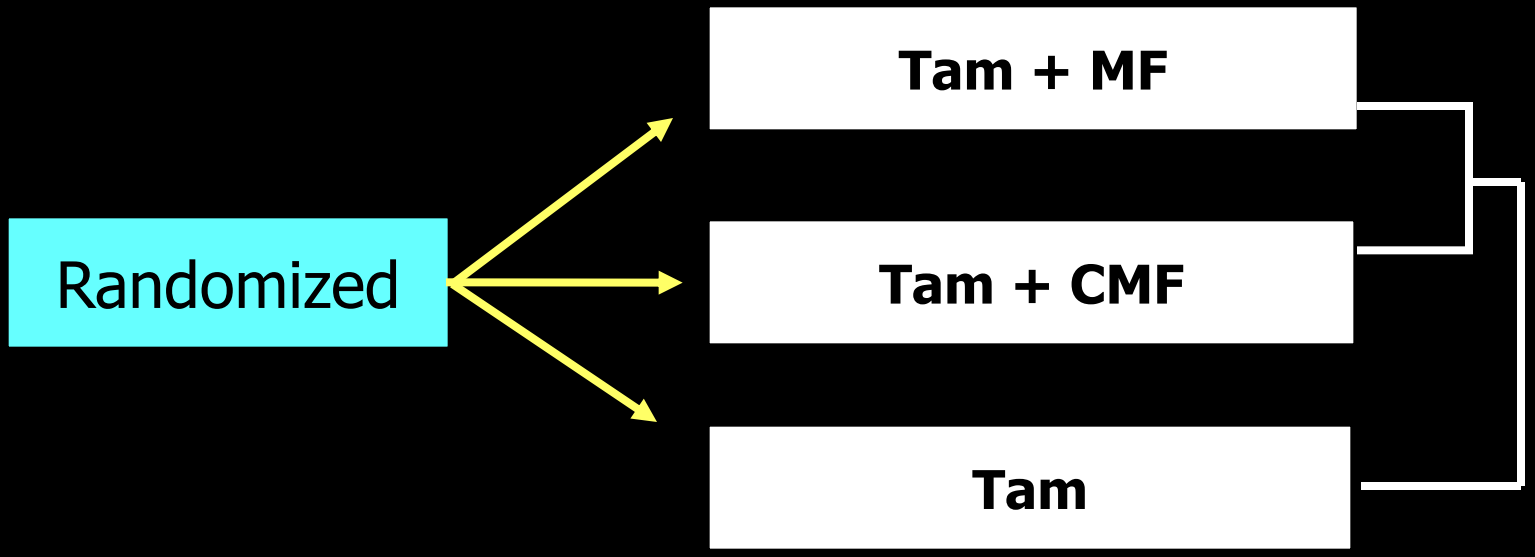
Category	NCCN		St Gallen		Recurrence Score	
	% of pts	$DRFS_{10}$	% of pts	$DRFS_{10}$	% of pts	$DRFS_{10}$
Low	**7.9**	0.93	**7.9**	0.95	**50.6**	0.93
Intermediate	-	-	33.2	0.91	22.3	0.86
High	92.1	0.85	58.8	0.81	27.1	0.69


Low risk
Optimize local therapy and hormonal therapy
Biopsy or Resection
Robust markers
High risk
Optimize chemotherapy and/or targeted therapy

Chemotherapy Response and Oncotype DX

NSABP Study B-20

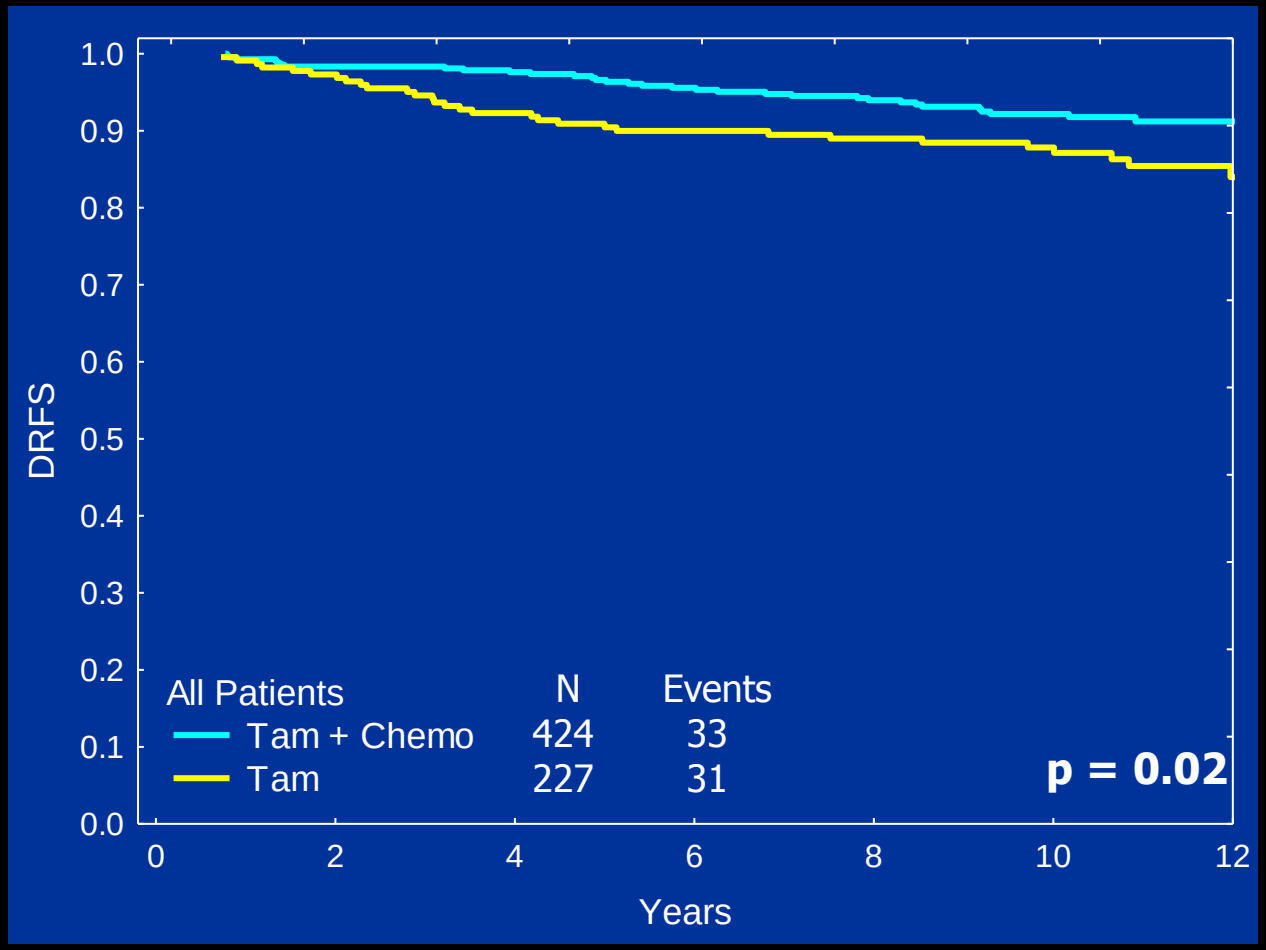
Design



Objective: Determine the magnitude of the chemotherapy benefit as a function of 21 gene Recurrence Score assay

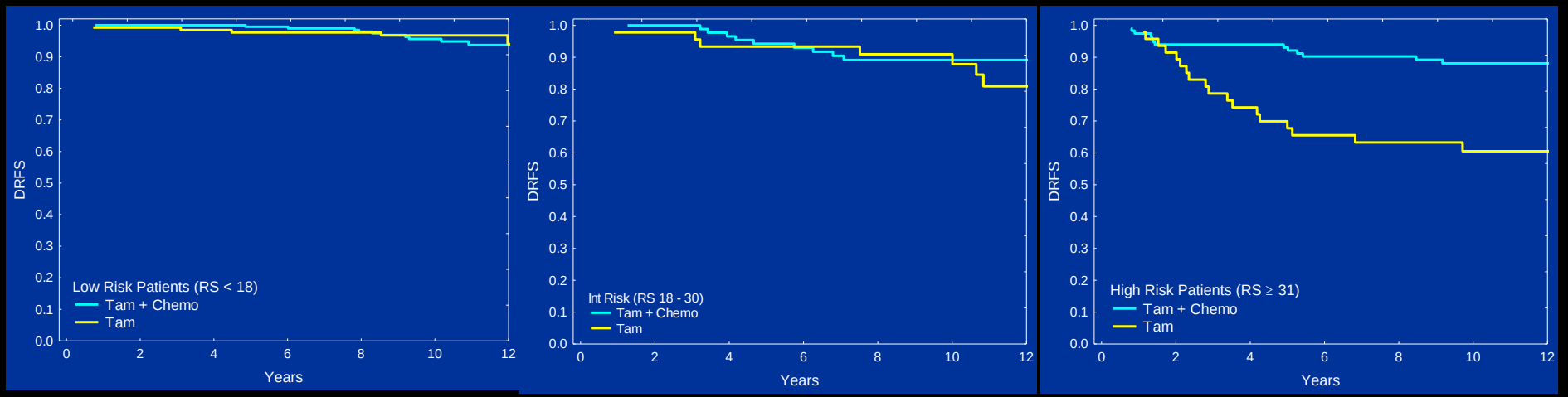
B-20 Results

- Tam vs Tam + Chemo – All



NSABP B-20 results are confirmatory

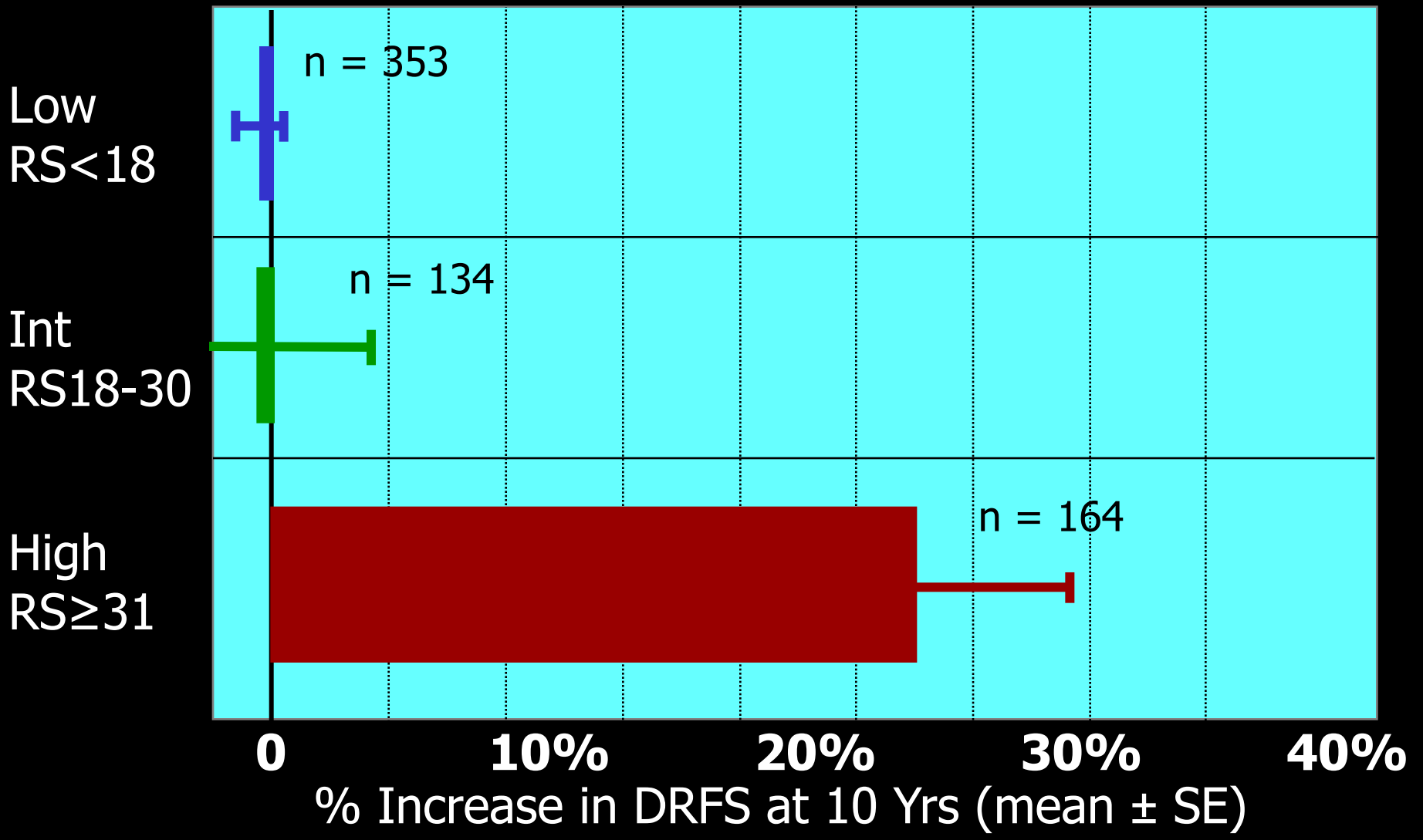
RS < 18 | RS 18-30 | RS ≥ 31



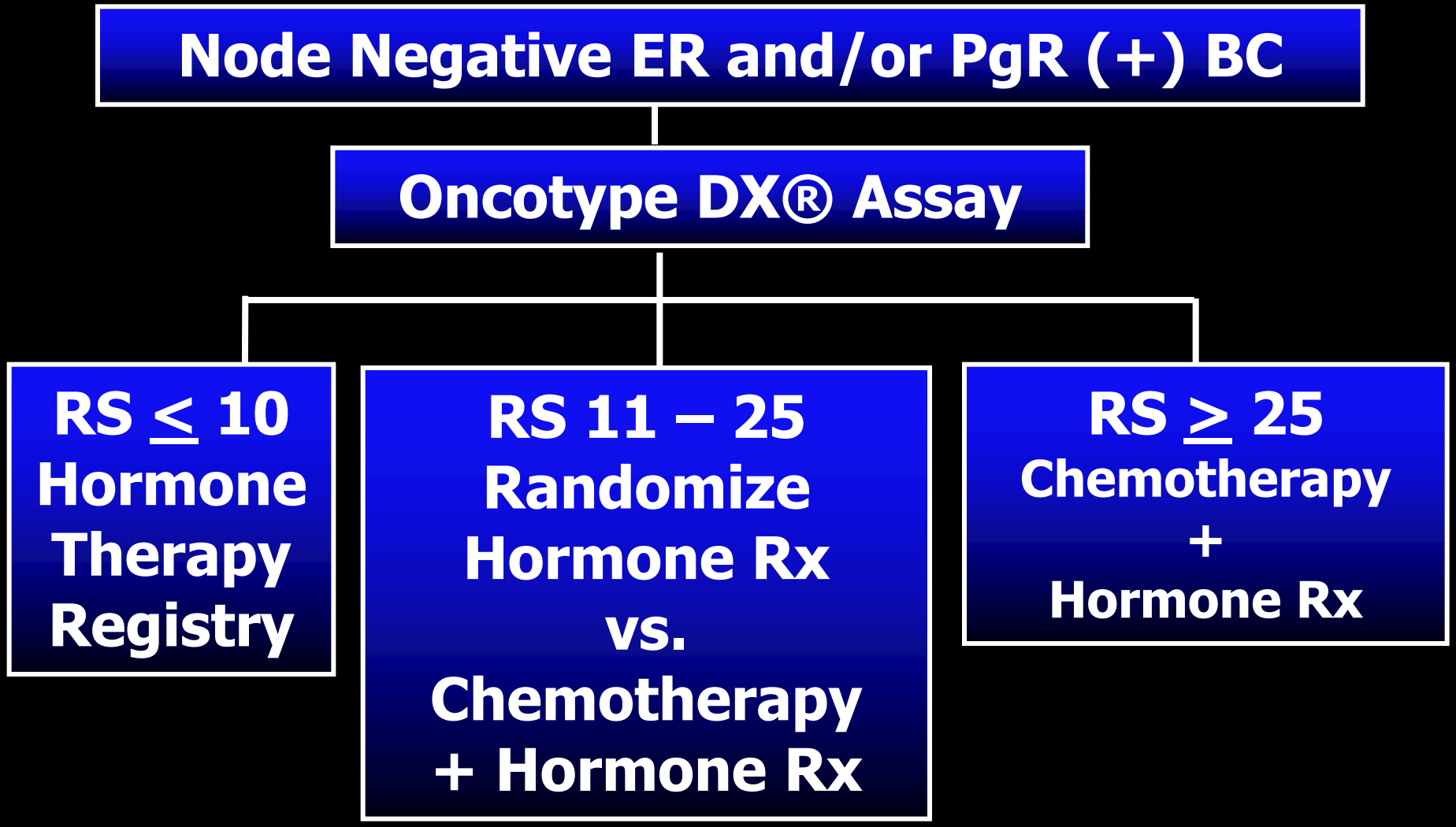
- Patients with tumors that have high Recurrence Scores have a large absolute benefit of chemotherapy (similar results with CMF and MF)
- Patients with tumors that have low Recurrence Scores derive minimal, if any, benefit from chemotherapy

B-20 Results

- Benefit (absolute) of Chemo Depends on RS



TAILORx


Node Negative ER and/or PgR (+) BC
Oncotype DX® Assay
RS ≤ 10
Hormone
Therapy
Registry
RS 11 – 25
Randomize
Hormone Rx
vs.
Chemotherapy
+ Hormone Rx
RS ≥ 25
Chemotherapy
+
Hormone Rx

Comparison of PACCT and MINDACT Trials

	PACCT	MINDACT
Groups	US Intergroup	EORTC, BIG
Population	Node-neg, ER+	Node-neg, ER+/-
Assay	21 gene ODX™	70 gene Mammaprint®
Utility Scale & Level of Evidence	+ or ++ II	+ or ++ III
Tissue	FPET	Fresh frozen
No.	~11,500	~6,000
No. randomized	4,390	1,920
Randomized group	RS 11-25 (40%)	Discordant risk (32%)
Randomization	*Treat with hormones +/- chemotherapy*	*Treat by clinical vs. genomic risk*
Non-randomized groups	RS < 11: Hormones RS > 25: Chemo + hormones	Both low risk (13%):Hormones Both high risk (55%): Chemo + hormones

Tumor Marker Utility Grading System

Hayes et al. JNCI 88: 156-1466, 1996

Scale	Utility Scale	Level	Level of Evidence
0	Adequately evaluated, no utility	V	Small pilot studies that estimate distribution of marker
+/-	Suggestive but not definitive data linking marker with biological process or clinical outcome	IV	Small retrospective studies without prospectively dictated therapy
+	Marker correlates with process/outcome, but further study required (correlates with another marker, marker information not useful, level of evidence lacking)	III	Large but retrospective studies without prospectively dictated therapy and/or followup
++	Standard practice in select situations: marker supplies information not otherwise available, cannot be used as sole criterion	II	Prospective therapeutic clinical trial not designed to test marker, but specimen collection for marker study & statistical analysis are prospectively defined as secondary objectives
+++	May be used as sole criterion for clinical decision making	I	Prospective, high-powered trial designed to test marker utility, or evidence from meta-analysis or overview of level II and/or III studies

Summary

- Molecular profiles to help prognosticate are (almost) here.
  - They do not replace traditional clinical variables.
- Molecular profiles to help predict response to therapy are here.
  - They do not exclude subsets from receiving adjuvant hormonal or chemotherapy.
  - They are reasonable adjuncts to other clinical decision-making.
- We are seeing the tip of the iceberg in breast cancer heterogeneity now…

Francisco de Zurbaran
1630-1633
Musee Fabre, Montpellier

Limitations

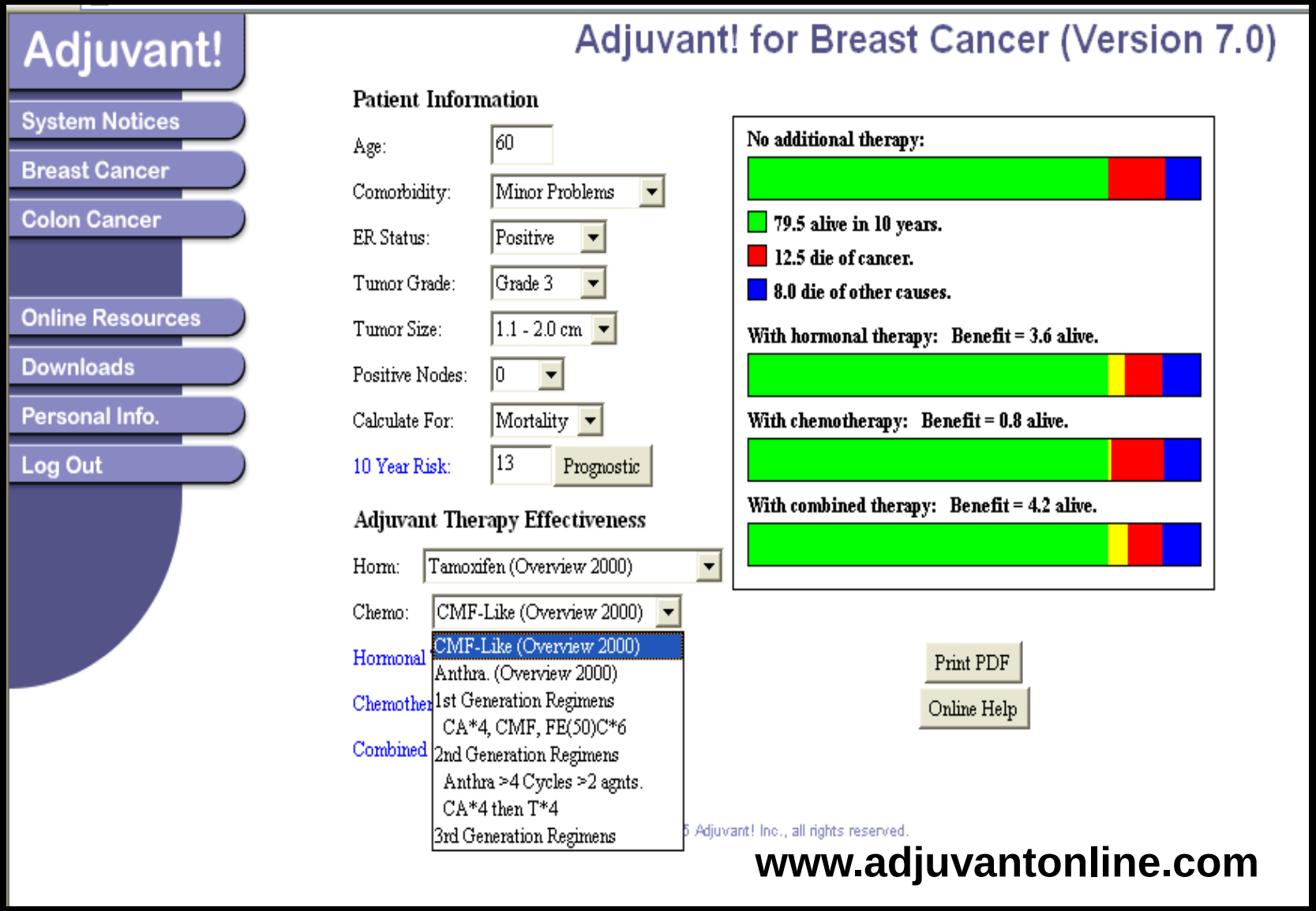
Some Methodological Challenges

- Getting adequate tissue samples, with good clinical information, for validation
- Plethora of potential markers and methods
- Adequacy of validation based on existing data, even when data analyses are prospectively planned
- What additional studies are needed?
- As standard of care changes, will continuous revalidation be necessary?

Assessing Clinical Relevance

- What evidence would it take for women and their docs to forego chemo?
- Can/should we try to assess whether there is a group of women who do not need Tamoxifen?
- What is on the horizon for identifying the best treatment for women with Stage III & IV breast cancer?
- Aren't predictive tests more important than prognostic tests for most patients?
- How do gene panels do by comparison with existing approaches?

Existing Approaches



www.adjuvantonline.com

An independent population-based validation of the adjuvant decision-aid for stage I-II breast cancer. (Olivotto,Bajdik,Ravdin et al. ASCO, 2004)

- Predictor variables
  - Demographic
  - Pathology
  - Staging
  - Treatment Plan
- Predicted variables
  - 10 Yr Overall Survival (OS)
  - Breast Cancer Specific Survival (BCSS)
  - Event-free survival (EFS)

- Validation
  - 4,083 women with pT2-2, pNO-1 breast cancer

	Pred	Obs
OS	71.7%	72.0%
BCSS	83.2%	82.3%
EFS	71%	70.1%

Adjuvant!

System Notices

Breast Cancer

Colon Cancer

Online Resources

Downloads

Personal Info.

Log Out

Adjuvant! for Breast Cancer (Genomic Version 7.0)

Patient Information:

Present Age: 60

Comorbidity: Minor Problems

ER Status must be initially positive.

Nodal status must be node negative.

GH Recurrence Score: 0

10 Yr Risk of Metastases: 3

Planned Therapy:

Horm: Tamoxifen (Validated for GH)

Chemo: CMF-Like (Overview 2000)

Chemotherapy Effectiveness: 12

(Proportional Risk Reduction)

Resulting Graphs

Only Hormonal Therapy:

- 88.7 % alive and without metastases in 10 years.
- 2.9 % relapse. (Develop metastatic disease)
- 8.4 % die of causes other than breast cancer.

Hormonal Therapy and Chemotherapy:

- 88.7 % alive and without metastases in 10 years. Plus...
- 0.4 % alive and without relapse due to chemotherapy.
- 2.5 % relapse. (Develop metastatic disease)
- 8.4 % die of causes other than breast cancer.

Print PDF | Online Help

Some Regulatory/Business Challenges

- How should these tests be regulated?
- Should insurance companies pay for them?
- Will drug companies invest in developing treatments targeted at small groups of patients?

Discussion