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: 20$^{\text{th}}$ and 21$^{\text{st}}$ 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

Treatment Plan

- Small tumour size
- Low tumour grade
- Patient old age
- Patient co-morbidities
- Patient preference
- Degree of ER expression

- Large tumour size
- High tumour grade
- Patient young age
- Patient good health
- Patient preference
- Degree of ER expression

Chemotherapy + hormonal therapy

Endocrine therapy only
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?
Patient A
68y, 1.1cm G2 IDCA, ER+ PR+ HER2-, LN-

No additional therapy:
- 82.1 alive in 10 years.
- 7.7 die of cancer.
- 10.2 die of other causes.

With hormonal therapy: Benefit = 2.3 alive.

With chemotherapy: Benefit = 1.9 alive.

With combined therapy: Benefit = 3.6 alive.

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).

<table>
<thead>
<tr>
<th>Nottingham Prognostic Index</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent prognosis group</td>
<td>&lt;=2.4</td>
</tr>
<tr>
<td>Good prognosis group</td>
<td>&lt;=3.4</td>
</tr>
<tr>
<td>Moderate prognosis group</td>
<td>&gt;3.4 and &lt;=5.4</td>
</tr>
<tr>
<td>Poor prognosis group</td>
<td>&gt;5.4</td>
</tr>
</tbody>
</table>


NPI calculator

Tumor size in cm
Histologic grade
Number of positive axillary lymph nodes

Calculate
<table>
<thead>
<tr>
<th>Assay</th>
<th>Prognosis</th>
<th>Chemo Benefit</th>
<th>Clinical Validation Studies</th>
</tr>
</thead>
</table>
| **Oncotype DX® Assay** | ![Checkmark](image) | ![Checkmark](image) | • 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®**    | ![Checkmark](image) |               | • Van De Vijiver et al.(1999); Buyse et al.(2006)                                          |
|                    |           |               | • *Not validated to predict chemo benefit*                                                  |
| **PAM50 ROR**      | ![Checkmark](image) |               | • Dowsett et al.(2011), Gnant et al 2013 (Post-Menopausal Patients)                         |
|                    |           |               | • *Not validated to predict chemo benefit*                                                  |
| **EndoPredict®**   | ![Checkmark](image) |               | • Filipits et al. (2011); Martin et al.(2011) (Post-Menopausal Patients)                    |
|                    |           |               | • *Not validated to predict chemo benefit*                                                  |

* Courtesy of C. Markopoulos*
### The Onco
type DX® Assay
The Only Multi-gene Assay Incorporated into all Major Guidelines to Predict Adjuvant Chemotherapy Benefit in ER+, HER2- EBC

<table>
<thead>
<tr>
<th><strong>NCCN Guidelines®</strong></th>
<th><strong>ASCO® Guidelines</strong></th>
<th><strong>ESMO</strong></th>
<th><strong>St Gallen Consensus</strong></th>
<th><strong>NICE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 0.5 cm, node negative, N1mi, and in select patients with N+ 1-3 nodes</td>
<td>Predicts the risk of recurrence and may be used to identify patients likely to benefit from tamoxifen or chemotherapy²</td>
<td>Provides additional prognostic and/or predictive information to complement pathology assessment and to predict response to adjuvant chemotherapy⁴</td>
<td>Provides not only prognostic but also predictive information regarding the utility of cytotoxic therapy in addition to endocrine therapy³</td>
<td>Recommended as an option for guidance of chemotherapy decisions in patients at intermediate risk* of distant recurrence⁴</td>
</tr>
</tbody>
</table>

4 NICE Diagnostics Guidance 2013.

---

ASCO is a trademark of the American Society of Clinical Oncology. NCCN and NCCN Guidelines are trademarks of the National Comprehensive Cancer Network. The guidelines do not endorse products or therapies.

*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**

Newly Diagnosed Early Stage Invasive Breast Cancer

- Node-negative or with 1 to 3 positive nodes
- Metastatic or locally advanced breast cancer with 4+ positive nodes
- ER-pos, HER2-neg
  - HER2-pos
  - Triple-neg

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

**NICE guidance**

Newly Diagnosed Early Stage Invasive Breast Cancer

- Node-negative, ER-positive, HER2-negative

The patient is assessed as being at intermediate risk; the decision to prescribe chemotherapy remains unclear, so that information on the biological features of the cancer provided by the Oncotype DX assay is likely to help in predicting the course of the disease

Accessed 14 Jan 2014

ER: Oestrogen receptor
HER2: Human Epidermal Growth Factor Receptor 2
Onco
type 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 biopsy¹

• 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 EBC²,³

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

**INVASION**
- Stromelysin 3
- Cathepsin L2

**CD68**

**HER2**
- GRB7
- HER2

**GSTM1**

**BAG1**

**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

<table>
<thead>
<tr>
<th>Category</th>
<th>Recurrence Score® Result (0 -100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Recurrence Score result &lt;18</td>
</tr>
<tr>
<td>Int risk</td>
<td>Recurrence Score result 18 - 30</td>
</tr>
<tr>
<td>High risk</td>
<td>Recurrence Score result ≥ 31</td>
</tr>
</tbody>
</table>

The Oncotype DX® Assay Process

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

ORDER ENTRY
- Online or Fax
  - Order Entry
  - Fax Request FedEx

SHIPPING
- Fax Request FedEx
  - Specimen Retrieval
  - Specimen Accessioning

PATHOLOGY
- Pathology Review
  - Histopath

ANALYTICAL LABORATORY
- Extraction
  - Quantitation
  - gDNA Detection
  - Reverse Transcription
  - QPCR

REPORT FULFILLMENT
- Results Generation
  - Report Delivery
  - Materials Return

MATERIAL RETURN
- FedEx
  - Secure Online Portal

10-14 working days

*Anderson JM et al, 2009.*
The Precision of the Onco\textit{type} 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

RS 30 = 20% risk of distant recurrence at 10 years

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

Onco\textit{type} DX® Clinical Validation: NSABP B-14 Trial (n=668)

Distant recurrence over time

- **10-Year rate of recurrence = 6.8%**
  - 95% CI: 4.0%, 9.6%

- **10-Year rate of recurrence = 14.3%**
  - 95% CI: 8.3%, 20.3%

- **10-Year rate of recurrence = 30.5%**
  - 95% CI: 23.6%, 37.4%

RS, Recurrence Score® result

*10-Year distant recurrence comparison between low- and high-risk groups: \( P < 0.001 \)

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

Likelihood of recurrence according to Recurrence Score categories¹

- Low RS <18
- Intermediate RS 18-30
- High RS > 31

UK decision impact data²

- 11% Low RS <18
- 34% Int. RS 18-30
- 54% High RS > 31

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

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.

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

Randomized

Tam + MF

Tam + CMF

Tam

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

RS, Recurrence Score result

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

RS Groups by Patient Age

- <50 yrs (n=367)
- ≥50 yrs (n=1497)

RS Groups by Tumor Size

- ≤2 cm (n=1447)
- >2 cm (n=402)

RS Groups by Tumor Grade

- Grade 1 (n=277)
- Grade 2 (n=964)
- Grade 3 (n=289)

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

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

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

1. Patient’s tumour

2. Oncotype DX® Assay

3. Analyze expression of tumour’s genes

4. Oncotype DX® Report

5. Shared Decision Making
31.9% of pts (95% CI: 27.9%-35.9%) had a recommendation change

Proportion of pts recommended CHT decreased from 45.4% pre-Onco
type DX® assay to 33.6% post-Onco
type 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

Pre-Recurrence Score® Recommendation

- 59.9% Hormonal Therapy Only
- 40.1% Chemo + Hormonal Therapies

Treatment Recommendation with Recurrence Score Report

- 85.9% Hormonal Therapy
- 14.1% Chemo + Hormonal Therapies
- 45.6% Hormonal Therapy
- 54.4% Chemo + Hormonal Therapies

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

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

Chemotherapy treatment in relation to Oncotype Dx Recurrence Score Risk Category

<table>
<thead>
<tr>
<th></th>
<th>RS&lt;18 n = 39</th>
<th>RS 18-30 n = 19</th>
<th>RS &gt; 30 n = 9</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No Chemo</strong></td>
<td>37 (94%)</td>
<td>7 (37%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>n = 44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chemo</strong></td>
<td>2 (6%)</td>
<td>12 (63%)</td>
<td>9 (100%)</td>
</tr>
<tr>
<td>n=23</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 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.
## Consistent Cost Effectiveness with OncoType DX® across Countries

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

Reinventing the Staging of Cancer

Do I need surgery?

Do I need chemotherapy?

Do I have aggressive disease?

INVASIVE BREAST CANCER

DCIS BREAST CANCER

STAGE II/III COLON CANCER

PROSTATE CANCER

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

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

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

250,000 U.S. Patients
460,000 Int’l Patients
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)

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%).