MammaPrint

Improving treatment decisions in breast cancer

Support and Involvement of EU

Bas van der Baan
VP Clinical Affairs
Irvine, California
Amsterdam, The Netherlands

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decoding cancer.

Leading Edge
Essay

Cell

It's Diagnostics, Stupid

René Bernards[1,*]
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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

opment 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?

Prognosis

Which therapy is most effective

Prediction

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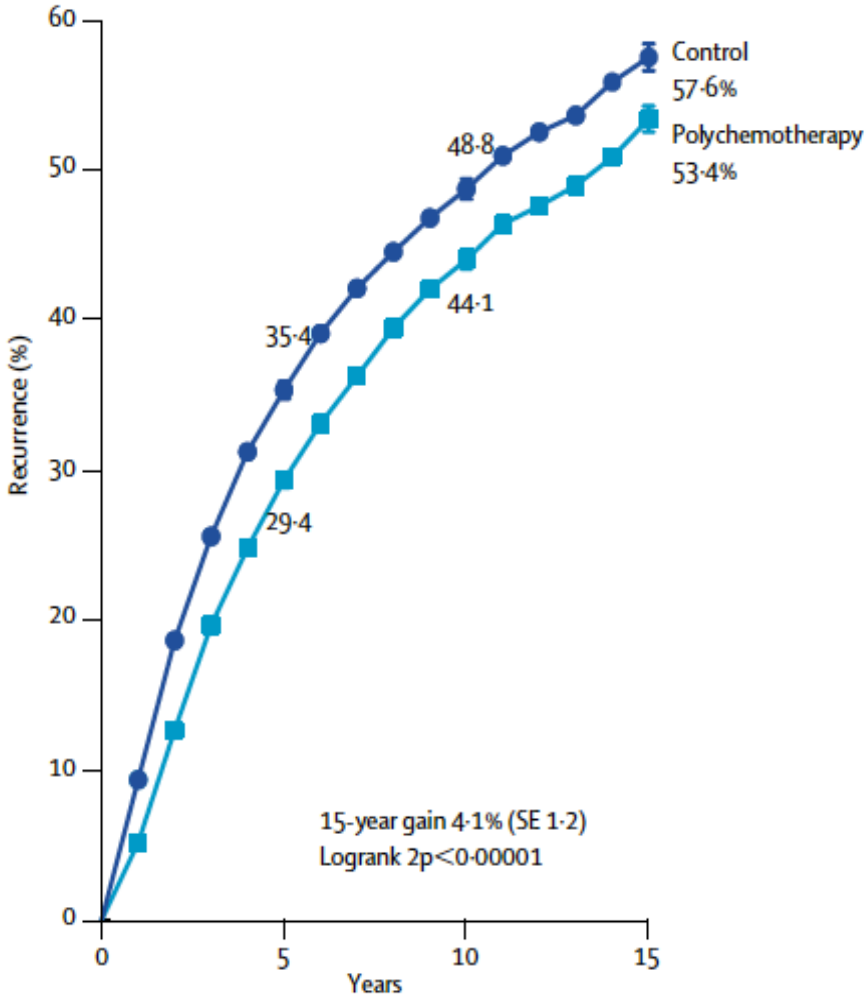
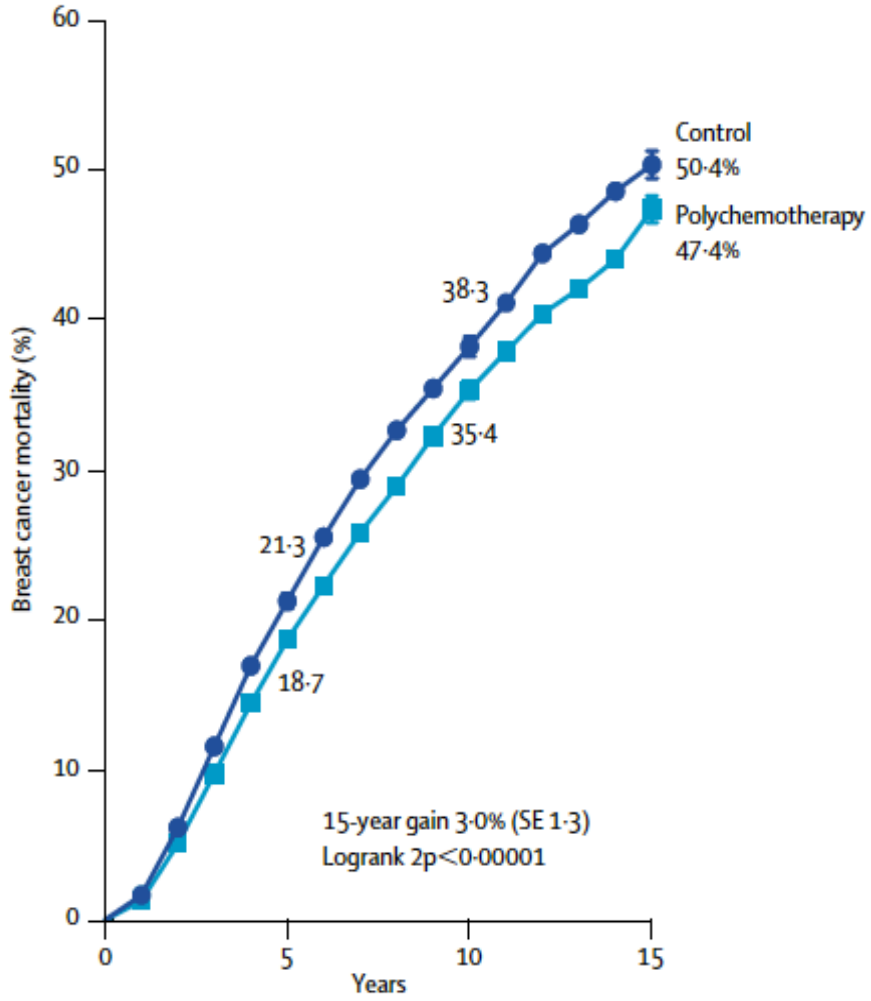
Recurrences and Mortality: >50 y

Entry age 50–69 years: recurrence



Entry age 50–69 years: breast cancer mortality



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?

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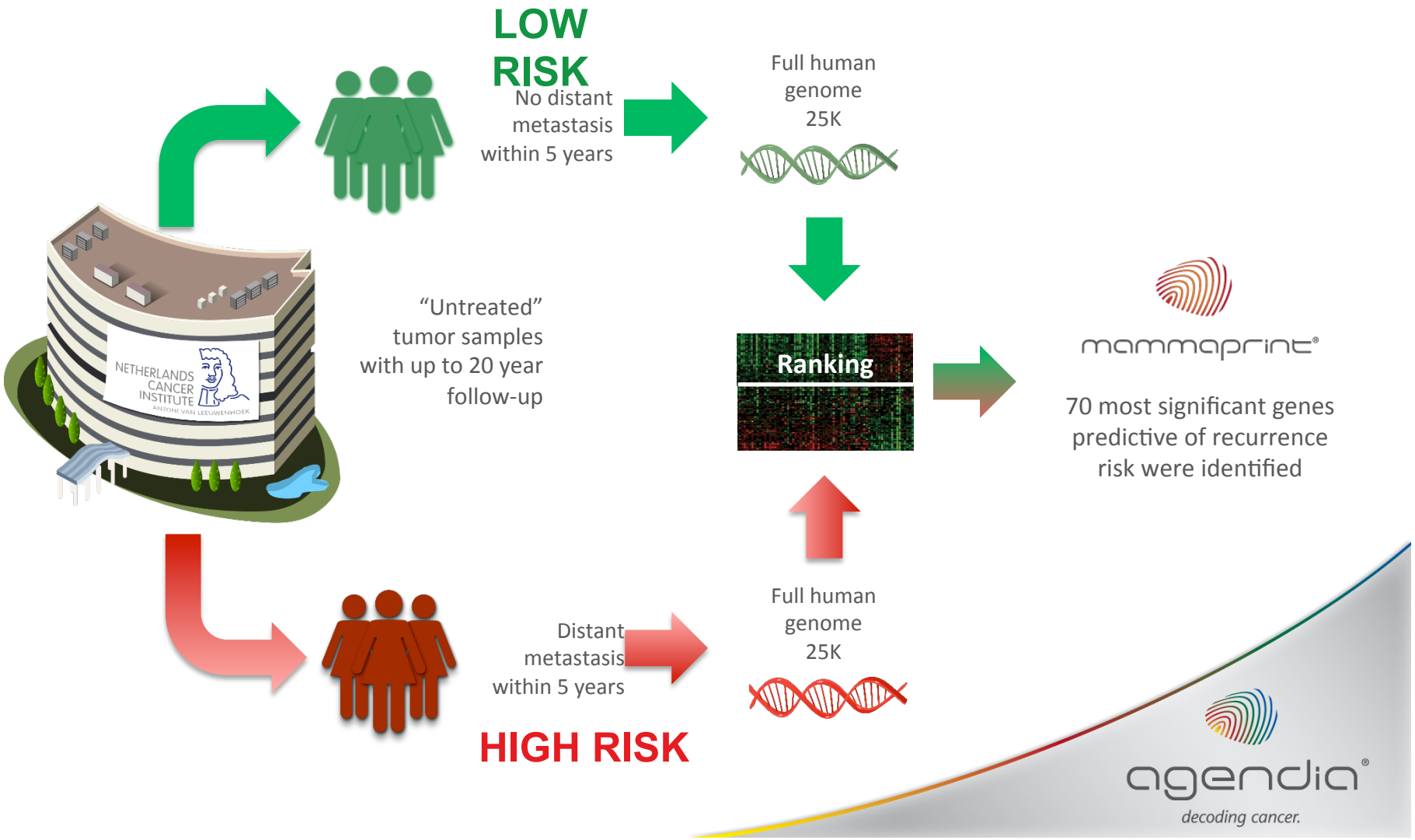
MammaPrint developed using unbiased gene selection based on patient outcomes



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. Schreiber‡, Ron M. Kerkhoven*, Chris Roberts‡, Peter S. Linsley‡, René Bernards* & Stephen H. Friend‡

** Divisions of Diagnostic Oncology, Radiotherapy and Molecular Carcinogenesis and Center for Biomedical Genetics, The Netherlands Cancer Institute, 121 Plesmanlaan, 1066 CX Amsterdam, The Netherlands*
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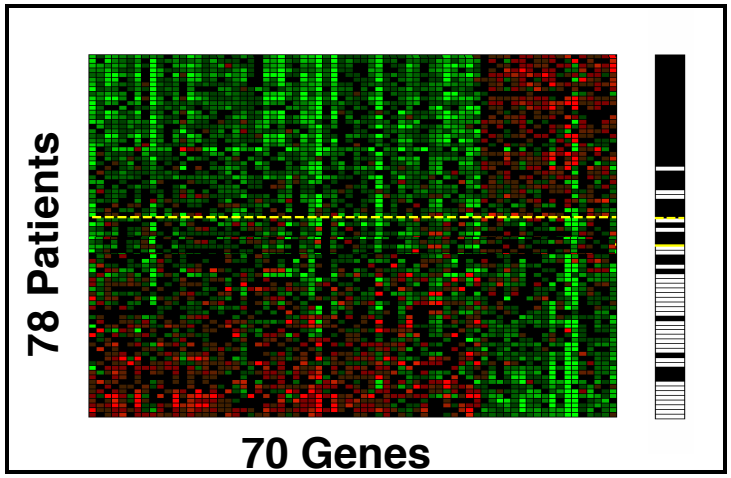
† These authors contributed equally to this work

Breast cancer patients with the same stage of disease can have markedly different treatment responses and overall outcome. The

(top and bottom of pi
tively), suggesting that
the basis of this set o
upper group only 34%
who developed distan
lower group 70% of t
(Fig. 1b). Thus, using
some extent, distingui
nosis' tumours.

To gain insight in
signatures, we associa
example, oestrogen re
immunohistochemical
stained tumours nega
clustered together in th
In the enlargement sh
genes is represented c
genes that are apparen
known ER target gene



NATURE | VOL 415 | 31 JANUARY 2002 | www.nature.com

Van 't Veer et al, *Gene expression profiling predicts clinical outcome of breast cancer*, Nature, Vol 415, 2002

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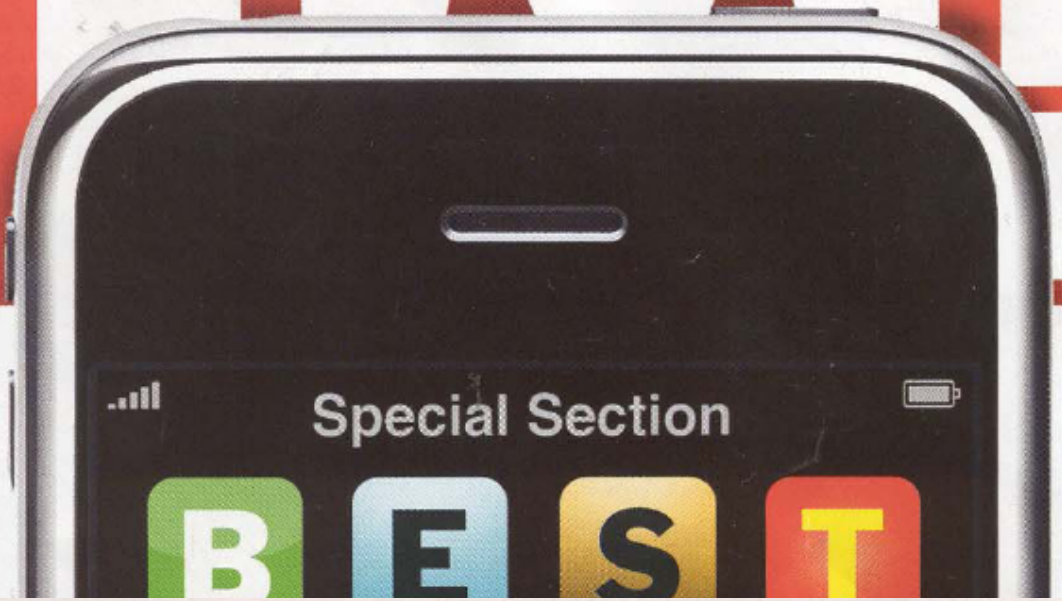
Clinical Validity NEJM 2002

The New England
Journal of Medicine

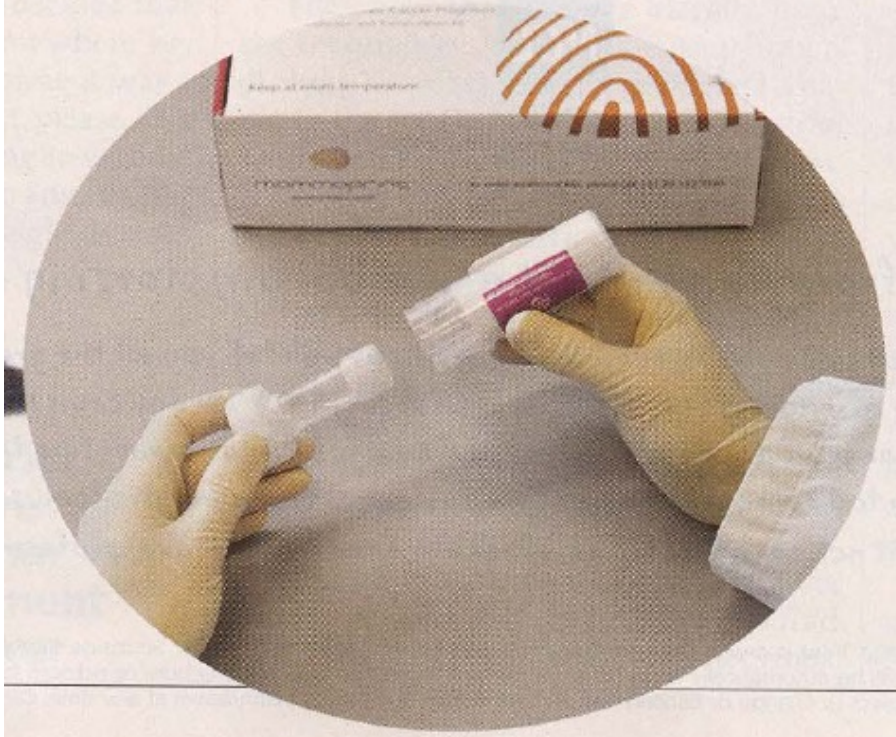
VOLUME 347 DECEMBER 19, 2002 NUMBER 25

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. VOSKUIL, 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.



From the phone that has changed



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

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JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

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

From the Jules Bordet Institute, Brussels, Belgium; Netherlands Cancer Institute, Amsterdam, the Netherlands; and Peter MacCallum Cancer Centre, Melbourne, Australia.

Submitted September 4, 2007; accepted November 30, 2007.

Supported by the European Commission Framework Programme VI, the Breast Cancer Research Foundation, the European Breast Cancer Confer-

A B S T R A C T

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

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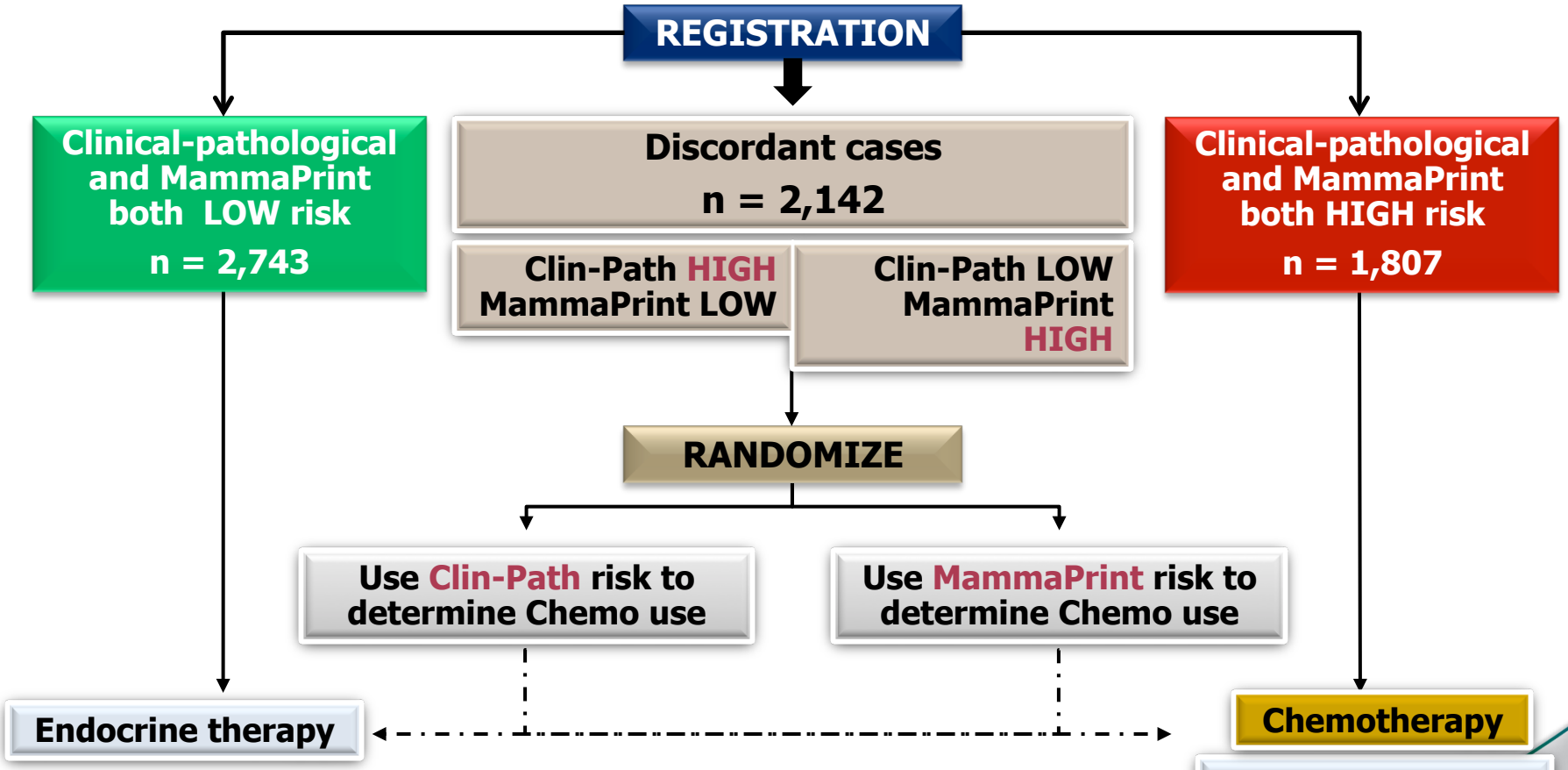
MINDACT Trial Design (n = 6,694);



Rutgers et al; ESMO 2013

Supported by the EU framework VI programme

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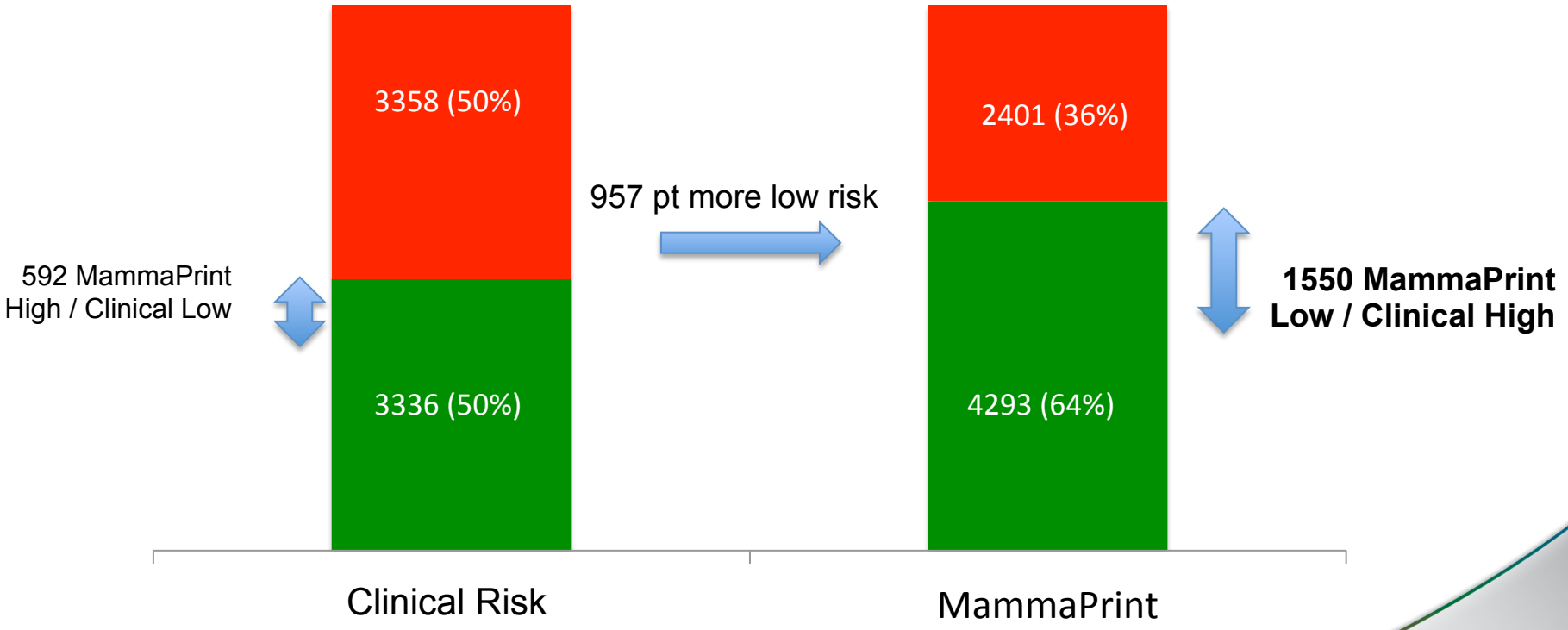
Influence health outcome
Discordance between Clinical Risk assessment and MammaPrint in MINDACT N = 6694



32% Discordance between MammaPrint and Clinical risk assessment

Rutgers et al ESMO 2013

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Category C: Clinical Utility

IJC
International Journal of Cancer

A prospective evaluation of a breast cancer prognosis signature in the observational RASTER study

C.A. Drukker[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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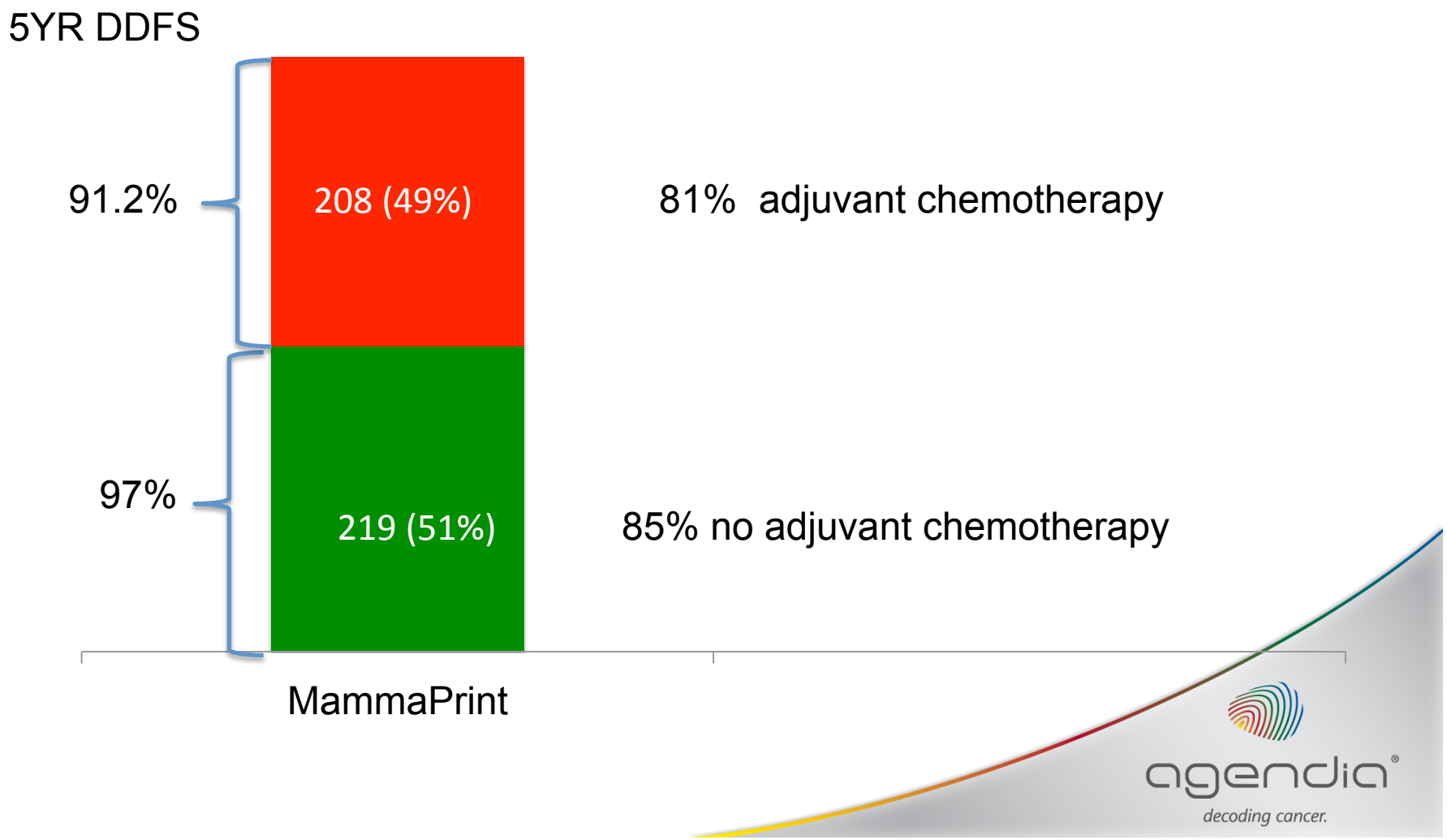
[9] Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands

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



MammaPrint Analytical and Clinical Validity Externally confirmed in 6 FDA clearances

Clearance	Year	Clearance
MammaPrint in Formalin Fixed Paraffin Embedded Tissue	2015	***K141142***
MammaPrint in all Agendia controlled Laboratories	2011	***K101454***
MammaPrint in post menopausal women	2009	***K81092***
Use of High Density Microarray Chip	2008	***K08252***
MammaPrint Ambient Temperature	2007	***K70675***
MammaPrint Fresh Frozen	2007	***K062694***

2007 DE Novo 510K

MammaPrint is the predicate devices for future multi gene assays for breast cancer prognosis FDA clearances

Feedback National Institute Clinical Excellence UK

- 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

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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

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