Australian Government

Department of Health

Application Form

Quantification of NT-proBNP in patients with systemic sclerosis and in patients with diagnosed pulmonary arterial hypertension

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 to determine whether a proposed medical service is suitable.

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

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

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): Janssen Australia and New Zealand (Janssen-Cilag Pty Ltd)
Corporation name: Janssen Australia and New Zealand (Janssen-Cilag Pty Ltd)
ABN: 47 000 129 975
Business trading name: Janssen-Cilag Pty Ltd

Primary contact name: REDACTED

Primary contact numbers
Business: Janssen Australia and New Zealand (Janssen-Cilag Pty Ltd)
Mobile: REDACTED
Email: REDACTED

Alternative contact name: REDACTED

Alternative contact numbers
Business: Janssen Australia and New Zealand (Janssen-Cilag Pty Ltd)
Mobile: REDACTED
Email: REDACTED

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

☐ Yes
☒ No

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

Not applicable

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

3. Application title

Quantification of NT-proBNP in patients with systemic sclerosis (scleroderma) in the screening of risk for pulmonary arterial hypertension that requires right heart catheterisation for definitive diagnosis.

Quantification of NT-proBNP in patients diagnosed with pulmonary arterial hypertension for ongoing risk assessment.

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

Population 1: Patients with systemic sclerosis (SSc)

Systemic sclerosis (SSc) is a rare disease with an estimated prevalence in the Australian population of ~ 6000 (Morrisroe et al., 2017a)[1]. Patients with SSc are at an increased risk of pulmonary arterial hypertension (PAH), irrespective of disease duration, gender, disease subtype, or other organ involvement. PAH occurs in approximately 10% of patients with SSc (Australian Rheumatology Association[1]). PAH is a major cause of mortality in SSc, accounting for approximately 30% of SSc-related deaths (Thakkar et al., 2012)[2]. In addition, systemic sclerosis-related pulmonary arterial hypertension (SSc-PAH) is associated with significant healthcare resource utilisation and associated economic burden predominantly driven by the severity of PAH (Morrisroe et al., 2017b[3], Morrisroe et al., 2019[4]).

In its earliest stages, SSc-PAH is often asymptomatic or minimally symptomatic. Patients often present late in the natural history of the disease and more than two thirds are in World Health Organisation functional class (WHO-FC) III and IV at presentation. Evidence suggests that earlier detection confers survival, and prognosis advantage (Brown et al., 2021[5]). In addition, earlier commencement of treatment has been shown to delay the progression of SSc-PAH and lead to improvement in functional class (Thakkar et al., 2012)[2].

Population 2: Patients with pulmonary arterial hypertension (PAH)

PAH is characterised by increased pulmonary vascular resistance and may be idiopathic or due to other underlying factors or disease associations such as connective tissue disease (CTD), most commonly SSc within CTD-PAH. PAH is defined as an increase in mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest along with pulmonary arterial wedge pressure (PAWP) ≤15 mmHg and pulmonary vascular resistance (PVR) > 3 Wood units (WU), as assessed by right heart catheterisation (RHC, Galie et al., 2016[6]). PAH is rare, severe, intractable, and debilitating progressive clinical condition characterised by a sustained elevation of pulmonary vascular resistance (due to narrowing of the pulmonary arteries), which if left untreated ultimately leads to right heart failure and death (Studer et al., 2019)[7].

Achievement and maintenance of low-risk status is a treatment goal in PAH. Risk assessment is often performed using multiparameter tools, such as ERS/ESC risk table (Galie et al 2016)[6], the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) risk calculator and REVEAL 2.0 (Benza et al 2019)[8]. These mentioned risk assessment methods contain invasive haemodynamic parameters from a RHC. . More recently, REVEAL 2.0 Lite has been validated, which is based on non-invasive parameters, and indicated that most highly predictive parameter was BNP/NT-proBNP (Benza et al., 2021)[9].

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

The proposed medical service is a screening service of plasma level for NT-proBNP (also known as N-terminal pro-brain natriuretic peptide, N-terminal pro-B-type natriuretic peptide or N-terminal prohormone of brain natriuretic peptide). NT-proBNP is a non-invasive screening strategy (i.e. a blood

[1] Australian Rheumatology Association https://rheumatology.org.au/patients/asig.asp

test) for systemic sclerosis related pulmonary arterial hypertension (SSc-PAH), and regular assessment of pulmonary arterial hypertension (PAH) disease progression.

NT-proBNP is a candidate biomarker that enables the early detection of SSc-PAH, and regular assessment of PAH progression. NT-proBNP is a 76-amino acid polypeptide that is released along with BNP, by cardiac myocytes, in response to increased ventricular wall stress, as typically occurs with volume overload and ventricular contractile dysfunction.

Population 1: Patients with systemic sclerosis (SSc)

Yearly screening for PAH in SSc in now standard of care in this disease (Quinlivan et al., 2015[10], Quinlivan et al., 2020[11]).

Population 2: Patients with pulmonary arterial hypertension (PAH)

NT-proBNP levels correlate with myocardial dysfunction and provide prognostic information at the time of PAH diagnosis, during follow-up assessments to monitor for clinical deterioration caused by progression of PAH, and to stratify patients into low, intermediate, and high-risk categories (Galie et al., 2016[6], Benza et al., 2021[9]).

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

☒ Yes
☐ No

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

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

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

N/A

Note, this current application is similar, i.e. measurement of NT-proBNP but not identical to the service covered by item number 66830 on MBS.

The MBS item number 66830 is for a different patient population (distinguishing between cardiac and respiratory causes of shortness of breath in patients presenting to an Emergency Department).

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

N/A

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

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

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

☐ Yes
☒ No

(g) If yes, please advise:

N/A

7. What is the type of service:

Investigative medical service

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

i. ☒ To be used as a screening tool in asymptomatic populations – for population 1
ii. ☒ Assists in establishing a diagnosis in symptomatic patients – for population 1
iii. ☒ Provides information about prognosis – for population 1
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 – for population 2

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

☐ Pharmaceutical / Biological
☐ Prosthesis or device
☒ No

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

☐ Yes
☒ No

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

N/A

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

N/A

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

N/A

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

☐ Yes
☒ No

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

N/A

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

N/A

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

N/A

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

N/A

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

N/A

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

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

A number of companies in Australia manufacture immunoassays for the detection of the inactive NT-proBNP. Janssen does not manufacture or provide the NT-proBNP assay. Based on our research the commercially available tests include

- Roche Diagnostics (CARDIAC® NT-pro-BNP),
- Siemens Healthineers (Stratus® CS Acute Care™),
- BioMerieux (VIDAS NT-proBNP2),

This application only applies to the NT-proBNP assays.

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

☐ Class III
☐ AIMD
☒ N/A

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

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

A search of the ARTG did not locate these tests, so it is our assumption that the tests are exempt from the Therapeutic Good Administrations Act 1998 because the diagnostic tests are not used for blood screening, are not used by consumers, do not contain material of human/animal origin, are not listed on the Pharmaceutical Benefits Scheme and are not used for human immunodeficiency or hepatitis B or C testing.

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

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

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

☐ Yes (please provide details below)
☐ No

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

☐ Yes (please provide details below)
☐ No

PART 4 – SUMMARY OF EVIDENCE

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

	Type of study design	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
Population 1: Patients with systemic sclerosis (SSc)					
1.	Analysis from the Australian Scleroderma cohort study (ASCS)	A comparison of the predictive accuracy of three screening models for pulmonary arterial hypertension in systemic sclerosis.	DETECT and ASIG algorithms performed equally in predicting PAH with sensitivity and NPV of 100%. The ESC/ERS guidelines had sensitivity of 96.3% and NPV of only 91%, missing one case of PAH. The ASIG algorithm had the highest specificity (54.5%).	https://pubmed.ncbi.nlm.nih.gov/25596924/	2015
2.	A cost comparison	Cost savings with a novel algorithm for early detection of systemic sclerosis-related pulmonary arterial hypertension: alternative scenario analyses	The new algorithm (NT-proBNP assessment) resulted in significant yearly cost savings of between AU$42 913.35 and AU$84 570 in screening and diagnosis of an Australian cohort which, if extrapolated to the Australian population, would result in a yearly cost saving of between AU$367 066 and AU$725 564. There was no scenario in which the proposed algorithm did not result in a cost saving.	https://pubmed.ncbi.nlm.nih.gov/31185523/	2019
3.	A case-control study	N-terminal pro-brain natriuretic peptide in a novel screening algorithm for pulmonary arterial hypertension in systemic sclerosis: a case-control study	A composite model wherein patients screened positive if NT-proBNP was ≥ 209.8 pg/ml, and/or DLCOcorr was < 70.3% with FVC/DLCOcorr ≥ 1.82, had a sensitivity of 100% and specificity of 77.8% for SSc-PAH.	https://pubmed.ncbi.nlm.nih.gov/22691291/	2012

	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.	A cohort study	Identifying early pulmonary arterial hypertension biomarkers in systemic sclerosis: Machine learning on proteomics from the DETECT cohort	Samples from an independent validation cohort (SSc-PAH, n=22 and non-PH, n=22) were obtained from University of Sheffield, UK. Random Forest (RF) analysis identified a novel panel of eight proteins, comprising Collagen IV, Endostatin, IGFBP-2, IGFBP-7, MMP-2, Neuropilin-1, NT-proBNP and RAGE, that discriminated PAH from non-PH in SSc patients in the DETECT discovery cohort (average area under the ROC values (ROC-AUC) of 0.741, 65.1 % sensitivity / 69.0 % specificity) was reproduced in the Sheffield cohort (81.1 % accuracy, 77.3 % sensitivity / 86.5 % specificity). This novel 8-protein biomarker panel has the potential to improve early detection of PAH in SSc patients and may provide novel insights into the pathogenesis of PAH in the context of SSc.	https://erj.ersjournals.com/content/early/2020/11/26/13993003.02591-2020	2020
5.	A multicentre prospective cohort study	Utility of B-type natriuretic peptides in the assessment of patients with systemic sclerosis-associated pulmonary hypertension in the PHAROS registry	The sensitivity and specificity for SSc-PAH detection using baseline BNP≥64 pg/mL was 71% and 59%; and for NT-proBNP≥210 pg/mL, 73% and 78%.	https://pubmed.ncbi.nlm.nih.gov/27908301/	2017
6.	A prospective case-control study	Non-invasive diagnostic and functional evaluation of cardiac involvement in patients with systemic sclerosis	NT-proBNP level correlated positively with TRPG, RV diameter, RV Tei index and negatively with 6MWT distance. ROC analysis identified >115 pg/ml as the best NT-proBNP threshold predicting PAH for SSc patients (sensitivity 92%, specificity 44%). Results of our study suggest that NT-proBNP measurement is a useful screening method for PAH in SSc patients.	https://pubmed.ncbi.nlm.nih.gov/18256871/	2008

	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
7.	A systematic review	Screening and Diagnostic Modalities for Connective Tissue Dieases-Associated Pulmonary Arterial Hypertension: A Systematic Review	Five studies assessed N- terminal prohormone of brain natriuretic peptide (NT-ProBNP) where a cut-off >239pg/ml has a sensitivity of 90–100%. ur systematic review revealed that most evidence exists for TTE, pulmonary function tests, and NT-ProBNP for screening and diagnosis of SSc-PAH	https://pubmed.ncbi.nlm.nih.gov/24012044/	2014
8.	A prospective cohort study	Disproportionate elevation of N-terminal pro-brain natriuretic peptide in scleroderma-related pulmonary hypertension	NT-proBNP levels are 1) significantly higher in PAH-SSc than IPAH despite less severe haemodynamic perturbations, and 2) stronger predictors of survival in PAH-SSc	https://erj.ersjournals.com/content/35/1/95	2010
9.	A single centre pilot study	Significance of plasma N-terminal pro-brain natriuretic peptide in patients with systemic sclerosis-related pulmonary arterial hypertension	NT-proBNP estimation in systemic sclerosis-related pulmonary hypertension is a potentially useful diagnostic tool with a high specificity and negative predictive value.	https://pubmed.ncbi.nlm.nih.gov/14635979/	2003
10.	An abstract	FRI0462 Does Serum NT-ProBNP Test Facilitate Diagnosis of PAH in Patients with SSc?	ROC curve analyses were performed to determine the optimal cut-off point for NT-proBNP and other variables in prediction of PAH. NT-proBNP at the level of >252,5 pg/mL, predicts the presence of SSc- PAH with sensitivity of 82% and specificity of 72%; positive predictive value for SSc-PAH was 86,6%, negative predictive value – 72,4%. Increased serum NT-proBNP can be considered as detecting factor of SSc-PAH provided left heart diseases are excluded.	https://ard.bmj.com/content/74/Suppl_2/595.1.abstract	2015
11.	A prospective case-control study	NT-proBNP levels in systemic sclerosis: Association with clinical and laboratory abnormalities	An ROC curve analysis (with an area under the curve of 0.89, 95% CI: 0.83–0.95) suggested a cutoff of 157.8 pg/mL to identify patients with suspected SSc-PAH, presenting a sensitivity of 100% (78.1–100) and specificity of 72.3% (62.3–80.5). NT-proBNP levels are related to clinical and laboratory abnormalities in SSc. The results indicate that NT-proBNP may be a useful tool in the evaluation of SSc-PAH.	https://pubmed.ncbi.nlm.nih.gov/20350538/	2010

	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
12.	A cohort study	The inclusion of N-terminal pro-brain natriuretic peptide in a sensitive screening strategy for systemic sclerosis-related pulmonary arterial hypertension: a cohort study	The sensitivity, specificity, PPV and NPV of the proposed algorithm for PAH was 94.1%, 54.5%, 61.5% and 92.3%, respectively. The combination of NT-proBNP with PFT is a sensitive, yet simple and non-invasive, screening strategy for SSc-PAH.	https://pubmed.ncbi.nlm.nih.gov/24246100/	2013
13.	A systematic literature review	Screening for pulmonary arterial hypertension in systemic sclerosis	The recent 6th World Symposium on PH recommends the use of TTE, the DETECT algorithm or FVC %/DLCO % ratio with NT-proBNP to screen for PAH in patients with SSc.	https://err.ersjournals.com/content/28/153/190023	2019
14.	A systematic literature review	Screening for pulmonary arterial hypertension in systemic sclerosis: A systematic literature review	DETECT and ASIG showed higher sensitivity and negative predictive value than ESC/ERS 2009.	https://www.sciencedirect.com/science/article/abs/pii/S0953620520302351	2020
15.	A systematic literature review	BNP/NT-proBNP in pulmonary arterial hypertension: time for point-of-care testing?	BNP/NT-proBNP POCT has been successfully implemented and is well established in multiple cardiovascular pathologies, including acute and chronic heart failure due to left ventricular dysfunction and dyspnoea.	https://err.ersjournals.com/content/errev/29/156/200009.full.pdf	2020
16.	A prospective cohort study	N-Terminal Pro–Brain Natriuretic Peptide as a Diagnostic Marker of Early Pulmonary Artery Hypertension in Patients With Systemic Sclerosis and Effects of Calcium-Channel Blockers	High NT-proBNP levels identified patients with PAH with a sensitivity of 90%, a specificity of 90.3%, a positive predictive value of 69.2%, and a negative predictive value of 96%. The NT-proBNP level correlated with the sPAP (r= 0.44; P= 0.006).	https://onlinelibrary.wiley.com/doi/epdf/10.1002/art.11345	2003

	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
17.	A prospective cohort study	High N-Terminal Pro–Brain Natriuretic Peptide Levels and Low Diffusing Capacity for Carbon Monoxide as Independent Predictors of the Occurrence of Precapillary Pulmonary Arterial Hypertension in Patients with Systemic Sclerosis	Kaplan-Meier analysis identified the following baseline parameters as being predictors of PAH: DLCO/VA ratio <70% or <60% (P < 0.01 for each comparison), elevated plasma NT-proBNP level (>97th percentile of normal; P 0.005), echocardiographically estimated systolic PAP >40 mm Hg (P= 0.08), and erythrocyte sedimentation rate >28 mm/hour (P= 0.015). This prospective study identified a decreased DLCO/VA ratio and an increased NT-proBNP as predictors of PAH in SSc.	https://onlinelibrary.wiley.com/doi/epdf/10.1002/art.23187	2008
18.	A single centre prospective cohort study	Prognostic value of N-terminal natriuretic peptides in systemic sclerosis: a single centre study	Patients diagnosed with heart ivolvement during the study had significantly higher levels of NT-proANP and NT-proBNP (791.4±379.9 pmol/l vs. 608.0±375.8 pmol/l, p<0.05 and 183.1±162.6 vs. 125.7±117.5 pmol/l, p<0.05, respectively). Receiver-operator-characteristic analysis identified <822.5 pmol/l as the best NT-proBNP and <154.5 pmol/l as the best NT-proBNP threshold (sensitivity 56.3%, specificity 79.5%, negative predictive value: 86.4% and sensitivity 50.0%, specificity 76.8%, negative predictive value: 83.7%, respectively). During the follow-up, lower NT-proBNP levels were significantly associated with a longer event-free survival (p<0.05), similar but a non-significant trend regarding NT-proBNP levels was also shown (p=0.052). NT-proBNP had a supplementary prognostic value for cardiac involvement in systemic sclerosis.	https://www.clinexprheumatol.org/abstract.asp?a=7931	2014
19.	A systematic review and meta-analysis	Screening for the early detection of pulmonary arterial hypertension in patients with systemic sclerosis: A systematic review and meta-analysis of long-term outcomes	This review demonstrates long-term benefit through the systematic screening of patients with SSc of varying disease duration for the early detection of PAH. Screened cohorts had improved survival, and were more likely to have better prognostic factors at the time of diagnosis with PAH.	https://pubmed.ncbi.nlm.nih.gov/33857705/	2021

	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
Population 2: Patients with pulmonary arterial hypertension (PAH)					
1.	Guidelines for the diagnosis and treatment of pulmonary hypertension	2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension	Regular assessment of patients with PAH in expert PH centres is strongly recommended.	https://erj.ersjournals.com/content/erj/46/4/903.full.pdf	2016
2.	A retrospective cohort study	Prognostic Significance of Biomarkers in Pulmonary Arterial Hypertension	In patients with PAH, higher NT-proBNP levels at baseline were associated with an increased risk of death or transplantation.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4722842/pdf/AnnalsATS.201508-543OC.pdf	2016
3.	A prospective cohort study	N-Terminal Pro-B-Type Natriuretic Peptide as an Indicator of Disease Severity in a Heterogeneous Group of Patients With Chronic Precapillary Pulmonary Hypertension	Plasma NT–proBNP can be used to determine the clinical severity of disease and is independently associated with long-term mortality.	https://www.ajconline.org/action/showPdf?pii=S0002-9149%2806%2900827-7	2006
4.	A prospective cross-sectional study	NT-proBNP can be used to detect right ventricular systolic dysfunction in pulmonary hypertension	In pulmonary hypertension, a baseline N-terminal B-type natriuretic peptide concentration of >1,685 $ng.L^{-1}$ suggests right ventricular systolic dysfunction, and thus an increased risk of early death. N-terminal B-type natriuretic peptide could prove useful as an objective, noninvasive means of identifying patients with pulmonary hypertension who have right ventricular systolic dysfunction at presentation	https://erj.ersjournals.com/content/erj/29/4/737.full.pdf	2007

	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
5.	A post-hoc analysis of the GRIPHON RCT	Association of N-Terminal Pro Brain Natriuretic Peptide and Long-Term Outcome in Patients With Pulmonary Arterial Hypertension	Baseline and follow-up NT-proBNP categories were highly prognostic for future morbidity/mortality events during the study (P< 0.0001). Analyses further establish the prognostic relevance of NT- proBNP levels in PAH and provide first evidence for the association of NT-proBNP level and treatment response.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6530970/pdf/cir-139-2440.pdf	2019
6.	A cohort study	Noninvasive Prognostic Biomarkers for Left-Sided Heart Failure as Predictors of Survival in Pulmonary Arterial Hypertension	Higher ST2 and NT-proBNP were associated with higher pulmonary pressures and vascular resistance and lower 6-min walk distance. Higher ST2 and NT-proBNP levels were associated with increased risk of death (hazard ratios: 2.79; 95% CI, 2.21-3.53; P < .001 and 1.84; 95% CI, 1.62-2.10; P< .001, respectively). ST2 and NT-proBNP are strong, noninvasive prognostic biomarkers in PAH.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7268446/pdf/main.pdf	2020
7.	A prospective cohort study	NT-proBNP as a tool to stratify disease severity in pulmonary arterial hypertension	The levels of NT-proBNP showed a high correlation with hemodynamic parameters, such as pulmonary vascular resistance (r= 0:80, P< 0.001). A significant difference was found among patients with different functional classes, addressed by NYHA classification (P< 0.02 for all groups comparison). The discriminant analysis reinforced the ability of NT-proBNP to stratify patients according to NYHA functional class. Compared to the other variables studied (hemodynamics and 6MWT), NT- proBNP had the lowest level of overlap in the stratification of IPAH patients. We conclude that NT-proBNP differs among the different functional classes and correlates with other measures of disease severity	https://www.resmedjournal.com/action/showPdf?pii=S0954-6111%2806%2900225-3	2007

	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
8.	A prospective cohort study	Role of N-terminal brain natriuretic peptide (NT-proBNP) in scleroderma-associated pulmonary arterial hypertension	The patients without PAH had a mean N-TproBNP level of 139 pg/mL (SD 151); those with SSc-PAH had a significantly higher mean NT-proBNP level of 1474 pg/mL (SD 2642) (P= 0.0002). Among patients with PAH for every order of magnitude increase in NT-proBNP level there was a four-fold increased risk of death (P= 0.002 for baseline level and P= 0.006 for follow-up level). Baseline NT-proBNP levels were correlated positively with mean PAP (r= 0.62; P< 0.0001), pulmonary vascular resistance (PVR) (r= 0.81; P< 0.0001), and inversely with SMWD (r= -0.46; P< 0.0001). Among patients with SSc-PAH, 13 patients (19%) were in WHO functional classes II and had mean NT-proBNP levels of 325 pg/mL (SD 388). Fifty-three patients (78%) were in WHO classes III and IV and had significantly higher mean NT-proBNP levels of 1677 pg/mL (SD 2835) (P= 0.02). Raised NT-proBNP levels are directly related to the severity of PAH. In screening programs, SSc patients with an NT-proBNP in excess of 395 pg/mL have a very high probability of having pulmonary hypertension. Baseline and serial changes in NT-proBNP levels are highly predictive of survival. A 10-fold increase in NT-proBNP level on therapy is associated with a greater than three-fold increase in mortality, and may indicate therapeutic failure.	https://pubmed.ncbi.nlm.nih.gov/16682379/	2006
9.	A systematic review	Blood biomarkers and their potential role in pulmonary arterial hypertension associated with congenital heart disease. A systematic review	Right heart dysfunction, endothelial inflammation and proliferation are mirrored by plasma levels of the corresponding biomarkers among patients with CHD‐PAH. There is early evidence to suggest that natriuretic peptides, in particular, may be a simple and effective tool for determining prognosis and timing for therapeutic interventions in patients with CHD‐PAH	https://www.internationaljournalofcardiology.com/article/S0167-5273(14)00836-5/fulltext	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
10.	A prospective cohort study	Serum N-Terminal Brain Natriuretic Peptide as a Prognostic Parameter in Patients With Pulmonary Hypertension	NT-proBNP level is related to the right heart morphology and dysfunction in PH patients. A serum NT-proBNP level of > 1,400 pg/mL was found to be useful in identifying patients with poor long-term prognosis both in the whole studied group and in the IPAH subgroup.	https://pubmed.ncbi.nlm.nih.gov/16685024/	2006
11.	A systematic review	The natriuretic peptides and their role in disorders of right heart dysfunction and pulmonary hypertension	BNP is a predictor of mortality in patients with primary pulmonary hypertension (PPH). These are important clinical implications in that a noninvasive blood test may be used to identify high-risk patients for more invasive procedures such as cardiac catheterisation. BNP or NT-proBNP measurements may also be used to guide therapy (e.g., pulmonary vasorelaxants) in PAH since upregulation of the natriuretic peptide pathway has been shown to reduce cardiac hypertrophy and PAH. Additionally, there may be therapeutic potential via recombinant BNP or neutral endopeptidase inhibitors in RV dysfunction and PAH.	https://pubmed.ncbi.nlm.nih.gov/15369714/	2004
12.	Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL)	Development and Validation of an Abridged Version of the REVEAL 2.0 Risk Score Calculator for Use in Patients With Pulmonary Arterial Hypertension	The purpose of this report is to describe the development of the updated REVEAL risk score calculator, REVEAL 2.0, and compare it with the original REVEAL calculator. We also compared the risk discrimination of REVEAL 2.0 with other contemporary risk assessment strategies to provide clinicians with information on the relative strength of each risk assessment strategy.	DOI: 10.1016/j.chest.2019.02.004	2019
13.	Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL)	Development and Validation of an Abridged Version of the REVEAL 2.0 Risk Score Calculator, REVEAL Lite 2, for Use in Patients With Pulmonary Arterial Hypertension	REVEAL Lite 2 includes six noninvasive variables—functional class (FC), vital signs (systolic BP [SBP] and heart rate), 6-min walk distance (6MWD), brain natriuretic peptide (BNP)/N- NT-proBNP, and renal insufficiency (by estimated glomerular filtration rate [eGFR])—and was validated in a series of an- alyses (Kaplan-Meier, concordance index, Cox proportional hazard model, and multivariate analysis).	DOI: https://doi.org/10.1016/j.chest.2020.08.2069	2021

	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
14.	Retropsective Registry Study	Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension	The objective of the study was to apply the risk assessment criteria from the 2015 ESC/ERS guidelines to an incident cohort of patients with PAH from the French pulmonary hypertension registry. Aim to determine survival according to the number of low-risk criteria at diagnosis and the number achieved during the first year of treatment. The study also validated risk assessment witn non-invaive parmeters including NT-proBNP	DOI: 10.1183/13993003.00889-2017	2017
15.	Retropsective Registry Study	Retrospective Validation of the US Registry to Evaluate Early and Long-Term PAH Disease Management 2.0 Risk Score With the Australian and New Zealand Pulmonary Hypertension Registry Cohort	The REVEAL 2.0 risk score was validated in a large external cohort from the PHSANZ Registry. The REVEAL 2.0 model can be applied for risk assessment of patients with PAH at follow-up. The simplified three-category model may be preferred for clinical use and for future comparison with other prognostic models.	DOI: https://doi.org/10.1016/j.chest.2019.08.2203	2019

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

No unpublished identified

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

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

Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ)

Australian Rheumatology Association (ARA) (Australian Scleroderma Interest Group (ASIG) is an ARA subcommittee)

Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ)

Australian Rheumatology Association (ARA) (Australian Scleroderma Interest Group (ASIG) is an ARA subcommittee)

Cardiac Society of Australia and New Zealand (CSANZ)

Thoracic Society of Australia and New Zealand (TSANZ)

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

Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ)

ASIG (Australian Scleroderma Interest Group, subcommittee of ARA)

Cardiac Society of Australia and New Zealand (CSANZ)

Thoracic Society of Australia and New Zealand (TSANZ)

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

Scleroderma Australia

Lung Foundation Australia

Pulmonary Hypertension Association of Australia Inc (PHAA)

Pulmonary Hypertension Network Australia (PHNA)

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

A number of companies in Australia manufacture immunoassays for the detection of the inactive NT-proBNP. Janssen does not manufacture or provide the NT-proBNP assay. Based on our research the commercially available tests include the following:

- Roche Diagnostics (CARDIAC® NT-pro-BNP),
- Siemens Healthineers (Stratus® CS Acute Care™),
- BioMerieux (VIDAS NT-proBNP2),

This application only applies to the NT-proBNP assays.

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

REDACTED

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

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

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

Population 1: Patients with systemic sclerosis (SSc)

Systemic sclerosis (SSc) is a multi-organ autoimmune disease characterised by vasculopathy and fibrosis. Australia has one of the highest prevalence of SSc worldwide with a prevalence of around 20/100,000. Among the rheumatic diseases, SSc is associated with one of the greatest increases in mortality and morbidity compared with age, and sex-matched peers. There is no cure for SSc, leading to significant morbidity, mortality, and poor health-related quality of life (Morrisroe et al., 2017)[12]. A meta-analysis in 2012 reported standardised mortality ratios (SMRs) for SSc ranging from 2.5 to 4.5, with a pooled SMR of 3.5 (95% CI: 3.03, 4.11, p<0.0001, Elhai et al., 2012)[13].

In Australia, SSc is associated with an average reduction in life expectancy of 11.3 years for women, and 25.8 for men, compared with the general population (Hao et al., 2017)[14]. Furthermore, the chronic nature of the disease and the involvement of multiple organ systems over time, makes SSc one of the most costly rheumatic diseases in terms of health care utilisation. In recent data linkage studies from the Australia Scleroderma Cohort, the average total annual direct and indirect costs were estimated to be $15,127 per annum per patient (Morrisroe et al., 2017[3]; Morrisroe et al., 2018[15]).

Pulmonary arterial hypertension (PAH) occurs in approximately 10% of patients with SSc but early detection is challenging (Australian Rheumatology Association). Early recognition of sclerosis-related pulmonary arterial hypertension (SSc-PAH) is difficult as early disease is clinically silent and the heterogeneous nature of SSc makes interpretation of fatigue and dyspnoea challenging. PAH is a major cause of mortality in SSc, accounting for approximately 30% of SSc-related deaths (Thakkar et al., 2012)[2], and is the second most common cause of PAH after idiopathic PAH (Morrisroe et al., 2017) [1]. Collectively, the pulmonary complications of interstitial lung disease (ILD), and pulmonary arterial hypertension (PAH), are the leading cause of mortality (Tyndall et al., 2010; Steen et al., 2007).

The use of advanced pulmonary vasodilators for PAH improves functional class, exercise capacity, haemodynamic, quality of life, and survival. Patients who undergo screening for PAH in specialised clinics have better survival compared with those who are found to have SSc-PAH during routine clinical care (Australian Rheumatology Association[2]). Survival is improved even after adjustment for lead-time bias in SSc-PAH when diagnosed by screening compared with diagnosis during routine care. Consequently, annual screening with transthoracic echocardiogram (TTE) and pulmonary function tests (PFTs) is recommended, regardless of the presence or absence of the aforementioned risk factors, to identify patients who should undergo right-heart catheterisation (RHC) to confirm the diagnosis (Morrisroe et al., 2017)[1].

SSc is associated with substantial healthcare utilisation and direct economic burden. The healthcare utilisation cost to the Australian government extrapolated to all Australian SSc patients from 2011 to 2015 was Australian Dollar (AUD)$297,663,404.77, which is an average annual cost of AUD $59,532,680.95 (US Dollar [USD]$43,816,040.08) and annual cost per patient of AUD$11,607.07 (USD$8,542.80). Hospital costs, including inpatient hospitalisation, and emergency department presentations, accounted for the majority of these costs (44.4% of total), followed by medication cost (31.2%), and ambulatory care cost (24.4%). PAH and gastrointestinal (GIT) involvement were the major determinants of healthcare cost (OR= 2.3 and 1.8, P= 0.01 for hospitalisations; OR= 2.8 and 2.0, P= 0.01

[2] Australian Rheumatology Association - https://rheumatology.org.au/patients/asig.asp

for ambulatory care; OR= 7.8 and 1.6, P< 0.001 and P=.03 for medication cost, respectively). The most costly aspects of SSc are PAH and GIT involvement (Morrisroe et al., 2017)[3].

Population 2: Patients with pulmonary arterial hypertension (PAH)

PAH is characterised by increased pulmonary vascular resistance and may be idiopathic or due to other underlying factors or disease associations such as connective tissue disease (CTD), most commonly SSc within CTD-PAH. PAH is defined as an increase in mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest along with pulmonary arterial wedge pressure (PAWP) ≤15 mmHg and pulmonary vascular resistance (PVR) > 3 Wood units (WU), as assessed by right heart catheterisation (RHC) (Galie et al., 2016)[6]. PAH is a rare, severe, intractable, and debilitating progressive clinical condition characterised by a sustained elevation of pulmonary vascular resistance (due to narrowing of the pulmonary arteries), which if left untreated ultimately leads to right heart failure and death (Studer et al., 2019).

PAH is a type of pulmonary hypertension (PH), which has been classified into five categories sharing similar pathological findings, hemodynamic characteristics, and management. PAH is Group 1 (Table 1) of PH and there are four subgroups of PAH by aetiology as follows.

1- Idiopathic PAH (IPAH).
2- Heritable PAH.
3- Drug and toxin induced PAH.
4- PAH associated with connective tissue disease, HIV infection, portal hypertension, congenital heart diseases or schistosomiasis (a parasitic infection).

The impact of PAH on health-related quality of life (HRQOL) is substantial and increases with severity of the disease, despite more aggressive treatments (Small et al., 2014)[16]. Patients experience symptoms such as fatigue, and shortness of breath that are associated with worse HRQOL in physical components of rating scales (Gu et al., 2016[17]; Matura et al., 2016[18]). Many patients also suffer from symptoms of stress, depression, and anxiety (Vanhoof et al., 2014[19]; White et al., 2006[20]).

The symptoms of PAH are non-specific and mainly related to progressive right ventricular (RV) dysfunction. Initial symptoms are typically induced by exertion and include shortness of breath, fatigue, weakness, angina, and syncope. Less commonly, patients may also describe dry cough and exercise-induced nausea and vomiting. Symptoms at rest occur only in advanced cases. Abdominal distension, and ankle oedema develop with progressing RV failure (Galie et al., 2016)[6]. Long durations, and high incurred costs for PH-related hospitalisations reveal the severe morbidity, health care, and patient burden of PAH (Lacey et al., 2013)[21].

Targeting therapy to achieve low risk status has been shown to improve survival and reduce clinical worsening events including hospitalisation (Galie et al., 2016[6], Sitbon and Gaine 2016[22]).

Table 1:Classification of Pulmonary Hypertension

Group	Subgroups	
1. Pulmonary Arterial Hypertension (PAH)	1.1 Idiopathic PAH	
	1.2 Heritable PAH	1.2.1 BMPR2 1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3 1.2.3 Unknown
	1.3 Drug and toxin induced	
	1.4 Associated with:	1.4.1 Connective tissue disease 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart diseases 1.4.5 Schistosomiasis
2. Pulmonary hypertension due to left heart disease	2.1 Left ventricular systolic dysfunction 2.2 Left ventricular diastolic dysfunction 2.3 Valvular disease 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies	
3. Pulmonary hypertension due to lung diseases and/or hypoxia	3.1 Chronic obstructive pulmonary disease 3.2 Interstitial lung disease 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern 3.4 Sleep-disordered breathing 3.5 Alveolar hypoventilation disorders 3.6 Chronic exposure to high altitude 3.7 Developmental lung diseases	
4. Chronic thromboembolic pulmonary hypertension (CTEPH)	-	
5. Pulmonary hypertension with unclear multifactorial mechanisms	5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH	

Source: [23] Consensus from the 5th World Symposium held in Nice, France, in 2013.
Abbreviations: BMPR = bone morphogenic protein receptor type II; CAV1 = caveolin-1; ENG = endoglin; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension

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

Population 1: Patients with systemic sclerosis (SSc)

Annual screening of all systemic sclerosis (SSc) patients to identify patients at risk of pulmonary arterial hypertension (PAH) is recommended by the American College of Cardiology Foundation/American Heart Association (ACCF/AHA), the European Society of Cardiology and European Respiratory Society (ESC/ERS), the National Pulmonary Hypertension centres of the UK and Ireland, and the Australian Scleroderma Interest Group (ASIG).

PAH screening is delivered in 15 centres across Australia (ASIG screening centres). Screening recommendations rely mainly on abnormal findings on transthoracic echocardiography (TTE). Other clinical tools include NT-proBNP as a marker of myocardial stress, and disproportionately reduced pulmonary diffusing capacity for carbon monoxide (DLCO) (Coghlan et al., 2013). The aim of screening is to identify patients at highest risk of developing PAH who should then undergo right heart catheterisation (RHC) to confirm the diagnosis.

The gold standard diagnostic tool in PAH is RHC, which determines a diagnosis of pulmonary hypertension, and further characterises the aetiology according to the WHO classification (Hoeper et al., 2013[24]; Galie et al., 2016[6]). PAH is determined as:

- a mean pulmonary arterial pressure (mPAP) equal to or higher than 25 mmHg,
- a normal back pressure from the heart, defined as a pulmonary arterial wedge pressure equal to or less than 15 mmHg, and
- a pulmonary vascular resistance (PVR) more than 3 Wood units measured during right heart catheterisation.

A pulmonary arterial wedge pressure higher than 15 mmHg indicates contributing left heart dysfunction.

Beyond confirmation of the diagnosis, RHC and other baseline tests assist to stratify the risk of disease progression, which assists in determining treatment options.

Population 2: Patients with pulmonary arterial hypertension (PAH)

The 2015 European Society of Cardiology and the European Respiratory Society (ESC/ERS) guidelines recommend a series of variables to stratify patients into low, intermediate, and high-risk categories, which corresponds to estimated one-year mortality rates of <5%, 5–10% and >10% respectively (Figure 1) and subsequently guides management. Not all of these assessments need to be measured at each visit; however, the basic program should include determination of the WHO FC, at least one measurement of exercise capacity (6MWD or CPET), and information on RV function (either BNP/NT-proBNP or echocardiography, Galie et al., 2016[6]).

These guidelines to determine risk and prognosis are used in Australian clinical practice. NT-proBNP levels correlate with myocardial dysfunction and provide prognostic information at the time of diagnosis, and during follow-up assessments.

These are commonly used in routine clinical practice and clinical trials.

Figure 1: Risk assessment in pulmonary hypertension

Determinants of prognosis[a] (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5–10%	High risk >10%
Clinical signs of right heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope[b]	Repeated syncope[c]
WHO functional class	I, II	III	IV
6MWD	>440 m	165–440 m	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.9	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 slope ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

Source: Galie et al., 2016[6]

Disease severity classification and risk stratification

The World Health Organization functional class (WHO FC) (Table 2) adopted from a modified New York Heart Association (NYHA) rating in 1998, remains one of the most powerful predictors of survival, not only at diagnosis, but also during follow-up (Galie et al., 2016)[6]. A worsening FC while on treatment is one of the most alarming indicators of disease progression, which triggers further investigations to identify the causes of clinical deterioration and would usually require consideration of a change in clinical management of the condition. Analysis of 3-year data from the REVEAL registry (n=982) has shown a significantly higher rate of

survival for patients whose FC improved than those who remained unchanged, within subtypes of PAH and whether newly diagnosed or previously diagnosed (Barst et al., 2013[25] and Benza et al., 2021[9]).

Table 2:Functional classification of pulmonary hypertension

Class	Description
I	Patients with pulmonary hypertension in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnoea, fatigue, chest pain, or presyncope.
II	Patients with pulmonary hypertension who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnoea, fatigue, chest pain, or presyncope.
III	Patients with pulmonary hypertension who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnoea, fatigue, chest pain, or presyncope.
IV	Patients with pulmonary hypertension who are unable to perform any physical activity at rest and who may have signs of right ventricular failure. Dyspnoea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity.

Source: Barst et al., 2013[25]

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

Population 1: Patients with systemic sclerosis (SSc)

The current Australian clinical pathway in identifying patients with sclerosis-related pulmonary arterial hypertension (SSc-PAH) is generally in line with several organisations and guidelines recommendations including the American College of Cardiology Foundation/American Heart Association (ACCF/AHA), the European Society of Cardiology/European Respiratory Society (ESC/ERS), and the DETECT algorithm that have published a variety of screening recommendations relying mainly on symptoms and abnormal findings on transthoracic echocardiography (TTE). Other clinical tools include NT-proBNP as a marker of myocardial stress, and disproportionately reduced pulmonary diffusing capacity for carbon monoxide (DLCO) on pulmonary function testing (PFT, Coghlan et al., 2013[26]). Following the 6th World Symposium on pulmonary hypertension (PH), the recommended diagnostic workup for SSc-PAH was updated. Annual screening of asymptomatic patients with SSc and SSc-spectrum disorders is recommended (Figure 2) (Brown et al., 2020[27]; Lechartier et al., 2021[28]).

Both the ESC/ERS 2015, and ACCP/AHA 2009 guidelines recommend initial screening upon SSc diagnosis by echocardiography (ECHO) with subsequent right heart catheterisation (RHC) if positive screen on ECHO (Figure 3) (Saygin et al., 2019)[29]. But there are limitations in symptom- and TTE-based algorithms. In the early stages, the symptoms of PAH are usually very mild and non-specific, making it difficult to identify patients who are developing PAH. In patients with SSc, coexisting organ involvement such as interstitial lung disease (ILD) makes the diagnosis of PAH even more challenging. In addition, the most widely used echocardiographic parameter, tricuspid regurgitant jet velocity (TRV), is not present in all patients. In fact, TRV cannot be obtained in 20% to 39% of patients, potentially decreasing the sensitivity of TTE-based algorithms. Another consideration is the cost-effectiveness of TTE-based screening (Hao et al., 2015)[30]. TTE can be costly in terms of resources and financially is dependent on operator technique and is unable to estimate systolic pulmonary artery pressure (sPAP) in up to 30% of patients due to lack of a tricuspid regurgitant jet. Furthermore, access to good-quality echocardiography for estimation of sPAP is very limited in regional Australia, with prolonged waiting times in many metropolitan areas (Quinlivan et al., 2019)[31].

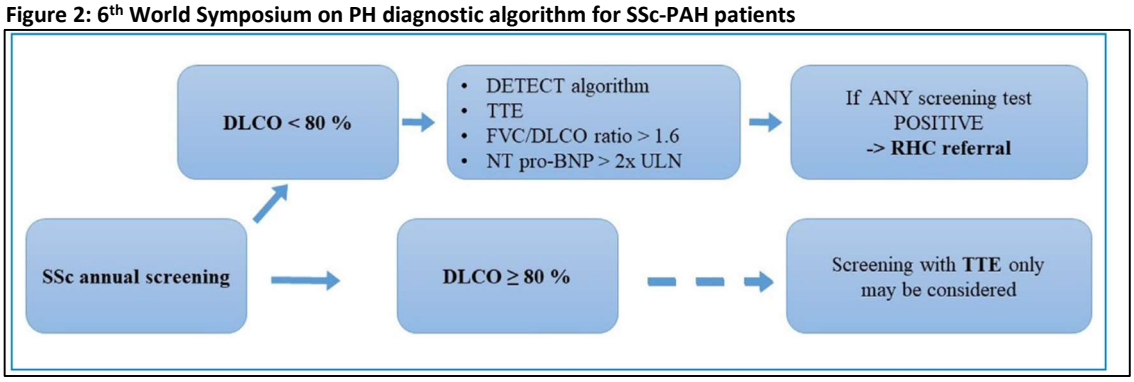
These limitations of TTE-based screening algorithms emphasise the need for alternative approaches to improve the selection of patients for referral for RHC, the 'gold standard' test for the diagnosis of PAH. Emerging screening algorithms incorporate pulmonary function tests (PFTs), and biomarkers such as NT-pro-BNP(Kiely et al., 2019[32]).

The DETECT algorithm is another commonly used clinical pathway that proposes a two-step approach to assessing patients with SSc for PAH (Figure 4). In Step 1, patients undergo a series of six tests, including clinical assessment for the presence of telangiectasia, PFTs, electrocardiogram, and serum biomarkers (anticentromere antibody, NT-pro-BNP, and uric acid) to identify those requiring further assessment by TTE (Step 2). Those with a high-risk score should then be referred for a RHC (Kiely et al., 2019)[32]. The two-step algorithm improved the sensitivity of screening for SSc-PAH from 71% to 96% in comparison with the ESC/ERS guidelines (Hao et al., 2015)[30].

The Australian Scleroderma Interest Group (ASIG) developed a screening algorithm for SSc-PAH by using serum NT-proBNP level and PFT (Figure 5); this was found to have similar sensitivity and higher specificity and positive (PPV) and negative (NPV) predictive value in comparison with the ESC/ERS guidelines. The ASIG clinical pathway recommends annual screening of all asymptomatic SSc patients with a non-invasive screening algorithm for PAH based on NT-proBNP levels and lung function parameters as the first tier screening for PAH. All positive patients for both or either tests should then be referred for a RHC, which is the confirmatory diagnosis for PAH. This algorithm had sensitivity, specificity, positive, and negative predictive values for the detection of PAH of 94.1%, 54.5%, 61.5%, and 92.3%, respectively. The ASIG algorithm showed significantly improved diagnostic accuracy compared with the use of PFTs or NT-pro-BNP alone and has a potential advantage of not using TTE (Kiely et al., 2019)[32]. This is the screening algorithm proposed in this application and the application is requesting MBS funding of the NT-proBNP test.

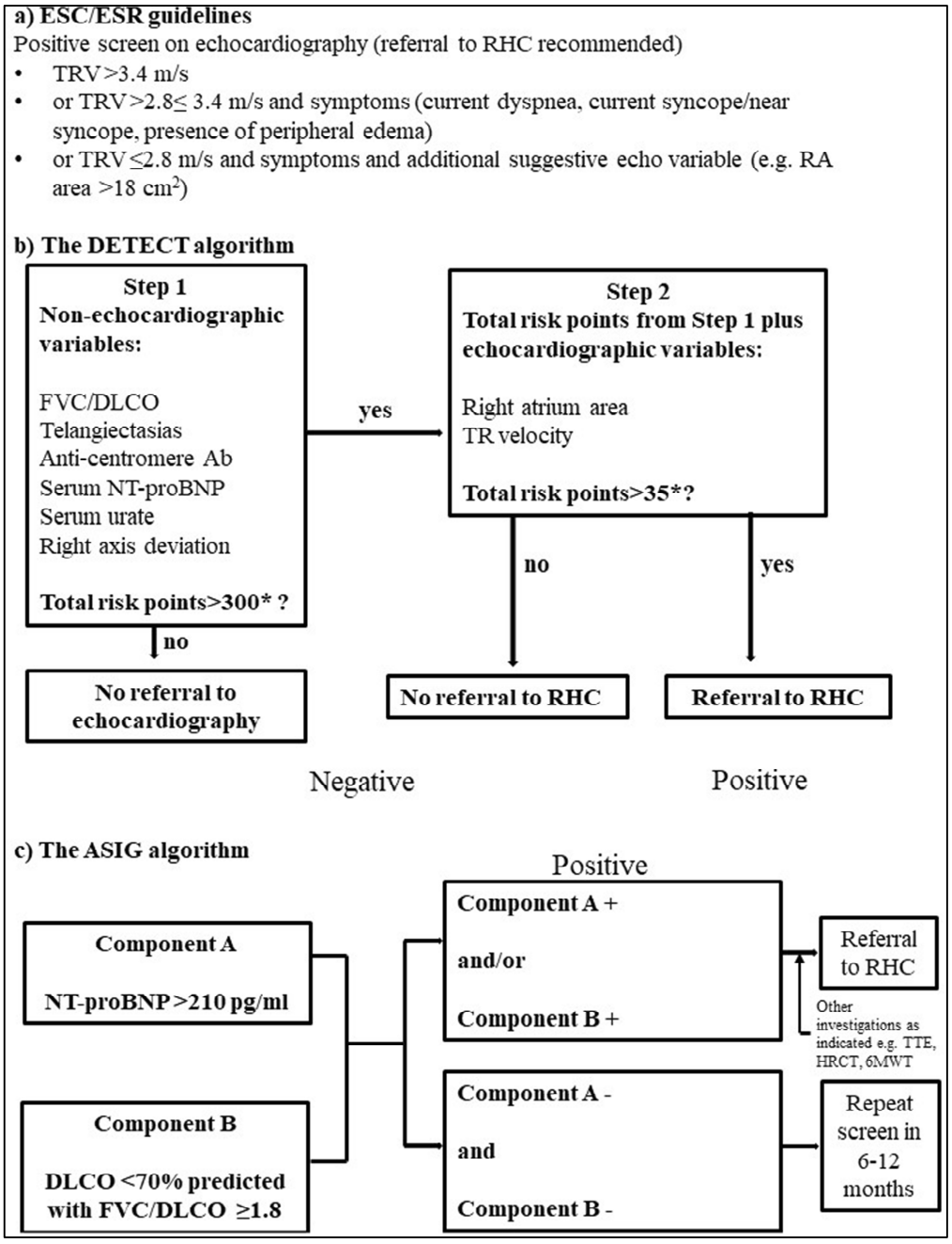
A comparison of the predictive accuracy of the DETECT and the Australian Scleroderma Interest Group for SSc-PAH with the commonly used ESC/ERS guidelines showed that both the DETECT and ASIG algorithms outperform the ESC/ERS guidelines, detecting all patients with PAH, albeit the ASIG algorithm had the highest specificity (54.5%). Compared with the DETECT algorithm, the ASIG algorithm performed equally well in sensitivity (100%) and NPV (100%), a little better in PPV (60%), and moderately better in specificity (54.5%). The referral rate for RHC was 68%, and the proportion of RHCs that did not confirm a diagnosis of PAH was 40% (Hao et al., 2015)[30].

Figure 2: 6th World Symposium on PH diagnostic algorithm for SSc-PAH patients



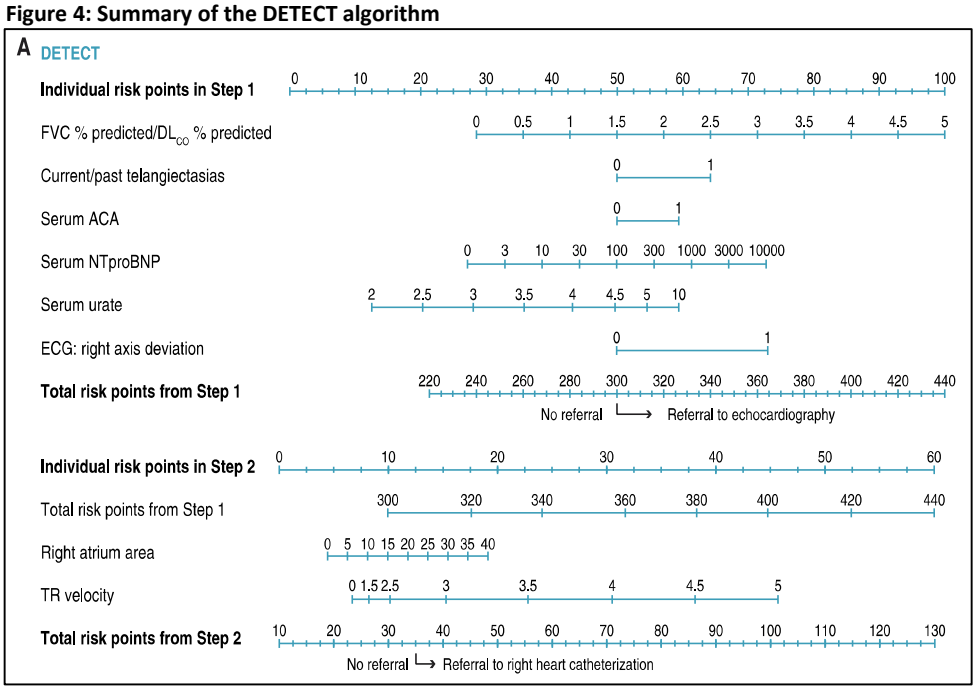
Source: Lechartier et al., 2021[28]

Figure 3: Summary of the ESC/ESR algorithm



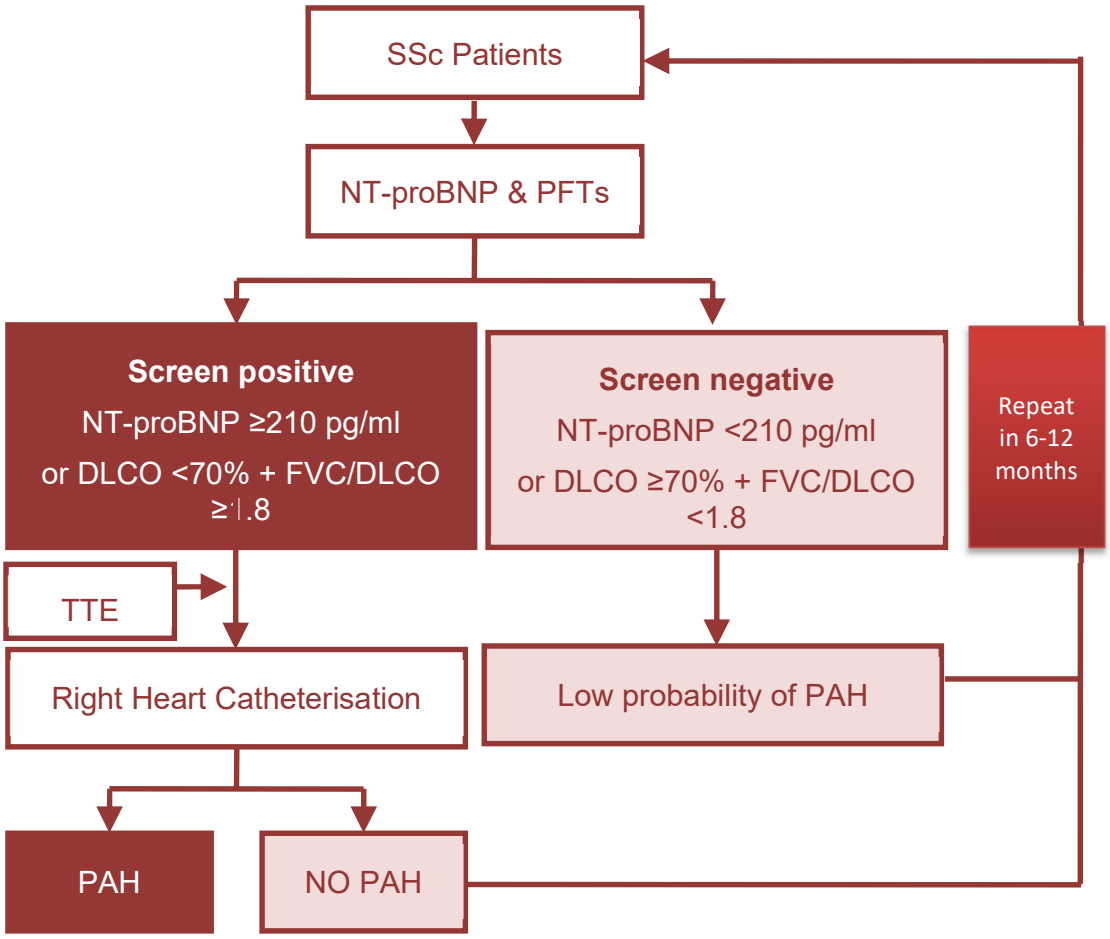
Source: Figure 1, Saygin et al., 2019[29]

Figure 4: Summary of the DETECT algorithm



Source: Kiely et al., 2019[32]

Figure 5: Summary of the Australian Scleroderma Interest group algorithm



Source: Adapted from Quinlivan et al., 2015[10]

Population 2: Patients with pulmonary arterial hypertension (PAH)

Following diagnosis of patients with PAH, regular assessment of patients in expert PH centres is strongly recommended. The most important questions to be addressed at each visit are

(i) is there any evidence of clinical deterioration since the last assessment?

(ii) if so, is clinical deterioration caused by progression of PH or by a concomitant illness?

(iii) is RV function stable and sufficient? and

(iv) is the current status compatible with a good long-term prognosis, i.e. does the patient meet the low-risk criteria. In order to answer these questions, a multidimensional approach is needed.

Not all of these assessments need to be measured at each visit; however, the basic program should include determination of the WHO FC, at least one measurement of exercise capacity (6MWD or CPET), and information on RV function (either BNP/NT-proBNP or echocardiography, Galie et al., 2016[6]). Figure 6 provides recommendations on the assessment, and timing for the follow-up of patients with PAH. These guidelines to determine risk and prognosis are used in Australian clinical practice.

Figure 6: Suggested assessment and timing for the follow-up of patients with in pulmonary arterial hypertension

	At baseline	Every 3–6 months[a]	Every 6–12 months[a]	3–6 months after changes in therapy[a]	In case of clinical worsening
Medical assessment and determination of functional class	+	+	+	+	+
ECG	+	+	+	+	+
6MWT/Borg dyspnoea score	+	+	+	+	+
CPET	+		+		+[e]
Echo	+		+	+	+
Basic lab[b]	+	+	+	+	+
Extended lab[c]	+		+		+
Blood gas analysis[d]	+		+	+	+
Right heart catheterization	+		+[f]	+[e]	+[e]

ALAT = alanine aminotransferase; ASAT = aspartate aminotransferase; BGA = blood gas analysis; BNP = brain natriuretic peptide; CPET = cardiopulmonary exercise testing; Echo = echocardiography; ECG = electrocardiogram; ERAs = endothelin receptor antagonists; FC = functional class; INR = international normalized ratio; lab = laboratory assessment; NT-proBNP = N-terminal pro-brain natriuretic peptide; RHC = right heart catheterization; TSH = thyroid stimulating hormone; 6MWT = 6-minute walking test.
[a]Intervals to be adjusted according to patient needs.
[b]Basic lab includes blood count, INR (in patients receiving vitamin K antagonists), serum creatinine, sodium, potassium, ASAT/ALAT (in patients receiving ERAs), bilirubin and BNP/NT-proBNP.
[c]Extended lab includes TSH, troponin, uric acid, iron status (iron, ferritin, soluble transferrin receptor) and other variables according to individual patient needs.
[d]From arterial or arterialized capillary blood; may be replaced by peripheral oxygen saturation in stable patients or if BGA is not available.
[e]Should be considered.
[f]Some centres perform RHCs at regular intervals during follow-up.

Source: Galie et al., 2018[6]

However, to expedite risk assessment in the clinic, where comprehensive data for all patients may be lacking and time constrained, risk assessment tools using fewer variables are preferable. REVEAL Lite 2 is based on the recently developed and validated REVEAL 2.0 risk calculator (Benza et al 2012[33], Anderson 2020[8], Kanwar et al., 2020[34] in an abridged format. REVEAL Lite 2 uses six modifiable and non-invasive variables (Figure 7). The model indicated that the most highly predictive parameter included in REVEAL Lite 2 (based on the c 2 value) was BNP/NT- proBNP, followed by 6MWD and NYHA or WHO FC. This risk assessment algorithm obviates the needs to perform the invasive procedures of RHC. This non-invasive risk assessment allows for NT-proBNP to be ordered prior to the patients visiting their specialist so results can be discussed at the consultation.

Figure 7: Variables included in the REVEAL 2.0 and REVEAL Lite 2 Risk Calculators and Associated Risk Scores

Parameter	REVEAL 2.0 (13 Variables)	REVEAL Lite 2 (6 Variables)
Cause	Connective tissue disease: +1 Portopulmonary hypertension: +3 Heritable: +2	—
Demographics	Men > 60 y: +2	—
Renal insufficiency	eGFR < 60 mL/min/1.73 m^2 or defined by clinical judgment if eGFR is not available: +1	
NYHA or WHO FC	FC I: −1 FC III: +1 FC IV: +2	
All-cause hospitalization within the previous 6 mo	+1	—
Vital signs	SBP < 110 mm Hg: +1 HR > 96 bpm: +1	
6MWD	≥ 440 min: −2 320-< 440 min: −1 < 165 min: +1	
BNP/NT-proBNP	BNP < 50 pg/mL OR NT-proBNP < 300 pg/mL: −2 BNP 200-< 800 pg/mL: +1 BNP ≥800 pg/mL OR NT-proBNP ≥1100 pg/mL: +2	
Echocardiogram	Pericardial effusion: +1	—
Pulmonary function test	% predicted D_{LCO} < 40%: +1	—
RHC within 1 y	mRAP > 20 mm Hg: +1 PVR < 5 Wood units: −1	—
Total score	Sum of above scores +6	Sum of above scores +6

Source: Table 1, Benza et al 2021[9].

NOTE: The dashes denote parameter not included in REVEAL Lite 2. 6MWD 1⁄4 6-min walk distance; BNP 1⁄4 brain natriuretic peptide; bpm 1⁄4 beats per minute; DLCO 1⁄4 diffusing capacity of the lungs for carbon monoxide; eGFR 1⁄4 estimated glomerular filtration rate; FC 1⁄4 functional class; HR 1⁄4 heart rate; mRAP 1⁄4 mean right atrial pressure; NT-proBNP 1⁄4 N-terminal prohormone of brain natriuretic peptide; NYHA 1⁄4 New York Heart Association; PAH 1⁄4 pulmonary arterial hypertension; PVR 1⁄4 pulmonary vascular resistance; REVEAL 1⁄4 Registry to Evaluate Early and Long-Term PAH Disease Management; RHC 1⁄4 right heart catheterization; SBP 1⁄4 systolic BP; WHO 1⁄4 World Health Organization.

PART 6b – INFORMATION ABOUT THE INTERVENTION

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

Population 1: Patients with systemic sclerosis (SSc)

In the absence of MBS funded NT-proBNP assessment, current clinical assessment for risk of pulmonary arterial hypertension (PAH) in patients with systemic sclerosis (SSc), is dependent on annual screening with transthoracic echocardiogram (TTE), and pulmonary function tests (PFTs), regardless of the presence or absence of the risk factors, to identify patients who should undergo right-heart catheterisation (RHC) to confirm the diagnosis.

The proposed medical service facilitates for annual screening in line with the Australian Scleroderma Interest Group (ASIG) clinical algorithm for the early detection of sclerosis-related pulmonary arterial hypertension (SSc-PAH) (population 1) (Figure 5), and the European Society of Cardiology/European Respiratory Society (ESC/ERS 2015) guidelines for regular assessment of patients with PAH (population 2) (Figure 6) with MBS funding of the NT-proBNP test

The proposed medical service NT-proBNP biomarker assay as part of a screening algorithm for pulmonary hypertension, to select patients requiring right heart catheterisation (RHC), would apply to all patients with systemic sclerosis **(**SSc). The NT-proBNP test would be ordered by a specialist physician caring for patients with SSc as part of screening for pulmonary arterial hypertension (PAH) usually undertaken once to twice annually per patient.

NT-proBNP biomarker level assessment requires venepuncture for a sample of blood that is sent to an accredited pathology service with appropriate accreditation, where the assay to measure the circulating level of this neurohormone would be performed.

The result would be made available by the pathology service in the usual way e.g. by electronic or paper report, and used in conjunction with other parameters e.g. clinical features and pulmonary function tests, to determine the patient's risk of PAH and the need for further tests such as echocardiography and diagnosis through right heart catheterisation (RHC).

The proposed medical service (NT-proBNP biomarker assay) would occur once to twice annually in combination with pulmonary function tests (PFT) as part of a screening algorithm used to select patients at increased risk of PAH for referral for diagnosis with a RHC.

Screening is positive if both or either NT-proBNP is at least 210 pg/mL, and DLCO is less than 70% predicted with an FVC/DLCO of at least 1.8. A screen is negative if both tests are absent. All patients with a positive screen move on to transthoracic echocardiography (TTE) mainly in order to exclude the other contributing factors for PH (left heart dysfunction, ILD, and pulmonary embolism). If no alternative explanation is found for a positive screen, patients undergo confirmatory RHC. Screening will be repeated every 6-12 months in all patients with a negative screen.

Population 2: Patients with pulmonary arterial hypertension (PAH)

Regular assessment is a key part of the evaluation of patients with PAH, as it provides valuable information for determining disease severity, improvement, deterioration, or stability. NT-proBNP levels correlate with myocardial dysfunction and provide prognostic information at the time of diagnosis and during follow-up assessments. The medical service would occur up to a maximum of every 3 months (i.e. up to 4 times per year) according to patients needs and physician discretion (Figure 7).

However, to expedite risk assessment in the clinic, where comprehensive data for all patients may be lacking and time constrained, risk assessment tools using fewer variables are preferable (REVEAL Lite 2 risk calculator (Benza et al 2021).[9] REVEAL Lite 2 uses six modifiable and non-invasive variables (Figure 7). The model indicated that the most highly predictive parameter included in REVEAL Lite 2 was BNP/NT-proBNP, followed by 6MWD and NYHA or WHO FC. Utilising NT-proBNP testing into non-invasive risk assessment algorithms obviates the needs to perform the invasive procedures of RHC and still discriminates among PAH risk groups.

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

Insert description of registered trademark component here

A number of companies in Australia manufacture immunoassays for the detection of the inactive NT-proBNP. Jannsen does not manufacture or provide the NT-prpBNP assay. Based on our research the commercially available tests include

- Roche Diagnostics (CARDIAC® NT-pro-BNP),
- Siemens Healthineers (Stratus® CS Acute Care™),
- BioMerieux (VIDAS NT-proBNP2),

This application only applies to the NT-proBNP assays.

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

N/A

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

Population 1: Patients with systemic sclerosis (SSc)

The proposed medical service (NT-proBNP biomarker assay) would occur up to twice annually per patient.

Population 2: Patients with pulmonary arterial hypertension (PAH)

The proposed medical service (NT-proBNP biomarker assay) would occur up to 4 times annually per patient.

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

Population 1: Patients with systemic sclerosis (SSc)

The proposed medical service NT-proBNP biomarker assay would occur once to twice annually in systemic sclerosis (SSc) patients in combination with pulmonary function test (PFT) as part of a screening algorithm used to select patients at increased risk of pulmonary arterial hypertension (PAH) for referral for right heart catheterisation (RHC).

At physician discretion, most patients with a positive screen move on to transthoracic echocardiography (TTE) mainly in order to exclude the other contributing factors for pulmonary hypertension (left heart dysfunction, ILD, and pulmonary embolism). If no alternative explanation is found for a positive screen, patients undergo a confirmatory RHC for PAH.

Population 2: Patients with pulmonary arterial hypertension (PAH)

The proposed medical service, NT-proBNP biomarker assay would occur up to 4 times annually as part of a regular non-invasive assessment and be part of a routine non-invasive heamodynamic assessment of the risk of PAH patients. In addition to NT-proBNP, the 6MWD, NYHA or WHO FC, vital signs and renal insufficiency would be assessed to complete a validated multiparameter risk assessment

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

The assay would be performed by an accredited pathology service and only requested and evaluated by PAH specialist physicians involved in the management of patients with SSc and/or PAH.

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

The assay would be performed by an accredited pathology service and only requested and evaluated by PAH specialist physicians involved in the management of patients with SSc and/or PAH.

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

The assay would be performed by an accredited pathology service and only requested and evaluated by PAH specialist physicians involved in the management of patients with SSc and/or PAH.

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

If applicable, insert advice regarding training or qualifications

Fellows of the Royal Australasian College of Physicians (RACP) would interpret the result of the assay performed by a NATA accredited pathology service with appropriate facilities and likely under the supervision of a Fellow of the Royal College of Pathologist of Australasia (RCPA[3]) (biochemistry).

36. (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)

[3] RCPA NT-proBNP - https://www.rcpa.edu.au/Manuals/RCPA-Manual/Pathology-Tests/N/NT-proBNP

☐ 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:

N/A

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

☒ Yes
☐ No – please specify below

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

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

Population 1: Patients with systemic sclerosis (SSc)

In the absence of MBS funded NT-proBNP assessment, current clinical assessment for risk of pulmonary arterial hypertension (PAH) in patients with systemic sclerosis (SSc), is dependent on annual screening with transthoracic echocardiogram (TTE), and pulmonary function tests (PFTs), regardless of the presence or absence of the risk factors, to identify patients who should undergo right-heart catheterisation (RHC) to confirm the diagnosis.

The appropriate comparator for the proposed medical service is considered annual TTE. NT-proBNP assessment would replace TTE.

Population 2: Patients with pulmonary arterial hypertension (PAH)

The ongoing risk assessment in the PAH population is multi-dimensional approach. Not all of these assessments need to be measured at each visit; however, the basic program should include determination of the WHO FC, at least one measurement of exercise capacity (6MWD or CPET), and information on RV function (either BNP/NT-proBNP or echocardiography) (Galie et al., 2018)[6]. These guidelines to determine risk and prognosis in Australian clinical practice and non-invasive haemodynamic assessment (Figure 7 above) provides risk assessment for discriminating low, intermediate, and high-risk patients. The most highly predictive parameter REVEAL Lite 2 is BNP/NT-proBNP, followed by 6MWD and FC, thus obviating the need to include TTE or an invasive RHC test to assess risk in PAH patients.

The appropriate comparator for the proposed medical service in this population is TTE and RHC as risk assessment can be made using a validated non-invasive algorithm including NT-proBNP and excluding TTE and RHC.

39. 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

Population 1: Patients with systemic sclerosis (SSc)

For TTE

MBS Item 55133

Note: the service only applies if the patient meets one or more of the following and the requirements of Note: IR.1.2

Frequent repetition serial real time transthoracic echocardiographic examination of the heart with real time colour flow mapping from at least 3 acoustic windows, with recordings on digital media, if the service:

(a) is for the investigation of a patient who:

(i) has an isolated pericardial effusion or pericarditis; or

(ii) has a normal baseline study, and has commenced medication for non-cardiac purposes that has cardiotoxic side effects and is a pharmaceutical benefit (within the meaning of Part VII of the National Health Act 1953) for the writing of a prescription for the supply of which under that Part an echocardiogram is required; and

(b) is not associated with a service to which:

(i) another item in this Subgroup applies (except items 55137, 55141, 55143, 55145 and 55146); or

(ii) an item in Subgroup 2 applies (except items 55118 and 55130); or

(iii) an item in Subgroup 3 applies (R)

Fee: $212.65 Benefit: 75% = $159.50 85% = $180.80

The reimbursed cost of PFT (including spirometry and DLCO) is $144.25 (MBS item number 11503).

Population 2: Patients with pulmonary arterial hypertension (PAH)

For TTE
MBS Item 55133 (as above).

For RHC:

MBS Item 13818

RIGHT HEART BALLOON CATHETER, insertion of, including pulmonary wedge pressure and cardiac output measurement

Fee: $118.30 Benefit: 75% = $88.75 85% = $100.60

MBS Item 13818

INITIATION OF MANAGEMENT OF ANAESTHESIA for central vein catheterisation or insertion of right heart balloon catheter (via jugular, subclavian or femoral vein) by percutaneous or open exposure

(5 basic units)

Fee: $103.00 Benefit: 75% = $77.25 85% = $87.55

MBS Item 22015

RIGHT HEART BALLOON CATHETER, insertion of, including pulmonary wedge pressure and cardiac output measurement, when performed in association with the administration of anaesthesia

(6 basic units)

Fee: $123.60 Benefit: 75% = $92.70 85% = $105.10

MBS Item 38254

Right heart catheterisation:

(a) performed at the same time as service to which item 38244, 38247, 38248, 38249, 38251 or 38252 applies; and

(b) including any of the following (if performed):

(i) fluoroscopy;

(ii) oximetry;

(iii) dye dilution curves;

(iv) cardiac output measurement;

(v) shunt detection;

(vi) exercise stress test

Multiple Operation Rule

(Anaes.)

Fee: $463.50 Benefit: 75% = $347.65 85% = $394.00

40. Define and summarise the current clinical management pathway/s 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):

Population 1: Patients with systemic sclerosis (SSc)

The current clinical assessment of sclerosis-related pulmonary arterial hypertension (SSc-PAH) is based on annual transthoracic echocardiography (TTE), and pulmonary function tests. If abnormal findings suggest increased risk of heart or lung complications, definitive investigations such as right-heart catheterisation (RHC) or high resolution CT scan of the chest (HRCT chest) are indicated in a patient at high risk of PAH or interstitial lung disease (ILD), respectively (Australian Rheumatology Association).

Those identified at low risk of PAH, based on the NT-proBNP biomarker (combined with PFT), will be excluded from further testing (No TTE or RHC) and re-screened in 6-12 months. Those identified at high risk of PAH, based on the NT-proBNP biomarker (combined with PFT), will be referred forRHC, which is mandatory for the diagnosis of PAH but may include a TTE as an intermediate test at physician discretion. See Figure 8: Summary of the Australian Scleroderma Interest group algorithm

Population 2: Patients with pulmonary arterial hypertension (PAH)

Regular multiparameter risk assessment of patients with PAH is strongly recommended (Galie et al., 2018)[6]. While risk stratification strategies include investigations such as cardiopulmonary exercise testing (CPET), the current practice is to monitor patients through clinical assessment (including functional class) and with TTE or RHC. Six-minute walk distance is a useful measure of exercise capacity in those without other comorbidities. Utilising NT-proBNP testing into non-invasive risk assessments algorithms obviates the needs to perform the invasive procedures of RHC and still discriminates among PAH risk groups. The comparator test is used to assess the need for additional therapy be that additional medical therapy or moving towards lung transplantation. Use of NT-proBNP will not affect the decision to add therapy but may mean that the more expensive investigations are not required.

41. (a) Will the proposed medical service 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 instead of (i.e. alternative service), please outline the extent to which the current service/comparator is expected to be substituted:

Population 1: Patients with systemic sclerosis (SSc)

The NT-proBNP assay will replace the routine use of TTE for screening patients at high risk of PAH. Pulmonary function tests will continue to be used in all patients to determine the FVC/DLCO ratio which is part of the NT-proBNP-based screening algorithm. Only those identified as high risk based on the initial tests with NT-proBNP (combined with PFT) will go on to receive RHC but may have an intermediate test with TTE at physician discretion. Those identified at low risk of PAH, based on the NT-proBNP biomarker (combined with PFT), will be excluded from further testing (No TTE or RHC) and re-screened in 6-12 months.

Population 2: Patients with pulmonary arterial hypertension (PAH)

The NT-proBNP assay as part of a multiparameter validated non-invasive risk assessment will replace the use of TTE and RHC in invasive multiparameter regular risk assessment of patients with PAH. Risk assessments will predict prognosis and determine disease progression.

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

Population 1: Patients with systemic sclerosis (SSc)

The current Australian clinical practice for assessment of risk from pulmonary arterial hypertension (PAH) in patients with systemic sclerosis (SSc) is based on annual transthoracic echocardiography (TTE), and pulmonary function tests. Following a positive screen of increased risk of heart or lung complications, definitive investigations such as right-heart catheterisation (RHC) or high-resolution CT scan of the chest (HRCT chest) are indicated in a patient at high risk of PAH or interstitial lung disease (ILD), respectively.

Assessment of NT-proBNP plasma level in the estimated population of SSc patients in Australia is expected to reduce the number of transthoracic echocardiograms (TTEs) required compared with current practice. In all positive screens, patients will also be offered a TTE to identify other cardiac causes, at physician discretion. A definitive investigation with RHC is indicated in a patient at high risk of PAH

All negative screens will be retested once to twice annually as part of a risk assessment used to select patients at increased risk of PAH for referral for RHC. This will reduce the number of TTE and RHC tests required compared with current practice.

In a cost comparison of screen-naïve patients from the ASCS, the proposed medical service resulted in 64% fewer TTE, and 10% fewer RHC compared with current practice, with $1936 (15%) saved for each case of PAH diagnosed. When the costs were extrapolated to the entire Australian SSc population, there was an estimated screening cost saving of $946,000 per annum with the proposed medical service, with a cost saving of $851,400 in each subsequent year of screening (Quinlivan et al., 2015)[10].

Once a diagnosis of PAH has been made, the management pathway remains unchanged except for assessment of risk in PAH patients (see Population 2 in this application).

Population 2: Patients with pulmonary arterial hypertension (PAH)

The current Australian clinical practice for risk assessment of PAH patients is based on the 2018 European Society of Cardiology and the European Respiratory Society (ESC/ERS) guidelines and other algorithms that include multiparamaters with measures from TTE and RHC. However, assessment of NT-proBNP as part of a non-invasive risk assessment in the estimated population of PAH patients in Australia will provide validated evaluation of risk stratification during regular clinical consultations. With the adoption of routine measured of NT-proBNP, the utilization of other tests in the risk assessment of PAH, such as TTE and an invasive RHC will be decreased.

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

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

Population 1: Patients with systemic sclerosis (SSc)

The Australian Scleroderma Interest Group (ASIG) algorithm has sensitivity, specificity, positive, and negative predictive values for the detection of PAH of 94.1%, 54.5%, 61.5%, and 92.3%, respectively. The ASIG algorithm showed significantly improved diagnostic accuracy compared with the use of PFTs or NT-pro-BNP alone and has a potential advantage of not using TTE (Kiely et al., 2019)[32].

A comparison of the predictive accuracy of the DETECT and the Australian Scleroderma Interest Group for SSc-PAH with the commonly used ESC/ERS guidelines showed that both the DETECT and ASIG algorithms outperform the ESC/ERS guidelines, detecting all patients with PAH, albeit the ASIG algorithm had the highest specificity (54.5%). Compared with the DETECT algorithm, the ASIG algorithm performed equally well in sensitivity (100%) and NPV (100%), a little better in PPV (60%), and moderately better in specificity (54.5%). The referral rate for RHC was 68%, and the proportion of RHCs that did not confirm a diagnosis of PAH was 40% (Hao et al., 2015)[30].

Population 2: Patients with pulmonary arterial hypertension (PAH)

Raised NT-proBNP levels are directly related to the severity of PAH. A post-hoc analysis showed that baseline and follow-up NT-proBNP categories were highly prognostic for future morbidity/mortality events during the study (P< 0.0001). Analyses further establish the prognostic relevance of NT-proBNP levels in PAH and provide first evidence for the association of NT-proBNP level and treatment response (Chin 2019)[35].

NT-proBNP testing has the ability to stratify patients according to risk status when used with other non-invasive parameters (Benza et al., 2021)[9]. The most highly predictive parameter (REVEAL Lite 2) was BNP/NT-proBNP, followed by 6MWD and FC (the variables TTE and invasive RHC were not needed). Including NT-proBNP in the non-invasive risk assessment (REVEAL Lite 2), provides a simplified method of risk assessment that can be implemented routinely in daily clinical practice and is a robust tool that provides discrimination among patients at low, inter- mediate, and high risk of 1-year mortality (Benza et al., 2021[9]).

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

☐ Superiority
☒ Non-inferiority for Population 1 and Population 2

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

Safety Outcomes:

Population 1
Reduction of TTE required with a commensurate reduction in morbidity and mortality associated with this test.

Population 1 and 2
Reduction of TTE and RHCs with current practice with a commensurate reduction in morbidity and mortality associated with this test.

Clinical Effectiveness Outcomes:

Population 1 and 2

1- Sensitivity

2- Specificity

3- Positive predictive value

4- Negative predictive value

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

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

Population 1: Patients with systemic sclerosis (SSc)

The prevalence of systemic sclerosis (SSc) in Australia is 20/100,000 per population. Pulmonary arterial hypertension (PAH) occurs in approximately 10% of patients with SSc (8-12%, in Morrisroe et al;, 2017[36], Australian Rheumatology Association). The annual incidence of PAH in SSc is approximately 0.7-1.4% (Morrisroe et al., 2016[37] and Morrisroe et al., 2017[36]). Thus based on the prevalence rate, the current (2021) number of SSc patients in Australia is estimated to be approximately 5,260 patients.

Population 2: Patients with pulmonary arterial hypertension (PAH)

The DUSC review of PAH treatments (DUSC, 2015), found that the prevalence and incidence rates of PAH treatment are 87.6 and 18.6 per million population.

A literature search did not locate more recent estimates of prevalence or incidence of PAH in Australia. Application of the DUSC's estimates to the total Australian population of 26,301,277 (estimated for 2021 (ABS 3222.0 Population Projections Series B), results in an estimated prevalence of 2,229 and an incidence of 473.

Additionally, we analysed the 10% PBS script data[4] (July 2020-June 2021) and we estimated that between 2,900 – 3,200 PAH patients are being treated. We can assume that 100% of diagnosed PAH are treated given the severity and mortality impact of PAH.

Thus the estimated diagnosed (prevalent pool) of patients in the current year can be assumed to be between 2,229 to 3,200 and thus would be eligible for ongoing risk assessment with measurement of NT-proBNP.

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

Population 1: Patients with systemic sclerosis (SSc)

In patients with SSc, once to twice (maximum) yearly until diagnosis of pulmonary arterial hypertension is made.

Population 2: Patients with pulmonary arterial hypertension (PAH)

In patients with PAH, up to a maximum of once every 3 months (4 times per year).

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

Population 1: Patients with systemic sclerosis (SSc)

In patients with SSc, twice yearly until diagnosis of pulmonary hypertension is made and then these patients enter or become part of Population 2, ongoing risk assessment.

Population 2: Patients with pulmonary arterial hypertension (PAH)

In patients with PAH, regular assessment is recommended up to a maximum of once every 3 months (i.e. 4 times/year) for the life of the patient.

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

Population 1: Patients with systemic sclerosis (SSc)

Using the estimates from Question 46, Table 3 shows that in the first full year on NT-proBNP being funded on the MBS, the projected number of patients who will utilise the proposed medical service (NT-

[4] PBS 10% SampleData Source: Prospection HealthCare Analytics, Pharmadash, accessed July 2021

proBNP test is 5,260. In Year 2 the expected number of patients is 5,339 and in Year 3 it is 5,419 (eg. 27,096,234 * 0.02%).

Table 3: Patients with systemic sclerosis (SSc) who will use the medical service

	Year 1	Year 2	Year 3
Australian Population*	26,301,277	26,695,797	27,096,234
Prevalent number of patients	5,260	5,339	5,419

Source: Australian population of 26,301,277 (estimated for 2021 (ABS 3222.0 Population Projections Series B) and assume 1.5% annual growth

Population 2: Patients with pulmonary arterial hypertension (PAH)

Using the estimates from Question 46, Table 4 shows that in the first full year on NT-proBNP being funded on the MBS, the projected number of patients who will utilise the proposed medical service (NT-proBNP test is between 2,229 and 3,200 and in years 2 and 3 the projected number of patients varies between 2,726-3,697 (year 2) and 3,230-4,201 (year 3).

Table 4: Patients with pulmonary arterial hypertension (PAH) who will use the medical service

	Year 1	Year 2	Year 3
Australian Population*	26,301,277	26,695,797	27,096,234
Low Estimate of PAH Patients			
PAH Prevalent Patients	2,229		
PAH Incident patients		497	504
Total PAH Patients	2,229	2,726	3,230
High Estimate of PAH Patients			
PAH Prevalent Patients	3,200		
PAH Incident patients		497	504
Total PAH Patients	3,200	3,697	4,201

Source: Australian population of 26,301,277 (estimated for 2021 (ABS 3222.0 Population Projections Series B) and assume 1.5% annual growth

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

Population 1: Patients with systemic sclerosis (SSc)

Table 5 shows that in the first full year on NT-proBNP being funded on the MBS, the projected uptake proposed medical service (NT-proBNP test) is 9,468 tests. In Year 2 the projected uptake proposed medical service is 9,610 test and in Year 3 it is 9,755 tests.

The risk of leakage to populations other than SSc is very low.

Table 5: Anticipated uptake of the proposed medical service in patients with systemic sclerosis (SSc)

	Year 1	Year 2	Year 3
SSc Patients (Table 3)	5,260	5,339	5,419
Uptake of medical service	90%	90%	90%
SSc Patients	4,734	4,805	4,877
NT-proBNP test/pt/year	2	2	2
NT-proBNP tests/year	9,468	9,610	9,755
NTproBNP Test Fee	$58.50	$58.50	$58.50
Cost to MBS	$553,905	$562,213	$570,647

Population 2: Patients with pulmonary arterial hypertension (PAH)

Table 6 shows that in the first full year on NT-proBNP being funded on the MBS, the projected uptake of the proposed medical service (NT-proBNP test) is between 8,028 and 11,520 tests and in years 2 and 3 the projected uptake of the proposed medical service varies between 9,816-13,312 tests (year 2) and 11,628-15,124 tests (year 3). The risk of leakage to populations other than PAH is very low.

Table 6: Anticipated uptake of the proposed medical service in patients with pulmonary arterial hypertension (PAH)

	Year 1	Year 2	Year 3
Low Estimate of Medical Service			
PAH Patients (Table 4)	2,229	2,726	3,230
Uptake of test	90%	90%	90%
PAH Patients	2007	2454	2907
NT-proBNP test/pt/year	4	4	4
NT-proBNP tests/year	8,028	9,816	11,628
NTproBNP Test Fee	$58.50	$58.50	$58.50
Cost to MBS	$469,638	$574,236	$680,238
High Estimate of Medical Service			
PAH Patients (Table 4)	3,200	3,697	4,201
Uptake of test	90%	90%	90%
PAH Patients Low	2,880	3,328	3,781
NT-proBNP test/pt/year	4	4	4
NT-proBNP tests/year	11,520	13,312	15,124
NTproBNP Test Fee	$58.50	$58.50	$58.50
Cost to MBS	$673,920	$778,752	$884,754

Taking both the populations into account (SSc and the high estimate for PAH), it is estimated that the maximum incremental cost to the MBS would be $1.23million in year 1 and increasing to $1.46million in year 3.

PART 8 – COST INFORMATION

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

The proposed NT-proBNP assay is the same service as currently covered under the MBS item no. 66830 (provided below). This application is requesting two additional populations, so the cost of the proposed MBS items will be the same (ie. $58.50, Table 7).

Table 7: Current NT-proBNP MBS Item 66830

Category 6 - PATHOLOGY SERVICES Group P2 – Chemical
66830 Quantitation of BNP or NT-proBNP for the diagnosis of heart failure in patients presenting with dyspnoea to a hospital Emergency Department (Item is subject to rule 25) Fee: $58.50 Benefit: 75% = $43.90 85% = $49.75

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

The proposed NT-proBNP assay is a standard assay already performed by Australian pathology services (i.e MBS item 66830). The estimated time to complete the assay varies between 12-20 minutes and in the emergency department setting (MBS Item 66830), the results are available to the clinician within hours.

It is anticipated that similar timeframes will be achieved for Populations 1 and 2 in this application.

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

Population 1: Patients with systemic sclerosis (SSc)

The proposed MBS item descriptor for Population 1, patients with SSc is presented in Table 8. The fee and benefit are the same as the current MBS Item 66830 (NT-proBNP). The proposed item descriptor does not include BNP, as does MBS Item 66830.

Table 8: Proposed MBS Item Descriptor for Population 1: Patients with systemic sclerosis (SSc)

Category 6 - PATHOLOGY SERVICES – (proposed category description) Group P2 – Chemical (proposed group description)
Proposed item descriptor: Quantification of NT proBNP in patients with systemic sclerosis (scleroderma) in the assessment of risk of pulmonary arterial hypertension that requires right heart catheterisation for definitive diagnosis. Fee: $58.50 Benefit: 75% = $43.90 85% = $49.75

Population 2: Patients with pulmonary arterial hypertension (PAH)

The proposed MBS item descriptor for Population 2, patients with PAH is presented in Table 9. The fee and benefit are the same as the current MBS Item 66830 (NT-proBNP) and also the proposed MBS Item Descriptor for Population 1 and similarly this proposed item descriptor does not include BNP, as does MBS Item 66830.

Table 9: Proposed MBS Item Descriptor for Population 2: Patients with pulmonary arterial hypertension (PAH)

Category 6 - PATHOLOGY SERVICES – (proposed category description) Group P2 – Chemical (proposed group description)
Proposed item descriptor: Quantification of NT proBNP in patients with diagnosed pulmonary arterial hypertension for ongoing risk assessment. Maximum of 4 tests per patient in any one year. Fee: $58.50 Benefit: 75% = $43.90 85% = $49.75

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