Australian Government

Department of Health

MSAC Application 1408.1

A prognostic RT-qPCR test for prediction of risk of distant recurrence of breast cancer under endocrine treatment

PART 1 – APPLICANT DETAILS

1. **Applicant details (primary and alternative contacts)**

Corporation / partnership details (where relevant):

Corporation name: Myriad Genetics

ABN: 168356572

Business trading name: Myriad Genetics Australia Pty Ltd

Primary contact name: **REDACTED**

Primary contact numbers

Business: Myriad Genetics Australia Pty Ltd

Mobile: **REDACTED**

Email: **REDACTED**

Alternative contact name: **REDACTED**

Alternative contact numbers

Business: Myriad Genetics Australia Pty Ltd

Mobile: **REDACTED**

Email: **REDACTED**

2. **(a) Are you a consultant acting on behalf on an applicant?**

☐
☒ No

(b) If yes what is the Applicant(s) name that you are acting on behalf of?

Not applicable

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

☐
☒ No

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

☐
☐ No

(c) Have you engaged a consultant on your behalf?

☐
☒ No

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

4. Application title

A prognostic RT-qPCR test for ER+ve /HER2-ve breast cancer that determines the risk of early and late metastasis in node negative and positive cancer treated with endocrine treatment.

5. 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)

EndoPredict® is an in vitro prognostic gene expression assay for patients with primary ER+/HER2–early-stage breast cancer. The final test result of the product, which includes a molecular signature combined with clinical markers assessed by a pathologist, scores the 10-year risk of distant metastasis with 5 years of Endocrine therapy only. The test score (EPclin) helps guide treatment decisions, allowing clinicians to determine whether adjuvant chemotherapy should be administered in cases where the established prognosis factors such as grading, Ki67, quantitative immunohistochemistry of the oestrogen receptor, and nodal status do not enable a clear-cut decision (i.e. the pre-test risk of distant metastases is considered intermediate). The report also provides the estimated absolute chemotherapy benefit at 10 years (for patients treated with 5 years of ET only) and the likelihood of late distant recurrence (5–15 years) (for patients with no recurrence after 5 years of ET only).

6. 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)

EndoPredict® is an in vitro prognostic product which uses RT-qPCR technology in combination with the two clinical markers tumour size and nodal status (assessed by the pathologist) to score individual breast cancer patients for risk of distant recurrence up to 10 years (on a continuous scale) if treated with endocrine therapy only. RT-qPCR is conducted in a local laboratory under Australian regulatory standards using the EndoPredict® Kit manufactured by Myriad Genetics GmbH and distributed by Myriad Genetics Pty Ltd. Online software is used in conjunction with the qPCR module, analyses expression data and clinical information (node status and tumour size) is entered and calculates an EPclin score. The report also provides estimated absolute chemotherapy benefit at 10 years and the likelihood of late distant recurrence (5–15 years). The oncologist will decide on treatment of endocrine therapy alone, extended endocrine therapy or endocrine and chemotherapy, based on the calculated risk.

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

☒ Yes
☐

(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?

☐
☒ 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/technology:

MSAC Application 1408

(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):

1. Demonstrate Evidence of Incremental Prognostic Value
2. Illustrate Confirmatory Evidence of Clinical Utility within Australia
3. Improve the Definition of the Descriptor, remaining test agnostic
4. Exemplify the Differentiation from Grouped GEP Assays as a Class Value
5. Offer a Price to Volume Fee
6. Recognise the Discrepancy between TGA Approval, IVD regulatory, Global Guidelines and the Position taken by MSAC regarding prognostic versus predictive

(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?

☐
☒ No

(g) If yes, please advise:

Not applicable

8. What is the type of medical service/technology?

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

9. 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

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

☐ Pharmaceutical / Biological
☐ Prosthesis or device
☒ No

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

☐
☒ No

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

Not applicable

(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

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

Not applicable

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

☐ Yes
☒ No

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

Not applicable

(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

(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
☐

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

Exact Sciences

Agendia

Veracyte

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

Single use consumables: EndoPredict® Kit and associated disposable laboratory consumables (e.g. laboratory pipette tips and laboratory safety ware)

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

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

Type of therapeutic good: Acquired Genetic Alteration IVDs

Manufacturer's name: Myriad International GmbH

Sponsor's name: Myriad Genetics Pty Ltd

(b) Has it been listed on the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)? If the therapeutic good has been listed on the ARTG, please state the ARTG identification numbers, TGA-approved indication(s), and TGA-approved purpose(s).

ARTG ID: 285557

TGA approved indication(s), if applicable: CT929 Acquired genetic alteration IVDs

TGA approved purpose(s), if applicable: An in vitro diagnostic kit for patients with estrogen-receptor-positive, HER-2 negative primary breast cancer to determine the risk of distant recurrence and to estimate the adjuvant chemotherapy benefit

(c) If a medical device is involved, has the medical device been classified by TGA as a Class III OR Active Implantable Medical Device (AIMD) under the TGA regulatory scheme for devices?

☒ Class III
☐ AIMD
☐ N/A

(d) Is the therapeutic good classified by TGA for Research Use Only (RUO)?

No, the Product Type is an IVD

15. (a) If not listed on the ARTG, is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?

Not applicable

(b) If the therapeutic good is not ARTG listed, is the therapeutic good in the process of being considered by TGA?

Not applicable

(c) If the therapeutic good is NOT in the process of being considered by TGA, is an application to TGA being prepared?

Not applicable

PART 4 – SUMMARY OF EVIDENCE

16. **Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology. At 'Application Form lodgement', please do not attach full text articles; just provide a summary.**

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
1	R-RCT A combined cohort from ABCSG-6 a phase III RCT comparing Tam alone for 5 years with Tam+Ana for the first 2 years and ABCSG-8 a phase III RCT comparing Tam for either 5 or 2 years followed by Ana for 3 years	Filipits M et al., A new molecular predictor of distant recurrence in ER-positive, HER2-negative breast cancer adds independent information to conventional clinical risk factors.	ABCSG-6 & 8 n=1702 Prospective- retrospective in design The multigene EP risk score provided additional prognostic information to the risk of distant recurrence of breast cancer patients, independent from clinicopathologic parameters. The EPclin score outperformed all conventional clinicopathologic risk factors	https://clincancerres.aacrjournals.org/content/17/18/6012.long	September 2011
2	R-CT ABCSG 6&8 (Same as 1)	Dubsky et al., EndoPredict improves the prognostic classification derived from common clinical guidelines in ER positive, HER2 negative early breast cancer .	ABCSG-6 & 8 n=1702 The EPclin score is able to predict favourable prognosis in a majority of patients that clinical guidelines would assign to intermediate or high risk. EPclin may reduce the indications for chemotherapy in ER-positive postmenopausal women with a limited number of clinical risk factors.	https://www.sciencedirect.com/science/article/pii/S0923753419371200	2013

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
3	RCT GEICAM 9906 a phase III RCT comparing two adjuvant chemotherapy regimens – four 21-day cycles of FEC followed by eight weekly courses of paclitaxel (FEC-P) vs six 21-day cycles of 5-fluorouracil, epirubicin and cyclophosphamide (FEC) experimental arm), and then followed by 5-year hormonal therapy – in 1246 women with lymph node positive disease, Prospective-retrospective design	Martin et al., Clinical validation of the EndoPredict test in node positive, chemotherapy treated ER+/HER2 breast cancer patients: results from the GEICAM 9906 trial	N=555 EP is an independent prognostic parameter in node-positive, ER+/HER2– BC patients treated with adjuvant chemotherapy followed by hormone therapy. EP did not predict a greater efficacy of FEC-P compared to FEC alone.	https://breast-cancer-research.biomedcentral.com/articles/10.1186/bcr3642	2014

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
4	Comparator to other GEPs RCT Arimidex, Tamoxifen, Alone or in Combination trial (ATAC) an RCT evaluated efficacy and safety of anastrozole vs tamoxifen given for five years in post-menopausal women with localised primary breast cancer TransATAC the translational substudy of the ATAC served as a validation study prospective-retrospective design	Sestak et al., Comparison of the Performance of 6 Prognostic Signatures for Estrogen Receptor–Positive Breast Cancer A Secondary Analysis of a Randomized Clinical Trial	Retrospective biomarker analysis of 774 postmenopausal women with ER-positive HER2 negative breast cancer. The signatures included the Oncotype Dx recurrence score, PAM50-based Prosigna risk of recurrence (ROR), Breast Cancer Index (BCI), EndoPredict (EPclin), Clinical Treatment Score, and 4-marker immunohistochemical score. Prognostic value was compared.	https://pubmed.ncbi.nlm.nih.gov/29450494/	2018
5	Comparative multicohort non-randomised analysis	Sestak et al., Prediction of chemotherapy benefit by EndoPredict in patients with breast cancer who received adjuvant endocrine therapy plus chemotherapy or endocrine therapy alone	N=3746 2630 patients received 5 years of ET alone (ABCSG-6/8, TransATAC) and 1116 patients received ET + C (GEICAM 2003-02/9906). The primary objective was to evaluate the ability of EPclin to provide an estimate of the 10-year DR rate as a continuous function of EPclin separately for ET alone and ET + C.	https://pubmed.ncbi.nlm.nih.gov/31041683/	2019

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
6	Follow up of DR free rate of the ABCSG 6 & 8 after 10 and 15yrs Prospective-retrospective design	Filipits et al., Prediction of Distant Recurrence using EndoPredict among Women with ER+, HER2-Node Positive and Node Negative Breast Cancer Treated with Endocrine Therapy Only	EndoPredict (EP; molecular score, EPclin score) was evaluated in women with ER-positive, HER2-negative node-positive and node-negative breast cancer who received 5 years of endocrine therapy only (median follow-up, 9.6 years; N = 1,702). Distant recurrence-free rate (DRFR; 95% confidence interval) was assessed 10 and 15 years after diagnosis.	https://clincancerres.aacrjournals.org/content/25/13/3865	2019

17. Identify <u>yet-to-be-published</u> research that may have results available in the near future (that could be relevant to your application). Do not attach full text articles; this is just a summary.

	Type of study design	Title of research (including any trial identifier if relevant)	Short description of research	Website link to research	Date
1	Clinical Utility Study Australia	Impact of the EndoPredict Genomic Assay on Treatment Decisions for ER Positive Early Breast cancer Patients: Benefits of Selective Physician Testing (PI: Dr. Nirmala Pathmanathan, Westmead Breast Cancer Institute) ACTRN12618001284257	This study evaluated the clinical utility of EndoPredict, and its impact on adjuvant therapy recommendations in patients with breast cancer in Australia. The significant impact of the test result on the treatment decision in patients who were selectively recruited based on clinical team discretion undersored the value of EndoPredict.	https://link.springer.com/article/10.1007/s10549-021-06456-5	2022

	Type of study design	Title of research (including any trial identifier if relevant)	Short description of research	Website link to research	Date
2	Prospective observational care research study	Reaching for Evidence-based Chemotherapy Use in Endocrine Sensitive Breast Cancer (RESCUE) NCT03503799 PI: Marion Kiechle, Technical University Munich, Germany)	Prospective assessment of the clinical outcome (distant metastasis-free survival) of patients with primary breast cancer who have been tested with EndoPredict; ER+/HER2- early-stage BC, N0-N1, T1-T3 (N=1191).		First results with 5 years follow-up expected 2026
3	Prospective randomized phase III study	Safety Study of Adding Everolimus to Adjuvant Hormone Therapy in Women With High Risk of Relapse, ER+ and HER2- Primary Breast Cancer, Free of Disease After Receiving at Least One Year of Adjuvant Hormone Therapy (UNIRAD) NCT01805271 PI: Thomas Bachelot, Centre Leon Berard, Lyon, France; Fabrice Andre, Gustave Roussy, Villejuif, France	Prospective assessment of disease-free and metastasis-free survival according to EndoPredict risk class and the ability to predict benefit from everolimus ER+/HER2-, early-stage BC, N1, Any T (N=767)		First results with 5 years follow-up presented at SABCS Dec 2021 Publication expected 2022

	Type of study design	Title of research (including any trial identifier if relevant)	Short description of research	Website link to research	Date
4	Retrospective cohort study	Clinical validation of EndoPredict® in pre-menopausal patients with estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-) primary breast cancer who received endocrine therapy only. PI: Anastasia Constantinidou, Bank of Cyprus Oncology Centre, Nicosia, Cypru	This clinical validation study showed that EPclin score is highly associated with DRFS in pre-menopausal women who received adjuvant endocrine therapy alone. Patients with a low risk EPclin classification had such a low risk of recurrence that they may safely forgo adjuvant chemotherapy. ER+/HER2- N0-N1, T1-T3 (N=385).	https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.537	Presented at ASCO 2021; publication expected in 2022
5	Prospective-retrospective real-life registry	Retrospective evaluation of prospective EndoPredict Assays for assessment of prognosis in luminal breast cancer – correlation with clinical parameters and outcome (Charité Registry) PI: Carsten Denkert, University of Marburg, Germany	Retrospective assessment of distant recurrence-free survival of patients prospectively tested with EndoPredict in a real-world setting in a German lab from 2011-2016; HR+, HER2-, N0/N+ (N=1726)		Expected publication end 2022

	Type of study design	Title of research (including any trial identifier if relevant)	Short description of research	Website link to research	Date
6	Prospective real-life registry	SiMoSein, a real -life prospective evaluation of EndoPredict use in early ER positive, HER2-ve breast Cancers PI: Jaqueline Lehmann-Che, St. Louis Hospital, Paris, France; Frederique Penault-Llorca, Jean Perrin Center, Clermont-Ferrand, France	This French National Registry, SiMoSein, includes 4,766 patients from 14 laboratories tested in a real-life setting with EndoPredict from 2016-2019. Patients are monitored and survival by EndoPredict risk class will be evaluated; HR+, HER2-, N0/N+ (N=4766).		First results with 5 years follow-up expected 2022

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

18. **List all appropriate professional bodies/organisations representing the health professionals who provide the service. For <u>MBS-related applications</u> ONLY, please attach a brief 'Statement of Clinical Relevance' from the most relevant college/society.**

    RCPA: The Royal College of Pathologists of Australasia

    MOGA: The Medical Oncology Group of Australia

    Breast Surgeons of Australia and New Zealand

    ASBD: Australian Society for Breast Disease

    A 'Statement of Clinical Relevance' is not required taking into consideration RCPA hosted the Stakeholder Meeting on 21stJune to 'break the stalemate'

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

    No medical services are impacted by this service

20. **List the consumer organisations relevant to the proposed medical service (noting there is <u>NO NEED</u> to attach a support letter at the 'Application Lodgement' stage of the MSAC process):**

    BCNA: Breast Cancer Network Australia

    Cancer Australia

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

    Exact Sciences

    Agendia

    Veracyte

22. **Nominate two experts that can be contacted about the proposed medical service, and current clinical management of the condition:**

    Name of expert 1: **REDACTED**

    Telephone number(s): **REDACTED**

    Email address: **REDACTED**

    Justification of expertise: **REDACTED**

    Name of expert 2: **REDACTED**

    Telephone number(s): **REDACTED**

    Email address: **REDACTED**

    Justification of expertise: **REDACTED**

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

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

23. **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 the most common cancer in females where therapy is based on subtypes. The most predominant subtype (65%) is ER+/HER-, which falls in the intermediate risk group where treatment is not well defined. While many patients require chemotherapy, the majority of these patients could be sufficiently treated with anti-hormonal therapy alone, which has fewer side effects.

EndoPredict® reliably determines early and late risk of recurrence in these patient subtypes. By understanding a patient's prognosis, this valuable information can be used to select appropriate therapy without jeopardizing the overall treatment success. Many patients can be spared unnecessary toxic chemotherapy and at times the associated debilitating side effects. EndoPredict® is a useful tool to help patients and clinicians guiding

treatment decisions for chemotherapy as well as extended anti-hormonal therapy.

EndoPredict® is a 2nd generation test which combines the molecular biology of the tumour with the two classical clinical markers tumour size and nodal status. The results provide a clear unambiguous prognosis of high or low risk and it can be performed in local pathology laboratories under Australian regulatory standards.

EndopPredict® is available globally. Recent studies have showed that using EndoPredict® reduces chemotherapy usage and overall associated treatment costs in primary breast cancer patients. EndoPredict® is available on the private market only to those with the ability to pay for it; the test cost can be out of reach for many. A Medicare rebate will provide access to EndoPredict® in an equitable manner for all Australian eligible patients diagnosed with breast cancer. Better access to this valuable test will result in improved treatment allocation benefiting both the patient's wellbeing and our healthcare system.

24. **Specify the characteristics of patients with (or suspected of having) the medical condition, who would be eligible for the proposed medical service/technology (including details on how a patient would be investigated, managed and referred within the Australian health care system, in the lead up to being eligible for the service):**

The characteristics of the patients eligible for the service are pre- or post- menopausal women with primary breast cancer who have had no prior adjuvant treatment and have been assessed by an oncologist as suitable for adjuvant chemotherapy.

Additional criteria are:

- ER+ (either PgR+ or PgR–) determined by immunohistochemistry (IHC)[1]
- HER2– (either Luminal A or B type) determined by in situ hybridisation [ISH])[2]
- have an operable T1, T2, or T3 tumour, with or without lymph node (N+ or N0) involvement (up to three nodes)

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[1] IHC involves examination of the cells under microscope after application of a stain. The stain shows how many cells have hormone receptors and the amount of hormone receptors in the cells.
[2] ISH involves a probe that specifically binds to the HER2 gene.

- are assessed as having a pre-test *intermediate clinical risk* of distant metastases based on postsurgical pathological examination of the tumour tissue, which requires at least one of the following characteristics:
  - tumour size > 2 cm
  - tumour grade 2/3
  - one to three lymph nodes involved in metastatic disease (including micrometastases but excluding isolated tumour cells).

Patients assessed to be at *low clinical risk* of distant metastases and those at *high clinical risk* of distant metastases are not eligible for the proposed service as treatment decisions for these patients do not require additional guidance.

PART 6b – INFORMATION ABOUT THE INTERVENTION

25. Describe the key components and clinical steps involved in delivering the proposed medical service/technology:

Patients with primary breast cancer diagnosed by core needle biopsy are assessed for surgical removal of the tumour. After surgery, a pathologist will determine ER and HER2 status, assess tumour size and nodal status, and report the histological results to the treating oncologist. The oncologist (sometimes in consultation with a multidisciplinary team [MDT]), will decide whether the tumour is considered at low, intermediate, or high clinical risk of distant recurrence, and, after consultation with the patient, make a treatment decision.

Patients with ER+, HER2– cancer who are assessed to be at intermediate risk of distant metastases and suitable for adjuvant chemotherapy, will have the EndoPredict® test requested from pathology. Here, a 10 μm section of the routine formalin-fixed paraffin-embedded (FFPE) is used to prepare RNA for RT-qPCR using the EndoPredict Kit reagents. The prepared tissue sample along with quality control samples are run on the RT-qPCR instrumentation to produce data which are exported into the reporter software. Combined with additional clinical information, the reporter software uses an algorithm to generate the EPclin risk assessment score, which predicts the risk of distant recurrence within 10 years (on a continuous scale). Using the EPclin score, the patient is categorised as being at high or low risk of distant recurrence, which may be used by the oncologist and patient to guide treatment decisions.

Patients who fall into the low risk category according to the EndoPredict tool would be offered ET alone (short or extended term), whereas those in the high risk category would be offered chemotherapy plus ET.

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

The test is registered with the Registered/Protected trademarks

AUS: 1672186 filed February 3, 2015, registered February 5, 2016

EU: 009612409 filed December 20, 2010; registered April 29, 2011

US: 85520009 filed 1/2012; registered January 5, 2016

27. 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?

Not applicable

28. 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 test is a once off test only relevant to primary breast cancer, not recurrence.

29. **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:**

Archival block retreival via pathology networks

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

Oncologist

Pathologist

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

Possibly a surgeon, as this is typically the patients first specialist in contact.

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

The proposed service should be restricted to a qualified and accredited oncologist, surgeon and/or pathologist.

33. **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:**

Laboratory training is required to perform the test (which is typically a one-off fee service), along with NATA accreditation.

34. **(a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select <u>ALL</u> relevant settings):**

- ☒ Inpatient private hospital (admitted patient)
- ☒ Inpatient public hospital (admitted patient)
- ☒ Private outpatient clinic
- ☒ Public outpatient clinic
- ☐ Emergency Department
- ☐ Private consulting rooms - GP
- ☒ Private consulting rooms – specialist
- ☐ Private consulting rooms – other health practitioner (nurse or allied health)
- ☐ Private day surgery clinic (admitted patient)
- ☐ Private day surgery clinic (non-admitted patient)
- ☐ Public day surgery clinic (admitted patient)
- ☐ Public day surgery clinic (non-admitted patient)
- ☐ 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:

Inpatient/outpatient/specialist: The service is being recommended for primary breast cancer patients and could be offered in a public or private hospital setting following surgery or biopsy, or when the patient attends a hospital outpatient service or consulting room.

Laboratory: The test can be conducted in local public or private pathology laboratories if they have the appropriate equipment and training.

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

- ☒ Yes
- ☐ No – please specify below

36. **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 <u>Australian health care system</u>). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service):**

    Three sets of comparators are described in the ratified PICO Confirmation.
    1. Main comparator (base case): Current standard of care (SOC) clinical practice based on IHC/ISH analysis of tumour tissue (ER+, HER2– status) and including Ki67 status and tumour grade and utilising a 5 Australian public hospital Multi-Disciplinary Teams
    2. Secondary comparator: International breast cancer clinical guidelines such as St Gallen, NCCN, ESMO, and the German S3 guidelines.
    3. Secondary comparator: Other prognostic tests

    The service is not expected to change current adjuvant treatment options or treatment algorithms. However, women currently classified as intermediate risk of distant recurrence based on clinical assessment and treated with chemotherapy may be classified as low risk under the new service; therefore, would receive ET alone and avoid the risks and side effects of chemotherapy. Conversely, women currently classified as intermediate risk of distant recurrence and not treated with chemotherapy may be classified as high risk under the new service, thus avoiding a potential distant recurrence. Patients who receive the same treatment following risk classification with EndoPredict as they did with current clinical practice alone will not be affected by the new service.

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

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

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

    ☒ In addition to (i.e. it is an add-on service)
    ☐ Instead of (i.e. it is a replacement or alternative)

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

    In patients with ER+/HER2– cancer who are assessed to be at intermediate risk of distant metastases and considered suitable for adjuvant chemotherapy, would be offered the GEP test requested from pathology.

    The results will be used by the oncologist and patient to guide treatment decisions.

*PART 6c CONTINUED – INFORMATION ABOUT ALGORITHMS (CLINICAL MANAGEMENT PATHWAYS)s*

39. **Define and summarise the CURRENT clinical management pathway (algorithm) that patients follow when they receive the COMPARATOR service (i.e. the landscape <u>before</u> the proposed service is introduced). An easy-to-follow flowchart is preferred, depicting the current <u>clinical management pathway</u>), but dot-points would be acceptable. Please include health care resources used in the current landscape (e.g. pharmaceuticals, diagnostics and investigative services, etc.).**

    Clinical management algorithm (current clinical practice OR international guidelines) for patients who have ER+/HER2– primary breast cancer
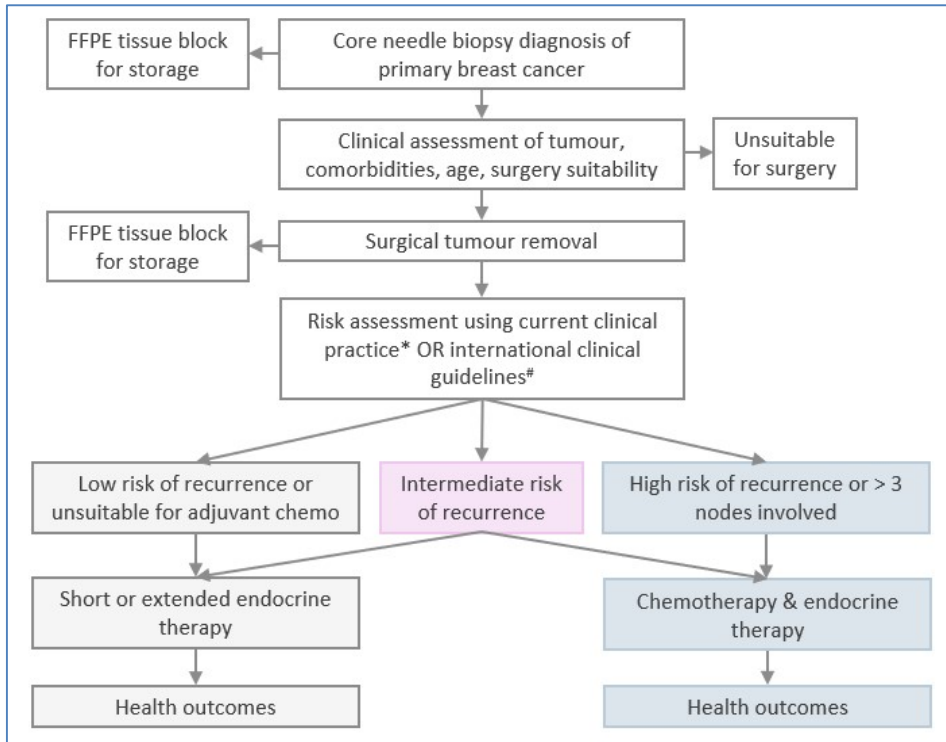
40. Define and summarise the PROPOSED clinical management pathway (algorithm) that patients would follow after the proposed service/technology is introduced, including variation in health care resources.

Clinical management algorithm with the proposed medical service for patients who have ER+/HER2– primary breast cancer
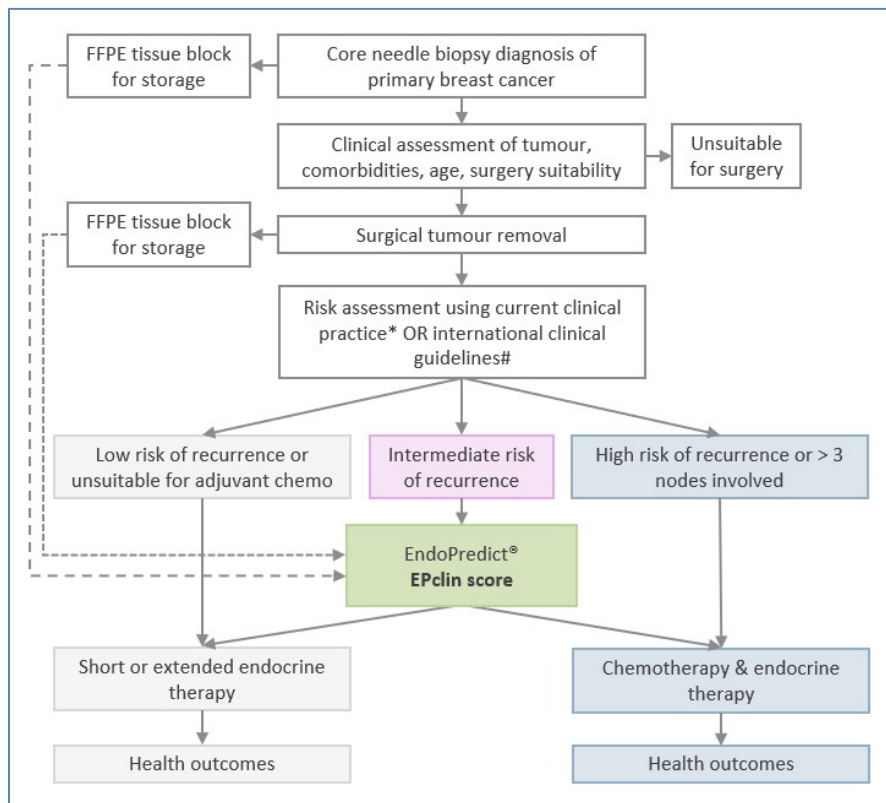
PART 6d – INFORMATION ABOUT CLINICAL OUTCOMES

41. **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 EndoPredict test is an in vitro diagnostic product for determining the risk of distant recurrence in patients with estrogen-receptor-positive, HER2–negative primary breast cancer treated exclusively with adjuvant ET.

EndoPredict improves the targeted use of systemic therapy in patients with ER+/HER2– breast cancer who have been assessed to be at intermediate clinical risk of distant recurrence. Currently, optimal treatment for patients in this group is regarded as the most difficult to determine, resulting in variable treatment decisions and outcomes between centres. Although chemotherapy can reduce the likelihood of cancer recurrence and death for women with breast cancer, it has considerable adverse effects and reduces quality of life. Improved information on a patient's risk of recurrence (i.e. prognostic risk) and/or likely response to chemotherapy (i.e. predictive benefit) may help target chemotherapy to those patients who will benefit the most.

Ultimately, EndoPredict is expected to influence the proportions of patients receiving ET alone and those receiving endocrine with adjuvant chemotherapy by providing better guidance for treatment decisions. Unnecessary chemotherapy can be reduced without negatively affecting the quality of treatment and more precise diagnostics can reduce the risk of undertreatment, thereby facilitating more effective patient treatment than current clinical practice.

42. **Please state what the overall clinical claim is:**

The clinical claim is that in women with ER+, HER2– breast cancer at intermediate clinical risk of developing metastatic breast cancer, the EndoPredict test and validated EPclin score has non-inferior safety and superior effectiveness compared with the main comparator – current SOC clinical practice.

EndoPredict demonstrates incremental prognostic value over current SOC clinical practice.

43. **List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):**

Primary Outcomes:

1. No distant/local recurrence
2. Distant/local recurrence
3. Chemotherapy

Secondary Outcomes:

Toxicity
Febrile neutropenia
Severe (grade3-5) cardiotoxicity
Leukemic/myelodysplastic syndrome
Severe (grade 3-5) neurotoxicity
Venous thromboembolic events

Metastatic state

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

44. Estimate the prevalence and/or incidence of the condition in the proposed population:

	Description	Source	2021	2022	2023	2024
A	Projected incidence in 2019: 19371*	AIHW 19371				
B	Projected incidence of breast cancer *	A x 3.25%	20643	21309	21998	22708
C	Early breast cancer	B x 80%	16,514	17,048	17,598	18,167
D	eBR HR+	C x 67%	11,064	11,422	11,791	12,172
E	eBR HR+ve Her2-ve	D x 80%	8,852	9,137	9,433	9,737
F	Suitable for adjuvant therapy	E x 75%	6,639	6,853	7,074	7,303
G	Intermediate clinical risk of metastases (eligible population)	F x 80%	5,311	5,482	5,660	5,842

Source: EndoPredict® for ER+ve, HER2-ve breast cancer – MSAC SBA 1408', pg. 140

*Row B in Table E-2 of MSAC SBA 1408, projected incidence of breast cancer 3.25%

45. Estimate the number of times the proposed medical service/technology would be delivered to a patient per year:

The test may be used once per new primary breast cancer diagnosis

46. How many years would the proposed medical service/technology be required for the patient?

The service would be expected to be delivered once per primary cancer diagnosis per patient at the point of primary tumour analysis. In the instance where primary breast cancer is detected a second or additional time (in either breast), the test cannot be requested anymore. Therefore, the service would be requested only once in a patient's lifetime.

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

	Description	Source	2022
A	Uptake rate	Assumption	60%
B	Number of MBS services	Row G in above table from question 44 x A	3289

Source: EndoPredict® for ER+ve, HER2-ve breast cancer – MSAC SBA 1408', pg. 141

48. **Estimate the anticipated uptake of the proposed medical service/technology 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.**

	Description	Source	2022	2023	2024
A	Uptake rate	Assumption	60%	70%	80%
B	Number of MBS services	Row G in above table from question 44 x A	3289	3962	4674

PART 8 – COST INFORMATION

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

REDACTED

50. Specify how long the proposed medical service/technology typically takes to perform:

Turnaround time of eight hours when performed in Australia

51. If public funding is sought through the <u>MBS</u>, please draft a proposed MBS item descriptor to define the population and usage characteristics that defines eligibility for the medical service/technology.

Category PATHOLOGY SERVICES – Group P7 – GENETICS
Proposed item descriptor: A gene expression profiling test that demonstrates statistically significant incremental prognostic value of multivariant clinical features. Clinically validated gene expression profiling of FFPE, core needle biopsy or surgical tumour sample in primary breast cancer tissue. The test may be used when all the following criteria are met: • New primary breast cancer, suitable for adjuvant chemotherapy, and not requiring neoadjuvant chemotherapy   • Oestrogen positive and HER2 negative as determined by IHC and ISH respectively on surgically removed tumour   • Node negative or positive (up to 3 nodes) and tumour size determined by histopathology on surgically removed tumour   • Pre-test intermediate clinical risk of distant metastases defined by at least one of the following characteristics: tumour size ≥ 2cm; or Grade 2; or Grade 3; or one to three lymph nodes involved in metastatic disease (nodes include micrometastases but not isolated tumour cells)   Laboratory pathologist can determine if required as a reflex test when criteria is met.   The test may be used once per new primary breast cancer diagnosis.   Fee: To be determined   Agreed price to volume fee, pricing is reduced annually based on volume achieved the previous year

52. If public funding is sought through an <u>alternative (non-MBS) funding arrangement</u>, please draft a service description to define the population and usage characteristics that defines eligibility for the service/technology.

Not applicable