The Promise of Predictive Biomarkers
MammaPrint in Breast Cancer

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Conflict of interest statement

• No conflict of interest to declare.
Early Stage Breast Cancer

Localized disease
Curable

Generalized disease
Very difficult to cure

But risk of:
• overtreatment
• undertreatment
• wrong treatment
• suboptimal treatment

« Adjuvant »
medical therapies
Precision Oncology is evidence based, targeted & allows escalation or de-escalation.
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.

MammaPrint developed at the NKI in 2002

van’t Veer et al., Nature 415, p. 530-536, 2002
70-Gene Prognosis Signature - MammaPrint

van’t Veer et al., Nature 415, p. 530-536, 2002

70 significant prognosis genes

Tumor samples

MammaPrint Index

LOW RISK
~10% chance (95% CI 4-15) of cancer recurrence within 10 years without any additional adjuvant treatment

HIGH RISK
~29% chance (95% CI 22-35) of cancer recurrence within 10 years without any additional adjuvant treatment
Prognostic value MammaPrint

From “One Size Fits All“

Informed decision on chemotherapy
yes/no

International Validation 70-gene signature MammaPrint

MammaPrint
Low risk

MammaPrint
High risk

Buyse et al., 2006
70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer


Among 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.

for the MINDACT Investigators*
Farewell to chemotherapy?

With all the good news about precision medicine, it can be difficult to explain why many patients are still being treated with expensive and toxic drugs that do not benefit them. Pia Heinemann, science editor for the German newspaper Die Welt, won the 2016 Cancer World Best Reporter prize for an article, republished below, that helped readers make sense of the complex reality.

Breast cancer patients could be spared the misery of chemotherapy with new test which predicts if their tumour will return

“There have been great advances in pathology, but patients are not benefiting as they should”
From invention to marketable product

Invention: Research microarray profile

Clinical validation

Convert invention: High throughput lab & informatics

Independent clinical & technical validations

Regulatory & certification

Test available for patient

AGENDIA
All positive news.......what could possibly go wrong?
Opnieuw Kamervragen over niet vergoeden MammaPrint

SP-Kamerlid Henk van Gerven wil dat de MammaPrint wordt opgenomen in het basispakket voor de zorg. Zorginstituut Nederland vindt dat in tegenstelling tot oncologen en patiënten geen goed idee.

‘We moeten er alles aan doen om die chemokuur alleen te geven aan vrouwen die er echt baat bij hebben’

De MammaPrint ligt onder vuur. Moet er uitsluitend een andere chemokuur of geneesmiddel worden gegeven bij borstkanker? Een interview met medisch verdienste Lauta Van ’t Veer.

Zorginstituut geeft negatief gebruiksaids voor MammaPrint, genetische test die noodzaak chemo voorspelt

Het Zorginstituut waarschuwt voor mogelijk extra sterkgeven bij het gebruik van de MammaPrint, een genetische test die kan voorspellen of vrouwen met een hoge kans hebben. Talloze patiënten hebben nog niet de mogelijkheid de test en de behandeling te maken die MammaPrint, een genetische test en gebruiksaids. ‘Wij hopen dat de behandeling van zowel de ziekte als de test het helpen bij hun genezing’.

MammaPrint niet in basisverzekering

‘Trieste dag voor alle vrouwen met borstkanker’

AMSTERDAM - Een zeer onterechte, foutieke beslissing! En een bultengewoon trieste dag voor alle vrouwen met borstkanker in Nederland.”
Current patient access to MammaPrint

Netherlands

- 95% of health insurers reimburse MammaPrint in the Netherlands.
- However MammaPrint is still not included in the basic insurance package in 2019….

Despite 15 years of development and support by medical communities and clinical guidelines.
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

Challenges for diagnostics in precision medicine

**Reimbursement, reimbursement, reimbursement**

**Patient Access**
- Without reimbursement patients are delayed access to these innovations

**Recognition of value**
- The value of the test is not being recognized by HTA or is thought to not be demonstrated adequately
  - Clinical utility
  - Health economics
HTA organizations today do not provide consistent parameters of acceptability*

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

- Analytical and clinical performance
- Clinical utility
- Economic impact

HTA organizations today do not provide consistent parameters of acceptability*

**WHY**

- HTA programs are most advanced for pharmaceuticals
- Few systems have established processes specifically delineated for predictive biomarkers
- HTA bodies continue to take existing systems set up to evaluate pharmaceuticals and applying them to predictive biomarkers with little modification of process or requirements

“Without establishing standards for diagnostics devices, HTA is left to subjective judgment rather than an objective assessment as to which tests meet, exceed, or fail to meet standards”
2017-2019 HTA landscape for MammaPrint

IQWiG
NICE
HAS
KCE
ZIN
EUnetHTA
1 Recommendations

1.1 EndoPredict (EPin score), Oncotype DX Recurrence Score and Prosigna are recommended as options for guiding adjuvant chemotherapy decisions for people with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative and lymph node (LN)-negative (including micrometastatic disease; see section 5.9) early breast cancer, only if:

- they have an intermediate risk of distant recurrence using a validated tool such as PREDICT or the Nottingham Prognostic Index
- information provided by the test would help them choose, with their clinician, whether or not to have adjuvant chemotherapy taking into account their preference
- the companies provide the tests to the NHS with the discounts agreed in the access proposals and
- clinicians and companies make timely, complete and linkable record-level test data available to the National Cancer Registration and Analysis Service as described in the data collection arrangements agreed with NICE (see section 5.29).

MammaPrint is not recommended for guiding adjuvant chemotherapy decisions for people with ER-positive, HER2-negative and LN-negative early breast cancer because it is not cost effective.

Gene test for breast cancer - limits of certainty

Chemotherapy or not? To make this decision due to a gene expression test is too uncertain for breast cancer patients, following the Institute of Quality and Efficiency in Health Care.

Difficult Decision. It is not always clear which breast cancer patient really needs chemotherapy ...

PHOTO: MAURITUS IMAGES

"Overall, the IQWiG concludes that there is currently no evidence for a benefit or damage to a biomarker-based strategy to decide whether or not to undergo adjuvant chemotherapy for primary breast cancer. For patients,
Each European HTA has used different criteria to evaluate MammaPrint

- **Trial endpoints evaluated** – primary or secondary endpoint most important
- **Patient outcome** – is DMFS or DFS to be evaluated
- **Trial design** accepted or not - only randomized phase 3, nonrandomized prospective data, other studies included/not included
- **Patient population** of the trial (intention to treat or per protocol)
- **Length of follow-up** which is deemed acceptable (5 vs 10yrs?)
- **Quality of life** (QoL) data required vs not necessary for evaluation
- **Country specific data** on impact for treatment decisions
**Stakeholders & MammaPrint current status**

- **Positive/Negative Clinical Utility**
- **Positive Cost-Effective***

*Cost-effective in 6 EU countries and USA, Retel et al., 2019 in preparation*
Future Outlook....lessons learned?
Stakeholders & MammaPrint current status

- **Positive/Negative Clinical Utility**
- **Positive Cost-Effective***

*Cost-effective in 6 EU countries and USA, Retel et al., 2019 in preparation
A new gold standard to assess value of predictive biomarkers?

Consideration of evidence other than RCT required in precision medicine
  - HTA bodies cannot continue evaluate predictive biomarkers solely on large RCT
  - Other evidence must be considered. e.g. retrospective, real world evidence

Precision Healthcare is ushering in new trial designs
  - (Often) no longer classical format of RCTs, single arm evaluations
  - Precision medicine will mean smaller cohorts
  - Companion diagnostics must be evaluated within trials for targeted therapies

❖ Relying on evaluation of randomized prospective data from large RCT delays patient access
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**, including test selection for formal HTA and review criteria

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Recommendations for policy decision makers, payers, health technology assessors, and industry members*

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

Statement by FDA Commissioner Scott Gottlieb, M.D  14 March 2019

Precision guided medicines can demonstrate strong efficacy signals in early clinical trials, including in trials where small groups of patients are selected based on biomarkers or other criteria suggesting they’re likely to benefit:

To take advantage of these innovations, the agency is also seeking new ways to modernize its approaches to accommodate these novel opportunities.
There is a collective responsibility from all partners involved to communicate consistently so a consensus is reached and standards for evaluation are drawn.
THANK YOU