Genomics and Breast Cancer: A New Approach to Personalised Healthcare

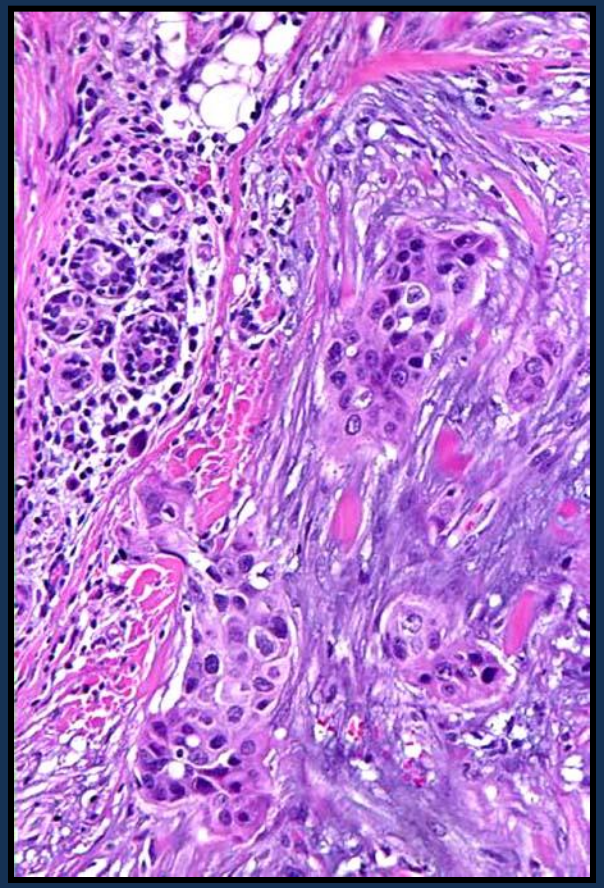
Calvin Chao, MD

Genomic Health Inc

Sr Director of Medical Affairs

Diagnosis of Breast Cancer: 20th and 21st Century

Size
Age



Phenotype
Nodal status

Protein/Gene
"Genomic Profiling"

What are Genetics and Genomics?

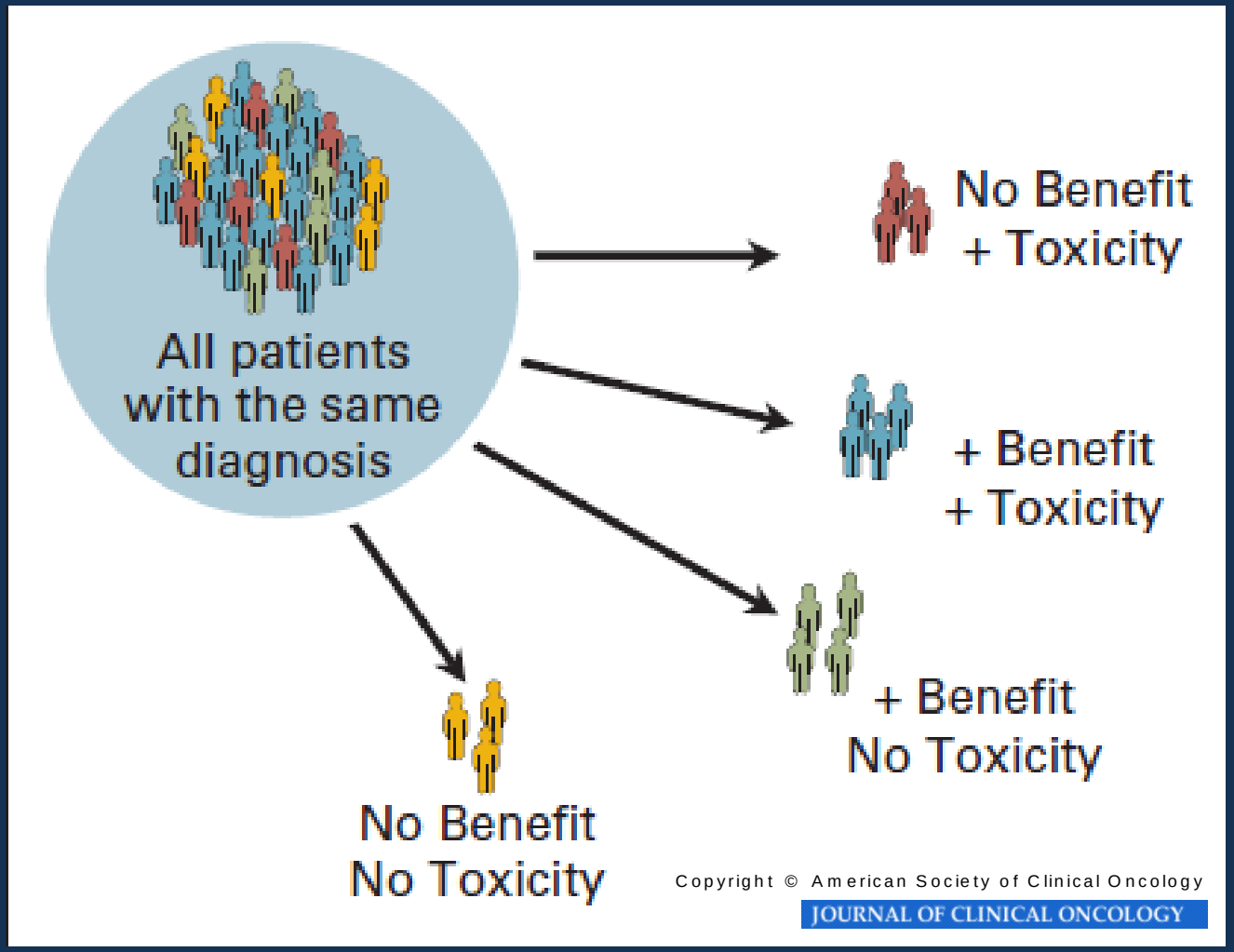
Genetics

- Genes (units of heredity) carry the instructions for making proteins, which direct the activities of cells and functions of the body
- Study of a single gene, its roles in inheritance and its effects
- Examples of genetic disorders include cystic fibrosis, Huntington's disease, and in oncology; BRCA

Genomics

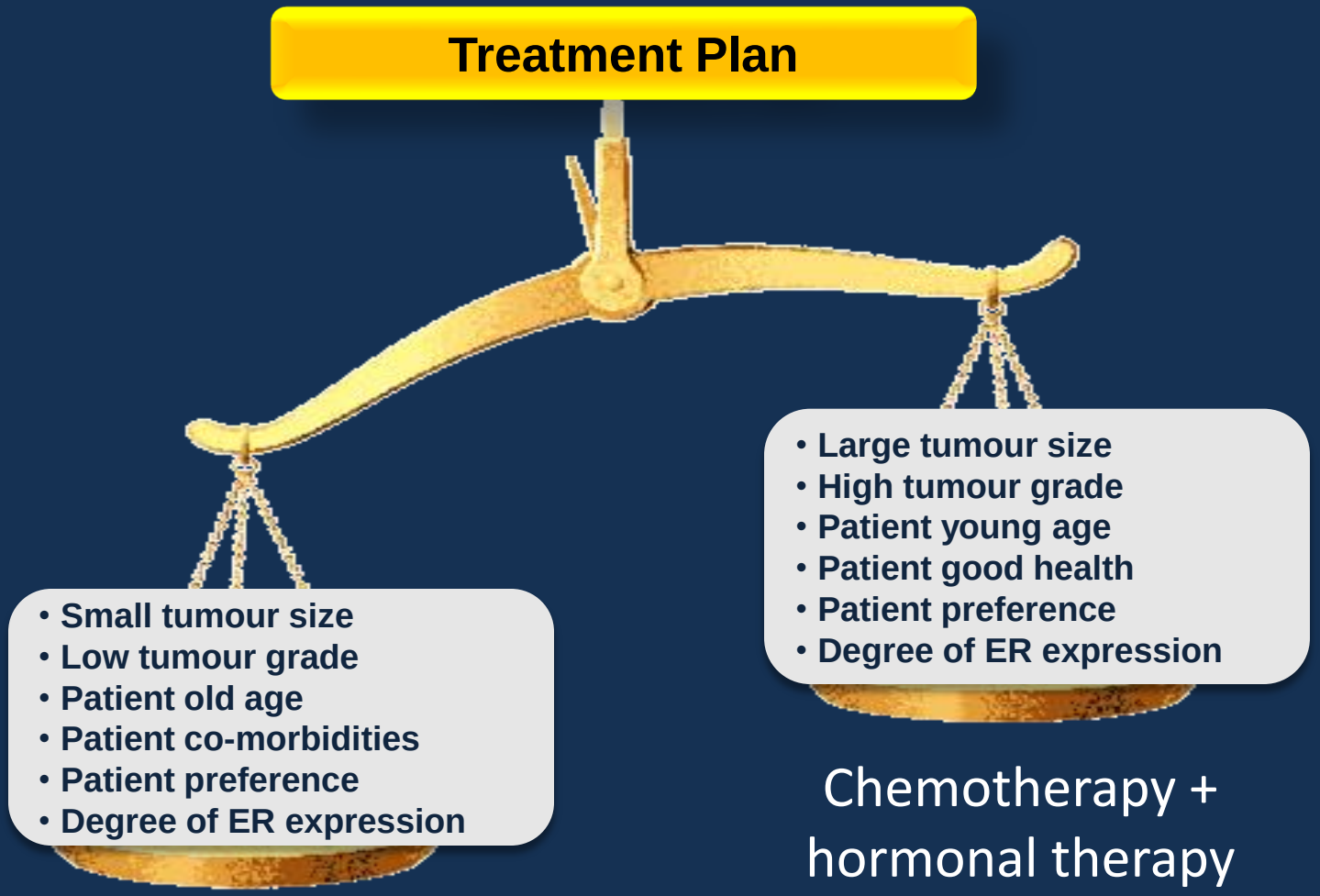
- Study of all of a person's genes (the genome), interactions of the genes with each other and with the environment
- Study of complex diseases such as heart disease, asthma, diabetes, and cancer because these diseases are typically caused more by a combination of genetic and environmental factors than by individual genes

Not all Patients Benefit from Adjuvant Chemotherapy



Walgren et al. JCO 2005;23:7342-7349

Many Factors Weigh into the Adjuvant Treatment Decision in ER+ BC



Current Standard Prognostication Tools

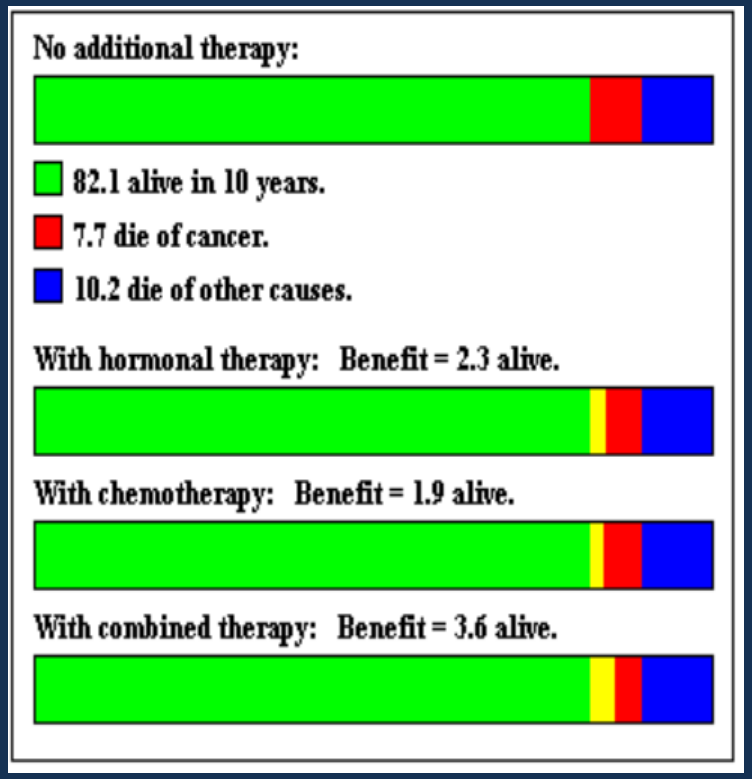
- Adjuvant! Online, the Nottingham Prognostic Index, and the AJCC staging system
  - Form the basis of many treatment guidelines (NIH Consensus Statement, St Gallen)
- Compare the patient question with the clinical trial average for similar patients with similar disease characteristics
  - Do not provide individual information about tumour biology
- Don’t address the fundamental question: who will benefit from therapy?

Adjuvant! Online

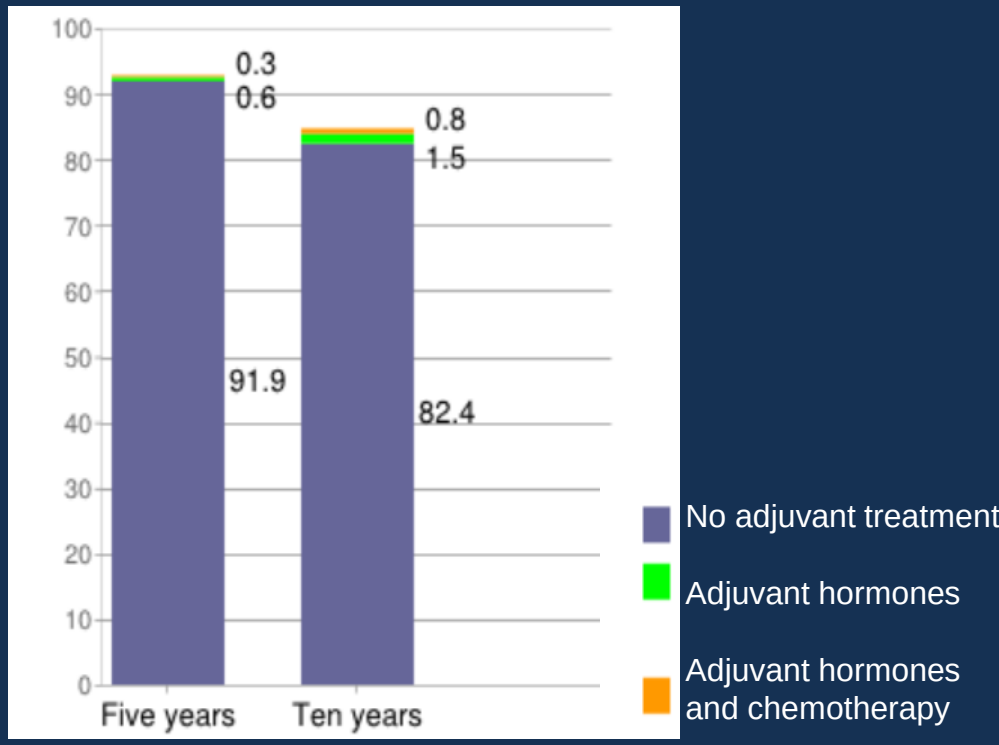
Decision making tools for health care professionals

PREDICT Tool:
Breast Cancer Survival

Patient A
68y, 1.1cm G2 IDCA, ER+ PR+ HER2-, LN-



Patient A
68y, 1.1cm G2 IDCA, ER+ PR+ HER2-, LN-



https://www.adjuvantonline.com/index.jsp Accessed 3 Sept 2014
Ravdin P et al. J Clin Oncol 2001;19:980-91
http://www.predict.nhs.uk/predict.html Accessed 3 Sept 2014

Nottingham Prognostic Index

The Nottingham Prognostic Index

The Nottingham Prognostic Index was calculated using the following formula: tumor size in cm x 0.2 + lymph-node stage (1, 2 or 3) + histologic grade (1, 2 or 3). When only node negative patients are analysed the lymph-node stage is 1 for all cases. The Nottingham "excellent prognosis" group was defined according to Galea et al. as those patients with an index value = 2.4 (ref).

Nottingham Prognostic Index	Score
Excellent prognosis group	<=2.4
Good prognosis group	<=3.4
Moderate prognosis group	>3.4 and <=5.4
Poor prognosis group	>5.4

Galea MH, Blamey RW, Elston CE, Ellis IO. The Nottingham Prognostic Index in primary breast cancer. Breast Cancer Research & Treatment 1992;22(3):207-19.

NPI calculator

Tumor size in cm

Histologic grade 1

Number of positive axillary lymph nodes 0

Calculate

Do all Genomic Tests Provide the Same Information?

Assay	Prognosis	Chemo Benefit	Clinical Validation Studies
Oncotype DX® Assay	✓	✓	• Paik et al.(2004), Habel et al.(2006), Goldstein et al (2008), Dowsett et al. (2009), Toi et al (2010), Mamounas et al (2012) • Paik et al.(2006); Albain et al.(2010)
MammaPrint®	✓		• Van De Vijiver et al.(1999); Buyse et al.(2006) • *Not validated to predict chemo benefit*
PAM50 ROR	✓		• Dowsett et al.(2011), Gnant et al 2013 (Post-Menopausal Patients) • *Not validated to predict chemo benefit*
EndoPredict®	✓		• Filipits et al. (2011); Martin et al.(2011) (Post-Menopausal Patients) • *Not validated to predict chemo benefit*

Courtesy of C. Markopoulos

The Oncotype DX® Assay
The Only Multi-gene Assay Incorporated into all Major Guidelines to Predict Adjuvant Chemotherapy Benefit in ER+, HER2- EBC

NCCN Guidelines® > 0.5 cm, node negative, N1mi, and in select patients with N+ 1-3 nodes	Quantifies risk of recurrence as a continuous variable and predicts responsiveness to both tamoxifen and chemotherapy1
ASCO® Guidelines Node negative	Predicts the risk of recurrence and may be used to identify patients likely to benefit from tamoxifen or chemotherapy[2]
ESMO Node negative	Provides additional prognostic and/or predictive information to complement pathology assessment and to predict response to adjuvant chemotherapy4
St Gallen Consensus Node negative, node positive	Provides not only prognostic but also predictive information regarding the utility of cytotoxic therapy in addition to endocrine therapy3
NICE Node negative	Recommended as an option for guidance of chemotherapy decisions in patients at intermediate risk* of distant recurrence4

1 NCCN Practice Guidelines in Oncology. V.3.2013.
2 Harris L, et al. *J Clin Oncol*. 2007.
3 Goldhirsch A, et al. *Ann Oncol*. 2013.
4 NICE Diagnostics Guidance 2013.

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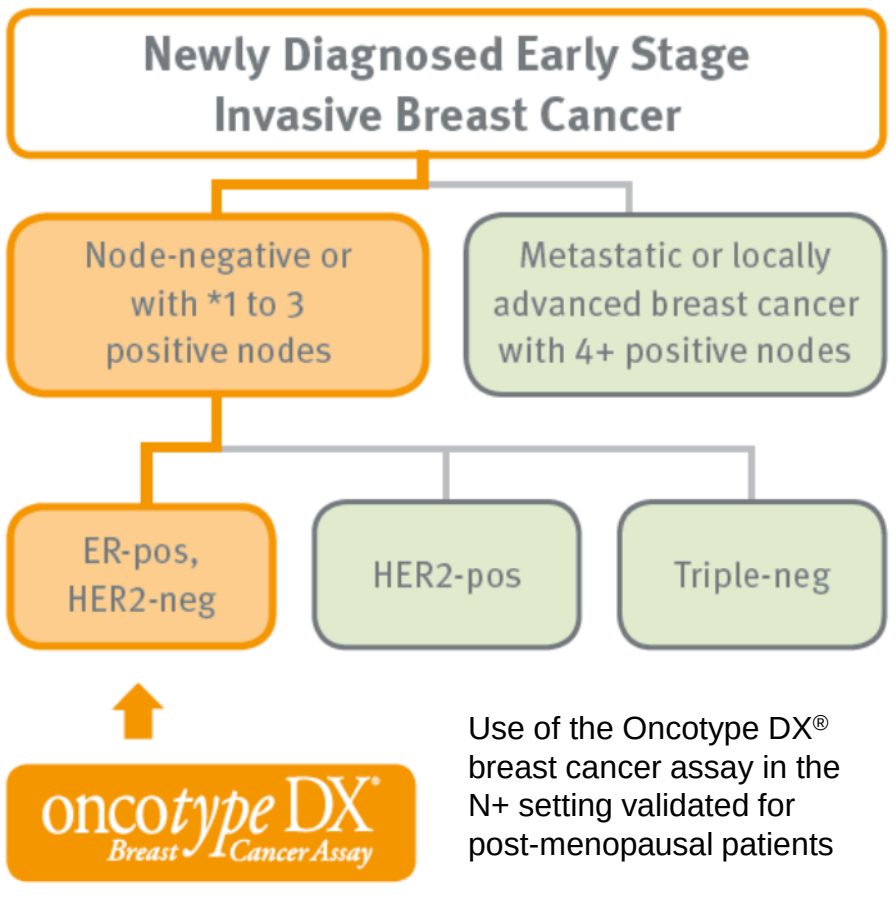
*Intermediate risk of distant recurrence is defined as NPI score ≥ 3.4 or at intermediate risk by other decision making tools or protocols

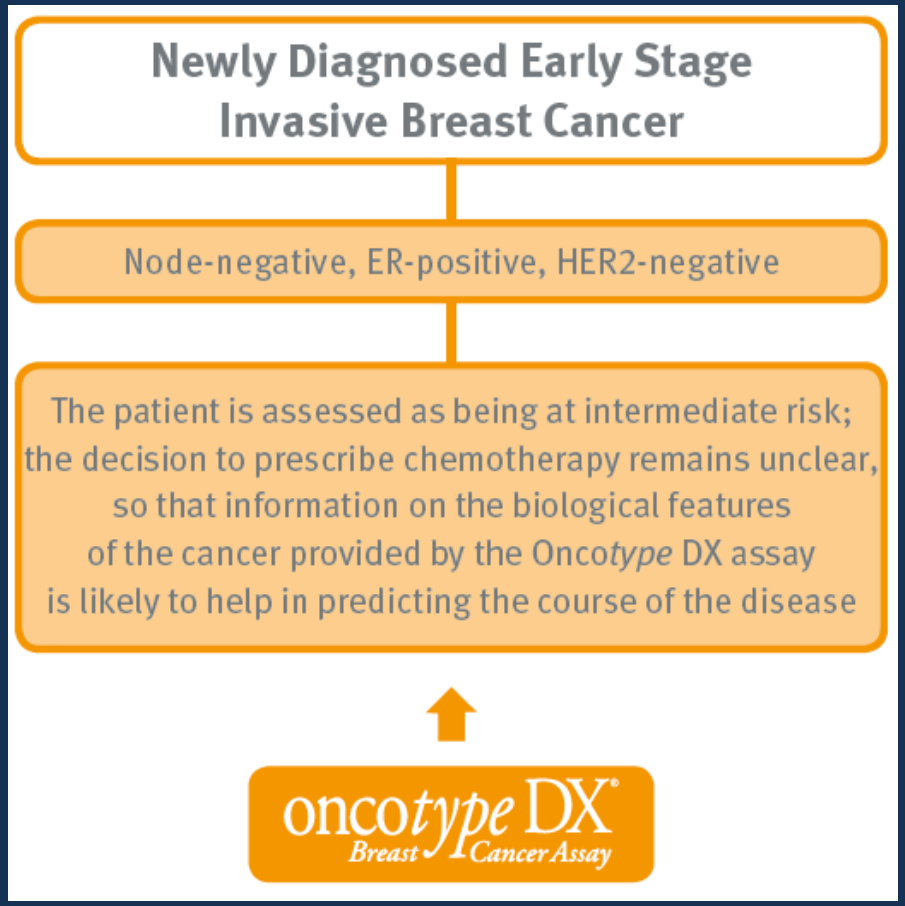
Which Patients may Benefit from the Oncotype DX® Test?

Clinical indication



Use of the Oncotype DX® breast cancer assay in the N+ setting validated for post-menopausal patients

NICE guidance



NICE guidance DG10. http://guidance.NICE.org.UK/DG10
Accessed 14 Jan 2014

ER: Oestrogen receptor
HER2: Human Epidermal Growth Factor Receptor 2

Oncotype DX® Breast Test

- 21 gene genomic test (16 tumour genes and 5 reference genes)[1]
- Uses RT-PCR technology performed on formalin fixed tissue obtained from the surgical specimen or biopsy[1]
- Diagnostic test that predicts the likely benefit of chemotherapy
- Provides prognostic information by quantitatively predicting the likelihood of breast cancer recurrence in women with newly diagnosed HR+ 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 4. NCCN Practice Guidelines in Oncology. V.3.2013.
5. Harris L, et al. *J Clin Oncol*. 2007. 6. Goldhirsch A, et al. *Ann Oncol*. 2013. 7. NICE Diagnostics Guidance DG10 2013.

The Oncotype DX® Assay Uses a Genomic Approach to Predict Recurrence Risk and Response to Adjuvant Therapy

16 Cancer and 5 Reference Genes From 3 Studies

PROLIFERATION
Ki-67
STK15
Survivin
Cyclin B1
MYBL2

OESTROGEN
ER
PR
Bcl2
SCUBE2

GSTM1

BAG1

CD68

INVASION
Stromelysin 3
Cathepsin L2

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	Recurrence Score® Result (0 -100)
Low risk	Recurrence Score result <18
Int risk	Recurrence Score result 18 - 30
High risk	Recurrence Score result ≥ 31

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

The Oncotype DX® Assay Process

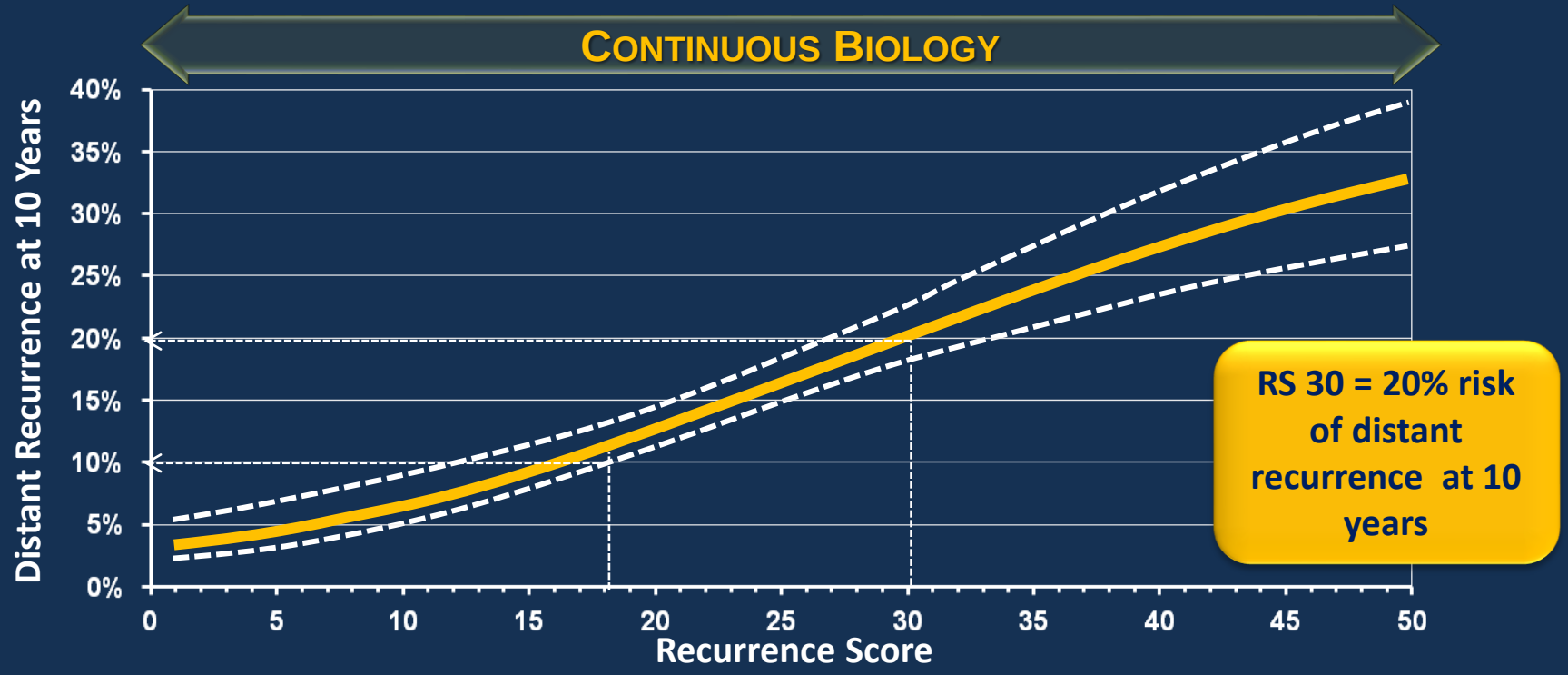
GHI has processed >500,000 tests from >70 countries; > 2,800 tests from the UK

ORDER ENTRY	SHIPPING	PATHOLOGY	ANALYTICAL LABORATORY	REPORT FULFILLMENT	MATERIAL RETURN
Online or Fax	Fax Request FedEx				FedEx
Order Entry	Specimen Retrieval	Pathology Review	Extraction	Results Generation	Report Delivery	Materials Return
	Specimen Accessioning	Histopath	Quantitation	Billing	Secure Online Portal	
			gDNA Detection			
			Reverse Transcription			
			QPCR			

10-14 working days

*Anderson JM et al, 2009.

The Precision of the Oncotype DX® Recurrence Score® Defines Individual Biology for ER Positive Breast Cancer



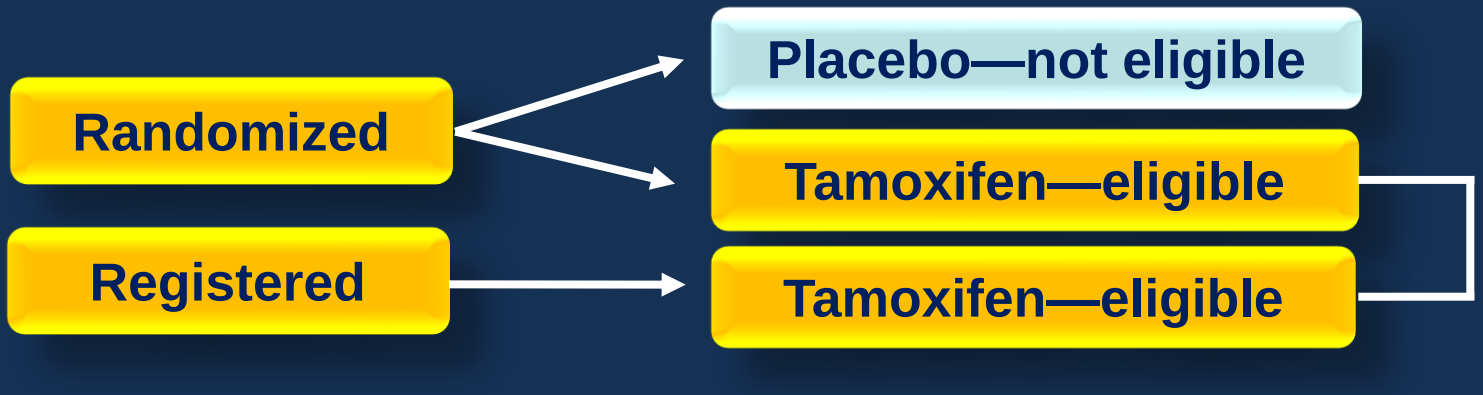
LOW RECURRENCE SCORE DISEASE
Indolent
Hormone Therapy Sensitive
Minimal, If Any, Chemotherapy Benefit

HIGH RECURRENCE SCORE DISEASE
Aggressive
Hormone Therapy Insensitive
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.

Oncotype DX® Clinical Validation in Node Negative Disease: NSABP B-14 Trial

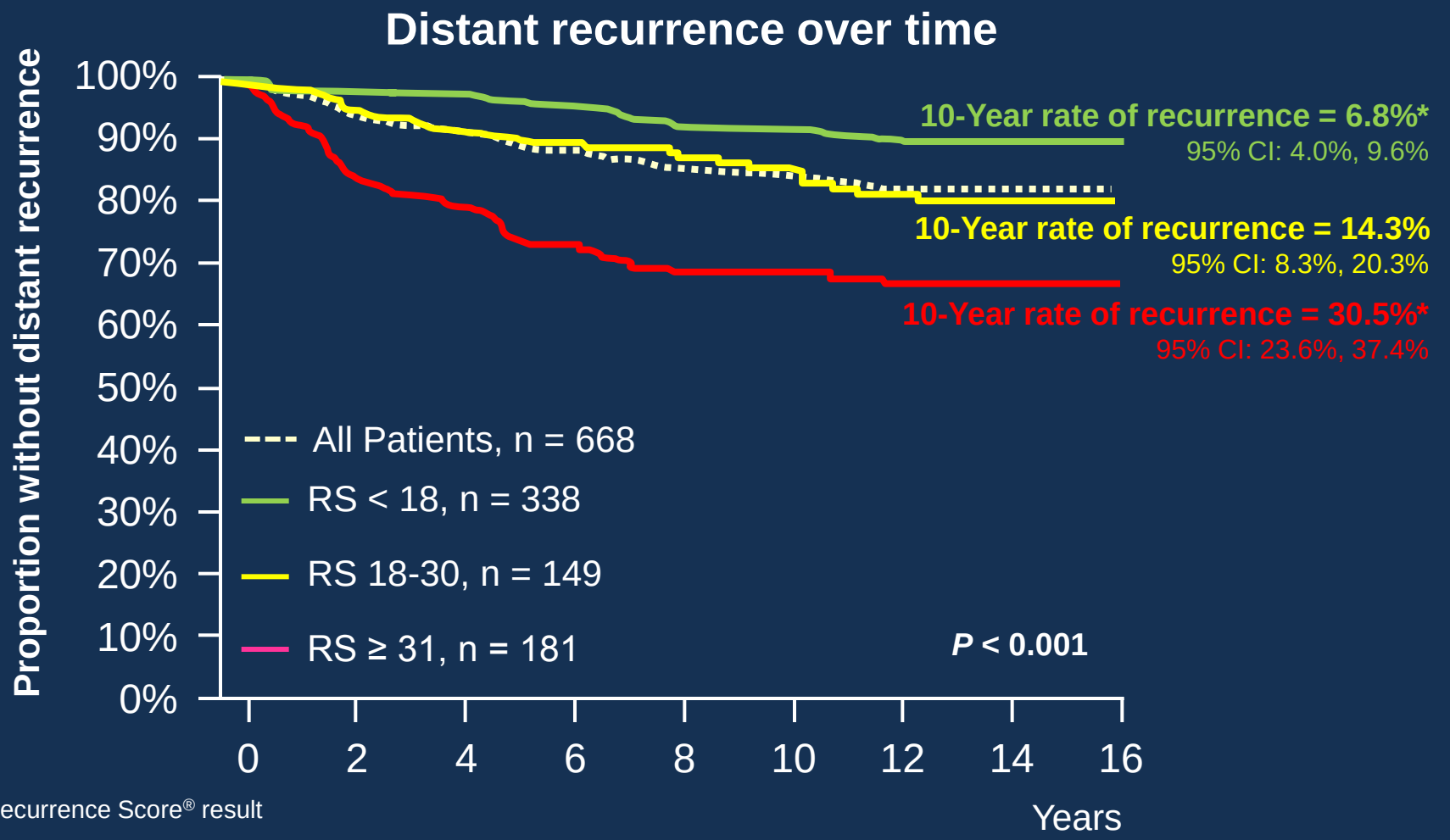
- Objective: Prospectively validate the Recurrence Score® result as a predictor of distant recurrence in node-negative, ER+ patients



- 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 Trial (n=668)



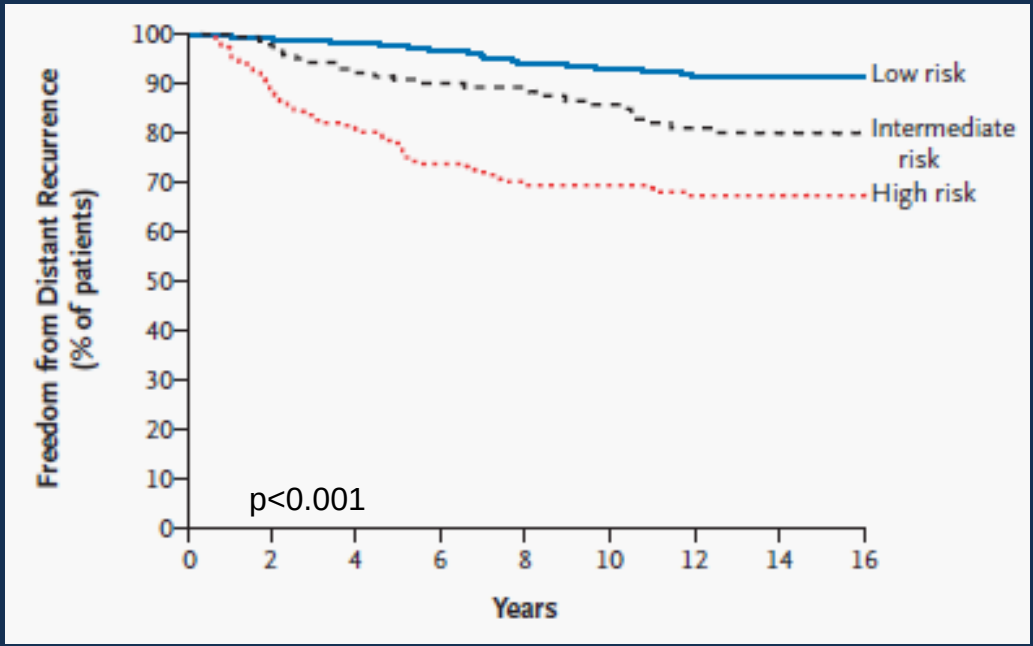
RS, Recurrence Score® result

*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.

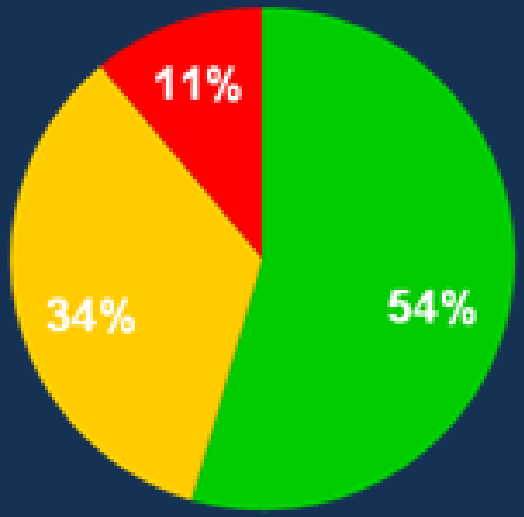
The Recurrence Score® Result Quantifies the Risk of Distant Recurrence (Prognosis)

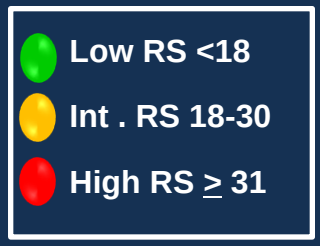
Likelihood of recurrence according to Recurrence Score categories[1]



28 recurrences in low risk group
25 in intermediate group
56 in high risk group

UK decision impact data[2]

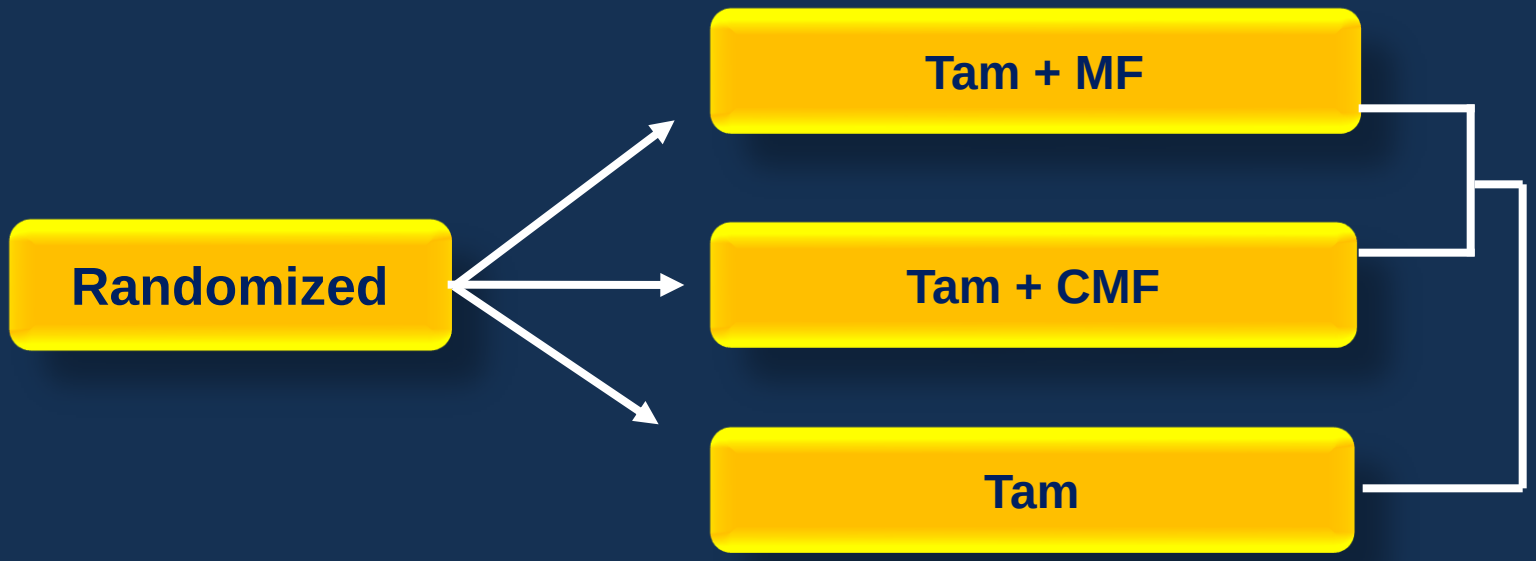




1. Paik et al. *N Engl J Med.* 2004;351:2817-2826
2. Holt S et al Br J Cancer 2013: 108(11):2250-8

Oncotype DX® Clinical Validation: NSABP B-20 Trial (n=651)

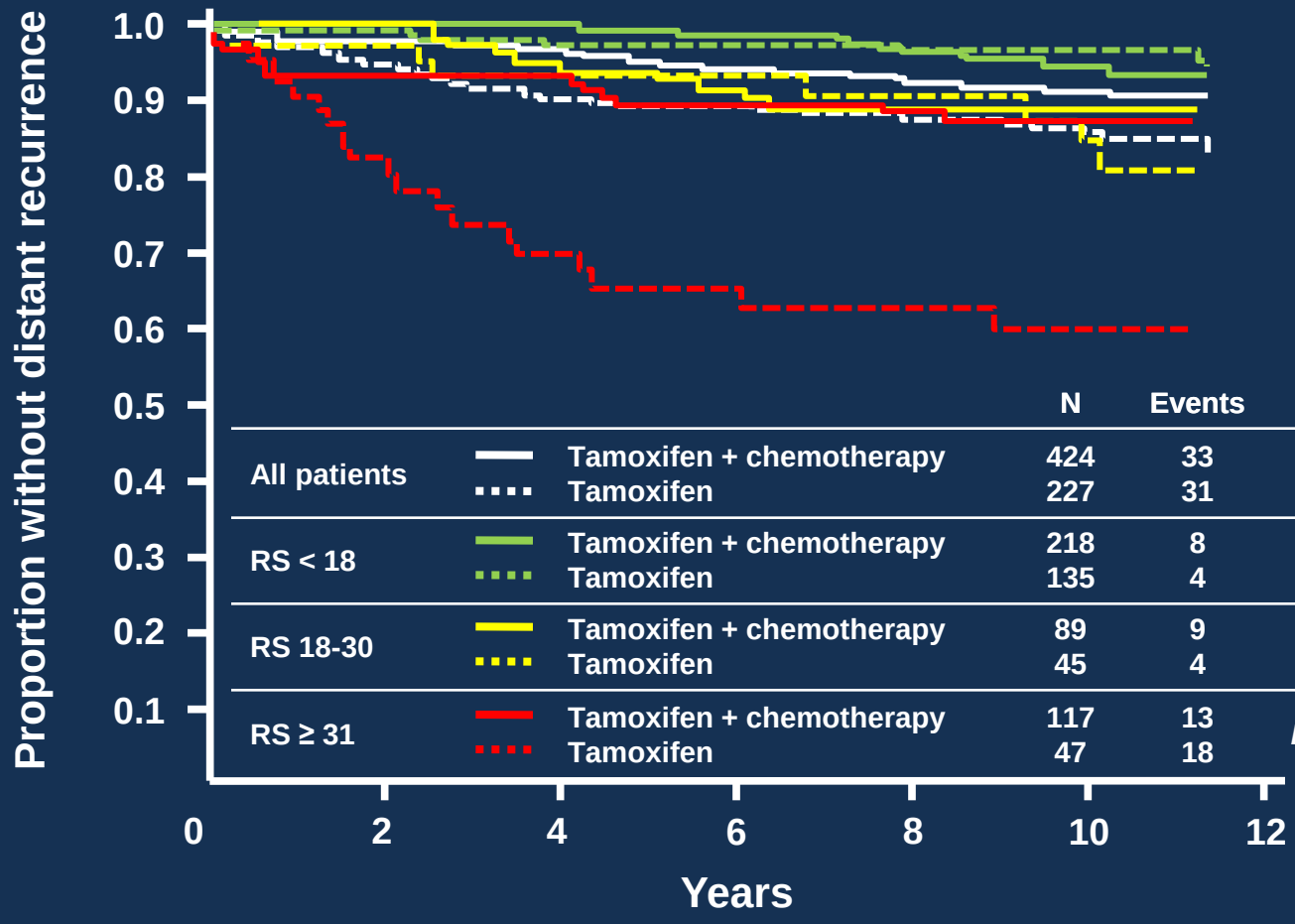
- Objective: Prospectively determine the relationship between Recurrence Score® result and chemotherapy benefit in node-negative, ER+ patients



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

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

Oncotype DX® Assay Was Predictive of Chemotherapy Benefit in the NSABP B-20



		N	Events	
All patients	Tamoxifen + chemotherapy	424	33	*P* = 0.02
	Tamoxifen	227	31	
RS < 18	Tamoxifen + chemotherapy	218	8	*P* = 0.61
	Tamoxifen	135	4	
RS 18-30	Tamoxifen + chemotherapy	89	9	*P* = 0.39
	Tamoxifen	45	4	
RS ≥ 31	Tamoxifen + chemotherapy	117	13	*P* < 0.001
	Tamoxifen	47	18	

PATIENTS WITH HIGH RS
28% absolute benefit from tamoxifen + chemotherapy

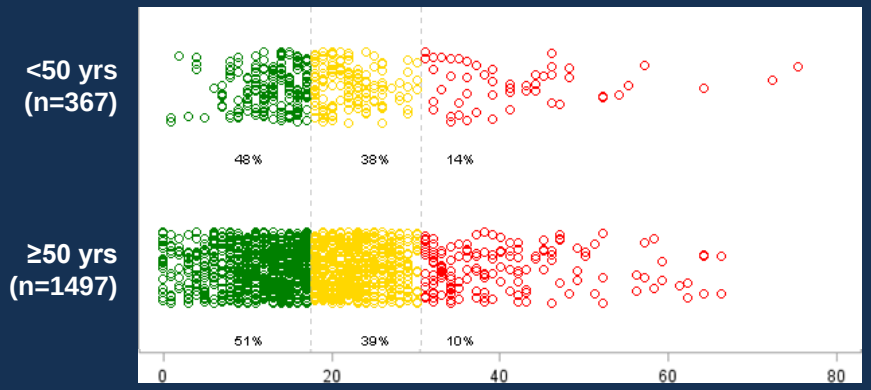
4.4% absolute benefit from tamoxifen + chemotherapy

RS, Recurrence Score result

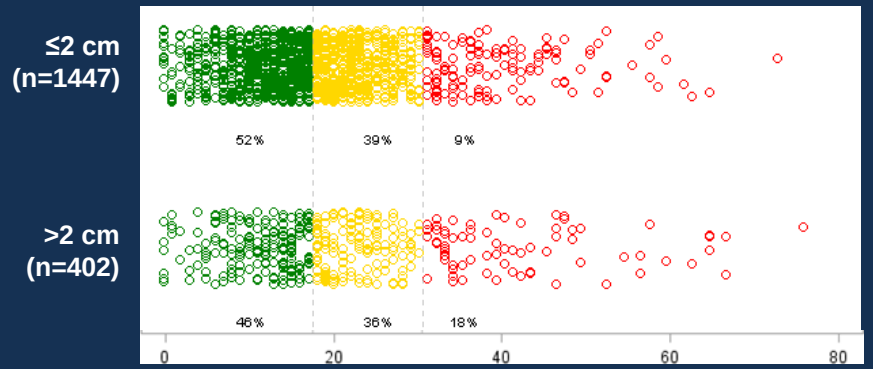
Paik S, et al. J Clin Oncol. 2006;24:3726-3734.

Clinical Experience Supports Findings from NSABP B-14 and NSABP B-20

RS Groups by Patient Age

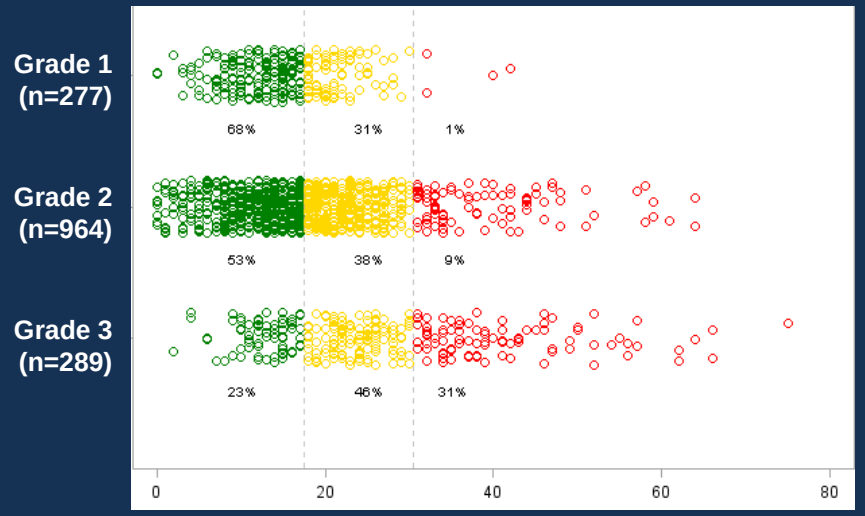


RS Groups by Tumor Size



- Small tumors have proportionately fewer high RS values.
- However, there is a range of RS values across both categories of tumor size.

RS Groups by Tumor Grade



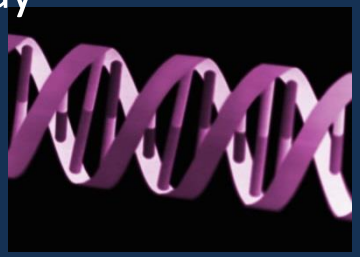
- Not all grade 1 tumors have low RS values.
- Only 31% of grade 3 tumors have high RS values.

Liebermann N, et al. ASCO 2011. Abstract 632 (poster presentation).

With Genomic Tools We Have a Deeper Understanding About Underlying Tumour Biology

1. Patient's tumour

2. Onco*type* DX® Assay



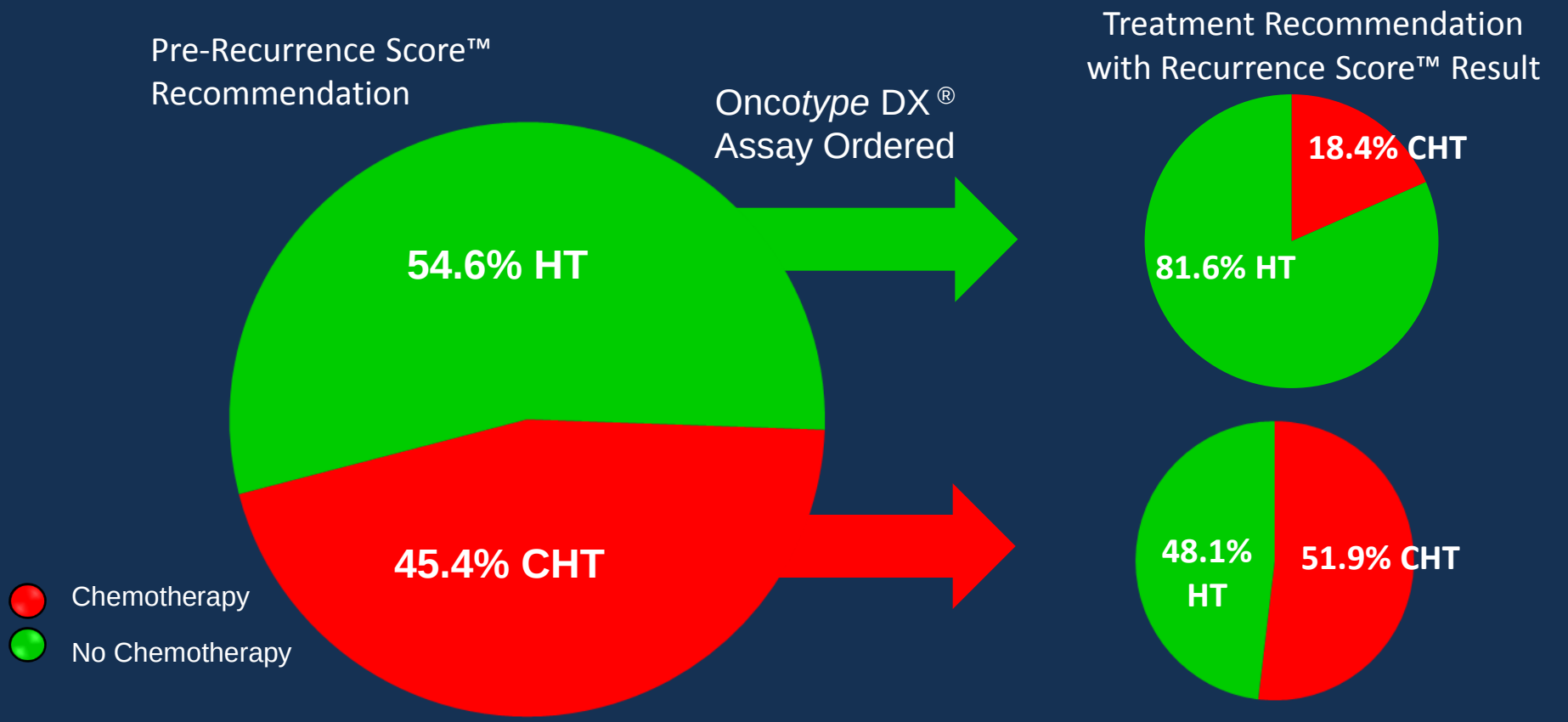
3. Analyze expression of tumour's genes

4. Onco*type* DX® Report

5. Shared Decision Making

Treatment recommendation changed in 31.9% of patients

(European meta-analysis, n=527 N0, ER+, EBC patients)

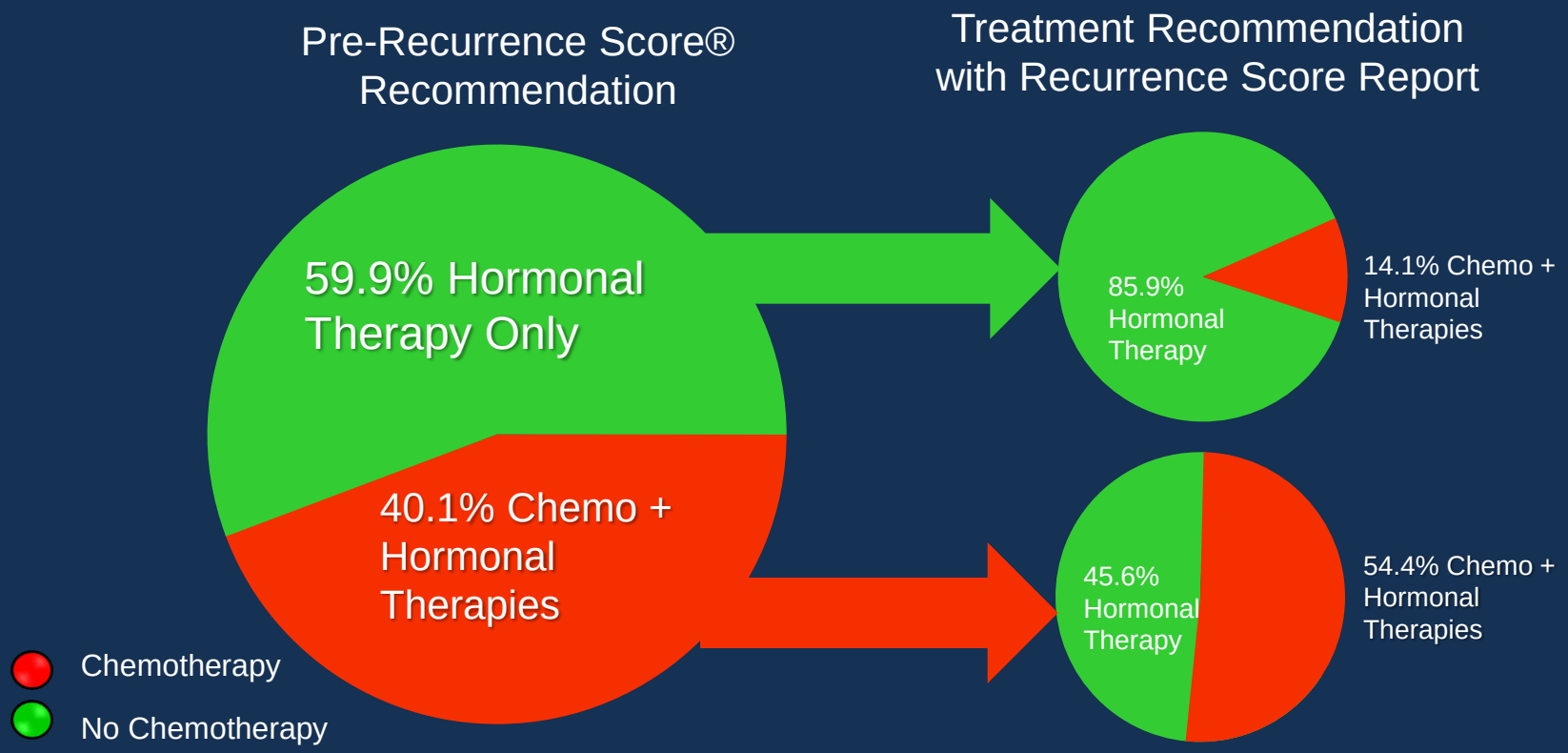


- **31.9%** of pts (95% CI: 27.9%-35.9%) had a recommendation change
- Proportion of pts recommended CHT decreased from 45.4% pre-Oncotype DX® assay to 33.6% post-Oncotype DX assay ($p<0.0001$ for McNemar's test)

Albanell et al. ESMO 2012. Abstract 252PD.

Treatment decision changed in 26.8% of patients after Oncotype DX®

Holt study (n=142), N0,1 ER+, EBC patients



Analysis based on 142 ER+ N- and N+ (micrometastatic) invasive breast cancer patients

Holt S et al. Br J Cancer 2013;08(11):2250-8

Experience with the Oncotype DX Assay in a UK Centre (n=67)

Chemotherapy treatment in relation to Oncotype Dx Recurrence Score Risk Category

	RS<18 n = 39	**RS 18-30** n = 19	**RS > 30** n = 9
No Chemo n = 44	37 (94%)	7 (37%)	0 (0%)
Chemo n=23	2 (6%)	12 (63%)	9 (100%)

- No patients with a RS <15 were given chemotherapy; only 2 patients with a RS < 18 received chemotherapy
- In this study there was a 66% reduction in the uptake of adjuvant chemotherapy in a population who would otherwise have been recommended chemotherapy

Armstrong A et al EBCC 2014

Consistent Cost Effectiveness with Oncotype DX® across Countries

Citation	Reported Findings (ICER in Cost per QALY gained with Oncotype DX)	Country Threshold (willingness to pay for 1 QALY)	Country	Comment
Davidson et al. 2013	CAD 6,630	CAD 75,000	Canada	✓**Cost Effective**
Lacey et al. 2011	EUR 9,462	EUR 20,000	Ireland	✓**Cost Effective**
Hall et al. 2011	GBP 5,529	GBP 20,000	UK	✓**Cost Effective**
Holt et al. 2011	GBP 6,232	GBP 20,000	UK	✓**Cost Effective**
Klang et al. 2010	USD 10,700	USD 35,000	Israel	✓**Cost Effective**
Kondo et al. 2010	USD 3,848	USD 50,000	Japan	✓**Cost Effective**
Lamond et al. 2012	CAD 9,591	CAD 75,000	Canada	✓**Cost Effective**
Madaras et al. 2011	EUR 9,730	EUR 12,600-25,300	Hungary	✓**Cost Effective**
O'Leary et al. 2010	AUS 9,986	AUS 18,000	Australia	✓**Cost Effective**
Paulden et al. 2011	>CAD 29,000	CAD 75,000	Canada	✓**Cost Effective**
Tsoi et al. 2010	CAD 63,421	CAD 75,000	Canada	✓**Cost Effective**
Vanderlaan et al. 2011	Improved outcomes (QALYs) Reduced costs		USA	✓**Cost Saving**
De Lima Lopez et al. 2011			Singapore	✓**Cost Saving**
Cosler et al. 2009			USA	✓**Cost Saving**
Blohmer et al. 2012			Germany	✓**Cost Saving**
Valtaire et al. 2012			France	✓**Cost Saving**
Hornberger et al. 2011			USA	✓**Cost Saving**
Hornberger et al. 2005			USA	✓**Cost Saving**
Lyman et al. 2007			USA	✓**Cost Saving**

How can Patients Currently Access the Oncoype DX Breast Assay in the UK?

- As of April 1, 2015, the Oncotype DX test became available through an access scheme, as an option to help National Health Service (NHS) clinicians in England decide whether to prescribe chemotherapy in people with early-stage breast cancer. Genomic Health UK is working with local trusts to provide equitable access for patients throughout the country through the scheme.

- Private health insurers in the UK will reimburse the Oncotype DX breast assay (by pre-authorisation)

- If a patient wishes to pay for the assay, he or she can do so. Genomic Health has a payment scheme to help patients pay for the assay. To find out more about payment options, please contact Genomic Health Customer Service on :

  020 3031 8087 Europeansupport@genomichealth.com

Questions on patient access to the Oncotype DX assay

- Does the company that supplies Oncotype DX have provision to offer the test on a case by case basis? Yes. We have representatives across the UK and they can facilitate all requests. Call Customer Service on 020 3031 8087 for details.
- What is the future provision going to be? We are working hard and with NHS to achieve equal access for eligible patients across England and the rest of the UK
- What is happening in Scotland and Wales? Oncotype DX assay is available in parts of Wales and ongoing work with Health Boards in the other parts. Working with NHS Scotland and hoping available soon but at the moment it is available in the private sector and self pay only. In N Ireland, situation similar to Scotland

Conclusions

- Recurrence Score® results reflects individual tumour biology
- The risk of distant recurrence or chemotherapy benefit can't be accurately predicted by relying on conventional tools alone
- Oncotype DX is the only assay demonstrated to be predictive of benefit from chemotherapy allowing chemotherapy to be given to those most likely to benefit[2,3] (Level I Evidence)
- Only assay incorporated into ASCO®, NCCN® , ESMO, St Gallen and NICE guidelines
- More than 500,000 patients tested to date worldwide, with ~5,000 patients tested in the UK by June 2014
- Oncotype DX® was shown to be consistently cost effective across different countries and is expected to generate cost savings

ASCO is a trademark of the American Society of Clinical Oncology and NCCN is a trademark of the National Comprehensive Cancer Network.
ASCO and NCCN do not endorse any therapy or product.

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 4. NCCN Practice Guidelines in Oncology. V.3.2013. 5. Harris L, et al. *J Clin Oncol*. 2007. 6. Goldhirsch A, et al. *Ann Oncol*. 2013. 7. NICE Diagnostics Guidance DG10 2013.

Reinventing the Staging of Cancer

INVASIVE BREAST CANCER

110,000 U.S. Patients
240,000 Int'l Patients

DCIS BREAST CANCER

50,000 U.S. Patients
100,000 Int'l Patients

STAGE II/III COLON CANCER

20,000 U.S. Patients
80,000 Int'l Patients

PROSTATE CANCER

250,000 U.S. Patients
460,000 Int'l Patients

oncotype DX®

Patient Cases

Can You Guess the Recurrence Score®?

68 & 69 year-old patients, small node-negative tumors, grade 2 & 3

PATIENT A

68-year-old patient with 1.1-cm tumor

Menopausal Status: Postmenopausal
Tumor Type: Infiltrating Ductal Carcinoma (IDC)
Tumor Size: 1.1 cm
ER Status (IHC): Positive
PR Status (IHC): Positive
HER2/neu Status: Negative
Histologic Grade: 2
Lymph Node Status: Negative
General Health: Fair

CASE SUBMITTED BY:

Victor G. Vogel, MD

PATIENT B

69-year-old patient with 1.3-cm tumor

Menopausal Status: Postmenopausal
Tumor Type: Infiltrating Ductal Carcinoma (IDC)
Tumor Size: 1.3 cm
ER Status (IHC): Positive (2)
PR Status (IHC): Positive (2)
HER2/neu Status: Negative (IHC)
Histologic Grade: 3
Lymph Node Status: Negative
General Health: PS 0

CASE SUBMITTED BY:

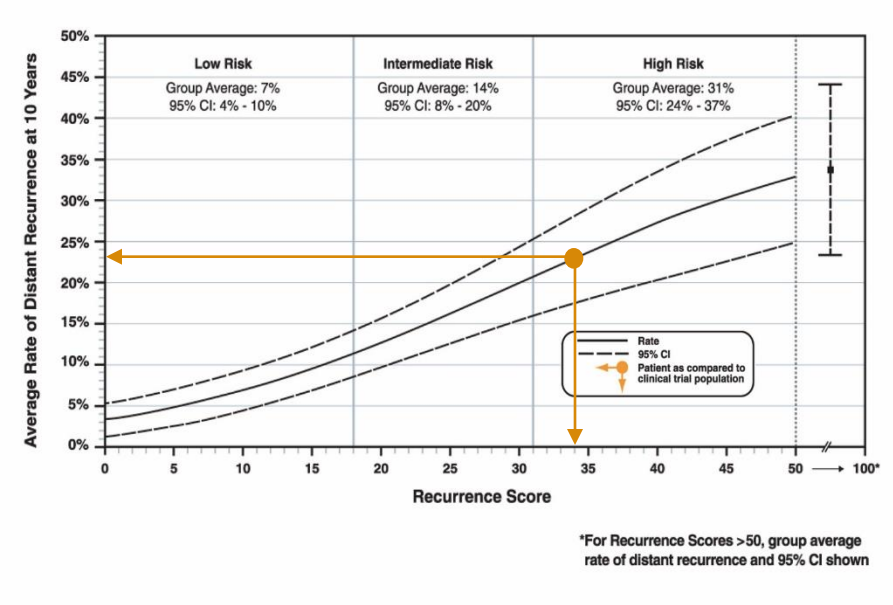
Ella Tepper, MD

Can You Guess the Recurrence Score®?

68 & 69 year-old patients, small node-negative tumors, grade 2 & 3

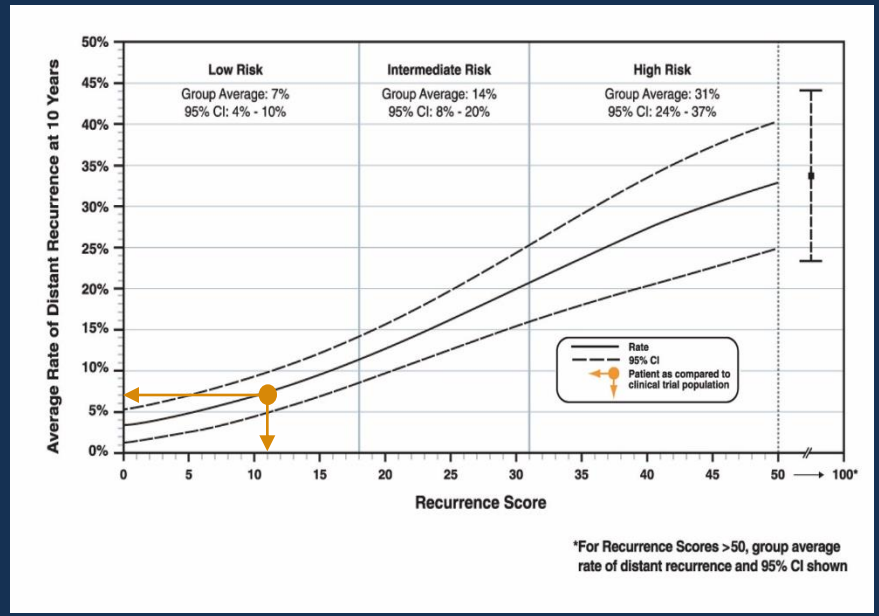
PATIENT A RESULTS
Clinical Experience

Patients with a Recurrence Score of **34** in the clinical validation study had an Average Rate of Distant Recurrence at 10 years of **23% (95% CI: 18%-28%).**



PATIENT B RESULTS
Clinical Experience

Patients with a Recurrence Score of **11** in the clinical validation study had an Average Rate of Distant Recurrence at 10 years of **7% (95% CI: 5%-10%).**



Can You Guess the Recurrence Score®?

45 & 46 year-old patients, small node-negative tumors, grade 2 & 3

PATIENT A

45-year-old patient with 0.9-cm tumor

Menopausal Status: Premenopausal
Tumor Type: Infiltrating Ductal Carcinoma (IDC)
Tumor Size: 0.9 cm
ER Status (IHC): Positive (99%)
PR Status (IHC): Positive (13%)
HER2/neu Status: Negative (1.7 by FISH)
Ki-67: 38%
Histologic Grade: 2
Lymph Node Status: Negative (0/2 SLNs)

CASE SUBMITTED BY:

Barbara Schwartzberg, MD

PATIENT B

46-year-old patient with 0.7-cm tumor

Menopausal Status: Premenopausal
Tumor Type: Infiltrating Ductal Carcinoma (IDC)
Tumor Size: 0.7 cm
ER Status (IHC): Positive (91%)
PR Status (IHC): Positive (99%)
HER2/neu Status: Negative (0.7 by FISH)
Ki-67: 35%
Histologic Grade: 3
Lymph Node Status: Negative

CASE SUBMITTED BY:

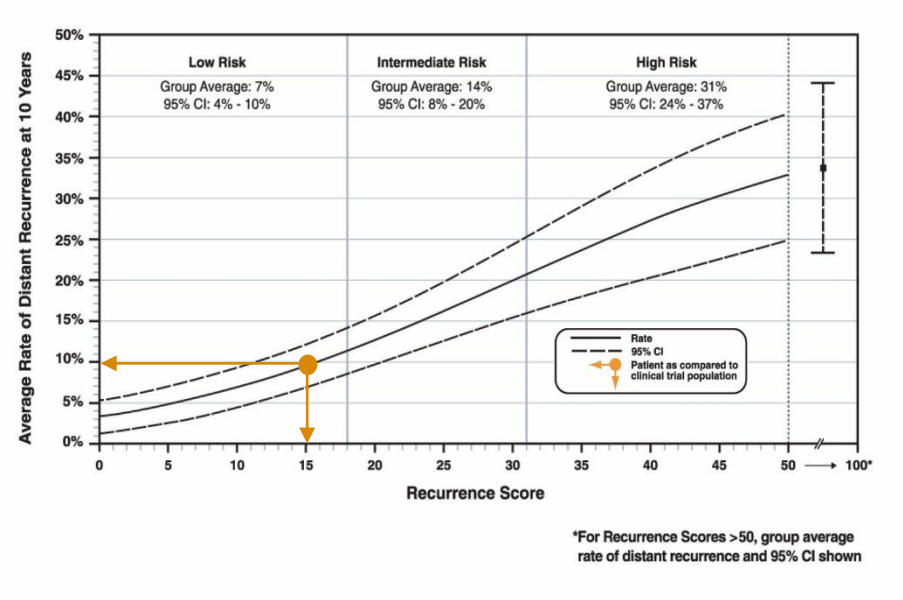
Barbara Schwartzberg, MD

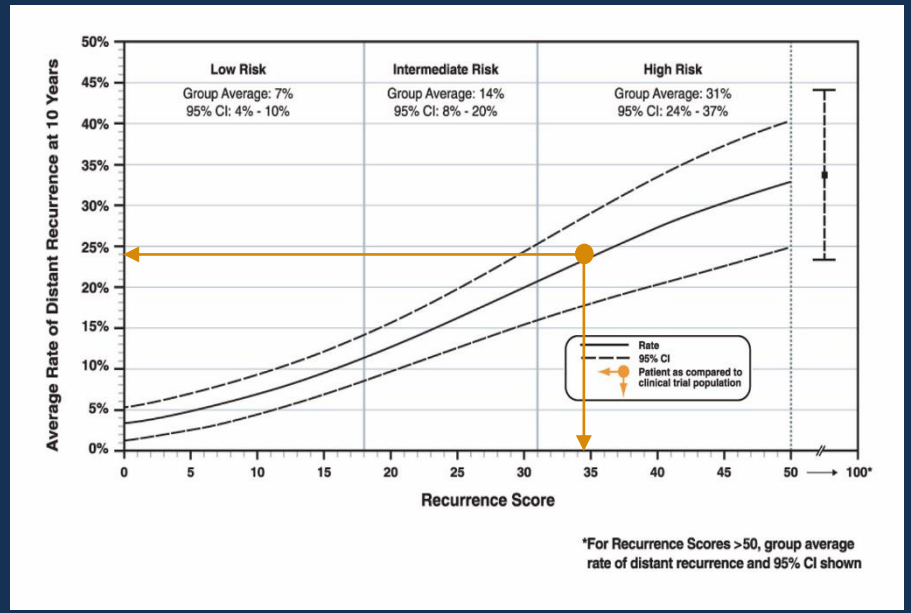
Can You Guess the Recurrence Score®?

45 & 46 year-old patients, small node-negative tumors, grade 2 & 3

PATIENT A RESULTS
Clinical Experience

Patients with a Recurrence Score of **15** in the clinical validation study had an Average Rate of Distant Recurrence at 10 years of **10% (95% CI: 7%-12%)**.



PATIENT B RESULTS
Clinical Experience

Patients with a Recurrence Score of **35** in the clinical validation study had an Average Rate of Distant Recurrence at 10 years of **24% (95% CI: 18%-30%)**.