

*NIH Symposium:  
Why Do We Get It Wrong?*

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*Methods of Oncology  
BioMarker Validation:  
Trying to Get it Right!*

**Daniel F. Hayes, M.D.**



# *ASCO Tumor Marker Guidelines Panel*

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- **ER, PgR**                      **Select Endocrine Therapy**
- **HER2**                              **Select Trastuzumab**
- **CA15-3, CA27.29, CEA**      **Monitor Selected Pts with Metastatic Disease**

*Bast RC, Jr., Ravdin P, Hayes DF, et al.: J Clin Oncol 19:1865, 2001*

# *ASCO Tumor Marker Guidelines*

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- **Why Are the Guidelines So Conservative?**
  - Only recommended markers for which results would change clinical decisions
  - Evidence-based
  - Lack of Level of Evidence I or II studies:
    - *A Tumor Marker Utility Grading Scale*

*Hayes, et al; J Nat Cancer Institute 88:1456, 1996*

# ***TMUGS: Levels of Evidence***

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<b><u>Level</u></b>	<b><u>Definition</u></b>
<b>I</b>	<b>Prospective, Marker Primary Objective, Well-powered OR Meta-analysis</b>
<b>II</b>	<b>Prospective, Marker Secondary Objective</b>
<b>III</b>	<b>Retrospective, Outcomes, Multivariate Analysis</b>
<b>IV</b>	<b>Retrospective, Outcomes, Univariate</b>
<b>V</b>	<b>Retrospective, Correlation with Other Marker, No Outcomes</b>

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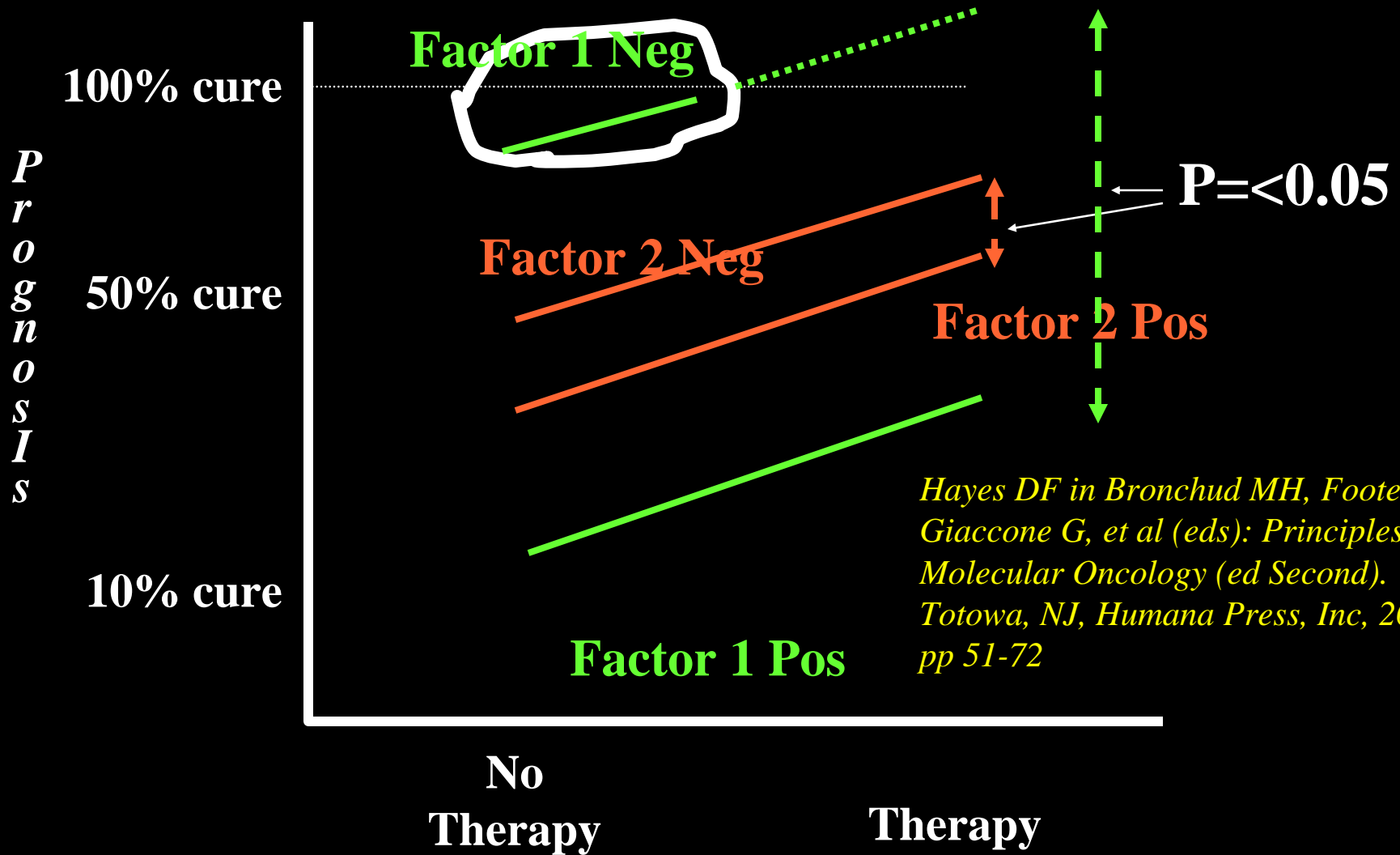
# *When is a Marker Clinically Useful?*

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- It is either **prognostic** or **predictive**
- The **magnitude** of effect is sufficiently large that clinical decisions based on the data result in outcomes that are acceptable
  - Greater chance for benefit
  - Smaller toxicity risk
- The estimate of magnitude of effect is **reliable**
  - Assay is reproducible
  - Clinical trial/marker study design is appropriate
  - Results are validated in subsequent well-designed studies

# PURE PROGNOSTIC FACTOR

*(Unfavorable)*



*Hayes DF in Bronchud MH, Foote M, Giaccone G, et al (eds): Principles of Molecular Oncology (ed Second). Totowa, NJ, Humana Press, Inc, 2004, pp 51-72*

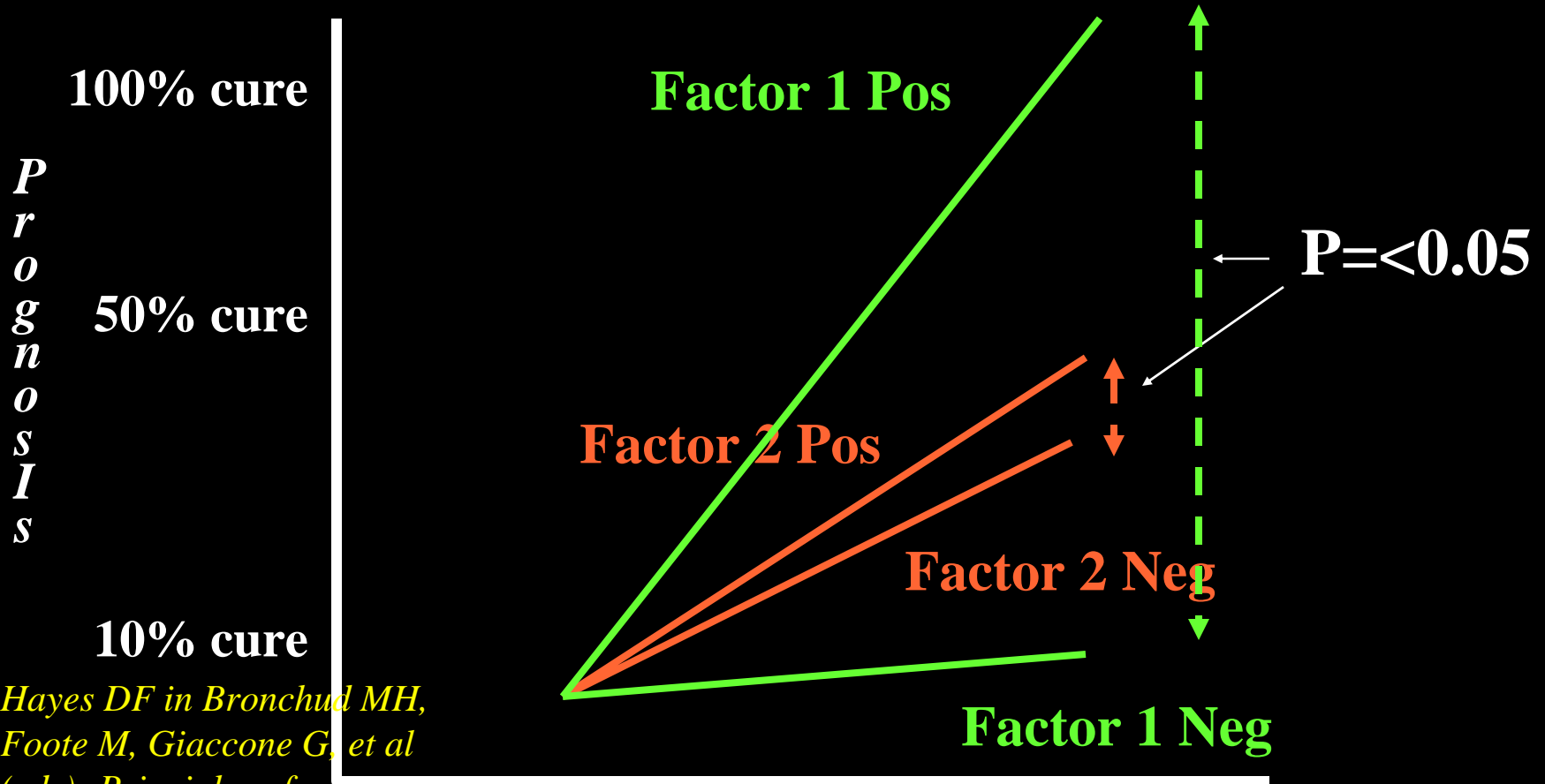
# *Prognostic Factors: Clinical Utility*

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- **How much added benefit is required to justify treatment?**
  - **Depends on toxicity of treatment**
  - **Depends on perspective of patients**

# PURE PREDICTIVE FACTOR

*(For Sensitivity to Therapy)*



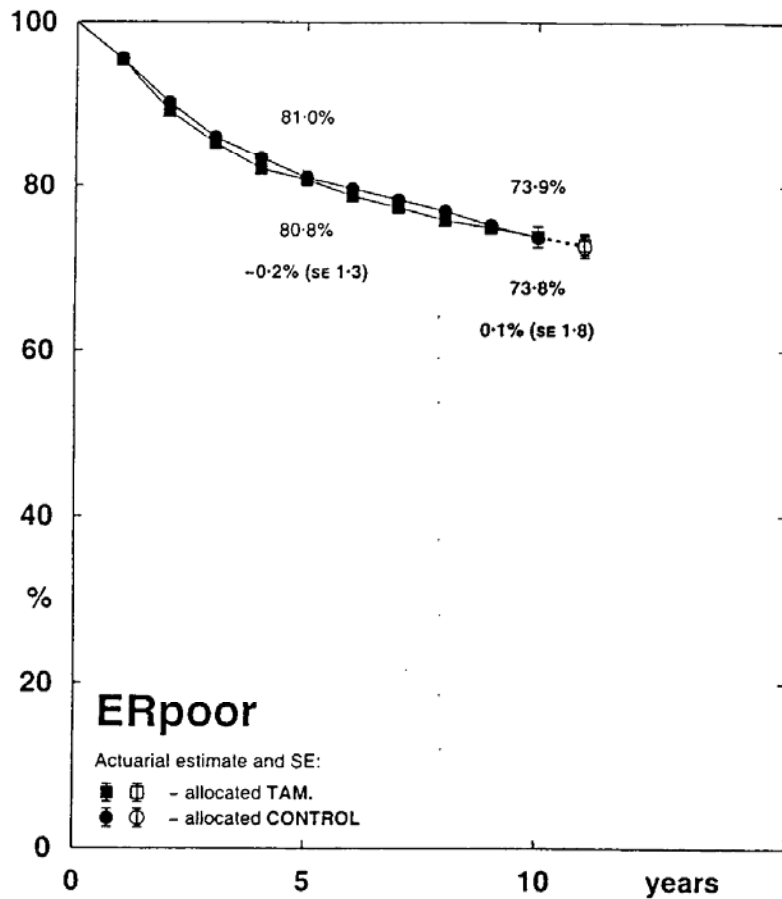
Hayes DF in Bronchud MH,  
Foote M, Giaccone G, et al  
(eds): Principles of  
Molecular Oncology (ed  
Second). Totowa, NJ,  
Humana Press, Inc, 2004,  
pp 51-72

No  
Therapy

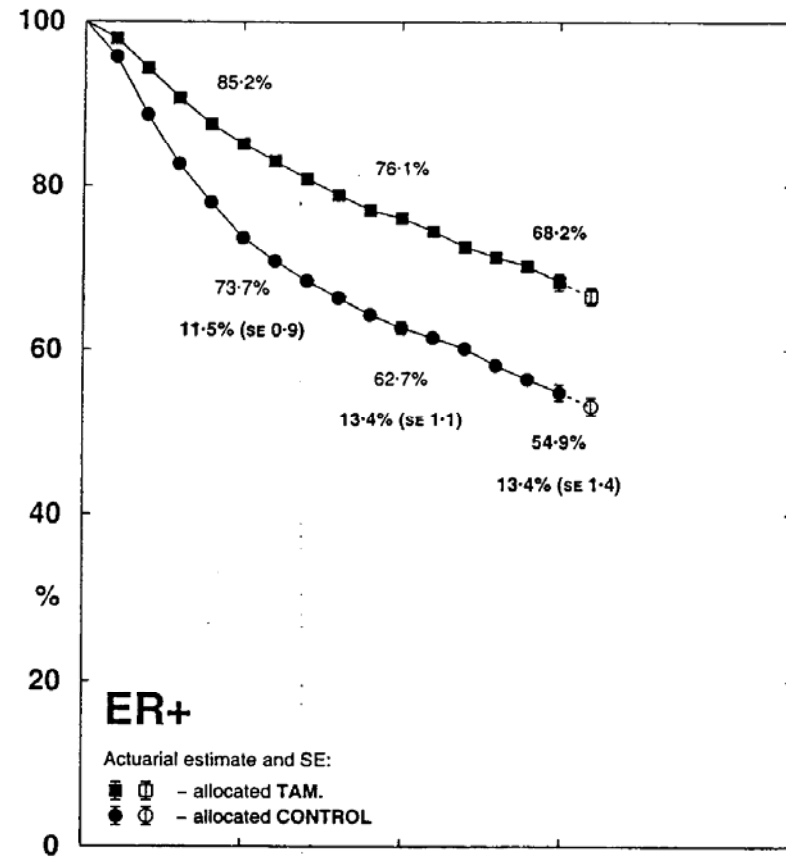
Therapy

# Tamoxifen vs. Not RECURRENTES Effect of ER

## POOR



## POSITIVE



*Oxford Overview 9/2000*

# *Tumor Marker Validation*

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## ● **Examples: Breast Cancer**

### ASSAY

*Multi-Gene Expression*

**Rosetta/DNA Array**

**GHI/Multi-gene RT-PCR**

*Circulating Tumor Cells*

**Immunicon/Immunomagnetic Separation**

### SETTING

*Adjuvant*

*Metastatic*

# *Tumor Marker Validation*

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## ● **Examples: Breast Cancer**

### ASSAY

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# 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

$$RS = + 0.47 \times \text{HER2 Group Score} \\ - 0.34 \times \text{ER Group Score} \\ + 1.04 \times \text{Proliferation Group Score} \\ + 0.10 \times \text{Invasion Group Score} \\ + 0.05 \times \text{CD68} \\ - 0.08 \times \text{GSTM1} \\ - 0.07 \times \text{BAG1}$$

GSTM1

BAG1

### INVASION

Stromolysin 3  
Cathepsin L2

CD68

### REFERENCE

Beta-actin  
GAPDH  
RPLPO  
GUS  
TFRC

HER2  
GRB7  
HER2

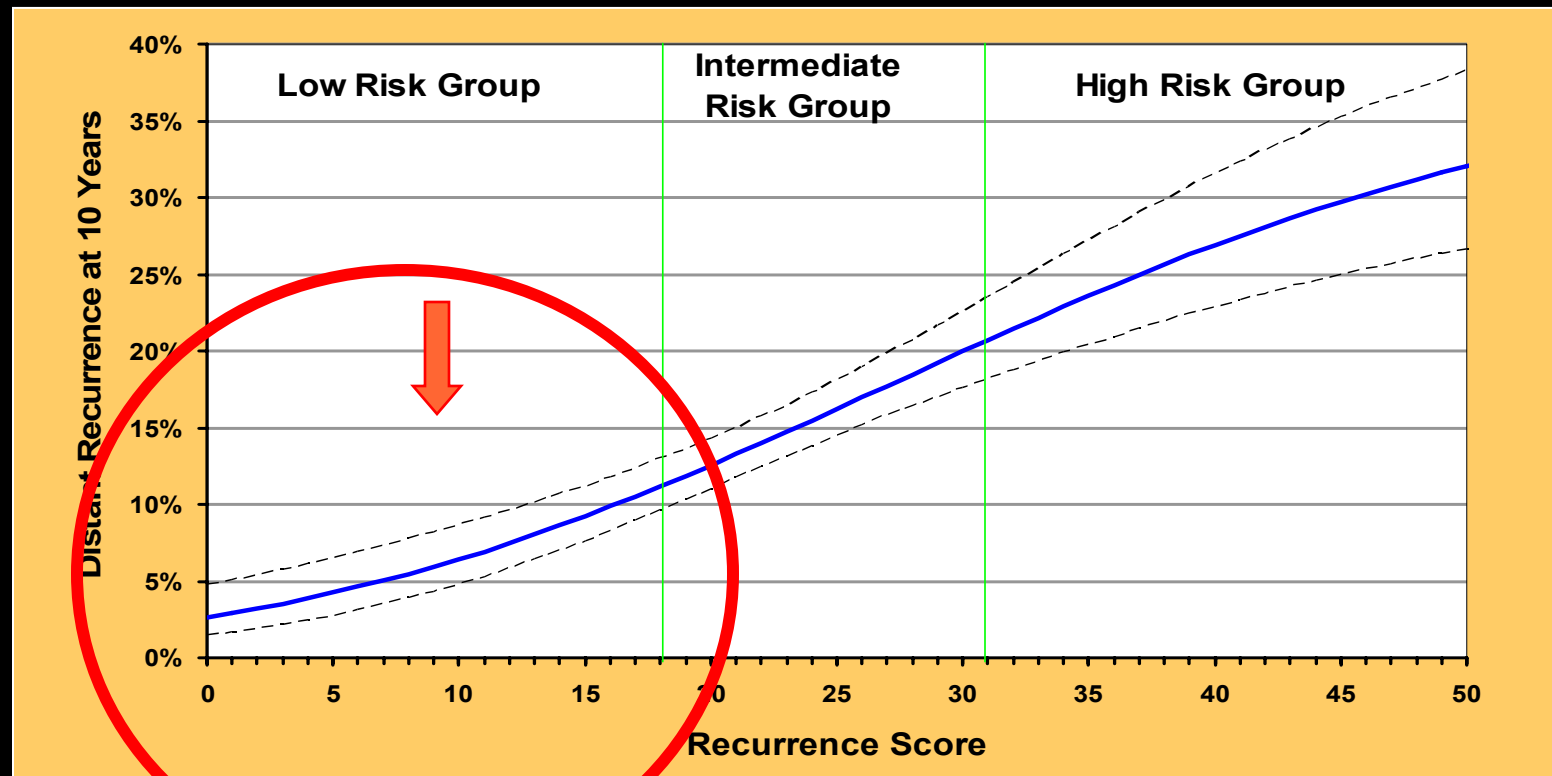
Category	RS (0 – 100)
Low risk	RS < 18
Int risk	RS ≥ 18 and < 31
High risk	RS ≥ 31

*Paik et al, NEJM 35:2817, '04*

## *NSABP: Clinical Validation Study of Oncotype DX*

- ***NSABP 20***: Node Neg, ER+, Tam treated patients
- **10 yr Distant Recurrence**

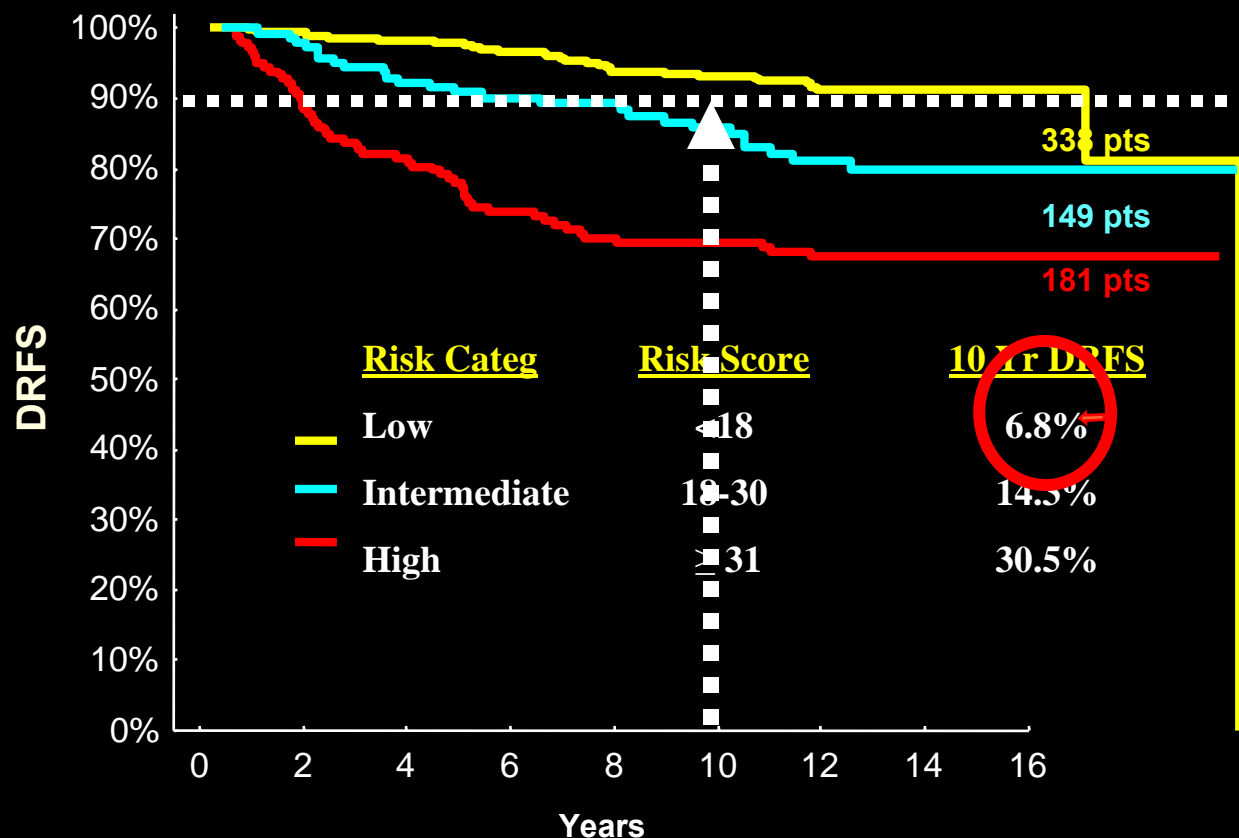
**Recurrence Score/Cont. Variable**



*Paik et al, NEJM 35:2817, '04*

# NSABP B-14 Clinical Validation Study of Oncotype DX

- **NSABP 14:** Node Neg, ER+, Tam treated patients
- Tam treated patients: 10 year Distant Recurrence



Paik et al, NEJM 35:2817, '04

# Proposed US Breast Intergroup Trial

Node Negative ER and/or PgR (+) BC

Oncotype DX® Assay

RS < 15  
Hormone  
Therapy  
Registry

RS 15 – 30  
Randomize

RS > 30  
Chemotherapy  
+  
Hormone Rx  
(Registry or  
Other Trials)

Hormone Rx

Hormone Rx  
+ ChemoRx

n~4400 for randomized arm

# *Conclusions*

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- **Many proposed tumor markers**
- **Most studies are LOE III or worse**
- **Cooperative Groups are now performing LOE II associated with prospective therapeutic clinical trials**
- **New Cooperative Group studies will be LOE I**