



# MammaTyper in vitro diagnostic test for determining breast cancer subtypes

Medtech innovation briefing

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## Summary

- The **technology** described in this briefing is MammaTyper. It is used for determining different molecular subtypes of breast cancer to decide on systemic therapy.
- The **innovative aspects** are that MammaTyper differs from standard immunohistochemistry (IHC) testing: it offers a quantitative test, which distinguishes more tumour subtypes and is easier to do.
- The intended **place in therapy** would be to replace IHC testing in people with early-stage breast cancer.
- The **main points from the evidence** summarised in this briefing are from randomised controlled trials (RCTs) and diagnostic reproducibility studies (UK, US and Europe) including a total of 1,460 adults (1,138 evaluable tumour samples) with early-stage breast cancer in secondary care. It shows that MammaTyper is more effective than IHC in defining breast cancer subtype to guide chemotherapy.

- **Key uncertainties** around the evidence include the need for further studies on clinical outcomes after MammaTyper-guided therapy and on the relative utility of MammaTyper compared with other gene-based tests.
- The **cost** of MammaTyper is £300 to £400 per unit (exclusive of VAT). The **resource impact** would be potentially cost saving if using the test leads to avoiding unnecessary chemotherapy, optimising treatment regimens and potentially reducing the need for expensive further multigene testing.

## The technology

The MammaTyper (BioNTech Diagnostics GmbH) test is a molecular in vitro diagnostic test for the relative gene expression quantification of the genes ERBB2, ESR1, PGR and MKI67 in human breast cancer tissue. It is used as a diagnostic test on biopsy samples of invasive breast cancer tissue from surgical resection or pre-operative core needle biopsies. The test is based on reverse transcription quantitative real-time polymerase chain reaction (RT-qPCR). MammaTyper classifies breast cancer into 4 subtypes that have different treatments according to St Gallen (2017) guidelines:

- Luminal A-like (oestrogen receptor [ER]-positive and generally human epidermal growth receptor 2 [HER2]-negative); treated with endocrine therapy.
- Luminal B-like subdivided according to the ERBB2 expression into:
  - luminal B-like (ER-negative and HER2-positive); treated with anti-HER2 therapy and chemotherapy
  - luminal B-like (ER-positive and generally HER2-negative); treated with endocrine therapy.
- HER2-positive (non-luminal); treated with anti-HER2 therapy and chemotherapy.
- Triple-negative (generally ER, progesterone receptor [PR]- and HER2-negative); treated with chemotherapy.

Luminal B-like tumour subtypes are associated with different prognoses and therapy recommendations. Knowing the luminal B-like subtype is designed to enable treatment to be optimised, which may avoid over- or under-treatment. Information about hormone-receptor status and ERBB2 expression can also be used to identify people for whom further multigene testing is not needed. This may avoid the unnecessary use of expensive

multigene tests.

The MammaTyper 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 a RT-qPCR machine with the MammaTyper test and controls supplied with the test.

## Innovations

MammaTyper measures ER and HER2 status on routinely collected FFPE material. It offers an objective, sensitive, and precise test, based on measuring the upregulation of genes on standard RT-qPCR equipment. It would be an alternative to IHC, which is a subjective test that has no defined cut off and may have inter-observer and inter-laboratory variability for some measures, such as those relating to MKI67. It would also provide additional information on luminal B-like tumour subtypes that cannot be assessed using IHC.

Results of the MammaTyper test would be used to guide treatment decisions (based on established St Gallen guidelines).

## Current NHS pathway

NICE's guideline on [diagnosing and treating early and locally advanced breast cancer](#) recommends people with invasive breast cancer should have postoperative assessment of ER status using IHC with a standardised and qualitatively assured methodology, and report the results quantitatively. HER2 status of all invasive breast cancers should also be assessed using a standardised and qualitatively assured methodology. The results of ER and HER2 assessments can be used to guide systemic treatment.

Using chemotherapy in ER-positive tumours is influenced by assessing MKI67. IHC cannot reliably assess this and so luminal B-like tumours cannot be subdivided by ER status. This means that for people with luminal B-like disease, those who have ER-positive disease may inappropriately have chemotherapy, and those with ER-negative disease may not be offered this potentially beneficial treatment. NICE's guideline on [diagnosing and treating early and locally advanced breast cancer](#) also recommends that all people with early invasive breast cancer should be considered for adjuvant treatment after surgery. The choice of treatment should be made by assessing prognostic and predictive factors and the potential benefits and side effects of the treatment. Decisions should be made after

discussing these factors with the person and using online prognostic tools such as PREDICT to estimate individual prognosis and the absolute benefit of a treatment.

NICE guidance on [gene expression profiling and expanded IHC tests in early breast cancer management](#) is being updated but does not include MammaTyper as it does not provide a result that describes the risk of cancer recurrence.

MammaTyper would be used in place of IHC to identify breast cancer subtype, and further subdivide people with luminal B-like disease by ER status to guide adjuvant treatment based on established methods (St Gallen guidelines).

NICE is aware of the following CE-marked device that appears to fulfil a similar function as MammaTyper:

- IHC4 AQUA (Genoptix Inc) – assesses risk (low, intermediate, high) and subtype.

## Population, setting and intended user

MammaTyper would be used to guide treatment decisions in people with breast cancer. The test would be done in secondary care on a surgical resection of the breast cancer tissue (or the initial diagnostic core biopsy) so results are available to guide post-surgical chemotherapy or initial treatment. It would be used in the same place in the care pathway as IHC, to identify people likely to have a low-risk subgroup of ER-positive luminal A-like or B-like disease and to avoid using chemotherapy in these groups.

The test uses industry-standard RT-PCR machines (including Roche LightCycler, Versant kPCR Cycler, cobas z480 Analyzer and others) and is done on routine clinical samples such as FFPE material, so additional training is not needed.

## Costs

### Technology costs

The company state the price per patient of MammaTyper is £400, including RNXtract to extract RNA. It states that there is potential for preferential NHS pricing. The test can be run on a range of industry-standard RT-PCR devices and needs 45 minutes of technician time (about £16).

## Costs of standard care

IHC tests are done using standard pathology laboratory techniques and cost about £152 per test. This includes 30 to 45 minutes of a consultant pathologist's time to do the test (£117), and the costs of consumables (£35).

## Resource consequences

The MammaTyper test would add costs compared with the standard IHC test in initial testing and treatment of breast cancer. It has the potential to make resource savings in avoiding unnecessary chemotherapy, optimising treatment regimens and potentially avoiding the need for more expensive multigene testing. As MammaTyper is an objective test, it does not need expert histopathology clinicians to read the result, and so can release staff time.

The test runs on a range of standard PCR devices and would need no changes to infrastructure beyond buying the relevant technology.

## Regulatory information

MammaTyper was CE marked as an in vitro diagnostic medical device in 2014.

## Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to: promote race and disability equality and equality of opportunity between men and women, eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

There are no equality issues associated with using this test but all people diagnosed with breast cancer would be recognised as disabled under the 2010 Equality Act. Women of African family origin are more likely to develop breast cancer at an earlier age and to have a more aggressive form of the disease compared with other women.

## Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the [interim process and methods statement](#). This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting [mibs@nice.org.uk](mailto:mibs@nice.org.uk).

### Published evidence

Five studies are summarised in this briefing, including 1,138 tumour samples analysed from 1,460 patients.

The evidence consists of 2 studies comparing the MammaTyper test to IHC as a part of an RCT and 2 further studies confirming the reliability of the test with different PCR machines, machine operators and pathology laboratories. One further large UK RCT examined using different breast cancer tests and compared their clinical and cost effectiveness.

Table 1 summarises the clinical evidence as well as its strengths and limitations.

### Overall assessment of the evidence

The evidence shows that the MammaTyper test is a reliable way to subtype breast cancer compared with conventional IHC testing and can provide clinical information to guide subsequent chemotherapy. It also shows there is little intra- and inter-site variability in the test results, which can happen with IHC testing.

The size of the studies are appropriate to show the validity of the assay but are from non-NHS sources. The most relevant study for the NHS shows that different breast cancer tests relying on testing for the upregulation of different genes give different results in defining breast cancer subtypes. Further clinical trials on clinical outcomes for adjuvant chemotherapy treatments chosen on the basis of MammaTyper testing would be useful.

**Table 1 Clinical evidence**

<u>Wirtz et al. 2016</u>	
Study size, design and location	769 archived breast cancer tumour samples from a cohort of 1,010 women with breast cancer in a RCT in Finland (the FinHer trial).
Intervention and comparator(s)	RCT comparing docetaxel plus FEC and vinorelbine plus FEC subtyping of the breast cancer was done using MammaTyper (RT-qPCR) and IHC.
Key outcomes	Both IHC and MammaTyper assessed ER and PGR accurately and gave a prognosis for DDFS (HR=0.42 [95 % CI 0.25 to 0.71] p=0.001; and HR=0.56 (0.37 to 0.8), p=0.005, respectively]. Women with luminal B-like subtype identified using MammaTyper had a better DDFS and OS when treated with docetaxel-FEC (DDFS, HR 0.52 (95 % CI 0.29 to 0.94) p=0.031), compared with those identified using IHC.
Strengths and limitations	Breast cancer subtypes defined using RT-qPCR and IHC show good concordance, but cancer MKI67 mRNA content correlated better with DDFS than Ki-67 expression. This shows MammaTyper could be used to more reliably identify patients likely to benefit from specific adjuvant therapy.
<u>Sinn et al. 2017</u>	
Study size, design and location	101 core needle biopsies from a 105-patient RCT on primary invasive breast cancer, Germany. Company sponsored.
Intervention and comparator(s)	Ki-67 assessed by manual scoring of slides stained by vIHC compared with automatic scoring using digital image analysis (qIHC) or MKI67 gene expression with RT-qPCR (MammaTyper).

Key outcomes	<p>Overall agreement for measuring ER and PGR between the 3 methods was high, with qIHC and MammaTyper showing slightly higher agreement than manual IHC and MammaTyper (all &gt;90%).</p> <p>A moderate correlation was seen for qIHC and RT-qPCR for Ki-67/ MKI67 (Spearman's <math>r=0.50</math>, <math>p=0.0001</math>).</p> <p>There is no agreed cut off for measuring Ki-67 using IHC, so the authors set sensitivity=100%. Specificity for the prediction of pathological complete response was higher for MammaTyper (measuring mRNA) compared with IHC (measuring protein) (68.9% compared with 22.2%). MammaTyper showed patients whose disease achieved pathological complete response had much greater variability in proliferation levels compared with qIHC or vIHC. The authors conclude that digital image analysis can be used for assessing ER, PR and Ki-67.</p>
Strengths and limitations	<p>This study shows that, while results from IHC and MammaTyper show good concordance for ER and PR, correlation for Ki-67 is only moderate and MammaTyper is more specific in measuring Ki-67 compared with IHC.</p> <p>This is a relatively small study but on the back of a carefully defined group of patients in a RCT for neoadjuvant therapy for breast cancer.</p>
<u>Varga et al. 2017</u>	
Study size, design and location	<p>Multicentre prospective study to test inter- and intra-site reproducibility of the MammaTyper test, 10 international pathology labs in Switzerland, Germany, China, France, Italy, US, Finland and Canada.</p>
Intervention and comparator(s)	<p>Testing samples from 1 tumour sample multiple times across 10 sites over several days and testing samples from 16 different tumour samples across 10 sites and several days using MammaTyper on both centrally and locally extracted RNA from FFPE breast cancer specimens.</p>
Key outcomes	<p>ICC=0.980 to 0.998 (excellent agreement) for quantitative measurements. Positive/negative single-marker results were reproducible and subtype agreement was excellent (<math>kappa=0.90</math> to 1.00).</p>



Strengths and limitations	This shows the MammaTyper test is precise and reproducible for measuring breast cancer biomarkers and identifying cancer subtypes in pathology laboratory sites and across different sites.
<u>Laible et al. 2016</u>	
Study size, design and location	Test accuracy study across 3 sites, different device operators, different PCR devices, standard RNA samples and 16 subtyped breast cancer tumour samples.
Intervention and comparator(s)	MammaTyper and RNA standards, no comparators.
Key outcomes	The individual PCR machines showed good (>90%) between-site concordance for all 4 markers: ERBB2, ESR1, PGR, MK167 and low inter-site variability (SD=<0.7 Cqs). The intra-site agreement was high (>97%) for individual markers and was stable up to a 64-fold sample dilution. The assay was reliable using different RNA isolation methods and with samples containing up to 80% of non-tumour tissue/in situ carcinoma.
Strengths and limitations	The mRNA expression rates of the ERBB2 ESR1, PGR and MKI67 genes measured using MammaTyper allows cancer subtyping of the luminal A-like or B/HER2 positive or negative/triple-negative subgroups. This study shows MammaTyper has robust results across different PCR devices, different sites and operators and the initial RNXtract RNA kit used on the tissue before MammaTyper, gives reliable results.
<u>Bartlett et al. 2016</u>	
Study size, design and location	313 women with early breast cancer, RCT, UK. NIHR-funded.
Intervention and comparator(s)	Standard (chemotherapy and endocrine therapy) or test-directed (chemotherapy if Oncotype DX recurrence score >25) treatment. Risk stratification was also determined with Prosigna (PAM50), MammaPrint/Blueprint, MammaTyper, NexCourse Breast (IHC4-AQUA), and conventional IHC4 (IHC4).

Key outcomes	<p>Data were available for 302 patients and results from all tests were available for 236 patients. The 5 tests producing risk estimates (not including MammaTyper) showed modest agreement when defining high compared with low/intermediate risk: 119 (39.4%) tumours were clearly either high or low/intermediate risk and 183 (60.6%) had different risk estimates depending on the test used. Discordant subtyping between tests was seen in 123 (40.7%) tumours. MammaTyper showed moderate agreement with BluePrint, kappa=0.39 (0.29 to 0.50) and Prosigna, kappa=0.44 (0.34 to 0.54). The authors conclude that evidence provided by different tests suggests that they present broadly equivalent risk information for women with ER-positive breast cancers and individual patients may benefit from some of the specific information provided by different tests.</p>
Strengths and limitations	<p>This was a large RCT centrally funded in an NHS population of women with breast cancer and so represents high-quality, relevant evidence. The tests compared all rely on different combinations of genes and use different technologies (IHC, PCR, array-based technologies) and had been shown in computer-based comparisons to be discordant. This study tested direct in vivo comparisons and showed the disagreement between the tests is genuine.</p>
<p>Abbreviations: CI, confidence interval; Cqs, quantification cycles; DDFS, distance disease-free survival; ER, oestrogen receptor; FEC, fluorouracil [5FU] epirubicin and cyclophosphamide; FFPE, formalin-fixed, paraffin-embedded; HR, hazard ratio; ICC, inter-class correlation coefficient; IHC, immunohistochemistry; mRNA, messenger ribonucleic acid; NIHR, National Institute for Health Research; OS, overall survival; PCR, polymerase chain reaction; PR, progesterone receptor; qIHC, IHC scoring using digital image analysis; RCT, randomised controlled trial; RNA, ribonucleic acid; RT-qPCR, quantitative real-time polymerase chain reaction; SD, standard deviation; vIHC, visual IHC scoring.</p>	

## Recent and ongoing studies

The company have noted that, in the neoadjuvant therapy setting, 2 MammaTyper-related studies are ongoing. They contain together about 1,100 people with breast cancer comparing MammaTyper with IHC and fluorescence in situ hybridisation and respective

therapy outcome.

## Expert comments

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

Two of the 3 experts were familiar with the technology but had not used it before.

## Level of innovation

The experts felt the test was a minor variation of established technology but offered a potentially more accurate or faster result. One expert said that other tests can measure the same genes but MammaTyper can be done in a local laboratory and is straightforward compared with more complex tests that need centralised laboratories, such as Oncotype DX.

## Potential patient impact

All experts agreed this test could have a positive patient benefit by identifying disease unlikely to need chemotherapy and by delivering a quicker result, possibly avoiding surgery and other neoadjuvant treatments.

## Potential system impact

All experts agreed this test has the potential to change the patient care pathway and improve clinical outcomes, such as allowing people to choose neoadjuvant therapy and even avoiding surgery.

## General comments

One expert noted that this test would free up consultant histopathologist time, which is especially important as there is a national shortage. Another expert commented that this test is much easier and cheaper than other tests. Using MammaTyper in local laboratories could save money as fewer of the more expensive tests, such as Oncotype DX, would be

needed.

One expert felt that MammaTyper is still early in development and the evidence is based on a small number of studies. Further validation would be needed before the NHS could adopt it.

## Specialist commentators

The following clinicians contributed to this briefing:

- Prof Rob Stein, consultant, University College London Hospitals NHS Foundation Trust; chief investigator of the OPTIMA trial, which seeks to investigate the ability of tumour gene expression tests to predict chemotherapy sensitivity for ER-positive HER2-negative breast cancer. There are no plans to assess the MammaTyper technology in the main OPTIMA study. However, with the collaboration of the vendor it was one of 6 related technologies evaluated in the OPTIMA feasibility study. That data is published in the formal report of OPTIMA-prelim and in Bartlett et al. 2016, which is referenced in the briefing document.
- Dr Roger Hunt, consultant histopathologist, Manchester University NHS Foundation Trust.
- Mr Simon Pain, consultant breast surgeon, Norfolk and Norwich University Hospitals NHS Trust, sat on advisory boards organised by Genomic Health to discuss use of the Oncotype DX test; gave talks to healthcare professionals about this test. He received honoraria for this work.

## Development of this briefing

The [interim process and methods statement](#) sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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