# Cancer Association of South Africa (CANSA)

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## Fact Sheet on MammaPrint Test

**Introduction**

[Picture Credit: MammaPrint]


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.

**Brandão, M., Pondé, N. & Piccart-Gebhart, M.** 2018.
"The number of breast cancer (BC) cases is growing worldwide, being most frequently diagnosed in the early-setting. Mammaprint™ is a 70-gene-expression signature, originally designed for selecting early BC patients with low risk of developing metastasis, so that they could be spared adjuvant chemotherapy. Its use as a prognostic biomarker has been extensively validated, both retrospectively and prospectively. However, its value as a predictive tool and as a clinically useful tool remains controversial."

**Viale, G., de Snoo, F.A., Slaets, L., Bogaerts, J., van 't Veer, L., Rutgers, E.J., Piccart-Gebhart, M.J., Stork-Sloots, L., Glas, A., Russo, L., Dell'Orto, P., Tryfonidis, K., Litière, S., Cardoso, F. & MINDACT investigators.** 2018.
**PURPOSE:** This study compares immunohistochemical (IHC) versus molecular subtyping (BluePrint and MammaPrint) in the population of patients enrolled in MINDACT and outcome based on molecular subtyping (MS) versus surrogate pathological subtyping (PS) as defined by the 2013 St. Gallen guidelines.
**METHODS:** MS classified patients in the following subtypes: Luminal A, Luminal B, HER-2-, and Basal-type. IHC/FISH for pathological subtyping (ER, PgR, HER-2, and Ki67) was centrally assessed in the European Institute of Oncology (n = 5806). Hazard ratios for distant-metastasis-free survival (DMFS) by subtype were adjusted for chemotherapy and endocrine therapy administration and thus independent of adjuvant treatment allocation.

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**RESULTS:** PS Luminal cancers classified as HER-2+ or Basal-type by MS did not have a significantly lower DMFS than the Luminal-type cancers by MS (95.9%): HR = 1.40, 95% CI 0.75-2.60 (p = 0.294). More patients were identified with Luminal A disease by MS (63%) as compared with PS (47%) with comparable 5-year DMFS (≥96.0%). Among the 500 patients with PS TN cancers, MS identified 24 (5%) patients as Luminal-type with 5-year DMFS estimated at 100% versus 71.4% for MS HER-2+ or 90.1% for MS Basal-type.
**CONCLUSIONS:** MS was able to re-stratify 54% of patients with a Luminal-B PS subtype to a low-risk Luminal A-type group with comparable outcome. Among TN EBC, 5% were classified as Luminal by MS with Luminal-like outcome. Molecular classification can help to identify a larger group of patients with low risk of recurrence compared with the more contemporarily used classification methodology including high-quality assessed Ki67.

**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. |

(MyBreastCancerTreatment.org).

**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

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., Kassar, 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

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*.).

**Beumer, I.J., Persoon, M., Witteyeen, A., Dreezen, D., Chin, S.F., Sammut, S.J., Snel, M., Caldas, C., Linn, S., van't Veer, L.J., Bernards, R. & Glas, A.M.** 2016.

**BACKGROUND:** MammaPrint® is a microarray-based gene expression test cleared by the US Food and Drug Administration to assess recurrence risk in early-stage breast cancer, aimed to guide physicians in making neoadjuvant and adjuvant treatment decisions. The increase in the incidence of invasive lobular carcinomas (ILCs) over the past decades and the modest representation of ILC in the MammaPrint development data set calls for a stratified survival analysis dedicated to this specific subgroup.
**STUDY AIM:** The current study aimed to validate the prognostic value of the MammaPrint test for breast cancer patients with early-stage ILCs.
**MATERIALS AND METHODS:** Univariate and multivariate survival associations for overall survival (OS), distant metastasis-free interval (DMFI), and distant metastasis-free survival (DMFS) were studied in a study population of 217 early-stage ILC breast cancer patients from five different clinical studies.
**RESULTS AND DISCUSSION:** A significant association between MammaPrint High Risk and poor clinical outcome was shown for OS, DMFI, and DMFS. A subanalysis was performed on the lymph node-negative study population. In the lymph node-negative study population, we report an up to 11 times higher change in the diagnosis of an event in the MammaPrint High Risk group. For DMFI, the reported hazard ratio is 11.1 (95% confidence interval = 2.3-53.0).
**CONCLUSION:** Study results validate MammaPrint as an independent factor for breast cancer patients with early-stage invasive lobular breast cancer. Hazard ratios up to 11 in multivariate analyses emphasize the independent value of MammaPrint, specifically in lymph node-negative ILC breast cancers.

**Medical Disclaimer**

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**Breastcancer.org**
http://www.breastcancer.org/symptoms/testing/types/mammaprint

**Gknowmix**
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**MammaPrint**
http://knowyourbreastcancer.com/agendia-test-suite/mindact-publication/

**MyBreastCancerTreatment.org**
http://www.mybreastcancertreatment.org/en-US/LearnAboutOncotypeDX/WhatIsGenomicTesting

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