Australian Government

Department of Health

Application Form

(New and Amended

Requests for Public Funding)

(Version 2.4)

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires in order to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment Team (HTA Team) on the contact numbers and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

Phone: +61 2 6289 7550
Fax: +61 2 6289 5540
Email: hta@health.gov.au
Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant): N/A
Corporation name: Genome Investigation P/L
ABN: 54 164 892 540
Business trading name: Genome Investigation

Primary contact name: REDACTED

Primary contact numbers
Business: REDACTED
Mobile: REDACTED
Email: REDACTED

Alternative contact name: REDACTED

Alternative contact numbers
Business: REDACTED
Mobile: REDACTED
Email: REDACTED

2. (a) Are you a lobbyist acting on behalf of an Applicant?

☒ Yes
☐ No

(b) If yes, are you listed on the Register of Lobbyists?

☒ Yes
☐ No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

3. Application title

Application for funding of the 70 gene signature (MammaPrint) for use in breast cancer to quantify the risk of disease recurrence and predict adjuvant chemotherapy benefit.

4. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

In 2012, there were 15,166 new cases of breast cancer diagnosed in Australia and it is estimated that this number will rise to 16,084 in 2016 (Cancer Australia). In 2012 this made breast cancer the 2nd most commonly diagnosed cancer in Australia (AIHW). For those diagnosed in 2008-2012, their chance of surviving 5 years was 90% (AIHW).

Surgery is usually considered as the first treatment option for primary breast cancer. 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, HER-2 status and proliferation index (Ki67).

Subsequent planning of treatment is then undertaken on the basis of these prognostic and predictive factors (in combination with information on patient characteristics). Systemic therapy options for breast cancer management include endocrine treatments, targeted biological agents and chemotherapy, and genomic testing is now indicated to assist with choice of treatment.

5. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

Microarray 70 gene signature expression profiling of breast cancer, performed on either core biopsy or surgically resected formalin fixed paraffin embedded histological specimen.

May only be used once to test a breast cancer tissue sample from a patient considering chemotherapy treatment with the following characteristics as determined by the referring specialist oncologist:

·early stage breast cancer (stages I-II)

·invasive tumour size up to 50mm in diameter

·node negative or up to 3 positive nodes

·oestrogen positive as determined by immunohistochemistry

-HER2 negative as determined by immunohistochemistry

6. (a) Is this a request for MBS funding?

☒ Yes
☐ No

(b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

☐ Amendment to existing MBS item(s)
☒ New MBS item(s)

(c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:

N/A

(d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

i. ☐ An amendment to the way the service is clinically delivered under the existing item(s)
ii. ☐ An amendment to the patient population under the existing item(s)
iii. ☐ An amendment to the schedule fee of the existing item(s)
iv. ☐ An amendment to the time and complexity of an existing item(s)
v. ☐ Access to an existing item(s) by a different health practitioner group
vi. ☐ Minor amendments to the item descriptor that does not affect how the service is delivered
vii. ☐ An amendment to an existing specific single consultation item
viii. ☐ An amendment to an existing global consultation item(s)
ix. ☐ Other (please describe below):

N/A

(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?

i. ☐ A new item which also seeks to allow access to the MBS for a specific health practitioner group
ii. ☒ A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)
iii. ☐ A new item for a specific single consultation item
iv. ☐ A new item for a global consultation item(s)

(f) Is the proposed service seeking public funding other than the MBS?

☐ Yes
☒ No

(g) If yes, please advise:

N/A

7. What is the type of service:

☐ Therapeutic medical service
☒ Investigative medical service
☐ Single consultation medical service
☐ Global consultation medical service
☐ Allied health service
☐ Co-dependent technology
☐ Hybrid health technology

8. For investigative services, advise the specific purpose of performing the service *(which could be one or more of the following)*:

i. ☐ To be used as a screening tool in asymptomatic populations
ii. ☐ Assists in establishing a diagnosis in symptomatic patients
iii. ☒ Provides information about prognosis
iv. ☒ Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
v. ☐ Monitors a patient over time to assess treatment response and guide subsequent treatment decisions

9. Does your service rely on another medical product to achieve or to enhance its intended effect?

☐ Pharmaceutical / Biological
☐ Prosthesis or device
☒ No

10. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

☐ Yes
☐ No

N/A

(b) If yes, please list the relevant PBS item code(s):

N/A

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

☐ Yes (please provide PBAC submission item number below)
☐ No

N/A

(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

Trade name: N/A
Generic name: N/A

11. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?

☐ Yes
☐ No

N/A

(b) If yes, please provide the following information (where relevant):

Billing code(s): N/A
Trade name of prostheses: N/A
Clinical name of prostheses: N/A
Other device components delivered as part of the service: N/A

(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?

☐ Yes
☐ No

N/A

(d) Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?

☐ Yes
☐ No

N/A

(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):

N/A

12. Please identify any single and / or multi-use consumables delivered as part of the service?

Single use consumables: N/A
Multi-use consumables: N/A

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

13. (a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following details:

Type of therapeutic good: Class III In vitro diagnostic device
Manufacturer's name: Agendia Incorporated
Sponsor's name: Genome Investigation P/L

(b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

☒ Class III
☐ AIMD
☐ N/A

14. (a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?

☐ Yes (If yes, please provide supporting documentation as an attachment to this application form)
☒ No

(b) If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

☐ Yes (if yes, please provide details below)
☒ No

15. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?

☒ Yes (please provide details below)
☐ No

Date of submission to TGA: November 2013
Estimated date by which TGA approval can be expected: TBA
TGA Application ID: DV-2014-IVA-02071-1
TGA approved indication(s), if applicable: TBA
TGA approved purpose(s), if applicable: TBA

16. If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?

☐ Yes (please provide details below)
☐ No

N/A

PART 4 – SUMMARY OF EVIDENCE

17. **Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only).** ***Please do not attach full text articles, this is just intended to be a summary.***

	Type of study design*	**Title of journal article or research project (including any trial identifier or study lead if relevant)**	**Short description of research (max 50 words)****	**Website link to journal article or research (if available)**	**Date of publication*** **
1.	Randomised, phase-3, prospective randomised trial.	Cardoso et al (2016) MINDACT Trial. (Microarray In Node negative and 1-3 lymph node positive Disease may Avoid ChemoTherapy Trial) 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer.	MINDACT is a trial of 6,693 early stage breast cancer patients across 112 centers in Europe. It is a prospective randomized trial proving the clinical utility of the 70 gene assay, in helping to predict patient outcomes and response to chemotherapy.	http://www.nejm.org/doi/full/10.1056/NEJMoa1602253	August 25, 2016.
2.	Editorial	Increasing Precision in Adjuvant Therapy for Breast Cancer.	Editorial published in NEJM authored by Hudis and Dickler. Concluded that the above MINDACT study allows clinicians to consider ordering MammaPrint for chemotherapy patients who wish to avoid it should they be genomically low-risk.	http://www.nejm.org/doi/full/10.1056/NEJMe1607947	August 25, 2016.

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
3.	5 Year Prospective observation study	Drukker et al IJC 2013. A prospective evaluation of a breast cancer prognosis signature in the observational RASTER (MicroarRAy-prognoSTics-in-breast-cancER) study.	A prospective evaluation of the utility of the 70-gene signature to identify those breast cancer patients that may safely forgo chemotherapy. As compared to standard clincopathological classification, MammaPrint re-stratified 20% of Clinical High Risk patients to Low risk. 97% of this Low Risk patient group which primarily chose to forgo chemotherapy, were disease free at 5 years.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3734625/	March 2013

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
6.	Test Development	Van't Veer et al (2002) Gene expression profiling predicts clinical outcome of breast cancer. Nature, 415:530-536.	Development of MammaPrint study, 78 patients. DNA microarray analysis on primary invasive breast carcinoma less than 5 cm (T1 or T2), no axillary metastases (N0), age at diagnosis less than 55 years. Results indicate that breast cancer prognosis can be derived from the gene expression profile of the primary tumour.	http://www.nature.com/nature/journal/v415/n6871/full/415530a.html	31 January, 2002.

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
7.	Observation	Van de Vijver et al (2002) A gene expression signature predicts survival in lymph node negative and positive breast cancer patients. NEJM;347, 1999-2009.	Clinical validation of MammaPrint in consecutive series of breast cancer patients. 295 patients (151 LN-, 144 LN+, 7.3yrs follow-up). Metastasis-free survival by MammaPrint at 10 years for LN- patients: Low risk: 87%, High risk: 44%. Indicates GEP may be a useful means of guiding adjuvant therapy.	http://www.nejm.org/doi/full/10.1056/NEJMoa021967#t=article	December 19, 2002.

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
8.	Technical	Glas et al. (2006) Converting a breast cancer microarray signature into a high-throughput diagnostic test. BMC Genomics; 7:278.	Conversion to diagnostic test study. 162 patients used to compare data to original study (no. 6 above). Demonstrated reproducibility and robustness of microarray results suggesting its utility as a tool to predict disease outcome.	http://bmcgenomics.biomedcentral.com/articles/10.1186/1471-2164-7-278	October 30, 2006.
9	Technical comparison of methods.	Sapino et al. (2014) MammaPrint Molecular Diagnostics on Formalin-Fixed, Paraffin-Embedded Tissue. J Mol Diagn; 16(2): 190-197.	Validation of MammaPrint in FFPE specimen. 211 patients. Comparison made between FFPE and fresh tissue equivalents. Demonstrated FFPE results substantially equivalent to fresh tissue results.	http://jmd.amjpathol.org/article/S1525-1578(13)00253-5/abstract	March, 2014.

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words)**	Website link to journal article or research (if available)	Date of publication***
10.	Cost-effectiveness study	Retèl et al. (2013) Prspective cost-effectiveness analysis of genomic profiling in breast cancer.	Prospective cost-effectiveness study based on 5-year survival date from the RASTER study. Costs and outcomes (QALYs) were calculated for 427 patients (node negatve), subgroup analysis performed based on tumour characteristics. The omission of chemotherapy for patients with a low risk score was both a cost-effective and oncological safe choice.	http://www.ejcancer.com/article/S0959-8049(13)00735-1/abstract	December, 2013
11.	Review	Azim Jr et al. (2011) Long-term toxic effects of adjuvant chemotherapy in breast cancer.	A review of the long-term toxic effects of adjuvant chemotherapy, with focus on adverse events such as cardiac toxicity, secondary leukaemia, cognitive function, fertility, and neurotoxicity.	http://annonc.oxfordjournals.org/content/early/2011/02/02/annonc.mdq683.full	February 2, 2011.

** Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes.*

**** If the publication is a follow-up to an initial publication, please advise.*

18. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

	Type of study design*	Title of research (including any trial identifier if relevant)	Short description of research (max 50 words)**	Website link to research (if available)	Date***
1.	Observation study	Tsai et al. The 70-gene signature provides risk stratification and treatment guidance for patients classified as intermediate by the 21-gene assay.	The PROMIS trial includes 840 ER+, LN+ or LN- women with an intermediate (18-30) score on the 21-gene assay. These patients obtained a risk categorisation based on the MammaPrint signature. Distribution and the impact the new score had on physician decisions was evaluated. Results showed a 33% change in treatment decisions, following significant discordance.	http://meetinglibrary.asco.org/content/170416-176	TBA

** Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment.*

****Date of when results will be made available (to the best of your knowledge).*

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

19. **List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):**

    MOGA – Medical Oncology Group of Australia

    RACP – Royal Australasian College of Physicians

    BreastSurgANZ – Breast Surgeons of Australia and NZ

    RACS – Royal Australasian College of Surgeons

20. **List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):**

    N/A

21. **List the relevant consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):**

    Breast Cancer Network of Australia (see letter attached)

22. **List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:**

    Myriad Genetics – EndoPredict

    Nanostring Technologies - Prosigna

    Genomic Health – OncotypeDX

23. **Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):**

    REDACTED

    Please note that the Department may also consult with other referrers, proceduralists and disease specialists to obtain their insight.

PART 6 – POPULATION (AND PRIOR TESTS), INDICATION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

24. Define the medical condition, including providing information on the natural history of the condition and a high level summary of associated burden of disease in terms of both morbidity and mortality:

Breast cancer is a malignant neoplasm of the breast, resulting in a highly significant annual mortality and morbidity. It 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). In 2012, there were 15,166 new cases of breast cancer diagnosed in Australia and it is estimated that this number will rise to 16,084 in 2016 (Cancer Australia). In 2012 this made breast cancer the 2nd most commonly diagnosed cancer in Australia (AIHW). For those diagnosed in 2008-2012, their chance of surviving 5 years was 90% (AIHW).

Breast cancer can be further classified based upon a number of factors, primarily the histological type, size, lymph node involvement and receptor status.

The number of deaths from breast cancer in 2013 was 2,892, an increase of nearly 1500 over the previous 45 years, in 2016, it is estimated that this number will rise to 3,073 (AIHW). For 2013, the age-standardised mortality rate was 11 deaths per 100,000 persons (AIHW). In 2007, the median age at death for this population was 68 (AIHW). “Breast cancer was the sixth leading cause of burden of disease for females, accounting for 61,300 DALYs, 4% of all female burden of diseases and 24% of all female burden due to cancer” (AIHW). The years of healthy life which these women are losing is primarily due to side effects during and after treatment (chemotherapy, radiotherapy etc.), potential changes in menopause, lymphedema and psychosocial changes (AIHW). Furthermore, “breast cancer is expected to contribute more years of life lost (40,800) (YLL) than years of healthy life lost disability (20,500) (YLD)” (AIHW).

Breast cancer causes a significant amount of patient admissions for women, specifically 113,000 in 2009-10, 85% of which were same-day, 56% were in females aged 50-69, 62% were in private hospitalisations, 75% involved a surgical procedure and 91% involved administration of pharmacotherapy (AIHW). However the AIHW does note that hospitalisations involving same-day chemotherapy administration for breast cancer patients, who were coded with breast cancer as an additional diagnosis, are not included in these numbers which likely represent a minimum (AIHW).

This results in a high level of financial expenditure, in the 2004-05 financial year, the total health expenditure on breast cancer for females was estimated to be $331 million, 16% of which was used for prescription pharmaceuticals (AIHW).

25. Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service:

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 (14,818×0.70). It is estimated that approximately one third of these patients would be potentially eligible for MammaPrint testing based on having ER+ positivity, HER2 negativity, 0-3 nodes involved and also be considered candidates for chemotherapy. Other reasons patients may not receive the test include patient/physician preference and contraindications or intolerance to chemotherapy. Patients are only tested if oncologists are in doubt regarding the value of chemotherapy in their specific situation. The MammaPrint® test will only be required once per new primary breast cancer diagnosis for patients who are eligible.

With this in mind, patients who have an early stage breast cancer (stages I-II), invasive tumour size up to 50mm, node negative or up to 3 positive nodes, ER positive and HER2 negative will be eligible for the 70 gene test, provided they are candidates for chemotherapy. Referrals will be made by either surgical oncologists or medical oncologists.

Table 1. TNM staging of breast cancer

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

Source:- American Joint Committee on Cancer Staging resources [accessed September 2011].

Table 2. American Joint Committee on Breast Cancer TNM stage grouping

Stage grouping	T stage	N stage	M stage
Stage 0	T1	N0	M0/M0(i+)
Stage IA	T0	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+)
Stage IIIB	T3	N2	M0/M0(i+)
	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].

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

26. Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):

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

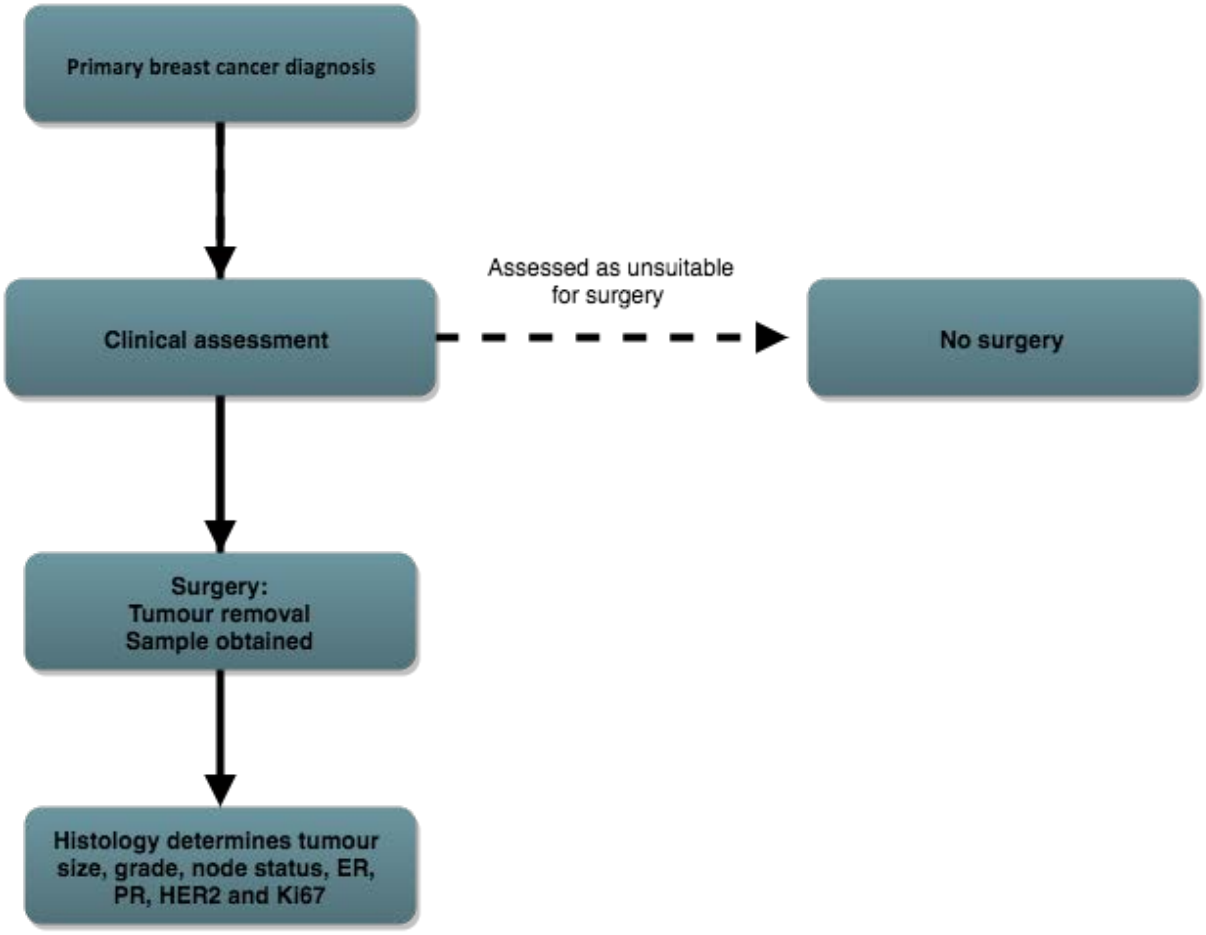
recommend that primary systemic therapy (neoadjuvant therapy) may be used in an attempt to shrink the size of the primary tumour to enable breast conserving treatment and surgery. In addition, some patients are considered unfit for surgery, and often these patients are elderly.

A core biopsy is performed by the radiologist or surgeon preoperatively, and sent to a laboratory, at which point an FFPE sample is prepared. During surgery the tumour plus or minus 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 by a pathologist then provides information relating to a number of prognostic factors including histological grade, nodal status, tumour size, hormone (ER and PR) receptor, HER-2 status and proliferation index (Ki67).

It is at this stage that the classification of the patient's stage of illness takes place. Planning of treatment is undertaken with the above information considered, along with patient characteristics.

For patients who fit the aforementioned criteria of an ER+, HER2-, primary stage I or II tumour, size up to 50mm and 0-3 lymph nodes involved, the MammaPrint 70-gene signature can be utilised to provide additional information to the multidisciplinary team, primarily the medical oncologist, who will subsequently use these factors to determine the course of treatment from this point onwards.



PART 6b – INFORMATION ABOUT THE INTERVENTION

27. Describe the key components and clinical steps involved in delivering the proposed medical service:

Clinical Step 1: Identification and request

The first step is to identify a patient who is eligible for the test using the established criteria discussed in the above sections. The information required for this identification is already part of standard clinical practice and is routinely provided to all professionals involved in the care of the patient. No extra investigation is required to identify an eligible patient.

For eligible patients, a medical or surgical oncologist will complete an Agendia Test Request Form and fax or email it to Genome Investigation. Along with the establishment of the specific nature of the tumour, this is the only active role required of the treating doctor.

Upon receipt of this request, Genome Investigation will then immediately contact the Australian pathology laboratory which initially reported the presence of invasive breast cancer on either the invasive tumour core biopsy or invasive tumour resection specimen. The pathology laboratory is then requested to send the designated sample (with a minimum of 30% of representative invasive cancer), via conventional priority international courier methods, either inside the MammaPrint Specimen Kit or in conventional FFPE packaging material, for export processing prior to sending on to the Agendia laboratory in Los Angeles, California.

The Australian pathology laboratory must prepare the specimen using the appropriate instructions provided with the MammaPrint Specimen Kit, consisting of 10 unstained slides each with (5 microns) section of tissue. Each slide must be numbered labelled with the Agendia specific patient code label. Charged (coated) slides are preferred. All specimens are labelled with barcode labels which are also placed on the patient's MammaPrint Test Request Form. An arrangement currently exists whereby Agendia pays a commercial-in-confidence administrative fee to Genome Investigation who then reimburses the Australian pathology company for any costs of sample preparation.

The main factor that influences the preparation of the specimen is the correct selection of invasive tumour sampling (not in-situ or non malignant tissue). However, even though the Australian pathology laboratory sends the exact portion of invasive tumour tissue, all tissue samples received by Agendia are assessed independently by a pathologist from Agendia to verify the diagnosis, review for adequate tumour content (>30%) and perform manual microdissection as needed in accordance with American pathology guidelines. Very rarely, the sending Australian pathologist is required to repeat the FFPE slide preparation and send these further slides to Genome Investigation and then on to Agendia in California for analysis. Genome Investigation will meet the separate cost of this repeated exercise in Australia. To date, this occurrence has only happened once - where in situ tumour was sent across rather than invasive tumour.

The results of the MammaPrint test should be available in 10 days from the date the tumour sample is sent. The results of the test will be returned immediately upon reporting by email securely online to the ordering medical or surgical oncologist as well as the submitting pathologist, and any additional specified physician, involved in the care of the patient as noted on the Agendia Test Request Form. The remaining tumour sample is then returned to the originating Australian pathology laboratory with costs covered by Agendia.

Although the 70 gene MammaPrint signature test is a complicated microarray mRNA analysis which is performed in Irvine, California, USA, the report, by design, returns a straight forward binary low risk result or high risk result. This binary result for both patients and specialist medical and surgical oncologists is straight forward to understand, therefore professional training and accreditation in the area of GEP has not yet been recommended by either MOGA or BreastSurgANZ. The simple binary low risk:high risk 70 gene result has not lead to either MOGA or BreastSurgANZ recommending any particular accreditation for medical or surgical oncologists ordering the 70 gene assay. Further, as the pathological analysis is being conducted in California, there are no specific training or accreditation requirements for pathologists or Australian laboratories sending cancer specimens abroad over and above their current standards.

Laboratory Process

The single laboratory performing the test for Australian patients is located in Irvine, California, USA. There have been over 40,000 tests performed on breast cancer patients from many countries in Europe, North & South America, Asia, Australia and New Zealand.

Gene expression levels are measured by a modern mRNA microarray analysis technique, as reported in Glas et al (BMC Genomics 2006). Fluorescent-dye labelled RNA to microarrays containing 15,000 60-mer oligonucleotide probes are hybridized to perform this test. To increase measurement precision, each of the signature genes are spotted 9 times and an error-weighted average of the intensity ratios is calculated. Since different measurement quantities are used (Xdev versus Log Ratio), the 'good prognosis template' is constructed using the data of the 44 good outcome patients generated on the original mini-array based on log ratios. Disease outcome classification of individual samples is then determined by the cosine correlation of this recreated template in a leave-one-out cross validation procedure.

The expression intensities of the 70 signature genes for the 78 original samples are hybridized to the customized array. The tumours are rank-ordered according to their correlation coefficients with the re-established 'good prognosis template'. Genes are ordered according to their correlation coefficient with the two prognostic groups as described in the original 2002 Nature article by Van't Veer et al. Tumours with correlation values above or below this original Van't Veer et al determined threshold are assigned to the good or poor prognosis profile group, respectively.

The 70 gene MammaPrint analysis is designed to determine the gene activity of specific genes in a tissue sample compared to a reference standard. The result is an expression profile, or fingerprint, of the sample. The correlation of the sample expression profile to a template (the mean expression profile of 44 tumours with a known good clinical outcome) is calculated and the molecular profile of the sample is determined (Low Risk, High Risk, Low Risk Borderline, High Risk Borderline).

The algorithm used to calculate the risk of relapse is as follows. Data analysis is performed according to a specific 70 gene MammaPrint algorithm (the 70 gene MammaPrint Index). The algorithm calculates the similarity ("cosine correlation") of the patient sample expression profile against two templates; a Low Risk template containing patient samples with a known good clinical outcome, and a High Risk Template containing patient samples with a known poor clinical outcome. This determines the correlation of the molecular profile of the patient sample to either Low Risk or High Risk.

This algorithm is designed and programmed by Agendia and compiled into a stand alone software program called "X-Print Analysis Software". The "X-Print Analysis Software" loads a data file (CSV) which is created by the laboratory technician by extracting specific information from the laboratory database. The CSV data file contains: external sample ID, internal sample ID, Technician name, Bio-analyzer ratio, RNA integrity number, location of straight and dye-swap data file (TXT), Microarray chip Layout (8-pack) and additional comments by the technician. The "X-Print Analysis Software" reads the CSV file, opens the Feature Extraction Software data files (TXT), performs quality control checks, determines the sample expression profile, calculates the correlation of sample profile to the "Low Risk" template profile on a scale of – 1 (High Risk) to + 1 (Low Risk). This is termed the MammaPrint Index, and it compares the calculated correlation to a pre-defined cutoff value and determines the samples prognostic profile (Low Risk or High Risk). The analysis software output is an internal report (PDF) for every sample. In this report quality control values and analysis results are reported.

To determine the cutoff point used to categorize patients as low or high risk, the abovementioned 70 gene MammaPrint Index is used. This index ranges from -1.0 to +1.0. Tumour samples with the 70 gene MammaPrint Index above the threshold of 0 (zero), are classified as low risk, and tumour samples with the 70 gene MammaPrint Index equal to or lower than the threshold are classified as high risk. De Snoo et al (Surg Oncol 2009) determined that a 10% risk of recurrence in untreated patients was used to determine the low risk category, as this would translate into a 5-6% recurrence risk if hormonal therapy was given. This was deemed sufficiently low so that patients would not be considered candidates for adjuvant chemotherapy. Conversely, the high risk threshold was set at a 30% risk of recurrence for untreated

patients. All such patients would be appropriate candidates for adjuvant chemotherapy based on their risk of developing metastases at the accepted 30% benefit of adjuvant treatment.

The clinical threshold was chosen to permit the creation of the largest group of 'Low Risk' intended use patients who could safely forego adjuvant chemotherapy without compromising their outcome. This equates to an untreated patient with lymph-node negative breast cancer having an average of a 10% risk (95% CI 4-15) of developing distant metastasis over the subsequent 10 years.

The above forms the basis for the binary result presented to patient and clinician 10 days later.

Clinical Step 2: Consultation

With the patient's genomic risk profile established, patients and clinicians are afforded an extra prognostic factor to guide their treatment decision. The clinical utility and body of evidence supporting this are discussed elsewhere in this document. However, it is at this stage that MammaPrint must be considered for its clinical utility in allowing patients to consider forgoing chemotherapy if their genomic profile shows their tumour to be low risk. In cases such as these, endocrine therapy alone would be provided and chemotherapy reserved for those who are high risk.

28. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?

MammaPrint is registered with Australian trademark number 1234096. It was lodged on 27/11/2007 and has a status of Registered/Protected. The applicant/owner of the trademark is registered as AGENDIA BV.

Similar health components are other gene profiling tests. The primary point of difference between these tests, with respect to the nature of the trademark, is the genes utilised in the analysis and the methods and algorithms involved.

29. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?

Yes, as reported and confirmed with Level 1A evidence in the MINDACT trial.

30. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency):

The primary limitations on the provision of the proposed medical services are quantity and duration. As this test is only indicated in primary tumours, the average patient will only require this test once.

As discussed above, there is a 10 day turnaround for the provision of results to treating clinicians. Expert opinion sought on the time to commence adjuvant chemotherapy after surgery indicates that treatment usually commenced within 6 weeks after surgery. The results of the MammaPrint test are available within 10 days of the sample being sent to Genome Investigation in Australia (including delivery to the Agendia laboratory in Irvine, California, USA) therefore imposing no delay for treatment to commence.

In around 3%, there is a requirement for repeat testing. Sapino et al (Journal of Molecular Diagnostics 2013) state in their review entitled "MammaPrint Molecular Diagnostics on Formalin-Fixed Paraffin-Embedded Tissue" that "FFPE sample processing had a success rate of 97%." This is a significant improvement over the earlier fresh tissue processing where higher failure rates were reported. Causes of failures are derived from insufficient invasive tumour, insufficient RNA or unevaluable slides. In such cases it is necessary to resubmit a sample for MammaPrint testing or repeat the MammaPrint test, in both circumstances the costs are borne by Agendia. Whilst this is a foreseeable possibility, it is not envisaged to apply to the majority of cases however it should be noted as a limitation nonetheless.

31. If applicable, identify any healthcare resources or other medical services that would need to be delivered <u>at the same time</u> as the proposed medical service:

N/A

32. If applicable, advise which health professionals will primarily deliver the proposed service:

Qualified and accredited medical and surgical oncologists will be the primary referrers of this service. Australian pathologists will provide the tissue and the Agendia laboratory in Los Angeles will perform the MammaPrint test.

33. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:

Not as yet.

34. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:

Agendia Incorporated in the USA deliver the proposed service, and Australian surgical and medical oncologists provide a referral for the MammaPrint service.

35. If applicable, advise what type of training or qualifications would be required to perform the proposed service as well as any accreditation requirements to support service delivery:

To perform the proposed service, a laboratory accredited by Agendia is required. Currently, only two such facilities exist – one in Irving, Los Angeles, and the other in Amsterdam, Holland - although Australian patient's specimens only get delivered to the Los Angeles Agendia laboratory. However, should MSAC advise the government to fund MammaPrint, then Agendia will consider accrediting a single laboratory in Australia to perform these services.

36. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select all relevant settings):

- ☐ Inpatient private hospital
- ☐ Inpatient public hospital
- ☐ Outpatient clinic
- ☐ Emergency Department
- ☐ Consulting rooms
- ☐ Day surgery centre
- ☐ Residential aged care facility
- ☐ Patient's home
- ☒ Laboratory
- ☐ Other – please specify below

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

N/A

37. Is the proposed medical service intended to be entirely rendered in Australia?

- ☐ Yes
- ☒ No – please specify below

All patient interaction, specimen collection and preparation is to be rendered entirely in Australia.

However, all specimen analysis and reporting is performed in the Agendia laboratory in Irvine, California, USA. As such, there are no direct costs of any equipment or resources that are used in Australia, over and above those required to send FFPE tissue from the Australian reporting pathology laboratory via Genome Investigation to the Agendia laboratory in Irvine California. These dispatch and return costs are included in the Agendia fee outlined below.

However, should MSAC advise the Australian Government to fund MammaPrint, then Agendia will consider accrediting one (only) laboratory in Australia to perform these services.

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

38. Nominate the appropriate comparator(s) for the proposed medical service, i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system (including identifying health care resources that are needed to be delivered at the same time as the comparator service):

1. *Current clinical practice:* The primary comparator for this application is the current clinical practice in Australia. Under this model, patients receive endocrine therapy with or without the addition of adjuvant chemotherapy. The decision to utilise adjuvant chemotherapy is guided by a variety of clinical and pathological measures. Primary amongst these is the hormone and HER2 receptor status of the tumour. This information is determined by IHC or ISH (in the case of HER2) for which the MBS item numbers are 72848, 73061 and 73332. The level of ER and PR are useful in predicting the efficacy of endocrine therapy, with ER/PR positive tumours often treated with endocrine therapy alone if other factors do not indicate otherwise. One such factor is HER2 status which is also assessed and forms a key component of the decision to offer trastuzumab. Other factors which form part of the decision process are the Ki67 molecular marker, tumour grade and size, age, menopausal status, lymph node involvement and other comorbidities. Tools such as NHS Predict and Adjuvant! Online are also used, and this latter tool was a focal point of comparison in the MINDACT study. Other guidelines that are currently utilised are the St. Gallen International Expert Consensus (Coates et al. 2015), National Comprehensive Cancer Network guideline (NCCN 2015), European Society for Medical Oncology (ESMO 2015) and Australian NHMRC Guidelines in breast cancer management.

2. OncotypeDX® uses RT-qPCR to produce an expression panel of 21 genes and calculate a Recurrence Score® (10 year risk of distant recurrence for node negative patients, 5 year risk of recurrence or death for node positive patients) to determine the likelihood of benefiting from combined adjuvant chemotherapy and endocrine therapy. The eligible population are those with early stage breast tumours classified as oestrogen positive, HER2 and lymph node negative. REDACTED

3. EndoPredict® uses RT-qPCR to determine the expression level of eight genes. This result is combined with clinical markers to produce a risk score for patients in the intermediate risk category. Eligible patients are those with primary, operable, T1, T2 or T3, ER+ve and HER2-ve breast cancer, with or without lymph node involvement (up to 3 nodes). REDACTED

4. PAM50® is another promising genomic test, REDACTED

39. Does the medical service that has been nominated as the comparator have an existing MBS item number(s)?

☒ Yes (please provide all relevant MBS item numbers below)
☐ No

MBS numbers included in current clinical practice:

- 72847
- 72848
- 73061
- 73332

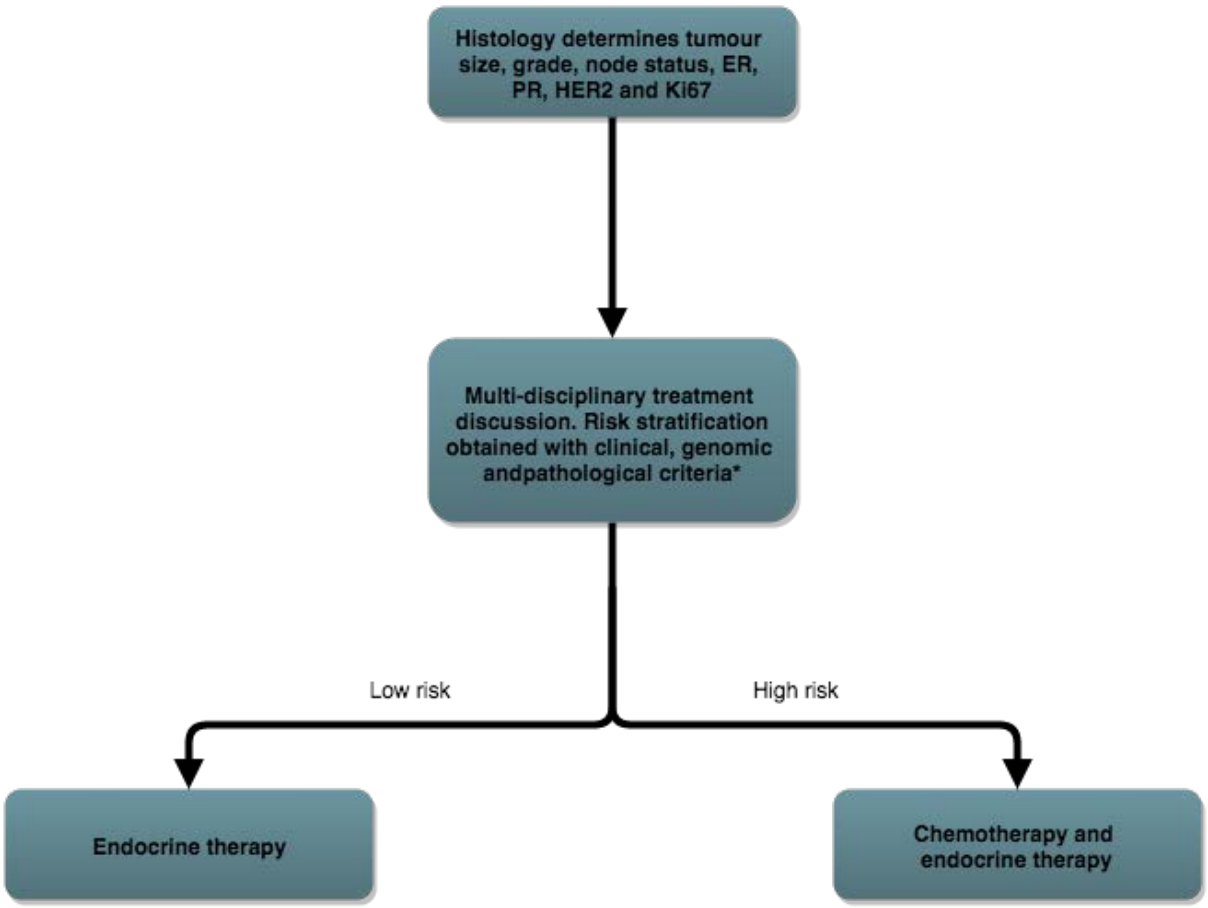
40. Define and summarise the current clinical management pathways that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards including health care resources):

The second clinical step noted in the previous portion of this clinical management pathway summary is consultation. During which the information provided by the pathologist (hormone and growth factor status, tumour size and grade, Ki67 status nodal status etc.) is used in conjunction with other clinical factors to establish risk of recurrence and subsequently the appropriateness of chemotherapy. All patients currently receive endocrine therapy, with chemotherapy being offered only to those in the

intermediate-high risk group in conjunction with endocrine therapy. The primary principle is that the recommendation for chemotherapy in combination with endocrine therapy is based on a balance of risk of recurrence against the potential for adverse effects during therapy.

All chemotherapy agents used to treat early breast cancer are all available on the PBS under the General Schedule or Streamlined authority.

It has been observed that in other similar applications, PASC has requested that international clinical guidelines and alternative GEP tests be included. This application supports this comparison, however notes that they are not the current mainstay of clinical practice and unlike MammaPrint, do not have Level 1A support. In light of this they will not be represented in the below management algorithms.



*It is at this stage that tools such as NHS Predict and Adjuvant! Online are utilised. Similarly, guidelines like the St. Gallen International Expert Consensus (Coates et al. 2015), National Comprehensive Cancer Network guideline (NCCN 2015), European Society for Medical Oncology (ESMO 2015) and Australian NHMRC Guidelines in breast cancer management may also be used.

41. (a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?

☒ Yes
☐ No

(b) If yes, please outline the extent of which the current service/comparator is expected to be substituted:

The proposed medical service is expected to complement existing clinical care. Its use requires the main tenets of clinical care to be maintained. It is envisaged that the only change in clinical practice will be a change in the individual recommendation for or against chemotherapy.

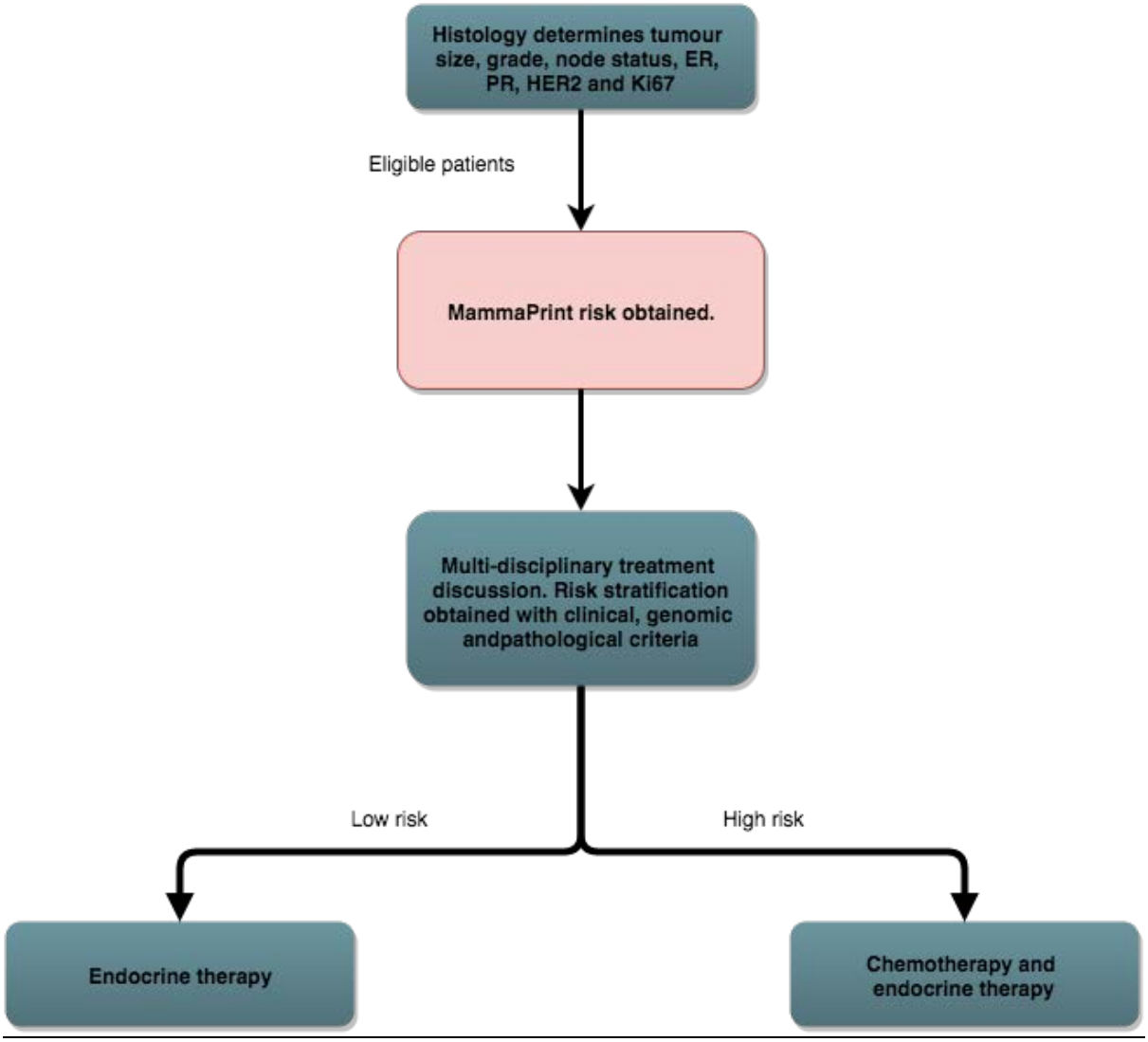
42. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service including variation in health care resources (Refer to Question 39 as baseline):

The key difference in the clinical management pathway from the point of service delivery is the addition of a new factor in the stratification of patients into risk groups and, consequently, treatment plans. For eligible, intermediate-risk patients as described above, the oncologist will assess the MammaPrint risk score in conjunction with currently employed clinical and pathological factors to further stratify their risk and chemotherapy eligibility. It is envisaged that this process will augment and improve, rather than replace, current clinical management. Thus the below algorithm contains only an addition to the process. For patients who are eligible, MammaPrint can assign a risk after the histological investigation and then serve to provide a clear picture for the treatment discussion which follows.

The MammaPrint® score provided is a binary score, making its inclusion simple and easily communicable to patients. With this information, the oncologist and patient will decide on the course of treatment. The result provides both prognostic and predictive genomic information for determining the correct risk group and who will and who wont benefit from chemotherapy, as shown conclusively in MINDACT.

It is the primary purpose of this application to convey the claim that MammaPrint will lead to a reduction in the utilisation of chemotherapy – which MINDACT suggests could be as high as a 46% reduction in utilisation of chemotherapy. The basis for this claim is the reclassification of women who would have previously been administered chemotherapy due to their low risk score. Their reclassification into a low-risk group by the MammaPrint test would lead to a cost saving to Medicare. However, its primary impact would be to spare women the arduous process, risks and problems of chemotherapy (see aforementioned Azim 2011 paper). The services which establish ER, PR, HER2 status etc. which are primarily determined in the pathology laboratory will not be altered. Furthermore, for patients whose treatment remains as it would have proceeded without the MammaPrint score then they will not experience a variation in health care resources.

(Algorithm below)



PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

43. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):

The primary clinical claim for the proposed medical service is that it can provide valuable information in deciding which patients might benefit from adjuvant chemotherapy. More specifically, patients at a high clinical risk but low genomic risk, as determined by the MammaPrint assay, can avoid chemotherapy and its associated toxicity and adverse effects. Whilst many of the above studies have investigated the clinical utility of MammaPrint, the cornerstone for this claim lies in the findings of the 2016 MINDACT study. The findings of which, in short, showed that those at a high clinical risk (as determined by Adjuvant! Online) but low genomic risk could avoid chemotherapy (Cardoso et al MINDACT, 2016). This is the primary point of comparison for primary comparator of current clinical care.

Therefore, this application is claiming a comparative benefit in this regard, as more women can avoid chemotherapy and reduce the associated adverse effects and drug toxicities with the added cost-saving benefit for Medicare. On a broader scale, this can result in less chemotherapy, less adverse outcomes and less expenditure.

This claim is in relation for those who are classified as genomic low risk, but clinical high risk. It is not the claim of this application that for those who are classified as clinical low risk, and genomic high risk, that chemotherapy should be given.

A small minority of patients classified as low genomic risk who experience a form of recurrence and who elected to avoid chemotherapy that would have otherwise been advised, may represent a comparative harm. The primary clinical claim in this regard is that the difference to current clinical care is not significant and does not outweigh the benefits. However, it should be noted that treatment with chemotherapy is ultimately a decision of the patient, augmented by advice from the treating oncologist who is armed with the results of various investigations. MammaPrint claims to improve this process, not to replace it.

REDACTED

44. Please advise if the overall clinical claim is for:

☐ Superiority
☒ Non-inferiority

45. Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:

Safety Outcomes:

Comparison of distant metastasis-free survival, disease-free survival and overall survival between the comparators.

Comparison of adverse-effects.

Clinical Effectiveness Outcomes:

Comparison of influence of treatment.

Cost-effectiveness analysis.

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

46. Estimate the prevalence and/or incidence of the proposed population:

Approximately 15,000 Australian women develop breast cancer each year, of which less than one quarter would be eligible for 70 gene signature expression profiling.

47. Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:

Once

48. How many years would the proposed medical service(s) be required for the patient?

Once only, at the time of the initial diagnosis

49. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:

100

50. Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of 'leakage' to populations not targeted by the service:

1,000

PART 8 – COST INFORMATION

51. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

$USD4,200 – current international fee for service. Includes collection of tissue from Australian pathology laboratory, dispatch to Agendia laboratory in Los Angeles, complete 70 gene microarray testing and reporting back to Australia.

52. Specify how long the proposed medical service typically takes to perform:

10 days.

53. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.

Category – MBS Pathology Category 6 - Group P7 Genetics
Proposed item descriptor: 733XX Microarray 70 gene signature expression profiling of breast cancer, performed on either core biopsy or surgically resected formalin fixed paraffin embedded histological specimen. May only be used to test samples from patients considering chemotherapy treatment with the following characteristics as determined by the referring specialist oncologist: ·early stage breast cancer (stages I-II) ·invasive tumour size up to 50mm in diameter ·node negative or up to 3 positive nodes ·oestrogen positive as determined by immunohistochemistry -HER2 negative as determined by immunohistochemistry May only be used once per new primary breast cancer tumour diagnosis Fee: $USD4,200

PART 9 – FEEDBACK

The Department is interested in your feedback.

54. How long did it take to complete the Application Form?

One week

55. (a) Was the Application Form clear and easy to complete?

☒ Yes
☐ No

(b) If no, provide areas of concern:

N/A

56. (a) Are the associated Guidelines to the Application Form useful?

☒ Yes
☐ No

(b) If no, what areas did you find not to be useful?

N/A

57. (a) Is there any information that the Department should consider in the future relating to the questions within the Application Form that is not contained in the Application Form?

☐ Yes
☒ No

(b) If yes, please advise:

N/A