Introducing a Genomic Innovation to Clinical Practice

Steven Shak

December 4, 2007

Disclosure: Steven Shak, M.D.

I have the following financial relationships to disclose:

Employee of: Genomic Health, Inc.

Stockholder in: Genomic Health, Inc.

Onco*type* DX

- Diagnostic multi-gene expression test for breast cancer treatment planning commercially available since 2004 with clinical evidence validating its ability to predict the:
  - Likelihood of breast cancer recurrence
  - Magnitude of chemotherapy benefit
- Growing physician use and reimbursement
  - Over 6,600 ordering physicians and 39,000 tests since launch
  - Reimbursed by Medicare and major payers
- ASCO guidelines recommend use of Oncotype DX for node negative ER positive breast cancer (Journal of Clinical Oncology on-line, Oct 23, 2007)

Oncotype DX—Bringing the Promise of Genomics to Clinical Practice

- Innovation
- Multiple independent clinical studies – rigor in design, performance, analysis (with comparison to standard measures)
- Assay precision, standardization, control
- Clinical utility – Meet the needs of patients, physicians, payers, regulators, and investors
- Continuing research

Technology Breakthrough

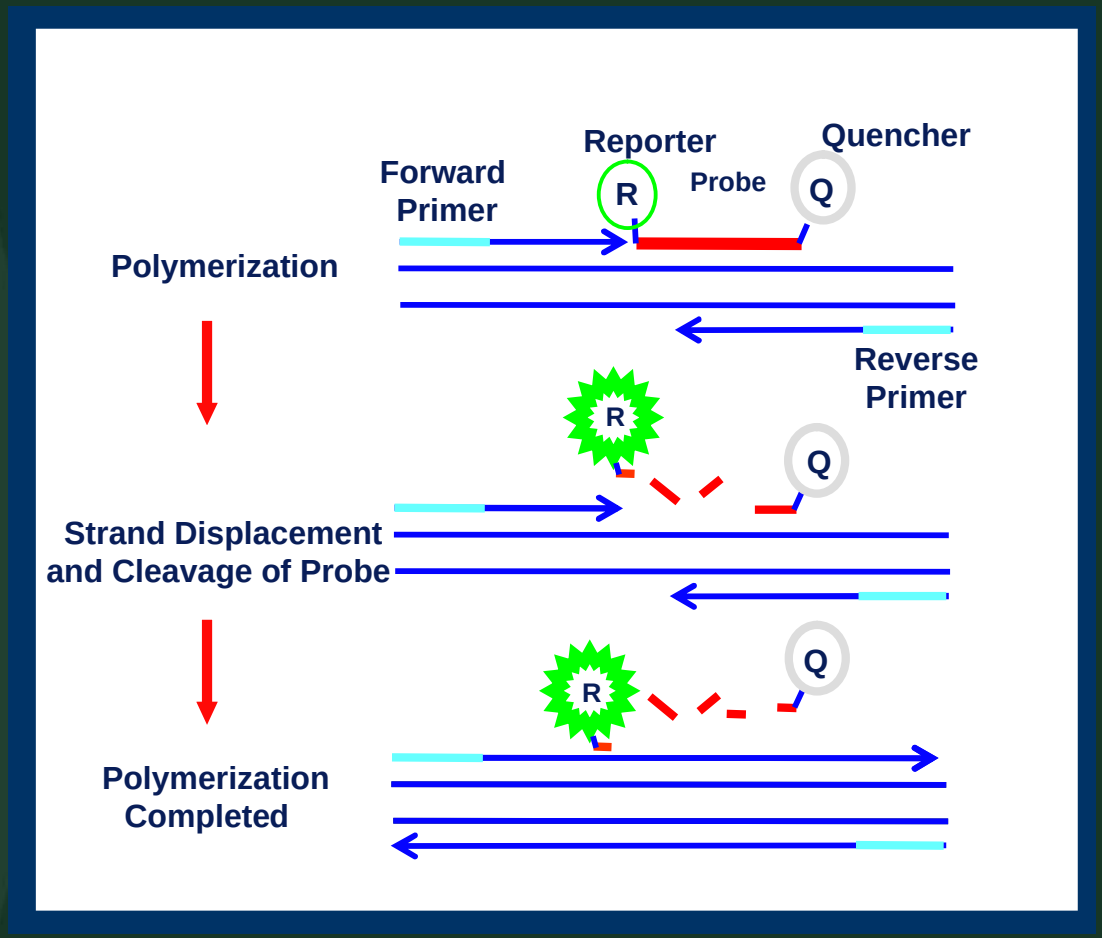
- Assay gene expression for many genes

“Unlocking the Block”

- Standardized quantitative analysis from tumor blocks

Real-time RT-PCR for RNA Quantification

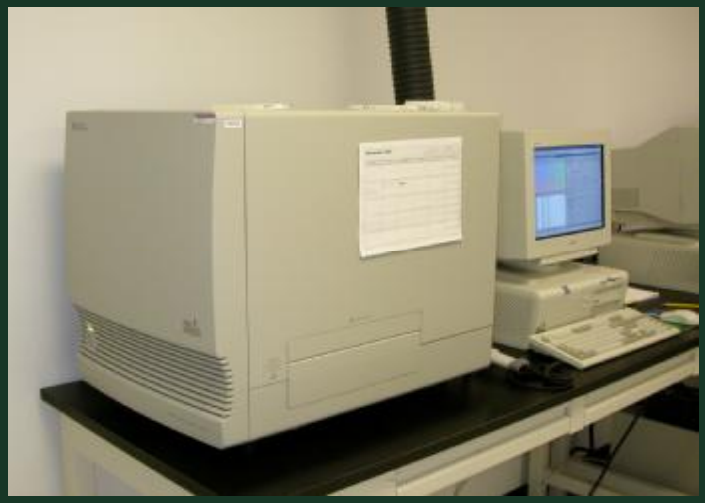
- Sensitive
- Specific
- Wide dynamic range
- Reproducible
- ~800 genes from three 10µ fixed paraffin embedded sections
- Mature technology used for clinical assays for viral infections



Cronin et al. *Am J Pathol.* 2004;164:35-42
Cronin et al. *Clin Chem*. 2007;53:1084-1091

Assay Development Studies

- Sensitivity and specificity, calibration with RNA controls
- Fresh frozen versus FPET
- Variability in preparation
- Tumor block age
- Heterogeneity within and between blocks
- Comparison with IHC/FISH (ER, PR, HER2)
- Dissection
- Robotics and miniaturization



Oncotype DX—Bringing the Promise of Genomics to Clinical Practice

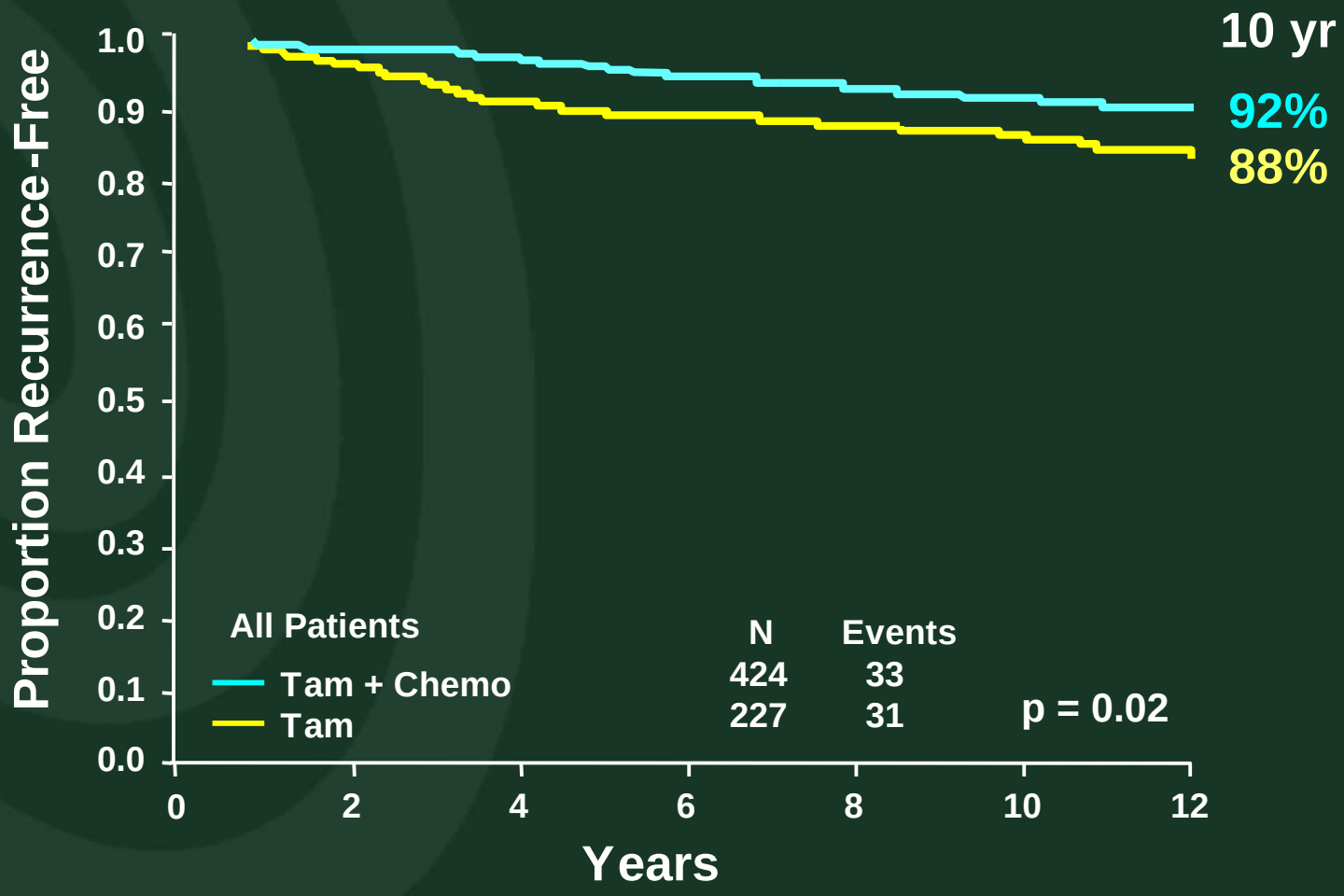
- Innovation
- Multiple independent clinical studies – rigor in design, performance, analysis (with comparison to standard measures)
- Assay precision, standardization, control
- Clinical utility – Meet the needs of patients, physicians, payers, regulators, and investors
- Continuing research

What We Need for N- ER+ Breast Cancer

- The ability to distinguish truly low risk patients
- The ability to determine who benefits from chemotherapy

NSABP B-20 Clinical Trial (1988-1997)

Tam vs Tam + Chemo – All 651 Pts



Case Study

ASCO 2002 CASE STUDY SURVEY

40 yr old woman with ductal carcinoma
Node negative
1.1 cm tumor
ER PR positive
HER2 negative
Grade 2

Case Study

ASCO 2002 CASE STUDY SURVEY

40 yr old woman with ductal carcinoma
Node negative
1.1 cm tumor
ER PR positive
HER2 negative
Grade 2

Physician Recommendation

54% Hormonal therapy
46% Hormonal therapy + Chemotherapy

Oncotype DX Development

Technical Feasibility

↓

Development Studies

Providence ● Rush ● NSABP B-20 (n=447)

↓

Analytical Methods Validation

↓

Clinical Validation Study - Prognosis

NSABP B-14 (n=668)

↓

Community Based Study - Prognosis

Kaiser Permanente (n=790)

↓

Treatment Benefit Studies

Tamoxifen Benefit: NSABP B-14 Placebo (n=645)

Chemo Benefit: NSABP B-20 (n=651), Milan (n=89), Baylor (n=72)

Final Gene Set Selection

Objective

Gene expression and relapse-free survival correlations across three independent studies—testing 250 genes in 447 patients

Study Site	N	Node Status	ER Status	Treatment
NSABP B-20, Pittsburgh, PA	**233**	**N–**	**ER+**	**Tamoxifen (100%)**
Rush University, Chicago, IL	**78**	**>10 positive nodes**	**ER+/–**	**Tamoxifen (54%)** **Chemotherapy (80%)**
Providence St. Joseph's Hospital, Burbank, CA	**136**	**N+/–**	**ER+/–**	**Tamoxifen (41%)** **Chemotherapy (39%)**

→ 21 genes and Recurrence Score (RS) algorithm

Paik et al. *SABCS 2003*. Abstract #16.
Cobleigh et al. Clin Cancer Res. 2005;11:8623-31.
Esteban et al. *Proceedings of ASCO 2003.* Abstract #3416.

Oncotype DX™ Technology: Final Gene Set

PROLIFERATION
Ki-67
STK15
Survivin
Cyclin B1
MYBL2

HER2
GRB7
HER2

ESTROGEN
ER
PGR
Bcl2
SCUBE2

GSTM1

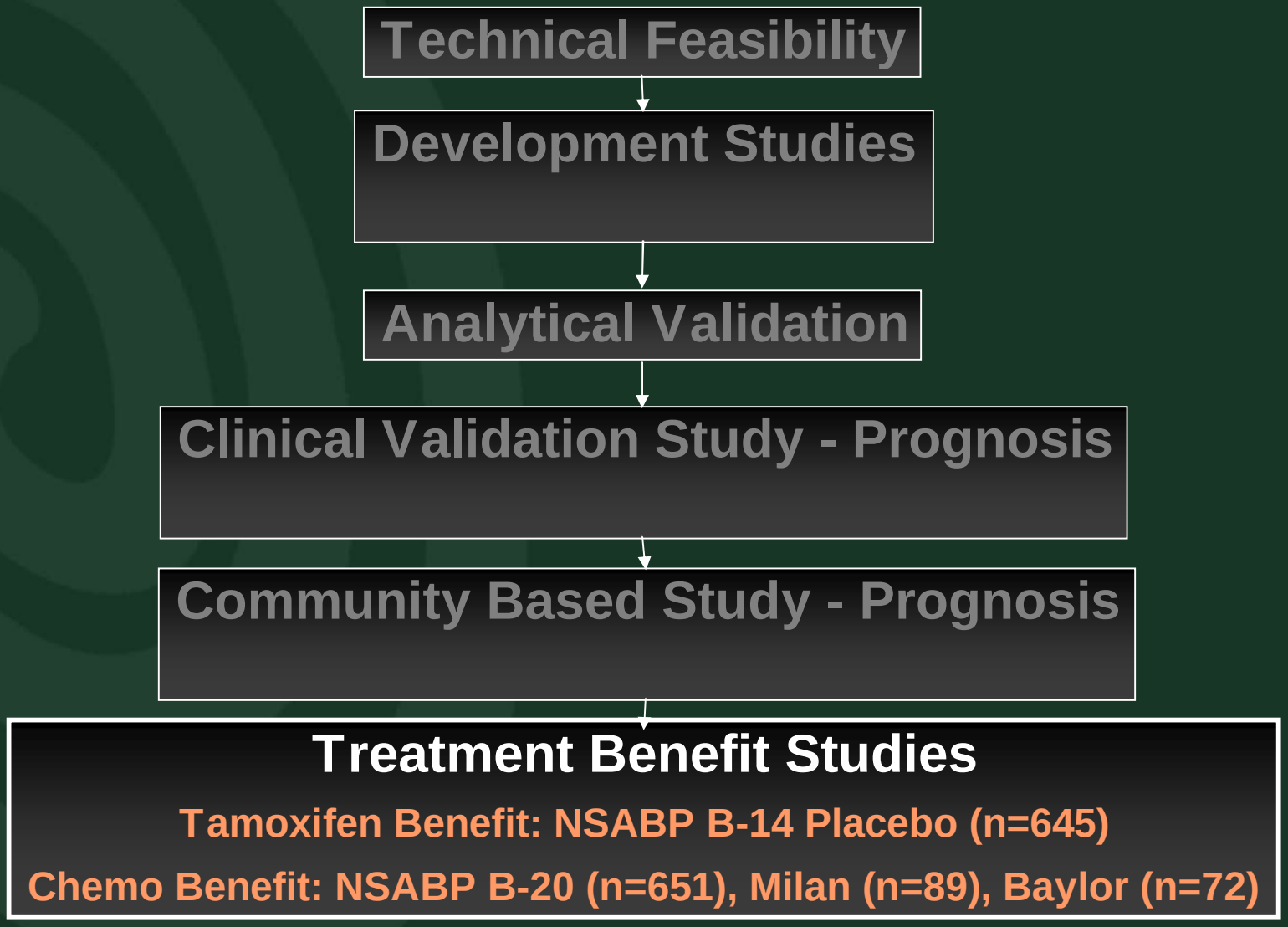
INVASION
Stromelysin 3
Cathepsin L2

CD68

BAG1

REFERENCE
Beta-actin
GAPDH
RPLPO
GUS
TFRC

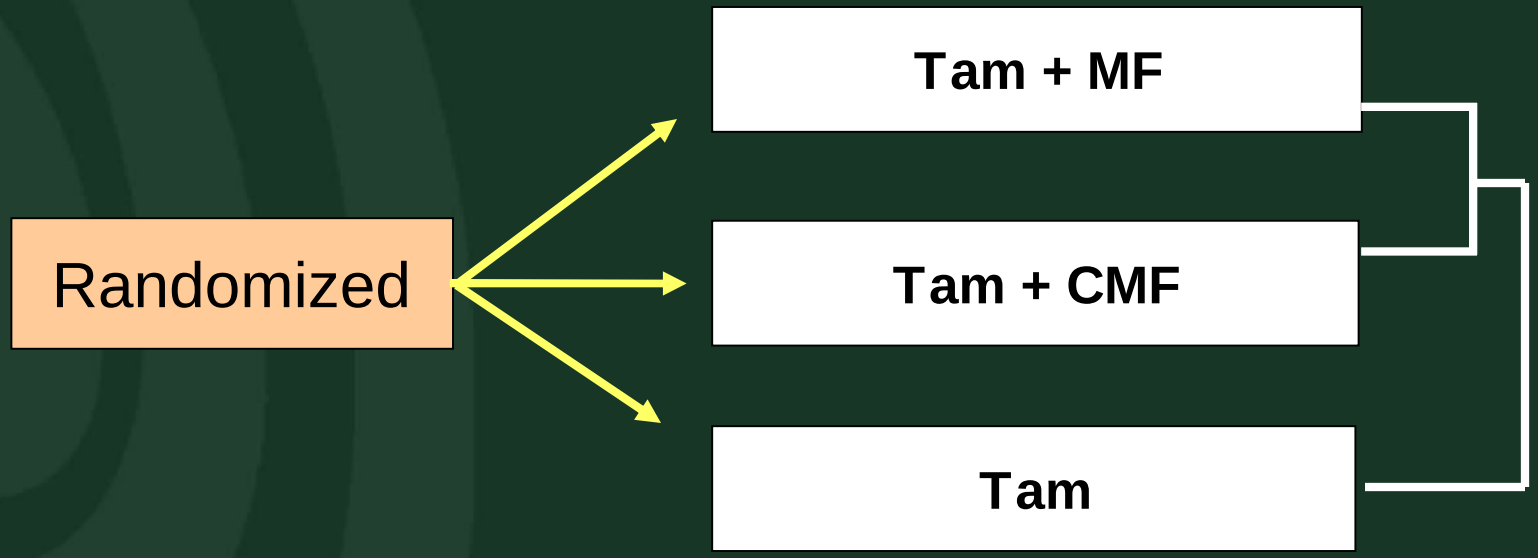
Oncotype DX Development



Chemotherapy Benefit and Oncotype DX

NSABP B-20 Chemo Benefit Study in N–, ER+ Pts

Design

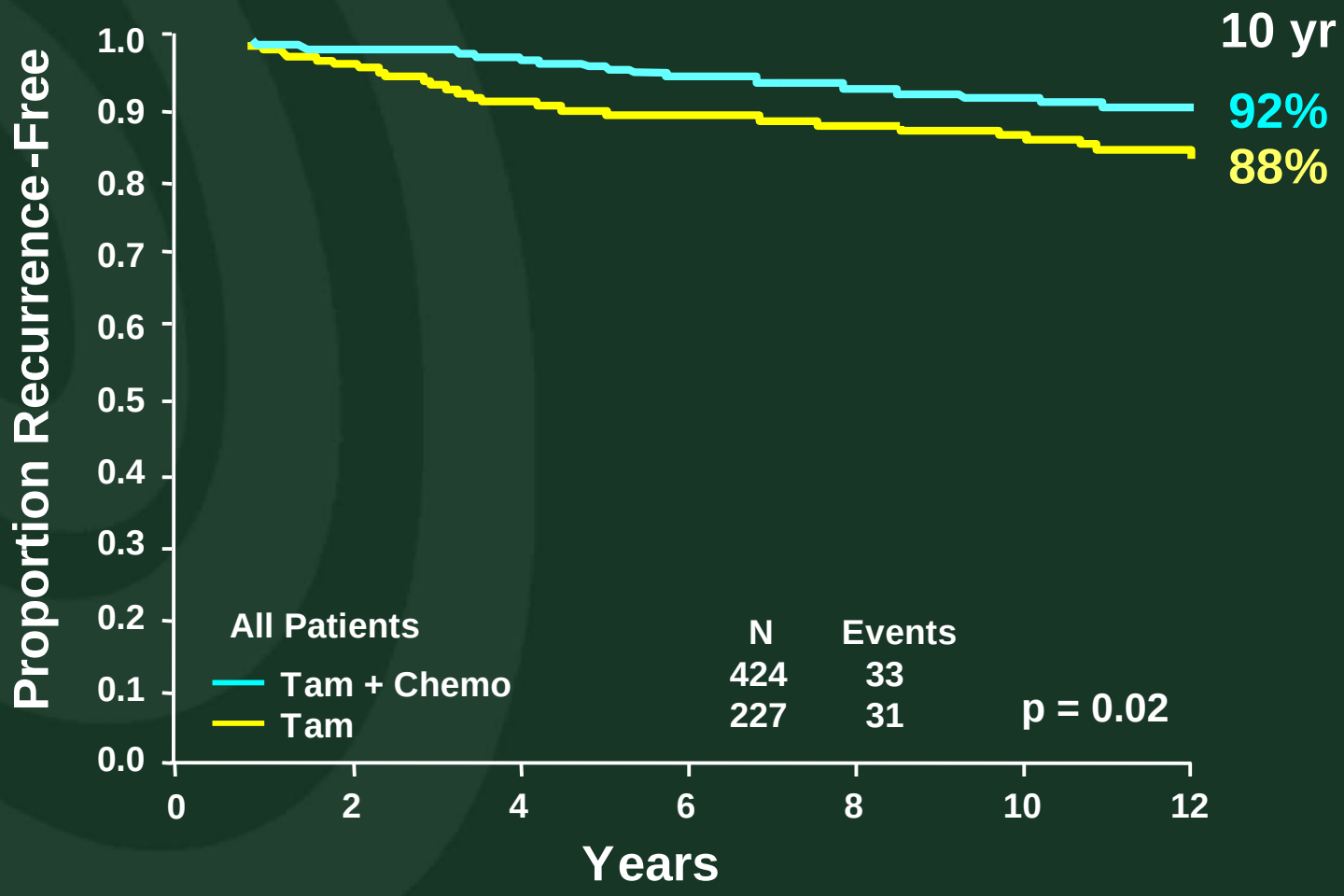


Multicenter study with prospectively defined assay, algorithm, endpoints, analysis plan

***Paik et al, *J Clin Oncol.* 2006;24:3726-3734. Epub May 23**

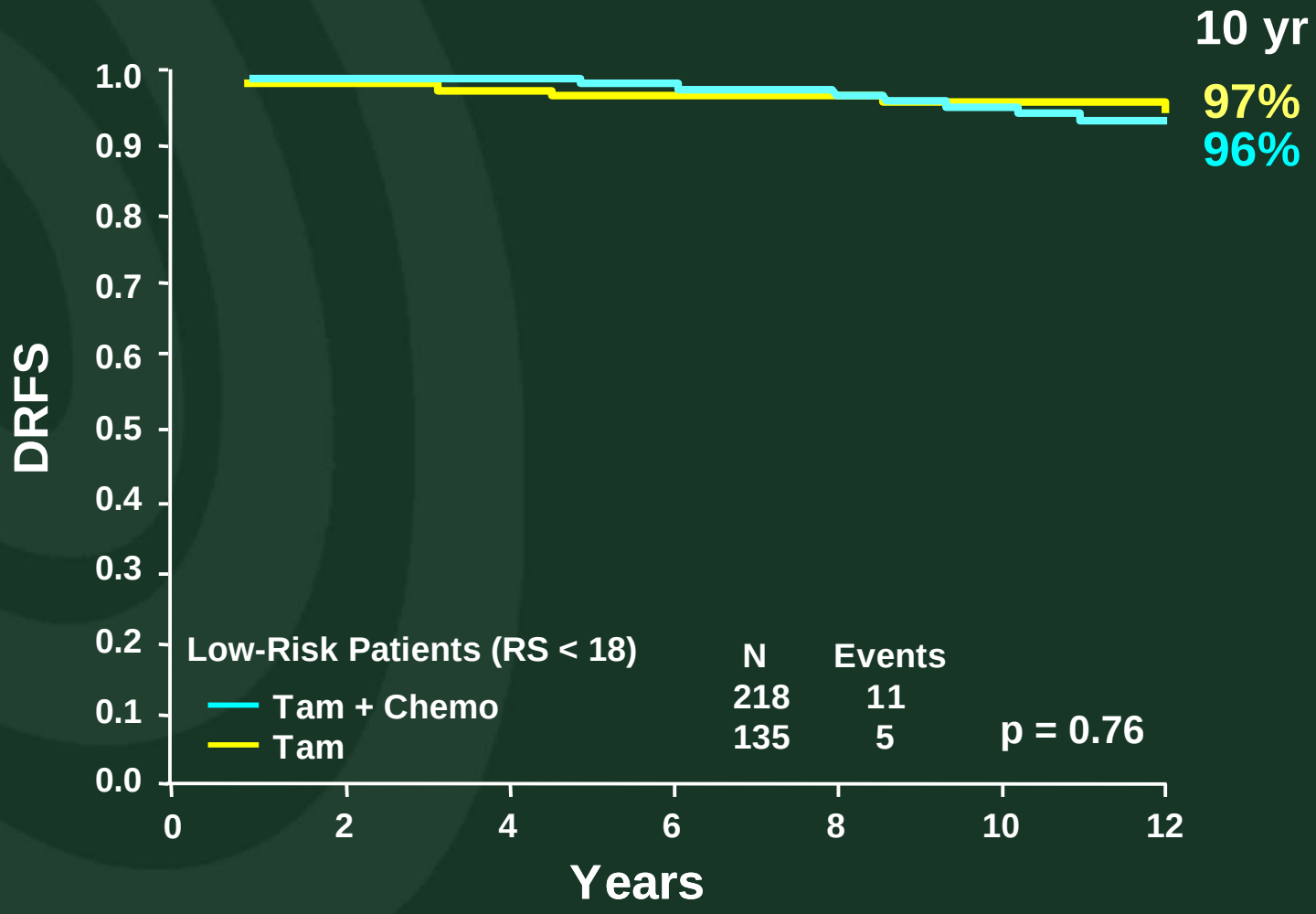
NSABP B-20 Clinical Trial (1988-1997)

Tam vs Tam + Chemo – All 651 Pts



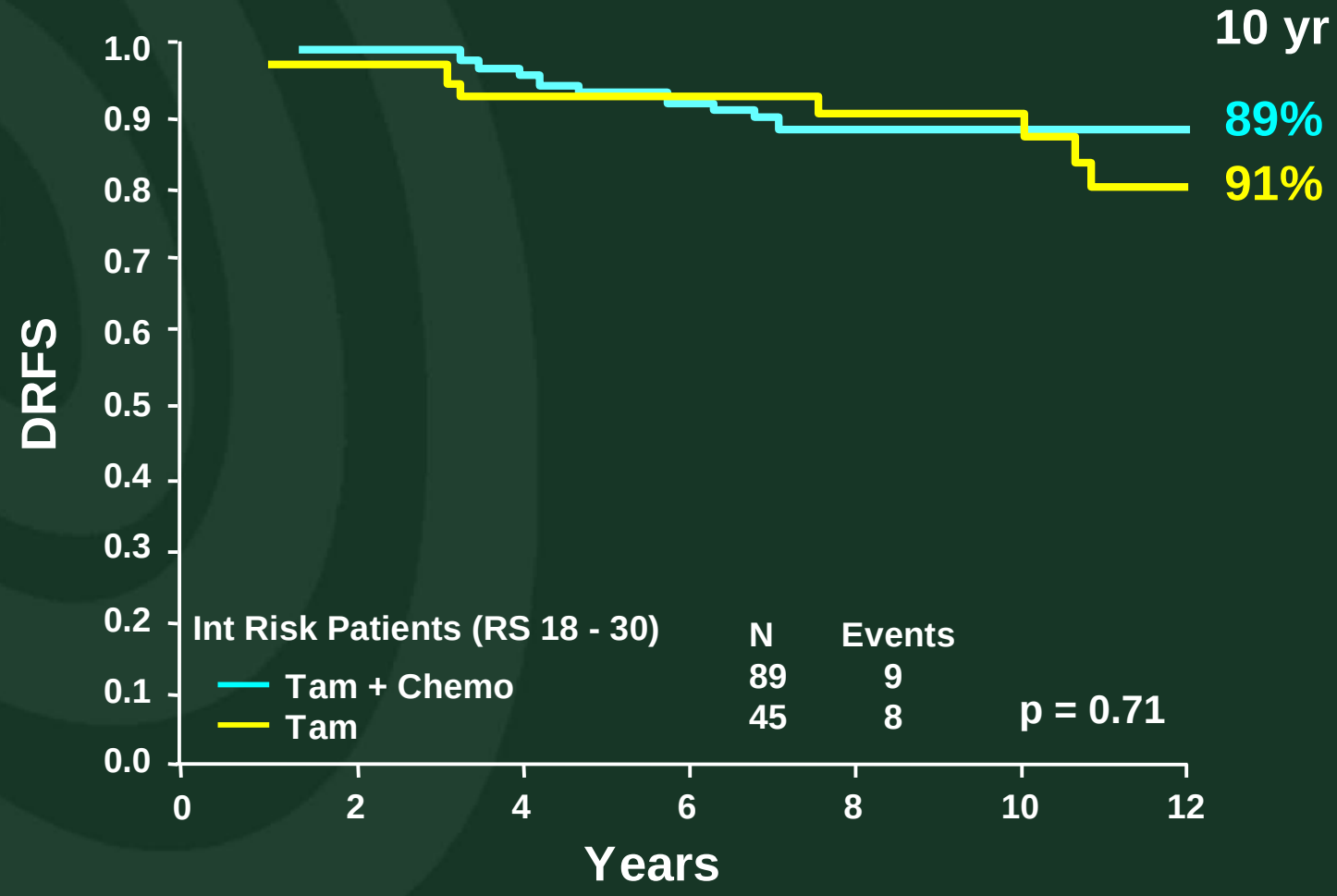
NSABP B-20 Genomic Health Study

Tam vs Tam + Chemo – Low Risk (RS <18)



NSABP B-20 Genomic Health Study

Tam vs Tam + Chemo – Intermediate Risk (RS18-30)



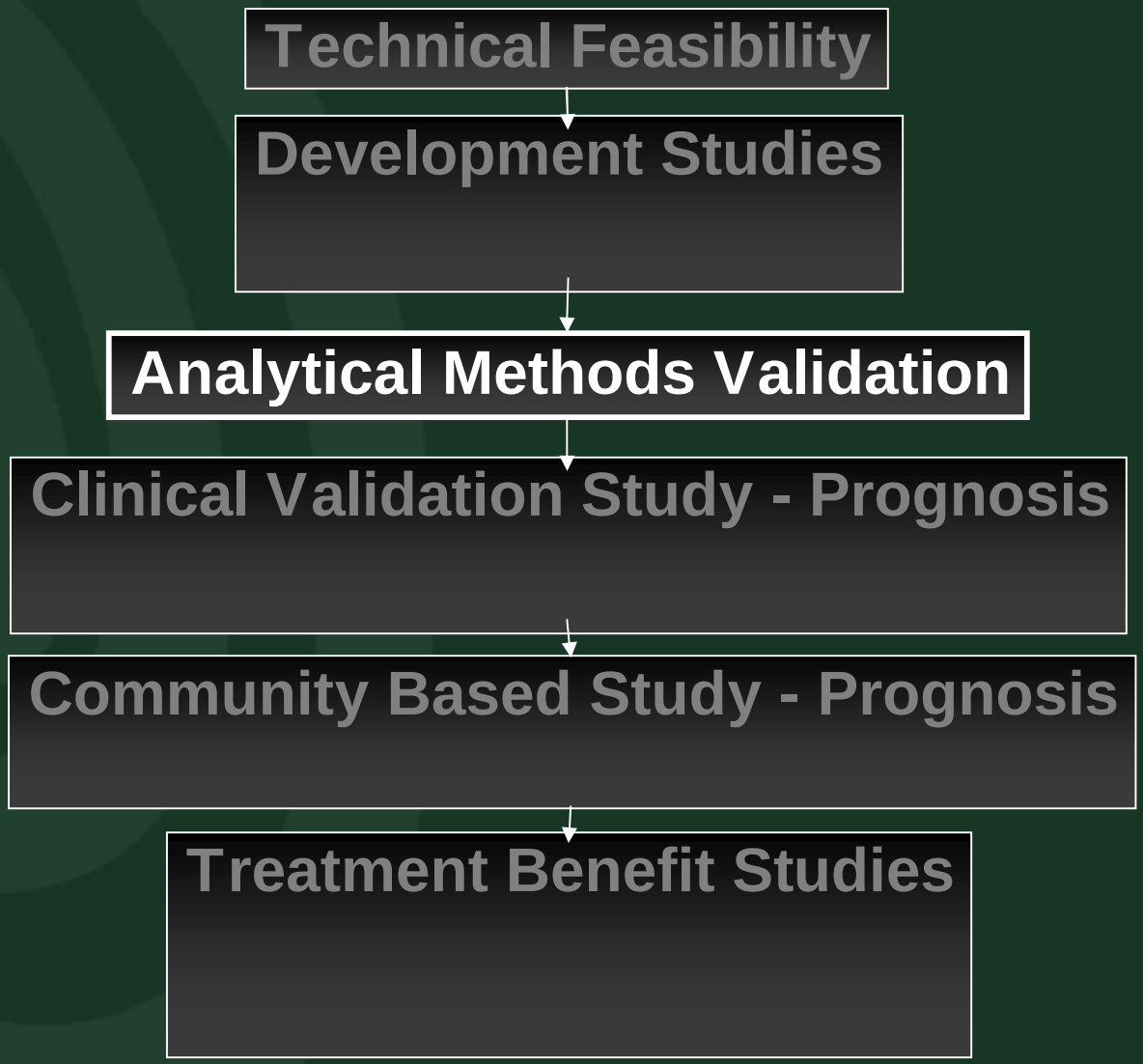
NSABP B-20 Genomic Health Study

Tam vs Tam + Chemo – High Risk (RS≥31)

Oncotype DX—Bringing the Promise of Genomics to Clinical Practice

- Innovation
- Multiple independent clinical studies – rigor in design, performance, analysis (with comparison to standard measures)
- Assay precision, standardization, control
- Clinical utility – Meet the needs of patients, physicians, payers, regulators, and investors
- Continuing research

Oncotype DX Development



CLIA Regulations and the Principles of Laboratory Medicine

- All assay methods and procedures defined prior to clinical validation studies, for example:
  - Specimen eligibility
  - Reagent qualification
  - Instrument validation
  - Controls and calibrators
  - Linearity, precision, reproducibility

Genomic Health CLIA-Certified and CAP-Accredited Reference Laboratory

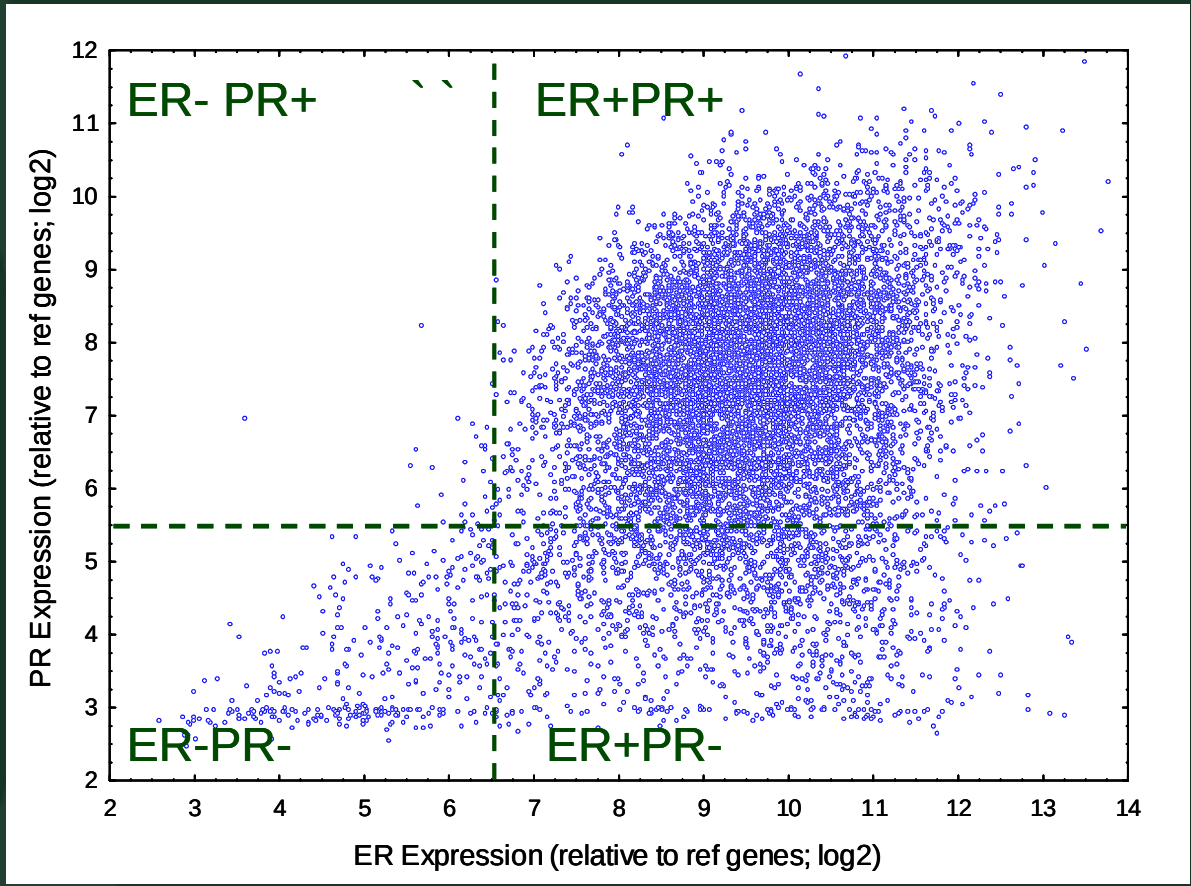
Oncotype DX Process
Number of Standard Operating Procedures (SOPs) and Forms:

Category	Number of SOPs	Number of Forms
Equipment	33	18
Finance	1	0
Histopathology	6	6
IT	23	10
Materials Management	7	6
Pre and Post Analytical	13	3
Production and Quality Control	52	15
QA	15	36
Safety and Facilities	4	0
Total	**154**	**94**

Precision and Reproducibility for Each Gene

- Quantitative ER and PR by Onco*type* DX in 10,618 breast cancers*
  - ER: > 3,000-fold range
  - PR: > 1,000-fold range
- High precision and reproducibility (SD < 0.4 units)

*Shak et al, SABCS 2006



Oncotype DX—Bringing the Promise of Genomics to Clinical Practice

- Innovation
- Multiple independent clinical studies – rigor in design, performance, analysis (with comparison to standard measures)
- Assay precision, standardization, control
- Clinical utility – Meet the needs of patients, physicians, payers, regulators, and investors
- Continuing research

Onco*type* DX

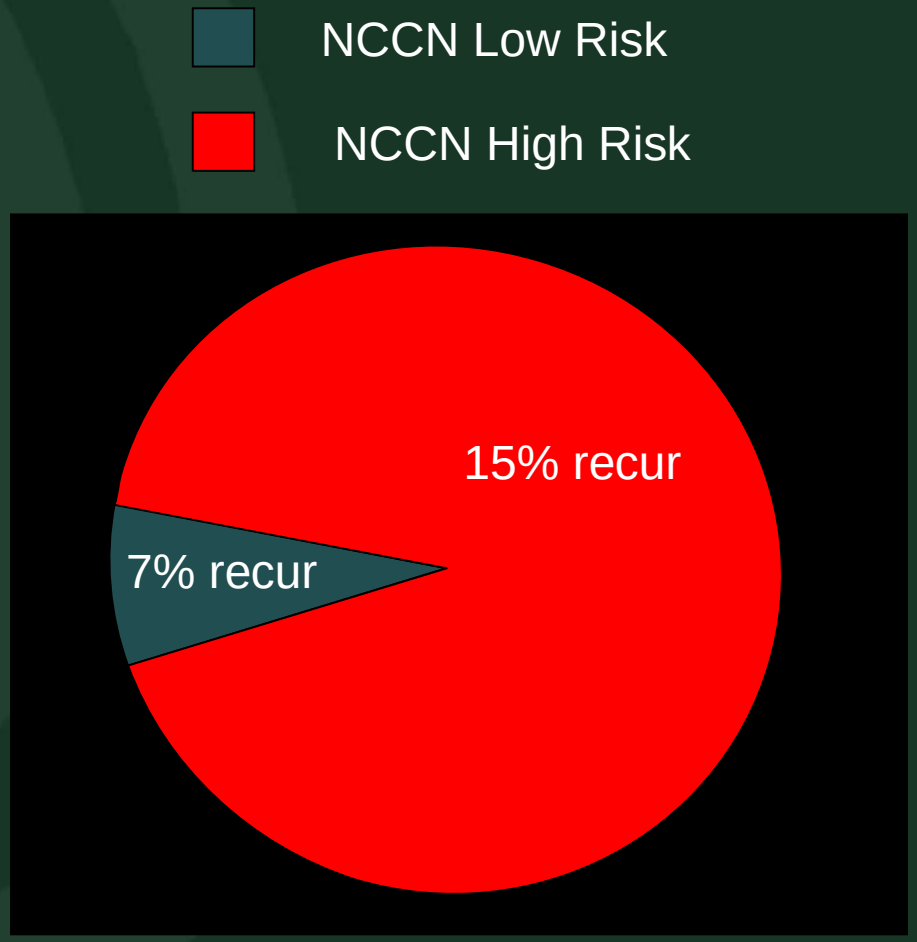
- Diagnostic multi-gene expression test for breast cancer treatment planning commercially available since 2004 with clinical evidence validating its ability to predict the:
  - Likelihood of breast cancer recurrence
  - Magnitude of chemotherapy benefit
- Growing physician use and reimbursement
  - Over 6,600 ordering physicians and 39,000 tests since launch
  - Reimbursed by Medicare and major payers
- ASCO guidelines recommend use of Oncotype DX for node negative ER positive breast cancer (Journal of Clinical Oncology on-line, Oct 23, 2007)

Oncotype DX Use/Reimbursement

- Facilitators
  - Evidence, publications, and education
  - Putting breast cancer patients first in defining the conceptual framework for evaluation of clinical effectiveness
  - Treatment decision studies
  - Health economic studies
- Threats
  - Historical incentives – poor reimbursement for diagnostics
  - Regulatory uncertainty

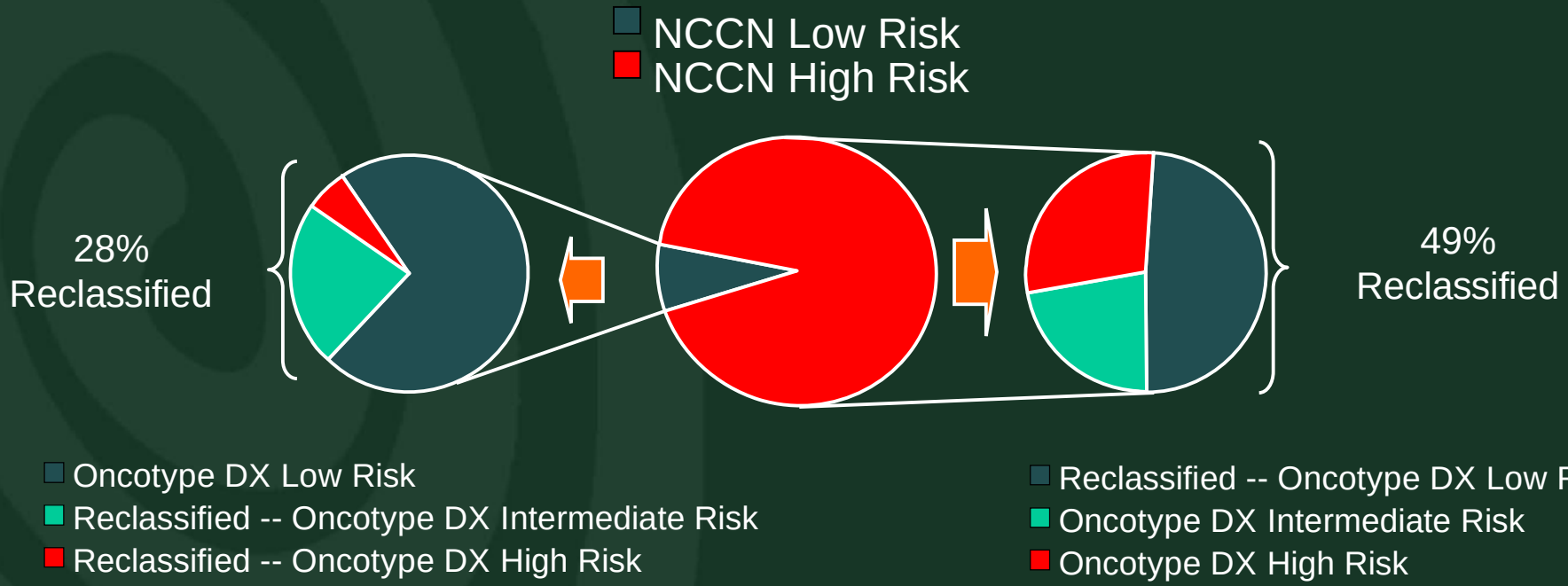
NCCN Guidelines in NSABP B-14

Distribution of patients with node negative, ER positive breast cancer based on patient age, tumor size, and tumor grade



Reclassification by the Recurrence Score

Many patients are reclassified



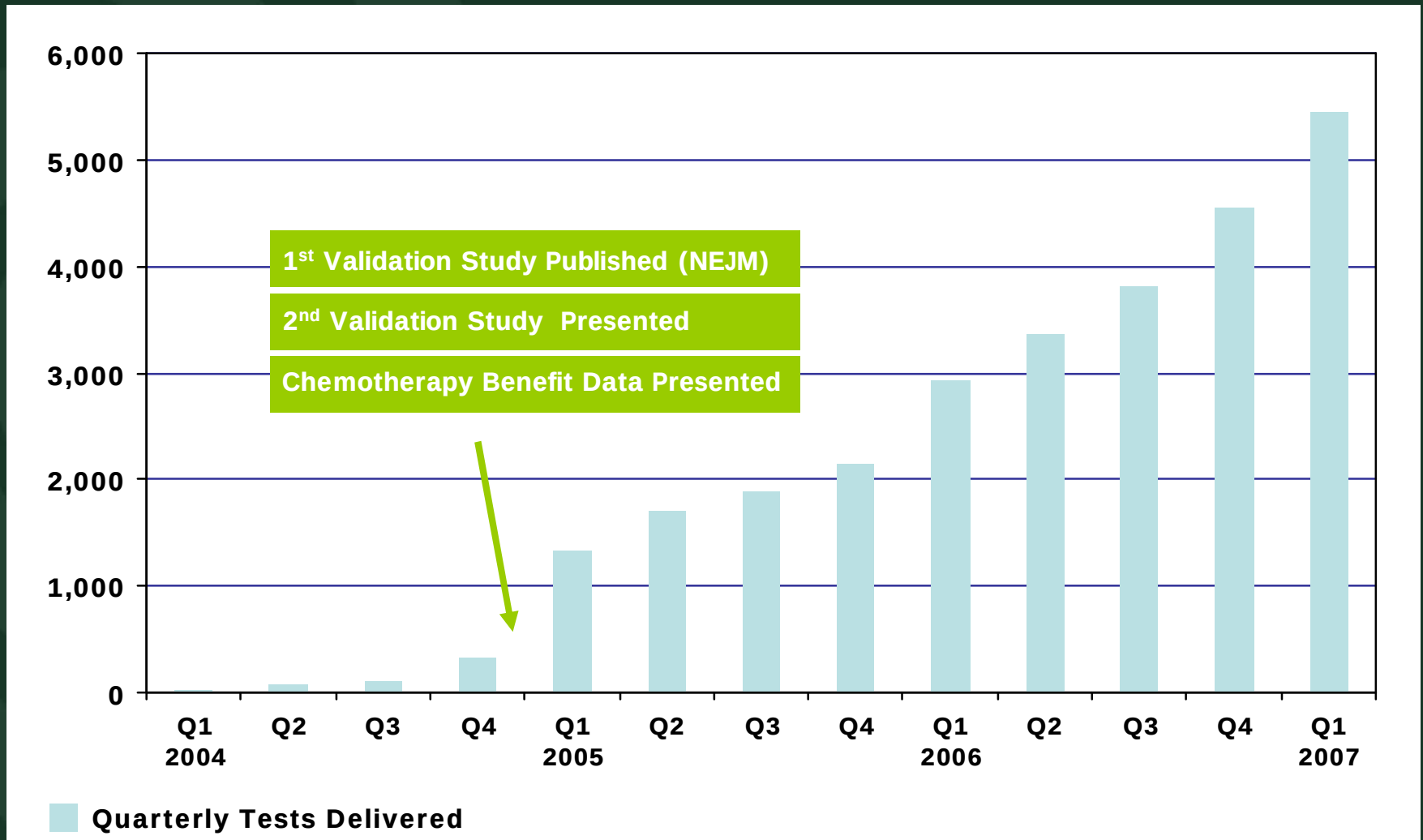
Oncotype DX Treatment Decisions in a Community Hospital Setting*

	Pre-Oncotype DX	Post-Oncotype DX
	Physician Recommendation (n=68)	Actual Therapy (n=68)
Hormonal Therapy Alone	51%	68%
Chemotherapy + Hormonal Therapy	49%	32%

25% of patients changed treatment compared to MD's original recommendation

*Oratz et. al, Journal of Oncology Practice 3:182, 2007

Publication Driving Oncotype DX Use



Oncotype DX—Bringing the Promise of Genomics to Clinical Practice

- Innovation
- Multiple independent clinical studies – rigor in design, performance, analysis (with comparison to standard measures)
- Assay precision, standardization, control
- Clinical utility – Meet the needs of patients, physicians, payers, regulators, and investors
- Continuing research

Ongoing and/or Planned New Studies

- Breast Cancer
  - Node positive disease
  - Other chemotherapy regimens
  - Aromatase inhibitors
  - NCI Large Adjuvant Trial - TAILORx
  - DCIS
- Colon Cancer
- Prostate Cancer
- Targeted drugs (e.g., Cetuximab)
- Other tumor types

The Promise of Genomics is a Reality

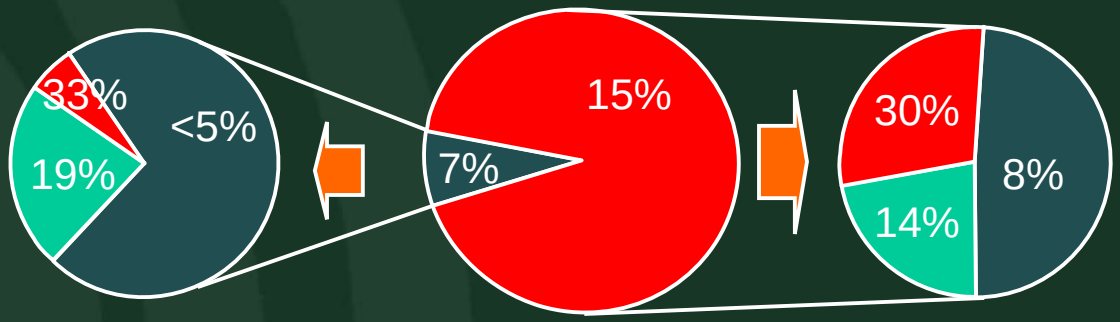
- It takes:
  - Innovation
  - Multiple well-designed clinical studies
  - Assay precision and standardization
  - Clinical utility and reimbursement
  - Great collaborations

Acknowledgements

- Drs. Paik, Bryant, Tang, Costantino, Wolmark (NSABP)
- Drs Habel and Quesenberry (Kaiser Permanente)
- Drs. Mena and Esteban (Providence-St. Josephs Medical Center)
- Drs. Cobleigh and Bitterman (Rush University Medical Center)
- Dr. Gianni (Istituto Milano)
- Dr. Sledge, Miller (Indiana University)
- Dr. Esteva, Sahin, Hortobagyi (MDACC)
- Dr. Baehner (UCSF)
- NCI and the Cooperative Groups
- Genomic Health colleagues
- Breast cancer advocates
- Patients and their families

Reclassification by the Recurrence Score

Recurrence rates at 10 years



- Oncotype DX Low Risk
- Reclassified -- Oncotype DX Intermediate Risk
- Reclassified -- Oncotype DX High Risk

- **NCCN Low Risk**
- **NCCN High Risk**

- Reclassified -- Oncotype DX Low Risk
- Oncotype DX Intermediate Risk
- Oncotype DX High Risk