

Cancer Association of South Africa (CANSA)



CANSA Fact Sheet on MammaPrint Test

Introduction

The MammaPrint Test, made by Agendia, is a genomic test that analyses the activity of certain genes in early-stage breast cancer. Research suggests the MammaPrint Test may eventually be widely used to help make treatment decisions based on the risk of cancer coming back (recurrence) within 10 years after diagnosis. Knowing if a woman has a high or low risk of early-stage breast cancer coming back might help women and their doctors decide if chemotherapy or other treatments to reduce risk after surgery are needed.

[Picture Credit: MammaPrint]



Haan, J.C., Bhaskaran, R., Ellappalayam, A., Bijl, Y., Griffioen, C.J., Lujinovic, E., Audeh, W.M., Penault-Llorca, F., Mittempergher, L. & Glas, A.M. 2021.

“MammaPrint® (MP) is a 70-gene signature that stratifies early-stage breast cancer patients into low- and high risk of distant relapse. Further stratification of MP risk results identifies four risk subgroups, ultra-low (UL), low, high 1, and high 2, with specific prognostic and predictive outcomes. BluePrint® (BP) is an 80-gene signature that classifies breast tumors as basal, luminal, or HER2 molecular subtype. To gain insight into their biological significance, we annotated the MP 70- and BP 80-genes with respect to the 10 hallmarks of cancer (HoC). Furthermore, we related gene expression profiles of the extreme ends of the MP low- and high-risk patients (here called, ultra-low (UL) and ultra-high (UH) or High2, respectively), to the 10 HoC per BP subtype by differential gene expression and pathway analysis. MP and BP gene functions reflected all 10 HoCs. Most MP and BP genes were associated with sustaining proliferative signaling, followed by genome instability and mutation categories. Based on the gene expression profiles, UL and UH subgroup pathways were down -or upregulated, respectively, reflecting proliferative and metastatic features, such as G2M checkpoint, DNA repair, oxidative phosphorylation, immune invasion, PI3K/AKT/mTOR signaling, and hypoxia pathways. Notably, the UH HER2-type was enriched in several immune signaling pathways, such as IL2/STAT5 signaling and TNF α signaling via NF κ B. Our results show that MP and BP gene signatures represent and capture all 10 HoCs and highlight underlying biological processes of MP extreme samples, which might guide treatment decisions as the signature captures the full spectrum of early breast cancers.”

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Dubsky, P., Van't Veer, L., Gnant, M., Rudas, M., Bago-Horvath, Z., Greil, R., Lujinovic, E., Buresch, J., Rinnerthaler, G., Hulla, W., Moinfar, F., Egle, D., Herz, W., Dreezen, C., Frantal, S. & Filipits, M. 2020.

Background: MammaPrint is a prognostic assay based on gene expression in tumors from patients with early breast cancer. MammaPrint has been extensively validated and Food and Drug Administration cleared in fresh and formalin-fixed and paraffin-embedded (FFPE) tissue. We aimed to assess its prognostic performance in the biomarker cohort of the Austrian Breast and Colorectal Cancer Study Group 8 (ABCSG-8) patient population, and to obtain a higher level of evidence with regard to its clinical validity after RNA extraction from FFPE biobank tissue.

Patients and methods: A prespecified retrospective analysis to test the prognostic performance of the MammaPrint test to predict distant recurrence-free survival at 5 and 10 years as primary end point was carried out. MammaPrint risk, clinicopathological factors (after central pathological review), and clinical risk (using a modified version of Adjuvant! Online) were evaluated by Cox regression analyses.

Results: From 1347 available samples, 607 (45%) failed quality control after RNA extraction. In total, 658 (49%) patients were included in survival analyses: MammaPrint low risk versus high risk is a significant prognostic factor for distant recurrence-free survival at 5 years (94.0% versus 91.6%) with a significant risk reduction of 6.5% at 10 years (log-rank P value = 0.017, low risk 91.3% versus high risk 84.8%). The multivariable models suggest that hazard ratio (HR) is primarily driven by tumor stage (5-year HR 3.89; confidence interval 1.97-7.71) and nodal status (5-year HR 1.73; confidence interval 0.91-3.21). After adjustment for clinical risk groups, MammaPrint HRs remain stable with values just below 2.0 after the first 3 years.

Conclusions: The MammaPrint test showed significant prognostic performance at 5 and 10 years of follow-up. In the particular cohort of ABCSG-8, the statistical independence from clinically assessed covariates remains unclear, and no conclusions concerning the clinical validity of the test can be drawn.

Puppe, J., Seifert, T., Eichler, C., Pilch, H., Mallmann, P. & Malter, W. 2020.

Background: Breast cancer is a very heterogeneous disease and luminal breast carcinomas represent the hormone receptor-positive tumors among all breast cancer subtypes. In this context, multigene signatures were developed to gain further prognostic and predictive information beyond clinical parameters and traditional immunohistochemical markers.

Summary: For early breast cancer patients these molecular tools can guide clinicians to decide on the extension of endocrine therapy to avoid over- and undertreatment by adjuvant chemotherapy. Beside the predictive and prognostic value, a few genomic tests are also able to provide intrinsic subtype classification. In this review, we compare the most frequently used and commercially available molecular tests (OncotypeDX[®], MammaPrint[®], Prosigna[®], EndoPredict[®], and Breast Cancer IndexSM). Moreover, we discuss the clinical utility of molecular profiling for advanced breast cancer of the luminal subtype.

Key messages: Multigene assays can help to de-escalate systemic therapy in early-stage breast cancer. Only the Oncotype DX[®] and MammaPrint[®] test are validated by entirely prospective and randomized phase 3 trials. More clinical evidence is needed to support the use of genomic tests in node-positive disease. Recent developments in high-throughput sequencing technology will provide further insights to understand the heterogeneity of luminal breast cancers in early-stage and metastatic disease.

Jacob, L., Witteveen, A., Beumer, I., Delahaye, L., Wehkamp, D., van den Akker, J., Snel, M., Chan, B., Floore, A., Bakx, N., Brink, G., Poncet, C., Bogaerts, J., Delorenzi, M., Piccart, M., Rutgers, E., Cardoso, F., Speed, T., van 't Veer, L. & Glas, A. 2020.

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“Gene expression data obtained in large studies hold great promises for discovering disease signatures or subtypes through data analysis. It is also prone to technical variation, whose removal is essential to avoid spurious discoveries. Because this variation is not always known and can be confounded with biological signals, its removal is a challenging task. Here we provide a step-wise procedure and comprehensive analysis of the MINDACT microarray dataset. The MINDACT trial enrolled 6693 breast cancer patients and prospectively validated the gene expression signature MammaPrint for outcome prediction. The study also yielded a full-transcriptome microarray for each tumor. We show for the first time in such a large dataset how technical variation can be removed while retaining expected biological signals. Because of its unprecedented size, we hope the resulting adjusted dataset will be an invaluable tool to discover or test gene expression signatures and to advance our understanding of breast cancer.”

Genetics and Genomics

Genetics can help to tell pme’s risk for getting cancer, while **genomics** can help once one has cancer, to choose one’s course of care.

Genetics	Genomics
Study of inherited traits, such as hair or eye colour, that are passed from one generation to the next through genes.	Study of the activity and interaction of certain genes in the body, including their role in certain diseases.
One’s risk for certain cancers can be inherited, or passed through one’s genes.	Once one has cancer, the activity and interaction of certain genes in one’s tumour tissue influences the behaviour of the tumour, including how likely it is to grow and spread.
The test for the BRCA1 and BRCA2genes is a genetic test that can help to predict one’s risk for getting breast or ovarian cancer.	The Oncotype DX breast cancer test is a genomic test that can help to predict the aggressiveness of a tumour and whether or not one will benefit from chemotherapy.
Once one knows one’s genetic risk for cancer, one can take steps to lower that risk, such as making lifestyle changes.	Once one has the personalised information from one’s Oncotype DX breast cancer test, patients and their doctors can decide what kind of treatment one might need following surgery.

Understanding a Breast Cancer Patient's Risk of Breast Cancer Risk Recurrence

MammaPrint analyses 70 critical genes identified in breast cancer metastasis to determine a woman's biological risk of recurrence. It provides a definitive result, Low Risk or High Risk, which is significantly correlated with differences in probability of metastasis free survival.

Many surgeons and oncologists rely on MammaPrint with other clinical criteria to assist in their therapeutic decision making. When combined with traditional risk factors, if a breast cancer patient is Low Risk by MammaPrint, endocrine therapy (e.g. Tamoxifen) alone may be sufficient to further reduce the recurrence risk. Conversely, if a breast cancer patient is High Risk by MammaPrint and has additional risk factors, she may benefit from more aggressive treatment including chemotherapy.

MammaPrint is a 70-gene test that will assess one's cancer's risk of recurrence, in other words, how likely the cancer is to return in the future. The patient is given definitive results, either a Low Risk or High Risk result, with no intermediate or indeterminate results which are common with other genomic tests.

In patients with the most common type of breast cancer (hormone receptor positive, HER2 negative, lymph node negative [ER+ / HER2- / LN -]) a Low Risk MammaPrint result showed an excellent 97.8% chance of being metastasis free at 5 years with hormonal therapy alone (tamoxifen or aromatase inhibitor), with no significant benefit of adding chemotherapy. In patients with a High Risk MammaPrint and treated with hormonal therapy and chemotherapy, these women had a 94.6% chance of being metastasis free at 5 years. These results are based on the landmark MINDACT clinical trial and represent the average risk of recurrence for these two groups.

MammaPrint Low Risk Result - a "Low Risk" MammaPrint result means that a patient has on average a 10% chance that her cancer will recur within 10 years without any additional adjuvant treatment, either hormonal therapy or chemotherapy/.

MammaPrint High Risk Result - a "High Risk" MammaPrint result means that a patient has a 29% chance that her cancer will recur within 10 years without any additional adjuvant treatment, either hormonal therapy or chemotherapy.

A Low Risk result does not guarantee that the cancer will not recur. A High Risk result does not guarantee that the cancer will recur. These results, in addition to all other factors, will help patients and their doctors make the most appropriate breast cancer treatment decisions.

MammaPrint Test Helps Some Women Avoid Chemotherapy

It is stated that the MammaPrint breast cancer test can dramatically reduce the number of women who need to undergo chemotherapy to treat the disease, according to a newly published study.

The prospective, outcome-based study of 427 breast cancer patients showed the genomic test, which analyses 70 key genes, accurately determines which patients are at low risk of breast cancer recurrence and can, therefore, safely choose not to undergo chemotherapy.

Of the 219 patients in the five-year study who were determined to be "low risk" based on the MammaPrint test, 85 percent chose not to have chemotherapy. Of those patients, 97 percent were

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disease-free after five years. Of the 208 patients who were determined to be 'high risk,' 81 percent chose chemotherapy and 91% were disease-free after five years.

"MammaPrint correctly stratified patients into Low Risk and High Risk categories based on prognosis of a recurrence of the disease," said Prof Linn, M.D., the principal investigator. "The outcome data generated in the study confirmed it was safe for the Low Risk patients to choose not to undergo chemotherapy and still have excellent outcomes".

The results of the peer-reviewed study, called MicroarRAY PrognOSTics in Breast CancER (or RASTER), conducted in 16 community-based clinics in the Netherlands, were published online by *The International Journal of Cancer*.

The RASTER study is considered unique by its co-authors because it is the first and only study to prospectively evaluate the performance of a genomic breast cancer test by using outcome data -- in this case through follow-up of the patient cohort for five years. The study also showed that MammaPrint identified 30 percent more patients as Low Risk than traditional clinical parameters such as; tumour size, grade, patient age and lymph node status, which are often used to determine risk of recurrence. MammaPrint is a 70-gene, breast cancer assay performed on both fresh and FFPE tumour tissue, developed by Agendia.

Of the prognostic tests commercially available for breast cancer, this is the first and only prospective validation to include outcome data. MammaPrint can be administered to virtually all early-stage breast cancer patients, not just those with certain disease characteristics as with other tests limited to certain receptor and lymph node status. Finally, MammaPrint results benefit the physician by clearly categorising all patients as high or low risk, eliminating the uncertainty of indeterminate scores reported by other genomic test methods.

Soliman, H., Shah, V., Srkalovic, G., Mahtani, R., Levine, E., Mavromatis, B., Srinivasiah, J., Kassab, M., Gabordi, R., Qamar, R., Untch, S., Kling, H.M., Treece, T. & Audeh, W. 2020.

Background: Increased usage of genomic risk assessment assays suggests increased reliance on data provided by these assays to guide therapy decisions. The current study aimed to assess the change in treatment decision and physician confidence based on the 70-gene risk of recurrence signature (70-GS, MammaPrint) and the 80-gene molecular subtype signature (80-GS, Blueprint) in early stage breast cancer patients.

Methods: IMPACT, a prospective, case-only study, enrolled 452 patients between November 2015 and August 2017. The primary objective population included 358 patients with stage I-II, hormone receptor-positive, HER2-negative breast cancer. The recommended treatment plan and physician confidence were captured before and after receiving results for 70-GS and 80-GS. Treatment was started after obtaining results. The distribution of 70-GS High Risk (HR) and Low Risk (LR) patients was evaluated, in addition to the distribution of 80-GS compared to IHC status.

Results: The 70-GS classified 62.5% (n = 224/358) of patients as LR and 37.5% (n = 134/358) as HR. Treatment decisions were changed for 24.0% (n = 86/358) of patients after receiving 70-GS and 80-GS results. Of the LR patients initially prescribed CT, 71.0% (44/62) had CT removed from their treatment recommendation. Of the HR patients not initially prescribed CT, 65.1% (41/63) had CT added. After receiving 70-GS results, CT was included in 83.6% (n = 112/134) of 70-GS HR patient treatment plans, and 91.5% (n = 205/224) of 70-GS LR patient treatment plans did not include CT. For patients who disagreed with the treatment recommended by their physicians, most (94.1%, n = 16/17) elected not to receive CT when it was recommended. For patients whose physician-

recommended treatment plan was discordant with 70-GS results, discordance was significantly associated with age and lymph node status.

Conclusions: The IMPACT trial showed that treatment plans were 88.5% (n = 317/358) in agreement with 70-GS results, indicating that physicians make treatment decisions in clinical practice based on the 70-GS result. In clinically high risk, 70-GS Low Risk patients, there was a 60.0% reduction in treatment recommendations that include CT. Additionally, physicians reported having greater confidence in treatment decisions for their patients in 72% (n = 258/358) of cases after receiving 70-GS results.

Trial registration: "Measuring the Impact of MammaPrint on Adjuvant and Neoadjuvant Treatment in Breast Cancer Patients: A Prospective Registry" ([NCT02670577](#)) retrospectively registered on Jan 27, 2016.

Ordering a MammaPrint Test from South Africa

Only a licensed healthcare provider (i.e. surgeon, medical oncologist, radiation oncologist, pathologist) can submit an order request for genomic testing. Ask a licensed doctor to order the Agendia Breast Cancer Test Suite for breast cancer. Local Agendia Molecular Oncology Specialists can assist with the ordering process.

From South Africa, one should contact Agendia Customer Service in The Netherlands at +31 20 462 1500, or alternatively contact customerservice@agendia.com.

Patients diagnosed with stage I or II invasive breast cancer that is lymph node negative or lymph node positive (up to 3 nodes) and < 5cm, are eligible for Agendia Breast Cancer testing. Unlike other assays, the Agendia Breast Cancer Suite of tests has no restrictions on other factors such as hormone receptor status (oestrogen receptor/progesterone receptor), HER2 status, or hormonal therapy prescription.

Gknowmix is the exclusive distributor of *MammaPrint*[®] in Southern Africa and signed a collaborative agreement with the University of Stellenbosch, South Africa, to promote genome research innovation. A research protocol has been ethically approved to study the clinical utility of transcriptional profiling in the South African population in comparison with the use of conventional prognostic markers.

Agendia B.V., headquartered in Amsterdam in The Netherlands, provides innovative diagnostic testing for the treatment of cancer patients which is based on gene expression analysis.

For any enquiries, please email customerservices@gknowmix.com or phone 021 9389324 / 0828799108.

(Agendia; Gknowmix).

MammaPrint Testing

MammaPrint is a 70-gene microarray test which is used to assess the risk of metastases at an early stage of breast cancer with greater accuracy than is possible using conventional methods. MammaPrint reveals the activity (expression) of 70 specific genes in the tumour sample to indicate a 'Low Risk' or 'High Risk' profile (no intermediate). The risk of tumour recurrence is determined

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according to the degree of similarity between the tumour's gene expression profile and reference profiles.

The test is performed on a tumour biopsy obtained from formalin fixed paraffin embedded (FFPE) tissue by the local pathologist following the test request on this website. The sample is then shipped overnight to Agendia's ISO certified laboratory in The Netherlands where the test is performed under an export permit obtained from the South African Department of Health. In general, results will be available within 10 working days after receiving a tumour biopsy.

To be eligible for a MammaPrint Test, a breast cancer patient should fulfil the following international criteria:

- Tumour size < 5.0 cm
- Up to 3 positive lymph nodes
- Stage 1 and Stage 2 invasive breast cancer
- Oestrogen receptor (ER) + or -
- Tamoxifen independent

The test selection criteria for reimbursement by certain medical schemes in South Africa has been further redefined following a Health Technology Assessment (HTA) performed in 2009. A pre-screen algorithm has been developed and was incorporated into the Gknowmix Database for easy identification of breast cancer patients eligible for testing. An application form with the selection criteria stipulated is provided by some medical schemes. This represents a unique development in the application of pathology supported genetic testing aimed at the exclusion of inappropriate genetic testing.

The 80-gene Blueprint test is generally used together with the 70-gene MammaPrint test for tumour subtyping into four treatment groups: Luminal A, Luminal B, HER2-enriched and basal-like.

Local experience of the MammaPrint service in routine clinical practice led to the following quotes from opinion leaders in breast cancer:

"Genomics is now an established and frequently used tool in medical research, and particularly in the oncology field. In breast cancer, genomics has led to a better understanding of the biology and to a molecular reclassification of the disease." – Dr Rika Pienaar, GVI Oncology, Panorama Hospital, Cape Town, South Africa.

"With the help of MammaPrint many early-stage breast cancer patients can safely forego chemotherapy. This is a major relief to patients with good prognosis as chemotherapy is the most dreaded part of breast cancer therapy." – Prof J Apffelstaedt, Faculty of Health Sciences, University of Stellenbosch, Tygerberg, South Africa.

In the resource-poor South African context in 2009, results indicated a break-even-point for cost-effectiveness of the MammaPrint Test (at R22 000 per test) at approximately R88 000 for the cost of chemotherapy. (Gknowmix; Grant, *et al.*).

Medical Disclaimer

This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet.

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Gknowmix

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MammaPrint

<http://knowyourbreastcancer.com/agendia-test-suite/mindact-publication/>

MyBreastCancerTreatment.org

<https://www.mybreastcancertreatment.org/en-US/LearnAboutOncotypeDX/WhatIsGenomicTesting>

News Medical Life Sciences

<https://www.news-medical.net/news/20130205/MammaPrint-breast-cancer-test-can-help-women-avoid-chemotherapy.aspx>

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