Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Gene expression profiling tests to guide adjuvant chemotherapy decisions in early-stage breast cancer:

Protocol for a Rapid Health Technology Assessment

Published: February 2023

About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.

- **Regulating social care services** — The Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.

- **Regulating health services —** Regulating medical exposure to ionising radiation.

- **Monitoring services** — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.

- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.

- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.

- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

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Abbreviations

GEP	gene expression profiling
HER2-	human epidermal growth factor receptor 2-negative
HIQA	Health Information and Quality Authority
HR+	hormone receptor positive
HTA	health technology assessment
LN-	lymph node negative
LN+ (1-3)	lymph node positive (1-3 = number of nodes to which the cancer has spread)
NCCP	National Cancer Control Programme
PICOS	Population, Intervention, Comparator, Outcomes, and Study design
RCT	randomised controlled trial

1. Introduction

1.1. Background

Breast cancer is the most commonly diagnosed female cancer in Ireland, with just over 3,000 cases annually, approximately 80% of which are diagnosed at an early stage (stage I or II).[1] Surgery is usually the first treatment for breast cancer in Ireland.[2] Patients with early and locally advanced breast cancer may benefit from further ('adjuvant') systemic therapies, including a combination of chemotherapy, endocrine therapy, radiotherapy, and or monoclonal antibodies (in the case of human epidermal growth factor receptor 2-positive (HER2+) breast cancer).[3] In Ireland, approximately 26% of stage I, 59% of stage II, and 72% of stage III breast cancers receive chemotherapy.[1] While chemotherapy can reduce the risk of recurrence and has contributed to declining breast cancer mortality,[4, 5] recurrence rates are low and not all women with early-stage breast cancer benefit from chemotherapy.[6, 7]

Historically, the choice of treatment for breast cancer was guided by clinical and pathologic factors.[8] More recently, gene expression profiling (GEP) tests have been developed to further inform decisions regarding the use of chemotherapy to treat breast cancer. These tests are intended to improve the categorisation of patients with respect to the risk of recurrence or death and to identify patients most likely to benefit from chemotherapy. In 2011, following a recommendation by the National Cancer Control Programme (NCCP) Technology Review Committee, the HSE began to reimburse the Oncotype DX® GEP test to guide adjuvant chemotherapy decisions in patients with lymph node negative (LN-) early-stage breast cancer.[9] In 2019, reimbursement of Oncotype DX® was extended to patients with HR+, HER2-, and LN+ (1-3 nodes) breast cancer. At the time of writing, there are three other commercially available GEP tests that are not currently reimbursed in Ireland:

- MammaPrint®
- EndoPredict®
- Prosigna®.

Following a request from the NCCP, HIQA agreed to undertake a rapid health technology assessment (HTA) on the use of commercially available GEP tests for the purpose of guiding adjuvant chemotherapy decisions in patients with early-stage invasive breast cancer. The primary aim of the rapid HTA is to provide advice to the HSE on alternatives to Oncotype DX® that may be used to inform decision-making in relation to the management of early-stage invasive breast cancer.

1.2. Purpose, aim, and terms of reference

The purpose of this protocol is to outline the process by which the Health Information and Quality Authority (HIQA) will conduct a rapid HTA to inform decision-making by the HSE NCCP in relation to GEP tests for guiding adjuvant chemotherapy use in patients with early-stage invasive breast cancer. The rapid HTA will comprise:

- a description of the role and use of four GEP tests (Oncotype DX®, EndoPredict®, MammaPrint®, and Prosigna®)
- an overview of the epidemiology of early-stage invasive breast cancer and the associated burden of disease
- a systematic review of the prognostic and predictive accuracy of four GEP tests.

The rapid HTA will follow national guidelines and the HTA Core Model® proposed by the European Network for Health Technology Assessment (EUnetHTA), covering the epidemiology, burden of disease, description of the technology, and clinical effectiveness domains.[10] Additionally, both the HIQA Guidelines for Evaluating the Clinical Effectiveness of Health Technologies in Ireland and the Guide to Health Technology Assessment at HIQA will be followed.[11, 12]

The terms of reference for the rapid HTA, agreed with the NCCP, are to:

- describe the commercially available gene expression profiling (GEP) tests used to inform decision-making in patients with early-stage invasive breast cancer and consider the organisational implications associated with their use.
- describe the burden of disease associated with breast cancer in Ireland, with a particular focus on hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) early-stage (I, II, or IIIa) invasive breast cancer.
- review the prognostic and predictive accuracy of commercially available GEP tests, along with their impact on clinical decision-making, in patients with early-stage invasive breast cancer.
- based on the evidence in this assessment, provide advice to the HSE on alternative GEP tests to Oncotype Dx® to inform decision-making in relation to the management of early-stage invasive breast cancer.

1.3. Establishment of the Expert Advisory Group

HIQA convened an Expert Advisory Group comprising representation from relevant stakeholders including the NCCP, clinicians with specialist expertise in medical oncology, breast cancer surgery and histopathology, and patient representation.

The role of the Expert Advisory Group is to inform and guide the process, provide expert advice and information, and to provide access to data where appropriate. A full list of the membership of the Expert Advisory Group will be available in the acknowledgements section of the HTA report.

2. Description of technology

A description of the role and use of the four GEP tests being assessed within this rapid HTA (that is, Oncotype DX®, EndoPredict®, MammaPrint® and Prosigna®) will be provided. This description will include a summary of:

- the existing clinical pathway for patients with breast cancer and the current use of Oncotype DX® in Ireland
- the technical characteristics and logistical considerations associated with the use of the four GEP tests
- international practice regarding the use of GEP tests to assist clinical decision-making regarding the use of adjuvant chemotherapy.

3. Epidemiology

An overview of the epidemiology of early-stage invasive breast cancer and the associated burden of disease will be provided. In particular, the rapid HTA will:

- define the target population for this rapid HTA
- summarise the natural history of breast cancer
- describe the associated burden of disease in Ireland (the incidence, treatment outcomes and survival) of women with early-stage breast cancer.

This description will be informed by international literature and national data. National data presented on the burden of disease will be based on data collected and made available by the National Cancer Registry Ireland (NCRI).

4. Clinical effectiveness

4.1. Systematic review methods

In 2020, a comprehensive HTA comparing EndoPredict®, MammaPrint®, Prosigna® and Oncotype DX® was conducted by the government agency Ontario Health and the Canadian Agency for Drugs and Technologies in Health.[13] Due to the recency of their review and overlap with the topic of this review, the current systematic review will update that conducted as part of the Ontario Health HTA. Therefore, a systematic review will be performed to identify research published since November 2018 (that is, when the Ontario Health HTA concluded its search) and new studies identified through this review will be synthesised in the context of the Ontario Health HTA findings. Five distinct steps in this process have been identified:

1. Quality assessment of prior review
2. Search of relevant databases
3. Screening of identified studies
4. Data extraction and quality appraisal of included studies
5. Summarise findings.

4.2. Review process

4.2.1. Research question

The research question was formulated according to the Population, Intervention, Comparator, Outcomes and Study design (PICOS) framework (see Table 1). The systematic review seeks to answer the following question:

- Among patients with HR+, HER2-, and LN- or LN+ (1-3) early-stage (stages I to IIIa) invasive breast cancer, how do the gene expression profiling (GEP) tests (that is, EndoPredict®, MammaPrint®, Prosigna® and Oncotype DX®) compare to each other in terms of their:
    - prognostic accuracy
    - predictive accuracy
    - impact on clinical decision-making.

Table 1. PICOS framework for research question

Populations	Patients (men and women) with: ▪ HR+, HER2-, and LN- or LN+ (1-3) early-stage (stages I to IIIa) invasive breast cancer Subgroups: ▪ LN+ and LN- ▪ pre-menopausal and post-menopausal women.
Interventions	Oncotype DX®, EndoPredict®, MammaPrint®, and Prosigna®
Comparator	Any (for example, no comparator, non-gene test, other prediction tools (such as clinical risk prediction tools)); Oncotype DX®, EndoPredict®, MammaPrint®, and Prosigna®
Outcomes	Prognostic performance: ▪ freedom from distant recurrence (that is, freedom from distant recurrence (that is, the cancer has travelled to distant parts of the body), second primary cancer, or death) ▪ disease-free survival (that is, freedom from disease recurrence (for example, ipsilateral breast tumour recurrence, local recurrence, regional recurrence, distant recurrence, contralateral second primary invasive cancer, second primary non-breast invasive cancer (excluding non-melanoma skin cancers)), second primary cancer, or death from any cause) ▪ overall survival (that is, freedom from death due to any cause). Prediction of chemotherapy benefit: ▪ freedom from distant recurrence ▪ disease-free survival ▪ overall survival. Decision impact of tests (that is, changes in the recommendation or use of chemotherapy based on GEP test results)
Study design	Include ▪ RCTs ▪ reanalyses/retrospective analyses of RCTs ▪ retrospective analyses of data from a prospectively assembled database/registry across two or more institutions. Exclude ▪ retrospective analyses of data from a prospectively assembled database/registry in a single institution ▪ analyses of data from a retrospective review of medical records.

Key: GEP – gene expression profiling; HER2- – human epidermal growth factor receptor 2-negative; HR+ – hormone receptor-positive; LN- – lymph node negative; LN+ (1-3) – lymph node positive (1-3 – number of nodes to which the cancer has spread); RCTs – randomised controlled trials.

4.2.2. Quality assessment of prior review

The Ontario Health HTA searched for literature published between January and November 2018 and identified relevant literature published before that from two preceding reviews which searched from 2002-2016 and 2016-2017, respectively.

As part of scoping work, the quality of the Ontario Health HTA was appraised by two researchers independently using the AMSTAR 2 critical appraisal tool.[14] This assessment identified two items that warranted consideration:

- Study selection was not performed in duplicate for studies published from 2016
- Data extraction was not performed in duplicate

To mitigate potential risks, studies included in the Ontario Health HTA will be compared with a related review[15] and a limited electronic search in Clinicaltrials.gov and the World Health Organisation International Clinical Trials Registry Platform portal will be run to ensure no key research was missed. Manufacturers will also be invited to submit lists of relevant studies. The data extracted from six randomly selected studies published 2016-2018 in the Ontario Health HTA will be compared against the original studies from which data were extracted to check for errors.

4.2.3. Search of relevant databases

Electronic searches will be conducted in Medline (EBSCO), Embase (OVID), the Cochrane Library, Clinicaltrials.gov, and the WHO's International Clinical Trials Registry Platform portal. The search strategy is presented in Appendix 1. The search strategy in Medline will be peer-reviewed by a Health Library Ireland Librarian using the Peer Review of Electronic Search Strategies checklist.[16] Electronic searches will be supplemented by a grey literature search in the International Network of Agencies for Health Technology Assessment database, Epistemonikos, National Institute for Health and Care Excellence, and Google, and forward and backward citation searching of included studies will also be undertaken. Results retrieved from databases and other methods will be de-duplicated in Endnote and imported to Covidence for screening.

4.2.4. Screening of identified studies

Titles and abstracts of identified studies will be screened and full texts of those that are potentially eligible will subsequently be screened. For both the title and abstract and full text screening phases all papers will be screened by two people with any

disputes resolved by a third person. Screening will be undertaken using Covidence software.

Prognostic and predictive studies will be included if they:

- include HR+, HER2-, and LN- or LN+ (1-3) early-stage (stages I to IIIa) invasive breast cancer patients and
- assess the prognostic performance, predictive performance, or decision impact of Oncotype DX®, EndoPredict®, MammaPrint®, or Prosigna® and
- comprise 1) randomised controlled trials (RCTs), 2) reanalyses or retrospective analyses of RCTs, or 3) retrospective analyses of data from a prospectively assembled database or registry across multiple institutions.

Decision impact studies will be included if they:

- quantitatively assess the change in chemotherapy recommendations and or decisions before and after use of a GEP test
- are conducted in Europe (that is, the EU27 and Norway, Switzerland, and the UK due to regional differences in chemotherapy rates, such as higher rates in the US compared with Europe).

As decision impact studies included in the current review were limited to those conducted in Europe, due to expected geographical differences in chemotherapy uptake rate, only decision impact studies included in the Ontario Health review that were performed in a European setting will be discussed in this review.

Studies will be excluded if they comprise:

- retrospective nonrandomised (cohort) studies
- an assessment of the effectiveness of GEP tests in the context of extending adjuvant endocrine therapy and not chemotherapy
- exclusively patients with a specific subtype of breast cancer
- examination of non-genetic tests (for example, immunohistochemistry 4 plus clinical factors (IHC4-C)) but not genetic tests
- non-human studies
- publications dated prior to November 2018
- conference abstracts and preprints.

4.2.5. Data extraction and quality appraisal of included studies

Two reviewers will extract data independently, with disagreements resolved by discussion. A standardised data extraction template will be developed and piloted prior to undertaking the review. Data to be extracted are listed in Appendix 2.

Risk of bias will be assessed using the Cochrane Risk of Bias tool for RCTs (RoB 2),[17] the Prediction Model Risk of Bias Assessment Tool for prognostic studies (PROBAST),[18] and the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS) for nonrandomised predictive ability or clinical utility studies.[19]

4.2.6. Summarise findings

Direct comparisons of GEP tests will be reviewed, and, as it is anticipated that there will be few direct comparisons, the effectiveness of each test individually will be reviewed. Due to the expected heterogeneity of studies that will be included, meta-analysis will not be undertaken ,and findings of the included studies will be narratively reviewed. The certainty of the body of evidence directly comparing GEP tests will be assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group criteria.[20]

5. Summary

There are a number of commercially available alternative GEP tests to Oncotype Dx®. Numerous systematic reviews and HTAs have examined the effectiveness of these GEP tests, with mixed findings. As evidence continues to emerge on this topic, an additional review is warranted.

The rapid HTA will comprise a description of the four commercially available GEP tests, a description of the burden of disease, and a systematic review of the prognostic and predictive accuracy of these four GEP tests to inform the management of early-stage invasive breast cancer.

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Appendices

Appendix 1: Search terms

Medline (EBSCO) Search Strategy

S17	S5 AND S14 AND S15	Limiters - Date of Publication: 20180101-20221231 Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	578
S16	S5 AND S14 AND S15	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,285
S15	S6 OR S7 OR S8 OR S9 OR S10 OR S11	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	152,095
S14	S12 OR S13	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	3,062,831
S13	MH "Cohort Studies" OR MH "Longitudinal Studies" OR MH "Prospective Studies" OR MH "Follow Up Studies" OR MH "Retrospective Studies" OR TI (cohort OR longitudinal OR prospective OR "follow up" OR retrospective) N1 (study OR analys* OR design OR method*) OR AB (cohort OR longitudinal OR prospective OR "follow up" OR retrospective) N1 (study OR analys* OR design OR method*)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	2,303,458
S12	MH "Randomized Controlled Trial" OR PT "Randomized Controlled Trial" OR TI random* N2 trial OR AB random* N2 trial OR TI placebo* OR TI "single blind*" OR TI "double blind*" OR TI "triple blind*" OR AB placebo* OR AB "single blind*" OR AB "double blind*" OR AB "triple blind*"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	924,725

S11	(MH "Gene Expression Profiling/MT")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	28,227
S10	(TI (multigene* or multi-gene* OR gene or genome or genomic) N2 (profil* or signature* or assay* or test*)) OR (AB (multigene* OR multi-gene* or gene or genome or genomic) N2 (profil* or signature* or assay* or test*))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	129,432
S9	(AB Oncotype OR “Oncotype DX” OR 21-gene OR "recurrence score”) OR (TI Oncotype OR “Oncotype DX” OR 21-gene OR "recurrence score”)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	1,356
S8	(TI Mammaprint or 70-gene) OR (AB Mammaprint or 70-gene)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	409
S7	(TI Prosigna or “Predictor Analysis of Microarray 50 “ OR PAM50 OR “PAM 50” OR 50-gene) OR (AB Prosigna or “Predictor Analysis of Microarray 50 “ OR PAM50 OR “PAM 50” OR 50-gene)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	589
S6	(TI EndoPredict OR EPclin OR “EP test” or “EP score” or “12-gene”) OR (AB EndoPredict OR EPclin OR “EP test” or “EP score” or “12-gene”)	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	310
S5	S1 OR S2 OR S3 OR S4	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	390,753
S4	(MH "Carcinoma, Intraductal, Noninfiltrating")	Limiters - Date of Publication: 20090101-20101231 Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	462
S3	(MH "Breast Neoplasms+")	Limiters - Date of Publication: 20090101-20101231 Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	19,563

S2	TI ("invasive lobular" OR "invasive ductal" OR "infiltrating ductal") OR AB ("invasive lobular" OR "invasive ductal" OR "infiltrating ductal")	Limiters - Date of Publication: 20090101-20101231 Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	731
S1	TI (Breast* N4 (cancer* OR carcinoma* OR neoplasm* OR tumour* OR tumor* OR adenocarcinoma* OR malignan* OR sarcoma* OR dcis or ductal or infiltrat* or intraductal* or lobular or medullary)) OR AB (Breast* N4 (cancer* OR carcinoma* OR neoplasm* OR tumour* OR tumor* OR adenocarcinoma* OR malignan* OR sarcoma* OR dcis or ductal or infiltrat* or intraductal* or lobular or medullary))	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	387,389

Appendix 2: Data extraction template

Study Details	Test Details	Study Population	Study results
▪ Author ▪ Year ▪ Country ▪ Study Design ▪ Funder ▪ Competing interests	▪ EndoPredict® ▪ MammaPrint® ▪ Oncotype DX® ▪ Prosigna®	▪ Sample size ▪ Age ▪ Gender ▪ Time period, years ▪ Menopausal status ▪ Adjuvant chemotherapy received ▪ GEP test score/classification ▪ Lymph node status	▪ Freedom from distant recurrence ▪ Disease-free survival ▪ Overall survival ▪ Decision impact

Key: GEP – Gene Expression Profile.

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