Neoadjuvant Drug Treatment for Breast Cancer Response Prediction and Response Monitoring
Executive Summary

Neoadjuvant chemotherapy (NAC) may help to further improve survival of stage II and III breast cancer, as it allows adaptation of the drug regimen to the response of the primary tumor. To do this with optimal efficacy, biomarkers to guide treatment selection are urgently required, and a strategy to monitor and quantify the treatment response must be defined. In addition, NAC presents specific problems and opportunities for radiation oncology, as only part of the usual staging information is available (e.g., the number of initially tumor-positive lymph nodes is unknown).

This project has addressed these problems and opportunities in a program that involved a total of 479 patients who underwent NAC in the Netherlands Cancer Institute. Candidate biomarkers were identified in experiments with genetically engineered mice. Genomic and proteomic analyses were done on biopsies of the primary tumors and additional genomic analyses were done on tumors of patients with M1 disease. Imaging studies were performed to design and standardize response monitoring by a combination of Magnetic Resonance and Positron-Emission Tomography and to employ molecular imaging in an experimental setting.

In the biomarker field, the most definitive progress was made for triple-negative tumors. A aCGH assay for BRCAness was successfully converted into a low-cost and rapid MLPA test. This test was validated in retrospective series and put to the final test in an ongoing multi-center phase III trial, that aims to show that tumors with BRCAness are exquisitely sensitive to DNA damaging chemotherapy. Additional predictive markers were identified and are currently in varying stages of development. A functional assay was developed that is able to predict the significance of unclassified variants of the BRCA1 gene. A strategy to identify genes in clinical tumor samples, whose expression levels may cause chemotherapy resistance was designed, and validated.

Contrast-enhanced MRI remains the best approach for response monitoring. Its performance can be significantly enhanced by taking the breast cancer subtype into account, and when automated image analysis is employed, particularly in the ‘luminal’ subtype (Computer Assisted Response Prediction, CARP). The added value of PET/CT was shown to strongly depend on the breast cancer subtype; it may also help to interpret MRI findings in certain cases. A tumor control probability model for breast cancer irradiation was completed and a novel image-guided radiotherapy correction strategy was designed and implemented, which is currently employed in the PAPBI (Preoperative Accelerated Partial Breast Irradiation) study.

"Adjuvant chemotherapy is steadily improving the cure rate of breast cancer. Preoperative chemotherapy allows adaptation of the regimen to response and, increasingly, the tailoring of the treatment to the individual tumor. This project has yielded novel tools to predict and to monitor response. Cure is the primary objective: there is no substitute!"
Neoadjuvant drug therapy in breast cancer. The recent fall in breast cancer mortality is mainly caused by the addition of drug treatment (“adjuvant therapy”) to the local treatment modalities surgery and radiation therapy. Drug treatment aims to eradicate microscopic disease, the presence of which cannot be detected at the time of local treatment, but which may eventually give rise to distant metastases. Adjuvant drug therapy has been shown to reduce breast cancer mortality by nearly 50%. Both chemotherapy and targeted agents are used and are often administered after local treatment, when their efficacy in the individual tumor can no longer be determined. The use of adjuvant therapy before surgery is often called “neoadjuvant therapy”. In this setting, the effect of the drugs on the tumor can be assessed, and the complete disappearance of all tumor cells at microscopic examination (pathologic complete remission, or pCR) correlates closely with overall survival. Thus, achieving a pCR is an appropriate intermediate goal. Current drug treatment schedules achieve pCR in about 10% of luminal type breast cancers, and in 33% of basal-like and in half of the HER2/neu-positive tumors. The optimal neoadjuvant treatment regimen is unknown, and is almost certainly different for each individual tumor. In addition, the optimal dose, duration and sequence of drug combinations are not usually adapted to individual tumor properties.

Clinical Need

Improving the survival of stage II and III breast cancer through:

(i) the selection of chemotherapy
(ii) the adaptation of the regimen based on response monitoring

Tools

- Array CGH, high-complexity gene expression arrays, MLPA, next generation sequencing, proteomics
- Conversion of research tool to clinical tests (e.g., employing MLPA)
- Chemotherapy trials in mouse-models, controlled clinical studies in humans
- Computer-aided response prediction, Computerized image interpretation
Development of new imaging tools and specific biomarkers that guide the selection and adaptation of neoadjuvant chemotherapy

Academic partners
Supporting Foundations
Industrial partners
Advisory board
ISAC CTMM

SteeringCie
Partner Representatives
CTMM

Project Team
PI: Prof.dr. S. Rottenberg (NKI)
IP manager: K. Verhoef (NKI)
WP leaders
Industrial partners
Dr. E. Caldenhoven (CTMM)

Workpackage leaders
WP1: Dr. S. Rottenberg (NKI)
WP2: Dr. J.M.M. Jonkers (NKI)
WP3: Dr. F.W. van Leeuwen (NKI)
WP4: Dr. J.M.M. Jonkers (NKI)
WP5: Prof.dr. S. Rodenhuis (NKI)
WP6: J. Foekens (EUMC)
WP7: Prof.dr.M.J. v.d. Vijver (AMC)
WP8: Dr. K.G.A. Gilhuijs (UMCU)
WP9: Dr. J.J. Sonke (NKI)
WP10: Dr. L.F.A. Wessels (NKI)

Advice
CTMM

Operations
CTMM

Partners
Coordination
Finance
Publications

Coordination
Finance
Publications

CTMM
Budget: CTMM manages the flow of funds

Funding:
- 25% Academia
- 25% Industrial
- 50% Government Subsidy

Project costs:
- Personnel
- Materials
- Use of existing equipment
- Investments
- Third parties
- Management (5%)
Facts & Figures

Distribution of the BreastCARE consortium budgets to perform the R&D activities

**Budget**: 12.6 M €

**Start**: 2008

**End**: 2014

**Partners**: 7

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**Academic Cash Costs**

- PhD: 1,000,000
- PostDoc: 3,000,000
- Sen. Staff: 2,000,000
- Supp. Staff: 1,000,000
- IT Staff: 0
- M&S: 0
- Investments: 0

**Academic In Kind Costs**

- PhD: 1,000,000
- PostDoc: 2,000,000
- Sen. Staff: 3,000,000
- Supp. Staff: 4,000,000
- IT Staff: 0
- M&S: 0
- Investments: 0

**Industrial Cash Costs**

- PhD: 0
- PostDoc: 0
- Sen. Staff: 0
- Supp. Staff: 0
- IT Staff: 0
- M&S: 0
- Investments: 0

**Industrial In Kind Costs**

- PhD: 0
- PostDoc: 0
- Sen. Staff: 0
- Supp. Staff: 0
- IT Staff: 0
- M&S: 0
- Investments: 0
### Facts & Figures

<table>
<thead>
<tr>
<th>Budget</th>
<th>12.6 M €</th>
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<tr>
<td>Start</td>
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<td>End</td>
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<td>FTE</td>
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<td>7 planned for 2015/2016</td>
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<td>Personal Grants</td>
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<td>Patent Applications</td>
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<td>2 IDF/patent applications in preparation: WP1 – XIST gene expression predicts chemotherapy sensitivity; WP3 - Development of hybrid imaging labels for PET and fluorescence imaging</td>
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<td>Raising Capital (&gt; 1 M€)</td>
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<td>ERC Grant 2012 (F.W. van Leeuwen, NKI) - ERC advanced Grant 2011 (Prof. Dr. J.A. Foekens, EMC) – EU FP7 project ARTFORCE 2011 (Jan-Jakob Sonke, NKI) – NOW Zenith Roadmap subsidy 2012, 18,6 miljon euro for Mouse Clinic for Cancer and Aging (Jos Jonkers, NKI).</td>
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<td>Awards</td>
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<td>AACR – Translational Cancer Medicine Award for Sven Rottenberg in 2010;</td>
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<td>Public Media</td>
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<td>Press release 2013 – Test classificeert DNA varianten erfelijke borstkanker (NKI)</td>
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Scientific Value Creation - Breakthroughs

- 2011: CTMM researchers at NKI and UMCU have shown that the accuracy to monitor treatment response of positron emission tomography (PET) and magnetic resonance imaging (MRI) depends on the breast-cancer subtype.

- 2012: Workers at the NKI generate models of mouse mammary tumors that cannot acquire drug resistance by restoration of BRCA1 function or by Pgp-mediated drug efflux, allowing the study of additional clinically relevant resistance mechanisms.

- 2012: CTMM researches at MRC Holland and NKI collaborate to develop and validate a simple MLPA test that detects ‘BRCAness’ and BRCA1 promoter methylation in small tumor samples.

- 2013: CTMM Investigators at the NKI develop and validate a screening tool that links detects genes whose expression levels in tumor tissue are closely linked with clinical chemotherapy resistance.

- 2013: CTMM investigators at the EMC complete a comparative tissue proteomics pipeline for in-depth proteome profiling and biomarker discovery using high resolution mass spectrometry.

- 2013: CTMM researchers at NKI have shown that in patients with ER-positive breast cancer receiving neoadjuvant chemotherapy, MRI after chemotherapy is a better predictor of recurrence-free survival than pathological complete remission (pCR).

- 2013: CTMM researchers at the NKI have developed a functional assay that determines the clinical significance of unclassified BRCA1 variants in germ line DNA.

- 2013: CTMM investigators at the NKI develop and validate a screening tool that links detects genes whose expression levels in tumor tissue are closely linked with clinical chemotherapy resistance.

- 2014: Investigators at the NKI have established a database of a large cohort of patients who underwent neoadjuvant chemotherapy for stage II or III breast cancer (N > 500), linked to databases with molecular data of pre-chemotherapy tumor biopsies, MRI and PET-CT imaging details, and many other features.

Highest Impact Papers – mean 21.8


Mean Impact Factor

International - oncology: 4.4
CTMM - oncology: 5.7
## Scientific Value Creation - Theses

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<tr>
<th>BreastCARE Thesis</th>
<th>Partner</th>
<th>Year</th>
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<tr>
<td>J.J de Ronde</td>
<td>NKI</td>
<td>2013</td>
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<td>B.B. Koolen</td>
<td>NKI</td>
<td>2013</td>
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<tr>
<td>J.E. Jaspers</td>
<td>NKI</td>
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<td>K.E. Pengel</td>
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<td>H.R. Zhang</td>
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<td>W. Chen</td>
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<tr>
<td>C.D. Savci Heijink</td>
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</tr>
<tr>
<td>R.B.H. Braakman</td>
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</table>
Scientific Value Creation - Infrastructure

- Spontaneous K14cre;Brca1^{F/F};p53^{F/F} mouse model for hereditary breast cancer (NKI)
- Novel genetically engineered cell lines and mouse models for breast cancer, including the development of an ER+ breast cancer mouse model (NKI)
- Genetically engineered mouse models for Brca1-mutated hereditary breast cancer and E-cadherin-mutated lobular breast cancer (NKI)
- Generation of mouse mammary tumors that cannot acquire drug resistance by restoration of BRCA1 function or Pgp-mediated drug efflux (NKI)
- Introduction of a tumor cell-specific GFP reporter to discriminate tumor from stromal cells (NKI)
- CARP (Computer Aided Response Prediction) (UMCU)
- DIDS (Detection of chemotherapy resistance markers by imbalance of differential signals) (NKI)
- Data Mining in Imaging (combining principal component analysis, Bayesian neural networks and Binary logistic regression) (UMCU)
- Radiation therapy planning infrastructure to tailor the dose distribution to specific residual microscopic disease distributions and residual geometric uncertainties (NKI, Philips).

- N08RMB imaging database: prospective cohort of patients undergoing neoadjuvant chemotherapy N=295 (NKI & UMCU)
- Neoadjuvant chemotherapy patients – clinical database: N= 479 (NKI)
- Pre-neoadjuvant chemotherapy tumor bank (NKI)
- A collection of more than 1000 fresh-frozen samples of drug-sensitive or –resistant mouse mammary tumors. Of these samples FFPE material and small tumor fragments for orthotopic transplantation into syngeneic animals is available (NKI)
- Development of a comparative tissue proteomics pipeline for in-depth proteome profiling and biomarker discovery using high resolution mass spectrometry (EMC)
- MLPA for BRCAness and for BRCA1 methylation (NKI, MRC Holland)
- Functional test for unclassified BRCA1 variants (NKI)
- MRI/PET-CT combination – Response prediction (NKI/UMCU)
- A proteomics signature to predict neo-adjuvant and advanced chemotherapy resistance in ER negative breast cancer. (EMC)
- Dose calculation on CBCT scans in Pinnacle treatment planning system and advanced CBCT reconstruction techniques for improved target definition (NKI, Philips)
Clinical and Economic Value Creation of BREASTCARE

New ‘products’ for clinical care
Main Product Pipelines

- Discovery biomarkers
- Selection of promising markers
- Clinical & Experimental Verification
- Final measurement platform/protocol
- Clinical Validation platform

MLPA BRCAness
- Not financed by CTMM
- Partially financed by CTMM

Functional test for unclass. BRCA1 variants
- Not financed by CTMM

Prot. Profile anthracycline resistance

PI3K pathway Perturbation (NGS)
- Partially financed by CTMM

Comp. aided response pred.

Image-guided preop. breast irradiation
MLPA for BRCAness in triple-negative tumors

**Product**

BRCA1 and BRCA2 can be inactivated in sporadic cancers as well, which is referred to BRCAness. In BRCA1 mutation carriers breast tumour samples have a characteristic pattern of DNA gains and losses. BRCA1ness profile is present in about half of all triple negative sporadic breast cancers and is predictive for benefit from intensified chemotherapy.

**Leading company:**
MRC Holland

**Current Diagnostics**

Currently, the BRCA1-like aCGH assay is used in two multicenter clinical trials. Patient biopsies are tested for BRCAness, and BRCA1-like patients are randomised between different chemotherapy regimens. As such, the aCGH BRCA1-like assay has already impact on clinical decision making. In addition the assay is used in the clinical genetic testing.

**Main results in CTMM**

- The 191-probe aCGH BRCA1-like classifier was translated into a 34-probe MLPA assay
- The MLPA assay performs equally well as the aCGH to detect a BRCA1-like pattern in both clinical genetic testing as in treatment benefit prediction.
- In a randomized controlled trial, patients with a BRCA1-like tumor showed a remarkably better survival upon intensified alkylating chemotherapy compared to standard dose.
- The assay is rapid and robust, can be multiplexed and works well with FFPE material, prerequisites for a clinical application.

**Future Outlook**

- Selection of patients with BRCA1/2-like breast cancer for treatment with intensified chemotherapy
Computer-Aided Response Prediction (CARP)

Breast cancer response monitoring
PET/MR response Imaging interpretation for tumor response monitoring based on MRI and PET/CT is complex and prone to differences in interpretation between medical specialists. This limits the efficacy to switch patients away from ineffective drug regimens, hence compromising benefits of neoadjuvant drug therapy.

CARP workstation
It is desirable to have a standardized tool to assess the risk of a breast cancer treatment failure on the basis of MRI and PET/CT early after initiating drug therapy. This tool should minimize user interaction in order to reduce clinical workload and to achieve uniformity across medical centres worldwide. Together with the University Medical Center Utrecht, Philips has developed such a system, known as CARP (Computer-Assisted Response Prediction).

Main results in CTMM

Identification of clinical limitations:
Researchers at NKI and UMCU have shown that the accuracy to monitor treatment response using positron emission tomography (PET) and magnetic resonance imaging (MRI) depends on the breast-cancer subtype.

Merit of computerized image interpretation:
Automated analysis of treatment response using computer interpretation is not affected by breast cancer subtype and significantly raises the accuracy to monitor treatment response in ER-positive breast cancers.

Future Outlook
- Prospective validation
- Incorporation into commercial products

Quality of Life (QoL):
Better tools to monitor tumor response to therapy will reduce exposure of patients to ineffective drug regimens, avoiding side effects that reduce QoL and offering them a second chance for cure

Accessibility:
Ultimately, all doctors must be able to purchase this technology and have access to these tools
MRI-PET/CT Breast Biopsy System

Breast cancer biopsy
Breast cancer is a highly heterogeneous disease. Systemic drug therapy is tailored to breast cancer subtype that is defined by the status of the receptors on the cancer-cell membranes. Tissue sampling by core needle biopsy may yield an estimate of breast cancer subtype that is not representative for the whole tumor, thus potentially limiting the efficacy of neoadjuvant drug therapy.

MRI-PET/CT biopsy system
In collaboration with Phillips, a prototype breast biopsy system was developed to obtain tissue samples guided to the most representative part of the cancer under PET/CT and MRI guidance. The system is based on a replica of the 7-channel MRI breast biopsy coil, and uses advanced automated deformable registration of PET/CT and previously acquired MRI.

Main results in CTMM

Setup and calibration:
Deviations in the trajectory of the biopsy needle have been calibrated and stored in a correction table, taking tangential forces into account exerted on the needle tip by surrounding breast tissue as function of distance to the template.

Longitudinal image registration:
Breast images in compressed and uncompressed state were successfully registered using robust automated deformable registration. Proof of concept to detect inhomogeneity in Her2/Neu receptor status has been reported\(^1\).

1. Dmitriev et al., PMB, 1221-33, 2013

Future Outlook
- Define the potential place of this technology in the workflow logistics of breast cancer therapy

Quality of Life (QoL):
Sampling of the most malignant part of the tumor may speed up discovery of predictive tissue biomarkers and help reduce exposure of patients to potentially ineffective drug regimens, thus improving their quality of life and increasing their changes of disease-free overall survival.

Accessibility:
We currently have a prototype of the system and are in the process of defining its potential place in the clinical logistics trajectory.
Functional test for unclassified BRCA1 variants

Approximately 2–3% of all breast and ovarian cancer cases are attributable to mutations in BRCA1. For most BRCA1 mutations it is known whether they increase the risk of cancer or not. However, for approximately 10% of all BRCA1 mutations the effect is unclear. The NKI has now developed a functional test to determine which of these so-called unclassified mutations result in a defective BRCA1 gene and which don’t. Using this test, they have determined the effect of 74 of these unclassified BRCA1 mutations. This information may provide clarity concerning the risks of cancer for the patient and her relatives. The test may also provide information for the tailored treatment of breast or ovarian cancer patients with unclassified BRCA1 mutations.

Current Diagnostics
In current clinical practice, genetic counselors determine the hereditary breast and ovarian cancer risk of women via assessment of medical records and family history of cancer, and via genetic testing of the BRCA1 and BRCA2 genes. This information is used to estimate the risk of breast and ovarian cancer for the family members and give advice on medical management, which can range from increased cancer surveillance to preventive surgery to reduce cancer risk.

Main results in CTMM

Assay development:
A functional assay was developed to test pathogenicity of BRCA1 variants of uncertain significance (VUS). This assay is based on complementation of inducible Brca1-knockout embryonic stem cells with human BRCA1 genes.

Demonstrator development:
The assay was validated using various BRCA1 variants of known significance. The assay system was subsequently used to classify 74 BRCA1 VUS.

Future Outlook:
• Functional classification of all BRCA1 VUS in the Netherlands

Quality of Life (QoL):
Better classification of BRCA1 mutation carriers results in better QoL. Women with non-pathogenic mutations are not exposed to prophylactic mastectomy and ovariectomy. Women with pathogenic mutations may opt for increased cancer surveillance or preventive surgery.

Accessibility:
Additional funding is currently requested from NutsOhra to run the assay for families with BRCA1 VUS.
Early HTA: Potential Impact of New Technologies

Value of response guidance by imaging

1. Switching chemotherapy based on ultrasound is contributing to cost-effectiveness

<table>
<thead>
<tr>
<th>Population</th>
<th>Monitoring</th>
<th>Costs (pp*)</th>
<th>QALYs (pp*)</th>
<th>ICER</th>
<th>Cost-effective?</th>
<th>Source</th>
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<tbody>
<tr>
<td>All breast cancer</td>
<td>No</td>
<td>103.625€</td>
<td>12.23</td>
<td>-</td>
<td>-</td>
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<td></td>
<td>Yes</td>
<td>111.441€</td>
<td>14.25</td>
<td>3.875</td>
<td>Yes</td>
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</table>

2. Switching chemotherapy by breast cancer subgroups is more cost-effective.

<table>
<thead>
<tr>
<th>Population</th>
<th>Monitoring</th>
<th>Costs (pp*)</th>
<th>QALYs (pp*)</th>
<th>ICER</th>
<th>Cost-effective?</th>
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<tr>
<td>All breast cancer</td>
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<td>85.716 €</td>
<td>7.99</td>
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<td>Stratified by ER status</td>
<td>Yes</td>
<td>85.526€</td>
<td>8.15</td>
<td>Dominant (-1.174)</td>
<td>Yes</td>
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Note: Differences in costs and QALYs between tables are due to differences in the chemotherapeutic regimens used (Table 1: TAC and switch to NX ; table 2: ddAC and switch ddDC in HER2- patients, and PTC in HER2+.)
3. Switching chemotherapy based on MRI and PET/CT (separately) is expected to be cost-effective, when compared to US, for its higher sensitivity (MRI&PET/CT) and specificity (PET/CT).

<table>
<thead>
<tr>
<th>Population</th>
<th>Monitoring technique</th>
<th>Costs (pp*)</th>
<th>QALYs (pp*)</th>
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<td>PET/CT</td>
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<td>PET/MRI (CARP SOFTWARE)</td>
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<td>t.b.d</td>
<td>assumption</td>
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**CARP SOFTWARE?**

with additional costs (fusion software (~110.000 €), training of the personnel (time & creation of new working paths), and (often) purchase of a new scanner (MRI or PET/CT ~ 3 million €)) is **likely to be cost-effective** if:

- The combined PET/MRI parameter(s) have higher sensitivity and specificity than that of cheaper alternatives (e.g. ultrasound, MRI, etc)
- Research focuses on subpopulations of breast cancer.

Value of novel biomarkers for response prediction:
MLPA for BRCAaness, MLPA for XIST and IHC for 53BP1

<table>
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<tr>
<th>Population</th>
<th>Biomarker</th>
<th>Costs (pp*)</th>
<th>QALYs (pp*)</th>
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<th>Probability of cost-effectiveness*</th>
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<tr>
<td>Triple negative breast cancer (TNBC)</td>
<td>No</td>
<td>29.439 €</td>
<td>7.30</td>
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<td>-</td>
<td>5%</td>
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<td></td>
<td>BRCAness (MLPA)</td>
<td>63.859 €</td>
<td>10.23</td>
<td>11.742</td>
<td>Yes</td>
<td>23%</td>
<td>(4)</td>
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<td></td>
<td>BRCAness (MLPA) + XIST (MLPA) + 53BP1 (IHC)</td>
<td>49.929 €</td>
<td>9.10</td>
<td>11.380</td>
<td>Yes</td>
<td>19%</td>
<td>(4)</td>
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</table>

Using the BRCAness MLPA alone (11.742 €/QALY) or combined with XIST and 53BP1 (11.380 €/QALY) has the potential to be cost-effective. Yet, due to the early stage of development of these biomarkers, there is a high degree of uncertainty in these results.

✓ Further research on the performance of the biomarkers and on the survival benefit, would increase its probability of cost-effectiveness.

(4) CTMM & Linn’s lab data (NKI). * Under the designed threshold in the Netherlands, 80.000€.
Partners

Academic Medical Center (AMC)  Amsterdam
Erasmus University Medical Center (EUMC)  Rotterdam
Netherlands Cancer Institute (NKI)  Amsterdam
University Medical Center Utrecht (UMCU)  Utrecht
Merck Sharp & Dohme BV (MSD)  Oss
MRC-Holland BV  Amsterdam
Royal Philips  Eindhoven


38. Gilhuijs KGA, Dmitriev I, Pengel KE, Koolen BB, Loo CE. Automatische PET/MR registratie van borstkanker voor het monitoren van therapie response. Gamma


42. Huijbers IJ, Krimpenfort P, Berns A, Jonkers J. Rapid validation of cancer genes in chimeras derived from established genetically engineered mouse models. Bioessays. 2011 Sep;33(9):701-10

List of Publications


### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AACR</td>
<td>American Association for Cancer Research</td>
</tr>
<tr>
<td>BRCA</td>
<td>BReast CAnce</td>
</tr>
<tr>
<td>CARP</td>
<td>Computer Assisted Response Prediction</td>
</tr>
<tr>
<td>CBCT</td>
<td>Cone Beam-CT</td>
</tr>
<tr>
<td>CGH</td>
<td>Complete Genome Hybridization</td>
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<tr>
<td>CT</td>
<td>Computer Tomogram</td>
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<td>ER</td>
<td>Estrogen Receptor</td>
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<td>ERC</td>
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<tr>
<td>FFPE</td>
<td>Formalin-fixed, paraffin-embedded</td>
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<td>GFP</td>
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<td>HER2</td>
<td>Human Epidermal growth factor Receptor</td>
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<td>ICER</td>
<td>Incremental Cost-Effectiveness Ratio</td>
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<td>IDF</td>
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<td>ISAC</td>
<td>International Scientific Advisory Committee</td>
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<td>MLPA</td>
<td>Multiplex Ligation-dependent Probe Amplification</td>
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<td>Variants of Unknown Significance</td>
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<td>Quality-Adjusted Life Years</td>
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<tr>
<td>XIST</td>
<td>X-inactive Specific Transcript</td>
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Co funded by Netherlands Enterprise Agency

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