**Mamma Typer**

- to determine breast cancer subtypes

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# INTRODUCTION

 Breast cancer is a heterogeneous disease with varying morphological, biological, and clinical phenotypes. Tumors may show phenotypic overlap but often display different biological behavior and response to therapy. Advances in high-throughput molecular techniques and bioinformatics have improved our understanding of breast cancer biology. Refinement of molecular taxonomy has led to the identification of specific molecular subclasses.

The traditional pathological morphological classification of breast cancer provides diagnostic and prognostic information. Despite being the most commonly used method for determining biomarker status in breast cancer. IHC has inter- and intraobserver variability. The accuracy and reproducibility of biomarker determination are crucial for effective therapeutic interventions in breast cancer management. Hence the current focus is on using gene assays to stratify breast cancer into distinct groups for guiding decisions on systemic therapy.

Several diagnostic assays like Oncotype DX, Prosigna, MammaPrint, NexCourse Breast, and MammaTyper are used to classify breast cancer into molecular subtypes. Oncotype DX and Prosigna are gene expression-based tests that predict the risk of recurrence and the likelihood of benefit from chemotherapy. MammaPrint is a 70-gene expression signature test that predicts the risk of distant metastasis. NexCourse Breast is an immunohistochemistry-based test that measures the expression of four biomarkers to predict the risk of recurrence. Mamma Typer is a multiplex PCR assay that measures the expression of 10 genes to classify breast cancer into four molecular subtypes: Luminal A, Luminal B. HER2-enriched, and Basal-like. 1

These diagnostic assays are used to guide treatment decisions and predict patient outcomes. The results of these tests can help doctors determine the most effective treatment approach and monitor the progression of the disease

**MAMMA TYPER**

The MammaTyper is a CE-marked in vitro diagnostic test developed by BioNTechDiagnostics, Mainz, Germany, used for determining different molecular subtypes of breast cancer to decide on systemic therapy.

This test uses a standard formalin-fixed paraffin-embedded (FFPE) biopsy sample, which is processed using RNXtract to extract ribonucleic acid (RNA). The sample is then run through an RT-qPCR machine with the Mamma Typer test and controls supplied with the test. 1

It quantifies the mRNA expression of four key marker genes, including ERBB2, ESRI, PGR, and MK167, using reverse transcription-quantitative real-time polymerase chain reaction (RT- qPCR). The main goal is to provide a precise and reproducible assessment of the four biomarkers, which is a significant concern in IHC-based semiquantitative assessment. 2

The MammaTyper® test can be integrated into local laboratory setups because it supports analysis on widely accessible qPCR platforms using total RNA extracted from clinical routine formalin-fixed, paraffin-embedded (FFPE) breast cancer samples from resections or core needle biopsies

**INNOVATION**

The test is objective, sensitive, and precise, and measures the upregulation of genes using standard RT-qPCR equipment. It is an alternative to IHC, which is subjective, lacks defined cut-offs, and may have variability in measures such as MKI67. MammaTyper provides additional information on luminal B-like tumor subtypes that cannot be assessed using IHC. 3

The process takes approximately 5 hours and analyses the expression levels of 50 genes, including

**ESRI:** encodes the estrogen receptor alpha protein and is involved in the regulation of breast cell growth and differentiation

**PGR:** encodes the progesterone receptor protein and is involved in the regulation of breast cell growth and differentiation

**ERBB2:** encodes the human epidermal growth factor receptor 2 (HER2) protein, which plays a role in the development and progression of breast cancer.

**MK167:** encodes the Ki-67 protein, which is a marker of cell proliferation and is commonly used to assess the aggressiveness of breast tumors.

**FOXCI:** encodes a transcription factor that regulates the expression of other genes and has been implicated in breast cancer development

**CDHI:** encodes the E-cadherin protein, which is a cell adhesion molecule that plays a role in maintaining the integrity of epithelial tissues,

The results are reported as a numerical value for each marker and can be used to classify breast cancer subtypes based on their molecular profiles 2

**INTERPRETATION OF TEST RESULTS :**

The results are interpreted using specialized software that compares the expression levels of the 50 genes to established reference values. The software then assigns the tumor to one of the four molecular subtypes based on the expression pattern of the genes. The results are reported in a clear and concise format that can be easily understood, helping healthcare providers to make informed decisions about patient care. The combination of marker results reveals the St Gallen subtypes: Luminal A-like, Luminal B- like (HER2 negative), Luminal B-like (HER2 positive), HER2 positive (non-luminal), and Triple negative tumors. 2

**CLINICAL APPLICATIONS :**

**Selection of appropriate treatment strategies**: The molecular subtype of the tumor can help guide treatment decisions. For example, patients with HER2-positive breast cancer may benefit from treatment with HER2-targeted therapies such as trastuzumab. 4

**Prediction of prognosis:** The molecular subtype of the tumor is a strong predictor of long-term outcomes, with Luminal A tumors having the best prognosis and triple-negative tumors having the worst prognosis. 5

**Assessment of treatment response:** Monitoring changes in gene expression over time can help evaluate treatment response and guide decisions about further treatment D. Identification of potential therapeutic targets: The MammaTyper test can identify specific genes and pathways that are dysregulated in breast cancer, providing targets for new therapies. 4

**LIMITATIONS :**

**Availability:** The MammaTyper test may not be widely available in all countries and healthcare systems. Now in India, it is available at Metropolis Health Care. 4

**Cost:** The cost of the MammaTyper test may be a barrier for some patients and healthcare systems. It cost around 48500 INR in India and 300 Pounds in the UK. 2,5

**Technical expertise required:** The MammaTyper test requires technical expertise to perform and analyze, which may limit its use in some settings. 2,6

**Sample size limitations:** The MammaTyper test requires a certain amount of tumor tissue for analysis, which may limit its use in patients with small tumors or limited biopsy samples. 7

**CONCLUSION:**

The MammaTyper test is a gene expression assay bat classifies breast tumors into molecular subtypes based on the expression levels of 50 genes. It has important applications in breast cancer management, including selection of appropriate treatment strategies, prediction of prognosis, assessment of treatment response, and identification of potential therapeutic targets. The MammaTyper test has the potential to be used in combination with other diagnostic modalities and may be developed further to identify targeted therapies based on subtype-specific gene expression

##### REFERENCES

1. MammaTyper in vitro diagnostic test for determining breast cancer subtypes Medtech innovation briefing [MIB135] Published: 18 January 2018. https://www.nice.org.uk/advice/mib135
2. Varga, Z., Lebeau, A., Bu, H. *et al.* An international reproducibility study validating quantitative determination of *ERBB2*, *ESR1*, *PGR*, and *MKI67* mRNA in breast cancer using MammaTyper®. *Breast Cancer Res* **19**, 55 (2017). https://doi.org/10.1186/s13058-017-0848-z
3. Finsterbusch K, Decker T, van Diest PJ, Focke CM. Luminal A versus luminal B breast cancer: MammaTyper mRNA versus immunohistochemical subtyping with an emphasis on standardised Ki67 labelling-based or mitotic activity index-based proliferation assessment. *Histopathology*. 2020;76(5):650-660. doi:10.1111/his.14048
4. Sapino A, Roepman P, Linn SC, et al. MammaPrint molecular diagnostics on formalin-fixed, paraffin-embedded tissue. *J Mol Diagn*. 2014;16(2):190-197. doi:10.1016/j.jmoldx.2013.10.008
5. Beumer I, Witteveen A, Delahaye L, et al. Equivalence of MammaPrint array types in clinical trials and diagnostics. *Breast Cancer Res Treat*. 2016;156(2):279-287. doi:10.1007/s10549-016-3764-5
6. Laible M, Schlombs K, Kaiser K, et al. Technical validation of an RT-qPCR in vitro diagnostic test system for the determination of breast cancer molecular subtypes by quantification of ERBB2, ESR1, PGR and MKI67 mRNA levels from formalin-fixed paraffin-embedded breast tumor specimens. *BMC Cancer*. 2016;16:398. Published 2016 Jul 7. doi:10.1186/s12885-016-2476-x
7. Sørlie T. Molecular portraits of breast cancer: tumour subtypes as distinct disease entities. Eur J Cancer. 2004;40(18):2667–75. doi: 10.1016/j.ejca.2004.08.021.