Genomic Health®

Scottish Association for Histotechnolegy

Monica Spence – Genomic Health

oncotype IQ™

Objectives

- Background for the need for better Prognostic tools
- Brief overview of the Onco*type* DX® assay
- Review assay development strategy and supporting studies
  - Technical feasibility
  - Gene discovery and refinement
  - Analytical validation
- Review clinical validation studies
  - Prognostic studies
  - Predictive studies
  - Prospective Data
- Technical Aspects – the GHI Laboratory

Not all patients benefit from adjuvant chemotherapy

All patients with the same diagnosis

- No Benefit + Toxicity
- + Benefit + Toxicity
- + Benefit No Toxicity
- No Benefit No Toxicity

Adapted from Walgren RA et al. *JCO* 2005;23:7342-7349

If you look at 100 women with ER+ node - breast cancer

If all 100 are treated with hormone therapy alone (such as Tamoxifen):

- 15 will relapse within 10 years in spite of getting hormonal treatment

Adapted from Paik S, et al. *J Clin Oncol*. 2006;24:3726-3734.

If you look at 100 women with ER+ node - breast cancer

If all 100 are treated with hormone therapy + chemotherapy:

- 4 will benefit

Adapted from Paik S, et al. *J Clin Oncol*. 2006;24:3726-3734.

If you look at 100 women with ER+ node - breast cancer

If all 100 are treated with hormone therapy + chemotherapy:

- 4 will benefit
- 11 will relapse in spite of adding chemotherapy to hormone treatment

Adapted from Paik S, et al. *J Clin Oncol*. 2006;24:3726-3734.

If you look at 100 women with ER+ node - breast cancer

If all 100 are treated with hormone therapy + chemotherapy:

- 4 will benefit
- 11 will relapse in spite of adding chemotherapy to hormone treatment
- 85 would have done fine without chemotherapy

Adapted from Paik S, et al. J Clin Oncol. 2006;24:3726-3734.

Prognostic & Predictive Markers Utilized in Breast Cancer Management

Prognostic (recurrence risk)

- **Axillary node status**
- **Histologic type/grade**
- **Tumor size**
- **Patient age**
- **Lymphatic/Vascular invasion**
- **ER/PR status**
- **HER2 *neu* status**
- **Onco*type* DX**

Predictive (treatment benefit)

- **ER/PR status**
- **HER2 *neu* status**
- **Onco*type* DX**

These markers can be used to estimate the risk of disease recurrence

These markers can be used to predict treatment benefit

Cianfrocca and Goldstein. *Oncologist*. 2004;9(6):606-616;
Lonning PE. *Ann Oncol*. 2007;18(suppl 8):viii3-viii7.

The Oncotype DX® Breast Recurrence Score™

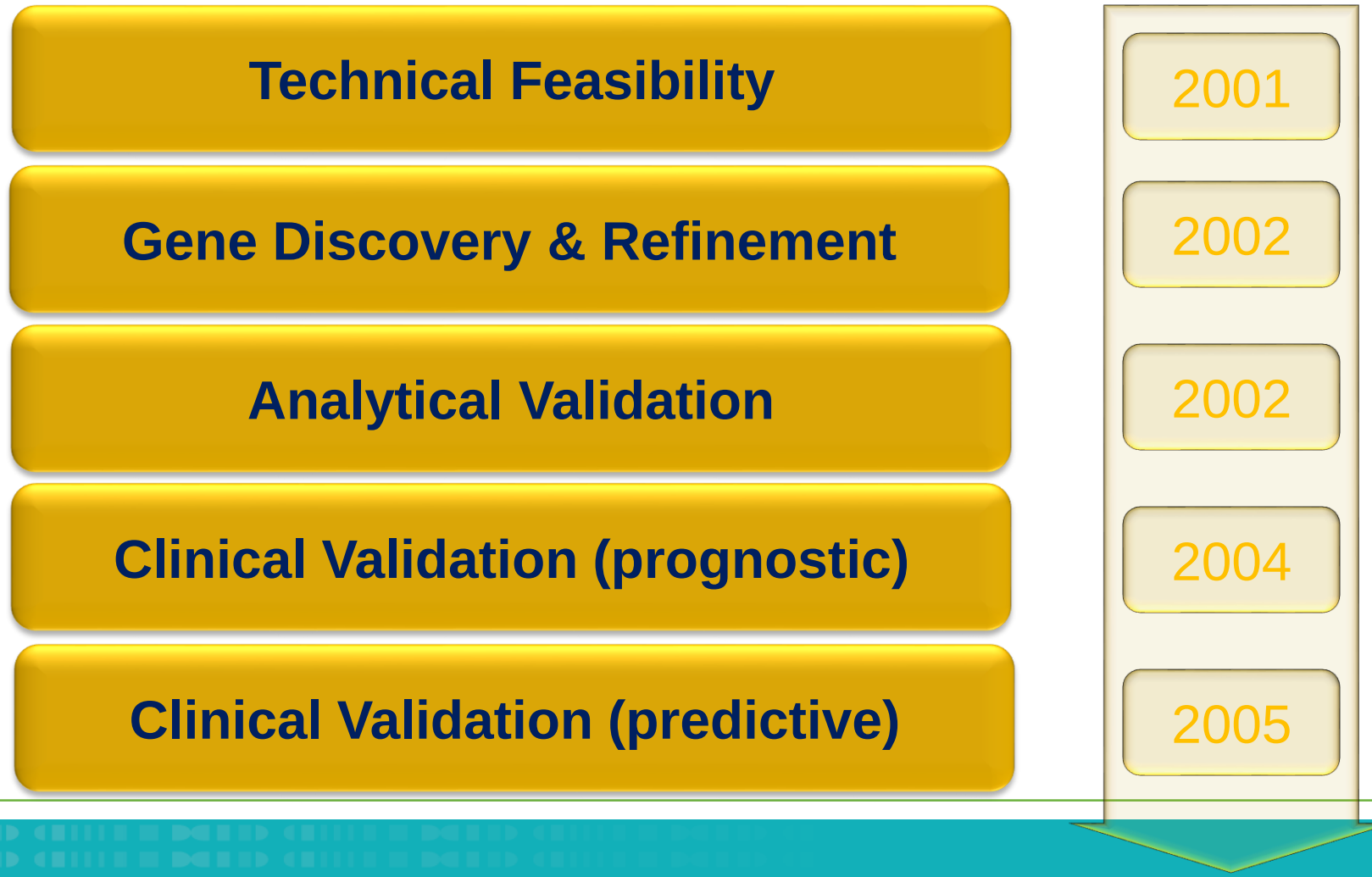
- It is a 21 gene genomic test (16 tumour genes and 5 reference genes)[1]
- Uses RT-PCR technology and is performed on formalin fixed tissue obtained from the surgical specimen or biopsy[1]
- It is a stand-alone diagnostic test innovation that does not predict benefit of any particular treatment (unlike HER2 and Herceptin), but predicts the likely benefit of chemotherapy[2]
- Provides prognostic information by quantitatively predicting the likelihood of breast cancer recurrence in women with newly diagnosed, invasive EBC[2,3]

1. Harris L, et al. *J Clin Oncol*. 2007;33(25):5287-5312.
2. Paik S, et al. *J Clin Oncol*. 2006;24:3726-3734.
3. Albain et al. *Lancet Oncol* 2010; 11: 55 - 65.

Genomic Health®

History of Development

Oncotype DX® Technology
Development Overview



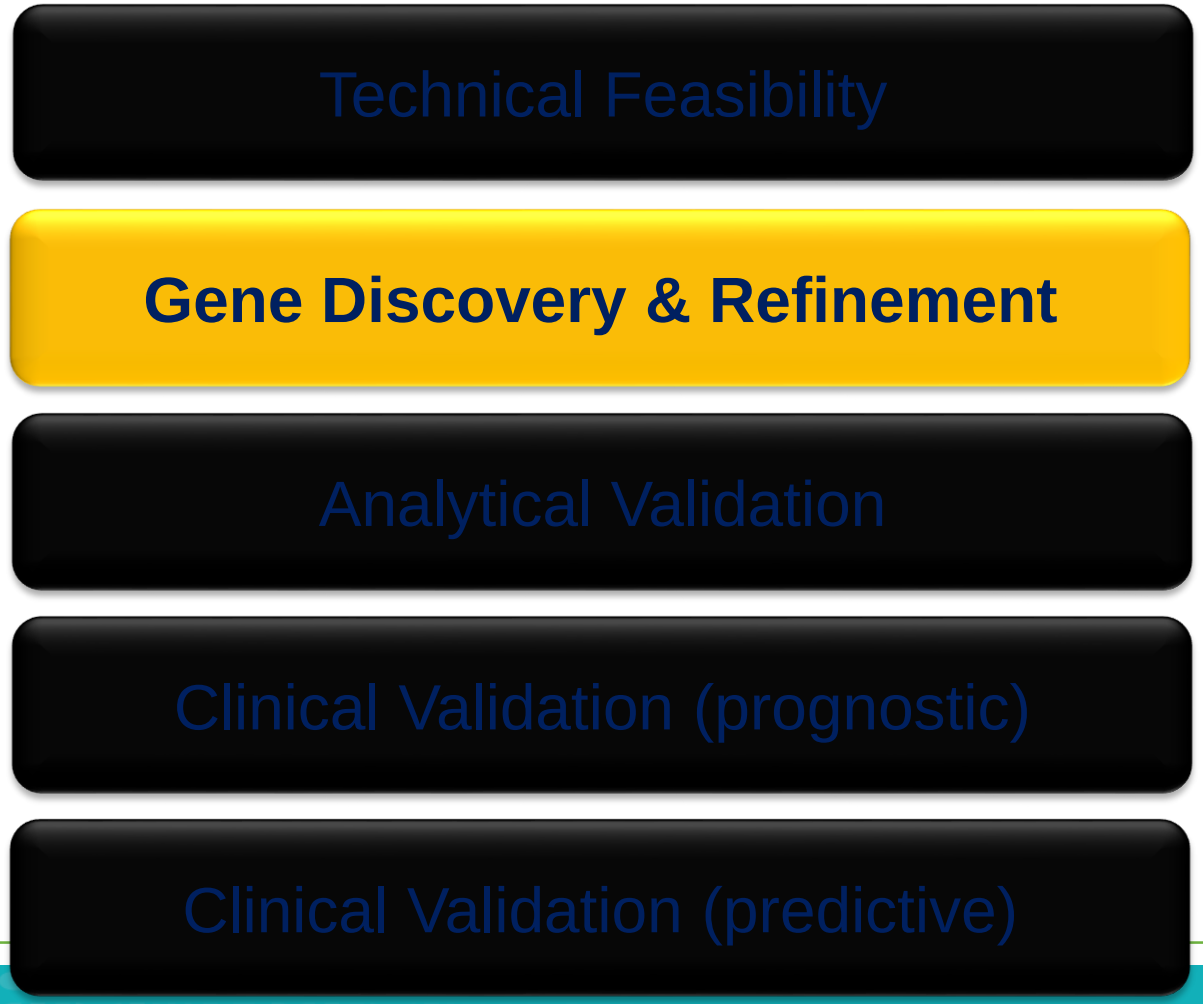
Oncotype DX® Technology
Development Overview

Purpose of Technical Feasibility Studies

Technical feasibility studies were designed to assess:

- RNA yield and the quality of RNA after extraction from FPET tissues
- Gene expression differences and similarities between whole section and enriched tumor tissue sections
  - To establish criteria for manual microdissection
- Gene expression heterogeneity within breast tumor tissues
  - Assess within block and between block gene expression heterogeneity
- Selection of reference genes (important for normalization of pre-analytical factors)
  - Delay to fixation, duration of fixation, fixative

Oncotype DX® Technology
Development Overview



The Oncotype DX® Breast Recurrence Score™ Assay

16 cancer and 5 reference genes from 3 studies

Proliferation
Ki-67 STK15
Survivin Cyclin
B1 MYBL2

Invasion
Stromelysin 3
Cathepsin L2

HER2
GRB7
HER2

Oestrogen
ER
PR
Bcl2
SCUBE2

GSTM1 BAG1

CD68

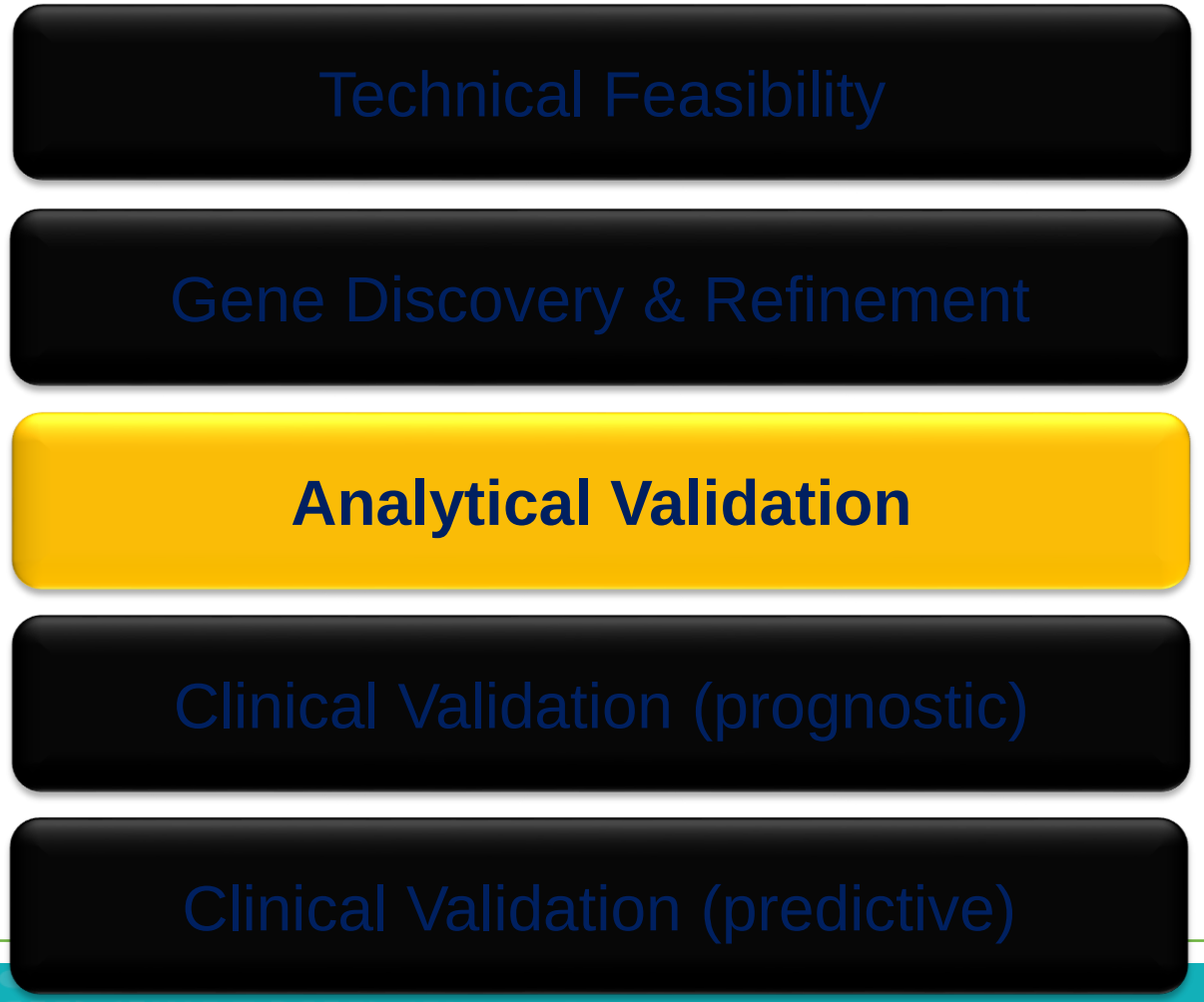
Reference
Beta-actin
GAPDH RPLPO
GUS
TFRC

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
Intermediate risk	RS 18-30
High risk	RS ≥31

Paik S, et al. *N Engl J Med*. 2004;351:2817-2826.

Oncotype DX® Technology
Development Overview



Oncotype DX® is Analytically Validated

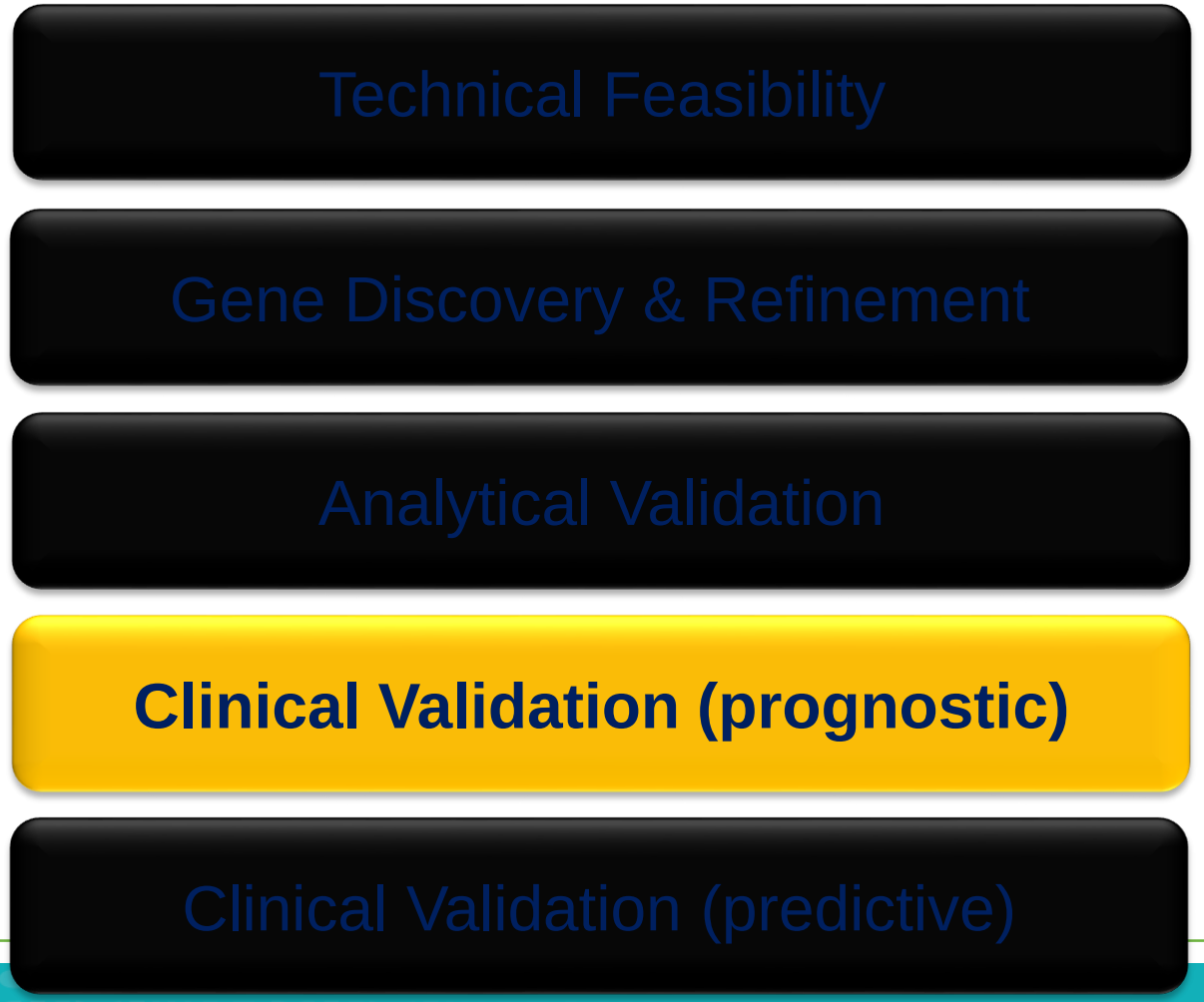
Analytical validation is the assessment of assay performance characteristics and the optimal conditions to generate accuracy, precision and reproducibility

Elements of Analytic Validation

- Analytical sensitivity
  (limits of detection and quantitation)
- Assay precision and linear dynamic range
- Analytical reproducibility
- PCR amplification efficiency
- Sample and reagent stability
- Reagent calibration
- Instrument validation and calibration

Chau CH, et al. *Clin Cancer Res.* 2008;14(19):5967-5976.

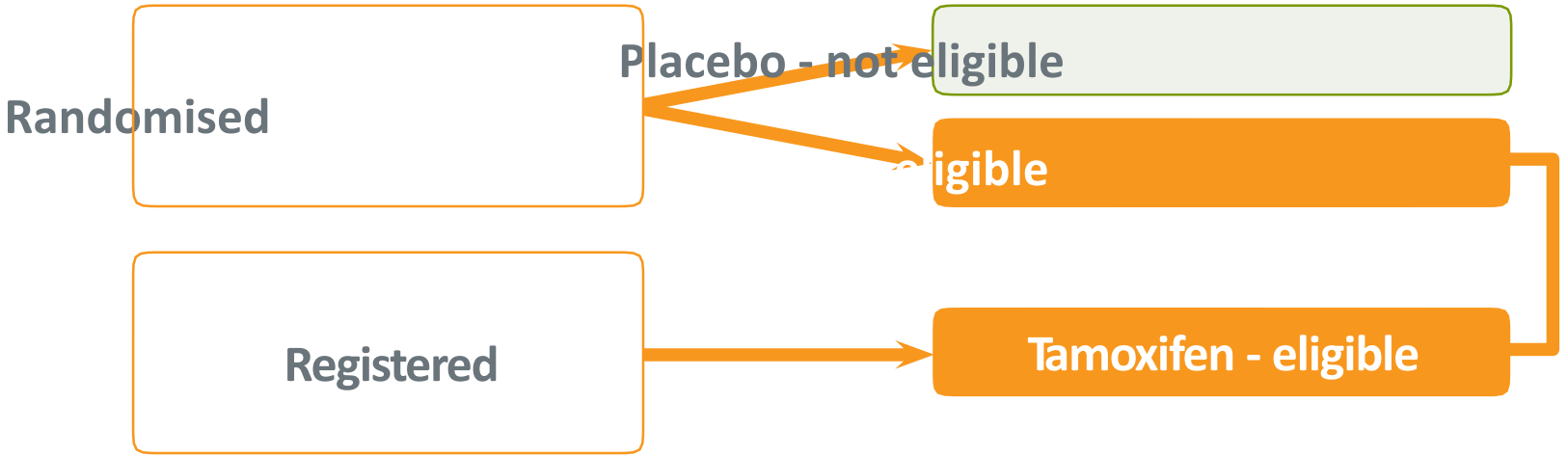
Oncotype DX® Technology
Development Overview



Clinical validation studies of the PROGNOSTIC value of the Oncotype DX® breast cancer assay

Oncotype DX® clinical validation: NSABP B-14

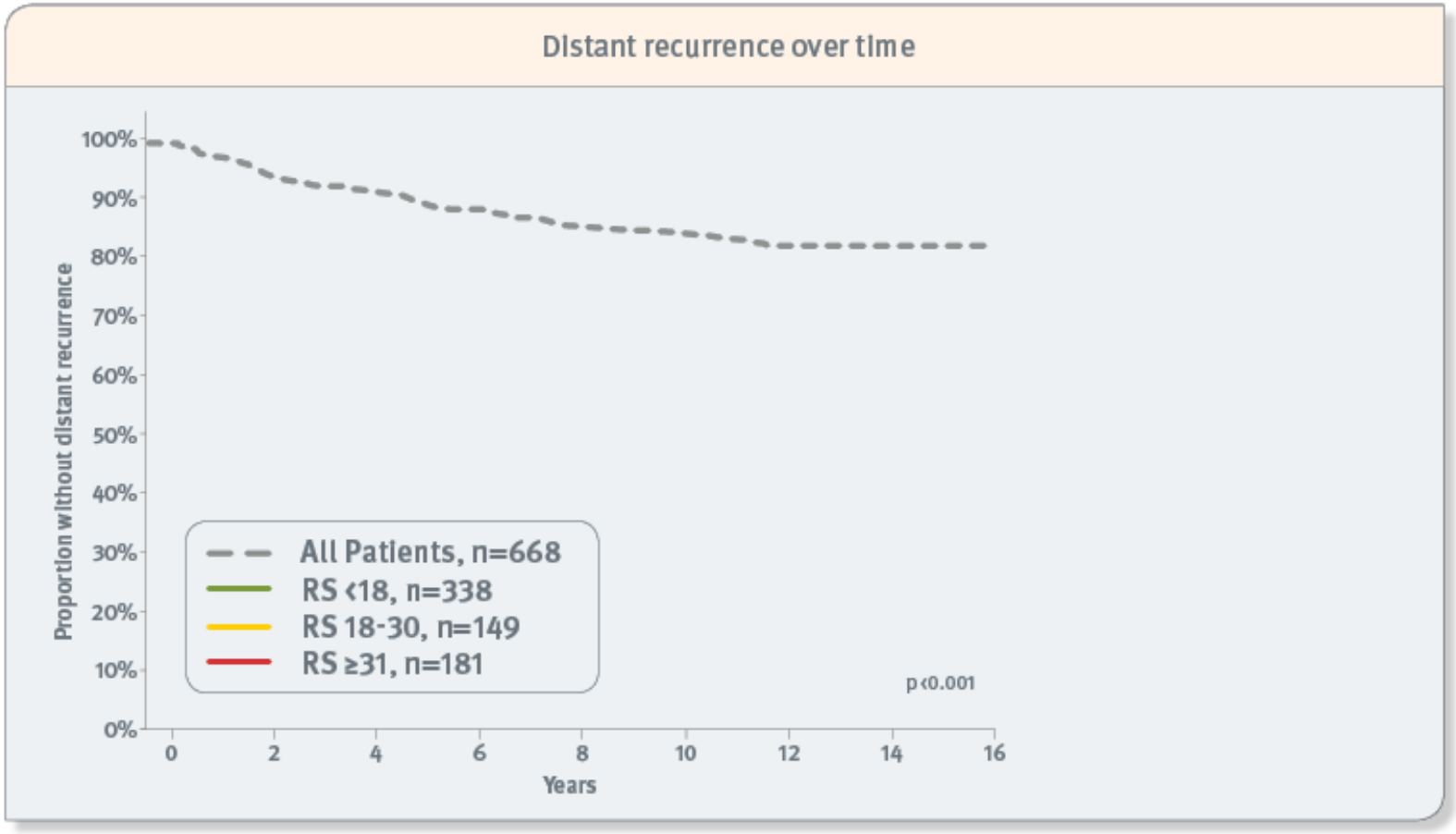
- Objective: Prospectively validate the Recurrence Score® result as a predictor of distant recurrence in axillary lymph node-negative, ER+ patients receiving tamoxifen



- Multicentre study with prespecified 21-gene assay, algorithm, endpoints, analysis plan

Paik S, et al. *N Engl J Med*. 2004;351:2817-2826.

Oncotype DX® clinical validation: NSABP B-14, distant recurrence

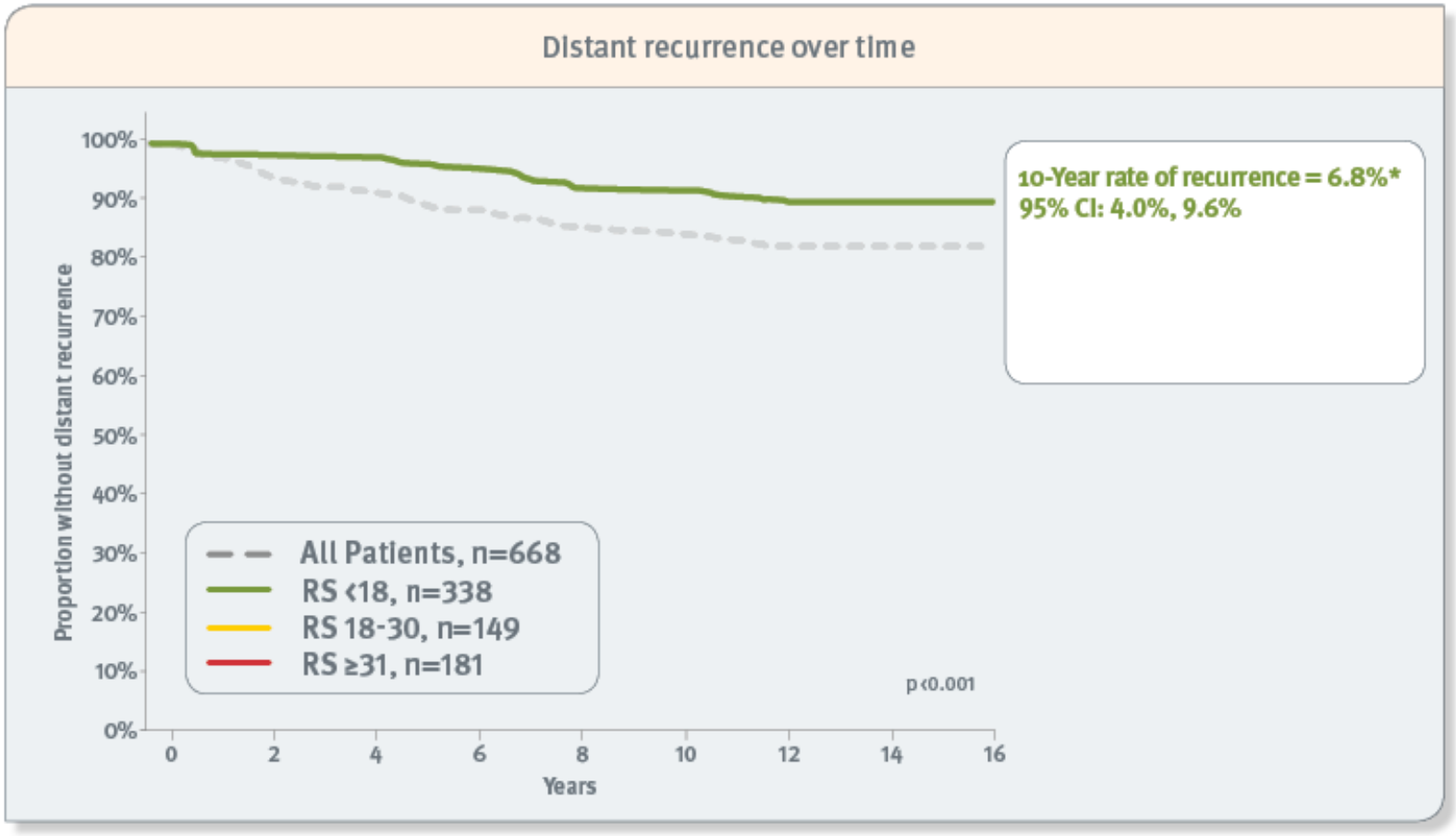


RS, Recurrence Score® result

*10-year distant recurrence comparison between low- and high-risk groups: p <0.001

Paik S, et al. *N Engl J Med*. 2004;351:2817-2826.

Oncotype DX® clinical validation: NSABP B-14, distant recurrence



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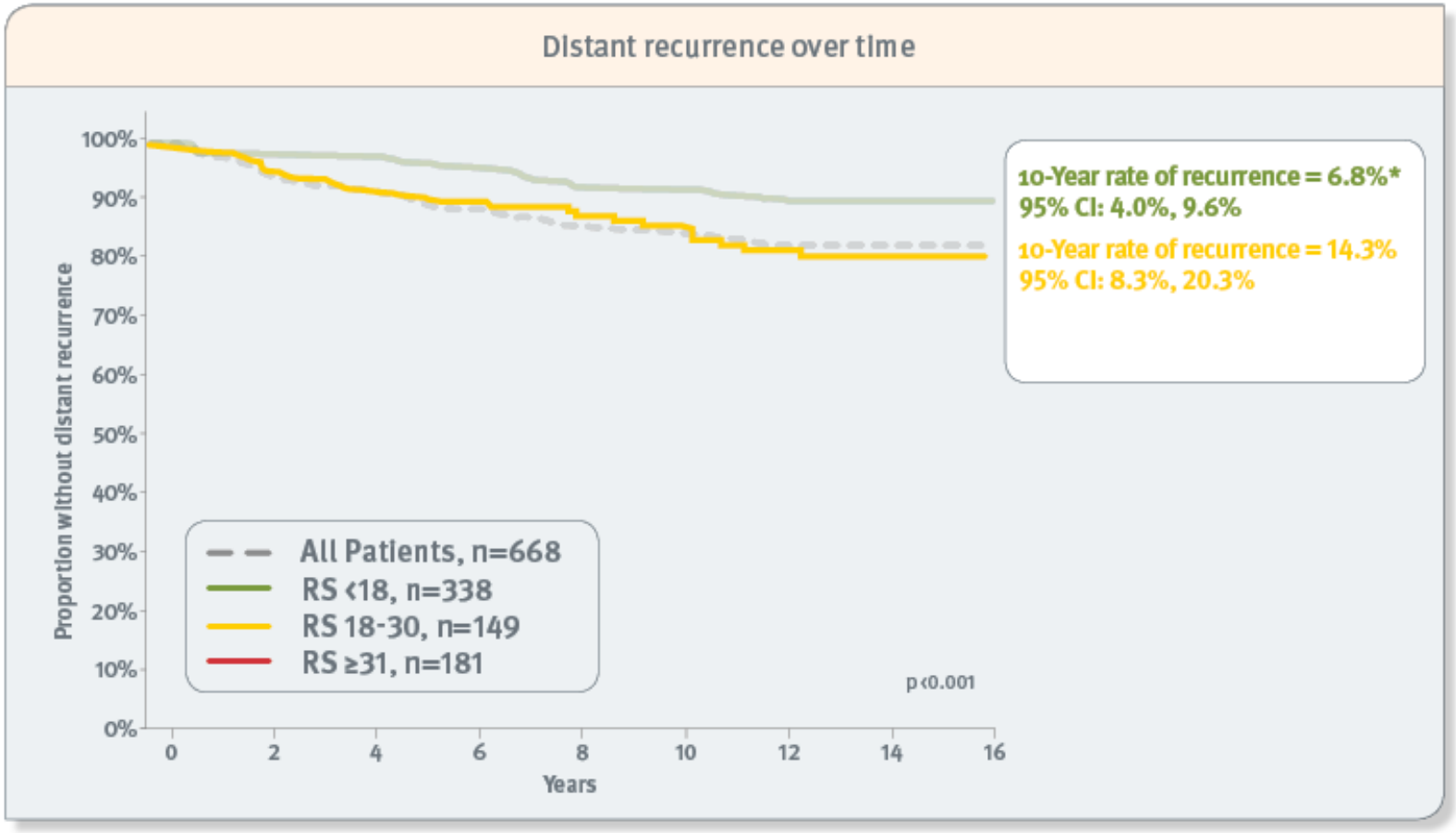

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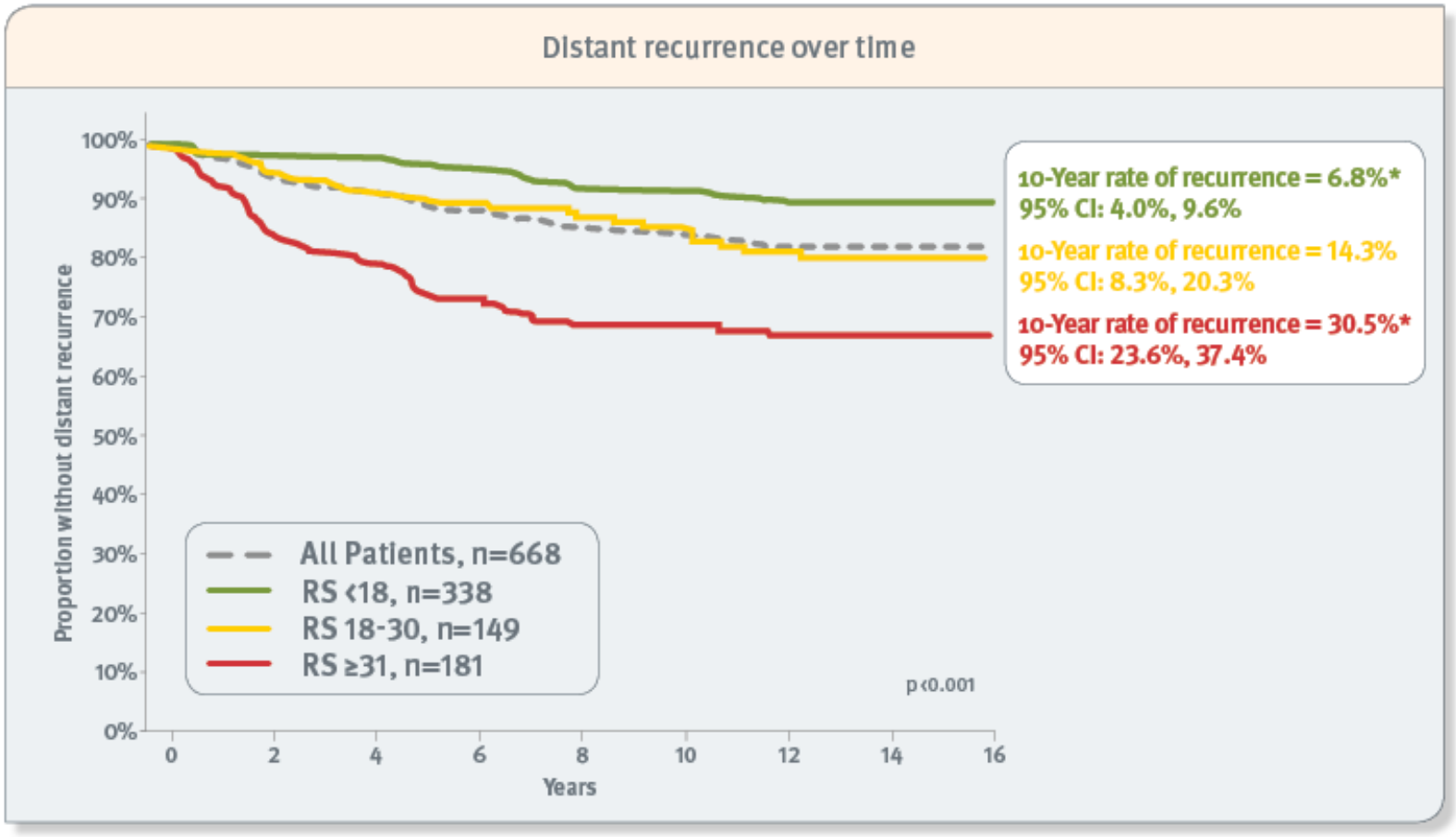

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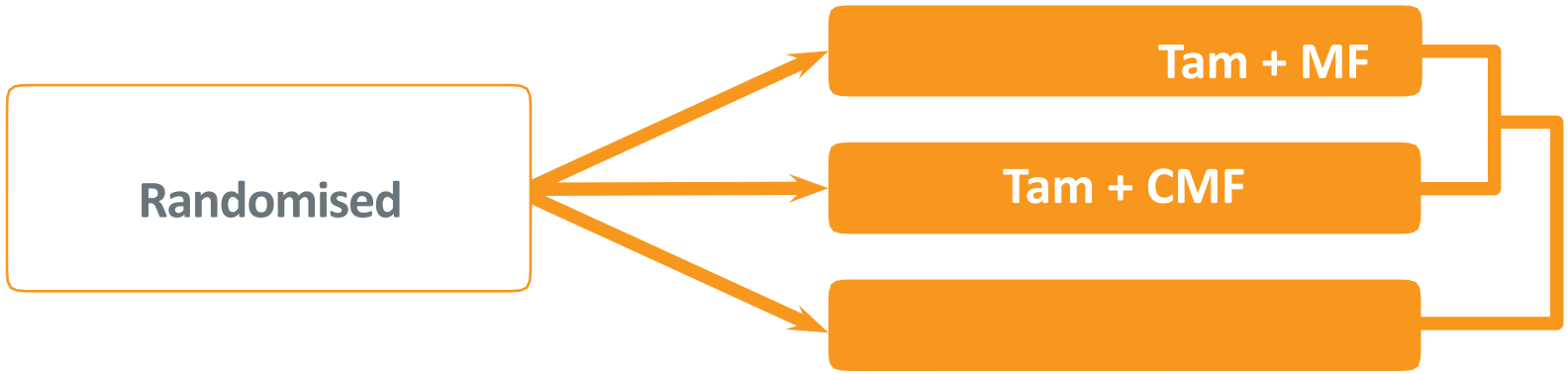
Paik S, et al. *N Engl J Med*. 2004;351:2817-2826.

Clinical validation studies of the PROGNOSTIC and PREDICTIVE value of the Oncotype DX® breast cancer assay

Oncotype DX® clinical validation: NSABP B-20

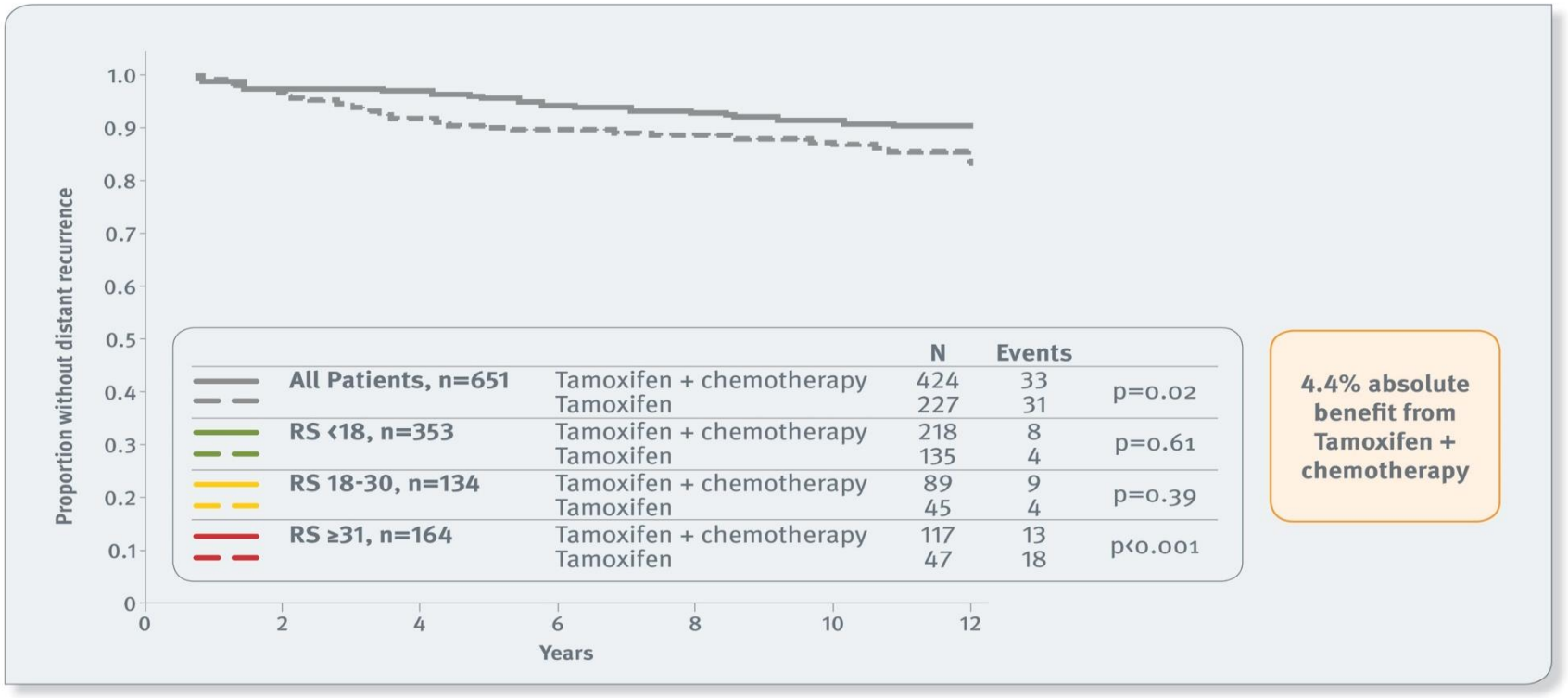
- Objective: Prospectively determine the relationship between Recurrence Score® result and chemotherapy benefit in node-negative, ER+ patients



- Multicentre study with prespecified 21-gene assay, algorithm, endpoints, analysis plan

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

High Recurrence Score® result correlates with greater benefit from chemotherapy (NSABP B-20)



RS, Recurrence Score® result

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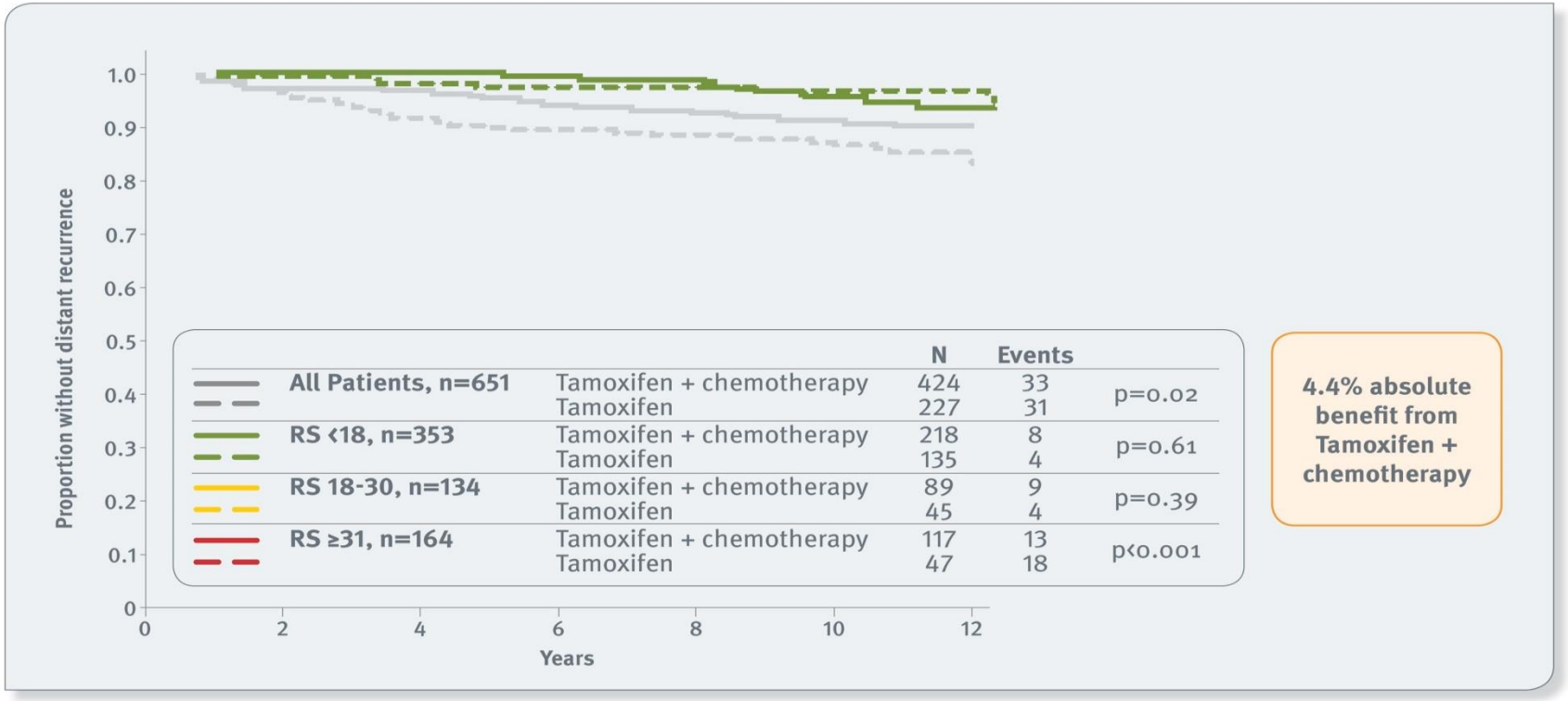

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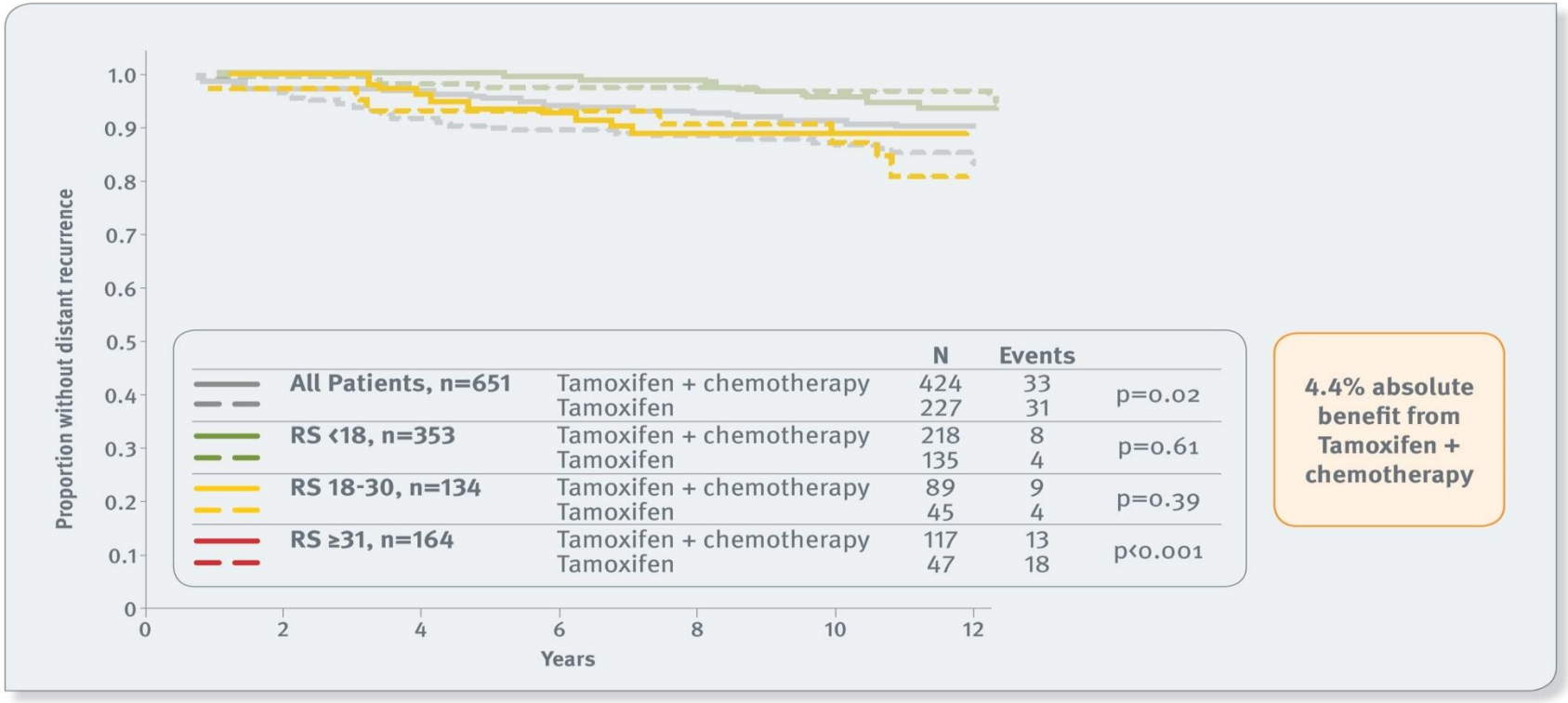

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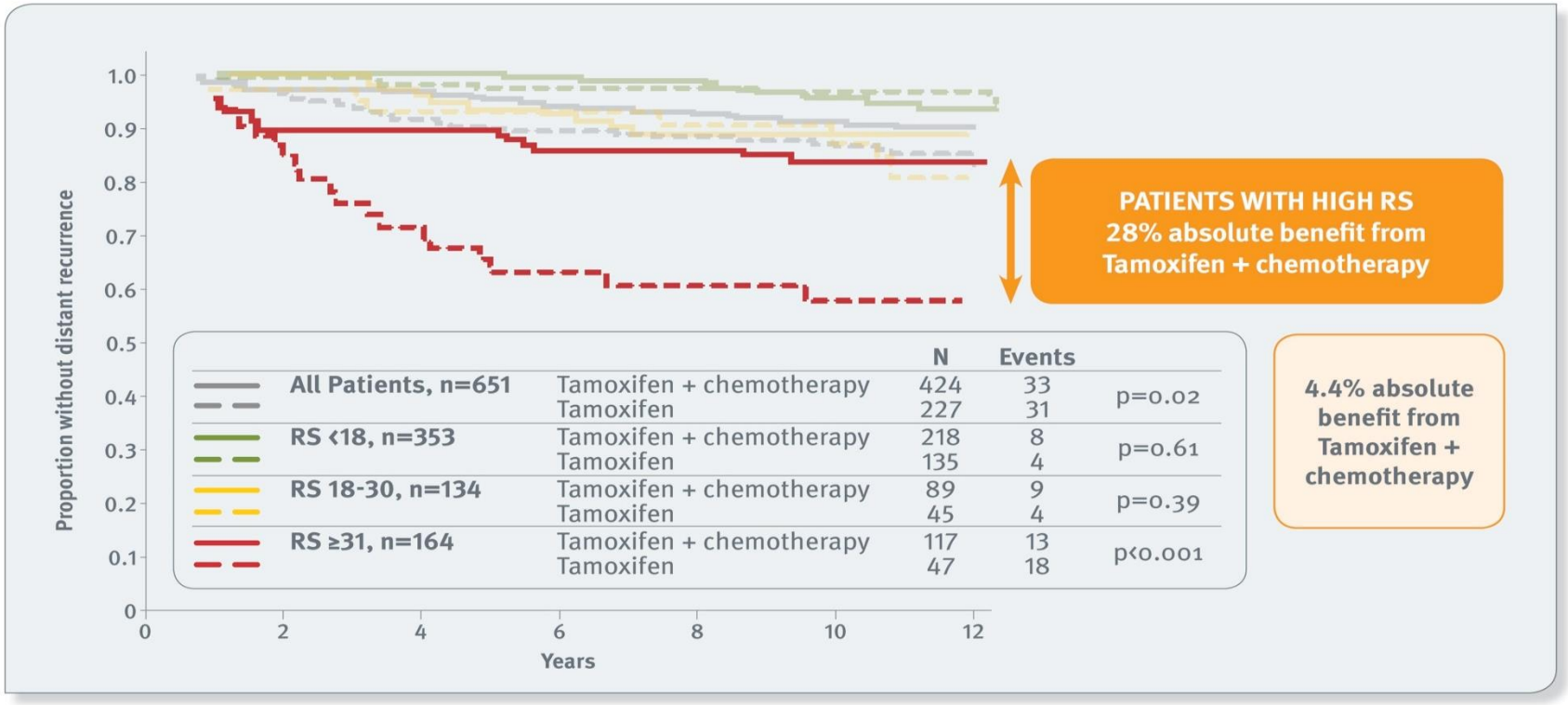
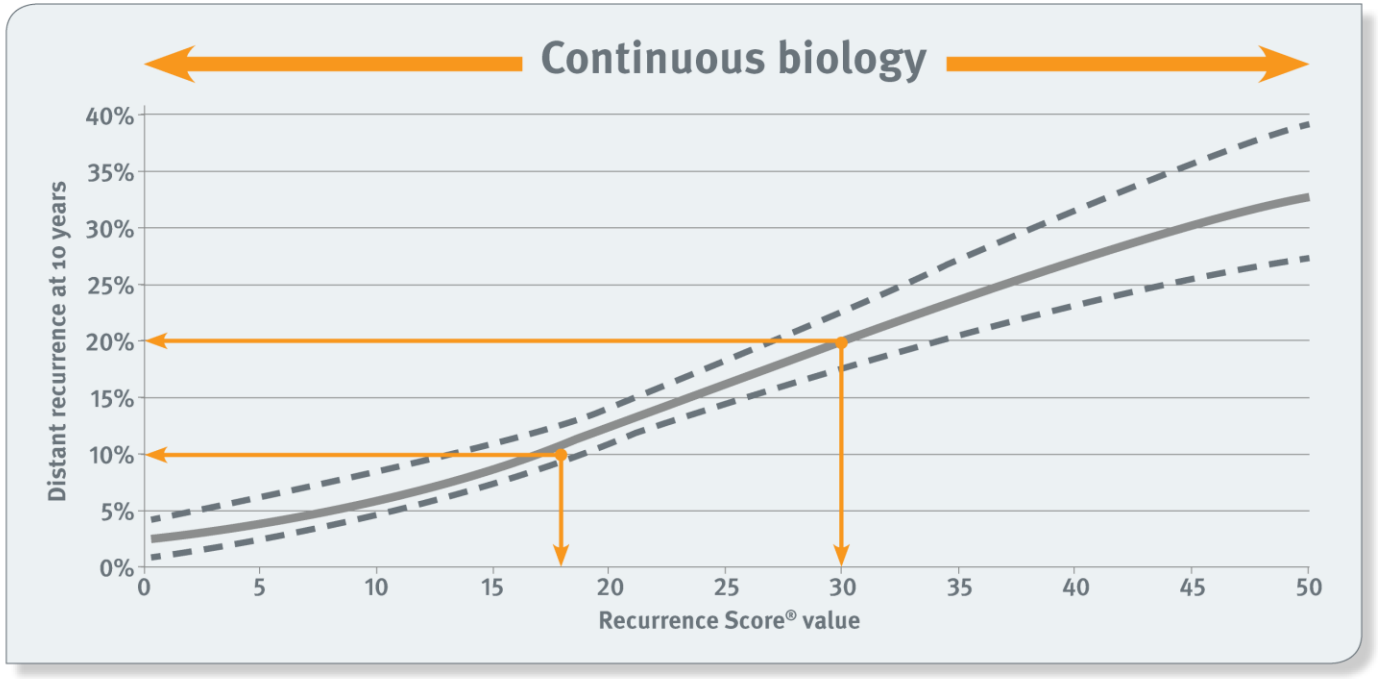


RS, Recurrence Score® result

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

The Recurrence Score® result assesses individual tumour biology for ER+ breast cancer



LOW RECURRENCE SCORE® DISEASE
Indolent
Hormone therapy-sensitive
Minimal, if any, chemotherapy benefit

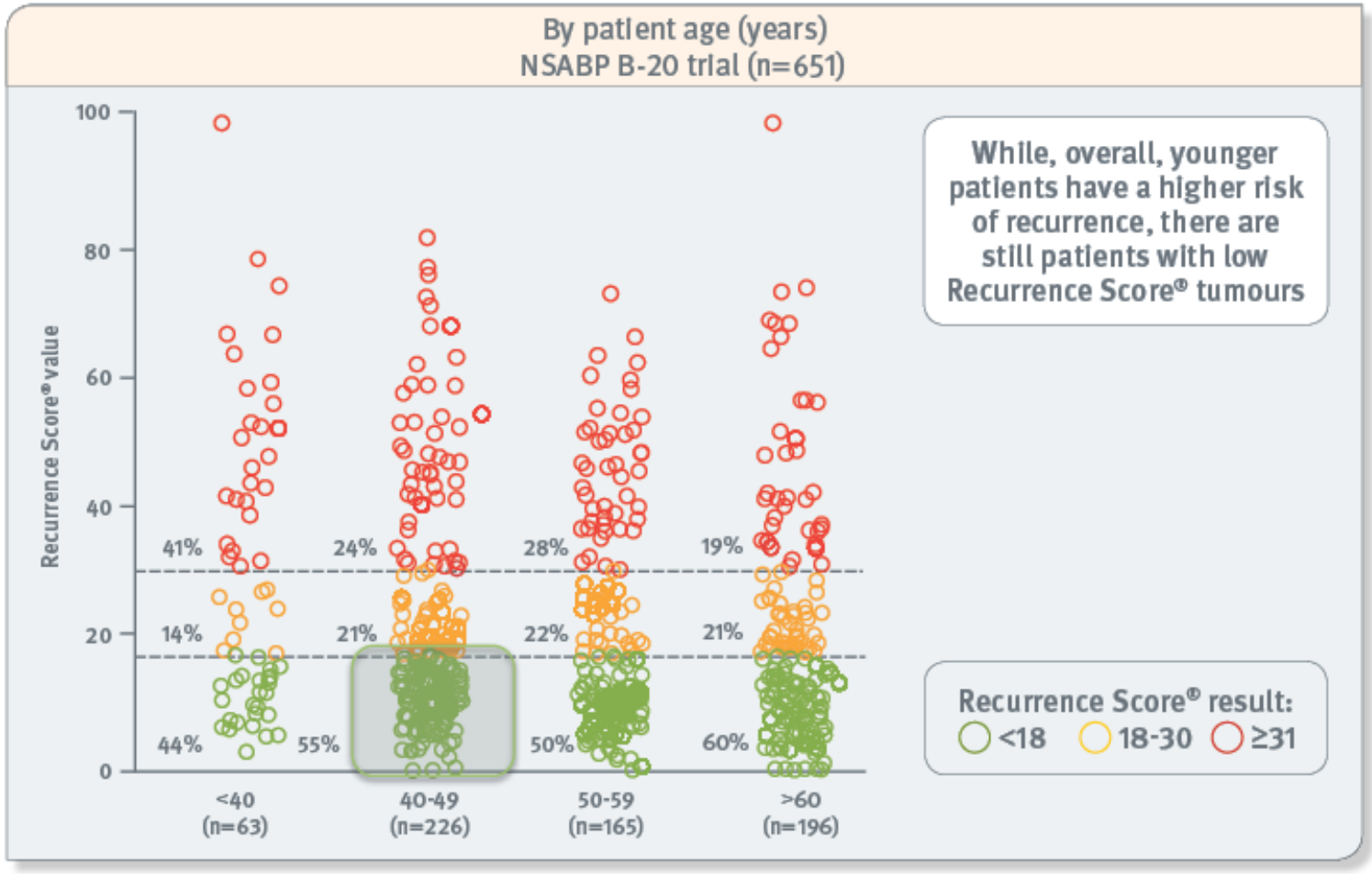
HIGH RECURRENCE SCORE® DISEASE
Aggressive
Less sensitive to hormone therapy
Large chemotherapy benefit

Paik S, et al. *N Engl J Med*. 2004;351:2817; Paik S, et al. *J Clin Oncol*. 2006;24:3726; Habel LA, et al. *Breast Cancer Res*. 2006;8:R25-R39.

Genomic Health®

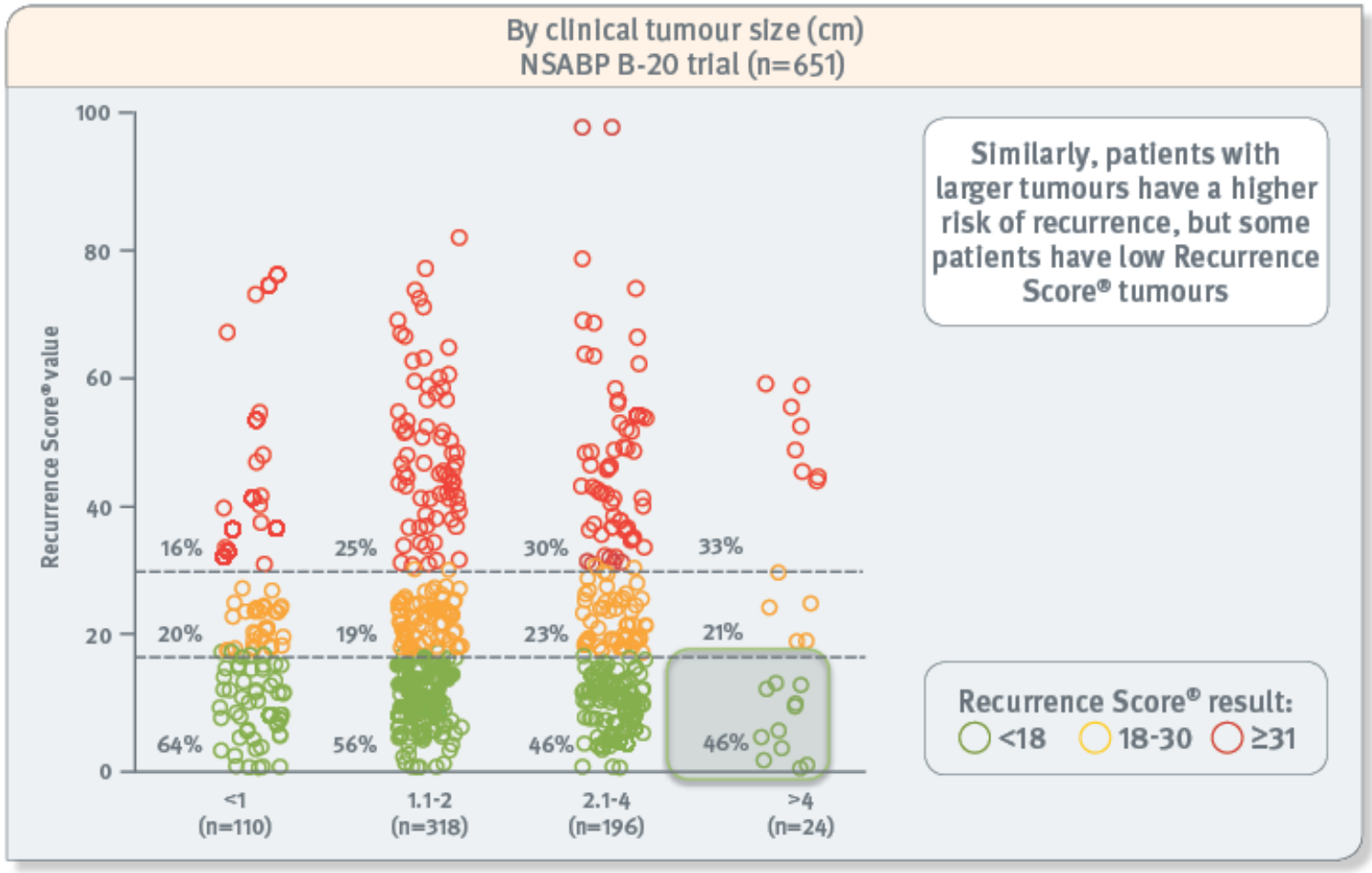
Can we predict Recurrene Score from Clinical Parameters?

Age



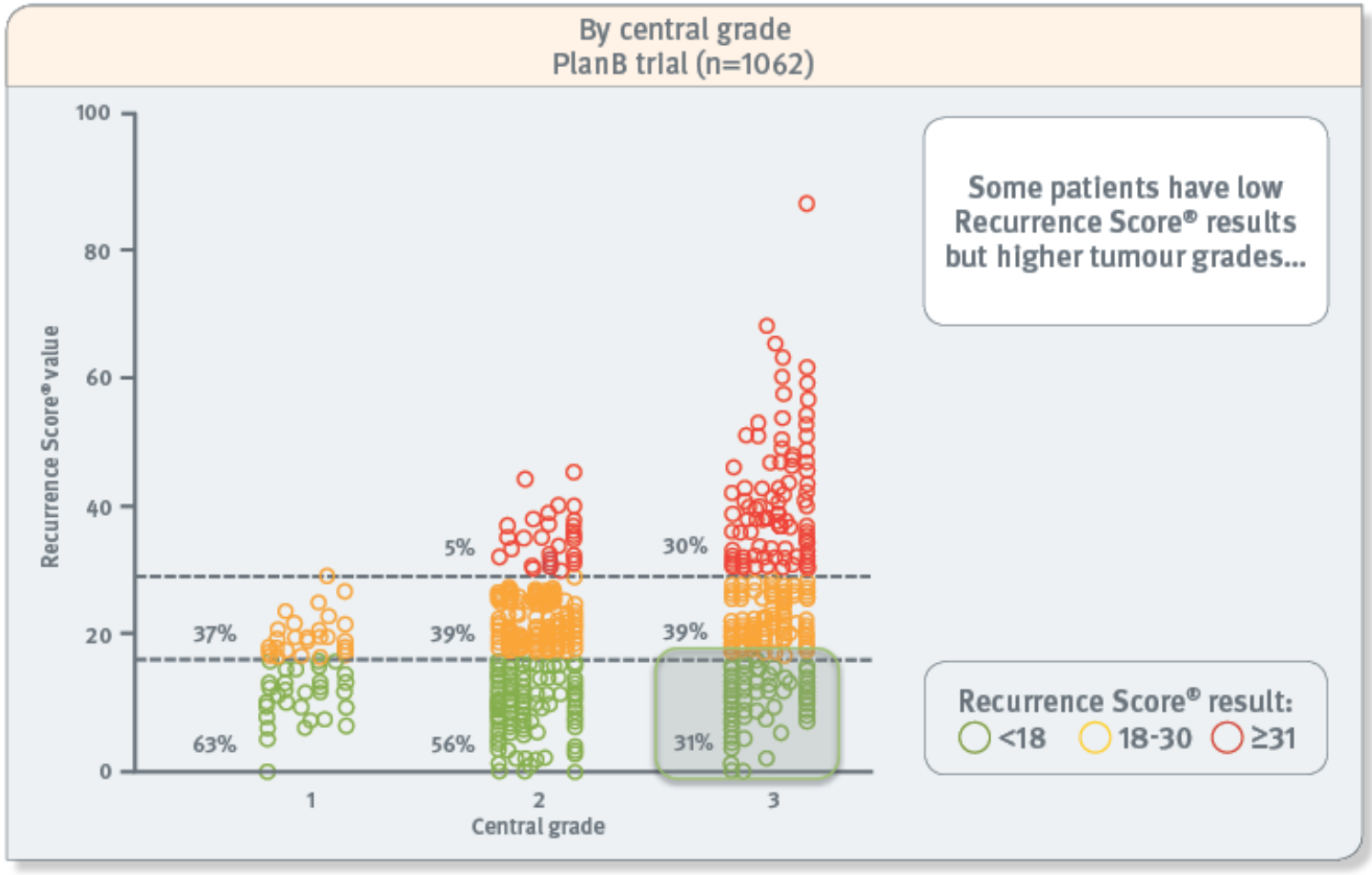
Paik S, et al. *N Engl J Med*. 2004;351:2817-2826

Size



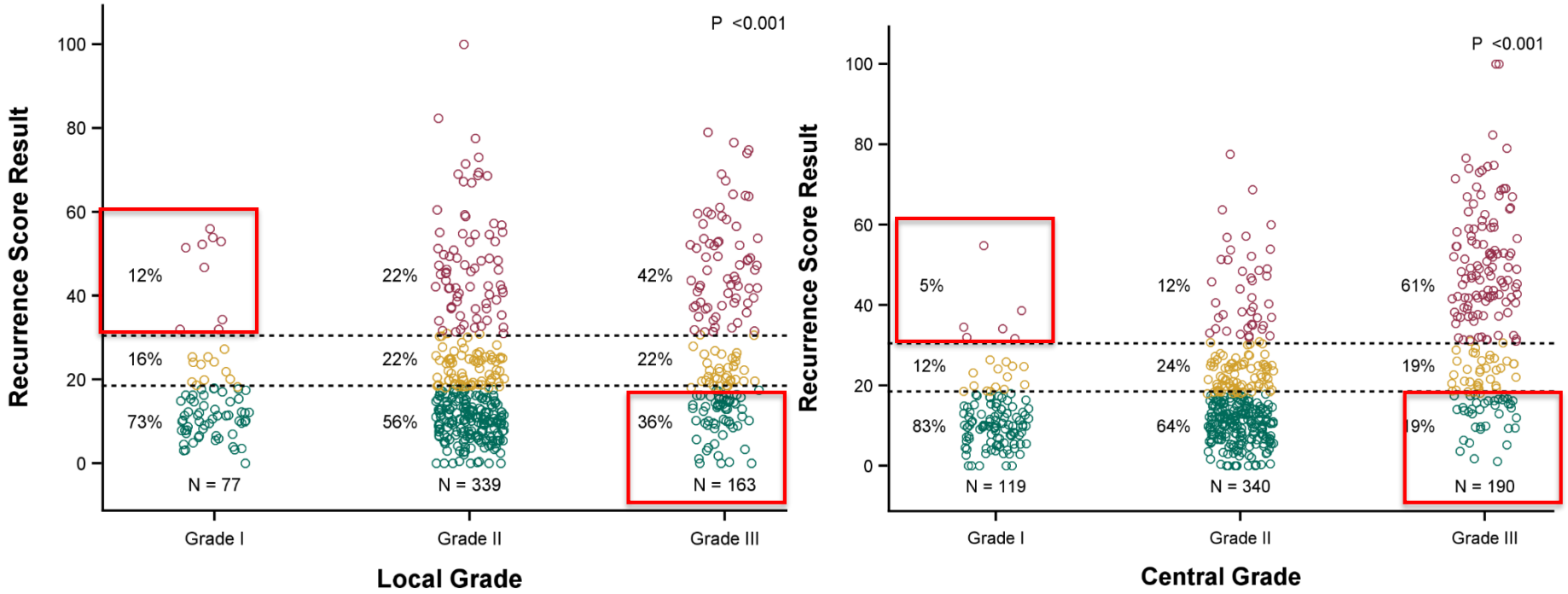
Paik S et al. *J Clin Oncol* 2006;24:3726-3734

Grade



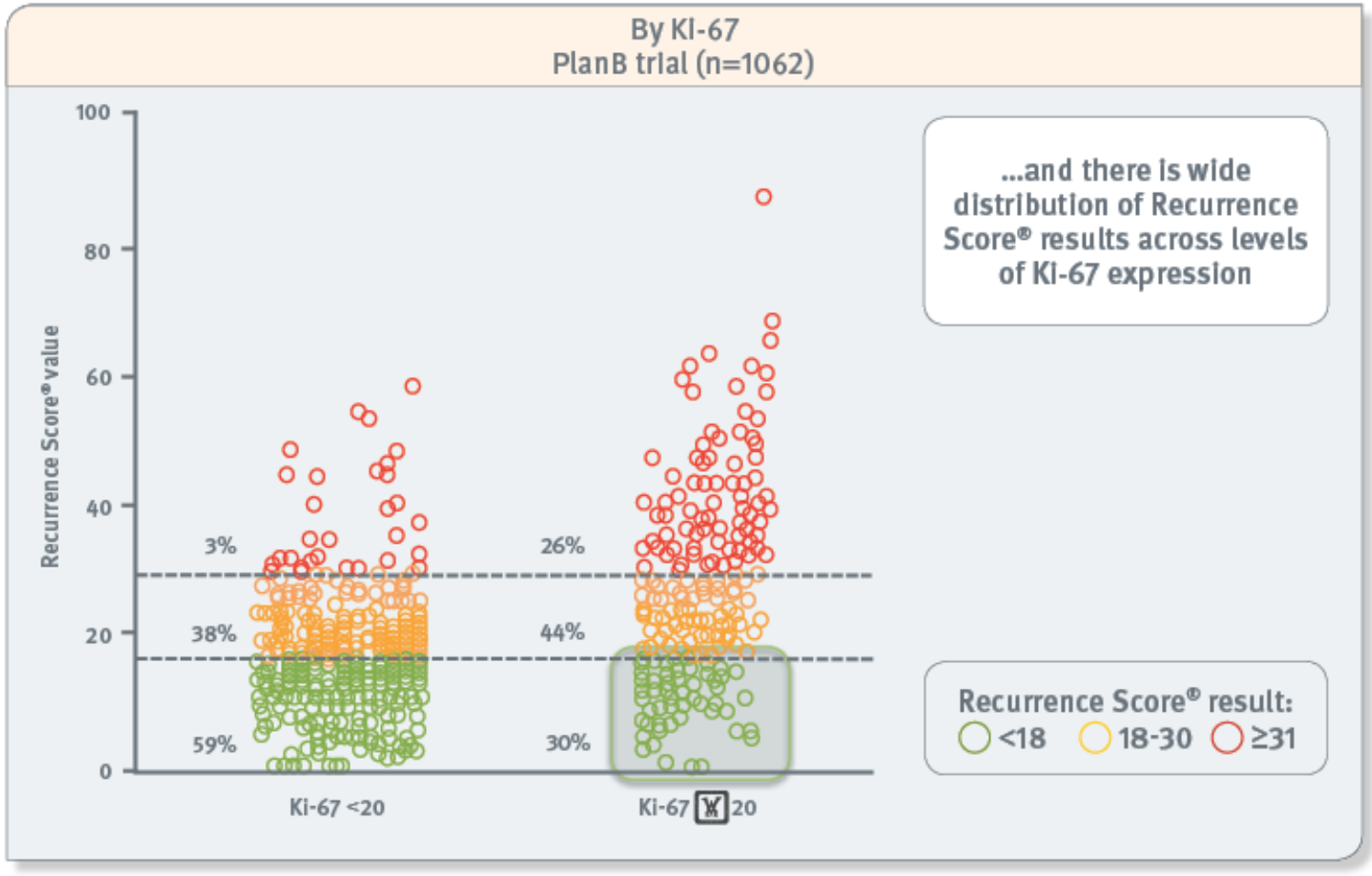
Gluz O et al. SABCS 2011;abstr S4-3

Significant Proportion of High-Grade Tumours Have Low Recurrence Score® Disease



Paik et al. *J Clin Oncol*. 2006.

Ki 67

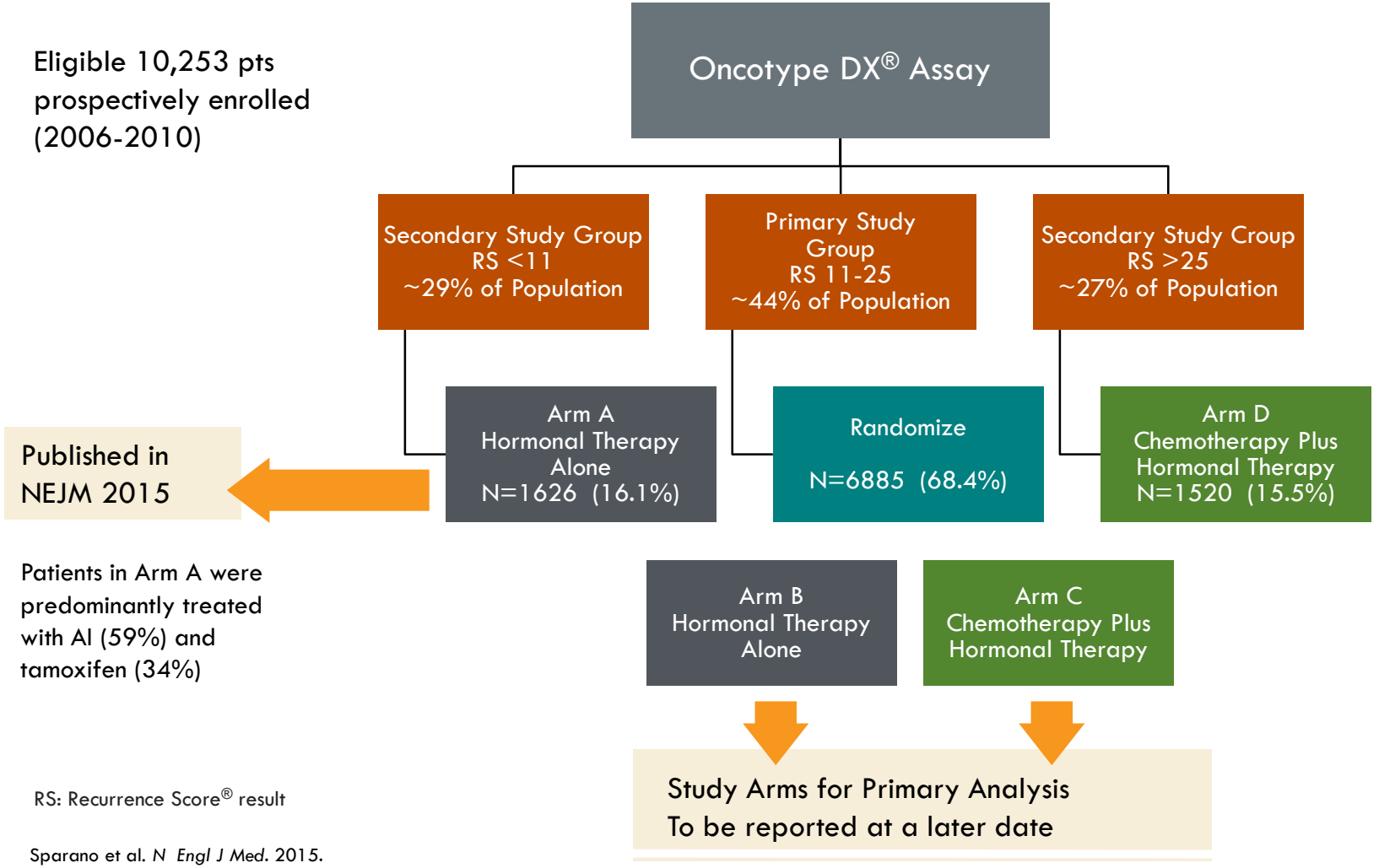


Gluz O et al. SABCS 2011;abstr S4-3

Identification of a Patient Population that May Not Benefit from Adjuvant Chemotherapy:
Outcomes from Large Population-based Genomic Studies

TAILORx: A Clinical Trial Assigning Individualized Options for Treatment (Rx)

Eligible 10,253 pts prospectively enrolled (2006-2010)



Patients in Arm A were predominantly treated with AI (59%) and tamoxifen (34%)

RS: Recurrence Score® result

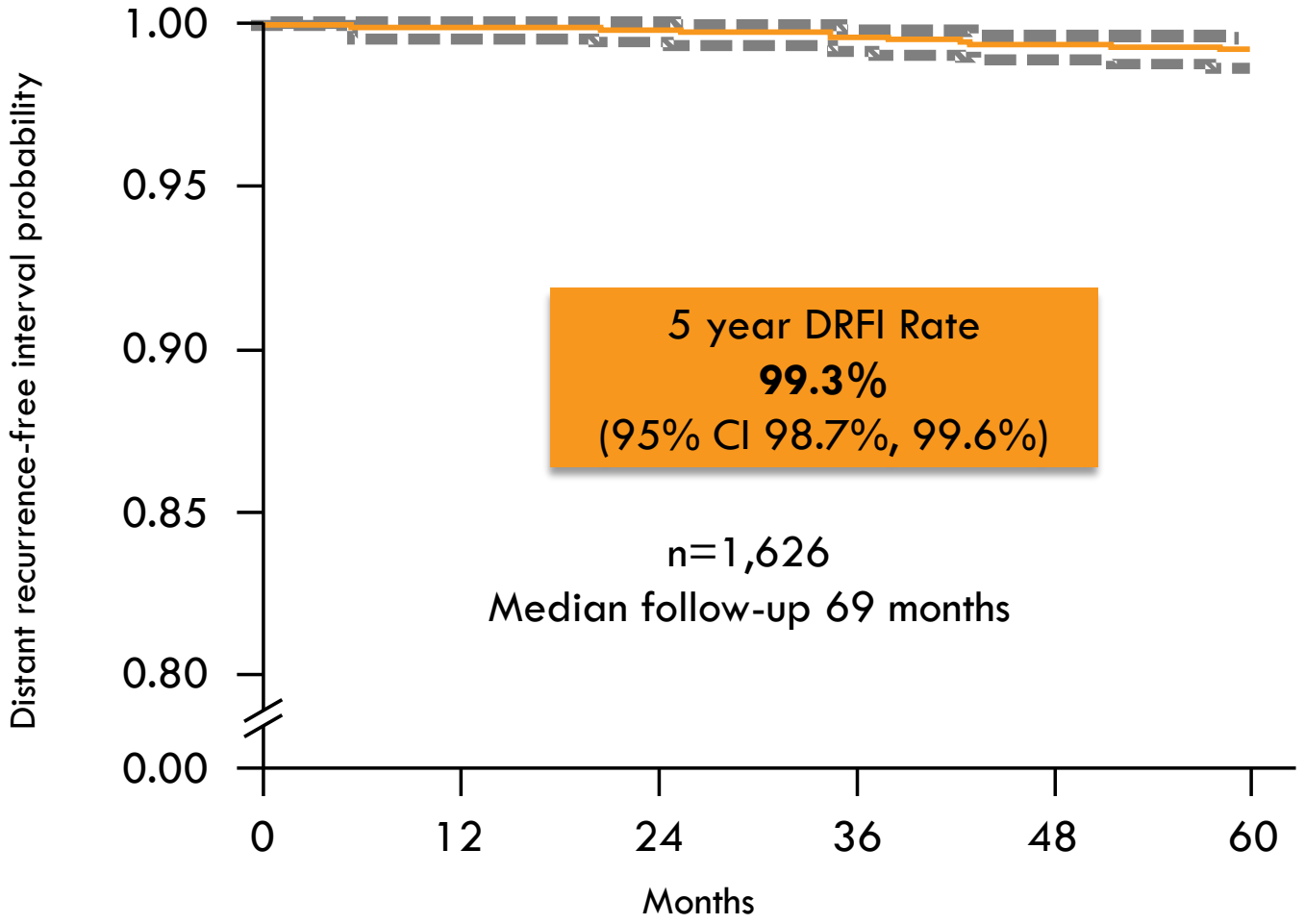
Sparano et al. *N Engl J Med*. 2015.

Most Patient Characteristics and Surgical Treatment Between Arms Were Similar

	Arm A (Recurrence Score® result <11)	Arm B/C (Recurrence Score® result 11-25)
No. eligible patients	1626	6897
Median age - yrs	58	55
Post-menopausal	70%	64%
Median tumor size - cm	1.5	1.5
Histologic grade		
Low	34%	29%
Intermediate	59%	57%
High	7%	14%
ER expression	>99%	>99%
PgR expression	98%	92%
Surgery		
Lumpectomy	68%	72%
Mastectomy	32%	28%

Differences between arms were clinically modest and would not allow a clinician to distinguish between patients having a low or mid-range Recurrence Score results

Patients with Recurrence Score® Results <11 Have Less than 1% Risk of Distant Recurrence at 5 Years



Sparano et al. *N Engl J Med*. 2015.

Neither Age, Size nor Grade Impacted the 5-year Distant Recurrence Risk or Overall Survival

Distant recurrence

		DRFI, HR (95% CI)	P Value
Age	≤50 vs 51-60 years ≤50 vs 61-75 years	1.28 (0.12-4.22) 3.49 (0.42-29.16)	0.27
Tumor size	>2 cm cm vs ≤2 cm	1.55 (0.38-6.31)	0.55
Tumor grade	2/3 vs 1	3.83 (0.48-30.69)	0.14

Event rates by grade

	DRFI, % (95% CI)	OS, % (95% CI)
All grades	99.3 (98.7-99.6)	98.0 (97.1-98.6)
Low grade	99.8 (98.3-100)	98.7 (97.0-99.4)
Intermediate grade	99.0 (98.0-99.5)	97.9 (96.8-98.7)
High grade	100 (NC-NC)	97.3 (91.9-99.1)

HR, hazard ratio; NC, not calculated; DRFI, distant recurrence-free interval; OS, overall survival.

Registry Studies

Clalit Breast Cancer Registry

- Clalit is the largest health services provider in Israel and accounts for ~60% of patients
- The 21-gene Oncotype DX® assay is a standard part of the initial diagnostic work-up for patients with ER+/HER2-negative early-stage breast cancer
- Physicians are mandated to follow the assay result for treatment; i.e. patients with a low score receive hormone therapy alone
- Began collecting prospective data on all patients in 2006

Stemmer et al. SABCS 2015.

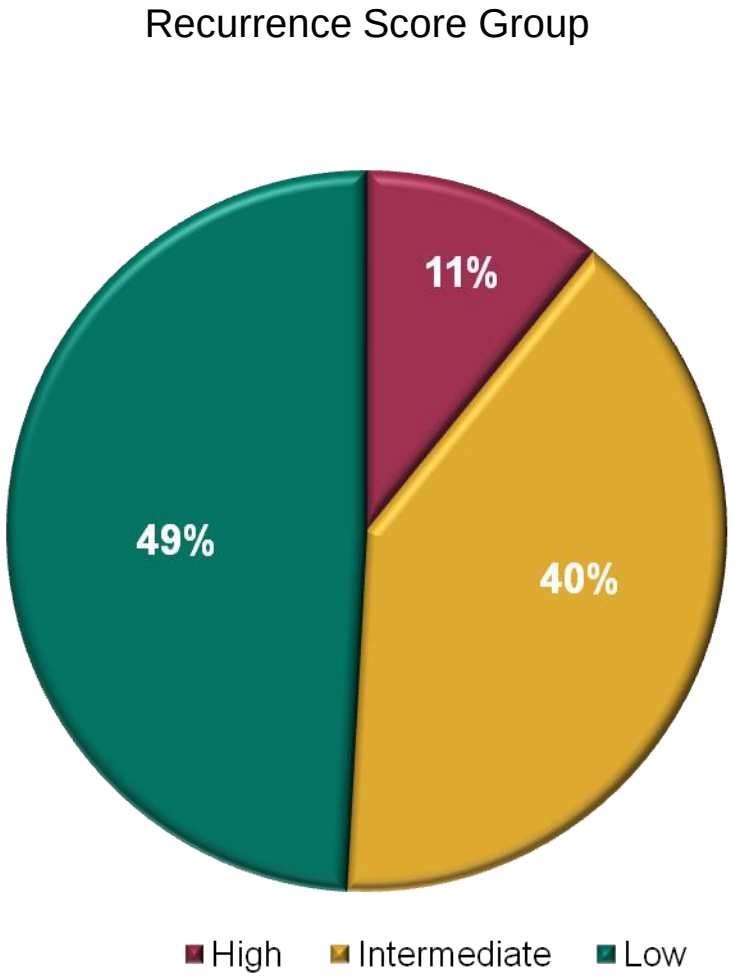
Clalit Registry: Patient Demographics are Similar to TAILORx

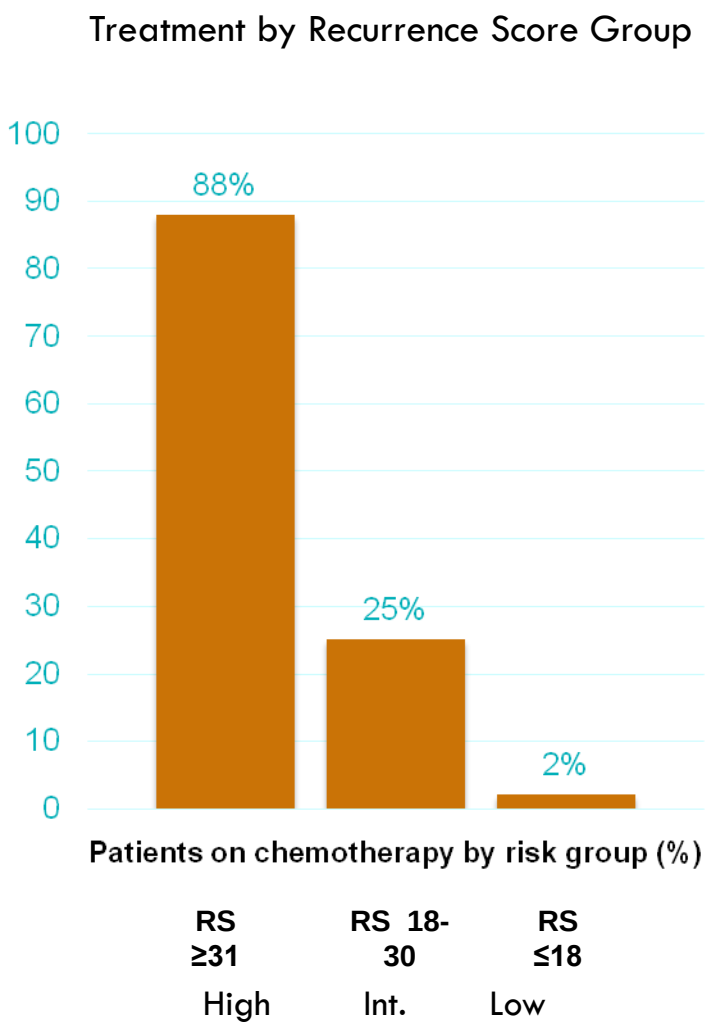
Variable	Mean
Age, years (range)	59.3
Nodal status	
N0	89%
N1mic	11%
Grade	
I	14%
II	51%
III	17%
N/A	18%
Size	
≤2 cm	77%
>2 cm	22%
N/A	1%
Histology	
IDC	81%
Lobular	12%
Other	7%

2,028 evaluable patients, median follow-up 6.1yrs

Stemmer et al. SABCS 2015.

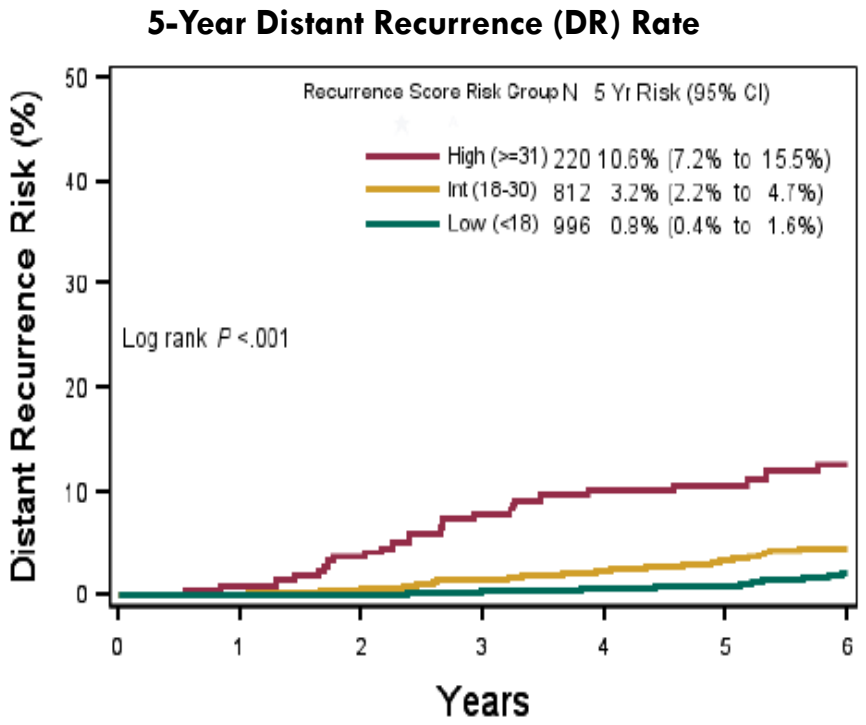
Clalit Registry: Chemotherapy Use is Consistent with the Recurrence Score® Result

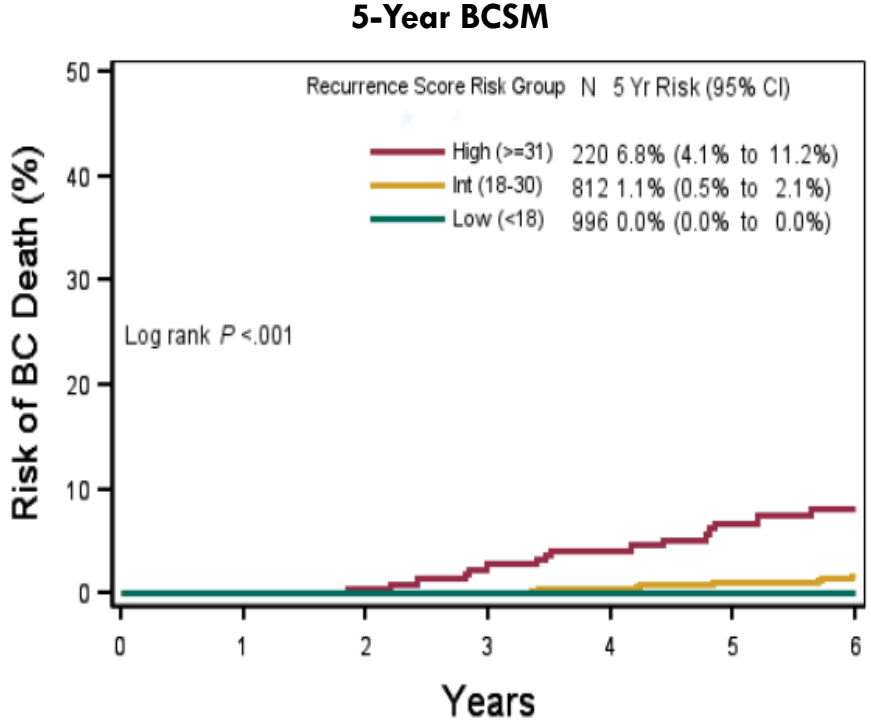




Stemmer et al. SABCS 2015.

Clalit Registry: Further Evidence that the Recurrence Score® Result Identifies Patients that Can Be Spared Chemotherapy





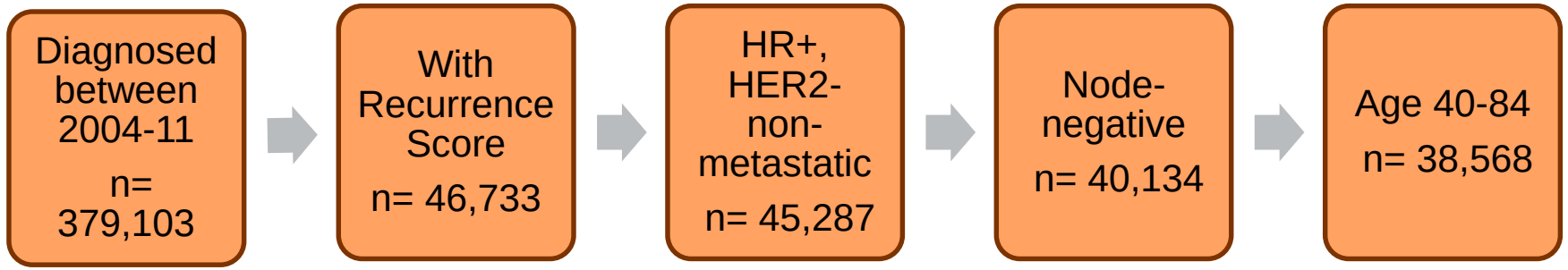
- The rate of 5-Year distant recurrence is 0.8% with Recurrence Score <18 compared to 10.6% with Recurrence Score ≥31
- The rate of breast cancer death within 5 years by Recurrence Score group is 0.0%, 1.1%, and 6.8%

Stemmer et al. ECC 2015.

SEER Survival Outcomes Data – Corroborating Oncotype DX® Clinical Utility with High Quality Registry Data

SEER Breast Cancer Registry Study Design

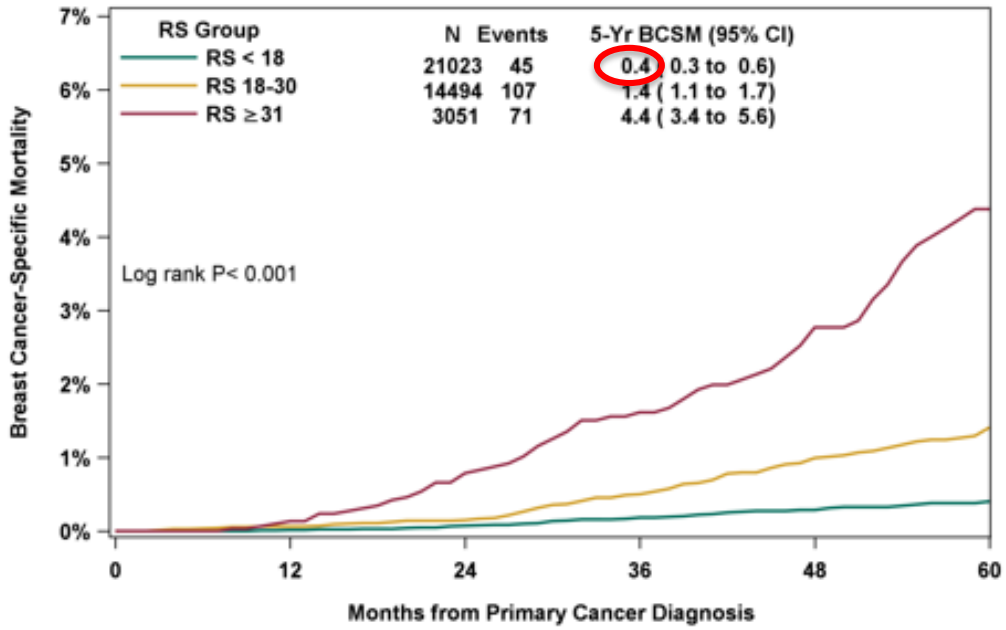
- Characterise the Oncotype DX® assay testing and known chemotherapy (CT) use by nodal status in hormone receptor-positive (HR+) invasive breast cancer
- Determine prospective breast cancer-specific mortality (BCSM) outcomes by Recurrence Score® result and clinical and pathologic features
  - In a pre-specified analysis of N0, HR+, HER2- patients aged 40-84 years
  - In subgroups with N0 and node-positive (N+; micrometastatic and 1-3 positive nodes) disease, including subgroups often under-represented in clinical trials



Shak et al. SABCS 2015.

5-yr BCSM by Recurrence Score® Group

Primary Analysis: N0, HR+, HER2- Patients 40-84 Years Old



Known Chemotherapy Use:

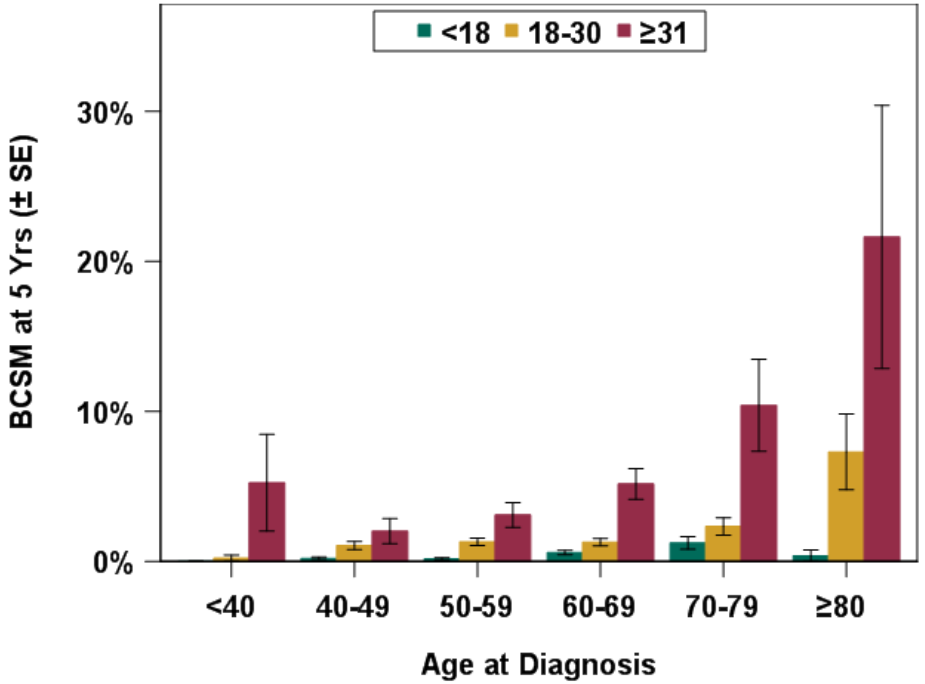
- 7% of Recurrence Score <18
- 34% of Recurrence Score 18-30
- 69% of Recurrence Score ≥31

- Only ***45 events*** in the 21,023 patients with Recurrence Score results <18 (0.4% BCSM)
- 5-yr BCSM for the low-risk group consistent with outcomes in patients treated with hormonal therapy alone in NSABP B-14 and B-20, TAILORx, and Clalit registry
- 5-yr BCSM results (1.4%) for RS 18-30 are consistent with Clalit registry despite 34% of patients receiving chemotherapy

Shak et al. SABCS 2015; Paik et al. *N Engl J Med*. 2004; Paik et al. *J Clin Oncol*. 2006; Stemmer et al. SABCS 2015.

SEER Subgroup Analysis of N0 by Patient Age

5-year BCSM by Recurrence Score® Group



- Chemotherapy use varied across age categories
- Regardless of age and chemotherapy use, the Recurrence Score results consistently predicted outcomes

Chemotherapy Use Consistent with Recurrence Score® Result

	N (% in each group known to have received chemotherapy)					
RS	**<40**	**40-49**	**50-59**	**60-69**	**70-79**	**≥80**
<18	682 (18%)	5185 (12%)	6799 (7%)	6471 (4%)	2360 (3%)	263 (1%)
18-30	637 (55%)	3550 (46%)	4924 (37%)	4438 (27%)	1439 (16%)	164 (6%)
≥31	161 (78%)	615 (75%)	1021 (74%)	1004 (67%)	374 (56%)	47 (32%)

Shak et al. SABCS 2015.

Genomic Health®

Oncotype DX™ Assay Process: the Genomic Health Clinical Laboratory

GHI Reference Laboratory

- Genomic Health Reference Laboratory is CLIA licensed (Lic. #05D1018272)
- GHI Reference Lab is CAP certified
- Since January, 2004 GHI has had five major laboratory audits and certifications
  - California Laboratory Field Services
  - CLIA, State of California (2x)
  - CLIA, State of New York (2 x)
  - CAP (2x)

Oncotype DX™ in Clinical Practice
Overview

- Oncotype DX™ has been offered by Genomic Health, Inc., since January 2004
  - Genomic Health is a CLIA-approved reference lab (Lic #05D1018272)
  - Send tumor block as fixed, paraffin-embedded sections (10 µm each) using the Oncotype DX™ Specimen Kit
  - Turnaround time: 10-14 days
  - Cost: £2580 (non NHS Cost)
  - Reimbursement: NHS Scotland via individual Health Boards

Unlocking the FPET Block

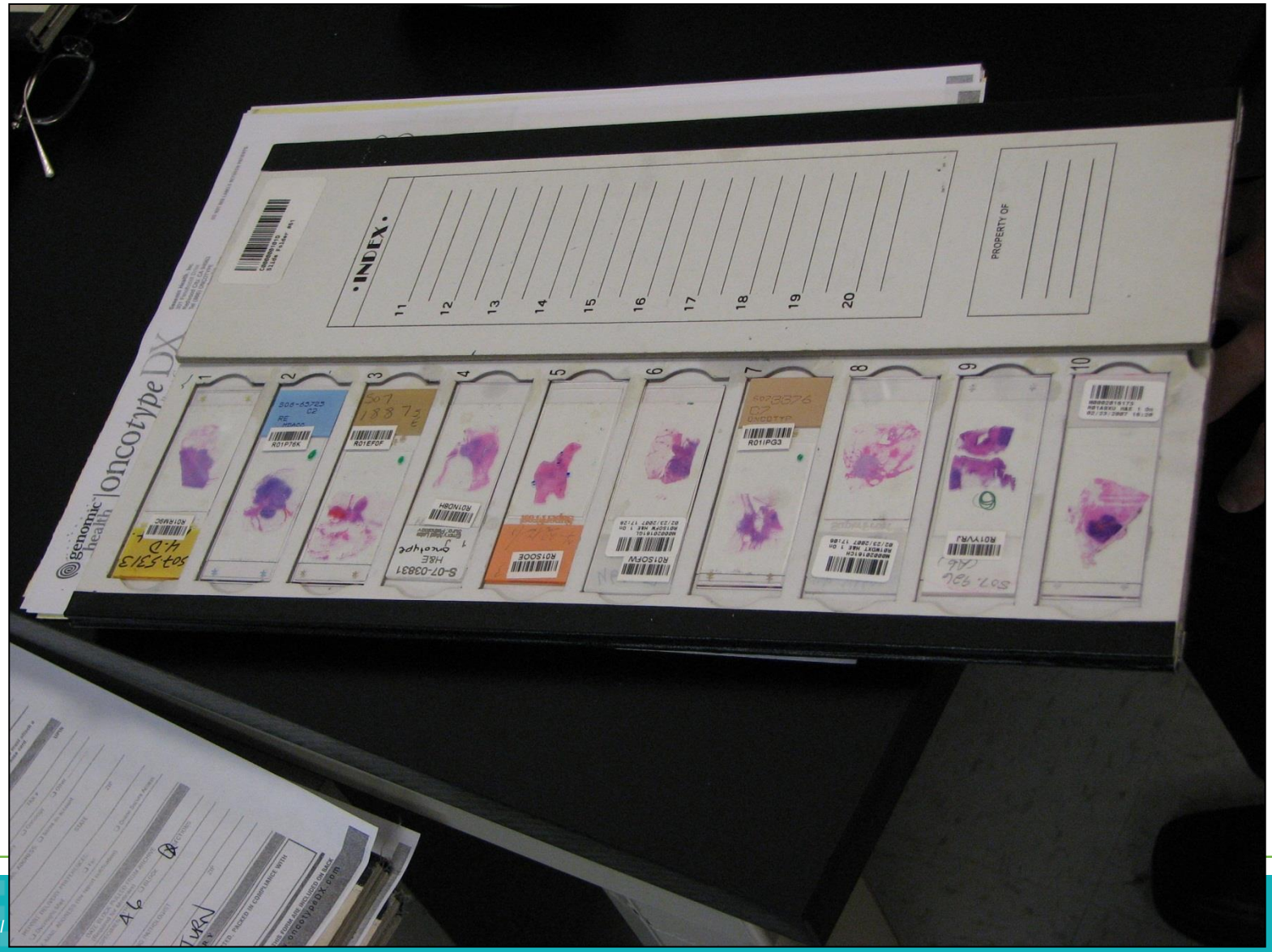
Patient Sample is Barcode Tracked from Submission to Report

All samples from Blocks to Slides to Assay tubes are uniquely barcode labeled

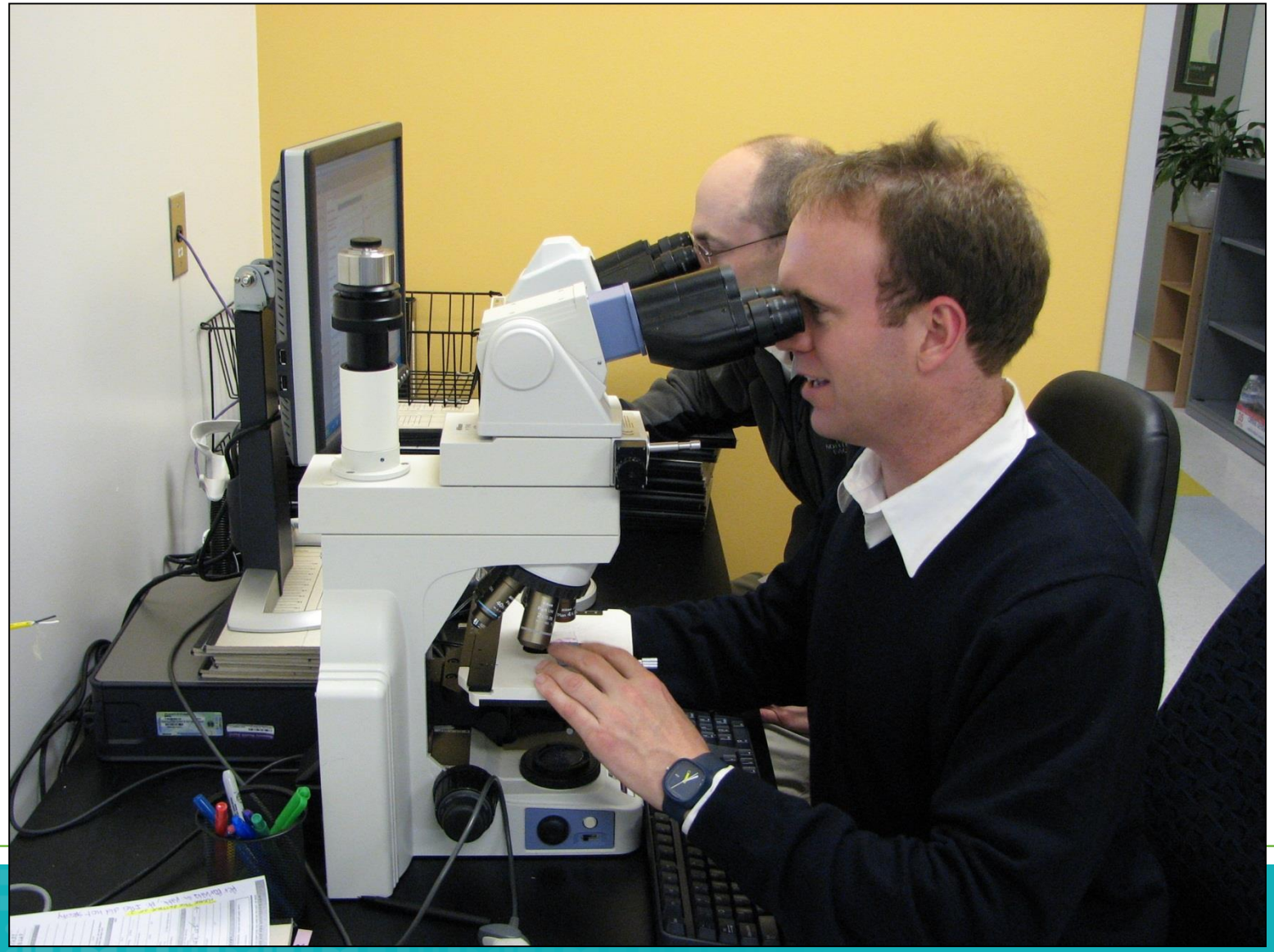
All sample locations are tracked by computer when on automated specimen platforms

GHI Bar-Coding Enables Sample Tracking with HIPAA Compliance

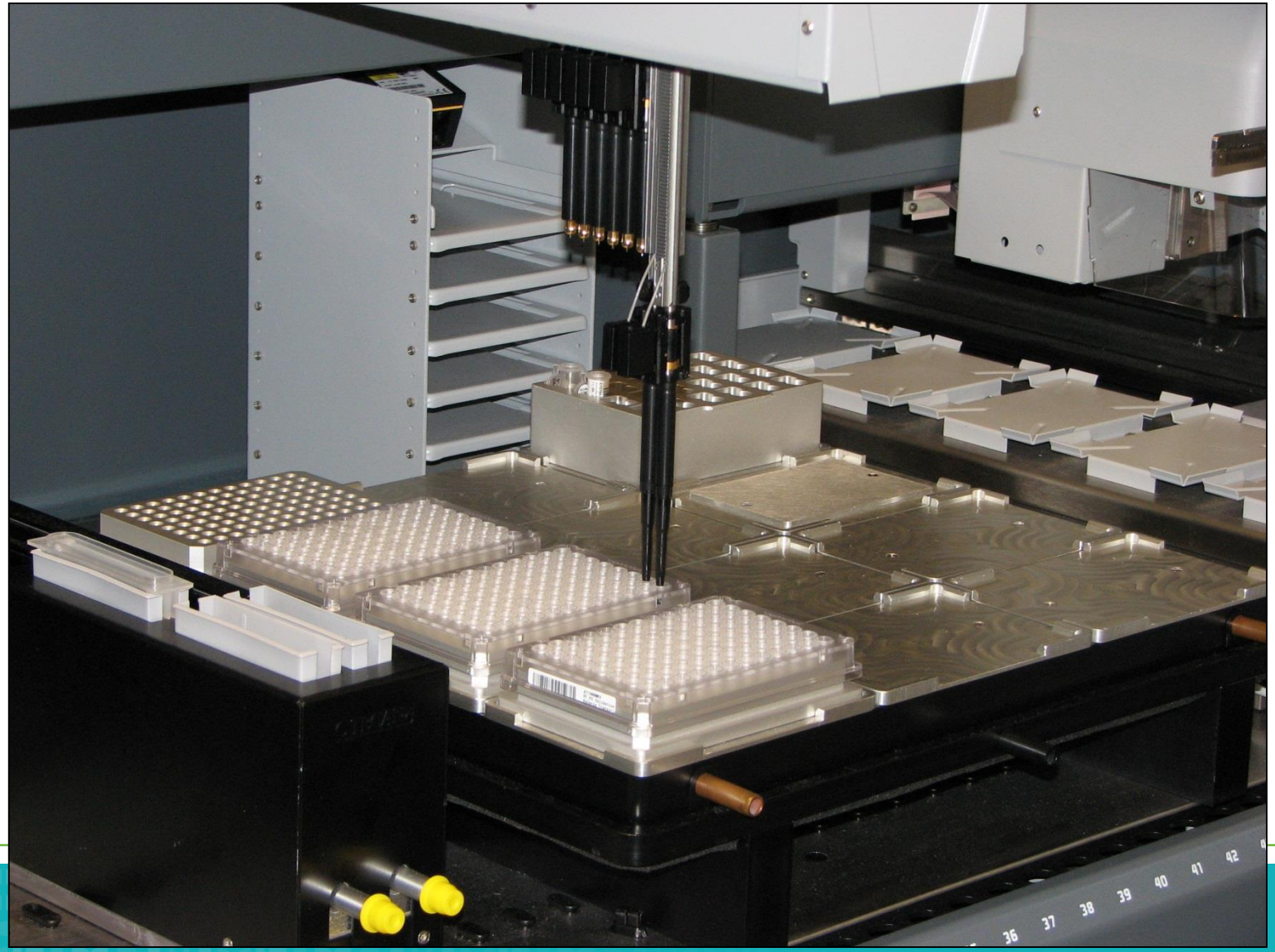
H&E Stained Slides are Prepared for All Submitted Samples



All Patient Samples are Reviewed by Pathologists to Confirm Sufficient Tumor for Assay



Most Assay Processes are Automated for Maximum Quality and Throughput



Tecan Freedom EVO 200-multifunction is the Basic Workhorse Robot

Equipment Replication Supports Scale up and Back up Functions

Plate and Sample Tracking

LIMS, Reagent, and Robotic integrated bar-coding, tracking, and Assembly

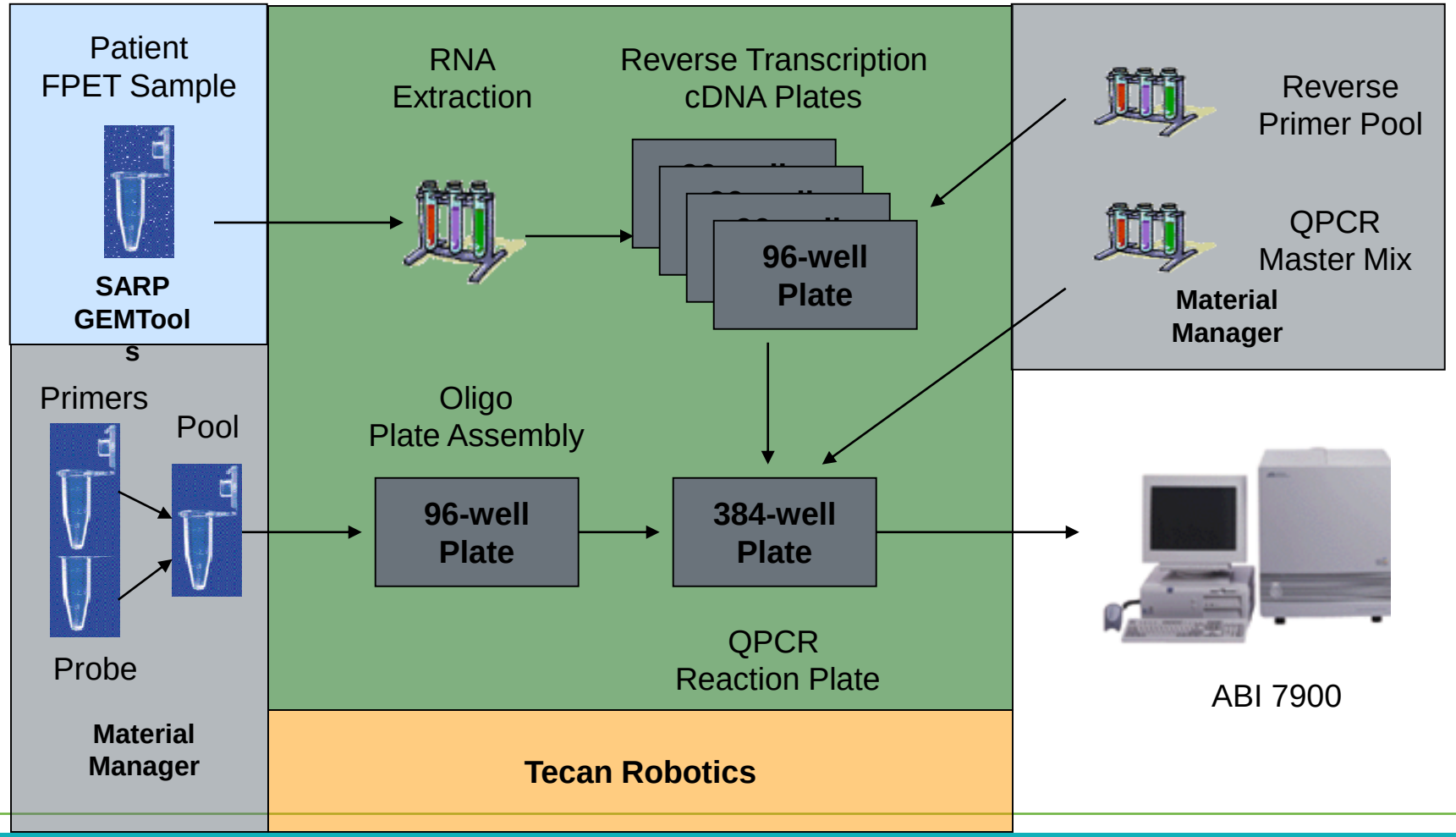
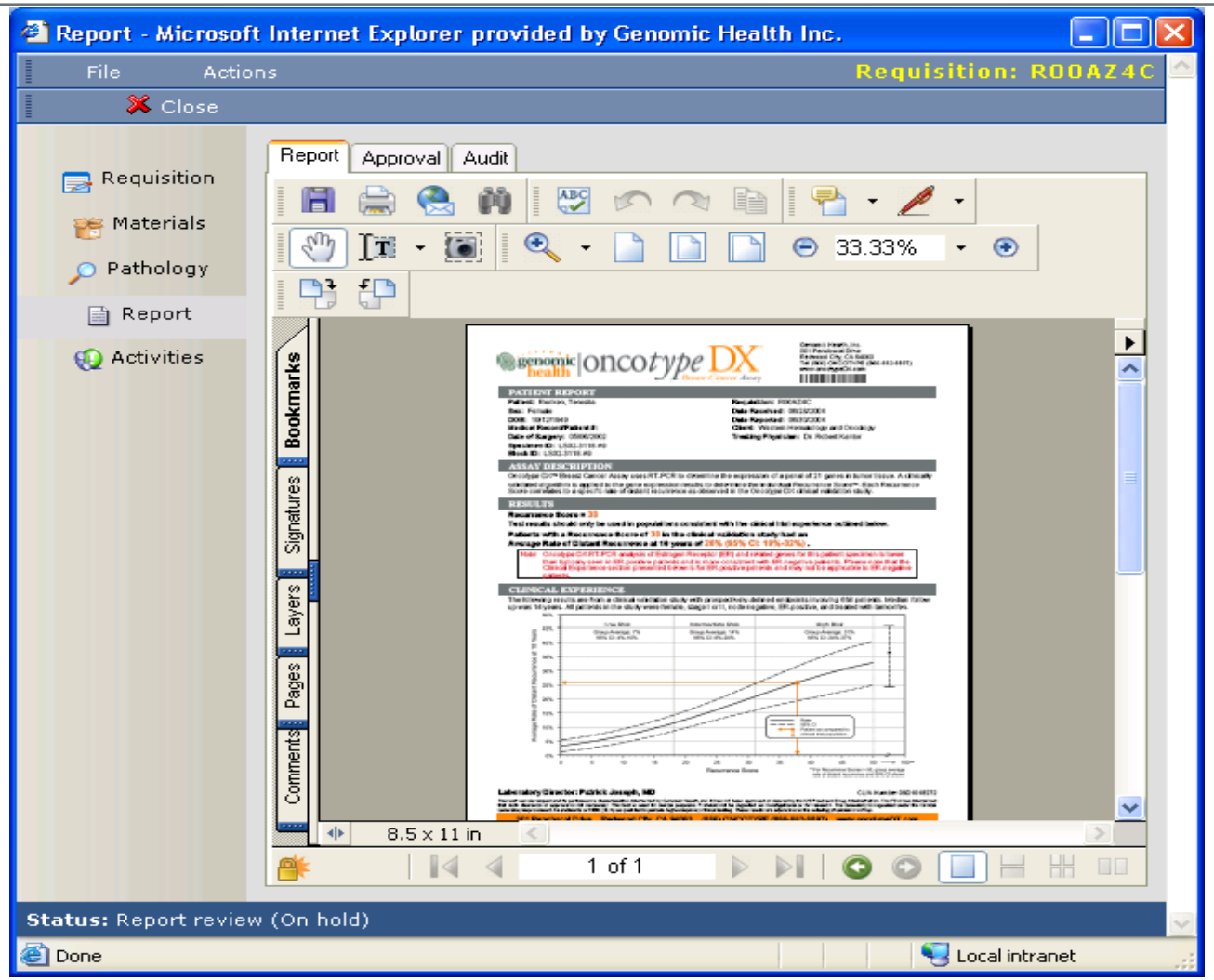


Plate Layout Template and Assembly for Primers and Samples

Report Generation and Approval

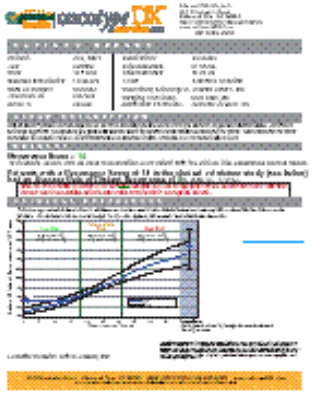


Result and Failure Reports

- Electronic PDF Format
- XML-Based Content Generation
- Optimized for Print, Fax, Online
- Reviewed Online by CLS
- Electronic Signature

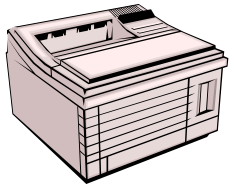
Report Delivery

Automated Report Output, Delivery, and Notification



Electronic PDF Result Report or Failure Report w/ Electronic Signature Approval

Report Distribution Service

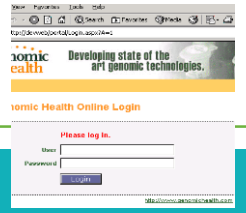


Printed Output

FedEx Waybill

E-mail Notification

Fax Delivery



Online

Conclusions

- Oncotype DX is quantitatively precise and reproducible
- Assay analytical validation resulted in process monitoring metrics that are applied at all stages of the process
- Each of 21 component gene assays is quantitatively controlled leading to highly reproducible RS values
- The overall process is highly integrated to support monitoring and tracking, HIPPA and CLIA compliance, resource management and process optimization

Genomic Health®

Thank You.