MammaPrint

Improving treatment decisions in breast cancer

Support and Involvement of EU

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VP Clinical Affairs
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It’s Diagnostics, Stupid

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To stem the spiraling cost of cancer treatment, a concerted effort is urgently needed to develop molecular diagnostics to better identify the patients that respond to expensive targeted therapies. Opportunities and obstacles in the development of such drug response biomarkers are discussed here.

In the United States, approximately 30% of total health care costs for an individual are incurred in the last year of life. Development of new classes of biomarkers to separate these apparently similar tumors into distinct subgroups that differ Nussenzweig and M.C. Nussenzweig on page 27 of this issue). Similarly, the presence of mutations in EGFR is correlated...
Two Crucial Questions in Cancer

Who needs additional therapy after surgery?

Which therapy is most effective?

Prognosis

Prediction
Recurrences and Mortality: >50 y
With an average 4% reduction in recurrence and 3% reduction in mortality in patients over age 50…

How can we identify patients who will benefit from adjuvant treatment?
MammaPrint developed using unbiased gene selection based on patient outcomes

LOW RISK
No distant metastasis within 5 years

“Untreated” tumor samples with up to 20 year follow-up

70 most significant genes predictive of recurrence risk were identified

HIGH RISK
Distant metastasis within 5 years

Full human genome 25K

Ranking
First to prove clinical utility
Nature Paper: The Breakthrough

Gene expression profiling predicts clinical outcome of breast cancer

Laura J. van 't Veer†, Hongyue Dai‡, Marc J. van de Vijver†, Yudong D. He†, Augustinus A. M. Hart†, Mao Mao†, Hans L. Peterse†, Karin van der Kooy†, Matthew J. Marton‡, Anke T. Witteveen‡, George J. Sausber†, Ron M. Kerkhoven†, Chris Roberts‡, Peter S. Linsley†, René Bernards‡ & Stephen H. Friend‡

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Breast cancer patients with the same stage of disease can have markedly different treatment responses and overall outcome. The (top and bottom of plotively), suggesting that the basis of this set of upper group only 34% who developed distant lower group 70% of the (Fig. 1b). Thus, using some extent, distinguishing tumours.

To gain insight in signatures, we associate example, oestrogen receptor immunohistochemical stained tumours negative clustered together in the In the enlargement the gene is represented by genes that are apparent known ER target gene

A GENE-EXPRESSION SIGNATURE AS A PREDICTOR OF SURVIVAL IN BREAST CANCER

MARC J. VAN DE VIJVER, M.D., PH.D., YUDONG D. HE, PH.D., LAURA J. VAN ’T VEER, PH.D., HONGYUE DAI, PH.D., AUGUSTINUS A.M. HART, M.SC., DORIEN W. VOSKUIJL, PH.D., GEORGE J. SCHREIBER, M.SC., JOHANNES L. PETERSE, M.D., CHRIS ROBERTS, PH.D., MATTHEW J. MARTON, PH.D., MARK PARRISH, DOUWE ATSMA, ANKE WITTEVEEN, ANNUSKA GLAS, PH.D., LEONIE DELAHAYE, TONY VAN DER VELDE, HARRY BARTELINK, M.D., PH.D., SJOERD RODENHUIS, M.D., PH.D., EMIEL T. RUTGERS, M.D., PH.D., STEPHEN H. FRIEND, M.D., PH.D., AND RENÉ BERNARDS, PH.D.
Cancer’s Crystal Ball

For anyone who has battled breast cancer, the threat of recurring tumors is one that no treatment can completely eliminate—yet. But with MammaPrint, a genetic test of a tumor’s DNA, patients and doctors can get a better handle on how likely it is that the cancer will spread. The 70-gene screen, developed by Amsterdam-based Agendia, is the first test approved by the FDA that measures the activity of genes at work.

Available Approved in February
agendia.com
Levels of evidence determination

Category A prospective, randomized clinical trial designs
Category B prospective studies using archived tissue samples
Category C prospective, observational registry studies

Level I  1 study from Cat A or ≥ 1 studies from Cat B
Level II 1 study from Cat B or ≥ 2 studies from Cat C
Level III 1 study from Cat C Levels

Simon JNCI 2009
Category A: Clinical Utility
A Prospect Randomized Controlled Trial Against Standard of Care

Clinical Application of the 70-Gene Profile: The MINDACT Trial

Fatima Cardoso, Laura Van’t Veer, Emiel Rutgers, Sherene Loi, Stella Mook, and Martine J. Piccart-Gebhart

Abstract

The 70-gene profile is a new prognostic tool that has the potential to greatly improve risk assessment and treatment decision making for early breast cancer. Its prospective validation is currently ongoing through the MINDACT (Microarray in Node-Negative Disease May Avoid Chemotherapy) trial, a 6,000-patient randomized, multicentric trial. This article reviews the several steps in the development of the profile from its discovery to its clinical validation.

J Clin Oncol 26:729-735. © 2008 by American Society of Clinical Oncology
MINDACT Trial Design (n = 6,694);
Influence health outcome
Discordance between Clinical Risk assessment and MammaPrint in MINDACT N = 6694

32% Discordance between MammaPrint and Clinical risk assessment

Rutgers et al  ESMO 2013
A prospective evaluation of a breast cancer prognosis signature in the observational RASTER study

C.A. Dukker\(^1\), J.M. Bueno-de-Mesquita\(^2\), V.P. Retèl\(^3\), W.H. van Harten\(^3\), H. van Tinteren\(^4\), J. Wesseling\(^2\), R.M.H. Roumen\(^5\), M. Knauer\(^1,6\), L.J. van 't Veer\(^2,7,8\), G.S. Sonke\(^9\), E.J.T. Rutgers\(^1\), M.J. van de Vijver\(^2\) and S.C. Linn\(^9\)

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MammaPrint High Risk Patients had a Relatively Good 5 Year Distant Recurrence Free Interval

5YR DDFS

91.2%  208 (49%)  81% adjuvant chemotherapy

97%  219 (51%)  85% no adjuvant chemotherapy
MammaPrint Analytical and Clinical Validity
Externally confirmed in 6 FDA clearances

<table>
<thead>
<tr>
<th>Clearance</th>
<th>Year</th>
<th>Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>MammaPrint in Formalin Fixed Paraffin Embedded Tissue</td>
<td>2015</td>
<td>K141142</td>
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<tr>
<td>MammaPrint in all Agendia controlled Laboratories</td>
<td>2011</td>
<td>K101454</td>
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<tr>
<td>MammaPrint in post menopausal women</td>
<td>2009</td>
<td>K81092</td>
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<tr>
<td>Use of High Density Microarray Chip</td>
<td>2008</td>
<td>K08252</td>
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<tr>
<td>MammaPrint Ambient Temperature</td>
<td>2007</td>
<td>K70675</td>
</tr>
<tr>
<td>MammaPrint Fresh Frozen</td>
<td>2007</td>
<td>K062694</td>
</tr>
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2007 DE Novo 510K
MammaPrint is the predicate devices for future multi gene assays for breast cancer prognosis FDA clearances
The Committee considered that the uncertainty in the clinical-effectiveness evidence for MammaPrint limited the validity of the economic analysis.
Clinical Utility

• Test influences treatment decision: impact
• Test improves health outcome
  – Improved survival
  – Less toxicity and cost without compromising outcome
Why H2020

• Limited reimbursement in Europe leads to limited clinical adoption, leads to over utilization of chemotherapy
  – New type of test
  – New levels of evidence required
  – Impact different in different EU countries
  – Returns in diagnostics can not justify the clinical trials necessary, it is not a drug
H2020 Project proposal

• Establish robust data on Clinical Utility
  – Retrospective analysis of a Prospective Randomized Trail for Prognosis
  – Retrospective analysis of a Prospective Randomized Trail for Therapy Benefit

• Establish impact data
  – Prospective PRIME trial Germany
Why successful?

• Extensive detailed feedback from reimbursement authorities on the limitations
• Concrete plan to overcome the limitations
• Clear path to clinical adoption after completion of the project
• Clear path for growth after completion
• Clear benefit for EU breast cancer patients
  – Up to 70% of patients can safely forego chemotherapy