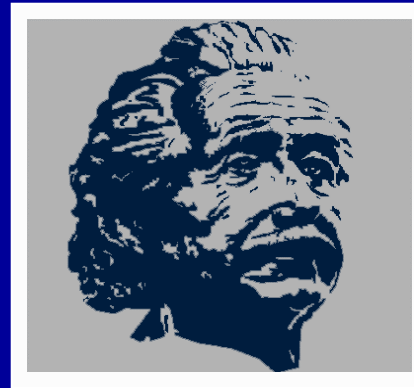


# ***Rationale For & Design of TAILORx***

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# Declining Breast Cancer Mortality & Event Rates in Adjuvant Trials: The Price of Progress

- **Breast cancer mortality declining**
  - Death rates in U.S. ↓ 24% in 2000 compared to 1990 (*Ries et al. SEER Cancer Statistics 1975-2000*)
  - Similar trends outside U.S. (*Parkin et al. Eur J Cancer 2003; 39; 848*)
- **Recurrence rates reduced after breast cancer diagnosis**
  - Better prognosis if mammogram detected (*Shen et al. JNCI 2005; 97: 1195*)
  - More accurate lymph node staging by sentinel lymph node biopsy
  - More effective cytotoxic regimens
  - More effective endocrine therapy for HR-positive disease
  - Adjuvant trastuzumab for Her2/neu positive disease
- **Incremental gains of chemotherapy driven largely by effects in HR-neg disease** (*Berry et al. JAMA 2006; 295: 1658*)
- **Adjuvant trials now typically require 5000-8,000 subjects because of low event rates, particularly in HR-Pos disease**

# Molecular Markers: A Potential Solution?

Reduce cancer mortality and treatment associated morbidity

- **More accurately identify high risk subjects likely to benefit from:**
  - More aggressive non-specific therapy (ie, chemotherapy)
  - Specific targeted therapies (ie, anti-Her2 therapy)
  - Clinical trials evaluating experimental therapies
- **Potential impact:**
  - Reduce overtreatment in low risk subjects
  - Reduce undertreatment in high risk subjects
  - Improve efficiency and reduce size and costs of adjuvant trials

# Program for the Assessment of Cancer Clinical Tests (PACCT)

(<http://www.cancerdiagnosis.nci.nih.gov/assessment/index.html>)

- **NCI program designed to:**
  - ensure translation of new knowledge about cancer into clinic
  - integrate/test new technologies in clinical practice
  - develop more informative laboratory tools to help maximize the impact of cancer treatments
- **Progress to date:**
  - REMARK Guidelines (Reporting Recommendations for Tumor Marker Prognostic Studies; JNCI 2005; 97: 1180-1184).
  - First clinical trial developed (PAACT-1): TAILORx

**What treatment should the marker be used for in order to spare or select ?**

# Non-Surgical Treatment Options

Treatment	Selection	Percent Eligible	Treatment Effect	Acute Toxicity	Estimated Cost
Chemotherapy	Recurrence Risk > 5-10%	Most	25-35%	High	\$26,500
Endocrine therapy	ER/PR+	70%	50%	Low	\$15,000
Trastuzumab	Her2+	15%	50%	Low	\$40,000
Radiation	Lumpectomy	40-60%	90%	Low	\$9,000 (Higher for PBI)

**Which population should  
the marker be evaluated in?**

# ER-Positive, Lymph-Node Negative Breast Cancer

- **Disease common**

- 137,000 diagnosed annually in North America
- ~ 50% of newly diagnosed breast cancer
- ~8% of all cancers in U.S.

- **Overtreatment common**

- 80-85% are adequately treated with
  - surgery +/- irradiation
  - hormonal therapy (ie, tamoxifen, A.I.)
- adding chemotherapy ↓ recurrence by ~ 25%
  - absolute benefit is small (~3-5% or less)
- current practice guidelines
  - chemotherapy recommendation based upon risk, not predictive factors
  - chemotherapy recommended for most

# What is the scientific rationale for selecting Oncotype DX for TAILORx?

*(Trial Assigning Individualized Options for Treatment)*

# 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

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

**GSTM1**

**BAG1**

## INVASION

Stromelysin 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 – 30

High risk

RS > 30

# Summary of Validation Study Results

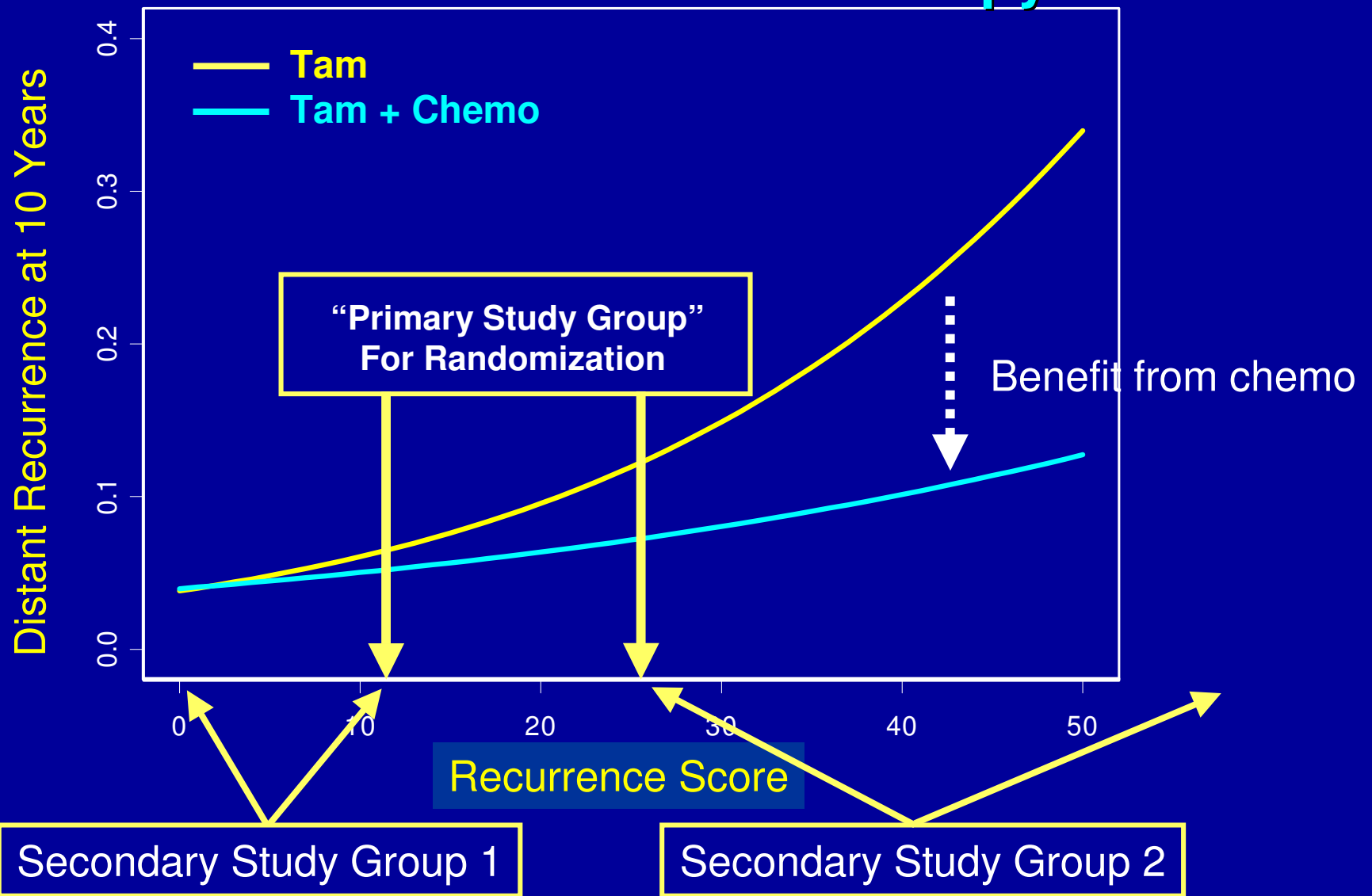
- **Prognostic**

- ↑ RS - ↑ distant recurrence at breast cancer death at 10 years
- Categorical or continuous variable
- Prognostic significance retained after adjustment for clinical features
- Prognostic if no therapy, tam therapy, or chemohormonal therapy
- Prognostic for local recurrence also
- More accurately predicts outcome than Adjuvant!

- **Predictive**

- Low RS predictive of benefit from hormonal therapy
- High RS predictive of benefit from chemotherapy

# Relationship Between RS as a Continuous Variable and Treatment with Tam or Tam + Chemotherapy



# Rationale for Choosing Oncotype DX

- **Level of Evidence**

- Prospective validation (B14) & external validation studies (Kaiser) in tamoxifen treated patients
- Experience in other populations including patients treated with chemohormonal therapy (B20) and no therapy

- **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 – facilitates retrospective clinical use
- Builds on prior public-private partnership
- Extensive post-marketing experience and precedent for payor reimbursement

# Molecular Markers: Potential Influence on Treatment Decisions

Treatment	Clinical	Genomic	Impact
<b>“Sparing”</b>	Yes	No	↓ Unnecessary Chemotherapy
<b>“Selection”</b>	No	Yes	↑ Curability
<b>“Direction”</b>	Equipoise	Yes or No	More appropriate treatment choices
<b>“Confirmation”</b>	Yes	Yes	Confirm clinical decision
	No	No	

**What trial design?**

# TAILORx Study Design

Pre-REGISTER

ONCOTYPE DX ASSAY

REGISTER  
Specimen Banking

## Key Eligibility:

- Node-negative
- HR-positive
- Her2-negative
- Age  $\leq$  75 years
- Meet standard criteria for chemo

Secondary Study Group 1  
RS < 11

Primary Study Group  
RS 11-25

Secondary Study Group 2  
RS > 25

ARM A  
Hormonal Therapy  
Alone

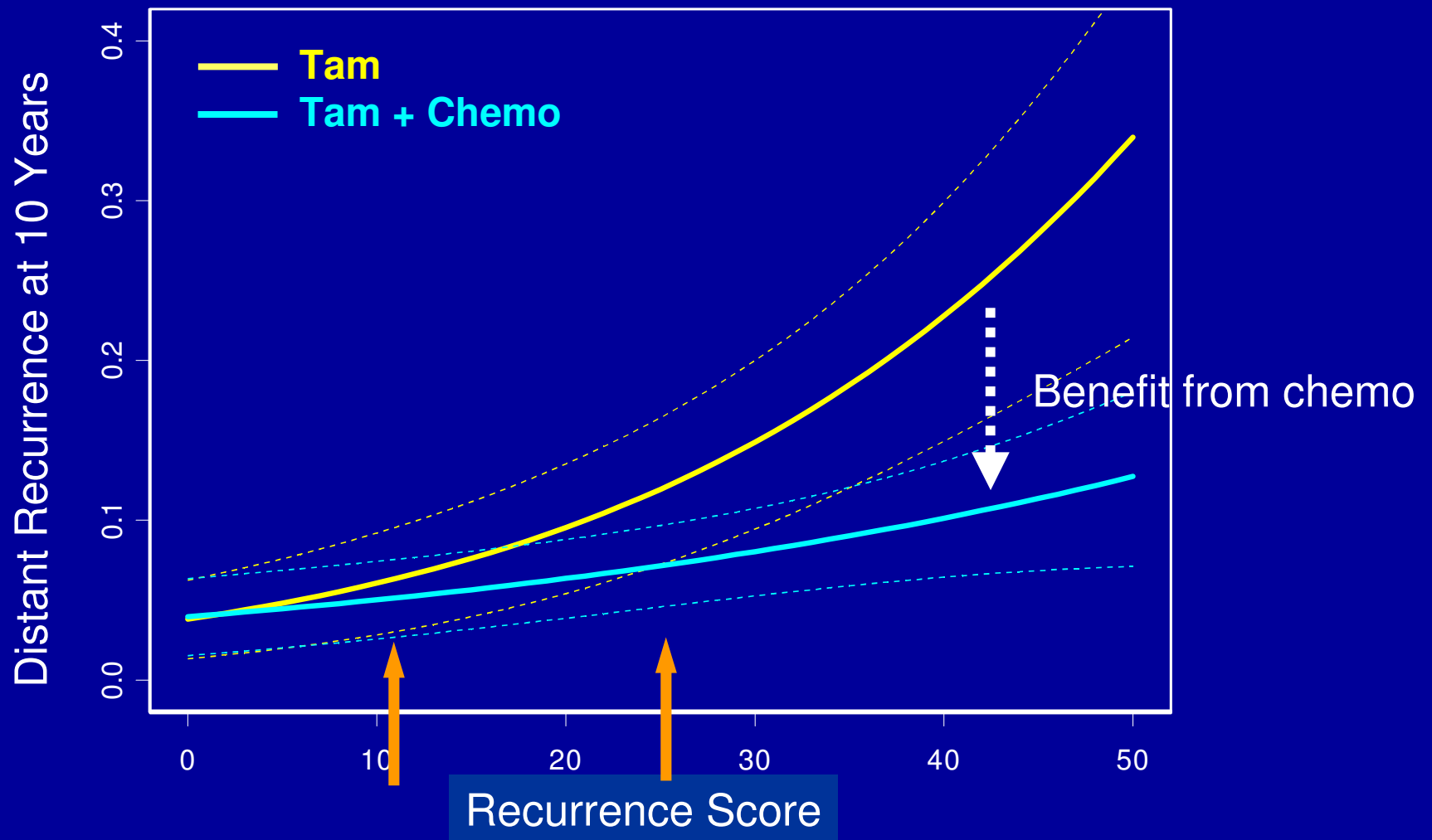
RANDOMIZE  
Stratification Factors:  
Tumor Size, Menopausal Status,  
Planned Chemo, Planned Radiation

ARM D  
Chemotherapy Plus  
Hormonal Therapy

ARM B  
Hormonal Therapy  
Alone

ARM C  
Chemotherapy Plus  
Hormonal Therapy

# Rationale for Primary Study Group RS Range of 11-25 Based upon B-20 Results (linear fit 95% CI)



# 10 year Distant Relapse Free Survival by TAILORx RS Ranges in B20 Trial

RS	No. (%)	Tam	Tam + Chemo	HR	P Value
<11	177 (27%)	98%	95%	1.79	0.47
11-25	297 (43%)	95%	94%	0.76	0.53
>25	195 (30%)	63%	88%	0.29	<0.0001

# Objectives

- **Primary:**

- Is ET inferior to chemo + ET in patients with a mid-range RS
- Create a tissue and specimen bank for evaluation of other cancer clinical tests in the future

- **Statistical considerations:**

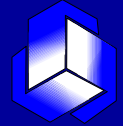
- RS 11-25:

- Non-inferiority design
- ↓5-year DFS rate from 90% (with chemo) to  $\leq$  87% (without chemo)
- one-sided type I error of 10%, 5% type II error
- Must screen ~10,046 to identify 4,390 patients with RS 11-25

- RS <11:

- distinguish between 10-year DFS rate of 95% vs.  $\leq$  93.5%
- one-sided test with type I error 2.5%, 80% power

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



Evaluate Clinical-Pathological risk and 70-gene signature risk

55%

32%

13%

Clinical-pathological and 70-gene both HIGH risk

Discordant	
Clin-Path HIGH 70-gene LOW	70% N=1344
Clin-Path LOW 70-gene HIGH	30% N=576

Clinical-pathological and 70-gene both LOW risk

N=1920

R1

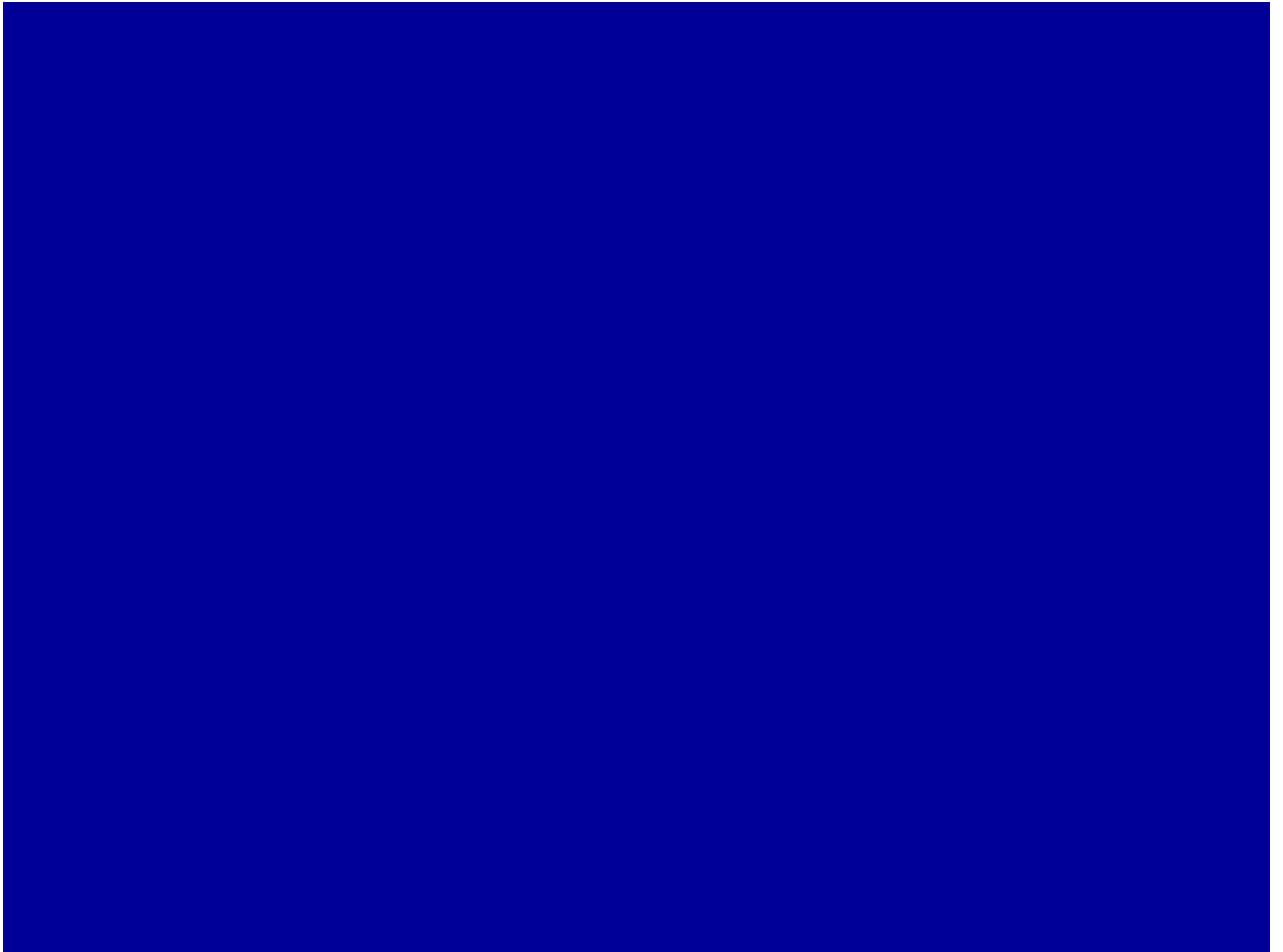
H<sub>0</sub>: 5y DMFS >92% (80% power)

Use Clin-Path risk to decide Chemo or not	
Clin-Path High 70-gene Low: CTx	70% 672
Clin-Path Low 70-gene High: no CTx	30% 288

Use 70-gene risk to decide Chemo or not	
<u>Clin-Path High</u> <u>70-gene Low: no Ctx</u>	<u>70%</u> <u>672</u>
Clin-Path Low 70-gene High: Ctx	30% 288

# Progress of TAILORx and MINDACT

- **MINDACT – Europe**
  - Pilot feasibility study ongoing
- **TAILORx – North America**
  - Activated in April, 2006
  - All NCI-sponsored cooperative groups participating
  - > 900 sites participating
  - > 2400 patients enrolled, > 1200 randomized
  - Non-compliance in randomized group manageable
  - Selection bias evident
    - Clinical: T 1-2 cm in 60%, intermediate grade in 60%
    - Genomic: 70% mid range RS



# 10 year Disease Free Survival by TAILORx RS Ranges in B20 Trial

RS	No. (%)	Tam	Tam + Chemo	HR	P Value
<11	177 (27%)	77%	85%	0.61	0.12
11-25	297 (43%)	81%	76%	1.11	0.69
>25	195 (30%)	53%	75%	0.29	0.01

DFS – includes second primary breast and non breast cancer