Personalized Treatment Breast Cancer
MammaPrint Science to Healthcare

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EC conference - 2019
Integrating Genomics into Personalized Healthcare
A Science-for-Policy Perspective
Personalized Healthcare for Breast Cancer

Healthy
Cancer Risk?

Diagnosis
Cancer Type
Aggressive?
Therapy choice

Outcome
Prognosis
Response?
Personalized Healthcare - Precision Oncology

Science based targeted escalation and de-escalation
Personalized Healthcare - Diagnostics

Diagnostics are the keys to precision medicine. Advanced diagnostic tests can stratify patients for response, non-response, and adverse events to costly therapies and interventions that do not yield improvement or positive outcome for patients. They can reduce diagnostic odysseys, monitor patients during drug holidays, and identify disease progression in time to intervene. not to forget the targeted drugs Pharma and Biotech

Personalized Healthcare - Diagnostics

Success of precision medicine hinges on reforming black box of diagnostics reimbursement

There is zero consensus on the level of evidence a diagnostic must show in order to prove clinical utility but establishing the right systems for coverage and reimbursement would allow modern diagnostics to drive a future of widespread precision medicine.

By LENA CHAIHORSKY

Post a comment / Jan 3, 2019 at 7:30 AM

Why do we need Genomic Assays in Early Stage Breast Cancer?

- To add greater precision beyond clinical and pathologic factors (not to confirm pathology)
- To guide therapy decisions (where there is greatest need for improved precision)
- DNA Gene Mutations (other than HER2) have not been useful
- RNA Gene Expression Analysis is most informative
Breast Cancer Diagnostic – Unmet need 1

low risk versus high risk of recurrence and the need for chemotherapy
use case: early stage breast cancer
Stage 1 and 2 (0-3 positive lymph nodes, max 5 cm)
EU: 380K and US: 230K patients/year

Priorities Breast Cancer Translational Research, Dowsett et al, BCR, 2007
Breast Cancer Diagnosis

- Localized disease: Curable
- Generalized disease: Very difficult to cure

« Adjuvant » medical therapies

But risk of:
- overtreatment
- undertreatment
- wrong treatment
- suboptimal treatment
Breast Cancer - Prognosis

Which Breast Cancers Return?

International Validation 70-gene signature MammaPrint

Buyse, 2006

From One Size Fits All to Informed decision on chemotherapy yes/no

EC Framework Program VI – TRANSBIG 2004-2011
MammaPrint: ‘07 FDA cleared IVDMIA for prognosis assessment technology – microarray

van’t Veer et al., Nature 415, p. 530-536, 2002
MINDACT Trial: Study Objective – Prospective Evidence

- **Microarray In Node** negative and 1-3 positive node **Disease** may **Avoid ChemoTherapy (MINDACT)**

- Designed to provide evidence for the clinical utility of MammaPrint:
  - Use of the **70-gene signature (MammaPrint)**
  - In addition to **standard clinical-pathological criteria**

- **Goal:** more accurate selection of patients for adjuvant chemotherapy

- 6693 Patients enrolled from 2007 – 2011 (9 Countries, 112 Centers)

- EORTC Sponsored + 6 Cooperative Groups

- €47 million investment, incl FPVI – TRANSBIG
MINDACT:
Microarray In Node negative (or 1-3 LN+) Disease may Avoid Chemotherapy

Methods
• Clinical Risk Assessment and Genomic Risk Assessment (MammaPrint)
• Concordant Low Risk did not receive CT
• Concordant High risk did receive CT
• Discordant groups were randomly assigned to a strategy using either their clinical or genomic risk to determine treatment
MINDACT Primary Test and End Point (single arm!)

Primary endpoint:

• Distant Metastasis Free Survival (DMFS) at 5 years

Primary test:

• To assess whether patients with clinical high risk features and a genomic Low Risk profile who did not receive CT would have a 5-year DMFS of ~95%.
  
  — A non-inferiority boundary of 92% (lower limit confidence)

![Diagram showing No Chemotherapy and R-T with C-high/G-low N=1550 and 23% discordant]
Primary Test Population, C-high / G-low tumors:
- 58% >2cm
- 93% Grade II or III
- 48% LN+ 1-3
- 98% HR+

- 5-Year DMFS for the C-high / G-low (MP Low) group with no CT = 94.7% (CI: 92.5 – 96.2%).
- Excludes 92%, positive outcome met.
MINDACT Secondary Test

Secondary endpoint:
- Distant Metastasis Free Survival of noCT vs CT

Secondary test:
- To assess significance of survival difference, *added clinical benefit of chemotherapy*, for patients with clinical high risk features and a genomic Low Risk
Chemo efficacy in Clin-High / MP Low (DMFS)

DMFS: distant relapses deaths all causes

- **No statistical difference** between CT vs no CT arms
- (1.5% non significant difference, considered not clinical relevant)
- **Excellent survival with no chemotherapy** for patients with clinically high risk features (94.4%)

Adapted from Figure 2

DMFS: distant Metastasis Free Survival

<table>
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<th>Years</th>
<th>5-year DMFS (95% CI)</th>
<th>adjusted HR (95% CI)</th>
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Adapted from Figure 2

NEJM, 2016
If ALL patients were treated using the clinical risk assessment or the MammaPrint risk assessment to guide treatment

Distant Metastasis Free Survival

- **Clinical Risk**
  - 3337 (50%) patients Low Risk
  - 3356 (50%) patients High Risk

- **MammaPrint Risk**
  - 4295 (64%) patients Low Risk
  - 2398 (36%) patients High Risk

46% reduction of chemotherapy prescription in clinical high risk patients (1550/3356)

Quality of Life and Cost Effectiveness Data from MINDACT

**5-year DMFS**

- C-risk: 95.0%
- G-risk: 94.7%

**Number of patients at risk:**

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Figure S 1

NEJM, 2016
Among the c-High risk patients, the trial shows that 46% who are MammaPrint low risk can safely forego chemotherapy, as the benefit is outweighed by the harm.
MammaPrint included in ASCO guidelines July 2017
Medical societies globally included or expanded recommendation of MammaPrint based on this pivotal clinical trial.
Avoid unnecessary chemotherapy
Reduce risk of not receiving chemo when needed

Defined financing of MammaPrint – Partial or full reimbursement
Financing/reimbursement for MammaPrint assessment ongoing (self-payer market)
No funding/reimbursement (self-payer market)

Global MammaPrint reimbursement
US Reimbursement, 200M Covered Lives

- Coverage CMS Since 2009
- CPT Code 81521 Category 1
- Medicaid Coverage

- Included in Medical Policy
- Contracted at Medicare Rate
- Tech Assessment
- Included in Policy
- Contracted
EU reimbursement status for MammaPrint

- Defined financing of MammaPrint – Partial or full reimbursement
- No defined financing/reimbursement for MammaPrint, but assessment ongoing (private-payer market)
- No funding/reimbursement (private-payer market)
Current HTA landscape

IQWiG

ZIN

EUnetHTA

NICE

KCE
EU countries currently under HTA assessment

**Base Coverage (HTA)**
- Netherlands* (in Guideline) (ZIN)
- Belgium (in pilot) (KCE)
- Germany* (AGO recommended) (IQWIG)

**Guidelines (HTA)**
- United Kingdom (NICE)
- Italy

**EUnetHTA (HTA)**
- EC Horizon2020 program
  - Workpackage MammaPrint

*Netherlands and Germany currently reimbursed Private Insurers as ‘additional’ (though all reimbursed also for ‘base insured’). Assessment by Dutch Insurance Board is for ‘base insurance package’.*
EUnetHTA (EU Horizon 2020 network)

• European collaborative effort for production of HTA information for national adaptation and reporting

• **What influence does it have:** European countries can adapt, and still conduct their own HTAs, taking EUnetHTA findings into account

• MammaPrint evaluation was a collaboration between NL and BE assessors

• Report published on Dec 29 2017, update published Feb 6 2018

• Clinical assessment (NL) and health economic assessment (BE) informed Dutch HTA by ZIN and KCE

• Other national HTAs consider and cite this evaluation in their own reports; UK NICE conducts its own HTA assessment
EUnetHTA report was published in end 2017 and raised a number of issues

• **Purpose**
  • Assessment of the relative effectiveness of MammaPrint (clinical utility)
  • Added value of using the gene expression signature test MammaPrint for adjuvant chemotherapy decision-making in early breast cancer (cost-effectiveness)

• **Outcome**
  • The EUnetHTA indicates that it is **uncertain whether it is safe to follow MammaPrint® and to refrain from treatment with chemotherapy** in patients in whom the risk for distant recurrence is high according to standard clinical risk-assessment but **low according to the MammaPrint (failed clinical utility)**

• **Criticism by oncology specialists**
  • EUnetHTA does not adopt MINDACT primary aim result (single arm evaluation, nor choice of endpoints (ASCO-Krop et al rebuttal, JCO 2017)(EORTC & NL-Onkos public statement 2017)
Stakeholders & MammaPrint Clinical Utility

Positive/Negative Clinical Utility
Positive Cost-Effective*

*Cost-effective in 6 EU countries and US, Retel, in preparation
Recommendations for policy decision makers, payers, health technology assessors, and industry members*

In 2016, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Devices and Diagnostics Special Interest Group reviewed diagnostic-specific HTA programs*

Clear and commonly accepted standards are needed across two dimensions:

1) Study types that are appropriate to demonstrate the value of diagnostic tests in the context of the respective care pathway – MINDACT is a clear case in point

2) Transparency of HTA processes, transparency of HTA processes, including test selection for formal HTA and review criteria

Recommendations included

• Clear guidance on study design preferences and prioritization criteria at regional and/or national level

• Early and ongoing opportunities for dialogue between health care decision makers, health technology assessors, payers, clinicians, patients, and industry

• Guidance on evidence development for molecular diagnostics

• Opportunities for stakeholders to comment on evaluation methods and evidence used in evaluations

• Harmonized HTA requirements across national/regional HTA groups for timely access to molecular diagnostic streamline the process and reduce workload for manufacturers and HTA bodies

There is a collective responsibility from all partners involved to communicate consistently so a consensus is reached and standards for evaluation are drawn.

Personalized Healthcare comes with new trial designs and new endpoints (often) no longer classical randomized controlled trials, but single arm evaluations.
Acknowledgements MammaPrint
The Netherlands Cancer Institute - Agenda

Marc van de Vijver
Hans Peterse
Floor van Leeuwen
Sjoerd Rodenhuis
Emiel Rutgers

Anuska Glas
Guido Brink
Arno Floore
Leonie Delahaye
Anke Witteveen

Agenda Founders
Bernhard Sixt
Laura van ’t Veer
René Bernards
Acknowledgements MINDACT

All National Teams and Participating Cooperative Groups

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Principal Investigators

- Fatima Cardoso
- Emiel Rutgers
- Martine Piccart
- Giuseppe Viale
- Laura van’t Veer

EORTC HQ Statistical & Medical Team

- Jan Bogaerts
- Leen Slaets
- Kostas Tryfonidis
### Acknowledgements

**MINDACT - Funding**

<table>
<thead>
<tr>
<th>Research Grants</th>
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<td>Association Le cancer du sein, parlons-en!</td>
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"Here are my genes..."