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Final Decision
Analytical Protocol
(DAP) to guide the
assessment of gene
expression profiling
of 21 genes in breast
cancer assay to
quantify the risk of
disease recurrence
and predict adjuvant
chemotherapy benefit

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FINAL

Abbreviations list

Abbreviation	Full Term
AAB	American Association of Bioanalysts
AACR	American Association of Cancer Registries
AC	doxorubicin and cyclophosphamide
AC-Taxol	doxorubicin and cyclophosphamide followed by paclitaxel
AIHW	Australian Institute of Health and Welfare
AJCC	American Joint Committee on Cancer Staging
BAG-1	BCL2-associated athanogene 1
BCL-2	B-cell lymphoma 2
CAP	College of American Pathologists
CD-68	Cluster of differentiation 68
CEA	Cost-effectiveness analysis
CI	confidence interval
CLIA	United States Clinical Laboratory Improvement Amendment
CMF	cyclophosphamide, methotrexate, 5-fluourouracil
CMS	Centers for Medicare and Medical Service
CUA	Cost-utility analysis
DAP	Decision Analytical Protocol
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
ER	oestrogen receptor
ER-	oestrogen receptor-negative
ER+	oestrogen receptor-positive
ESMO	European Society for Medical Oncology
FECD	5-fluourouracil, epirubicin, cyclophosphamide followed by docetaxel
FFPET	formalin fixed paraffin embedded tissue
FiSH	fluorescence in situ hybridization
FPE	paraffin-embedded tumour tissue
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
GEP	gene expression profiling
GHI	Genomic Health Inc.
GRB-7	Growth factor receptor-bound protein 7
GSTM-1	Glutathione S-transferase mu 1
GUS	Beta-glucuronidase
HER2	human epidermal growth factor receptor 2
HER2-	human epidermal growth factor receptor 2-negative
HER2+	human epidermal growth factor receptor 2-positive
IHC	Immunohistochemistry
IVDs	In Vitro diagnostic medical devices
KRAS	GTPase KRas or V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LN	lymph node
MBS	Medicare Benefits Scheme
MDM	Multidisciplinary Meeting
mRNA	messenger ribonucleic acid
MSAC	Medical Services Advisory Committee
MYBL-2	Myb-related protein B
N-	node-negative

N+	node-positive
NATA	National Association of Testing Authorities
NBOCC	National Breast and Ovarian Cancer Centre
NCCN	National Comprehensive Cancer Network
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Clinical Excellence
NPAAC	National Pathology Accreditation Advisory Committee
NSABP	National Surgical Adjuvant Breast and Bowel Project
PASC	Protocol Advisory Sub-Committee
PICO	Patients, Intervention, Comparator, Outcomes
PR	progesterone receptor
PR-	progesterone receptor-negative
PR+	progesterone receptor-positive
RNA	ribonucleic acid
RPLPO	Large ribosomal protein
RS	Recurrence Score
RT-PCR	reverse-transcriptase polymerase chain reaction
SCUBE-2	Signal peptide, CUB domain, epidermal growth factor-like 2
SD	standard deviation
STK-15	Serine/threonine kinase
TAC	docetaxel, doxorubicin, cyclophosphamide
TC	docetaxel, cyclophosphamide
TFRC	Transferrin receptor
TGA	Therapeutic Goods Administration
TNM	Classification of Malignant Tumours
uRS	unscaled recurrence score

MSAC and PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Australian Government Health Minister to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Health Minister on the evidence relating to the safety, effectiveness, and cost effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

The Protocol Advisory Sub-Committee (PASC) is a standing sub-committee of MSAC. Its primary objective is the determination of protocols to guide clinical and economic assessments of medical interventions proposed for public funding.

PURPOSE OF THIS DOCUMENT

This document is a Decision Analytical Protocol (DAP) that will be used to guide the assessment of a gene expression profiling (GEP) test by real-time reverse-transcriptase polymerase chain reaction (RT-PCR) technique for 21 genes that predicts the likelihood of adjuvant chemotherapy benefit in a subset of breast cancer patients. Specifically, it is proposed that the test should be used in patients with early breast cancer who are node-negative (N-) or node-positive (up to 3 nodes), oestrogen receptor-positive (ER+) or progesterone receptor-positive (PR+) and human epidermal growth factor receptor 2-negative (HER2-). It is the intent of this DAP to develop a protocol for the assessment and MBS listing for **any** GEP in breast cancer using 21-genes and the RT-PCR technique. The rationale behind performing such a test is to characterise and identify patients with different risk profiles for recurrence, thus allowing clinicians to better individualise their treatment recommendations.

There is only one such test that uses 21-genes and the RT-PCR technique in existence, the Oncotype DX[®] Breast Cancer Test which is marketed by Genomic Health Inc. (GHI). GHI hold the patent for the GEP algorithm from the 21-gene RT-PCR assay. Throughout the remainder of the DAP the GEP in breast cancer using 21-genes and the RT-PCR technique will be referred to as Oncotype DX.

Although reference is made to the Oncotype DX brand name in this DAP for simplicity, it should be noted that GHI is not seeking to include a brand name in an MBS item descriptor. If implemented, this MBS item would therefore apply to other GEPs assaying 21 genes using RT-PCR and an algorithm in competition with Oncotype DX.

This DAP has been updated by GHI based on requested changes received after an earlier version (dated November 2012) was reviewed by PASC at the 13-14 December 2012 PASC meeting. It is expected that this updated version will be reviewed at the April 2013 PASC meeting. Following a period of consultation the final DAP ratified by PASC will provide the basis for the assessment of the intervention.

The protocol guiding the assessment of the health intervention has been developed using the widely accepted “PICO approach”. This approach involves a clear articulation of the following aspects of the research question that the assessment is intended to answer:

Patients - specification of the characteristics of the population or patients in whom the intervention is intended to be used;

Intervention - specification of the proposed intervention;

Comparator - specification of the therapy most likely to be replaced, or added to, by the proposed intervention; and

Outcomes - specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention.

Purpose of the application

An application from GHI was received by the Department of Health and Ageing requesting a Medicare Benefits Schedule (MBS) listing for GEP Oncotype DX testing in a subset of early breast cancer patients who are node negative or positive (up to 3 nodes) ER+ or PR+ and HER2-. GEP is an emerging technology for identifying genes whose activity may be helpful in assessing disease prognosis and guiding therapy. In recent years, GEP has been successfully used in breast cancer research. For instance, distinct subtypes of breast tumours (such as tumours expressing HER-2) have been identified as having distinctive gene expression profiles, representing diverse biologic entities associated with differences in clinical outcome (Marchionni et al. 2008).

This application relates to a test that is conducted in a single laboratory in the United States and so is not subject to regulation by the Australian Therapeutic Goods Administration. The laboratory is however subject to regulation by the United States’ Centers for Medicare and Medical Service (CMS). The test is not currently funded on the MBS. This DAP originally drafted by GHI using the final DAP for other GEP tests assessed in Australia, HER2 testing for lapatanib (MSAC ID 1175), and other DAPs developed for gene expression tests such as BRAF testing (MSAC ID 1172) and epidermal growth factor receptor (EGFR) testing (MSAC ID 1173) as a guide. Consultation with experts in the treatment of breast cancer from across Australia was also sought in the development of the DAP.

It is proposed that this DAP guide the assessment of the safety, effectiveness and cost-effectiveness of Oncotype DX testing in early breast cancer in order to inform MSACs decision-making regarding public funding of the test.

Background

CURRENT ARRANGEMENTS FOR PUBLIC REIMBURSEMENT

Oncotype DX is a unique multigene assay using 21 genes and offers information on individual tumour biology that is not currently available from any other source. Currently Oncotype DX testing is not eligible for reimbursement under Medicare. However the Oncotype DX test is available on the private market but only those with the ability to pay for it.

The single laboratory performing the test is located in Redwood City, California, US. There have been over 250,000 tests delivered to breast cancer patients from 64 countries and over 400 Australian patients have received the test. GHI works with Australian laboratories and other partners to coordinate the delivery of the sample to the US for testing. The test does not have any workforce implications in Australia in terms of the need for investment in new technology, additional capacity or training – unlike other genetic tests recently reviewed by PASC and MSAC (HER2 testing using fluorescence in situ hybridization, FiSH, for example)(MSAC assessment report 38, June 2008 p.64).

In Australia, there were 12,567 new cases of breast cancer in 2007, and it is estimated that this will increase to approximately 14,818 cases in 2011 and 15,409 cases by 2015 (Cancer Australia 2011). Based on data from the NSW Central Cancer Registry between 2004 and 2008, 51.2% of patients have localised disease at the time of diagnosis, while 36.5% have advanced disease with regional lymph node involvement, 5.4% have distant metastases, and the extent of disease in 6.9% is unknown (New South Wales Central Cancer Registry 2010). It is estimated that half of the women with regional lymph node involvement will have involvement in less than 3 nodes. Thus, approximately 70% of patients have breast cancer with either no lymph node involvement or 1-3 lymph nodes involved. This equates to approximately 10,372 per annum ($14,818 \times 0.70$).

Immunohistochemistry (IHC) for the detection of oestrogen, progesterone and HER2, among other antibodies, is currently listed on the MBS (item number 72848, 72849 or 72850). These item numbers allow for examination of biopsy with 1 to 3, 7 to 10 and 11 or more antibodies, respectively and are currently not restricted by patient or clinical indication. Any of these tests are sufficient to determine patients ER and HER2 status to establish eligibility for the Oncotype DX test. The utilisation of these items indicates that between January 2010 and December 2011 there were approximately 28,874 services claimed for women (Table 1). Based on the estimated 14,818 new breast cancer cases in 2011, current usage of IHC testing in Table 1 suggests that all women with breast cancer are being tested for ER, PR and HER2.

Table 1 Medicare utilisation of MBS items 72848, 72849, 72850 by women between January 2010 and December 2011

Item number	2010	2011
72848	6,660	6,440
72849	5,599	5,995
72850	1,876	2,304
Total	14,135	14,739

Source: <https://www.medicareaustralia.gov.au/>

REGULATORY STATUS

The Oncotype DX assay is not registered in any other country other than the US as it is a test service that is exclusively performed in a single laboratory located in Redwood city, California, US. The Genomic Health Inc. laboratory is certified to perform such testing with the United States' Centers for Medicare and Medical Service (CMS) and accredited by the College of American Pathologists (CAP) under the United States Clinical Laboratory Improvement Amendment (CLIA) of 1988 and operates in accordance with federal and state laws.

Centralisation of the testing process is a significant strength of Oncotype DX with regard to reproducibility. It does not suffer from the same problems as other assays based on technologies that are difficult to standardise across different laboratories. Hence there is no need for an Australian laboratory to implement new testing strategies. Importantly, there are no issues with laboratory workforce limitations such as the need for additional expertise in performing or interpreting the test that could be a barrier to access and indeed has been with the implementation of other tests. For example, the review of tests for HER2 gene amplification found that some techniques would be restricted to central laboratories because of requirements for investment in specialised equipment and training. Furthermore widespread introduction of some techniques were not thought to be tenable due to the workload pressures facing Australian pathologists (MSAC assessment report 38, June 2008 p. 64).

INTERVENTION

Standard of Care and Rationale for Oncotype DX

The rationale for developing the Oncotype DX assay was to provide clinicians with a tool that would allow them to better select patients with early breast cancer who may benefit from adjuvant chemotherapy.

Breast cancer is a disease in which abnormal cells, most commonly originating from the terminal duct lobular unit of the breast, transform and develop into an invasive tumour. These tumours can invade and damage the tissue around them, and spread to other parts of the body, such as the bones, liver, lung and brain, through the lymphatic or vascular systems (AIHW & NBOCC 2009).

Breast cancer is the most common cancer among Australian women, accounting for 27% of all cancer diagnoses and with an average age of first diagnosis of 60 years in 2007 (AIHW & AACR 2010; AIHW & NBOCC 2009). Thus, one in nine women will be diagnosed with breast cancer before the age of 85. The BreastScreen Australia program screened 1,641,316 women (77.6% aged 50-69 years) for breast cancer in 2007-2008 (AIHW 2010). There was an increase in the rate of detection of invasive breast cancer between 1996 and 2008, from 56.5 to 71.7 per 10,000 women screened for the first screening round, and from 35.3 to 47.5 per 10,000 women screened for subsequent screening rounds. However, nearly two-thirds of all invasive breast cancers detected by BreastScreen Australia were small, improving the chances of survival for these patients.

The relative five-year survival rates for Australians has been increasing steadily in the last few decades; 72.6% of women diagnosed with breast cancer in 1982-1987 survived, compared to 88.3% of women in 2000-2006. The 2006 five-year relative survival rate can be further divided into 96.5% for women with negative nodal status and 80.2% for women with positive nodal status in 2006 (AIHW & NBOCC 2009). Despite the high survival rates, breast cancer was the leading cancer cause of burden of disease for women, accounting for 40,600 years of life lost due to premature death and 20,500 years of healthy life lost due to disease, disability or injury in 2010 (AIHW & AACR 2010).

In the current care paradigm a diagnosis of breast cancer is made by multiple assessments (clinical assessment, mammography and/or ultrasound imaging with core biopsy and/or fine needle aspiration) and upon pathological confirmation of cancer diagnosis and staging a treatment plan is suggested. Systemic therapy options for breast cancer management include endocrine treatments, targeted biological agents and chemotherapy.

Surgery is usually considered as the first treatment option for primary breast cancer. For patients who present with tumours that are considered too large for breast conservation surgery, guidelines recommend that primary systemic therapy (neoadjuvant therapy) may be used in an attempt to shrink the size of the primary tumour to enable breast conserving treatment and surgery. In addition some patients are considered unfit for surgery, these patients are usually elderly. During surgery the tumour and axillary lymph nodes are dissected. The aim of surgery is to eradicate the primary tumour and any local extension in the hope of achieving total disease control (NHRMC Clinical practice guidelines for the management of early breast cancer, 2001). Histological information obtained following surgery provides information relating to a number of prognostic factors including histological grade, nodal status, tumour size, hormone (ER and PR) receptor and HER-2 status, subsequent planning of treatment is then undertaken on the basis of these prognostic and predictive factors (in combination with information on patient characteristics). The strongest prognostic factors for predicting future recurrence or death from breast cancer are patient age, comorbidity, tumour size, tumour grade, number of involved axillary lymph nodes and HER2 status (NCCN 2011). Algorithms, such as Adjuvant online, have been published estimating the rates of recurrence but it has not been updated for some time and does not

include HER2 tumour status (Segelov and Yeo 2010). Based on expert opinion gathered to assist the development of this DAP, it is for these reasons that Australian clinicians are tending to use Adjuvant online less frequently. Information on risk of recurrence is used by clinicians and patients to make decisions regarding toxicities, costs and benefits of systemic adjuvant therapy (NCCN 2011). Systemic adjuvant therapy may comprise hormone therapy and or chemotherapy.

The intent is to include all “hormone receptor (HR)-positive” patients, defined as being ER+ and/or PR+ determined by immunohistochemistry (IHC), as eligible for the assay, as these are patients for whom adjuvant hormonal therapy with or without chemotherapy is usually recommended. The level of ER assessed immunohistochemically provides useful predictive information regarding efficacy of endocrine therapy (NICE 2011 Scoping document). ER status therefore forms part of the Australian minimum dataset for histopathology reporting of invasive breast cancer. ER status is routinely determined on all invasive breast cancers and reported using a standardised technique (such as the Allred scoring system). However, the prediction of likelihood of response of a breast cancer to endocrine therapies using ER assessment is not precise; some patients with ER-positive disease will not respond to endocrine therapies. Therefore, additional markers for response to endocrine therapy have been sought. Since progesterone receptor (PR) expression is induced by ER, it has been studied as a surrogate marker for ER activity and immunohistochemical assessment of PR has been used as an additional predictive factor for hormonal therapy in breast cancer. The results of overview analyses of randomised clinical trials in early breast cancer have shown that PR may add to the power of ER for predicting response to endocrine therapy. PR also predicts response to endocrine therapy in metastatic breast cancer (Mohsin et al. 2004). Divergent ER and PR status is uncommon (for example, less than 5% of cases are ER-negative but PR-positive). Nevertheless, PR examination is routinely performed on all invasive tumours by some laboratories (NICE 2011 Scoping document). Furthermore there have been instances where there are occasional discordances where a tumour is deemed ER- by IHC but ER+ by RT-PCR. In a report of the first 10,618 patients who received the Oncotype DX® assay, all of whom met the definition of HR-positivity based on IHC results from local laboratories, the distributions of the ER and PR status were 81.0% ER+, PR+; 15.4% ER+, PR-; 3.4% ER-, PR-; and 0.2% ER-, PR+ (Shak et al., Subtypes of Breast Cancer Defined by Standard Quantitative RT-PCR Analysis of 10,618 Tumors, SABCS 2006, Abstract #6118). Thus, instances of patients who are PR+ and ER- are exceedingly rare and those patients found to be ER-, PR- by reverse transcription–polymerase chain reaction (RT-PCR) were likely representative of true discordant results when compared with results by IHC.

Immunohistochemical assessment of the ER and PR status of a breast cancer tumour is currently used to predict the efficacy of hormone therapy (NHMRC 2001). HER2 status is also assessed and forms a key component of decision to offer trastuzumab. Ki-67 is a genetic marker in development however there still remain substantial challenges in its utility as reliable Ki-67 index assessments are not yet available and evidence predictive

(Goldhirsch et al. 2011, Li et al. 2012, Luporsi et al. 2012). Furthermore Ki-67 has not found to be predictive for long term follow-up after chemotherapy (Luporsi et al. 2012).

There is no tumour specific chemotherapy subtyping tool available to determine the likelihood of benefiting from adjuvant chemotherapy. It is well recognised that there is a significant overtreatment (and under treatment) with chemotherapy in the adjuvant setting in patients with ER+ early stage breast cancer based on conventional care paradigm. The selection of patients with ER+ (or PR+) early stage breast cancer for adjuvant chemotherapy remains an important clinical issue since the additional benefit of adjuvant chemotherapy in node negative breast cancer is modest (estimated absolute benefit of 4%; 92% with versus 88% without, in terms of 10-year distant recurrence in the NSABP-20 trial) but the toxicity is significant. There is great interest in developing, testing, and validating strong predictive markers that can be used in daily clinical practice to accurately identify those patients most likely to benefit from specific therapy options such as chemotherapy.

For node positive patients, who are HR+ (N=3383), there is also a relatively modest risk of relapse and modest treatment effect observed with taxane containing chemotherapy regimens (annual recurrence rate less than 0.1 and 7.0% absolute survival benefit due to chemotherapy for patients who survived to 5 years disease-free) (Berry et al. 2006). Additionally, patients with node positive disease are more likely to be initiated on chemotherapy than node-negative patients. Therefore, there exists the potential for Oncotype DX to prevent unnecessary exposure to chemotherapy regimens that are offering the patient no clinical effect.

Table 2 provides definitions for the TNM staging categories used by the American Joint Committee on Cancer Staging (AJCC) and Table 3 describes the TNM categories that define breast cancer stages 0-IV. Patients with breast cancer stage I-II would be eligible for Oncotype DX testing.

Table 2 TNM staging of breast cancer

Primary tumour (T)		Regional lymph node (N)		Distant metastasis (M)	
TX	Primary tumour cannot be assessed	NX	Regional lymph nodes cannot be assessed (for example, previously removed)	M0	No clinical or radiographic evidence of distant metastases
T0	No evidence of primary tumour				
Tis	Carcinoma in situ	N0	No regional lymph node metastasis	M0(i+)	deposits of tumour cells in circulating blood, bone marrow, or other non-regional nodal tissue that are no larger than 0.2 mm
(DCIS)	Ductal carcinoma in situ	N1	Metastases to movable ipsilateral level I, II axillary lymph node(s)		
(LCIS)	Lobular carcinoma in situ				
(Paget's)	Paget's disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ	N2a	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted	M1	Distant detectable metastases larger than 0.2 mm
T1	Tumour ≤ 20 mm in greatest dimension	N2b	Metastases in clinically detected ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases		
T2	Tumour > 20 mm but ≤ 50 mm in greatest dimension				
T3	Tumour > 50 mm in greatest dimension				
T4	Tumour of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)	N3a	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement;		
T4a	Tumour of any size with direct extension to the chest wall, not including only pectoralis muscle adherence/invasion	N3b	Metastases in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases;		
T4b	Tumour of any size with ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma	N3c	Metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement		
T4c	Both T4a and T4b				
T4d	Inflammatory carcinoma				

Source: American Joint Committee on Cancer Staging resources [Accessed, September 2011]
<http://www.cancerstaging.org/staging/index.html>;

(As presented in Decision Analytic Protocol for HER2 testing in breast cancer, application 1175, January 2012)

Table 3 American Joint Committee on Breast Cancer TNM stage grouping

Stage grouping	T stage	N stage	M stage
Stage 0	Tis	N0	M0/M0(i+)
Stage IA	T1	N0	M0/M0(i+)
Stage IB	T0	N1mi	M0/M0(i+)
	T1	N1mi	M0/M0(i+)
Stage IIA	T0	N1	M0/M0(i+)
	T1	N1	M0/M0(i+)
	T2	N0	M0/M0(i+)
Stage IIB	T2	N1	M0/M0(i+)
	T3	N0	M0/M0(i+)
Stage IIIA	T0	N2	M0/M0(i+)
	T1	N2	M0/M0(i+)
	T2	N2	M0/M0(i+)
	T3	N1	M0/M0(i+)
	T3	N2	M0/M0(i+)
Stage IIIB	T4	N0	M0/M0(i+)
	T4	N1	M0/M0(i+)
	T4	N2	M0/M0(i+)
Stage IIIC	Any T	N3	M0/M0(i+)
Stage IV	Any T	Any N	M1

Source: American Joint Committee on Cancer Staging resources [Accessed, September 2011]
<http://www.cancerstaging.org/staging/index.html>; orange shading denotes proposed eligibility for HER2 testing

(As presented in Decision Analytic Protocol for HER2 testing in breast cancer, application 1175, January 2012)

Oncotype DX: Design and technical background

The Oncotype DX test evaluates the expression of a panel of 21 genes from a tumour specimen (surgical resections or core biopsy) using a high-throughput, RT-PCR method to measure levels of gene expression. Standardised pathology guidelines instruct pathologists to select the most representative formalin fixed, paraffin-embedded tumour (FFPET) block (i.e., that which contains the greatest amount of invasive carcinoma that is morphologically consistent with the submitting diagnosis) when preparing unstained slides for the assay. Samples from surgical resections are preferred to core biopsies to ensure that the most representative invasive tumour component is sent for analysis. Core biopsies are accepted, however, in rare instances when surgical resection tissue is not available, as analytical methods have also been standardised to assay these tissue sources. All tissue samples are assessed by a pathologist at GHI to verify the diagnosis and to perform manual microdissection as needed in accordance with pathology guidelines. The assay generally requires 2 mm of invasive tumour tissue for successful analysis.

GEP examines the composition of cellular messenger ribonucleic acid (RNA) populations (Marchionni et al. 2008). The identity of the RNA transcripts that make up these populations and the number of these transcripts in the cell provide information about the global activity of

genes that give rise to them. The number of mRNA transcripts derived from a given gene is a measure of the “expression” of that gene. Given that messenger RNA (mRNA) molecules are translated into proteins, changes in mRNA levels are ultimately related to changes in the protein composition of the cells, and consequently to changes in the properties and functions of tissues and cells in the body. Technologies available for GEP include RT-PCR and microarray assays. The technology used for Oncotype Dx testing is RT-PCR.

The first step in developing the Oncotype DX test was to develop a method to accurately quantify gene expression with the use of sections of fixed, paraffin-embedded (FPE) tumour tissue. FPE tissue represents the most abundant supply of solid tissue specimens with frozen section examinations of breast specimens playing a limited role in the management of the patient with breast cancer (NHMRC 2001 p.46). It was previously considered impossible to perform RT-PCR on archival tissue, partly because the extracted RNA was extensively degraded and partly because the amounts present were too small to be amplified by conventional means. However, improved techniques for extracting RNA from fixed specimens have shown that it is possible to detect mRNA in FPE tissue (Abrahamsen et al. 2003, Cronin et al. 2004).

RT-PCR is the method of choice for quantifying absolute changes in gene expression. Moreover, this technique has become the preferred method for validating results obtained from microarray analyses and other techniques that evaluate gene expression changes on a global scale (Marchionni et al. 2008). RT-PCR is a highly sensitive and reproducible technology, and diagnostic accuracy studies show that Oncotype DX has a consistently low failure rate (Cronin et al. 2007).

The second step in the developing the assay was to identify a set of 250 candidate genes of genes from the published literature, genomic databases, and experiments based on DNA arrays performed on fresh-frozen tissue. Candidate genes were selected by surveying the breast cancer literature for evidence of a significant role in cancer pathologic processes, including proliferation, invasion, sensitivity to apoptosis, metastasis, angiogenesis, immune surveillance, tumour suppression activity, oncogene activity, and differentiation status (Cronin et al. 2004, Cobleigh 2005).

Thirdly, authors compared gene expression levels in matched FPE and frozen tissue specimens prepared from the same breast tumour. They showed that the relative expression profiles obtained from the two analyses were similar (correlation = 0.91, P value < 0.0001), although the magnitude of the measurements differed (Cronin et al. 2004). Five reference genes (ACTB (the gene encoding beta-actin), GAPDH, GUS, RPLP0, and TFRC) were identified to enable normalisation of the expression of cancer-related genes. Reference gene candidates were selected from among those well-known in the literature as commonly constitutively expressed genes across a wide range of tissues and biological conditions (Cronin et al. 2004). Combinations of these genes were tested for normalisation performance before selecting the mean of all 5 genes for the standard reference normalization method. Normalisation is of importance as it minimises pre-analytical sources

of variability due to different fixatives or protein/RNA degradation over time, for instance the authors successfully corrected the differences using normalization based on the expression of five reference genes. Convincing evidence supporting the use of the implemented protocols in assessing gene expression levels from archival (i.e., formalin-fixed, paraffin-embedded) tumour specimens was shown (Cronin et al. 2004).

Cobleigh et al. (2005) reported the findings from a study designed to investigate aspects of analytical validation of the expression of individual genes during the development of Oncotype DX as an aid to adjuvant chemotherapy decision-making in patients with ER+ breast cancer (Cobleigh et al. 2005). Archival fixed paraffin blocks were available from the primary tumour in 78 evaluable patients with ≥ 10 positive nodes in breast cancer. RNA was extracted from these paraffin blocks, and expression of 203 candidate genes was quantified using RT-PCR at the GHI central laboratory.

Follow up data (August, 2002) showed that 77% of patients had experienced distant recurrence or death due to breast cancer at the time of analysis. Univariate Cox analysis of clinical and immunohistochemistry variables suggested that the following factors were significantly associated with distant recurrence (or disease-free survival): HER2 (immunohistochemistry), number of involved nodes, PR+ (immunohistochemistry, percentage of cells), and ER+ (immunohistochemistry, percentage of cells). A total of 22 genes were identified by univariate Cox analysis as being associated with distant recurrence or disease-free survival (most of which went on to be used in the Oncotype DX test). These observations were supported using several multivariate analyses.

Importantly, the analysis showed that gene expression in FFPE tissue obtained at the time of surgery performed as long as 24 years ago was associated with the likelihood of distant recurrence in women with breast cancer and ≥ 10 positive nodes. Clinical and pathologic variables, such as age, tumour size, number of involved nodes, and systemic treatment, were shown to have only modest correlations with the likelihood of recurrence. The assay identified groups of co-expressed genes (that had previously been identified as cancer-related "candidate" genes) and 14 of the 16 genes used to compute the Recurrence Score were correlated with recurrence, 9 of them at a level of $p < 0.05$ and 14 at a level of $p < 0.10$. The accuracy and specificity of the RT-PCR assay was supported by comparison of the results with immunohistochemistry assays of protein for ER, PR, and HER2, which showed high concordance. It is not surprising that 3 of the genes found to be significantly associated with distant recurrence in the Oncotype Dx studies, HER2, ER and PR, are known prognostic factors in breast cancer.

A panel of 16 cancer genes has been selected based on the consistent and strong statistical association between the level of expression of these genes and distant breast cancer recurrence in 447 patients from three independent clinical studies (Esteban et al. 2003 abstract, Cobleigh et al. 2003 abstract, Paik et al. 2003 abstract). The panel of 16 genes are categorised into 5 functional groups associated with tumour proliferation and invasion, as

well as other genes related to HER-2/*neu* expression, ER expression and single gene expression (see Table 4).

Table 4 Overview of gene expression levels captured in the Oncotype DX breast cancer assay

Type	Gene
Proliferation	KI-67
	Serine/threonine kinase 15 (STK-15)
	Survivin
	Cyclin-B1
	Myb-related protein B (MYBL-2)
Invasion	Stromelysin-3
	Cathepsin-L2
Human epidermal growth factor receptor 2 (HER-2)	Growth factor receptor-bound protein 7 (GRB-7)
	HER-2
Oestrogen	Oestrogen receptor (ER)
	Progesterone receptor (PR)
	B-cell lymphoma 2 (BCL-2)
	Signal peptide, CUB domain, epidermal growth factor-like 2 (SCUBE-2)
Other	Glutathione S-transferase mu 1 (GSTM-1)
	Cluster of differentiation 68 (CD-68)
	BCL2-associated athanogene 1 (BAG-1)
Reference	Beta-actin (ACTB)
	Glyceraldehyde 3-phosphate dehydrogenase (GAPDH)
	Large ribosomal protein (RPLPO)
	Beta-glucuronidase (GUS)
	Transferrin receptor (TFRC)

Source: Paik et al. 2004

A recurrence score is used to correspond to a point estimate of the 10-year risk of distant recurrence with a 95% confidence interval for an individual patient. The validation of the Recurrence Score (RS) has been reported by Paik et al. (2004). The authors evaluated the reproducibility of the Oncotype DX assay within and between FFPET blocks from the same patient using 668 breast cancer tissue blocks. For the 16 genes considered in the RS, the SD of expression ranged from 0.07 to 0.21 expression units across serial sections from the same block. The within-block SD of the combined RS proved to be 0.72 RS units (with 95 percent CI: 0.55–1.04), while the within patient SD, which included both among-block and within-block variation, proved to be 2.2 RS units. The difference between the low- and high-risk groups is 14 RS units, far larger than the standard deviations reported.

In 2007, Cronin et al. reported on the analytical performance of the Oncotype DX assay (Cronin et al. 2007). The authors describe that the Oncotype DX assay normalises gene

expression measurements to the mean expression of 5 reference genes (ACTB (the gene encoding beta-actin), GAPDH, GUS, RPLP0, and TFRC). For each sample, normalised expression measurements are calculated as the mean cycle threshold (CT, the number of cycles required to achieve an RT-PCR cycle threshold) for the 5 reference genes minus the mean CT of triplicate measurements for each individual gene. Normalized expression measurements are scaled from 0 to 15 units, where 1 unit reflects an ~2-fold change in RNA quantity (Cronin et al. 2007). The unit of measurement of gene expression levels for inputting into the algorithm are “units”.

Cronin et al. (2007) also provides evidence regarding the high degree of precision and reproducibility in the Oncotype Dx assay. Standard deviations in cycle threshold measurements varied from approximately 0.06 to 0.15 cycle threshold units for each of the 21 genes, and the upper bounds on 2-sided 95% CIs for the coefficients of variation were all within 10%, indicating a high degree of precision and reproducibility in the assay. These standard deviations and coefficient of variation values are for the estimates of total analytical variability. The between-day standard values were close to 0 for all 21 genes. In addition, pairwise differences in (least-squares) mean cycle threshold values between operators, liquid-handling robots, and 7900HT instruments were calculated, with the largest differences being <0.5 cycle threshold units for each of the 21 Oncotype DX genes.

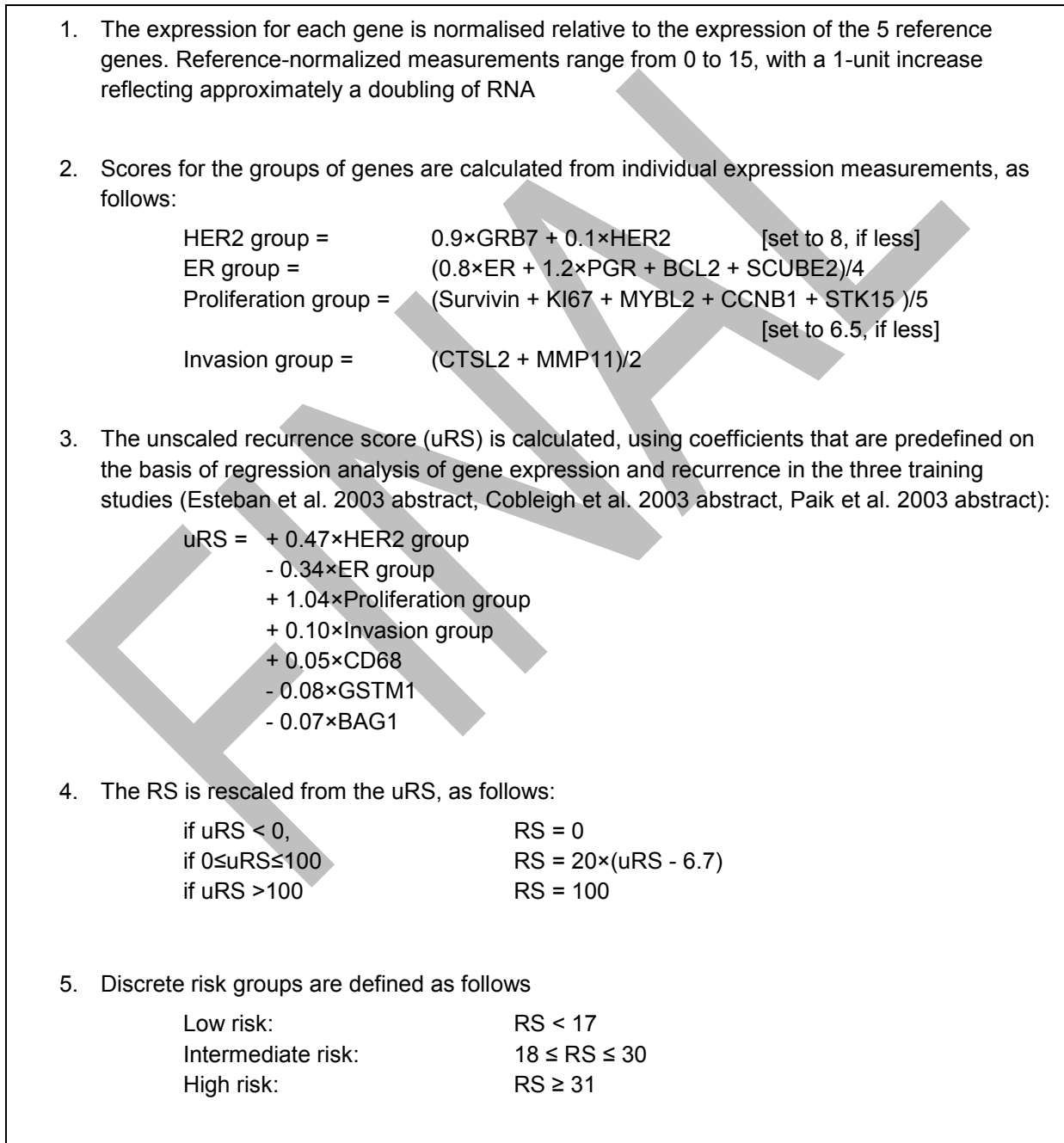
Clinical validation of the Oncotype DX assay has also been established by Cronin et al. (2007) after validating analytical performance with quality-control measures from the results of previous studies (Cronin et al. 2004, Paik et al. 2004, Cobleigh et al. 2005). The entire assay process, including process controls with associated performance-acceptance limits, is documented as a series of standard operating procedures that provide the basis for the current reference laboratory operation. In summary, a standard RNA control sample is assayed at least once per batch of patient samples (≤ 46 samples), and PCR controls are run in every assay plate to verify that the process and reagents continue to perform within specified ranges. RT-PCR failures, identified by analysing the amplification curve from every assay well, are excluded from analysis. Expression values are assigned when at least 2 of 3 assay wells provide acceptable RT-PCR results. All 21 genes must have an expression value assigned for a Recurrence Score to be calculated/reported.

Process monitoring shows that Recurrence Score reproducibility is very high (Cronin et al. 2007). Repeat testing with specific patient samples (de-identified) produced a cumulative standard deviation in the Recurrence Score of $\pm < 2$ units on a 100-unit scale, which represents all sources of analytical process variation.

The RS corresponds to a point estimate of the 10-year risk of distant recurrence with a 95% confidence interval for an individual patient. The Recurrence Score is calculated according to the algorithm in Figure 1 (Marchionni et al. 2008). It is then used to define three distinct risk groups: low-risk (RS < 18), intermediate-risk (RS 18-30), and high-risk (RS ≥ 31).

The RS cut-off points which classify patients as low risk (Recurrence Score <18), intermediate risk (Recurrence Score 18–30) and high risk (Recurrence Score ≥31) categories are based on a case-control study of 4,964 Kaiser Permanente patients diagnosed with node-negative invasive breast cancer from 1985 to 1994 and not treated with adjuvant chemotherapy (Habel et al. 2006). These cut-off points were later examined in randomised controlled trials of node-negative (Paik et al. 2006) and node-positive (Albain et al. 2010) patients. Evidence justifying the cut-off points will be presented in the submission.

Figure 1 The derivation of the Recurrence Score



Randomised controlled trials have shown that patients with a low RS were very unlikely to benefit from chemotherapy whereas the benefit from chemotherapy was important in patients with a high RS (Paik et al. 2006; Albain et al. 2010). This strong evidence led

independent experts to include Oncotype DX in all major breast cancer guidelines. The: Trial Assigning Individualized Options for Treatment (Rx) (TAILORx) trial will provide evidence for the benefit of chemotherapy in patients with an intermediate risk score.

The TAILORx trial is an ongoing multicentre trial in more than 10,000 patients initiated by the National Cancer Institute (NCI) and the Eastern Cooperative Oncology Group (ECOG) and includes 1,500 sites in the United States, Canada, Europe, South America and Australia. The trial's objective is to investigate if endocrine treatment is non-inferior to chemotherapy and endocrine treatment in patients with mid-range Recurrence Score disease. The TAILORx study started in 2006 and is ongoing (<http://www.ecog.org/general/tailorx.html>). Interim data only from the TAILORx trial should become available in 2015. However, it is important to note the TAILORx trial, a randomised phase III trial, which is trying to find out the best individual therapy for women who have node-negative, hormone-receptor positive, HER2 negative breast cancer by using the Oncotype DX test (<http://www.clinicaltrials.gov/ct2/show/NCT00310180>) will not necessarily answer many of the questions for public funding. For example, it is only applicable to a select group of node-negative women with a particular RS. Patients were included for randomisation in the TAILORx trial on the basis of their risk score. It does not compare health outcomes in women who do have the Oncotype DX test versus not having the Oncotype DX test. The validation of the Oncotype DX test has been established and is therefore an appropriate technology for consideration by MSAC – without waiting for the results of the TAILORx trial.

Delivery of the intervention

It is proposed that the Oncotype DX test will be reimbursed in women with early stage breast cancer who are:

- ER+ or PR+, and;
- HER2-, and;
- node-negative or with a maximum of 3 positive nodes

to determine the likelihood of benefiting from adding adjuvant chemotherapy to hormonal treatment. Importantly, the Oncotype DX test identifies patients who would not be recommended adjuvant chemotherapy based on current assessment of clinical and pathological information but are at high risk of recurrence. This offers the potential to prolong disease free survival and ultimately save lives. It also identifies many patients that will not benefit from chemotherapy, thus sparing them adverse effects and risks associated with chemotherapy.

A surgeon is responsible for removing the breast cancer and axillary lymph nodes. The tumour and all excised lymph nodes are sent to a pathologist for examination. Biopsy and surgical samples are stored in Australia for a period of at least ten years for subsequent testing according to the National Guidelines for Tissues Storage; many centres and institutions would keep samples indefinitely.

Physicians offering the Oncotype DX test will require that the pathology company who perform the histological examination of the tumour biopsy obtain the Oncotype DX Specimen Kit (through the distributors of Oncotype DX in Australia). An arrangement currently exists whereby GHI pays an administrative fee to the distributor who then reimburses the pathology company for the costs of sample preparation. The laboratory will need to prepare the specimen, using the appropriate instructions provided with the Oncotype DX Specimen Kit, consisting of either:

15 unstained slides each with (5microns) section of tissue, each slide must be numbered 1 through 15, in order of sequential sectioning

OR,

One fixed paraffin embedded tumour block

All specimens are labelled with barcode labels from the patients Oncotype DX Requisition form.

The Requisition form and specimen are sent to the distributors in Australia who then send the specimen via express post to the Genomic Health central laboratory in Redwood, CA in the US.

All tissue samples are assessed by a pathologist at Genomic Health to verify the diagnosis, review for adequate tumour content and to perform manual microdissection as needed in accordance with American pathology guidelines. The RNA is extracted from FFPE specimens and contaminant DNA removed by DNase I treatment. Total RNA yield is measured and the absence of DNA contamination is verified. Real time RTPCR is performed by TaqMan® technology in 384-well plates. The expression of the 16 cancer genes is measured in triplicate then normalized to the expression levels of the 5 reference genes. Finally, normalised gene expression levels of the 16 cancer related genes are used to compute the Recurrence Score™ (RS), on a scale from 1 to 100.

The results of the Oncotype DX test will be available in 10-14 days from the date the tumour sample is sent to Genomic Health. The results of the test will be returned by mail, secure online reporting and/or facsimile to the ordering physician, submitting pathologist, and any additional physician, involved in the care of the patient as noted on the Requisition form. Refer to Attachment 1 for an example of a sample report sent for a patient who has undergone Oncotype DX testing. The remaining tumour sample can be returned to the pathology lab if required with costs covered by GHI.

Prerequisites

Immunohistochemical (IHC) examination of biopsy material is routinely performed as a prior test to examine the ER, PR and HER2 status of all patients with breast cancer. Nodal status is also routinely assessed to inform the breast cancer staging of each patient. The information from these tests will be used to define the population eligible for the Oncotype DX test.

Ordering of the Oncotype DX test should be restricted to oncologists or surgeons, once patients are diagnosed with node-negative or 1–3 positive nodes, ER+ or PR+, HER2 -, early stage breast cancer. Data pertaining to the ability of Oncotype Dx test RS to predict patients likely to benefit from chemotherapy has only been ascertained in these patient groups.

Co-administered and associated interventions

The Oncotype DX test does not involve or require co-dependent assessment by MSAC and PBAC. The chemotherapy regimen(s) that Oncotype DX is used to triage patients towards (or away from) are all PBS listed and reimbursed.

Hormone therapy remains the mainstay for treatment of hormone receptor-positive (ER+ or PR+) breast cancer. Hormone therapy for breast cancer such as tamoxifen, anastrozole and letrozole are all available on the PBS for patients with breast cancer.

Adjuvant chemotherapy is also administered to patients with early breast cancer with and without nodal involvement based on improved recurrence free survival and overall survival. Although subsequent post hoc analysis of the pivotal trials demonstrating the benefits of chemotherapy in early breast cancer have shown that some patients benefit more than others. All chemotherapy agents used to treat early breast cancer are all available on the PBS under the General Schedule or Streamlined authority.

The chemotherapy regimens currently used in this patient population – and therefore the regimens that will be initiated (or not) on the basis of the Oncotype DX recurrence score include:

- AC-Taxol (doxorubicin and cyclophosphamide followed by paclitaxel)
- AC (doxorubicin and cyclophosphamide)
- TC (docetaxel, cyclophosphamide)
- CMF (cyclophosphamide, methotrexate, 5-fluourouracil)
- TAC (docetaxel, doxorubicin, cyclophosphamide)
- FECD (5-fluourouracil, epirubicin, cyclophosphamide followed by docetaxel)

The recommendation to prescribe adjuvant chemotherapy in combination with hormone therapy is based on a balance of the risk of recurrence against the potential for adverse effects of therapy. The patients that should be administered combination chemotherapy and hormone therapy are difficult to define because the ER/PR+ and HER2-, early stage breast cancer group includes patients with a spectrum of recurrence risks.

The advent of GEP now provides the ability to segment heterogeneous subsets of patients based on their degree of gene activity, whose response to a therapeutic intervention within each subset is homogeneous. This molecular profiling of tumour cells has a prognostic and

predictive value in women with early stage breast cancer. Prognostic value provides the risk of distant recurrence if one receives standard treatment (i.e. adjuvant hormone therapy alone) and predictive value provides the likely benefit from the addition of a specific treatment (e.g., adjuvant chemotherapy) to this standard treatment. A prognostic marker is clinically validated by demonstrating in a relevant patient population that the marker identifies subsets of patients at clinically meaningfully higher and lower risks of recurrence. Clinical validation of a predictive marker requires a randomised trial in a relevant patient population that compares standard treatment with standard treatment plus the addition of the specific treatment. Clinical validation of the RS requires demonstration that relative treatment benefit depends upon the value of the marker; this involves demonstration of a statistically significant interaction between treatment (i.e. chemotherapy) and the marker in predicting the risk of recurrence (i.e. recurrence score). For example, randomised controlled clinical trial data from Paik et al. (2006) [the NSAPB B-20 trial] shows that chemotherapy is ineffective in patients identified as low risk by Oncotype DX [relative risk (95% CI) for disease free survival of 1.31, (0.46 to 3.78)]; moderately effective in intermediate risk patients and [0.61, (0.24 to 1.59)] and most effective in high risk patients [0.26, (0.13 to 0.53)].

In the case of Oncotype DX, it poses an opportunity to select the most optimal and personalised treatment strategy on the basis of the individual predicted probability of relapse and sensitivity to chemotherapy. This is still a fairly new paradigm in Australian healthcare although in recent years the molecular profiling of tumours for HER2, KRAS, and EGFR has become widely accepted and implemented.

LISTING PROPOSED AND OPTIONS FOR MSAC CONSIDERATION

It is proposed that Oncotype DX should be used in patients with the following disease characteristics for whom physicians are in doubt of the value of chemotherapy:

- Early breast cancer (stages I-II)
- Suitable for hormone therapy
- Suitable for adjuvant chemotherapy
- ECOG status 0-2

and, as determined by an Australian pathology laboratory:

- Invasive tumour >2 mm
- Node negative or 1-3 positive nodes
- Oestrogen positive (ER+) or progesterone positive (PR+) as determined by IHC
- HER2 negative as determined by IHC and/or ISH

Proposed MBS listing

The proposed MBS item descriptors and fees for patients with early breast cancer according to IHC (and or ISH) results are provided in Table 5. It is anticipated that the listing would appear as a Pathology service (Category 6) in Group P7- Genetics. The text describing the eligibility criteria are separated into those aspects determined by an Australian pathology laboratory and those determined by the referring clinician.

Table 5 Proposed MBS item descriptor

MBS [item number] (proposed MBS item) Pathology Group P7 Genetics
Gene expression profiling of tumour samples (surgical resection preferably or core biopsy) by reverse-transcriptase polymerase chain reaction (RT-PCR) technique for 21 genes in breast cancer tissue.
May only be used to test samples from patients with the following characteristics as determined by the referring clinician:
<ul style="list-style-type: none">• early breast cancer (stages I-II)• suitable for hormone therapy• suitable for adjuvant chemotherapy• ECOG performance status 0-2
and
As determined by an Australian pathology laboratory
<ul style="list-style-type: none">• invasive tumour >2mm• node negative or 1-3 positive nodes• oestrogen positive or progesterone positive as determined by immunohistochemistry• HER2 negative as determined by immunohistochemistry and/or in situ hybridisation
May only be used once per new primary breast cancer diagnosis
Fee: TO BE DETERMINED

The proposed MBS fee is yet to be determined. The fee itself will cover administrative costs of collecting and preparing the sample performed in Australia, cost of shipping the sample overseas, the cost of performing the RT-PCR across the 21 genes, calculating the algorithm and all subsequent reporting of results. A commercial in-confidence arrangement currently exists whereby GHI pays an administrative fee to a distributor in Australia who then reimburses the pathology company for the costs of sample preparation. The costs of shipping the sample to the Genomic laboratory are covered by GHI within the proposed MBS fee. The remaining tumour sample can be returned to the pathology lab if required with costs covered by GHI. The MBS fee to be proposed in the application will be justified using cost-effectiveness analysis.

In Australia, a Multidisciplinary Meeting (MDM) has become the standard forum for determining treatment recommendations. A national goal is for all patients to have their treatment decisions discussed in an MDM, which includes medical oncologists and surgeons who treat early breast cancer, prior to definitive treatment recommendations being made.

The Recurrence Score information provided by the Oncotype DX test will help inform the treatment decision for the patient. There have been a number of studies examining the impact of the Oncotype DX assay on clinical decision-making (i.e. real life effectiveness of the test) for patients with hormone receptor-positive breast cancer. The results of these studies have been fairly consistent, showing changed treatment recommendations (for adjuvant chemotherapy) in approximately 35% of cases compared with conventional assessment.

Clinical place for proposed intervention

Oncotype DX is included as a test predictive of chemotherapy in all major international guidelines (St Gallen, ASCO, ESMO and NCCN) (Goldhirsch et al. 2011, Harris et al. 2007, Aebi et al. 2010 and NCCN 2011).

Australian clinical experts contacted during scoping felt that molecular classification would be used in the clinical setting as an adjunct to current clinical practice rather than replacing any part of it.

In different markets with varying therapeutic approaches, using the test has consistently resulted in a significant reduction of patients who are prescribed chemotherapy (and identifies a smaller subset of patients who would benefit from chemotherapy among patients who would otherwise be treated with endocrine therapy alone) (Hassett et al. 2012). In a meta-analysis of nine studies (two prospective analyses and seven retrospective chart reviews) with 1,154 eligible patients, Oncotype DX testing was shown to change treatment recommendations (for adjuvant chemotherapy) in approximately 35% of cases compared with conventional assessment (Hornberger et al. 2011). With a 51% change in patients initially recommended chemotherapy plus endocrine therapy and a 13% change in patients who were initially recommended endocrine therapy alone, Oncotype DX testing was associated with an overall reduction in the recommended use of adjuvant chemotherapy. Similar observations have been made in a trial of Oncotype DX testing in Australia (de Boer et al. 2011). In a study of 151 patients from three Australian medical centres, multidisciplinary team treatment recommendations changed after Oncotype DX results were obtained in 24 of 101 (24%) node-negative patients and 13 of 50 (26%) node-positive patients. In node-negative patients, 12 (40%) of the 30 pre-assay recommendations for chemotherapy changed to hormone therapy alone, while 12 (17%) of 71 pre-assay recommendations for hormonal therapy changed to chemo-hormonal therapy on the basis of assay. Oncotype DX is valuable in terms of informing patient choice as well as enhancing the discussion between clinician and patient about the risks and benefits of adjuvant therapy options. Studies suggest that use of Oncotype DX is associated with improvements in the confidence of patients and oncologists in their treatment recommendations in as many as 76% of cases (Lo et al. 2010, Albanell et al. 2012). Patient anxiety was also reduced with the introduction of Oncotype DX testing. Furthermore in a population in whom it is difficult to select patients that would benefit most from chemotherapy the introduction of Oncotype DX would standardise treatment decisions and improve the quality, equity and consistency of care across Australia.

Patients in Australia diagnosed with breast cancer currently follow the diagnosis/treatment pathway described in Figure 2. The pathway reflects the assessment of all patients diagnosed with breast cancer up to the point of surgery. The biopsies from all patients are tested using IHC to determine hormone and HER2 status. The post operative assessment of tumour size and degree of lymph node involvement is used to define the patient's stage of illness. It is proposed that the Oncotype DX test be positioned as an adjunctive test following surgery for a subgroup of patients who are classified as stage I or II, ER+ or PR+ and HER2 –with 0-3 positive lymph nodes. The Oncotype DX test will be used to guide the use of adjuvant chemotherapy in addition to existing prognostic approaches based on tumour staging, histological features and lymph node involvement. Any patients deemed not suitable for chemotherapy or unable to tolerate chemotherapy would not be eligible for the Oncotype DX test.

Expert opinion sought on the time to commence adjuvant chemotherapy after surgery indicates that treatment usually commenced within 3-6 weeks after surgery. The results of the Oncotype DX test are available within two weeks of the sample being sent to the Genomic Health laboratory in the US therefore imposing no delay for treatment to commence. In less than 10% of cases there is a need for repeat testing. A study of over 103,863 submissions for Oncotype DX testing from July 2005 –May 2009 demonstrated that of the 88.7% that were surgical resections and 11.3% that were core biopsies, the initial success rate were 95.7% and 91.6%, respectively (Anderson et al. 2009, Abstract). Causes of failures are derived from insufficient invasive tumor, PCR process failure, insufficient RNA, unevaluable slide, scant tissue in block, incomplete requisition. In such cases it is necessary to resubmit a sample for Oncotype DX testing or repeat the Oncotype DX test, in both circumstances the costs are borne by GHI.

The algorithm considers all patients with early breast cancer (stage I-II) who undergo primary surgical resection.

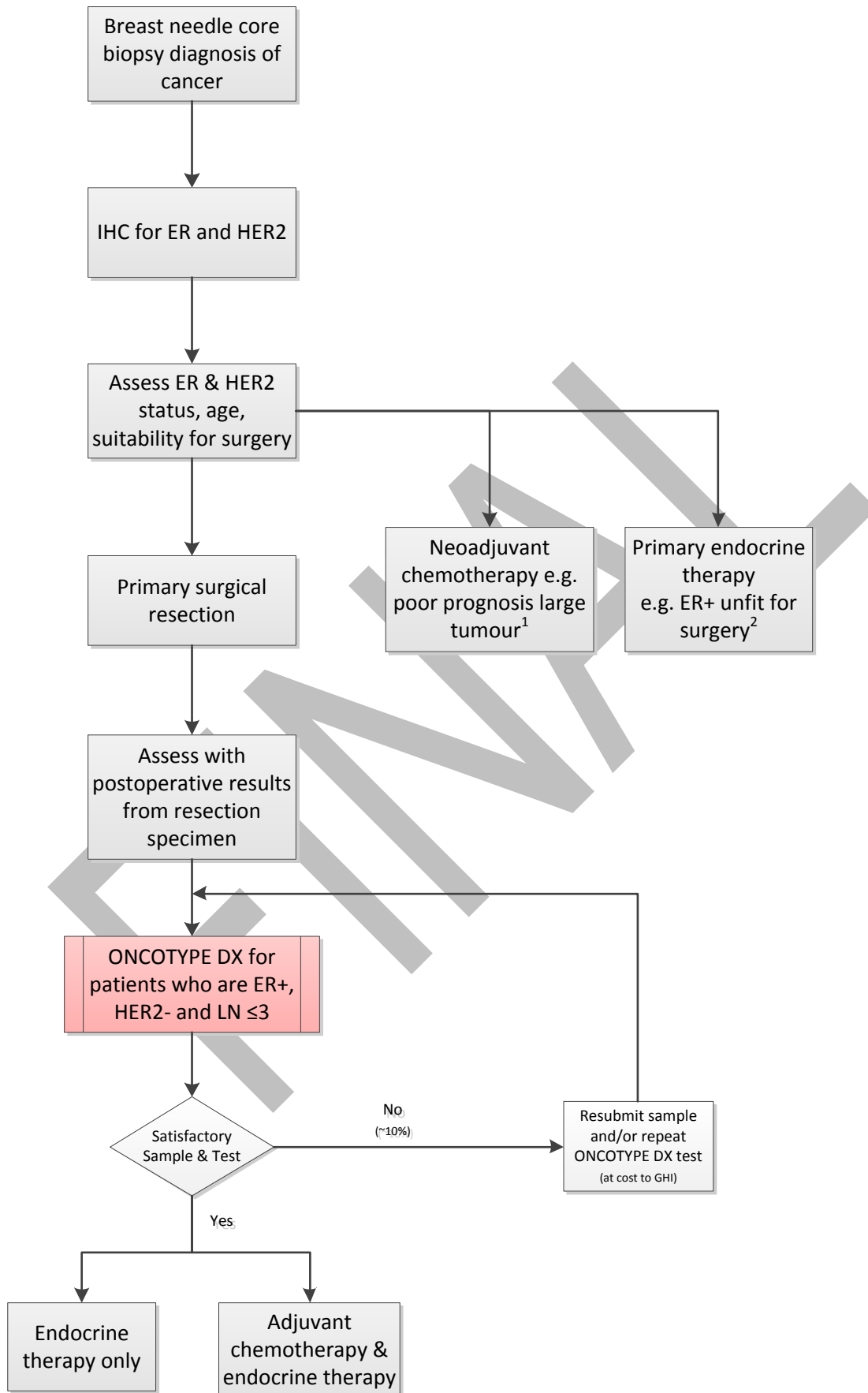


Figure 2 The current diagnosis and management pathway in breast cancer with proposed positioning of the Oncotype DX test.

¹ Patients who have received neoadjuvant chemotherapy will continue to receive chemotherapy and therefore Oncotype DX will not be required for the treatment decision

² Patients who are unfit for surgery would also be deemed unfit for chemotherapy and therefore Oncotype DX will not be required for the treatment decision

Size of the eligible patient population in Australia

As previously stated, in Australia there were 12,567 new cases of breast cancer in 2007, and it is estimated that this will increase to approximately 14,818 cases in 2011 and 15,409 cases by 2015 (Cancer Australia 2011). Based on data from the NSW Central Cancer Registry between 2004 and 2008, 51.2% of patients have localised disease at the time of diagnosis, while 36.5% have advanced disease with regional lymph node involvement, 5.4% have distant metastases, and the extent of disease in 6.9% is unknown (New South Wales Central Cancer Registry 2010). It is estimated that 60% of the women with regional lymph node involvement will have involvement in 0 to 3 nodes (Albain et al. 2010). Thus, approximately 70% of patients have breast cancer with either no lymph node involvement (50%) or 1-3 lymph nodes involved (60% of 36.5%). Based on the predicted incidence of breast cancer in 2011 this equates to approximately 10,372 per annum ($14,818 \times 0.70$). It is estimated, based on expert opinion, that approximately half of these patients would be potentially eligible for Oncotype DX testing based on ER, PR and HER2 criteria. This equates to approximately 5,366 patients per annum ($10,372 \times 0.50$).

It is expected that around 5,000 patients will be eligible for Oncotype DX each year, although only a proportion of these patients will necessarily receive the test. Patients would need to be considered candidates for treatment with systemic chemotherapy in addition to hormone therapy, for example a frail elderly patient may not be considered a candidate for chemotherapy. Alternatively a patient who has an ECOG performance status 3 or 4 (being bed ridden for >50% of the times with limited ability to self care) would not be considered a candidate for chemotherapy. Other reasons patients may not receive the test includes patient/physician preference and contraindications/intolerance to chemotherapy. Patients would only be tested It would only be used when physicians are in doubt of the value of chemotherapy. The Oncotype DX test will only be required once per new primary breast cancer diagnosis for patients who are eligible.

COMPARATOR

The comparator for Oncotype DX test plus usual care is usual care (without testing the tumour using the 21 gene signature). Consequently patients in the comparator arm would receive endocrine therapy with or without the addition of adjuvant chemotherapy based on traditional clinical and pathological measures, none of which have individually been shown to be predictive of adjuvant chemotherapy benefit.

There is no change in the treatment algorithm between the current and proposed pathways, rather the RS results in a change in the recommendation to treat with adjuvant chemotherapy in addition to endocrine therapy. The clinical validity and the clinical utility of the Oncotype DX test should be included in the assessment submitted to MSAC. There is no

reference or gold standard for determining the recurrence score. As described earlier, centralisation, using a standardised assay, reagents, procedures, and scoring is a significant strength of Oncotype DX with regard to reproducibility. Oncotype DX does not suffer from the same problems as other assays based on technologies that are difficult to standardise across different laboratories.

Evidence that the Genomic Health laboratory and the analytical and clinical validity of the test meet the standards required by the National Association of Testing Authorities and the Royal College of Pathologists of Australasia / Quality Assurance Program Pty Ltd, for medical testing will be provided.

The cost of the test option and test strategy should be assessed from the full healthcare system perspective (i.e., the provision of each relevant healthcare resource with a material increment fully costed irrespective of the source of the payment(s) and also disaggregated across these sources as appropriate).

OUTCOMES FOR SAFETY AND EFFECTIVENESS EVALUATION

Oncotype DX is expected to influence outcomes in two ways:

1. By reducing exposure to adverse event causing chemotherapies in those patient populations in whom chemotherapy is less likely to offer a survival benefit; and,
2. By increasing chemotherapy use in those patient populations in which chemotherapy is more likely confer a survival benefit

The health outcomes, upon which the comparative clinical performance of Oncotype DX testing versus usual care (according to funding scenario) will be measured, are based on the impact of a change in treatment decisions and treatment effectiveness.

These outcomes are listed below:

Effectiveness

- Primary outcomes: Disease free survival, overall survival, quality adjusted survival
- Secondary outcomes: Change in treatment decisions, uptake of chemotherapy, quality of life.

Direct evidence about the impact of testing for Oncotype DX testing on health outcomes will be sought. The literature search should not be limited by outcomes or comparators. In the absence of studies providing direct evidence, indirect evidence indicating the impact of Oncotype DX testing on clinical management and diagnostic accuracy should be assessed.

As stated in the MSAC assessment for HER2 (MSAC report 38, June 2008) proof of an effect on management change is a key component of the evidence base where an additional diagnostic test is to be used in the clinical pathway. The most appropriate design for investigation of effects on management change is a pre-test, post-test case series study.

Where a pre-test management plan is not reported, the outcomes of a study do not truly represent change in patient management, and thus, outcomes are likely to be biased.

Safety

Psychological and physical harms from testing.

Any adverse events related to a change in treatment including tolerability and toxicity.

Summary of PICO to be used for assessment of evidence (systematic review)

Table 6 provides a summary of the PICO used to:

- (1) define the questions for public funding,
- (2) select the evidence to assess the safety and effectiveness of Oncotype DX testing, and
- (3) provide the evidence-based inputs for any decision analysis modelling to determine the cost-effectiveness of Oncotype DX testing,

for the proposed and current clinical pathways.

Table 6 Summary of PICO to define research questions for Oncotype DX testing

Patients	Intervention	Comparator	Reference Standard	Outcomes to be assessed
<p>Women diagnosed with early (stage I or II) breast cancer who are ER+ or PR+, and HER2- node-negative or with a maximum of 3 positive nodes</p> <p>Patients must have an invasive tumour >2mm, ECOG status 0-2 and be a suitable candidate for chemotherapy.</p> <p>Subgroup analyses will be presented to define populations in which the degree of clinical benefit and cost-, effectiveness can be assessed to determine which patient subgroups would and would not be eligible for public funding</p>	<p>Oncotype DX test and RS guided usual care</p>	<p>No Oncotype DX test and current usual care without RS guidance</p>	<p><i>Not applicable</i></p>	<p><u>Safety</u> Psychological and physical harms from testing. Any adverse events related to a change in treatment including tolerability and toxicity.</p> <p><u>Effectiveness</u> <i>Direct evidence^{abc}</i> <u>Primary outcomes:</u> Disease free survival Overall survival Quality adjusted survival <u>Secondary outcomes:</u> Change in management Uptake of chemotherapy Quality of life</p> <p><u>Analytic Validity</u> Description of the genetic test Rationale for sample selection Development and validation of prognostic algorithm Clinical validity and utility <i>(see research questions to follow for more detail)</i></p> <p><u>Cost-effectiveness</u> Cost, cost per relevant health outcome (e.g. LYG, QALY)</p> <p>Assessment of the evidence will be made separately for patients who are node negative and those who are node-positive (1-3) nodes. This is because differences in nodal status are known to be prognostic for disease recurrence and thus is already taken into consideration in clinical decisions about whether to recommend adjuvant chemotherapy.</p>
<p><u>Research Questions</u></p> <p>1. What is the evidence describing and providing rationale for: a. the genetic testing intervention itself?</p>				

- b. the sample section for Oncotype testing?
 - c. the development and validation of prognostic algorithm?
 - d. the clinical validity and utility of Oncotype DX testing?
2. Is Oncotype DX testing, in addition to usual care, safe, effective and cost-effective compared to usual care alone in patients with early (stage I or II) breast cancer who are ER+ or PR+, HER2- and,
 - a. node negative?
 - b. node positive (up to 3 nodes)?
3. Will Oncotype DX change treatment decisions such that some patients who would otherwise be treated with chemotherapy will no longer and some patients who otherwise would not receive chemotherapy now will?
 - a. In node negative patients?
 - b. In node positive (up to 3 nodes) patients?
4. Assuming Oncotype DX does change treatment decisions, will this change in decision making improve health outcomes?
 - a. In node negative patients?
 - b. In node positive (up to 3 nodes) patients?

a. Direct evidence, as described in the PICO table above, can be employed when there are trials available (on patients with early breast cancer) that compare a management strategy that involves Oncotype DX test with a management strategy that does not involve Oncotype DX test and the differential impact on patient-relevant clinical outcomes is measured.

b. When this type of information is lacking, a linked evidence approach may be employed (i.e. linking evidence assessing evidence of a change in management as a consequence of testing, and then to the effect of that change in management (e.g. impact of treatment on patient health outcomes).

c. Adequate description of evidence and anticipated population is necessary to understand the applicability of the evidence and downstream health outcome and cost consequences.

^ Specific research questions relating to Oncotype DX test itself are provided in more detail to follow

Clinical claim

There is no change in the diagnostic practice or treatment options available to patients between the current and proposed pathway. Rather, it is a tool which provides new and additional information for the patient/physician decision as to whether or not to initiate chemotherapy. It is still the same decision to be made, however the outcome of the Oncotype DX test will result in triage of different patients through to different treatments (than is current practice).

The test will improve health outcomes in one of two possible ways:

- i) by identifying patients likely to benefit from chemotherapy that would not have been identified through standard clinical practice. This will result in improved disease free survival and reduction in breast cancer recurrence by the addition of chemotherapy to a patient who would have otherwise been treated with hormone therapy alone
- ii) by identifying patients that will not benefit from chemotherapy, thus sparing them adverse effects and other risks associated with chemotherapy.

The clinical claim depends on a linked approach which:

- (i) shows the impact of Oncotype DX on the decision to initiate chemotherapy, and

- (ii) shows that the change in allocation by Oncotype DX recurrence score of chemotherapy improves disease free survival and reduces unnecessary adverse effects

For example, data from an Australian decision impact study shows that the Oncotype DX recurrence score will have an effect on the types of patients being treated with chemotherapy. With less prescribing of chemotherapy overall and with the majority of chemotherapy reduction in patients with low risk recurrence scores (de Boer et al. 2011).

Randomised controlled clinical trial data from Paik et al. (2006) [the NSAPB B-20 trial] shows that chemotherapy is ineffective in patients identified as low risk by Oncotype DX [relative risk (95% CI) for disease free survival of 1.31, (0.46 to 3.78)]; moderately effective in intermediate risk patients and [0.61, (0.24 to 1.59)] and most effective in high risk patients [0.26, (0.13 to 0.53)]. A similar relationship between Oncotype DX recurrence score and response to chemotherapy was observed in node positive patients (Albain et al. 2010), however, this was a different patient population from the intended use population. It is important to note that the claimed predictive value of the Oncotype Dx recurrence score is derived from retrospective analysis of randomised controlled trial data and that the association has not yet been tested prospectively in a randomised controlled trial.

Therefore, the decision impact study shows fewer patients will get unnecessary chemotherapy thus decreasing exposure to chemotherapy risks and improving disease free survival in those who stand to benefit from chemotherapy.

These data are presented in this DAP by way of illustration only and will be fully evaluated in the assessment itself.

Relative to the comparator, Oncotype DX testing and consequent treatment may be considered superior in terms of safety (less chemotherapy adverse effects) and to be non-inferior to superior in terms of effectiveness (better disease free survival in patients using chemotherapy when they otherwise would not have). As such, the type of economic evaluation required is a cost-effectiveness analysis or cost-utility analysis (green shading in Table 7).

The applicant does not intend to make any claims about the comparative effectiveness of the various chemotherapy options (with or without hormone therapy) available for patients with breast cancer.

Table 7 Classification of an intervention for determination of economic evaluation to be presented

		Comparative effectiveness versus comparator				
		Superior		Non-inferior	Inferior	
Comparative safety versus comparator	Superior	CEA/CUA		CEA/CUA	Net clinical benefit	CEA/CUA
					Neutral benefit	CEA/CUA*
					Net harms	None^
	Non-inferior	CEA/CUA		CEA/CUA*	None^	
	Inferior	Net clinical benefit	CEA/CUA	None^	None^	
		Neutral benefit	CEA/CUA*			
Net harms		None^				

Abbreviations: CEA = cost-effectiveness analysis; CUA = cost-utility analysis

* May be reduced to cost-minimisation analysis. Cost-minimisation analysis should only be presented when the proposed service has been indisputably demonstrated to be no worse than its main comparator(s) in terms of both effectiveness and safety, so the difference between the service and the appropriate comparator can be reduced to a comparison of costs. In most cases, there will be some uncertainty around such a conclusion (i.e., the conclusion is often not indisputable). Therefore, when an assessment concludes that an intervention was no worse than a comparator, an assessment of the uncertainty around this conclusion should be provided by presentation of cost-effectiveness and/or cost-utility analyses.

^ No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

OUTCOMES AND HEALTH CARE RESOURCES AFFECTED BY INTRODUCTION OF PROPOSED INTERVENTION

Outcomes for economic evaluation

If differences in health outcomes, such as the rate of disease recurrence and incidence of chemotherapy adverse effects can be determined, cost-effectiveness and cost-utility analyses would be relevant, and health outcomes would need to be measured as life-years gained and quality-adjusted life-years gained.

Health care resources

As diagnosis and staging of breast cancer will occur in both comparative arms – that is with or without Oncotype DX testing – costs and resource use associated with these will not be needed in the economic evaluation of Oncotype DX testing.

The proposal includes the costs for the following health care resource items

- Costs for Oncotype DX testing (these costs will include; block retrieval of stored sample from tissue archive, preparation of tissue sample; transportation of the tissue sample; reporting of results including any the cost for retesting of any samples which were found to be insufficient)
- Costs associated with acquisition and administration of hormone therapy and chemotherapy used to treat patients with early (stage I-II) breast cancer.

- Costs associated with the management of adverse events associated with chemotherapy and hormone therapy.
- Costs associated with the management of stable disease and recurrent breast cancer

A non-exhaustive list of the resources that would need to be considered in the economic analysis is provided in Table 8.

FINAL

Table 8 List of resources to be considered in the economic analysis

Type of resource	Provider of resource	Setting in which resource is provided	Proportion of eligible patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost		
					MBS	Other ^	Total cost
Resources provided in association with proposed intervention							
Block retrieval of stored sample from tissue archive ^a	Pathologist		100%	1	1		Proposed MBS fee is to be determined
Preparation of tissue sample ^b	Pathologist						
Oncotype DX test, reporting of results	GHI	GHI laboratory					
Resources provided to deliver chemotherapy							
Chemotherapy treatment cost (chemotherapy regimen(s) including those regimens above)	Medical Oncologist	Outpatient / Inpatient	TBD based on uptake of chemotherapy in the clinical evaluation of Oncotype DX	Number infusions/patient			TBD
Supportive or prophylactic medication (e.g. G-CSF, anti emetics)	Medical Oncologist	Outpatient / Inpatient	As above along with evidence of concomitant medication use				
Monitoring of chemotherapy (test/ lab analyses performed before, during and after the chemotherapy treatment to monitor the impact of treatment on some of physiological functions)		Outpatients	As above				
Full day hospital admission for chemotherapy in a public hospital	Medical	Day patient	As above (along with split of settings of				

Type of resource	Provider of resource	Setting in which resource is provided	Proportion of eligible patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost		
					MBS	Other [^]	Total cost
setting (excluding average pharmacy cost component)	oncologist		chemotherapy administration in Australia)				
Full day hospital admission for chemotherapy in a private hospital setting (excluding average pharmacy cost component)	Medical oncologist	Day patient	As above				
Drug administration cost for 1 to 6 hour infusion in outpatient setting	Medical oncologist	Day patient	As above				
Chemotherapy follow up monitoring	Medical Oncologist	Outpatient/Inpatient	As above				
Resources provided to deliver hormone therapy							
Hormone therapy treatment cost (hormone therapy TBD)	Medical oncologist	Day patient	100% (all patients will get HT in both arms of the model)				
Hormone therapy administration cost	Medical oncologist	Day patient	100%				
Resources provided in association with chemotherapy: costs associated with treating adverse events for patients receiving chemotherapy							
Short and long term adverse events. Will depend on adverse events associated with chemotherapy usage		Inpatient	Patients receiving chemotherapy treatment who incur grade 3/4 adverse event				
Resources provided in association with hormone therapy: costs associated with treating adverse events for patients receiving hormone therapy							

Type of resource	Provider of resource	Setting in which resource is provided	Proportion of eligible patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost		
					MBS	Other [^]	Total cost
Will depend on adverse events associated with hormone therapy usage		Inpatient	Patients receiving hormone therapy who incur grade 3/4 adverse event				
Resources provided in association with the management of recurrent breast cancer							
Will depend on results of literature review for relevant information	TBD	TBD	Patients in the 'BC recurrence' health state of the model				
Resources provided in association with the management of stable disease breast cancer							
Will depend on results of literature review for relevant information	TBD	TBD	Patients in the 'disease free' health state of the model				

a The need to resend samples due to inability to test initial samples could be dealt with in sensitivity analyses of the model

b Samples that are shipped are formalin fixed and embedded in paraffin hence stable and non hazardous. The shipping costs are covered by GHI within the proposed MBS fee

[^]Safety nets*, Other govt budget, Private health insurer, Patient (Disaggregated results to be provided in the submission)

Proposed structure of economic evaluation (decision analysis)

The Oncotype DX RS is used to classify patients as low risk, intermediate risk and high risk. The structure of the economic evaluation will align with the linked evidence approach described earlier. That is, Oncotype DX RS testing impacts the decision to initiate chemotherapy treatment, and the change in allocation of chemotherapy treatment by Oncotype DX recurrence score improves disease free survival and reduces unnecessary adverse events.

The decision analysis presented in Figure 3 uses trial based analysis where staging the population suitable for Oncotype DX testing is identical to the staging of patients who would not undergo Oncotype DX testing. The introduction of Oncotype DX testing helps to inform the decision on adjuvant chemotherapy for patients based on their RS. Therefore the primary analysis compares current clinical practice with the adjuvant treatment decision based on the addition of Oncotype DX ('ODX') to current clinical practice ('USUAL CARE').

Patients in the model are either assigned adjuvant chemotherapy based on the conventional approach in the Australia (usual care) or based on the Oncotype DX Recurrence Score.

There are three states in the model:

- recurrence-free (in which all patients start the simulation),
- recurrence (following a distant recurrence event) and
- dead (following a mortality event).

All patients start the simulation in the recurrence-free state. In each cycle of the simulation, patients are exposed to the risk of competing mortality and recurrence. Patients who have a mortality event transition to the dead state (absorbing state). Patients who experience a distant recurrence event transition to the recurrence state, where they are exposed to the risk of breast cancer mortality in each subsequent cycle of the simulation.

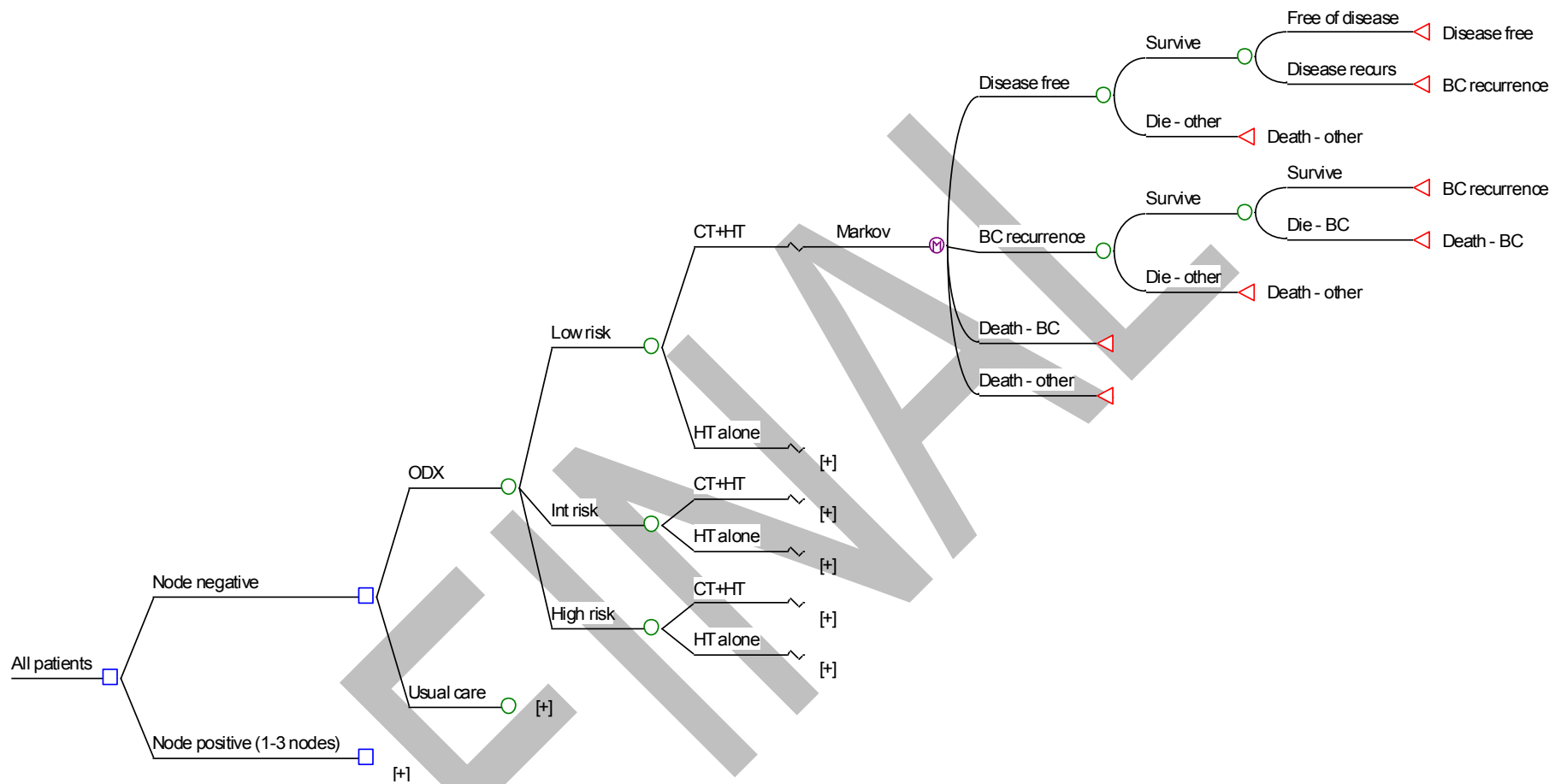


Figure 3 Decision tree representing cost effectiveness model structure for Oncotype DX test

[+] Nominates that the branch structure is identical to that of the adjacent node above. However, the probabilities, costs and other model variables will differ

Note: The 'usual care' branch is also stratified according to the ODX RS categories to maintain a symmetrical tree structure and control to the ODX treatment arm.

Addressing the questions for public funding

It is accepted that it would be informative for the assessment of evidence in response to the final DAP to assess the proposed intervention separately for:

- patients who are node negative
- patients who have 1-3 positive nodes

as these differences in nodal status are known to be prognostic for disease recurrence and thus is already taken into consideration in clinical decisions about whether to recommend adjuvant chemotherapy.

It is accepted that the assessment of evidence in response to the final DAP would need to provide additional information to address the following matters.

In relation to the proposed genetic testing intervention:

- a detailed explanation and justification (with a biological basis) for the selection of each of the 21 genes identified in Table 4, including how and why they were identified, how and why each were grouped into the 16 identified cancer genes for assessment and the 5 identified genes for reference, and how and why other genes with prognostic value in breast cancer were excluded from the 250 candidate genes originally identified
- a detailed explanation and justification for choosing RT-PCR as the method of analysis
- details of the analytical validation of the RT-PCR method for each of the 21 genes profiled
- details of the method used to normalise gene expression of the 16 cancer genes relative to the set of five reference genes
- details regarding the choice of the five reference genes used for normalisation, including evidence that their expression levels remain constant
- details of the variability of mRNA expression within each of the triplicate measurements for each of the 21 genes
- a demonstration that the measured expression levels of each of the 21 genes is in the linear range of measurement of the RT-PCR assay
- a demonstration of the effect of tumour spatial heterogeneity in mRNA expression on assay reproducibility.

In relation to pre-analytical variables, particularly to establish whether the origin and/or method of specimen preparation is a source of reduced confidence in the outputs of the proposed intervention despite the normalisation relative to the set of five reference genes:

- a detailed explanation and justification for relying on formalin-fixed paraffin-embedded tissues (FFPET) given the known instability of RNA
- a demonstration of the stability and reproducibility of mRNA detection, using RT-PCR, for each of the 21 genes from FFPET breast cancer samples obtained from different pathology laboratories.

In relation to the analyses undertaken to develop and validate the prognostic algorithm:

- details of the characteristics of the populations included in the studies used to develop and validate the algorithm
- details of how the weighting formulae for each of the 21 genes were derived
- details of and evidence supporting the choice and use of the algorithm used to determine the recurrence score
- a detailed explanation and justification for how and why the 16 genes for assessment were determined for the algorithm by aggregating 13 genes into four grouped inputs but leaving the remaining three genes as separate single inputs
- a detailed explanation of how each of the four gene group scores is calculated from the individual gene expression levels
- a detailed explanation of how the mathematical constant for each of the seven genes and gene groups was derived to weight each of these inputs for the algorithm
- a detailed explanation and justification for the cut-points used to categorise the overall recurrence score into high-risk, intermediate-risk and low-risk, and how individual scores with their 95% confidence intervals are to be interpreted in this context with regards to a decision to treat with chemotherapy
- a detailed explanation and justification for the method used to optimise the weighting of the individual assay scores, bearing in mind that errors will be compounded when the data is aggregated.

In relation to evidence of the clinical validity and utility of the proposed intervention:

- a detailed explanation and justification of how and why the patient population(s) to be tested was chosen in each of the studies conducted to provide evidence of the clinical validity and utility of the proposed intervention

- a demonstration of which of these studies were retrospective or prospective (with respect to when the data were collected and when the analysis was specified). It is noted that the randomised controlled trial evidence confirming the prognostic and predictive value of the Oncotype DX test was necessarily retrospective. No prospective data testing the prognostic or predictive ability of Oncotype DX is planned.
- a demonstration that prespecified endpoints were met in each study
- a demonstration of an improved performance of the 21 gene signature over the known IHC-based prognostic markers, ER, PR and HER2, alone
- a demonstration that women with a low risk of recurrence who forego or decline adjuvant chemotherapy have equivalent or better clinical outcomes to women with similar risk scores who are treated with adjuvant chemotherapy. Such demonstration would support the hypothesis that Oncotype DX has the propensity to improve outcomes by reducing exposure to ineffective, yet adverse event causing, chemotherapy
- a demonstration that women with a high risk of recurrence who receive adjuvant chemotherapy have better clinical outcomes to women with similar risk scores who were not treated with adjuvant chemotherapy. Such demonstration would support the hypothesis that Oncotype DX has the propensity to improve outcomes by extending disease free survival in patients who would not otherwise be treated with effective chemotherapy.
- a demonstration that the pathology laboratory involved in each study participated in an external quality assurance program measuring the same 21 gene signature on the same patient population.

In relation to evidence from studies undertaken to validate the downstream health outcome and cost consequences of adding the recurrence score to current clinical decision-making (noting the variation in Australian practice and the US-based evidence available):

- details of the characteristics of the populations and existing management strategies studied
- details of which studies were retrospective or prospective (with respect to when the data were collected and when the analysis was specified) – in this regard, PASC noted that the TAILORx prospective randomised trial in node-negative patients, which has completed accrual of participants, is estimated to be completed in 2014 and that a responder study in node-positive patients is currently accruing participants. PASC noted the TAILORx trial will not validate the assay in the intended use population. It is important to note the reason TAILORx will not validate the assay is because, by using Oncotype DX as a means of selecting patients for the trial (of

CT+HT versus HT alone) the TAILORx trial endorses Oncotype DX as a validated assay. It is possible the TAILORx trial will confirm the predictive ability of Oncotype DX by showing chemotherapy is ineffective in this intermediate risk group

- details of the proportions of patients tested who fall within the low, intermediate and high risk groups according to their recurrence scores
- a demonstration of the cost offsets for the population of patients being tested due to the reduction in cost for adjuvant chemotherapy in those patients with low risk recurrence scores and due to the improvement in health outcomes for those additional patients with high risk recurrence scores who otherwise would not have received adjuvant chemotherapy.

In relation to sources of data used to predict the risk of breast cancer recurrence across the two arms of the proposed decision analysis, with one arm representing the range of current management strategies and the other arm representing the addition of the proposed intervention (noting that a shift in the spectrum of disease is likely to be a confounding factor):

- an assessment of the comparability of the spectrum of disease of the patients across the two arms and their sources of data – in this regard, PASC noted that this is important to distinguish between the prognostic effect of better risk classification by the proposed intervention and the differential treatment effect as a consequence of the proportion of eligible patients for whom the decision as to whether to offer chemotherapy as well as hormone therapy was changed.

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Attachments

Attachment 1: *Sample Oncotype DX patient report*

PRELIMINARY