Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

- Determine the quantity of evidence available for a technology of interest.
- Identify any gaps in the evidence.
- Inform decisions on topics that warrant fuller assessment by Health Technology Wales (HTW).

Topic exploration report number:	TER323
Topic:	Tumour profiling tests that guide treatment decisions for early breast cancer
Summary of findings:	NICE guidance on tumour profiling test recommends that some tests (i.e. EndoPredict, Oncotype DX, Prosigna) are appropriate for use for patients judged to be moderate risk by other validated tools. While other tests did not have sufficient supporting evidence to recommend (i.e. MammaPrint, IHC4+C). A further review by EUnetHTA also concluded that MammaPrint did not have sufficient evidence to support use and there is uncertainty in long-term outcomes of the MINDACT trial with a suggestion that the test may be beneficial for some populations but harmful for others. There is emerging evidence that Digistain is associated with tumour grade, recurrence, and survival but further research is needed to confirm patient benefit.

Introduction and aims

Tumour profiling tests can provide information on the activity of genes in tumour samples from people with early breast cancer. Such profiles may provide information on the risk profile of a person's breast cancer and may be able to be used to better predict the risk of disease recurrence and guide treatment decisions. In particular, tumour-profiling tests may be able to identify patient cohorts with low or high risks of distant recurrence and may help guide decisions on whether chemotherapy is needed alongside hormone therapy. This may allow a group of people with low risk to avoid adverse events associated with chemotherapy.

Health Technology Wales (HTW) researchers searched for evidence on tumour profiling tests that guide treatment decisions for early breast cancer. The topic proposer highlighted Digistain that uses infrared imaging to profile tumours and may reduce the time needed for assessment compared to other approaches to tumour profiling, including gene expression assays.

Evidence overview

Technology Assessment/Guidance

HTW researchers identified two recent health technology assessments (HTA) of tumour profiling.

National Institute for Health And Care Excellence (NICE) Diagnostic Guidance (DG34) on tumour profiling tests to guide adjuvant chemotherapy decisions (NICE 2018) recommends the following:

- EndoPredict (EPclin score), Oncotype DX Breast Recurrence Score and Prosigna to be used as options for guiding adjuvant chemotherapy decisions for people with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative and lymph node (LN)-negative (including micrometastatic disease) early breast cancer, only if they have intermediate risk of distant recurrence assessed via a validated tools currently within use in the NHS (e.g. PREDICT) and the test would inform decision-making on adjuvant chemotherapy. This recommendation also required tests to be provided at agreed discounts and clinicians and companies to provide data to the National Cancer Registration and Analysis Service.
- MammaPrint is not recommended for guiding adjuvant chemotherapy decisions for people with ER-positive, HER2-negative and LN-negative early breast cancer because it is not cost effective.
- IHC4+C is not recommended for guiding adjuvant chemotherapy decisions for people with ER-positive, HER2-negative and LN-negative early breast cancer because the analytical validity of the test is uncertain.

A European Network for Health Technology Assessment (EUnetHTA) Rapid Assessment evaluated the clinical utility of the addition of MammaPrint, a gene expression signature test, to a standardised risk assessment web based algorithm in patients with a high clinical risk profile in order to limit the number of patients receiving chemotherapy and the associated adverse effects (EUnetHTA 2018). The review identified one randomised controlled trial (RCT). Based on this MINDACT trial, the authors concluded that it had not yet been demonstrated that patient outcomes are improved when treatment decisions are informed by MammaPrint testing.

Individual studies

HTW researchers identified long-term outcomes from the MINDACT trial that was identified in the EUnetHTA review (Piccart et al. 2021). The study randomised patients with high clinical risk and low

genomic risk with MammaPrint to receive chemotherapy or no chemotherapy. At five years, distant metastasis-free survival rate was 95.1% for the no chemotherapy group, which was considered above a predefined non-inferiority boundary. However, there was a significant difference between arms with those who received no chemotherapy having lower 8-year distant metastasis-free survival than those who received chemotherapy (89.4% vs. 92.0%, hazard ratio 0·66; 95% CI 0·48 to 0·92). In exploratory subgroup analyses, this difference was larger in a group of women who were 50 years of age or younger (88.6% vs. 93.6%) and smaller for those aged over 50 years of age (90.0% vs. 90.2%).

It appears that Digistain was not included in previous HTAs of tumour profiling. The topic proposer provided data from several studies and report that Digistain Index scores are associated with tumour grade established by haemotoxylin and eosis (H + E) protocols, as well as recurrence and survival.

Evidence standards

The technology submitted by the topic proposer incorporates a digital health technology (DHT) and would likely fall under Tier C technology according to the Evidence Standards Framework for Digital Health Technologies**.** Technologies within this classification are DHTs designed to provide or guide treatment, active monitoring and clinical calculations, to provide or guide a diagnosis, for preventative behaviour change, or to allow self-management of a diagnosed condition. For technologies of this classification, it is recommended that high quality randomised controlled studies or studies comparing the DHT with a relevant comparator is produced to demonstrate effectiveness of the technology.

Areas of uncertainty

NICE guidance and a EUnetHTA review from 2018 is available on tumour profiling for breast cancer. There may have been additional evidence developed since these HTAs were conducted. However, HTW researchers did not identify more recent meta-analyses on this issue. Further, recently published long-term outcomes for MammaPrint suggest that there is still uncertainty around the potential benefit for patients.

Digistain appears to be associated with outcomes of importance but it appears uncertain whether this can guide treatment decisions and lead to benefits for patients.

Literature search results

Health technology assessments and guidance
EUnetHTA. (2018). Added value of using the gene expression signature test MammaPrint® for adjuvant chemotherapy decision-making in early breast cancer [OTCA04]. European Network for Health Technology Assessment Available at: https://www.eunethta.eu/final-assessment-report-on-mammaprint-added-value-of-using-the-gene-expression-signature-test-mammaprint-for-adjuvant-chemotherapy-decision-making-in-early-breast-cancer [Accessed 14.12.2021]. NICE. (2018). Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer [DG34]. National Institute for Health and Care Excellence. Available at: https://www.nice.org.uk/guidance/dg34 [Accessed 13.12.2021].
Individual studies
Piccart et al. (2021). 70-gene signature as an aid for treatment decisions in early breast cancer: updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. *The Lancet Oncology, 22*, 476-488. https://doi.org/10.1016/S1470-2045(21)00007-3
Provided by the topic proposer
Digistain (2018). Data Summary. *Unpublished*

Date of search:	December 2021
Concepts used:	tumour profiling test; breast cancer

(Internal use only – delete before publication)

Proposed research question and evidence selection criteria

Proposed research question	**What is the clinical and cost-effectiveness of tumour profiling tests that guide treatment decisions for early breast cancer?**

	Included	Excluded
Population	Early stage breast cancer patients	
Intervention	Tumour profiling tests	
Comparison/ comparators	Standard of care	
Outcomes	Treatment decision Metastasis-free survival Overall survival Quality of life	
Study design		

Topic selection criteria:

[Italicised text is for guidance only – delete it once the table is completed/before circulating the TER.]

Criteria		Comments
Are there likely to be sufficient published research findings available upon which to base a technology assessment, and to allow HTW to provide clear advice to support decision making?	Unclear	In relation to NICE guidance, unlikely there'd be sufficient new evidence to update recommendations. Unlikely to be sufficient evidence for Digistain
Is a clear additional health benefit to patients or benefit to the NHS anticipated or evident from the use of this technology?	Unclear	Some benefits from some tests but no clear benefit for Digistain submitted by TP
Is there wide variation in provision or outcome of the technology across NHS Wales, and/or uncertainty about the effectiveness of the technology?	Unclear	No information
Is the technology likely to have an impact on NHS resources (consuming or releasing)?	Yes	Would require upfront spending on tests, may be outweight by savings in chemo.

Is the technology likely to have a major impact on NHS Wales?	Yes	Only if proved clinically and cost-effective – the technology could have the potential to release resources.
Is there potential for quality improvement from undertaking an assessment of this technology at this time?	No	NICE guidance is available and recommendations unlikely to be changed by evidence