ASSESSMENT OF RECURRENCE RISK IN EARLY BREAST CANCER:
Clinicopathologic and molecular prognosticators

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INTRODUCTION
Faculty

Christos Sotiriou  Giuseppe Curigliano  Carmen Criscitiello
INTRODUCTION

Programme

Introduction and Welcome
Christos Sotiriou

Assessment of recurrence risk in early breast cancer: Clinicopathologic and molecular prognosticators
Christos Sotiriou

Communicating breast cancer recurrence risk to patients: how to optimally navigate facts, unknowns and perceptions
Giuseppe Curigliano

Patient-Physician shared decision making and patient support- Case studies for practical tips and tricks
Carmen Criscitiello

Q&A
All faculty
INTRODUCTION

Learning Objectives

- To obtain expert insights on the clinicopathologic and molecular prognosticator tools available to date for the assessment of recurrence risk in patients with early breast cancer

- To be informed on principles of optimal physician-patient communication on recurrence risk and explanation of treatment strategies

- To enrich experiences on communication with, and support of patients via illustrative case studies and expert insights
Our decision - chemo no chemo – for ER+/HER2- breast cancer was based mainly on prognosis...
Nottingham Prognostic Index

NPI = (0.2 x T) + N + Grade

Prognostic information

Stage
Biology

Age, T, N, grade, ER, PR, HER2, Ki67
Gene **prognostic** signatures

C Sotiriou & L Pusztai, NEJM 2009
First gene expression **prognostic signature** in breast cancer: *All comers!*

The Amsterdam signature (70-gene signature)

Amsterdam signature **validation series** (295 patients)

Van’t Veer LJ et al., Nature 2002

Van de Vijver et al., NEJM 2002

**Table 1. Association between clinical characteristics and the Prognosis Signature.**

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>POOR-PROGNOSIS SIGNATURE (N=180)</th>
<th>GOOD-PROGNOSIS SIGNATURE (N=115)</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;40 yr</td>
<td>52 (29)</td>
<td>11 (10)</td>
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<tr>
<td>40–44 yr</td>
<td>41 (23)</td>
<td>44 (38)</td>
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<tr>
<td>45–49 yr</td>
<td>55 (31)</td>
<td>43 (37)</td>
<td></td>
</tr>
<tr>
<td>≥50 yr</td>
<td>32 (18)</td>
<td>17 (15)</td>
<td></td>
</tr>
<tr>
<td>No. of positive nodes</td>
<td>91 (51)</td>
<td>60 (52)</td>
<td>0.60</td>
</tr>
<tr>
<td>0</td>
<td>63 (35)</td>
<td>48 (37)</td>
<td></td>
</tr>
<tr>
<td>1–3</td>
<td>26 (14)</td>
<td>12 (10)</td>
<td></td>
</tr>
<tr>
<td>≥4</td>
<td>84 (47)</td>
<td>71 (62)</td>
<td>0.012</td>
</tr>
<tr>
<td>Tumor diameter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 mm</td>
<td>96 (53)</td>
<td>44 (38)</td>
<td></td>
</tr>
<tr>
<td>≥20 mm</td>
<td>84 (47)</td>
<td>71 (62)</td>
<td></td>
</tr>
<tr>
<td>Histologic grade</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>I (good)</td>
<td>19 (11)</td>
<td>56 (49)</td>
<td></td>
</tr>
<tr>
<td>II (intermediate)</td>
<td>56 (31)</td>
<td>45 (39)</td>
<td></td>
</tr>
<tr>
<td>III (poor)</td>
<td>105 (58)</td>
<td>14 (12)</td>
<td></td>
</tr>
<tr>
<td>Vascular invasion</td>
<td></td>
<td></td>
<td>0.38</td>
</tr>
<tr>
<td>Absent</td>
<td>108 (60)</td>
<td>77 (67)</td>
<td></td>
</tr>
<tr>
<td>1–3 Vessels</td>
<td>18 (10)</td>
<td>12 (10)</td>
<td></td>
</tr>
<tr>
<td>4+ Vessels</td>
<td>54 (30)</td>
<td>26 (23)</td>
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<tr>
<td>Estrogen receptor status</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Negative</td>
<td>66 (37)</td>
<td>3 (3)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>114 (63)</td>
<td>112 (97)</td>
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<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td>0.063</td>
</tr>
<tr>
<td>Breast-conserving therapy</td>
<td>97 (54)</td>
<td>64 (46)</td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td>83 (46)</td>
<td>51 (44)</td>
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<tr>
<td>Chemotherapy</td>
<td>114 (63)</td>
<td>71 (62)</td>
<td>0.79</td>
</tr>
<tr>
<td>No</td>
<td>66 (37)</td>
<td>44 (38)</td>
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<tr>
<td>Yes</td>
<td>157 (87)</td>
<td>98 (85)</td>
<td>0.63</td>
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<tr>
<td>Hormonal therapy</td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>23 (13)</td>
<td>17 (15)</td>
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<tr>
<td>Yes</td>
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</tbody>
</table>
First gene signature in low risk ER+, LN- breast cancer (using RT-PCR)

Oncotype DX
(21 genes)

NSABP-B14

S Paik et al., NEJM 2004
First link between proliferation genes and prognostication

Genomic grade index (GGI)

C Sotiriou et al., JNCI 2006

Histological grade

Histological grade 2

Gastrointestinal grade

MammaPrint

GG1
GG3

C Sotiriou et al., JNCI 2006
Molecular classification, clinical features and GEPs

Figure 3. Molecular Classification, Gene-Expression Signatures, and Clinical Outcome.
Genes that are associated with tumor differentiation and cell cycle drive the prognostic power of the intrinsic molecular classification and several gene-expression signatures.

C Sotiriou & L Pusztai, NEJM 2009
Tumor stage (N) still matters for prognosis

Trans ATAC (Oncotype DX)

- 70-Gene signature: MammaPrint (Agendia)
- 21-gene recurrence score: Oncotype Dx (Exact Sciences)

Dowsett et al., J Clin Oncol. 2010
Molecular Drivers of Oncotype DX, Prosigna, EndoPredict, and the Breast Cancer Index: A TransATAC Study

Buus R et al., J Clin Oncol 2020
High RS breast cancer patients benefit most from neo(adj) chemotherapy irrespective of stage (nodal status).

CMF regimen
LN-

CAF regimen
LN+

Paik et al., J Clin Oncol 2006

Albain et al., Lancet Oncology 2009

Neoadjuvant Breast Registry
Symphony Trial: ER+/HER2- cohort
N = 474 pts

TAILORx
Node negative
All ER+/HER2-
N=9719

RxPONDER
Node positive (1-3 N+)
All ER+/HER2-
N=5083

MINDACT
Node negative/positive
(1-3 N+ 21%)
81% ER+/HER2-
N=6693

21,495 patients
Validation of the **prognostic** value

**TAILORx**

N=1619 (17%); All node negative

- RS <11
- 9-year rate: 96.8 ± 0.7

**MINDACT**

CL/GL N=2745 (41%)

Sparano JA et al., NEJM 2015; 2018

Piccart et al., Lancet Oncol 2021
Validation of the *predictive* value – “*low*” clinical risk
No benefit of chemotherapy for postmenopausal pts

TAILORx

Sparano JA et al., NEJM 2018

9-year rate (ITT): 94.5% (ET) vs. 95.0% (C+ET)
Validation of the **predictive** value – “**high**” clinical risk

**RxPONDER**
- RS ≤ 25
- Node positive (1-3 N+)
- N=5083

**MINDACT**
- MammaPrint low
- 48% 1-3 N+ ; 50% T >2 cm
- N=1550

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N1, ER/PR+, HER2− breast cancer

- Trial-sponsored Oncotype DX testing
- Oncotype DX already performed and RS≤25
- Randomize Stratification factors: RS<14 vs. 14-25 menopausal status, axillary dissection vs. SN biopsy

- RS>25
  - RS>25
    - Discuss alternatives
  - RS<25
    - Hormonal therapy alone N=2000
    - Chemotherapy plus hormonal therapy N=2000

---

**MINDACT** N=6,693

- c-Low/g-Low N=2,745 (41.0%)
- c-Low/g-High N=592 (8.8%)
- c-High/g-Low N=1,550 (23.2%)
- c-High/g-High N=1,806 (27.0%)

Discordance Rate=32%

- NO CHEMOTHERAPY
- CHEMOTHERAPY
No benefit of chemotherapy for *postmenopausal pts*

Kalinsky et al., N Engl J Med 2021

RxPONDER

Piccart et al., Lancet Oncol 2021

MINDACT
Benefit of chemotherapy for premenopausal pts

Kalinsky et al., N Engl J Med 2021

Piccart et al., Lancet Oncol 2021

Sparano JA et al., NEJM 2018
Numerically improved IDFS in premenopausal pts no longer having regular menstrual periods in both Tx arms

Endocrine Tx alone (N=676)

Chemo then Endocrine Tx (N=677)
Take home messages

- **Three prospective de-escalation studies** validated the **prognostic and predictive** value of GEPs (TAILORx, RxPONDER and MINDACT)

- Clinical parameters (T, N) add significant prognostic **but not predictive** information

- There is **no benefit adding adjuvant chemotherapy** to endocrine therapy for **postmenopausal patients with up to 3 LN+ and RS <25 or MammaPrint low**

- The chemotherapy benefit observed in **premenopausal patients** may be due to **chemotherapy-induced premature menopause (TAILORx, RxPONDER, MINDACT)**
  
  → **Discuss the option of ovarian ablation vs chemotherapy (4-6 cycles of TC)**

- Patients with **high GEPs scores** should be offered chemoendocrine therapy
Communicating breast cancer recurrence risk to patients: how to optimally navigate facts, unknowns and perceptions

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Milano, Italia
Disclosures

- Board Member: Ellipses
- Consultant: Lilly, Novartis, Seattle Genetics, Roche-Genentech
- Research grants to my Institute: MSD, Astra Zeneca
- Speakers bureau: Pfizer, Lilly, Novartis, Roche-Genentech, Samsung, Celltrion
- Stock ownership: None
Risk of recurrence and patient’s perception

• How does recurrence risk interact with the patient’s cognitive processes in approaching his/her care pathway?

• Why patients react in different way to the same information context?
## Risk of recurrence and patient’s perception

<table>
<thead>
<tr>
<th>Multiparametric score</th>
<th>Variables considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nottingham Prognostic Index (NPI)*</td>
<td>Tumor size (cm), lymph node stage (1-3 by level), tumor grading (1-3)</td>
</tr>
<tr>
<td>Adjuvant! Online</td>
<td>Age at diagnosis, menopausal status, comorbidities (minor problems, perfect health, minor problems, average for age, major problems), ER status (positive/negative), tumor grade (1/2/3), tumor size (cm), positive nodes (number). + type of hormonal and chemotherapy to calculate risk reduction</td>
</tr>
<tr>
<td>PREDICT</td>
<td>Age at diagnosis, menopausal status, ER status (positive/negative), HER2 status (positive/negative/unknown), Ki67 status (positive/negative/unknown), invasive tumor size (mm), tumor grade (1/2/3), detection way (screening/symptoms/unknown), positive nodes (number).</td>
</tr>
<tr>
<td>CTSS (only for postmenopausal patients)</td>
<td>Tumor size (mm), nodal status (number of involved nodes, tumor grade (1-3), age at diagnosis (years).</td>
</tr>
<tr>
<td>TNM 8th edition (Clinical Prognostic Stage)</td>
<td>Tumor size (T0-4), nodal status (N0-3), tumor grade (1-3), ER status (positive/negative), PgR status (positive/negative), HER2 status (positive/negative).</td>
</tr>
</tbody>
</table>
### Risk of recurrence and patient’s perception

<table>
<thead>
<tr>
<th>Test</th>
<th>NUMBER OF GENES</th>
<th>PROFILING TECHNIQUE</th>
<th>RISK STRATIFICATION</th>
<th>VALIDATION STUDIES</th>
<th>OUTCOMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>ONCOTYPE DX</td>
<td>21 genes (16 genes + 5 reference)</td>
<td>RT-PCR</td>
<td>Recurrence Score (RS; range 0-100) Low &lt;18 Int 18-30 High &gt;30</td>
<td>NSABP B14 [47]</td>
<td>10-ys DR Low (51%): 6.8% Int (22%): 14.3% High (27%): 30.0%</td>
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<td>NSABP B20 [105]</td>
<td>10-ys DFS Low (54%): 97% (w/o CT), 96% (w CT) Int (21%): 91% (w/o CT), 89% (w CT) High (25%): 60% (w CT), 88% (w CT)</td>
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<td>SWOG 8814 [106]</td>
<td>10-ys DFS Low (40%): 60% (w/o CT), 64% (w CT) Int (28%): 49% (w/o CT), NR (w CT) High (32%): 43% (w CT), 55% (w CT)</td>
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<td>TransATAC [107]</td>
<td>9-ys DR Low: N0 4%; N+ 17% Int: N0 12%; N+ 28% High: N0 25% N+ 49%</td>
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<td>TAILORx [9]*</td>
<td>9-ys IDFS Low: 84% Int: 81% (w/o CT), 84% (w CT) High: 76%</td>
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<td>RxPonder[108]* (NCT01272037)</td>
<td>9-ys OS Low: 94% Int: 94% (w/o CT), 94% (w CT) High: 89%</td>
</tr>
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<td></td>
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<td></td>
<td>10253 pts, ER+/HER2-, N0. Low risk (17%) received ET only, High-risk (14%) received ET+CT, Int-risk (69%) randomized to ET only or ET+CT</td>
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<td>5083 pts, HR+/HER2-, N1 (1-3 positive nodes), RS &lt; 25, randomized to ET alone or ET+CT</td>
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</tbody>
</table>
Risk of recurrence and patient’s perception

<table>
<thead>
<tr>
<th>Test</th>
<th>NUMBER OF GENES</th>
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<th>OUTCOMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAMMAPRINT</td>
<td>70 genes</td>
<td>DNA microarray</td>
<td>MammaPrint Index (MPI; range -1; +1) Low risk (1.0; 0) High risk (0; +1.0)</td>
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<tr>
<td>TRANSBIG [109]</td>
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<td>10-year OS G-high risk: 69% (C-low risk), 69% (C-high risk) G-low risk: 89% (C-high risk), 88% (C-low risk)</td>
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<tr>
<td>RASTER [110]*</td>
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<td>5-yrs DDFS G-low/C-low (95%): 94% G-high/C-low (37%): 95% G-low/C-high (124%): 98% G-high/C-high (171%): 90%</td>
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<tr>
<td>MINDACT [54]*</td>
<td></td>
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<td></td>
<td>5-yrs DMFS G-low/C-low: 97.6% (w/o CT) G-high/C-low: 94.8% (95.8% w CT; 95.0% w/o CT) G-low/C-high: 95.1% (95.9% w CT; 94.4% w/o CT) G-high/C-high: 90.6% (w CT)</td>
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</table>

- **MAMMAPRINT**
  - 70 genes DNA microarray
  - MammaPrint Index (MPI; range -1; +1)
  - Low risk (1.0; 0)
  - High risk (0; +1.0)

- **TRANSBIG [109]**
  - 302 pts, <61 yrs, T1-T2, N0, ER+ (212) and ER- (90), all untreated with any adjuvant systemic therapy

- **MINDACT [54]**
  - 6693 pts, T1-2 or operable T3, N0 (79%) or N1 (21%); HER2+ (10%) or HER2- (90%)
  - 4 subgroups:
    - G-low/C-low (41%), receiving ET
    - G-high/C-low (8.8%): receiving ET or ET+CT
    - G-low/C-high (23.2%): receiving ET or ET+CT
    - G-high/C-high (27%): receiving ET+CT

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  - 6693 pts, T1-2 or operable T3, N0 (79%) or N1 (21%); HER2+ (10%) or HER2- (90%)
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    - G-high/C-low (8.8%): receiving ET or ET+CT
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    - G-high/C-high (27%): receiving ET+CT
### Risk of recurrence and patient’s perception

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<tr>
<th>Test</th>
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<th>OUTCOMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROSIGNA</td>
<td>50 (+ 5 control genes)</td>
<td>NanoString</td>
<td>Risk Of Recurrence score (ROR; range 0-100)</td>
<td>ABCSG-8 [48]</td>
<td>10-yrs DFS Low: 96.7% Int: 91.3% High: 79.9%</td>
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<td></td>
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<td></td>
<td>NO Low (0–40) Intermediate (41–60) High (61–100)</td>
<td>ATAC [51]</td>
<td>10% of risk of 10-yrs DR predicted by: - ROR score of 42 in N0 pts - ROR score of 25 in N+ (1-3 nodes) pts Specific 10-yrs DFS for low-int- and high-risk pts not reported</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>N+ (1-3 nodes) Low (0–40) High risk (41–100)</td>
<td>OPTIMA (ISRCTN42400492) (Stein Cancer Research 2019)*</td>
<td>Ongoing</td>
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<td>HR+/HER- EBC, 1-9 positive nodes or T≥3cm node-negative</td>
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<tr>
<td>Test</td>
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<tr>
<td>ENDOPREDICT</td>
<td>12 (8 genes + 3 RNA ref genes + 1 DNA ref gene)</td>
<td>RT-PCR</td>
<td>EPclin (genomic risk score + tumor size + nodal status) Low risk (EPclin &lt; 3.3) High (EPclin &gt; 3.3)</td>
<td>GEICAM 9906 [111]</td>
<td>10- yrs MFS: Low risk (25%): 93%; High risk (75%): 70%</td>
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<td></td>
<td>555 pts, ER+/HER2−, N+, all treated with adj CT ABCSG-6 [45]</td>
<td>10- yrs DR EP low: 8%; EP high: 22%</td>
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<td>1324 pts, postmenopausal, ER+, N0 and N+, treated with 5 yrs of TAM or 2 yrs of TAM followed by 3 yrs of AI</td>
<td></td>
</tr>
<tr>
<td>BREAST CANCER INDEX (BCI)</td>
<td>7 genes (5 genes + 2 genes ratio)</td>
<td>RT-PCR</td>
<td>BCI (0-10) Low risk (0-5) Intermediate risk (5–6.4) High risk (6.4–10)</td>
<td>TransATAC [112]</td>
<td>10- yrs DR BCI-low: 4.8%; BCI-int: 18.3%; BCI-high: 29%</td>
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<td></td>
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<td>665 pts, postmenopausal ER+, N0, treated with ET alone (TAM or ANA)</td>
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<td>Stockholm trial [44]</td>
<td>10- yrs DMR TAM-treated Low: 2.9%; Int: 16.9%; High: 16.3%</td>
</tr>
<tr>
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<td></td>
<td>588 pts, postmenopausal ER+, N0, treated with TAM alone or no ET</td>
<td>10- yrs DMR Untreated Low: 9.5%; Int: 21.0%; High: 25.4%</td>
</tr>
</tbody>
</table>
When chemotherapy?

**Generally Yes**
- High grade
- High Ki67
- Weak ER and PR
- Unfavorable signature
- Luminal B or surrogate
- Early recurrence risk

**MAYBE**
- IN
- B
- BETWEEN
- E

**Generally No**
- Low grade
- Low Ki67
- Strong ER and PR
- Favorable signature
- Luminal A or surrogate
- Late recurrence risk

**Disease Burden**
- Lower threshold to offer chemotherapy
- Consider: Preferences, Co-Morbidity
- Higher threshold to offer chemotherapy
Cognitive processes in genetic testing report

- **Value attribution**: The Prospect Theory explains individual differences in options evaluation.
- **Understanding information**: The heuristic thinking explains distortion in information processing.
- **Emotions in cognitive processes**: how emotions affect what we want.
- **Risk perception**: the affect heuristic and the importance of numbers.
The Prospect Theory explains individual differences in information interpretation.
Value attribution

• When faced with a problem, people form a mental representation of that problem

• The decision made about exactly the same problem will vary between individuals and across different contexts (Kahnemann and Tversky, 1984; Shoemaker and Russo, 2001)
Differences between professionals and patients in choice options evaluation

Individuals tend to evaluate the options using their status quo as reference point:

- Emotional state
- Physical state
- Family environment

- The reference point is affected by the personal past experiences
  - It determines the mental frame the person uses to approach and judge events

(Kahneman & Tversky, 1979)
Understanding information

• The heuristic thinking explains distortion in information processing
Context
- Ambient conditions
- Task difficulty
- Task ambiguity
- Affective state

Logical Thinking
- Rationality
- Intellectual ability
- Education
- Training
- Critical thinking
- Logical competence

Event Pattern Processor
- Recognized
  - System 1 (Experiential, intuitive Thinking)
- Not recognized
  - System 2 (analytical, deliberative Thinking)

Pattern recognition
- Practice
  - Rational/disrational override
  - Calibration
  - Decision

(Adapted from Croskerry, 2003)
Context
Ambient conditions, Task difficulty, Task ambiguity, Affective state

Recognized
Sistem1 (experiential, intuitive thinking)
Pattern recognition
Practice

Patient
Pattern Processor

Decision (diagnosis)
Heuristics and biases

Logical Thinking
Rationality, Intellectual ability, Education, Training, Critical thinking, Logical competence
Pattern recognition is easier if you have experience
Experience: A problem of perception
Slide from Slawson, Shaughnessy, Becker, 1999.

Do you see the Dalmation in the picture?
**Moral:** Clinical experience sometimes helps see, sometimes prevents seeing the right picture
Now that you see it, can you try to **not** see it?
**Moral:** Experience can result in ideas that are difficult to change
One learns the basic patterns
One sees them in new situations.
Then one can see the pattern where before it had been confusing
Emotions and information processing

• How emotions affect how we interpret information and how we act
Emotions and attention

• Almost any emotional stimulus captures attention at the expense of attention to other stimuli

• Especially true for negative stimuli
  • a frightening stimulus captures attention and narrows its focus
Emotions and heuristic information processing

Positive emotions:

• The information are elaborated more superficially

• Attention is distributed, but people do not exhaustively and efficiently search for more information (Keinan, 1987; Fiedler, 1988)

• Overestimation of positive outcomes
Emotions and heuristic information processing

**Negative emotions:**

- Induce a more deep information processing (the process gets slower)
- Higher attention to every single attribute (Luce, Bettman e Payne, 1997)

**But... Which attributes?**

- People tend to give greater weight to negative rather than positive events
- There is less adaptation to negative than positive situations
- People seem to seek more explanations for negative than positive events (attributional activity)

---

Rozin et al., *Personality and Social Psychology Review.* 2001
• Anxious individuals are more likely to access the more threatening meaning of ambiguous situation

• involuntary capture effects at relatively lower levels of threat

  • weak threats attract attention in anxious patients, particularly when the words match their concerns (Mathews & MacLeod, 1994), and

  • under prolonged stress (Broadbent & Broadbent, 1988; MacLeod & Mathews, 1988)
Risk Perception

• Uncertainty, Prospect Theory and the Affect Heuristic
Risk stratification in post menopausal

- Node neg
  - T.1.5cm
  - Her2 neg
  - PVI neg
  - ER 90%
  - PgR 80%
  - Ki-67 7%

- Node 3+
  - T.1.9cm
  - Her2 neg
  - PVI pos
  - ER 95%
  - PgR 75%
  - Ki-67 67%

- Node neg
  - T 2.1cm
  - Her2 pos
  - PVI neg
  - ER 75%
  - PgR 0%
  - Ki-67 35%

- Node 12+
  - T 2.5cm
  - Her2 neg
  - PVI pos
  - ER 80%
  - PgR 75%
  - Ki-67 20%

Viale Get al, JCO 2011
Risk stratification in post menopausal

Viale Get al, JCO 2011
Risk stratification in post menopausal
Risk stratification in post menopausal

DFS (%)

Years from Randomization

Viale Get al, JCO 2011
Risk stratification in post menopausal

Viale et al, JCO 2011
**Monarch E trial**

**COHORT 1:**
High-Risk based on clinical pathological features
- \( \geq 4 \) ALN OR
- 1-3 ALN and at least 1 of the below:
  - Grade 3 disease
  - Tumor size \( \geq 5 \) cm

Stratified for:
- Prior chemotherapy
- Menopausal status
- Region

First patient randomized July 2017: \( N = 5,120 \)

**COHORT 2:**
High risk based on Ki-67
- 1-3 ALN and Ki-67 \( \geq 20\% \)
- \(< \text{Grade 3 and/or tumor } \leq 5 \) cm

First patient randomized one year later: \( N = 517 \)

**ITT population**
(includes both Cohort 1 and Cohort 2)

**On-study treatment period**
2 years

**Follow-up period**
Endocrine Therapy 3-8 years as clinically indicated

**Abemaciclib**
(150mg twice daily) + Endocrine Therapy

**R 1:1**
\( N = 5637^* \)

**Primary Objective:** IDFS
**Secondary Objectives:** IDFS in high Ki-67 populations, DRFS, OS, safety, PK, PROs

\*Recruitment from July 2017 to August 2019. \*Endocrine therapy of physician’s choice [e.g., aromatase inhibitors, tamoxifen, GnRH agonist]. \*Ki-67 expression centrally assessed in all patients from both cohorts with suitable untreated breast tissue using Ki-67 immunohistochemistry Assay by Dako/Agilent.

HR+: HER2-, Node-Positive, High-Risk EBC

**ALN:** Axillary Lymph Nodes; **DRFS:** Distant Relapse-Free Survival; **EBC:** Early Breast Cancer; **GnRH:** Gonadotropin-releasing Hormone; **HER2:** Human Epidermal Growth Factor Receptor 2; **HR:** Hormone Receptor; **IDFS:** Invasive Disease-Free Survival; **ITT:** Intent-to-treat Population; **OS:** Overall Survival; **PK:** Pharmacokinetics; **PRO:** Patient-Reported Outcome; **R:** Randomized.


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IDFS

Absolute differences were calculated by subtraction of the IDFS rates between the two arms at each year.

CI: Confidence Interval; ET: Endocrine Therapy; HR: Hazard Ratio; IDFS: Invasive Disease-Free Survival; OS IA2: Overall Survival Interim Analysis 2; Y: Years.

IDFS Benefit in Cohort 1 Persists Beyond Completion of Abemaciclib

Absolute differences were calculated by subtraction of the IDFS rates between the two arms at each year.

CI: Confidence Interval; ET: Endocrine Therapy; HR: Hazard Ratio; IDFS: Invasive Disease-Free Survival; OS IA2: Overall Survival Interim Analysis 2; Y: Years.

Ki-67 is prognostic but not predictive of abemaciclib treatment benefit.

- IDFS rates in the ET only arm of Cohort 1 Ki-67 High vs Cohort 1 Ki-67 Low confirmed the prognostic value of Ki-67.

- Within Cohort 1, similar abemaciclib treatment effects were observed regardless of Ki-67 index.

<table>
<thead>
<tr>
<th>Population</th>
<th>Treatment Arm</th>
<th>Pts</th>
<th>Events</th>
<th>4-Year IDFS Rate</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1 Ki-67 High</td>
<td>Abemaciclib + ET</td>
<td>1017</td>
<td>147</td>
<td>83.6</td>
<td>0.618 (0.501, 0.762)</td>
</tr>
<tr>
<td></td>
<td>ET alone</td>
<td>986</td>
<td>224</td>
<td>74.7</td>
<td></td>
</tr>
<tr>
<td>Cohort 1 Ki-67 Low</td>
<td>Abemaciclib + ET</td>
<td>946</td>
<td>91</td>
<td>88.8</td>
<td>0.624 (0.478, 0.814)</td>
</tr>
<tr>
<td></td>
<td>ET alone</td>
<td>968</td>
<td>141</td>
<td>82.4</td>
<td></td>
</tr>
</tbody>
</table>

Ki-67 High: Ki-67 ≥20%; Ki-67 Low: Ki-67 <20%.
CI: Confidence Interval; ET: Endocrine Therapy; IDFS: Invasive Disease-Free Survival; OS IA2: Overall Survival Interim Analysis 2; Pts: Patients.

DRFS

Absolute differences were calculated by subtraction of the DRFS rates between the two arms at each year.

CI: Confidence Interval; DRFS: Distant Relapse-Free Survival; ET: Endocrine Therapy; HR: Hazard Ratio; OS IA2: Overall Survival Interim Analysis 2; Y: Years.

**DRFS Benefit in Cohort 1 Persists Beyond Completion of Abemaciclib**

Absolute differences were calculated by subtraction of the DRFS rates between the two arms at each year.

CI: Confidence Interval; DRFS: Distant Relapse-Free Survival; ET: Endocrine Therapy; HR: Hazard Ratio; OS IA2: Overall Survival/Interim Analysis 2; Y: Years.

## Location of First Recurrences

<table>
<thead>
<tr>
<th>LOCATION OF RECURRENCE</th>
<th>Abemaciclib + ET</th>
<th>ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any disease recurrence, n (%)</td>
<td>203</td>
<td>308</td>
</tr>
<tr>
<td>Distant recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Bone</td>
<td>62</td>
<td>119</td>
</tr>
<tr>
<td>• Liver</td>
<td>42</td>
<td>65</td>
</tr>
<tr>
<td>• Lung</td>
<td>31</td>
<td>35</td>
</tr>
<tr>
<td>Local/regional recurrence</td>
<td>33 (16.3)</td>
<td>50 (16.2)</td>
</tr>
<tr>
<td>Contralateral recurrence</td>
<td>8 (3.9)</td>
<td>12 (3.9)</td>
</tr>
<tr>
<td>Second primary neoplasm</td>
<td>19 (9.4)</td>
<td>20 (6.5)</td>
</tr>
</tbody>
</table>

Majority of recurrences were distant metastases, with lower incidence of recurrence in the abemaciclib arm

AFU1: Additional follow-up 1; ET: Endocrine Therapy.

Fewer deaths (147 vs 168) were observed in the abemaciclib + ET group versus the ET group.
When to escalate?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ET plus CDK4/6i and chemotherapy</th>
<th>ET plus CDK4/6i (chemotherapy in selected cases)</th>
<th>ET alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histological grade</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Genomic risk</td>
<td>High or intermediate</td>
<td>Intermediate</td>
<td>Low</td>
</tr>
<tr>
<td>Proliferative index</td>
<td>High</td>
<td>Intermediate</td>
<td>Low</td>
</tr>
<tr>
<td>HR expression level</td>
<td>Low</td>
<td>High or intermediate</td>
<td>High</td>
</tr>
<tr>
<td>Involved nodes</td>
<td>≥4</td>
<td>1–3</td>
<td>0</td>
</tr>
<tr>
<td>PVI</td>
<td>Present</td>
<td>–</td>
<td>Absent</td>
</tr>
<tr>
<td>Tumour diameter</td>
<td>&gt;5cm (pT3)</td>
<td>2.1–5 cm (pT2)</td>
<td>≤2 cm (pT1)</td>
</tr>
<tr>
<td>Post-operative ctDNA status</td>
<td>Positive</td>
<td>–</td>
<td>Negative</td>
</tr>
</tbody>
</table>
Thank You

Giuseppe Curigliano MD, PhD

giuseppe.curigliano@ieo.it
PATIENT-PHYSICIAN SHARED DECISION MAKING AND PATIENT SUPPORT- CASE STUDIES FOR PRACTICAL TIPS AND TRICKS

Carmen Criscitiello, MD, PhD
University of Milan
European Institute of Oncology
DISCLOSURE SLIDE

Advisory/consultancy role/speaker bureau from:
Eli Lilly
Pfizer
Novartis
Roche
AstraZeneca
MSD
Daiichi Sankyo
Gilead
Seagen
TRADITIONAL PARAMETERS USED TO INFORM TREATMENT DECISIONS

- Tumour size
- Lymph node status
- Grade
- Patient age
- ER / PR, HER2, Ki-67

Viale G et al. JNCI 2008;100:207-12
EVOLUTION OF AJCC CANCER STAGING MANUAL
From Anatomic Staging Towards Personalized Risk Assessment

AJCC 1st Edition
TNM Anatomic Staging Introduced
1978

AJCC 2nd Edition
Expands Cancer Staging Data Form
1984

AJCC 3rd Edition
Established Worldwide Staging System w/ UICC
1989

AJCC 6th Edition
Addition of Non-anatomic Factors as Stage Modifiers (e.g., serum markers in testis tumors)
2003

AJCC 7th Edition
Continues Introduction of Non-anatomic Factors (e.g., PSA/Gleason in prostate cancer)
2010

AJCC 8th Edition
Introduction of the Prognostic Stage Group in Breast Cancer
2018

“...Biologic factors – such as grade, hormone receptor expression, HER2 overexpression/amplication, and genomic panels – have become as or more important than the anatomic extent of disease to define prognosis, select the optimal combination of systemic therapies, and increasingly, influence the selection of locoregional treatments.”

UNCERTAINTY IN TREATMENT DECISION FOR HR+/HER2- EARLY BREAST CANCER

Current parameters and tools

Clear treatment decision for some patients

Uncertainty for many patients
- 10–15% of patients will relapse despite optimal endocrine therapy
- Many patients receive chemotherapy with modest, if any benefit and suffer treatment-related toxicities

MULTIGENE SIGNATURES IN HR+/HER2- BREAST CANCER
CLINICAL CASE 1

Higher risk clinical features
CLINICAL CASE 1

The patient

<table>
<thead>
<tr>
<th>Age</th>
<th>53 yrs old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menopausal status</td>
<td>Post-menopause</td>
</tr>
<tr>
<td>Family history</td>
<td>No</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Hypertension treated with ACE inhibitor</td>
</tr>
<tr>
<td>Clinical stage</td>
<td>cT2 cN0 M0</td>
</tr>
<tr>
<td>Biopsy</td>
<td>NST breast cancer</td>
</tr>
</tbody>
</table>
CLINICAL CASE 1

Surgery

Right quadrantectomy and axillary lymph node dissection

NST breast cancer
Grade 3 ER 80% PgR 20% HER2 1+ Ki-67 25%

Stage: pT2 (25 mm) pN1 (2/7) M0
CLINICAL CASE 1

Adjuvant therapy

pT2 pN1 M0
RS 14

Letrozole + abemaciclib
Radiotherapy
Follow up
HIGH RISK ≠ HIGH BENEFIT
COMMON (BUT WRONG) BELIEF

Tumor grade is predictive of chemotherapy benefit
TUMOR GRADE IS NOT PREDICTIVE OF CHEMOTHERAPY BENEFIT

**Anthracrycline-based *versus* no chemotherapy**

<table>
<thead>
<tr>
<th>Category</th>
<th>Events/woman-years</th>
<th>Anthr. events Logrank Variance of O-E</th>
<th>Ratio of annual event rates Anthr. / Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>(f) ER status ($\chi_1^2 = 0.7; 2p = 0.4; NS$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER-poor</td>
<td>484/8503 (5.6%/y)</td>
<td>-80.2</td>
<td>0.68 (se 0.06)</td>
</tr>
<tr>
<td>ER+</td>
<td>1118/24872 (4.5%/y)</td>
<td>-135.2</td>
<td>0.73 (se 0.04)</td>
</tr>
<tr>
<td>Subsets of ER+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+, chem+end. vs end. only $\dagger$</td>
<td>882/21412 (4.1%/y)</td>
<td>-92.3</td>
<td>0.76 (se 0.05)</td>
</tr>
<tr>
<td>ER+ PR-poor</td>
<td>273/5019 (5.4%/y)</td>
<td>-44.6</td>
<td>0.68 (se 0.08)</td>
</tr>
<tr>
<td>ER+ PR+</td>
<td>759/18187 (4.2%/y)</td>
<td>-92.9</td>
<td>0.74 (se 0.05)</td>
</tr>
<tr>
<td>(i) Tumour differentiation and ER ($\chi_3^2 = 1.1; p = 0.8; NS$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poorly, ER-poor</td>
<td>97/1789 (5.4%/y)</td>
<td>-17.1</td>
<td>0.67 (se 0.42)</td>
</tr>
<tr>
<td>Poorly, ER+</td>
<td>145/2707 (5.4%/y)</td>
<td>-19.3</td>
<td>0.74 (se 0.11)</td>
</tr>
<tr>
<td>Mod./Well ER-poor</td>
<td>77/1060 (7.1%/y)</td>
<td>-5.1</td>
<td>0.77 (se 0.07)</td>
</tr>
<tr>
<td>Mod./Well ER+</td>
<td>340/7386 (8.0%/y)</td>
<td>-41.5</td>
<td></td>
</tr>
</tbody>
</table>

EBCTCG Lancet 2012
TUMOR GRADE IS NOT PREDICTIVE OF CHEMOTHERAPY BENEFIT

Taxane/anthracycline-based versus non-taxane

<table>
<thead>
<tr>
<th>Category</th>
<th>Events/woman-years</th>
<th>Taxane events</th>
<th>Ratio of annual event rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>allocated taxane</td>
<td>allocated non-tax.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Logrank</td>
<td>Variance</td>
<td>Taxane : Non-tax.</td>
</tr>
<tr>
<td>(f) ER status ($\chi^2 = 0.1; 2p = 0.7; NS$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER-poor</td>
<td>1751/26414</td>
<td>2066/27845-1116</td>
<td>759.9</td>
</tr>
<tr>
<td>(6.2%/y)</td>
<td>(7.2%/y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+</td>
<td>2175/52322</td>
<td>2442/61006-167.3</td>
<td>1025.0</td>
</tr>
<tr>
<td>(3.5%/y)</td>
<td>(4.0%/y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subsets of ER+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+ PR-poor</td>
<td>440/9902</td>
<td>504/9452</td>
<td>45.2</td>
</tr>
<tr>
<td>(4.4%/y)</td>
<td>(5.0%/y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER+ PR+</td>
<td>1515/47333</td>
<td>1743/46525</td>
<td>124.0</td>
</tr>
<tr>
<td>(3.2%/y)</td>
<td>(3.7%/y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(j) Tumour differentiation and ER ($\chi^2 = 10.2; p = 0.02$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poorly, ER-poor</td>
<td>748/11023</td>
<td>881/10730</td>
<td>-59.7</td>
</tr>
<tr>
<td>(0.9%/y)</td>
<td>(8.2%/y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poorly, ER+</td>
<td>758/14309</td>
<td>760/14040</td>
<td>-11.6</td>
</tr>
<tr>
<td>(5.3%/y)</td>
<td>(5.4%/y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mod./Well ER-poor</td>
<td>571/6905</td>
<td>401/7000</td>
<td>-8.2</td>
</tr>
<tr>
<td>(6.4%/y)</td>
<td>(5.7%/y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mod./Well ER+</td>
<td>810/32621</td>
<td>1016/32092</td>
<td>-102.2</td>
</tr>
<tr>
<td>(2.5%/y)</td>
<td>(3.2%/y)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ER+ G3
ER+ G1/G2

EBCTCG Lancet 2012
THE TRUTH: CLASSICAL CLINICO-PATHOLOGICAL VARIABLES ARE NOT PREDICTIVE OF CHEMOTHERAPY BENEFIT
Clinico-pathological features provide independent **prognostic information** compared to multigene assays.

**RS=23**

<table>
<thead>
<tr>
<th>Age</th>
<th>Grade</th>
<th>pT</th>
<th>10-yr RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>2</td>
<td>1 cm</td>
<td>7% (5%-10%)</td>
</tr>
</tbody>
</table>

12% (9%-16%)

<table>
<thead>
<tr>
<th>Age</th>
<th>Grade</th>
<th>pT</th>
<th>10-yr RISK</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>3</td>
<td>3 cm</td>
<td>27% (20%-36%)</td>
</tr>
</tbody>
</table>
THE LOWER THE RS THE HIGHER THE ENDOCRINE THERAPY BENEFIT

Recurrence Score
ESR1 mRNA

Placebo
Degree of tamoxifen-benefit
Tamoxifen
CLINICAL CASE 2

Lower risk clinical features
## CLINICAL CASE 2

The patient

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>55 yrs old</td>
</tr>
<tr>
<td>Menopausal status</td>
<td>Post-menopause</td>
</tr>
<tr>
<td>Family history</td>
<td>no</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>no</td>
</tr>
<tr>
<td>Clinical stage</td>
<td>cT1c cN0 M0</td>
</tr>
<tr>
<td>Biopsy</td>
<td>NST breast cancer</td>
</tr>
<tr>
<td></td>
<td>ER 90% PgR 10% HER2 0</td>
</tr>
<tr>
<td></td>
<td>Ki-67 16%</td>
</tr>
</tbody>
</table>
CLINICAL CASE 2

Surgery

Quadrantectomy + sentinel node biopsy
Invasive breast cancer NST G2
ER: 100% PgR: 10% Ki-67: 16% HER2: 0
Stage: pT1c pN0 M0

Risultato Recurrence Score® (RS)

32

Rischio di recidiva a distanza di 9 anni
Solo con TAM

20%
IC 95% (15%, 27%)
NSABP B-14

Beneficio assoluto della chemioterapia (CT) nella media del gruppo*

>15%
IC 95% (9%, 37%)
NSABP B-20

*Per il recesso stadio della chemioterapia (CT) per i singoli risultati RS, vedere pagina 2.
CLINICAL CASE 2
Adjuvant therapy

- pT1c pN0 M0
- RS 32
- TC × 4
- Radiotherapy
- Letrozole
Some oncologists would have not performed the genomic test, and have prescribed endocrine therapy.

But, low degree of PgR is a negative prognostic factor.

PgR does not predict ET benefit.

PgR on itself does not predict ET benefit, but in the context of Oncotype Dx it could be more informative.
CLINICAL CASE 3
## CLINICAL CASE 3

### The patient

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>46 yrs old</td>
</tr>
<tr>
<td><strong>Menopausal status</strong></td>
<td>Pre-menopause</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td>Mother and sister with BC at a young age</td>
</tr>
<tr>
<td><strong>Comorbidity</strong></td>
<td>no</td>
</tr>
<tr>
<td><strong>Genetic test</strong></td>
<td>gBRCA1mut.</td>
</tr>
<tr>
<td><strong>Clinical stage</strong></td>
<td>Left cT1c cN0 M0</td>
</tr>
<tr>
<td><strong>Biopsy</strong></td>
<td>NST breast cancer ER 90% PgR 90% HER2 1+ Ki-67 25%</td>
</tr>
</tbody>
</table>
CLINICAL CASE 3

Surgery

Bilateral mastectomy (prophylactic right breast) + left axillary dissection

Left: Invasive breast cancer NST G2
ER: 90% PgR: 80% Ki-67: 28% HER2: 1+
Stage: pT1c (18 mm) pN1a (1/9) M0

Right: negative
CLINICAL CASE 3

Adjuvant therapy

pT1c (18 mm) pN1a (1/9) M0
ROR 14

LHRHa + exemestane
ONCOTYPE Dx MAY NOT BE CONSIDERED INFORMATIVE IN THIS CASE
INTERPRETATION BIAS RxPONDER FOR PREMENOPAUSAL PATIENTS
CHEMOTHERAPY BENEFIT IN PREMENOPAUSAL PTS WITH RS ≤ 25
RxPONDER (RS 0-25)

Invasive Disease–free Survival, Premenopausal Participants

- **OFS: 16%**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Participants</th>
<th>Events</th>
<th>5-Yr Disease–free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemoendocrine</td>
<td>829</td>
<td>57</td>
<td>93.9%</td>
</tr>
<tr>
<td>Endocrine Only</td>
<td>826</td>
<td>92</td>
<td>89.0%</td>
</tr>
</tbody>
</table>

Hazard ratio for invasive disease recurrence, new primary cancer, or death: 0.60 (95% CI, 0.43–0.83)
P=0.002

Kalinsky et al. NEJM 2021
Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer


OFS BENEFIT IN PREMENOPAUSAL PATIENTS

Disease-free Survival in All Patients

- **8-Yr DFS**
  - TAM: 78.9%
  - TAM + OFS: 83.2% HR 0.76
  - EXE + OFS: 85.9% HR 0.65

**RxPONDER**

- **CT + ET vs ET**
  - HR 0.60

**SOFT**

- **EXE + OFS vs TAM**
  - HR 0.65
AMENORRHEA AND SURVIVAL IN PREMENOPAUSAL PATIENTS

- **Status**: Amenorrhea, No amenorrhea
- **No. of Patients**: 1868, 475
- **No. of Events**: 424, 173

**Disease-free Survival (%)**
- Hazard ratio, 0.70
- P<0.001

**Years since Randomization**

**Overall Survival (%)**
- Hazard ratio, 0.76
- P=0.04

**No. at Risk**
- Total: 2343, 2101, 1838, 974, 323
- Amenorrhea: 1868, 1705, 1519, 797, 250
- No amenorrhea: 475, 396, 319, 177, 73

**Years since Randomization**

Swain et al. NEJM 2010
CHEMOTHERAPY BENEFIT IN PREMENOPAUSAL PATIENTS WITH RS ≤ 25

Is it all about OFS?
ESTIMATED PERCENTAGE OF CT BENEFIT DUE TO OFS IN PREMENOPAUSAL WOMEN WITH RS ≤ 25

- 41.9%
- 25.6%
- 14%
- 13.9%
- 4.6%

Categories:
- None
- <25%
- ~50%
- >75%
- All

Burstein et al. Ann Oncol 2021
CLINICAL CASE 4
Discordant tests
**CLINICAL CASE 4**

The patient

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>72 years old</td>
</tr>
<tr>
<td><strong>Menopausal status</strong></td>
<td>Post-menopause</td>
</tr>
<tr>
<td><strong>Family history</strong></td>
<td>no</td>
</tr>
<tr>
<td><strong>Comorbidity</strong></td>
<td>no</td>
</tr>
<tr>
<td><strong>Clinical stage</strong></td>
<td>cT2 cN0 M0</td>
</tr>
<tr>
<td><strong>Biopsy</strong></td>
<td>IDC</td>
</tr>
<tr>
<td></td>
<td>ER 90%, PgR 25%, Ki67 23%,</td>
</tr>
<tr>
<td></td>
<td>HER2 1+</td>
</tr>
</tbody>
</table>
CLINICAL CASE 4

Surgery

Right mastectomy and axillary dissection
IDC, G2, ER 90%, PgR 30%, Ki67 22%, HER2 1+
Stage: pT2 (2.5 cm) pN0, M0
**CLINICAL CASE 4**

Genomic tests

**EPclin risk score = 3.5**

Risk class: high risk → CT

**Oncotype RS = 8**

Risk class: low risk → NO CT
In T1-2 patients with ER+, HER2-, N- disease, an Oncotype DX RS <11 will downstage patients to Prognostic Stage Group 1A.

When Oncotype Dx Breast RS is <11, all of these patients are classified as Stage IA.
CLINICAL CASE 4
Adjuvant therapy

pT2 (2.5 cm) pN0 M0
EPClin 3.5, RS 8

Anastrozole
ARE MULTIGENE SIGNATURES INTERCHANGEABLE?

Different technologies
Different genes
Different ways to report results
COMPARISON OF MULTIGENE SIGNATURES IN THE SAME POPULATION

TransATAC study (N = 774)

adapted from Sestak et al. JAMA Onc 2018
COMPARISON OF MULTIGENE SIGNATURES IN THE SAME POPULATION

The OPTIMA study

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Oncotype DX® No. (%)</th>
<th>MammaPrint† No. (%)</th>
<th>Prosigna No. (%)</th>
<th>IHC4 No. (%)</th>
<th>IHC4-AQUA‡ No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (%)</td>
<td>301 (99.7)</td>
<td>298 (98.9)</td>
<td>299 (99.0)</td>
<td>257 (85.1)</td>
<td>271 (89.7)</td>
</tr>
<tr>
<td>Low risk</td>
<td>163 (54.2)</td>
<td>183 (61.4)</td>
<td>108 (36.1)</td>
<td>62 (24.1)</td>
<td>87 (32.1)</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>84 (27.9)</td>
<td>–</td>
<td>88 (29.4)</td>
<td>123 (47.9)</td>
<td>80 (29.5)</td>
</tr>
<tr>
<td>Mid risk</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>55 (20.3)</td>
</tr>
<tr>
<td>High risk</td>
<td>54 (17.9)</td>
<td>115 (38.6)</td>
<td>103 (34.5)</td>
<td>72 (28.0)</td>
<td>49 (18.1)</td>
</tr>
</tbody>
</table>

54.2% 61.4% 65.5%

Similar proportion of patients defined as low risk

Similar prognostic information at population level
COMPARISON OF MULTIGENE SIGNATURES IN THE SAME POPULATION

For individual patients, tests may provide different results

The OPTIMA study

Table 5. Number of tests agreeing with each test

<table>
<thead>
<tr>
<th>No. of other tests agreed with test</th>
<th>Oncotype DX No. (%)</th>
<th>Prosigna No. (%)</th>
<th>MammaPrint No. (%)</th>
<th>IHC4 No. (%)</th>
<th>IHC4-AQUA No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>119 (39.4)</td>
<td>119 (39.4)</td>
<td>119 (39.4)</td>
<td>119 (39.4)</td>
<td>119 (39.4)</td>
</tr>
<tr>
<td>3</td>
<td>84 (27.8)</td>
<td>77 (25.5)</td>
<td>73 (24.2)</td>
<td>67 (22.2)</td>
<td>75 (24.8)</td>
</tr>
<tr>
<td>2</td>
<td>54 (17.9)</td>
<td>52 (17.2)</td>
<td>47 (15.6)</td>
<td>36 (11.9)</td>
<td>33 (10.9)</td>
</tr>
<tr>
<td>1</td>
<td>31 (10.3)</td>
<td>33 (10.9)</td>
<td>34 (11.2)</td>
<td>25 (8.3)</td>
<td>27 (9.0)</td>
</tr>
<tr>
<td>0</td>
<td>13 (4.3)</td>
<td>18 (6.0)</td>
<td>25 (8.3)</td>
<td>10 (3.3)</td>
<td>17 (5.6)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (0.3)</td>
<td>3 (1.0)</td>
<td>4 (1.3)</td>
<td>45 (14.9)</td>
<td>31 (10.3)</td>
</tr>
</tbody>
</table>

High level of discordancy for individual patients:
40-60% discordancy
AND SO... WHICH TEST SHOULD WE CHOOSE?

The right test for the right patient
MULTIGENE SIGNATURES IN HR+/HER2- EBC

converting “average” benefit into “individual” benefit
The ultimate test of your knowledge is your capacity to convey it to another.

- Richard Feynman