Australian Government

Department of Health

Application Form

(New and Amended Requests for Public Funding)

(Version 2.5)

50 gene signature assay for predicting breast cancer recurrence

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.

The application form will be disseminated to professional bodies / organisations and consumer organisations that have been identified in Part 5, and any additional groups that the Department deem should be consulted with. The application form, with relevant material can be redacted if requested by the Applicant.

Should you require any further assistance, departmental staff are available through 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): NA
Corporation name: REDACTED
ABN: NA
Business trading name: REDACTED

Primary contact name: REDACTED

Primary contact numbers
Business: REDACTED
Mobile:
Email: REDACTED

Alternative contact name: REDACTED

Alternative contact numbers
Business:
Mobile: REDACTED
Email: REDACTED

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

☒ Yes
☐ No

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

NanoString Technologies, Inc.

3. (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

NA

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

4. Application title

50 gene signature assay for predicting breast cancer recurrence

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)

Prosigna® is a 50-gene test that is designed to identify intrinsic breast cancer subtypes and to generate a Risk of Recurrence (ROR) score. This is then used to tailor the most appropriate therapy for that type of primary breast cancer. It will be used for women with HER2 –ve, ER and/or PR +ve breast cancer who do not have clear cut treatment choices.

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)

The assay provides a 50 gene profile that is used to assess the prognosis and predict response to treatment of breast cancer patients. The Risk of Recurrence (ROR) score is based on the identification of the four intrinsic breast cancer subtypes, Luminal A, Luminal B, HER2-enriched, and Basal-like. The unique genetic profile is produced using a diagnostic kit which quantifies mRNA expression and can be performed in local laboratories provided they have the NanoString nCounter® Dx technology (Prosigna enabled).

7. (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:

NA

(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):

NA

(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

If yes, please advise:

NA

8. 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

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
vi. ☐ Is for genetic testing for heritable mutations in clinically affected individuals and, when also appropriate, in family members of those individuals who test positive for one or more relevant mutations (and thus for which the Clinical Utility Card proforma might apply)

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?

☐ Yes
☐ No

NA

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

NA

(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

NA

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

Trade name: Insert trade name here
Generic name: Insert generic name here

NA

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

☐ Yes
☐ No

NA

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

Billing code(s): Insert billing code(s) here
Trade name of prostheses: Insert trade name here
Clinical name of prostheses: Insert clinical name here
Other device components delivered as part of the service: Insert description of device components here

NA

(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

NA

(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

NA

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

NA

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

Single use consumables (consumables per test):

- Prosigna code set
- Preparation plates
- Cartridges
- Preparation pack

Multi-use consumables: NA

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

14. (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: Acquired genetic alteration IVD
Manufacturer's name: NanoString Technologies, Inc.
Sponsor's name: Bio-Strategy Pty Ltd

(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

15. (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

ARTG listing, registration or inclusion number: 226487
TGA approved indication(s), if applicable: NA
TGA approved purpose(s), if applicable: NA

16. 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
NA

Date of submission to TGA: NA
Estimated date by which TGA approval can be expected: NA
TGA Application ID: NA
TGA approved indication(s), if applicable: NA
TGA approved purpose(s), if applicable: NA

17. 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
NA – see 15(b) above.

Estimated date of submission to TGA: NA
Proposed indication(s), if applicable: NA
Proposed purpose(s), if applicable: NA

PART 4 – SUMMARY OF EVIDENCE

18. **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.***

Table 1 Key journal articles relevant to the proposed service

	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.	Retrospective cohort study Prognostic level III-3	Supervised risk predictor of breast cancer based on intrinsic subtypes Parker et al	Population: frozen and formalin fixed tissue samples from a number of different breast cancer cohorts (HER2 +ve or –ve, ER or PR +ve or –ve, Node +ve or –ve) Purpose: Development of a clinical genetic test to diagnose tumour subtype, and a score which reflects the risk of distant tumour recurrence. Development of prognostic and predictive models for risk according to subtype and score. Results: Intrinsic subtypes showed prognostic significance ($p = 2.26^{E-12}$) and remained significant in multivariate analyses (ER status, histologic grade, tumour size, node status). The intrinsic subtype model predicted neoadjuvant chemotherapy efficacy with a negative predictive value for pathologic complete response of 97%.	http://jco.ascopubs.org/content/27/8/1160.long	March 2009

	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***
2.	Retrospective cohort study Prognostic level III-3	Comparison of PAM50 risk of recurrence score with Oncotype DX and IHC4 for predicting risk of distant recurrence after endocrine therapy Dowsett et al ATAC trial: ISRCTN18233230	Population: mRNA from 1,017 patients in the ATAC trial (post-menopausal, ER +ve primary breast cancer treated with anastrozole or tamoxifen) Purpose: prognostic assessment using PAM50 compared with Oncotype DX (risk score, RS), clinical treatment score (CTS), and IHC4 Results: PAM50 risk of recurrence (ROR) score provided more prognostic information than RS in endocrine-treated node -ve, and more information (measured by c index) than RS and CTS in node +/-ve patients. ROR and IHC4 provided similar prognostic information except more was added (greater c index) by ROR in the HER2 -ve / node -ve group.	http://jco.ascopubs.org/content/early/2013/06/25/JCO.2012.46.1558.abstract	July 2013
3.	Analysis of prognostic factors amongst persons in a randomised controlled trial Prognostic level III-2	Predicting distant recurrence in receptor-positive breast cancer patients with limited clinico-pathological risk: using the PAM50 Risk of Recurrence score in 1478 postmenopausal patients of the ABCSG-8 trial treated with adjuvant endocrine therapy alone Gnant et al ABCSG-8: NCT00291759	Population: formalin fixed paraffin-embedded (FFPE) samples from 1,478 post-menopausal women with ER +ve early breast cancer treated with tamoxifen or tamoxifen/anastrozole from the ABCSG-8 trial. Purpose: to compare ROR prediction against other tools/scoring approaches, including use of standard clinical factors, to determine prognostic value and ability to predict distant recurrence at 10 years. Results: ROR added significant prognostic information when added to a clinical linear predictor ($p < 0.0001$) and when predicting 10 year distant recurrence free survival.	http://prosigna.com/x-us/downloads/publications/	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***
4.	Retrospective cohort study Prognostic level III-3	A 50-Gene Intrinsic Subtype Classifier for Prognosis and Prediction of Benefit from Adjuvant Tamoxifen Chia et al	Population: FFPE samples from premenopausal primary breast cancer, stage I to III, ER +ve or –ve, node +/-ve Purpose: to evaluate prognostic and predictive significance of intrinsic subtypes identified by PAM50 compared to an IHC panel Results: PAM50 subtype was prognostic for disease-free survival (p = 0.0003) and overall survival (p = 0.0002), whereas the IHC panel was not. Luminal subtypes were predictive of a non-significant tamoxifen benefit. The trend was the same irrespective of hormone status.	http://prosigna.com/x-us/downloads/publications/	2012
5.	Retrospective cohort study Prognostic level III-3	Molecular subtype and tumor characteristics of breast cancer metastases as assessed by gene expression significantly influence patient post-relapse survival Tobin et al TEX trial: NCT01433614	Population: Fine needle aspirates from 149 patients with distant breast cancer relapse, ER +ve or –ve, who were enrolled in the TEX trial Purpose: To determine whether tumour characteristics and PAM50 subtypes in breast cancer confer clinically relevant prognostic information Results: Subtyping provided statistically significant post-relapse survival information (basal-like HR 3.7 [95% CI 1.3–10.9] and HER2-enriched HR 4.4 [95% CI 1.5–12.8] subtypes compared with the luminal A subtype).	https://www.clinicaltrials.gov/ct2/show/nct01433614 https://www.clinicaltrials.gov/ct2/bye/rQoPWwoRrXS9-i-wudNgpQDxudhWudNzlXNiZip9Ei7ym67VZR08Fg0jxK4jA6h9Ei4L3BUgWwNG0it	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***
6.	Analysis of prognostic factors amongst persons in a randomised controlled trial Prognostic level III-2	PAM50 breast cancer intrinsic subtypes and effect of gemcitabine in advanced breast cancer patients Jorgenson et al DBCG trial	Population: 270 FFPE samples from the DBCG trial Purpose: to evaluate whether the basal-like subtype identifies patients with advanced breast cancer who would benefit from gemcitabine plus docetaxel compared to docetaxel alone Results: Intrinsic subtypes were associated with time-to-progression (TTP, $p = 0.0006$) and overall survival (OS, $p<0.0083$). Response rate (complete plus partial response) did not differ significantly among subtypes, nor between basal and non-basal like types. For predictivity – PAM50 subtypes were not significantly different for TTP but for OS was significant. Basal-like type had an improved OS associated with gemcitabine plus docetaxel ($P_{interaction} = 0.0016$). PAM50 subtype analysis - according to triple negative HER2 and ER status - showed no difference in treatment effect.	http://www.tandfonline.com/doi/full/10.3109/0284186X.2013.865076	2014
7.	Analysis of prognostic factors amongst persons in a randomised controlled trial Prognostic level III-2	Prediction of Late Distant Recurrence After 5 Years of Endocrine Treatment: A Combined Analysis of Patients From the Austrian Breast and Colorectal Cancer Study Group 8 and Arimidex, Tamoxifen Alone or in Combination Randomized Trials Using the PAM50 Risk of Recurrence score. Sestak et al ATAC trial: NCT00849030 ABCSG-8: NCT00291759	Population: 2,137 FFPE samples from the ATAC and ABCSG-8 trials from post-menopausal women with ER/PR +ve who did not have recurrence after 5 years of endocrine treatment Purpose: to assess the PAM50 ROR score for predicting distant recurrence after 5 years follow-up Results: CTS added more prognostic information for distant recurrence 5 years after diagnosis than the ROR score in the overall population (univariable: LR $\chi^2 = 94.12$) and when added to ROR score (bivariable: LR $\chi^2 = 61.43$). Agreement between ROR and CTS was weak ($r = 0.36$)	http://prosigna.com/x-us/downloads/publications/	2015

	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.	Before and after case-series Interventional level IV	Prognostic ability of EndoPredict compared to research-based versions of the PAM50 risk of recurrence (ROR) scores in node-positive, estrogen receptor-positive, and HER2-negative breast cancer. A GEICAM/9906 sub-study Martin et al GEICAM trial: NCT00129922	Population: 217 patients with post-menopausal, ER +ve, HER2 – ve, node -ve, stage 1 or 2 tumours (GEICAM trial patients) Purpose: to determine the influence of the Prosigna gene expression profile on physician adjuvant treatment selection for early breast cancer and treatment optimisation recommendations in clinical practice Results: treatment recommendations changed in 20% of patients following the gene expression profile result	http://www.tandfonline.com/doi/full/10.1185/03007995.2015.1037730	2015
9.	Analysis of prognostic factors amongst persons in a randomised controlled trial Prognostic level III-2	Responsiveness of intrinsic subtypes to adjuvant anthracycline substitution in the NCIC.CTG MA.5 randomized trial Cheang et al	Population: FFPE samples from premenopausal node +ve breast cancer patients (NCIC.CTG MA.5 trial) Purpose: to determine the association of qPCR PAM50 intrinsic subtypes with recurrence free survival (RFS) and OS; to determine the significance of the interaction between treatment (CMF versus CEF) and subtypes. Results: In the combined cohort treated with either CMF or CEF, subtypes were associated with RFS ($p = 0.0005$) and OS ($p = 0.0001$). The HER2 enriched subtype strongly predicted anthracycline (CEF) sensitivity, whereas for basal-like tumours there was no difference in benefit between CEF and CMF.	http://prosigna.com/x-us/downloads/publications/	2012

	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.	Retrospective cohort study Prognostic level III-3	Prediction of Response to Neoadjuvant Chemotherapy Using Core Needle Biopsy Samples with the Prosigna Assay Pratt et al	Population: 122 FFPE samples of core needle biopsy tissue from newly diagnosed breast cancer patients, and 216 samples from a Spanish HR +ve / HER2 –ve cohort bank. Purpose: to evaluate the performance of Prosigna on core needle biopsy tissue compared to surgical resection specimens; and determine whether Prosigna ROR score and intrinsic subtype could predict response to neoadjuvant chemotherapy Results: Correlation in ROR score between needle biopsy and surgical resection samples was high ($r \geq 0.90$) and 4- and 3-subtype classifications (kappa = 0.81 and 0.91 respectively). Both ROR ($p = 0.047$) and subtype (OR LumA versus non-LumA = 0.341, $p = 0.037$) were significant predictors of response to neoadjuvant chemotherapy.	http://prosigna.com/x-us/downloads/publications/	2015
15	Analysis of prognostic factors amongst persons in a randomised controlled trial Prognostic level III-2	Defining breast cancer intrinsic subtypes by quantitative receptor expression Cheang et al	Population: Data and FFPE samples of 1,557 patients from 3 trials – GEICAM/, NCIC CTG MA.5 and NCIC CTG MA.12 Purpose: to compare centrally performed clinical assays of ER, PR and HER2 expression with PAM50 intrinsic subtypes, a centroid based 50-gene prediction algorithm Results: There was significant discordance between clinical assay defined subsets and Prosigna intrinsic subtype.	http://theoncologist.alphamedpress.org/content/20/5/474.long	2015

ABCSG-8 = Austrian Breast and Colorectal Cancer Study Group 8; ATAC = Arimidex, Tamoxifen Alone or in Combination trial; c index = comparison of concordance index; CEF = cyclophosphamide, epirubicin and fluorouracil; CMF = cyclophosphamide, methotrexate and fluorouracil; CTS = clinical treatment score based on nodal status, tumour size, histopathologic grade, age and anastrozole or tamoxifen treatment; DBCG = Danish Breast Cancer Cooperative Group trial; DRFS = distant recurrence free survival; ER = estrogen receptor; FFPE = formalin fixed paraffin embedded; GEICAM = Grupo Espanol para la Investiacion del Cancer de Mama; GEP = gene expression profile; HER2 = human epidermal growth factor receptor 2; IHC4 = an

index of distant recurrence risk derived from immunohistochemical testing of oestrogen receptor, dprogesterone receptor, human epidermal growth factor receptor 2 and Ki67; N +/- = node positive or negative; mRNA = messenger ribonucleic acid; NCIC.CTG MA5 and MA12= National Cancer Institute of Canada Clinical Trials Group MA5 and MA12 trials; NPV = negative predictive value; OR = odds ratio; OS = overall survival; ROR = risk of recurrence score; PR = progesterone receptor; RS = Oncotype DX recurrence score;; TEX trial = first-line chemotherapy of epirubicin and paclitaxel alone or in combination with capecitabine; TTP = time to progression

** 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.*

19. **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.***

Table 2 Key trials relevant to the proposed service that have yet to publish evidence

	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.	Prospective cohort study Interventional level III-2	NCT02625935: Prospective Observational Study Evaluating Treatment Decision Impact of Prosigna® in Early Stage Breast Cancer Patients	Designed to examine whether Prosigna score influences physician and patients adjuvant treatment selection over currently used prognostic factors, in post-menopausal women with node –ve, ER +ve, HER2 –ve early stage breast cancer	https://clinicaltrials.gov/ct2/show/record/NCT02625935?term=Prosigna&rank=1	Estimated completion Dec 2016
2.	Prospective cohort study Interventional level III-2	NCT02395575: A Study of Clinical Outcomes for the NanoString® Technologies Prosigna™ Gene Signature Assay (prospective)	Designed to evaluate the impact of Prosigna on the therapeutic decision of adjuvant therapy in node –ve, ER +ve, HER2 –ve early stage breast cancer	https://clinicaltrials.gov/ct2/show/record/NCT02395575?term=Prosigna&rank=2	Estimated completion Dec 2016

	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***
3.	Evaluation of biomarkers Prognostic level IV	NCT02213042: Evaluation of Biomarkers Associated With Response to Subsequent Therapies in Subjects With HER2-Positive Metastatic Breast Cancer	To evaluate the changes in biomarkers associated with the HER family, immunomodulation, apoptosis, and Adenosine triphosphate binding cassette transporters between the pre-treatment and disease progression biopsy, in HER2 +ve metastatic breast cancer who received at least 2 prior lines of anti-HER2-targeted therapies including a Trastuzumab regimen	https://clinicaltrials.gov/ct2/show/record/NCT02213042?term=Prosigna&rank=6	Estimated completion Aug 2017
4.	Prospective cohort study Prognostic level II	NCT02400567: Efficacy of Letrozole + Palbociclib Combination as Neoadjuvant Treatment of Stage II-IIIA PAM 50 ROR-defined Low or Intermediate Risk Luminal Breast Cancer, in Postmenopausal Women (NeoPAL)	Outcomes include the determination of correlation of the PAM50 ROR score with prediction of residual cancer burden (RCB, 0-1 index) in neoadjuvant operable breast cancer	https://clinicaltrials.gov/ct2/show/record/NCT02400567?term=PAM50&rank=2	Estimated completion Dec 2018
5.	Analysis of prognostic factors amongst persons in a randomised controlled trial Prognostic level III-2	NCT01560663: Predictors of Response to Neoadjuvant Docetaxel-Carboplatin Chemotherapy for Patients With Stage II and III Triple Negative Breast Cancer	To identify predictors of response (defined as lack of invasive tumour in breast plus axilla) to docetaxel-carboplatin after neoadjuvant chemotherapy (PCR, pathological complete response), in patients with triple negative primary tumours	https://clinicaltrials.gov/ct2/show/NCT01560663?term=PAM50&rank=9	Estimated completion Mar 2017

** 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

20. 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):

Sonic Genetics

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

Royal College of Pathologists of Australasia

Clinical Oncology Society of Australia

Medical Oncology Group of Australia

22. 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 Australia (BCNA has agreed to provide a letter of support and this will be forwarded once it is received.)

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

Table 3 Similar products to the proposed service

Sponsor/manufacturer	Product
Genomic Health Inc. (US)	Oncotype DX
Sividon Diagnostics (GmbH), distributed by Myriad Genetics Australia Pty Ltd	EndoPredict®
Agendia	MammaPrint®

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

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

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

25. 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 type among women, representing 28% of all reported cancers in females in Australia (AIHW 2012). The incidence of breast cancer in Australia is increasing, and has risen from 5,303 new cases in 1982 to 14,181 new cases in 2010 (Cancer Australia 2015).

There are multiple classifications of breast cancer. The most important primary tumour markers in terms of prognosis and treatment have been considered recently to be the epidermal growth factor gene (HER2) and hormone receptor (HR) genes (oestrogen, ER; and progesterone, PR) (Coates et al. 2015; Rossi et al. 2015). Breast cancer guidelines recommend the categorisation of primary disease into the basic groups which constitute the four combinations of HER2 +ve or -ve and ER/PR +ve or –ve. The largest category is the HER2 –ve/ER +ve group, which makes up 65-70% of all breast cancer according to published evidence (Voduc et al. 2010; Wang-Lopez et al. 2015) (Table 4).

Table 4 Estimated breast cancer incidence for Australia (males and females)

Statistic	2012	2014	2016	2020
New cases	15,166[a]	15,270[b]	16,084[b]	17,210[c]
New ER +ve, HER2 -ve cases (assuming 65% of total)[d]	9857	9925	9972	11,187

[a] Australian Institute of Health and Welfare in 2016 (AIHW 2016)
[b](Cancer Australia 2016)
[c](AIHW 2012)
[d] Estimated from recent publications (Voduc et al. 2010; Wang-Lopez et al. 2015)

Another way of defining breast cancer is by intrinsic subtype categorisation – luminal A, luminal B, HER2 enriched and Basal-like. Luminal cell tumours which express low levels of Ki67 are called luminal A type and tend not to be responsive to chemotherapy. Those expressing high levels of Ki67 are called luminal B type tumours (Coates et al. 2015). There is some overlap of HER2+ve and -ve expression between luminal A and B groups. While most Luminal A type cancers will be HER2-ve, some will be HER2+ve. Some HER2-ve patients may fall into the luminal B type cancer group.

A further breakdown of breast cancer subgroups was reported by Voduc et al (2010) in a cohort of 2,985 primary tumours from breast cancer patients attending the British Columbia Cancer Agency. The 10-year local relapse-free survival (LRFS) data from those patients who had undergone surgical removal of the primary tumour (with negative surgical margins) and received adjuvant radiotherapy, but who did not have *in situ* or metastatic disease (no adjustment for age), are reported in Table 5.

Table 5 10-year LRFS after breast conserving surgery by subtype (Voduc et al, 2010)

Subtype	Patients N	Events N	10-year LRFS (%)	95% CI
Luminal A	587	55	92	90 to 95
Luminal B	295	27	90	86 to 94
Luminal-HER2	61	5	91	83 to 100

HER2 enriched	80	15	79	69 to 89
Basal-like	134	19	86	80 to 93
TNP-nonbasal	114	9	92	86 to 97

HER2 = human epidermal growth factor receptor 2; LRFS = local relapse-free survival; TNP = triple-negative phenotype

26. 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:

Patients with primary breast tumours of the subtype ER and/or PR +ve, HER2 -ve are often without clear-cut treatment options. Clinical factors and immunohistochemistry (IHC) test results may be predictive of risk of cancer recurrence for those at the low and high risk ends of the spectrum, but many patients fall into an intermediate risk group.

It is for this group that clinicians seek better information to direct treatment choices. Prosigna® would be offered to those patients who have been diagnosed with primary early invasive breast cancer classified as ER and/or PR +ve and HER2 -ve, that have undergone surgical tumour removal. Prosigna® can be conducted on tissue samples from formalin fixed paraffin embedded (FFPE) blocks used for tissue storage following tumour removal, or on fresh or frozen tissue.

Prosigna® would be used on samples from both pre and post-menopausal patients that are either node positive or negative.

27. 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):

In current clinical practice, patients suspected of having a breast tumour would undergo clinical investigation by an oncologist, as well as histological and IHC investigation of biopsy tissue by a pathologist. Following surgery, ER/PR and HER2 status and intrinsic subtype of the tumour tissue would be confirmed. The oncologist would then base their treatment recommendations on the tumour classification.

Patients with tumours classified as ER and/or PR +ve, HER2 –ve would be offered endocrine therapy. If a patient is categorised on a clinical and histological basis as having a low risk of distant recurrence they would be offered endocrine therapy alone. If categorised as having a high risk of recurrence, a patient may be offered adjuvant chemotherapy, to reduce the risk of recurrence. Those who fall into the intermediate risk category may be offered either of these options, depending on the individual circumstances and risk factors of the patient. International guidelines and/or other assessment tools such as Ki67, IHC4, Adjuvant! Online, and PREDICT may be used in the clinical assessment.

See attached flowchart – [Clinical management algorithms.ppt].

PART 6b – INFORMATION ABOUT THE INTERVENTION

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

The Prosigna® Clinical Summary (NanoString Technologies Inc. 2015) provided the following information:

- Prosigna® Breast Cancer Prognostic Gene Signature Assay is an *in vitro* diagnostic assay which measures the expression of 50 genes to provide an intrinsic subtype classification and risk of recurrence (ROR) score.
- The test is performed on RNA extracted from FFPE tumour samples and this is performed by running the sample through a gene expression measurement system called the nCounter® Analysis System. The nCounter needs to be enabled for Prosigna to run the assay.
- Prosigna® classifies patients into low, intermediate, and high risk groups by generating ROR scores on a scale of 0 – 100, based on the expression profile, intrinsic subtype and size of the tumour.
- Prosigna® (developed using the PAM50 gene signature but on a different platform) classifies tumours into 1 of 4 intrinsic subtypes – luminal A, luminal B, HER2-enriched and basal-like.
- The nCounter® Analysis System uses a highly sensitive hybridisation technique with labelled probes which enables detection of as little as one RNA copy per cell. The method is non-enzymatic and does not require amplification of the RNA.
- A patient's treatment decision would be based on the combined information from the ROR score and subtype.

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

The components of the proposed medical service that have a registered trademark are given in Table 6.

Table 6 Trademark registration details

Component	Australian trademark and entry date	International registration	Owner
Prosigna® assay kit	1732521 14 March 2016	1272305	NanoString Technologies, Inc.
nCounter® Analysis System	1732521 15 March 2016	1272305	NanoString Technologies, Inc.

30. 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?

N/A (no prosthesis or device)

31. 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 proposed for primary breast cancer patients, and would be expected to be delivered once per primary cancer diagnosis per patient ie at the point of primary tumour analysis. For most patients the test would be requested once in their lifetime, but in the instance where primary breast cancer is detected a second or additional time (in either breast), the test may be requested more than once.

32. 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:

Testing would be performed following surgical resection to assist decision making concerning the need for adjuvant treatment, in which case a request for an FFPE tissue sample would be required. A separate tissue biopsy would not be required from the patient in order to perform the test.

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

A core biopsy is performed by an oncology surgeon, and then sent to an accredited laboratory for testing and routine FFPE embedding. Patients with new primary breast cancer will be assessed for suitability for surgery. Following surgery, a pathologist assesses the tissue for ER/HER status (by IHC/ISH staining), tumour size and nodal status and provides a report to the oncologist or surgeon.

Gene profiling would be requested by the oncologist or surgeon. It would performed in a pathology laboratory, by a specialist molecular pathologist. Samples from FFPE blocks would be prepared for RNA extraction using the Prosigna® kit reagents. The Prosigna intrinsic subtyping and ROR score can only be produced using the Prosigna enabled nCounter® Analysis System. Results would be reported by the molecular pathologist to the requesting specialist.

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

Any molecular pathologist trained and accredited in the use of the Prosigna enabled nCounter® Analysis System would be able to interpret and report the results.

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

It is expected that a patient's oncologist or surgeon would be able to order the Prosigna® assay and that a suitably trained pathologist would be able to perform the assay on the Prosigna enabled nCounter® Analysis System and report on the results. NanoString Technologies, Inc. has validated procedures for training laboratory personnel to perform the assay.

36. 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:

Gene profiling should be performed within an appropriately accredited pathology laboratory, meeting the standards required for the National Association of Testing Authorities, Australia (NATA). In Australia, the technical competency of medical testing (of which genetic testing is a component) is ensured by the accreditation scheme operated by the NATA. NanoString Technologies, Inc. has validated procedures for training laboratory personnel to perform the Prosigna® assay using the nCounter® Analysis System which will also be required to meet NATA standards.

37. (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:

Any laboratory that is NATA accredited and has the Prosigna enabled nCounter® Analysis System can perform the assay using the Prosigna® kit reagents. This may occur in the private pathology sector or public hospital pathology setting.

Currently Sonic Healthcare is the only pathology laboratory with the nCounter® system enabled to run the Prosigna test. There are a number of other nCounter systems throughout Australia but within research settings.

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

☒ Yes
☐ No – please specify below

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

39. 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):

The comparator for the assessment of Prosigna® in women with HER2 –ve, ER and/or PR +ve primary breast cancer would be standard care.

Current standard care of primary breast cancer in Australia is largely determined by immunohistochemistry (IHC) and *in situ* hybridisation (ISH) analysis of tumour type, i.e. hormone receptor (ER/PR) positive or negative, and HER2 positive or negative. In Australia HER2 status is determined by ISH rather than IHC, as it is a requirement for access to trastuzumab under the Pharmaceutical Benefits Scheme (PBS) (MBS item 73332), although the result may be confirmed by IHC. MBS items 72848 and 73061 provide for the IHC analysis of oestrogen, progesterone and HER2 receptor status. However treatment benefit cannot be totally predicted by these subtypes. Other standard markers and factors used in the clinical risk assessment process are the molecular marker Ki67, IHC4 (an IHC test and algorithm for HER2, ER, PR and Ki67), intrinsic subtype, tumour grade, age, menopausal status, lymph node involvement, tumour size, and comorbidities.

Clinicians may additionally use predictive algorithmic tools such as Adjuvant! Online or PREDICT and recent clinical guidelines to determine the risk of breast cancer recurrence in their patients. Recently published clinical guidelines make varied recommendations regarding the use of gene expression profiling in addition to standard clinical factors in order to direct treatment choices in breast cancer patients (Coates et al. 2015; Harris et al. 2016; Senkus et al. 2015; Wockel & Kreienberg 2008). For example, the European Society for Medical Oncology (ESMO) guideline lists four gene expressions profiles (GEPs) which may be used, at the clinicians' discretion, in cases where there is uncertainty concerning the indications for adjuvant treatment with chemotherapy. Recommendations were based on lower level evidence, but with a strong expert consensus concerning the likely benefit (Senkus et al. 2015).

Considering current practice in Australia, the standard care comparator in the assessment of Prosigna® will be defined as:

- Determination of HER2, ER and PR status by IHC and ISH analysis
- Consideration of patient characteristics of age, menopausal status and comorbidities
- Post-surgical determination of lymph node status, tumour size, tumour grade, intrinsic subtype
- Discretionary input from other markers and tools such as Ki67, IHC4, Adjuvant! Online, PREDICT.

Alternative comparators of other GEPs may be included in the assessment, depending on the availability of suitable evidence.

Secondary comparators

Other risk prediction tools are currently in the process of seeking MBS reimbursement. Although not considered part of standard practice in Australia, they may become relevant comparators to Prosigna® in the future.

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.

Endopredict® is an algorithm which includes an expression panel of eight genes and clinical factors to assign patients to either a high or low risk of recurrence.

MammPrint® is a 70 gene profiling test performed by microarray to quantify the risk of disease recurrence and predict adjuvant chemotherapy benefit in breast cancer patients.

Current clinical practice guidelines (examples listed)

- ASCO Clinical Practice Guideline on Use of Biomarkers to Guide Decisions on Adjuvant Systemic Therapy for Women with Early-Stage Invasive Breast Cancer, 2016
- NCCN 2015, Breast Cancer, NCCN Clinical Practice Guidelines in Oncology National Comprehensive Cancer Network.
- Senkus E, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rutgers E, Zackrisson S, Cardoso F; ESMO Guidelines Committee. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol. 2015;26 Suppl 5:v8-v30. ESMO Guidelines Committee. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up
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40. 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 item 72848

	Category 6 –PATHOLOGY SERVICES
72848	Group P5 – TISSUE PATHOLOGY
Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen - 1 to 3 of the following antibodies - oestrogen, progesterone and c-erb-B2 (HER2) (Item is subject to rule 13) Fee: $74.50 Benefit: 75% = $55.90 85% = $63.35	

MBS item 73061

Category 6 – PATHOLOGY SERVICES

73061	Group P6 - CYTOLOGY
Immunocytochemical examination of material obtained by procedures described in items 73045, 73047, 73049, 73051, 73062, 73063, 73066 and 73067 for the characterisation of a malignancy by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen - 1 to 3 of the following antibodies - oestrogen, progesterone and c-erb-B2 (HER2) (Item is subject to rule 13) Fee: $51.20 Benefit: 75% = $38.40 85% = $43.55	

MBS item 73332

	Category 6 – PATHOLOGY SERVICES
73332	Group P7 - GENETICS
An in situ hybridization (ISH) test of tumour tissue from a patient with breast cancer requested by, or on the advice of, a specialist or consultant physician who manages the treatment of the patient to determine if the requirements relating to human epidermal growth factor receptor 2 (HER2) gene amplification for access to trastuzumab under the Pharmaceutical Benefits Scheme (PBS) or the Herceptin Program are fulfilled. Fee: $315.40 Benefit: 75% = $236.55 85% = $268.10	

As Oncotype DX®, Endopredict® and MammaPrint® are not currently listed on the MBS, there are no relevant MBS items for these tests.

41. 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):

Under the current clinical pathway, a diagnosis of primary breast cancer would be confirmed by core needle biopsy, following which a patient would be placed under the care of an oncologist and assessed for suitability for surgery. A pathologist would conduct a histological examination following surgical tumour removal or mastectomy, and make an assessment of ER and HER2 status, tumour characteristics and nodal status. Results would be reported to the surgeon and/or oncologist. The oncologist would further assess other clinical factors and classify the patient's risk of disease recurrence.

In a base case scenario, this decision would be based on (in addition to ER/PR+ve, HER2-ve status, tumour characteristics and nodal status) Ki67 status and/or other markers most likely to be used in the Australian population. Treatment with endocrine therapy is given to all patients, and adjuvant chemotherapy is administered to high risk and some intermediate risk patients.

In an alternative scenario, the decision for treatment would be based on recent clinical guidelines, or an available GEP in addition to standard clinical factors. Treatment with endocrine therapy is given to all patients, and adjuvant chemotherapy is administered to high risk and some intermediate risk patients.

(See attached document [Clinical management algorithms.ppt] for current clinical pathway algorithm.)

42. (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:

With regard to the primary comparator, the proposed test would be used in addition to current markers and characteristics to assist in the treatment decision.

With regard to the secondary comparators, Prosigna® would be an alternative to Endopredict®, Oncotype DX® and MammaPrint®. (As the secondary comparators are not currently MBS listed, a clinical comparison would be provided in the submission but not an economic comparison)

43. 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 proposed test would be used in addition to current clinical practice (primary comparator) for those patients who are not clearly suitable for endocrine therapy alone, or adjuvant chemotherapy. This group of patients, who could be classified as 'intermediate risk', are the most difficult for determining treatment decisions. To assist in the treatment decision, a patient's oncologist could order the Prosigna® assay, which would require retrieval of an FFPE sample of resected tumour. The assay would provide a ROR score generated by the nCounter® Analysis System which is based on intrinsic subtype, proliferation score and tumour size. The patient would be assigned to therapy based on the ROR score on a scale of 1 – 100 (Table 7) and nodal status. Risk categories identified by Prosigna® are described in Table 8.

Table 7 Prosigna® risk classification by ROR score and nodal status

Nodal status	Prosigna® score range	Risk classification
Node negative	0 - 40	Low
	41 - 60	Intermediate
	61 - 100	High
Node positive (1-3 nodes)	0 - 15	Low
	16 - 40	Intermediate
	41 - 100	High
Node positive (≥4 nodes)	0 - 100	High

ROR = risk of recurrence

Table 8 Risk categories as identified by Prosigna®

Category	Description
Low risk	< 10% predicted clinical risk of DR by 10 years
Intermediate risk	10 – 20% predicted risk of DR by 10 years
High risk	> 20% predicted risk of DR by 10 years

DR = distant recurrence

(See attached document [Clinical management algorithms.ppt] for proposed clinical pathway algorithm.)

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

44. 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):

If funded, the proposed new service would be added to the current decision pathway for treatment of ER and/or PR +ve, HER2-ve primary breast cancer. The claim is that Prosigna® provides incremental prognostic and predictive information over current markers and clinical characteristics, so that chemotherapy may be used in those breast cancer patients who are at the greatest risk of recurrence, and most likely to benefit from this treatment. The use of the Prosigna® assay to tailor treatment options according to risk of recurrence will mean that patients will be more likely to appropriately receive adjuvant chemotherapy.

The use of the Prosigna® assay to tailor treatment options according to risk of recurrence will mean that patients who are unlikely to benefit from chemotherapy (either because they are not at risk of recurrence, or they are unlikely to respond to chemotherapy) are able to avoid it. In those who avoid chemotherapy, there will be a reduction in harms associated with the treatment, and are likely to have an improved quality of life.

For patients who receive adjuvant chemotherapy, when with standard care they would have not received it, it is predicted they would have a reduced rate of disease recurrence (assuming that the treatment is effective).

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

☒ Superiority
☐ Non-inferiority

46. 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:

Harms associated with testing: rebiopsy rate, harms of undergoing rebiopsy

Harms associated with subsequent treatment: harms of chemotherapy

Clinical Effectiveness Outcomes:

Clinical utility:

- Overall survival
- Disease-free survival
- Metastasis-free survival
- Quality of life

Indirect outcomes (linked analysis):

Clinical validity of Prosigna® assay (including a comparison of Prosigna and PAM50)

Prognostic performance of Prosigna® or PAM50 assay

Predictive performance of Prosigna® or PAM50 assay

Change in management (treatment decisions made with and without the use of Prosigna®)

Likely impact of expected change in management (efficacy of endocrine therapy alone versus endocrine therapy plus chemotherapy in patients at intermediate risk of recurrence)

Cost utility

- cost per QALY

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

According to estimates of newly diagnosed cases of breast cancer in Australia there would be 17, 210 new cases in the 2020. Of these, it is estimated that 65% would be HER2 –ve, ER and/or PR +ve (proposed population) which would be 11,187 case in the same year. Only a proportion of these cases would be eligible to receive Prosigna® testing, as many would be clearly assigned to endocrine treatment alone or adjuvant chemotherapy (Table 9).

Table 9 Estimated number of new breast cancer cases eligible for Prosigna

Statistic	2012	2014	2016	2020
New cases	15,166[a]	15,270[b]	16,084[b]	17,210[c]
New ER +ve, HER2 -ve cases (assuming 65% of total)[d]	9857	9925	9972	11,187
Estimated new ER +ve, HER2 –ve cases of local or regional cancer in women under 80 years (assuming 68% of total)[e]	6703	4049	6781	7607

[a] Australian Institute of Health and Welfare in 2016 (AIHW 2016)
[b](Cancer Australia 2016)
[c](AIHW 2012)
[d] Estimated from recent publications (Voduc et al. 2010; Wang-Lopez et al. 2015)
[e] Estimation based on: localised or regional cancer – 75%; age < 80 years – 91% (Cancer Institute NSW http://www.statistics.cancerinstitute.org.au/, accessed 8.11.2016)

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

A patient would receive the test once per diagnosis of primary breast cancer, which would be once per lifetime in the vast majority of patients.

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

NA

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

For an estimate of the number utilising the proposed service see Table 9. The first full year of utilisation would be expected to be 2018. A gradual increase in uptake of the test is expected – approximately 10% of the eligible population in year 1, 20% in year 2, 30% in year 3, and 60% in year 4.

51. 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:

It is possible clinicians may use the service in all patients diagnosed with HER2 –ve, ER and/or PR +ve breast cancer, rather than just those who cannot be clearly assigned treatment without the proposed test. Clinicians may do this if they or the patient requires reassurance or evidence for their treatment decision, or if they feel there is benefit from the additional confirmation of the prognostic information provided. This might occur for reasons other than the decision-making regarding adjuvant chemotherapy. This would result in up to 11 187 Prosigna tests being performed in 2020 (Table 9).

PART 8 – COST INFORMATION

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

The market cost of the service in Australia is $2,900.00.

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

The process of macrodissection, RNA extraction, and testing with the Prosigna® assay can take 3 days from tissue processing to result (Nielsen et al. 2010).

Sonic Genetics currently perform this service and state their turnaround time from receipt of patient sample to test result is approximately 10 days.

54. 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.

Proposed MBS item descriptor

	Category – PATHOLOGY SERVICES
XXXXX	Group P7 – GENETICS
RT-qPCR gene expression profiling of FFPE, core needle biopsy or surgical tumour sample in primary breast cancer tissue. The test may be used when all of the following criteria are met: - New primary breast cancer, suitable for adjuvant chemotherapy but not requiring neoadjuvant chemotherapy - Oestrogen and/or progesterone positive and HER2 negative as determined by immunohistochemistry (IHC) and in situ hybridisation (ISH) respectively on a surgically removed tumour sample - Node negative or positive (up to 3 nodes) and tumour size determined by histopathology on surgically removed tumour sample - Pre-test intermediate risk of distant metastases defined by at least one of the following characteristics: tumour size ≥ 2cm*; or Grade 2[a]; or one to three lymph nodes involved in metastatic disease (nodes include micrometastases but not isolated tumour cells) The test may be used once per new primary breast cancer diagnosis. Fee: $2,900 Benefit: 75% = $2,175	

[a]The AJCC recommend that all invasive cancer is graded using the Nottingham combined histologic grade (Elston-Ellis modification of Scarff-Bloom-Richardson grading system)(AJCC 2012)

PART 9 – FEEDBACK

The Department is interested in your feedback.

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

22 hours

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

☒ Yes
☐ No

(b) If no, provide areas of concern:

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

☒ Yes
☐ No

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

It would be helpful to have a clear indication of an email address to use to submit the application.

58. (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:

Insert feedback here

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