Australian Government

Department of Health

MSAC Application 1689:

Quantification of NT-proBNP in patients with systemic sclerosis (scleroderma) and in patients previously diagnosed with pulmonary arterial hypertension (PAH)

Ratified

PICO Confirmation

Summary of PICO/PPICO criteria to define question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Table 1 PICO for NT-proBNP in systemic sclerosis associated pulmonary arterial hypertension: Population 1

Component	Description
Population	Patients with systemic sclerosis (SSc)
Prior tests	Assessment to confirm a diagnosis of systemic sclerosis includes: Clinical evaluation: determination of the skin thickness by the modified Rodnan skin score, nailfold capillaroscopy, multisystemic physical exam, and blood pressure monitoring. Laboratory testing: autoantibody testing, complete blood count, muscle enzymes-creatine kinase and aldolase, and urinalysis. Ancillary and radiographic evaluation:Holter monitor or telemetry, high-resolution CT (HRCT) of the chest, , X-rays of the extremities, evaluation for gastrointestinal (GI) involvement by upper GI endoscopy, oesophageal manometry, barium swallow studies, 24-hour pH probe, and cardiac magnetic resonance imaging.
Intervention	N-terminal proB-type natriuretic peptide (NT-proBNP) biomarker assay and pulmonary function testing (PFT)
Comparator/s	Transthoracic echocardiography (TTE) and PFT
Reference standard	Right heart catheterisation (RHC)
Outcomes	• **Diagnostic performance**: sensitivity, specificity, positive and negative predictive values. Assessment of the extent of and implications of discordance between Australian NT-proBNP testing and clinical utility standard, test-retest reliability, the test failure rate • **Prognosis**: prognostic utility of tests • **Clinical utility:** % change in management plan (e.g. changes in treatment, change in use of TEE, change in use of RHC) • **Therapeutic effectiveness:** quality of life, overall survival, disease-related survival, • **Safety**: adverse events related to changes in clinical management • **Cost-minimisation analysis**: cost of testing and any costs offsets • **Financial implications**: number and cost of patients tested
Assessment questions	What are the safety, cost- and clinical-effectiveness of NT-proBNP biomarker assay plus PFT versus TTE plus PFT in screening patients with SSc at risk for pulmonary arterial hypertension?

Table 2 PICO for NT-proBNP in patients previously diagnosed with pulmonary arterial hypertension: Population 2

Component	Description
Population	Patients with RHC-confirmed diagnosis of pulmonary arterial hypertension (PAH), of any aetiology, selected for ongoing risk assessment
Prior tests	Physical examination, chest radiography, electrocardiography, transthoracic echocardiography, pulmonary function testing
Intervention	NT-proBNP biomarker assay as risk assessment tool
Comparators	Transthoracic echocardiography
Reference standard	RHC is the accepted reference standard to confirm disease progression. In the context of risk assessment tools, the reference standard is the health outcome being considered by the risk assessment tool (mortality or transplant-free survival).
Outcomes	• **Risk assessment/prediction**: risk stratification into low-, medium- and high-risk PAH categories • **Prognosis**: prognostic effect of tests • **Disease monitoring**: Monitor disease progression and response to treatment • **Clinical utility:** % change in management plan (e.g. changes in treatment). • **Therapeutic effectiveness:** overall survival, disease-related survival, quality of life • **Safety**: adverse events related to change in clinical management. • **Cost-minimisation analysis**: cost of testing and any costs offsets • **Financial implications**: number and cost of patients tested
Assessment questions	What are the safety and cost- and clinical-effectiveness of NT-proBNP biomarker assay versus TTE when used as a part of a PAH risk assessment tool in (i) predicting severity of disease, and (ii) monitoring disease severity, or response to treatment, in patients with a confirmed diagnosis of pulmonary arterial hypertension?

Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of N-terminal pro B-type natriuretic peptide (NT-proBNP) biomarker assay for screening patients with systemic sclerosis and for risk assessment and monitoring of patients with pulmonary arterial hypertension was received from Janssen Australia and New Zealand (Janssen-Cilag Pty Ltd) by the Department of Health.

The use of the proposed technology is claimed to result in noninferior health outcomes compared to the nominated comparators.

PICO Set 1 - Quantification of NT-proBNP for screening of systemic sclerosis associated pulmonary arterial hypertension

Population 1

Scleroderma is a chronic but rare connective tissue disorder with unknown and complex pathogenesis. It is primarily characterised by the thickening and hardening of the skin. Scleroderma is categorised into two forms localised scleroderma and systemic sclerosis (SSc). Localised scleroderma mainly affects skin with a potential impact on the muscles and bones. Internal organs such as the digestive tract, heart, lungs, kidneys, and others may also be affected in SSc, which has a higher risk for onset of PAH than localised scleroderma. The severity and outcome of scleroderma are variable.

The causes of scleroderma are not fully known. There is some evidence that genetic and environmental factors play a role in scleroderma development. These triggers activate the immune system, causing blood vessel damage and tissue injury, resulting in scar tissue formation and excess collagen accumulation.

SSc is a rare disease. Its prevalence varies with ethnicity, gender, and geographic area. There is an overall female predominance with a female to male ratio of about 5:1 (Chifflot et al., 2008) and earlier disease onset in females than males. SSc can occur at any age; however, it is rare in children and the elderly. The disease is most prevalent in individuals aged 30-50 years. Worldwide prevalence rates of SSc varies with estimates ranging from 7/million (Japan) to 489/million (Italy) population, with relatively higher prevalence rates reported in the USA (276/million population in 1990) and Australia (233/million population in 1999) (Chifflot et al., 2008, Morrisroe et al., 2017a).

SSc is a multisystemic disorder with significant variation in clinical presentation among affected individuals. The most common clinical indications include Raynaud's phenomenon, skin manifestations and pulmonary impairment. The pulmonary lesions include cardiorespiratory manifestations, pulmonary arterial hypertension (PAH) and interstitial lung disease, which remain the leading causes of SSc-related mortality (Tyndall et al., 2010, Steen and Medsger, 2007). PAH is defined as pulmonary arterial pressure average ≥ 20 mmHg[1] measured at rest by right heart catheterisation (RHC) (Condon et al., 2019). PAH is suspected when pulmonary arterial systolic pressure exceeds 40 mmHg at rest in echocardiography. Patients can remain asymptomatic for an extended time, especially if they do not have high physical activity levels. Syncope, haemoptysis, and dysphonia (Ortner's syndrome) are signs of seriousness. PAH is typically progressive and can ultimately lead to right-sided heart failure.

Two major types of SSc are commonly recognized and are based on whether the extent of skin involvement is limited or diffuse (LeRoy and Medsger, 2001). Limited cutaneous systemic sclerosis (LcSSc), formerly known as the CREST syndrome, is associated with skin thickening distal to the elbows and knees, and/or face without trunk involvement (Adigun et al., 2021). Diffuse cutaneous systemic sclerosis (DcSSc) is associated with skin thickening that may involve skin proximal to the elbows, knees, face, and/or trunk (Adigun et al., 2021). Both LcSSc and DcSSc are associated with several systemic manifestations and autoantibody positivity. However, DcSSc is considered more severe and has a higher mortality rate than LcSSc (Adigun et al., 2021). PAH is more common in patients with LcSSc. The Australian scleroderma cohort study, estimated a prevalence *(cumulative incidence)* of PAH of 11.8% (10.3% in LcSSc, 8.5% in DcSSc and 12.0% in mixed connective tissue disease) (Morrisroe et al., 2017b). According to the PHARAOS registry,

[1] The definition was updated as per the applicant suggestion that the most recent World Symposium on PH (6th WSPH) defines PAH as mean pulmonary arterial pressure (mPAP) threshold in the definition of PAH to >20 mmHg at rest.
Reference: CONDON, D. F., NICKEL, N. P., ANDERSON, R., MIRZA, S. & DE JESUS PEREZ, V. A. 2019. The 6th World Symposium on Pulmonary Hypertension: what's old is new. F1000Res, 8.

comprising 22 US scleroderma expert centres, 70% of patients with SSc-PAH had limited cutaneous disease (Chung et al., 2014).

PAH occurs in up to 13% of patients with SSc (Phung et al., 2009, Legendre and Mouthon, 2014). A recent systematic review estimates a PAH prevalence of 8-12% in an asymptomatic cohort of Australian SSc patients (Morrisroe et al., 2017a). The annual incidence of PAH in SSc is approximately 0.7-1.4% in Australia (Morrisroe et al., 2017b, Morrisroe et al., 2016).

The diagnosis of SSc and related disorders is based primarily upon the presence of characteristic clinical findings and is supported by specific serological abnormalities (LeRoy and Medsger, 2001). If SSc is suspected, various tests can be done to establish the initial diagnosis, especially if the disease is oilgosymptomatic (LeRoy et al., 1988). Clinical evaluation includes determination of the skin thickness by the modified Rodnan skin score, nailfold capillaroscopy, multisystemic physical exam, and blood pressure monitoring (Adigun et al., 2021). Autoantibody testing includes anti-nuclear, anti-centromere, anti-topoisomerase I, anti-RNA polymerase III, and anti-U3-RNP (fibrillarin) (Adigun et al., 2021). Other autoantibodies may also be tested for diagnosing rare subtypes, including anti-Th/To, anti-PM/Scl, anti-U1-RNP and anti-Ku. In addition to autoantibody testing, additional laboratory tests may also be required for differential diagnosis (Adigun et al., 2021). These include complete blood count, muscle enzymes- creatine kinase and aldolase, and urinalysis. Ancillary and radiographic evaluation includes transthoracic echocardiography (TTE), Holter monitor or telemetry, high-resolution CT (HRCT) of the chest, pulmonary function testing (PFT), X-rays of the extremities, evaluation for gastrointestinal involvement by upper GI endoscopy, oesophageal manometry, barium swallow studies, and 24-hour pH probe (Adigun et al., 2021). Cardiac magnetic resonance imaging may be needed in patients where myocardial involvement is suspected. Once the diagnosis of SSc is established, additional tests such as electrocardiogram, urinalysis, complete blood count, renal and liver functions, upper gastrointestinal endoscopy and NT-pro-BNP serology may be performed for disease differentiation. Routine examination of SSc patients with PFT (spirometry and diffusing capacity of the lungs for carbon monoxide (DLCO)), TTE and NT-pro-BNP serology is usually performed annually (Khanna et al., 2013, Adigun et al., 2021).

PASC confirmed that population 1 consists of all patients with an established diagnosis of SSc.

PASC advised that tests for the diagnosis and initial assessment of SSc are out of the scope of this PICO Confirmation as the proposed intervention is not influenced by the tests used to establish the SSc diagnosis.

Utilisation

The application estimated the number of patients with diagnosed SSc disease who would be eligible for NT-proBNP screening to be 5,260 in 2021, increasing to 5,419 in 2023 (p39). These estimates were based on the Australian Scleroderma Cohort Study, a longitudinal multicentre study wherein patients with SSc were recruited from 13 participating centres assuming a prevalence of 20 per 100,000 or 200/million (Morrisroe et al., 2017b). The estimates provided in previous Australian studies are slightly variable. SSc prevalence was 20.8 and 23.3 per 100,000 people in two South Australian studies (Chandran et al., 1995, Roberts-Thomson et al., 2001). Total SSc prevalence rates within Sydney ranged from 4.5/100,000 in 1975 to 8.6/100,000 in 1988 (Englert et al., 1999). The total Australian population in 2021 and the projected growth to 2023 was based on the Australian Bureau of Statistics projections. Table 3 presents the patients with SSc who will be eligible to use the proposed service.

Table 3: Patients with systemic sclerosis who will use the NT-proBNP testing

	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: Table 3, p40 of the application.

Rationale for earlier screening

Early detection of PAH in SSc patients remains a challenge as SSc-PAH patients tend to be asymptomatic in the early course of the disease, and patients are often detected at an advanced stage. Data from the French PAH Network study reported that 79% of new SSc-PAH cases between 2006 and 2009 were diagnosed in the New York Heart Association (NYHA) class III/IV (Launay et al., 2013). Early symptoms related to PAH are often vague and nonspecific. Fatigue and exertional dyspnoea are common symptoms and are often misdiagnosed as more common respiratory conditions such as asthma or poor fitness. Patients with SSc have multifactorial causes with underlying musculoskeletal conditions, making the early detection of PAH challenging. Therefore, substantial delays from early disease onset to definitive diagnosis by RHC could have negative consequences for disease management.

Accumulating evidence from multiple large scale national PAH registries indicates that diagnosis at an early stage of SSc-PAH is associated with improved survival. Patients with SSc-PAH in the UK Pulmonary Hypertension Service had a more than two-fold increase in mortality for patients in NYHA class III or IV compared with those in NYHA class I or II (Condliffe et al., 2009). The main limitations of this study included its observational and uncontrolled design and the fact that much of the data were collected retrospectively.

In a prospective registry of SSc patients at high risk for PAH conducted in multiple centres in the US, the 1-year, 2-year, and 3-year cumulative survival rates were 93%, 88%, and 75%, respectively (Chung et al., 2014). Among other factors such as age, sex and DLCO, the functional class IV status (HR 6.5; 95% CI: 1.8-22.8) was reported as a significant predictor of mortality (Chung et al., 2014). Also, relative to the general population, a study showed that SSc related disease burden resulted in an average reduction in life expectancy in Australia of 11.3 years for women and 25.8 for men (Hao et al., 2017).

A case-control study was conducted to compare the baseline characteristics and long-term survival of two cohorts of patients with SSc-PAH. Each group comprised 16 incident SSc-PAH patients: one group diagnosed through an echocardiography-based detection programme and the other via routine clinical practice. The routine clinical care group enrolled consecutive adult patients with RHC confirmed PAH in patients with SSc. The detection cohort comprised consecutive patients with SSc who entered a systematic PAH detection program and subsequently had PAH on RHC (Humbert et al., 2011). Both groups included patients from the same management era (2002/2003), minimising therapeutic approach bias. The detection cohort had the significantly less severe pulmonary vascular disease at diagnosis measured by NYHA functional class (50.0% vs 12.5% in class I or II; p=0.036) and pulmonary haemodynamics (PVR index: 734 ± 486 vs 1,299 ± 428 dynes/sec/cm^5/m^2; p=0.01), compared with the routine clinical care cohort. Another interesting observation of this study was that significantly higher survival rates were observed in the detection programme than in the patients diagnosed through routine care. In the detection cohort, the 1-year, 3-year, 5-year, and 8-year survival rates were 100%, 81%, 73%, and 64% compared with 75%, 31%, 25%, and 17% in the routine-care cohort. The lead-time and length-time biases were acknowledged as potential contributors to the observed survival benefit. The small sample size and overdiagnosis bias were also identified as study weaknesses. Nevertheless, this study provided a compelling case for the screening of SSc patients for milder forms of PAH, potentially enabling earlier intervention and improved survival.

Despite the lack of randomised controlled trials, the observational studies suggest that implementation and development of early screening strategies in patients with SSc may be promising.

Intervention

The proposed intervention is N-terminal proB-type natriuretic peptide (NT-proBNP) serological testing in combination with pulmonary function testing (PFT) to screen for PAH in patients with established systemic sclerosis.

Natriuretic peptides are a family of hormones secreted primarily from the heart, kidneys and brain that cause vasodilation and natriuresis. They include atrial natriuretic peptide, BNP, C-type natriuretic peptide and urodilatin. BNP is the product of the early response gene *NPPB*. In PAH, transmural pressure, volume overload, hypoxia, or pro-inflammatory factors induce transcription of *NPPB* to produce 134-amino acid (aa) preproBNP. The end result of this process is two biomarkers of 32-aa BNP and 76-aa NT-proBNP. BNP is then rapidly metabolised in the blood with a short half-life of about 20 minutes, making rapid processing of samples necessary for its determination (Rehman and Januzzi, 2008). NT-proBNP, on the other hand, is cleared passively by organs with high blood flows, including the kidneys, resulting in a longer half-life of about 60-120 minutes (Rehman and Januzzi, 2008). NT-proBNP also offers good stability at different temperatures (Sokoll et al., 2004, Ordonez-Llanos et al., 2008). In contrast, the BNP assays have been shown to be more variable as BNP results of the same sample can vary 40% among the different methods (Rawlins et al., 2005). In clinical laboratory testing, the longer half-life of NT-proBNP may be beneficial if sample transportation time is high. Estimates of BNP stability recommend that it should be analysed or frozen within 4 hours, whereas NT-proBNP can reasonably be stored at room temperature for up to 2 days (Downie et al., 1999, Cowie et al., 2010).

Measurement of BNP or NT-proBNP is currently used to diagnose heart failure in patients presenting with dyspnoea to a hospital emergency department (MBS item number 66830).[2] The current MBS item number is subject to rule 25, implying that a maximum of six tests per year can be requested per patient. The current application exclusively proposes measurement of NT-proBNP for population 1.

There is no standard protocol for NT-proBNP sampling and testing. Risk stratification guidelines recommend specific threshold values to indicate PAH severity, accuracy, and analytical range can vary between tests, and there is conflicting evidence on the interchangeability of results. A study by Collin-Chavagnac et al. compared 10 different natriuretic peptide laboratory assays in patients with heart failure and reported that median NT-proBNP values varied between 1020 and 1450 ng/L^{-1} in different assays (Collin-Chavagnac et al., 2015). The authors concluded that, while practical diagnostically, none of the tests could be reliably cross-compared and recommended that patients should consistently use the same assay (NT-proBNP) over time (Collin-Chavagnac et al., 2015). Individual specific reference ranges and heart failure diagnostic cut-offs were also recommended for each commercial natriuretic peptide immunoassay.

There is a need for consistency among the testing platforms as different laboratories use different testing platforms. For example, NSW health pathology utilises the Abbott architect fluorescence immunoassay for NT-proBNP detection, which relies on specialised reagents compatible with a specific fluorescent microplate reader.[3] Information on methods used by the local hospital emergency departments and private pathology providers in Australia is unavailable.

The application has suggested three commercially available NT-proBNP laboratory-based immunoassays, none manufactured by the applicant. These include Roche Diagnostics (CARDIAC® NT-pro-BNP), Siemens Healthineers (Stratus® CS Acute Care™) and BioMerieux (VIDAS NT-proBNP2). The study by Collin-Chavagnac et al. in heart failure patients included the immunoassays provided by all three providers and reported variability in the test results (Collin-Chavagnac et al., 2015). If the requested intervention is made available in the outpatient or specialised PAH clinic settings, it is important to ensure that the same antibodies and instruments are used to make the assays relatively consistent. Given the potential for variation between kits, a UK-based consensus group set up to develop clinical guidance in PAH also recommends users participate in a quality assurance scheme and adhere to manufacturer recommendations (Cowie et al., 2010). The lack of standardisation between protocols and devices could

[2] Medicare Benefits Schedule - Item 66830.
http://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=66830&qt=item
[3] http://www.palms.com.au/php/labinfo/info_index.php?tab=5

pose logistical challenges and must be addressed for the successful implementation of NT-proBNP laboratory-based testing.

BNP/NT-proBNP testing is claimed using MBS item 66830. This item is for diagnosing heart failure in patients presenting with dyspnoea to a hospital Emergency Department, subject to rule 25, which limits the frequency of its use to not more than 6 times in a 12-month period. The proposed MBS item in this application does not include BNP but NT-proBNP only.

The application did not address whether:

- Different testing technologies lead to variable or discordant test results
- Steps to ensure standardisation between protocols and devices.

During the pre-PASC teleconference, the applicant has agreed to address these issues.

PASC recommended that the intervention should be one of the algorithms for determining the risk of PAH, which includes the NT-proBNP test, such as that the algorithm developed by the Australian Scleroderma Interest Group (ASIG).

PASC noted the application requested a maximum of two NT-proBNP tests per year, and the applicant's advice that the test would be part of the annual screening for PAH in patients with SSc, and a second NT-proBNP test would be performed where results are borderline or on worsening of symptoms. PASC advised to appropriately model the screening frequency in the assessment report.

PASC acknowledged that PFTs and laboratory-based NT-proBNP biomarker assay would be expected to partially replace TTE and PFTs to screen for PAH in patients with established SSc.

PASC also noted that TTEs are performed for other reasons and advised the assessment report would need to clarify the proportion of patients who might still require TTE following NT-proBNP testing.

PASC considered that information on the comparative access to TTE and NT-proBNP testing in Australia should be provided in the assessment report.

PASC considered the lack of a definitive reference range for NT-proBNP concentration for diagnosing PAH and issues around concordance given that the various NT-proBNP testing platforms are not standardised. The applicant stated that any discrepancy between assays is likely to be negligible and that the test performance and concordance amongst various laboratory-based NT-proBNP assays available in Australia would be discussed in the assessment report, which the PASC acknowledged.

Rationale

BNP and NT-proBNP are well-studied clinical biomarkers used in PAH and other cardiovascular disorders, such as acute/chronic heart failure, and they are used as surrogate markers of cardiac function (Galiè et al., 2016, Fu et al., 2018, Santaguida et al., 2014). The role of NT-proBNP in screening SSc-PAH has also been investigated (Coghlan et al., 2014).

Various clinical practice guidelines endorse the use of early detection and disease management tools such as NT-proBNP in combination with other diagnostic parameters for different cardiac pathologies, including PAH. NT-proBNP has been shown to correlate with several pulmonary haemodynamic metrics.

Also, given that NT-proBNP is released in response to either left or right ventricular wall stress, its measurement cannot be used to differentiate between PAH and left heart disease. NT-proBNP clearance is dependent on glomerular filtration, and its concentration can be influenced by kidney function (Luchner et al., 2005). Hence, specific cut-off values and a reference range in conjunction with an appropriate measure of kidney function may be required to confirm the NT-proBNP based findings.

PASC noted the applicant's advice that the application is limited to NT-proBNP laboratory-based testing and does not include BNP testing, as the latter is more likely to be spuriously affected by non-cardiac factors.PASC noted the clinician's advice that kidney function is considered alongside NT-proBNP testing as kidney function can influence the results of the NT-proBNP test. The clinician clarified that regular kidney function tests would be conducted as part of the regular screening protocol, and these tests are currently MBS funded. PASC advised to include these tests in the economic evaluation for the assessment report.

Comparator(s)

Population 1: The comparator for screening for SSc-PAH is TTE (also known as Doppler echocardiography or echocardiography).

TTE is the most widely used screening modality in clinical practice to guide referral for RHC for definitive diagnosis of PAH. The detection of PAH by TTE relies principally on measuring the tricuspid regurgitation jet velocity (TRV), which can be transformed into a pressure estimate using the Bernoulli equation to assess systolic P_{pa} (systolic P_{pa} = 4 × TRV2 + right atrial pressure) (Galiè et al., 2016). The right atrial area determined by TTE is also a frequently used metric in identifying PAH disease (Lechartier and Humbert, 2021).

TTE is the most widely used non-invasive tool because of its practicality and reliability in screening for SSc-PAH (Denton et al., 1997). However, tricuspid regurgitation can be absent in about 15-20% of patients, and PAH can be missed in up to 30% of cases (Fisher et al., 2009). Another potential limitation of TTE is the need for specific technical expertise and interpretation as well as issues related to accessibility and prolonged waiting times in regional and remote Australia (Quinlivan et al., 2019). Various clinical practice guidelines and algorithms recommend TTE as a primary screening tool for assessing SSc-PAH (Lechartier and Humbert, 2021). TTE allows the evaluation of the systolic and diastolic left ventricular function, measurement of left and right heart chambers, assessment of valves and pericardium, and estimation of systolic pulmonary artery pressure (sPAP) (Lechartier and Humbert, 2021). Elevated sPAP concentration (≥30 mmHg) ranging from 11 to 14 per cent have been reported in studies of SSc patients with and without known risk factors for PAH, correlating with the presence of PAH (Wigley et al., 2005, Hesselstrand et al., 2005).

While most experts agree on the need for PAH screening in SSc patients at the initial visit and re-evaluation at regular intervals, there is no consensus on the screening test/s choice and sequence before proceeding to diagnostic RHC. Recommendations developed by a diverse group of international experts provided valuable guidance on the role of TTE, NT-proBNP and PFTs for SSc-PAH screening (Khanna et al., 2013). It was recommended that screening with PFTs (single-breath diffusing capacity for carbon monoxide), TTE, and measurement of NT-proBNP be performed in all patients with SSc and scleroderma spectrum disorders (Khanna et al., 2013). Initially, asymptomatic patients with SSc and scleroderma spectrum disorders were recommended to undergo annual screening with TTE and PFTs. However, if any signs or symptoms were present, patients were recommended to be tested with the full screening panel consisting of TTE, PFTs and NT-proBNP (Khanna et al., 2013). In contrast, the Australian Scleroderma Interest Group (ASIG) algorithm prefers initial testing with NT-proBNP (instead of TTE) and PFTs as the first-line screening strategy in patients with SSc at risk for PAH. The clinical management algorithms section below provides a detailed discussion of various algorithms, guidelines, and recommendations.

Due to the lack of consensus on NT-proBNP instead of TTE for screening asymptomatic patients with SSc for PAH, there are chances that some clinicians might still prefer both. Therefore, NT-proBNP has the potential to become an add-on rather than a replacement test for certain patients. TTE would still be indicated following NT-proBNP testing to assess cardiac structure/function other than an estimation of pulmonary artery pressure but would not be necessary for all patients.

The applicant stated during the pre-PASC teleconference that the choice of either NT-proBNP or TTE as part of the screening strategy would be individualised for each patient as per the risk evaluation and clinical characteristics.

PASC considered that the comparator should be TTE and PFT, as TTE with PFT are the most widely used/validated tests to screen for PAH in patients with SSc, and are endorsed by various screening guidelines.

PASC acknowledged that TTE requires specific equipment and technical expertise, and there may be access/availability problems, particularly in regional or remote Australia.

PASC considered that some clinicians might still request both TTE and NT-proBNP testing due to the lack of consensus on the screening test/s choice and sequence before proceeding to diagnostic RHC in patients with SSc.

PASC also considered that given that TTE provides important additional information (e.g. presence of other SSc related cardiac disease), it would be likely to be performed in a significant number of patients even if screening with NT-proBNP becomes publically funded.

Reference standard

The reference standard to confirm any form of PAH is RHC, and it is well established (Hoeper et al., 2013). It is considered the gold standard test for diagnosing and validating PH/PAH (Rosenkranz and Preston, 2015). There is no other reference standard.

RHC provides a complete hemodynamic assessment, including measuring pulmonary artery pressure, pulmonary capillary wedge pressure, pulmonary vascular resistance, transpulmonary, and diastolic pressure gradients (Rosenkranz and Preston, 2015). RHC is a technically demanding procedure that requires meticulous attention to detail to obtain clinically useful information. To obtain high-quality results and be of low risk to patients, the procedure is generally limited to expert PAH/PH centres.

PASC acknowledged that RHC is the accepted reference standard to diagnose all types of PAH.

Outcomes

The evidence base for the NT-proBNP based screening (population 1) and prognostic testing and monitoring disease progression (population 2) mainly consisted of observational studies, which have been briefly discussed below.

Given the claim of non-inferiority, a truncated evidence approach may be appropriate. However, the application states that there may be a reduction in the use of TEE and RHC with current practice with a commensurate reduction in morbidity and mortality associated with this test.

<u>Patient relevant</u>

Diagnostic accuracy	Sensitivity, specificity, positive predictive value and negative predictive value compared to the reference standard (RHC) in patients with SSc; assessment of the extent of and implications of discordance between Australian NT-proBNP testing and clinical utility standard, test-retest reliability, the test failure rate
Clinical utility	proportion of tested patients who might have a change in management (e.g., change in use of TEE, change in use of RHC, changes in treatment in terms of monotherapies or combination therapies and increased uptake of the treatments due to earlier diagnosis and treatment initiation)

Therapeutic effectiveness	Overall survival, progression free survival, disease-related survival, quality of life
Prognosis	Prognostic utility of testing in patients with SSc and PAH
Safety	Adverse events related to the change in clinical management
Healthcare system	
Cost-minimisation	Cost of testing and any costs offsets
Financial implications	Number and cost of patients tested

It is recommended that patients should consistently use the same assay over time (Collin-Chavagnac et al., 2015).

Rationale

Population 1: Patients with SSc at risk for PAH (screening test performance)

The application has presented the results of an Australian study comparing the ASIG algorithm (including NT-proBNP) for screening patients with SSc and the ESC/ESR guidelines (TTE, but no NT-proBNP) and the DETECT algorithm (includes NT-proBNP) (Hao et al., 2015). In this study, 79 consecutive patients with SSc with suspected PAH were screened, out of which 29 (37%) had RHC confirmed PAH. The three algorithms were then compared in PAH patients and non-PAH patients, with the ASIG algorithm showing the best diagnostic estimates followed by DETECT and the Risk Assessment in PAH in the ESC/ESR[4] guidelines. The clinical management algorithms section below presents a detailed discussion of various algorithms and guidelines, including the test results.

While the study by Hao et al. compared the algorithms comprising multiple tests, including NT-proBNP and TTE, the specific diagnostic performance of the intervention and the comparator was not presented in the application. The diagnostic efficacy of NT-proBNP alone (Williams et al., 2006, Allanore et al., 2003, Mukerjee et al., 2003) and TTE alone (Mukerjee et al., 2004, Rajaram et al., 2012) in patients with SSc has been investigated. The assessment report should also compare the stand-alone diagnostic performance of these tests.

PASC advised that the most important outcome would be the comparative diagnostic accuracy of the intervention and comparator screening algorithms and that the patient outcomes are unlikely to be different if the accuracies are similar.

PASC noted no significant risks to NT-proBNP testing as it is a simple blood test. However, if the test leads to more false positives followed by confirmatory RHC, it may result in safety issues associated with invasive RHC.

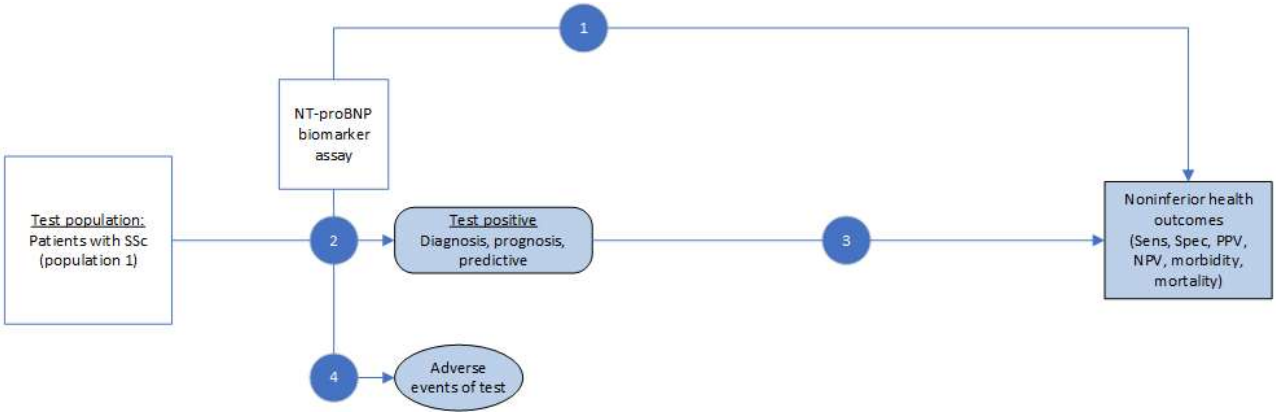
PASC advised that the assessment report should provide a summary of the NT-proBNP laboratory tests used in Australia, including the analytical performance of these tests.

Assessment framework

The clinical claim is of noninferiority in terms of comparing the diagnostic and prognostic performance of NT-proBNP with the comparator TTE (population 1). Given this, and that the proposed test claims to replace the existing MBS test (TTE), an assessment framework truncated at test accuracy seems appropriate (p82, TG 9.3, MSAC Technical Guidelines).

[4] ESC/ESR = European Society of Cardiology (ESC) / European Respiratory Society (ERS)

Figure 1 Assessment framework that has been truncated at test accuracy (concordance, test accuracy) with the inference that identical test accuracy will result in the same health outcomes



SSc= systemic sclerosis; Sens= sensitivity, Spec= specificity; PPV= positive predictive value; NPV= negative predictive value; NT-proBNP= N-terminal proB-type natriuretic peptide.
Figure notes: 1: direct from test to health outcomes evidence; 2: concordance of NT-proBNP testing with TTE in patients with SSc (population 1); 3: similar test results from both proposed test (NT-proBNP) and the comparator (TTE) will result in the same management decisions, and noninferior health outcomes; 4: adverse events due to testing.
Source: Adapted from p82, Figure 9, MSAC Guidelines for preparing assessments for the Medical Services Advisory Committee 2021.

PASC agreed that a truncated assessment framework at test accuracy may be appropriate.

PASC advised that the assessment report would need to demonstrate that the use of NT proBNP in an algorithm such as the ASIG algorithm is non-inferior to TTE and lung function testing.

Clinical management algorithms

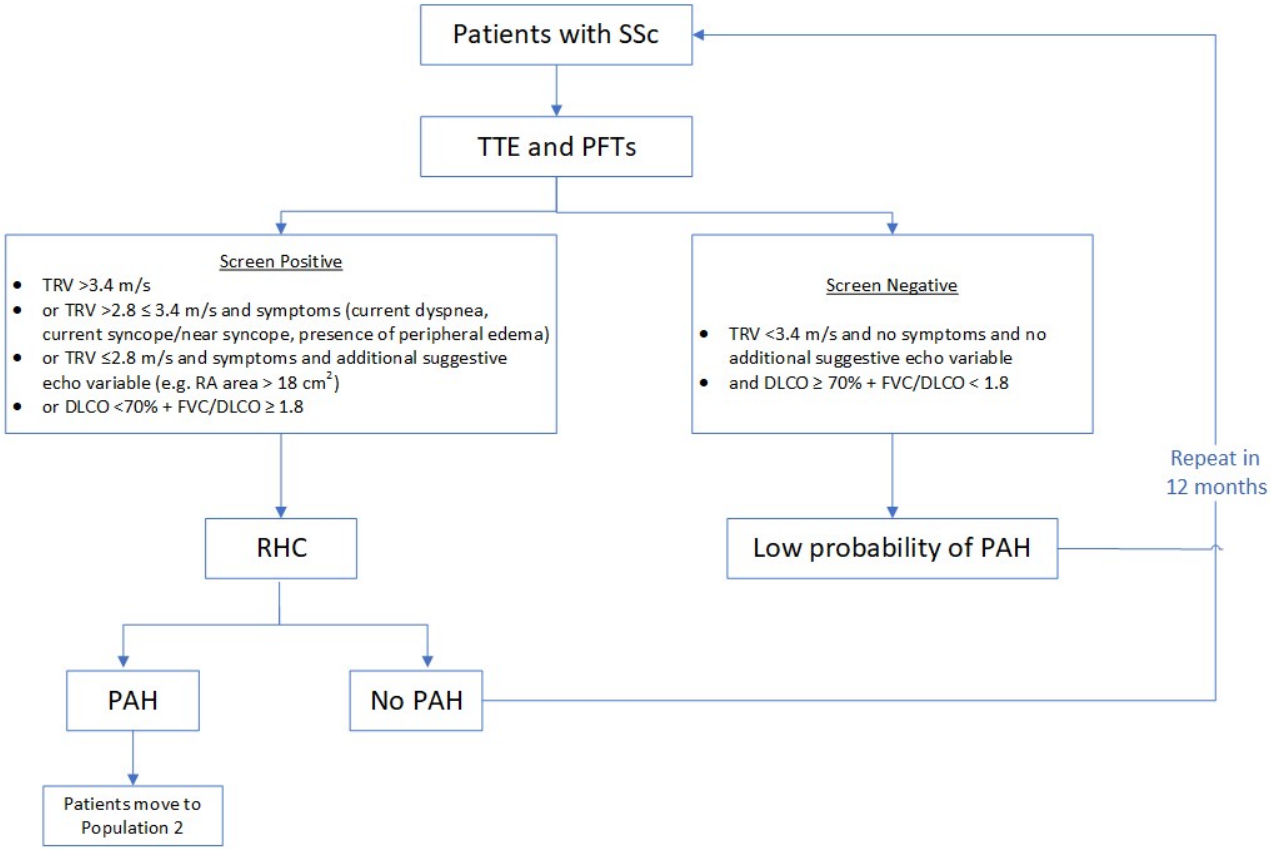
Population 1: Patients with systemic sclerosis

Current clinical management algorithms

Several international clinical management guidelines have been developed for the early detection and screening for PAH in connective tissue disease (CTD) associated PAH, including SSc-PAH. Although universal consensus on the best practice guidelines is not available as most guidelines are region-specific and tend to vary slightly, most have adopted TTE and PFTs for the initial screening of patients with SSc. The application did not propose the current management algorithm (in the absence of NT-proBNP testing) but instead discussed the commonly used ones, which are summarised in the Appendix.

Although the application did not provide the current clinical management algorithm in the absence of NT-proBNP testing, the algorithm based on the ESC/ESR guidelines appears to be the most suitable as it is based on the comparator, TTE, for the initial screening of patients with SSc. However, it lacks PFTs. Figure 2 presents an overview of the ESC/ESR algorithm incorporating PFT values from the ASIG screening algorithm.

Figure 2: Current clinical management algorithm for population 1



TRV= tricuspid regurgitant velocity, SSc= systemic sclerosis; TTE= transthoracic echocardiography; PAH= pulmonary arterial hypertension; RA= right atrium area; m/s= metre per second; DLCO= diffusing capacity of lung for carbon monoxide; FVC= forced vital capacity.
Note: The applicant suggested annual testing, but a maximum of 2 NT-proBNP tests per year could be requested if the results are borderline or there is worsening of symptoms.
Source: Figure compiled during the evaluation from (Saygin and Domsic, 2019).

In addition, the literature search conducted during the PICO preparation revealed the consensus recommendations developed by a task force of international experts from various specialities (Khanna et al., 2013). The guidelines were derived from a systematic review of the literature on the screening and diagnosis of PAH in connective tissue disease (CTD) associated PAH, including SSc-PAH. The quality assessment of the included studies was performed by Quality Assessment of Diagnostic Accuracy Studies (QUADAS) and Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group. It was recommended that screening PFTs (spirometry with lung volumes) with single-breath DLCO (high-quality evidence), TTE (high-quality evidence), and measurement of NT-proBNP (moderate-quality evidence) be performed in all patients with SSc and scleroderma spectrum disorders (Khanna et al., 2013). The panel also endorsed the use of the DETECT (DETECTion of PAH in SSc) algorithm in these patients if their DLCO was <60% predicted and if the duration of their SSc was >3 years from the time of their first non–Raynaud's phenomenon symptom (moderate-quality evidence). The recommendations are shown diagrammatically in Table 4.

These guidelines are similar to the proposed Australian Scleroderma Interest Group (ASIG) algorithm in that the screening recommendations include NT-proBNP. However, the difference lies in the strong recommendation of annual screening with TTE and PFTs, but not NT-proBNP. The combination of TTE, PFTs and NT-proBNP was recommended if any new signs or symptoms of PH/PAH appear.

Table 4: General recommendations, initial screening evaluation, and frequency of non-invasive tests for early detection of CTD-associated PAH*

General recommendations	
-	All patients with SSc should be screened for PAH (Moderate)
-	Patients with MCTD or other CTDs with scleroderma features (scleroderma spectrum disorders) should be screened in a similar manner to patients with SSc (Very low)
-	Screening is not recommended for asymptomatic patients with MCTD or other CTDs (including SLE, rheumatoid arthritis, inflammatory myositis, Sjögren's syndrome) without features of scleroderma (Low to moderate)
-	For unexplained signs and symptoms of PH in patients with MCTD, SLE, or other CTDs without scleroderma features, one may consider the diagnostic algorithm evaluation for PH (Moderate)
-	All patients with SSc and scleroderma spectrum disorders with a positive result on a non-invasive screen (see below) should be referred for RHC (High)
-	RHC is mandatory for diagnosis of PAH (High)
-	Acute vasodilator testing is not required as part of the evaluation of PAH in patients with SSc, scleroderma spectrum disorders, or other CTDs (Moderate to high)
Initial screening evaluation	
-	PFTs with DLCO (High)
-	Transthoracic echocardiogram (High)
-	**NT-proBNP (Moderate)**
-	DETECT algorithm if DLCO <60% predicted and disease duration >3 years (Moderate)
Frequency of non-invasive tests	
-	Transthoracic echocardiogram annually as a screening test (Low)
-	Transthoracic echocardiogram if new signs or symptoms develop (High)
-	PFTs with DLCO annually as a screening test (Low)
-	PFTs with DLCO if new signs or symptoms develop (Low)
-	**NT-proBNP if new signs or symptoms develop (Low)**

* The quality of evidence, which was assessed according to the Grading of Recommendations Assessment, Development and Evaluation Working Group, is shown in parentheses at the end of each statement.
CTD= connective tissue disease; PAH= pulmonary arterial hypertension; SSc= systemic sclerosis; MCTD= mixed connective tissue disease; SLE= systemic lupus erythematosus; PH= pulmonary hypertension; RHC= right-sided heart catheterization; PFTs= pulmonary function tests; DLCO= diffusing capacity for carbon monoxide; NT-proBNP= N-terminal pro–brain natriuretic peptide; DETECT= DETECTion of PAH in SSc.
Source: Khanna 2013 (Khanna et al., 2013).

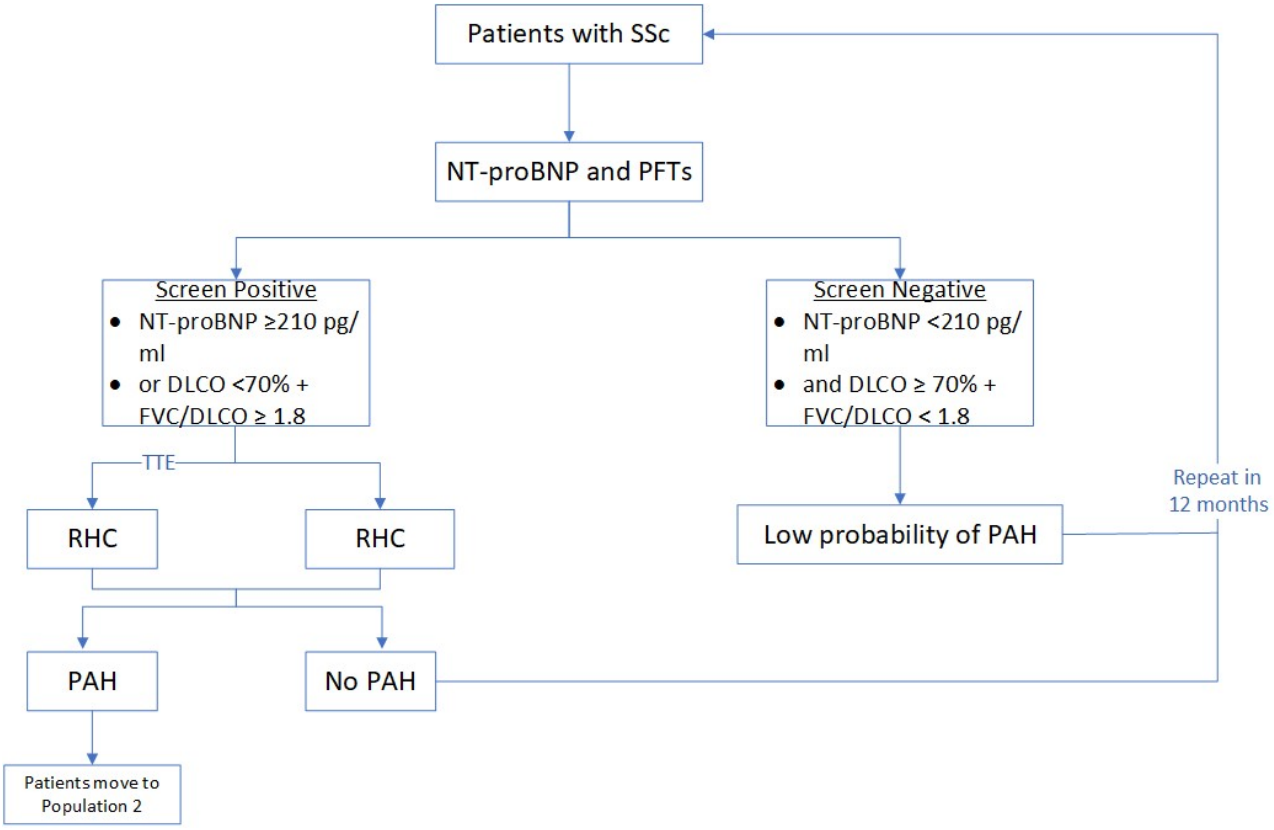
PASC noted that a current clinical management algorithm in the absence of NT-proBNP testing was not proposed in the application. The applicant clarified that the most relevant current algorithm would include TTE instead of NT-proBNP in combination with PFTs as the first-tier screening strategy. PASC requested this change be reflected in the current clinical management algorithm.

Proposed clinical management algorithm

The applicant has proposed the Australian Scleroderma Interest Group (ASIG) screening algorithm, developed based on findings from an Australian cohort of patients with SSc (Figure 3). Patients screened positive if NT-proBNP was greater than or equal to 209.8 pg/mL, and/or DLCO was less than 70.3% with FVC (forced vital capacity), %/DLCO% greater than or equal to 1.82 (Thakkar et al., 2012). Patients who test positive for NT-proBNP or fulfil the PFT criteria are referred for RHC and other investigations, including TTE (where applicable). Patients with negative results for NT-proBNP and PFT are recommended to undergo repeat screening in 6-12 months. Figure 3 shows an overview of the ASIG algorithm.

The ASIG clinical pathway recommends annual screening of all asymptomatic SSc patients with a non-invasive screening algorithm for PAH based on NT-proBNP concentration and lung function parameters as the first-tier screening for PAH. All positive patients for both or either test are then recommended for RHC confirmation.

Figure 3: Proposed clinical management algorithm (population 1): Summary of the Australian Scleroderma Interest group (ASIG) algorithm, as proposed in the application



ASIG= Australian Scleroderma Interest Group; NT-proBNP= N-terminal pro-B-type natriuretic peptide; PFTs= pulmonary function tests; DLCO= diffusing capacity of lung for carbon monoxide; FVC= forced vital capacity; TTE= transthoracic echocardiography; RHC= right heart catheterisation; PAH= pulmonary arterial hypertension.
Note: The applicant suggested annual testing, but a maximum of 2 NT-proBNP tests per year could be requested if the results are borderline or there is worsening of symptoms.
Source: Figure compiled during the PICO preparation based on Figure 5, p28 of the application and (Saygin and Domsic, 2019).

Comparison of the current and proposed guidelines/algorithms for population 1

A comparative summary of the various guidelines regarding the use and frequency of the proposed intervention and the comparator is provided in Table 5.

Table 5: Comparative summary of various guidelines regarding the use and frequency of the proposed test and the comparator test

Guidelines/algorithm	Initial screening		Follow-up annual screening		Frequency of testing
	NT-proBNP included	TTE (comparator) included	NT-proBNP included	TTE (comparator) included	
ASIG[1]	Yes	No	Maybe	Maybe	Up to 2 times per year
ESC/ESR	No	Yes	Maybe	Yes	Annually
International task force	Maybe	Yes	Maybe	Maybe	Annually
DETECT	Yes	NA[1]	Yes	Yes	NR
ItinerAIR	No	Yes	Yes	No	NR
6th WSPH	Conditional[2]	Yes	Conditional[2]	Yes	Annually

WSPH= World Symposium for Pulmonary Hypertension; NR= not reported; ASIG= Australian Scleroderma Interest Group; DETECTion (DETECT) of PAH in SSc algorithm; ESC= European Society of Cardiology; ESR = European Respiratory Society.
[1] **Proposed clinical management algorithm**
[2] Included in the second step
[3] NT-proBNP recommended if DLCO < 80%.

Table 6 compares the diagnostic performance of commonly used consensus recommendations for screening patients with SSc. Substantial variation was observed in the test performance of various algorithms. The ASIG algorithm showed a specificity of 54.5%, whereas the specificity ranged from 35.3% to 48.0% in DETECT and from 31.8% to 85.7% in the ESC/ESR guidelines. Sensitivity was comparatively less variable for ASIG and DETECT algorithms and slightly more variable in the ESC/ESR guidelines (71.0 to 96.3%).

Table 6: Comparison of the diagnostic performance of commonly used consensus recommendations for screening patients with SSc

Algorithms/ guidelines	Sensitivity (95% CI), %	Specificity (95% CI), %	PPV (95% CI), %	NPV (95% CI), %	Study Reference
ASIG	100 (78.2-100)	54.5 (32.2-75.6)	60.0 (38.7-78.8)	100 (73.5-100)	(Hao et al., 2015)
	100 (73.2-99.3)	77.8 (51.9-92.6)	NR	NR	(Thakkar et al., 2012)
DETECT	100 (87.2-100)	35.3 (19.7-53.5)	55.1 (40.2-69.3)	100 (63.1-100)	(Hao et al., 2015)
	100 (90.1-100)	42.9 (26.5-60.9)	68.6 (55.0-79.7)	100 (75.7-100)	(Guillén-Del Castillo et al., 2017)
	96 (NR)	48 (NR)	35 (NR)	98 (NR)	(Coghlan et al., 2014)
ESC/ESR	96.3 (81.0-99.9)	32.3 (16.7-51.4)	55.3 (40.1-69.8)	90.9 (58.7-99.8)	(Hao et al., 2015)
	91.4 (77.6-97.0)	85.7 (68.5-94.3)	88.9 (74.7-95.6)	88.9 (71.9-96.1)	(Guillén-Del Castillo et al., 2017)
	71.0 (NR)	69.0 (NR)	40.0 (NR)	89.0 (NR)	(Coghlan et al., 2014)

NR=not reported; NPV=negative predictive value; PPV=positive predictive value; CI=confidence interval; ESC= European Society of Cardiology; ESR = European Respiratory Society; DETECTion (DETECT) of PAH in SSc algorithm.
Source: Table compiled during the PICO preparation and (Saygin and Domsic, 2019).

Key differences and similarities in the various algorithms include:

- Most algorithms propose annual screening of patients with SSc, whereas ASIG proposes screening up to two times per year.
- Compared with the ASIG algorithm, which prefers NT-proBNP and PFTs, most algorithms endorse TTE and PFTs as the initial and annual screening strategy.
- The ASIG algorithm stratifies patients for further testing based on the screen-positive results for either NT-proBNP (>210 pg/ml) or a predefined PFTs threshold (DLCO < 70.3% with FVC%/DLCO% ≥1.8). In contrast, the other screening algorithms propose considering a variety of variables.
- Universal consensus on the use of a particular screening algorithm is lacking.
- The test performance of various algorithms is highly variable and difficult to compare.

PASC advised that the proposed clinical management should reflect the use of NT-proBNP as a part of a screening process such as the ASIG algorithm.

Proposed economic evaluation

The application has proposed a non-inferior clinical claim, implicitly suggesting the non-inferior safety and effectiveness for the NT-proBNP testing compared to TTE for population 1 (p37). Based on this claim, the appropriate type of economic evaluation would be cost minimisation analysis (Table 7).

Table 7: Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	**Uncertain[a]**	**Noninferior[b]**	**Superior**
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis

? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis

[a] 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations

[b] An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

PASC advised that the most appropriate approach for the economic evaluation would be a cost minimisation analysis, given the claim of non-inferior safety and effectiveness.

Proposal for public funding

The applicant stated during the pre-PASC teleconference that NT-proBNP is exempt from the Therapeutic Goods Administration evaluation process. Table 8 presents commercial tests registered on the Australian Register of Therapeutic Goods (ARTG). A list of additional laboratory-based assays was provided by the applicant post PASC and is presented in Table A 1.

Table 8 NT-proBNP tests on the Australian Register of Therapeutic Goods

Test	Laboratory-based test
Roche Diagnostics (CARDIAC® NT-pro-BNP)	ARTG 200461, Class 2 IVD, Specific Protein IVDs
Siemens Healthineers (Stratus® CS Acute Care™)	ARTG 179719 includes NT-proBNP, it is on the Immulite platform. ARTG 175075 includes NT-proBNP on the ADVIA Centaur and the Atellica Immunoassay module.
BioMerieux (VIDAS NT-proBNP2)	Not supplied in Australia

Source: Provided to the Department by the Therapeutic Goods Administration
ARTG = Australian Register of Therapeutic Goods; IVD = in vitro diagnostic medical device

Population 1: Patients with SSc

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

Table 9: 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 *laboratory-based* NT proBNP *testing* in patients with systemic sclerosis (scleroderma) in assessing the risk of pulmonary arterial hypertension that requires right heart catheterisation for definitive diagnosis. Maximum of two tests per patient in any one year.
Fee: $58.50 Benefit: 75% = $43.90 85% = $49.75

Suggested changes to the item descriptor in italics

PASC enquired whether point of care NT-proBNP tests are included in this application. The applicant confirmed that these tests are not a part of this application and requested laboratory-based tests of NT-proBNP only.

The applicant accepted the amendment in the proposed item descriptor reflecting laboratory-based NT proBNP testing only, which was acknowledged by the PASC.

PASC considered whether the proposed service should be amalgamated with existing MBS item 66830 or whether new items should be created, and was supportive of a creation of a separate item. The need for requester restrictions and strengthening the frequency restrictors were also discussed and is to be developed as part of the ESC and MSAC process.

PICO Set 2 – Quantification of NT-proBNP for risk stratification in patients previously diagnosed with pulmonary arterial hypertension

Population 2

Pulmonary hypertension (PH) is defined as mean pulmonary artery pressure ≥20[5] mm Hg measured during RHC (Prins and Thenappan, 2016, Condon et al., 2019). The term pulmonary artery hypertension represents a subset of patients who also have the presence of pre-capillary hypertension, including an end-expiratory pulmonary artery wedge pressure (<15 mm Hg) and a pulmonary vascular resistance greater than 3 Woods units. PAH is a progressive disease characterised by vasoconstriction, hyperplasia, hypertrophy, fibrosis, and thrombosis that involves all three layers of the vascular wall (intima, media, adventitia). PAH subgroups include idiopathic, heritable, PAH related to risk factors or associated conditions and others, as shown in Table 10.

Table 10: Classification of PAH

1. Pulmonary Arterial Hypertension
1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drug and Toxin induced
1.4 PAH 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
1.5 PAH long-term responders to CCBs
1.6 PAH with overt features of PVOD/PCH
1.7 Persistent PH of the newborn

CCB, calcium channel blocker; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary hemangiomatosis; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease. Source: (Klinger et al., 2019, Prins and Thenappan, 2016, Simonneau et al., 2019)

Epidemiology

PAH is a rare disorder with worldwide estimates varying from 15 to 52 persons per million (Peacock et al., 2007, Jansa et al., 2014, Humbert et al., 2006). Idiopathic, heritable, and drug/toxin-induced PAH make up 52.6% of all PAH cases, with idiopathic PAH accounting for nearly half of all PAH cases. The mean age of all PAH patients at time of diagnosis in the Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ) cohort (n=1071) was 49.9 ± 20.4 years and more than two thirds of patients were female.[6] However, it can occur in males and is often associated with worse clinical outcomes (McLaughlin et al., 2015). Country-specific registries were established to provide detailed information on patient demographics. The National Institutes of Health (NIH) registry in the United States (US) collected PAH data from 1981 to 1985 and included 187 individuals of various aetiologies (Rich et al., 1987). The registry

[5] The definition was updated as per the applicant suggestion that the most recent World Symposium on PH (6th WSPH) defines PAH as mean pulmonary arterial pressure (mPAP) threshold in the definition of PAH to >20 mmHg at rest.
Reference: CONDON, D. F., NICKEL, N. P., ANDERSON, R., MIRZA, S. & DE JESUS PEREZ, V. A. 2019. The 6th World Symposium on Pulmonary Hypertension: what's old is new. F1000Res, 8.

[6] https://www.pbs.gov.au/reviews/pah-review-files/pmr-pah-final-report-tor2-redacted.PDF

reported a mean age of PAH presentation of 36 years, mainly included Caucasian women and reported a poor median survival of 2.8 years (1 year- 68%, 3 year- 48%, and 5 year- 34%), mainly due to limited treatment options at that time. The 2002 French PAH registry, including 674 people with PAH, reported improved survival 82.9% at 1 year and 58.2% at 3 years (Benza et al., 2012b, Humbert et al., 2010a). REVEAL (Registry to Evaluate Early and Long-Term PAH Disease Management) is a multicentre, observational, US-based registry that enrolled 2,967 patients between 2006 and 2007 information in 2006 from 2,967 individuals (Badesch et al., 2010). The mean age of patients was 53 years at baseline with a female to male ratio of 5:1. Idiopathic PAH accounted for about 46% of patients, 25% associated with connective tissue diseases, and 10% with congenital heart diseases. In the REVEAL registry, the 1-year, 3-year, 5-year, and 7-year survival rates were 91%, 85%, 68%, and 49%.

Clinical Presentation and Diagnosis

The underlying disease entities frequently mask the clinical manifestations of PAH. Obtaining a thorough history, physical examination, and complete workup are required to differentiate PAH from groups 2-5 pulmonary hypertension. Patients may present with one or more symptoms, including exertional dyspnoea, weakness, and fatigue (Simonneau et al., 2019, Nickel et al., 2020, Schermuly et al., 2011). As the disease progresses, other symptoms such as chest pain, syncope, jugular venous distension, edema, and other symptoms may appear (Simonneau et al., 2019). Based on the loss of physical activity, patients are generally placed in a World Health Organization functional class (WHO FC) system (Barst et al., 2013). Developed initially for heart failure by the NYHA and adapted for pulmonary hypertension by the WHO, patients fall into one of four classes according to limits on physical activity imposed by the disease (Barst et al., 2013). Patients in WHO FC I suffer from no physical activity limitations, whereas patients in WHO FC II are distinguished by a slight reduction in physical activity, which may be accompanied by undue dyspnoea, fatigue, chest pain, or near syncope. Patients in WHO FC III are characterised by a marked reduction in physical activity with no discomfort at rest, but less than ordinary activity causes undue dyspnoea, fatigue, chest pain, or near syncope. Finally, patients in WHO FC IV cannot perform any physical activity without symptoms with signs of right ventricular failure and symptoms at rest with discomfort increasing by any physical activity.

In addition to a detailed clinical examination, initial tests such as chest radiography and electrocardiography are performed with a follow-up TTE if the initial tests suggest pulmonary hypertension (Simonneau et al., 2019). RHC is the gold-standard test to confirm the diagnosis of PH and PAH (Frost et al., 2019).

Risk Assessment

The risk stratification of PAH is an assessment of prognosis and is considered an important step in determining the individualised treatment options (Galiè et al., 2019). Several risk assessment stratification tools have been developed over the years. Most have used retrospective analysis of large patient registries to aid in determining prognosis and deciding therapy options. These tools have been designed based on demographics, laboratory tests, functional status, and hemodynamic information to stratify patients into low, intermediate, or high risk according to the expected one-year mortality. The risk categories are then used as a baseline for initiating treatment, determining prognosis, and monitoring response and disease progression (Beshay et al., 2020, Galiè et al., 2019, Levine, 2021). Table 11 summarises the commonly used risk assessment tools (Galiè et al., 2019). The 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) pulmonary hypertension (PH) guidelines are also a valuable tool (Galiè et al., 2016). The clinical management algorithms section provides a detailed discussion of the risk stratification scores/calculators and guidelines.

The risk stratification and regular monitoring of patients have been shown to help clinicians determine which individuals with PAH are at high risk for 1-year mortality, prioritisation of therapies, and referral for

lung transplantation (Thomas et al., 2020). The ESC/ESR guidelines recommend that risk assessment be conducted regularly (3-6 monthly in stable patients) using multiple parameters to evaluate disease progression and patients' response to treatment (McLaughlin et al., 2013, Galiè et al., 2016). It is recommended that risk assessment in these patients should include a range of clinical, haemodynamic and exercise parameters, as there is no single variable that provides definitive prognostic information (Humbert et al., 2010b). Based on the evaluation of multiple variables, including NT-proBNP levels, PAH patients are categorised as low, intermediate, or high risk with an estimated 1-year mortality of <5%, 5–10% and >10%, respectively (Galiè et al., 2016).

Table 11: Summary of four registries assessing risk scores

	REVEAL	Swedish PAH Register	COMPERA	French Pulmonary Hypertension Network#
Required variables, n	12-14	8	8	4
Patients at baseline, n	2716	530	1588	1017
Patients at follow-up, n	2529	383	1094	1017
Associated PAH included	Yes	Yes	Yes	No
Definition of low risk	⩽6 REVEAL risk score	<1.5 average risk score	<1.5 average risk score	3–4 out of 4 low-risk criteria
1-year mortality by risk group (low/intermediate/high), %	⩽2.6/7.0/⩾10.7	1.0/7.0/26.0	2.8/9.9/21.2	1.0/NA/13.0–30.0

PAH= pulmonary arterial hypertension; NA= not available. # incident patients only; REVEAL= Registry to Evaluate Early and Long-term PAH Disease Management. Source: (Galiè et al., 2019)

PASC acknowledged that the population for PICO set 2 consists of all patients with an established diagnosis of PAH.

Utilisation

The application estimated the number of patients with diagnosed PAH disease who would be eligible for NT-proBNP testing to be 2,229 (low estimate) to 3,200 (high estimate) in 2021, increasing to 3,230 (low estimate) to 4,201 (high estimate) in 2023 (p40). These estimates were based on the Drug utilisation subcommittee (DUSC) report on PAH utilisation, which assumed the prevalence and incidence rates of PAH to be 87.6 and 18.6 per million population.[7] The projected number of patients who will utilise the proposed medical service is presented in Table 12.

[7] Pulmonary Arterial Hypertension (PAH) medicines utilisation analysis. Drug utilisation sub-committee (DUSC). February 2015. Public Release Document, February 2015 DUSC Meeting.

Table 12: Patients with previously diagnosed pulmonary arterial hypertension (PAH) who will be eligible for NT-proBNP testing, as presented in the application

	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: Table 4, p40 of the application

Additionally, the application analysed the 10% PBS script data[8] from July 2020 to June 2021 and estimated that between 2900 to 3200 PAH patients are being treated in Australia, assuming 100% of diagnosed patients received treatment for PAH (p39). The source of these estimates could not be verified because of the lack of access to these data.

There are no published national prevalence and incidence figures for PAH in Australia. The subgroup-specific incidence and prevalence rates were not discussed in the DUSC report, and the relevant Australian data are not available. The DUSC estimate of 87.6 million per million population seems to be higher than the international prevalence estimates of 15 to 52 persons per million (Peacock et al., 2007, Jansa et al., 2014, Humbert et al., 2006). Incidence rates ranged from 2.4 to 10.7 in these studies, lower than the DUSC estimate of 18.6 per million. The application has assumed that all patients diagnosed with PAH will undergo PAH-specific therapy.

The applicant clarified during the pre-PASC teleconference that Population 1 patients with SSc who have been diagnosed with SSc-PAH will move to Population 2 (all patients with PAH).

Given that all patients with PAH were assumed to receive PAH-specific therapy, PASC noted that the assessment report should clarify whether additional patient numbers are anticipated, i.e., would there be patients who may not receive therapy.

Rationale for risk assessment

The main treatment goal of PAH therapy is to reach a low-risk status, as determined by a risk assessment instrument. The benefit of reaching a low-risk profile was demonstrated in a retrospective analysis of 530 PAH patients in a Swedish registry (Kylhammar et al., 2018). Patients were categorised as low-risk, intermediate-risk or high-risk according to the cut-off values for FC, 6-min walking distance (6MWD), NT-proBNP, right atrial area assessed by TTE, mean right atrial pressure (mRAP), pericardial effusion, cardiac index (CI), and mixed venous oxygen saturation (SvO2), as defined in the risk assessment instrument from the 2015 ESC/ESR guidelines. The results showed that patients in the low-risk group exhibited a reduced mortality risk (hazard ratio 0.2; 95% confidence interval: 0.1-0.4 in multivariable analysis adjusted for age, sex and PAH subset), as compared to patients in the intermediate-risk or high-risk groups (Kylhammar et al., 2018). Among patients who remained in the low-risk group at follow-up, 1-, 3- and 5-year survival rates were 100%, 98% and 89%; for those who improved to low-risk, it was 98%, 96% and 96%; for those who remained in the intermediate-risk or high-risk groups, it was 90%, 68% and 50%; and for those who worsened to intermediate-risk or high-risk, it was 81%, 60% and 43%.

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

Another registry-based analysis included 1,588 newly diagnosed PAH patients enrolled into COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension), a European-based PH registry (Hoeper et al., 2017). Risk assessment was applied using the following variables: WHO-FC, 6MWD, BNP/NT-proBNP, RAP assessed by TTE, CI, and SvO2. The observed mortality rates one year after diagnosis were 2.8% in the low-risk cohort (n=196), 9.9% in the intermediate-risk cohort (n=1,116) and 21.2% in the high-risk cohort (n=276). In addition, the risk assessment strategy proved valid at follow-up and in major PAH subgroups.

Similar results were reported in a retrospective analysis of 1,017 PAH patients risk-stratified using a simplified version of the ESC/ESR guidelines (Boucly et al., 2017). Risk classification was performed using four variables: WHO-FC, 6MWD, RAP, and CI. Exploratory analysis for a subset of patients was also performed using BNP/NT-proBNP and SvO2. Each of the four low-risk criteria independently predicted transplant-free survival at first re-evaluation, with the number of low-risk criteria present at diagnosis ($p<0.001$) and at first re-evaluation ($p<0.001$), discriminating the risk of death or lung transplantation. In addition, in a subgroup of 603 patients with BNP or NT-proBNP measurements, the number of three non-invasive criteria (WHO/NYHA FC, 6MWD and BNP/NT-proBNP) at first re-evaluation discriminated prognostic groups ($p<0.001$). Patients attaining only one or two low-risk criteria at follow-up had a worse long-term prognosis than those who attained three or four low-risk criteria. Furthermore, patients achieving or maintaining all four low-risk criteria had a better long-term prognosis than those with three low-risk criteria at re-evaluation.

Although the registry-based studies show the value of early identification of worsening disease, their retrospective nature lacks rigorous study design. In addition, data collection was not standardised in all published registries, and significant missing data and numbers of patients lost to follow-up were reported. Another source of uncertainty is the optimal screening frequency and choice of the risk stratification variables. An individual patient is unlikely to have all variables indicative of low, medium, or high risk. Therefore, sound clinical judgement is crucial, as some variables may indicate low risk and some indicative of intermediate or high risk. The application has suggested that the basic program should include determination of the WHO-FC, at least one measurement of exercise capacity (6MWD or CPET), and information on right ventricle (RV) function (either BNP/NT-proBNP or echocardiography) (p24).

Intervention

The proposed intervention is N-terminal proB-type natriuretic peptide (NT-proBNP) serological testing to (i) screen for risk stratification and monitor patients with PAH.

Natriuretic peptides are a family of hormones secreted primarily from the heart, kidneys and brain that cause vasodilation and natriuresis. They include atrial natriuretic peptide, BNP, C-type natriuretic peptide and urodilatin. BNP is the product of the early response gene *NPPB*. In PAH, transmural pressure, volume overload, hypoxia, or pro-inflammatory factors induce transcription of *NPPB* to produce 134-amino acid (aa) preproBNP. The end result of this process is two biomarkers of 32-aa BNP and 76-aa NT-proBNP. BNP is then rapidly metabolised in the blood with a short half-life of about 20 minutes, making rapid processing of samples necessary for its determination (Rehman and Januzzi, 2008). NT-proBNP, on the other hand, is cleared passively by organs with high blood flows, including the kidneys, resulting in a longer half-life of about 60-120 minutes (Rehman and Januzzi, 2008). NT-proBNP also offers good stability at different temperatures (Sokoll et al., 2004, Ordonez-Llanos et al., 2008). In contrast, the BNP assays have been shown to be more variable as BNP results of the same sample can vary 40% among the different methods (Rawlins et al., 2005). In clinical laboratory testing, the longer half-life of NT-proBNP may be beneficial if sample transportation time is high. Estimates of BNP stability recommend that it should be analysed or frozen within 4 hours, whereas NT-proBNP can reasonably be stored at room temperature for up to 2 days (Downie et al., 1999, Cowie et al., 2010).

Measurement of BNP or NT-proBNP is currently used to diagnose heart failure in patients presenting with dyspnoea to a hospital emergency department (MBS item number 66830).[9] The current MBS item number is subject to rule 25, implying that a maximum of six tests per year can be requested per patient. The current application exclusively proposes the measurement of NT-proBNP for both populations.

There is no standard protocol for NT-proBNP sampling and testing. Risk stratification guidelines recommend specific threshold values to indicate PAH severity, accuracy, and analytical range can vary between tests, and there is conflicting evidence on the interchangeability of results. A study by Collin-Chavagnac et al. compared 10 different natriuretic peptide laboratory assays in patients with heart failure and reported that median NT-proBNP values varied between 1020 and 1450 ng/L^{-1} in different assays (Collin-Chavagnac et al., 2015). The authors concluded that, while practical diagnostically, none of the tests could be reliably cross-compared and recommended that patients should consistently use the same assay (NT-proBNP) over time (Collin-Chavagnac et al., 2015). Individual specific reference ranges and heart failure diagnostic cut-offs were also recommended for each commercial natriuretic peptide immunoassay.

There is a need for consistency among the testing platforms as different laboratories use different testing platforms. For example, NSW health pathology utilises the Abbott architect fluorescence immunoassay for NT-proBNP detection, which relies on specialised reagents compatible with a specific fluorescent microplate reader.[10] Information on methods used by the local hospital emergency departments and private pathology providers in Australia is unavailable.

The application has suggested three commercially available NT-proBNP laboratory-based immunoassays, none manufactured by the applicant. These include Roche Diagnostics (CARDIAC® NT-pro-BNP), Siemens Healthineers (Stratus® CS Acute Care™) and BioMerieux (VIDAS NT-proBNP2). The study by Collin-Chavagnac et al. in heart failure patients included the immunoassays provided by all three providers and reported variability in the test results (Collin-Chavagnac et al., 2015). If the requested intervention is made available in the outpatient or specialised PAH clinic settings, it is important to ensure that the same antibodies and instruments are used to make the assays relatively consistent. Given the potential for variation between kits, a UK-based consensus group set up to develop clinical guidance in PAH also recommends users participate in a quality assurance scheme and adhere to manufacturer recommendations (Cowie et al., 2010). The lack of standardisation between protocols and devices could pose logistical challenges and must be addressed for the successful implementation of NT-proBNP laboratory-based testing.

BNP/NT-proBNP testing is claimed using MBS item 66830. This item is for diagnosing heart failure in patients presenting with dyspnoea to a hospital Emergency Department, subject to rule 25, which limits the frequency of its use to not more than 6 times in a 12-month period. The proposed MBS item in this application does not include BNP but NT-proBNP only.

The application did not address whether:

- Different testing technologies lead to variable or discordant test results
- Steps to ensure standardisation between protocols and devices.

During the pre-PASC teleconference, the applicant has agreed to address these issues.

PASC noted that a risk assessment approach is to be used to monitor treatment response and to guide treatment decisions in patients with PAH. PASC noted that the proposed NT-proBNP test would be used in combination with other tests or variables for this purpose.

[9] Medicare Benefits Schedule - Item 66830.
http://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=66830&qt=item
[10] http://www.palms.com.au/php/labinfo/info_index.php?tab=5

PASC noted that NT-proBNP would be a part of a risk assessment tool such as the REVEAL 2.0 Lite or the European Respiratory Society and European Society of Cardiology (ERS/ESC) guidelines–derived score.

PASC noted the applicant's advice on the screening frequency of NT-proBNP testing for patients with PAH, who suggested testing would be undertaken twice per year in most patients, but a maximum of four NT-proBNP tests per year was proposed to provide flexibility for clinical worsening or monitoring response to a change in therapy. PASC advised that the screening frequency should be appropriately modelled in the assessment report.

PASC considered the lack of a definitive reference range for NT-proBNP concentration for risk assessment and monitoring progress in patients with PAH and issues around concordance, given that the various NT-proBNP testing platforms are not standardised. The applicant stated that any discrepancy between assays is likely to be negligible, and that the test performance and concordance amongst various laboratory-based NT-proBNP assays available in Australia would be discussed in the assessment report, which the PASC acknowledged.

Rationale

BNP and NT-proBNP are well-studied clinical biomarkers used in PAH and other cardiovascular disorders, such as acute/chronic heart failure, and they are used as surrogate markers of cardiac function (Galiè et al., 2016, Fu et al., 2018, Santaguida et al., 2014). Typically, NT-proBNP is measured when patients are assessed by their PAH physician, and this information is integrated with the results of other investigations.

The ESC/ERS guidelines strongly recommend regular risk assessment of patients with PAH in specialised PH centres (Galiè et al., 2016). A multidimensional approach consisting of several variables has been recommended, including determining the right ventricular function by echocardiography or NT-proBNP testing (Galiè et al., 2016). However, these guidelines specify that the approach should be patient-specific, which considers the individual risk factors such as the rate of disease progression and the presence or absence of signs of right heart failure, or syncope, and also by co-morbidities, age, sex, background therapy, and PAH subtype (Galiè et al., 2016).

The ESC/ESR and other algorithms do not recommend stand-alone NT-proBNP (or TTE) testing for PAH as these markers can be elevated in almost any heart disease (Galiè et al., 2016). Also, given that NT-proBNP is released in response to either left or right ventricular wall stress, its measurement cannot be used to differentiate between PAH and left heart disease. NT-proBNP clearance is dependent on glomerular filtration, and its concentration can be influenced by kidney function (Luchner et al., 2005). Hence, specific cut-off values and a reference range in conjunction with an appropriate measure of kidney function may be required to confirm the NT-proBNP based findings.

The application noted that in the REVEAL Lite 2 risk assessment tool, which categorises patients as having low, intermediate, and high risk of 1-year mortality, BNP/NT-proBNP was most highly predictive parameter.

PASC noted the applicant's advice that the application is limited to NT-proBNP laboratory-based testing and does not include BNP testing, as the latter is more likely to be spuriously affected by non-cardiac factors.

PASC discussed the requirement of renal function tests alongside NT-proBNP testing as its concentration can be influenced by kidney function. The applicant clarified that regular kidney function tests would be conducted as part of the regular risk assessment protocol, and these tests are currently MBS funded. PASC advised to include these tests in the economic evaluation for the assessment report.

Comparator(s)

Population 2: The comparators for population 2 is TTE.

Risk stratification in patients with established PAH is generally performed by a comprehensive analysis including TTE and RHC after the initial check-up, with further assessments at regular intervals. TTE is a frequently used tool in the risk stratification of PAH patients, whereas RHC is the reference standard test to confirm the presence of PAH (Galiè et al., 2016). The ESC/ESR guidelines recommend that risk assessment be conducted regularly (3-6 monthly in stable patients and intervals adjusted as per patient needs) using multiple parameters to monitor for signs of disease progression and response to therapy. Other guidelines/algorithms also recommend similar approaches (Galiè et al., 2019).

Uncertainty around the optimal timing of follow-up TTE and RHC has been noticed in the ESC/ESR guidelines, as risk assessment strategies may vary across PAH centres, from regular invasive haemodynamic assessments to a predominantly non-invasive follow-up strategy (Galiè et al., 2016). There is no evidence that an approach involving regular RHC is associated with better outcomes than a predominantly non-invasive follow-up strategy (Galiè et al., 2016). However, experts agree that RHC should be performed whenever therapeutic decisions can be expected from the results, including changes in medications and/or decisions regarding listing for transplantation (Galiè et al., 2016). Choosing which test to perform is usually reliant on patient characteristics and clinician preference.

There is no clear consensus on choosing NT-proBNP over TTE and RHC at regular check-ups. If the clinician sees the need for it, they might order a comprehensive panel including TTE, NT-proBNP and RHC, or they may opt for a non-invasive strategy including both TTE and NT-proBNP, among other variables. Therefore, NT-proBNP might become an add-on rather than a replacement prognostic/monitoring test for a subset of patients.

Considering that TTE is a non-invasive tool widely recommended in the various clinical practice algorithms and more frequently assessed than RHC, TTE might be a more appropriate comparator than TTE and RHC for population 2. RHC is usually reserved for disease confirmation and whenever therapeutic decision making is implicated.

PASC noted the lack of clarity on the most appropriate comparator for population 2.

PASC advised that the most appropriate comparator for population 2 would be a risk assessment tool that does not use NT-proBNP testing, such as the French Pulmonary Hypertension Network ItinérAIR-HTAP predictive equation tool. PASC further advised the assessment report to include the comparison of different risk assessment tools and choose the most appropriate tool that does not include NT-proBNP testing. PASC also considered whether the comparator would be similar to the intervention algorithm without NT-proBNP testing. The applicant was advised to clarify this issue further out of session.

Reference standard

The application did not nominate a reference standard for Population 2. RHC provides a complete hemodynamic assessment, including measuring pulmonary artery pressure, pulmonary capillary wedge pressure, pulmonary vascular resistance, transpulmonary, and diastolic pressure gradients (Rosenkranz and Preston, 2015). RHC is a technically demanding procedure that requires meticulous attention to detail to obtain clinically useful information. To obtain high-quality results and be of low risk to patients, the procedure is generally limited to expert PAH/PH centres.

PASC acknowledged that RHC is the accepted reference standard to confirm disease progression.

The MSAC Guidelines (p102) note that in longitudinal accuracy studies, the reference standard is more likely to be clinical outcomes at a later time point; this is relevant to prognostic tests (health outcomes).

PASC noted (out-of-session) that the risk assessment tools predict mortality or another clinical outcome (such as transplant-free survival). PASC advised that reference standard in this context should be the outcome measured by the risk assessment tools.

Outcomes

The evidence base for the NT-proBNP based prognostic testing and monitoring disease progression (population 2) mainly consisted of observational studies, which have been briefly discussed below.

Given the claim of non-inferiority, a truncated evidence approach may be appropriate. However, the application states that there may be a reduction in the use of TEE and RHC with current practice with a commensurate reduction in morbidity and mortality associated with this test.

Patient relevant

Test accuracy	Sensitivity, specificity, positive predictive value and negative predictive value compared to the reference standard in patients with SSc; assessment of the extent of and implications of discordance between Australian NT-proBNP testing and clinical utility standard, test-retest reliability, the test failure rate
Clinical utility	proportion of tested patients who might have a change in management (e.g., change in use of TEE, change in use of RHC, changes in treatment, change in the proportion of patients achieving a low risk status)
Therapeutic effectiveness	Overall survival, progression free survival, disease-related survival, quality of life
Prognosis	Prognostic effect of testing in patients with PAH
Risk assessment	Risk stratification (prediction) and disease monitoring of patients with PAH
Safety	Adverse events related to changes in clinical management.
Healthcare system	
Cost-minimisation	Cost of testing and any costs offsets
Financial implications	Number and cost of patients tested

It is recommended that patients should consistently use the same assay over time (Collin-Chavagnac et al., 2015).

PASC acknowledged that the primary outcome would be whether risk assessment including an NT-ProBNP measurement is non-inferior in classifying patients into low-, medium- and high-risk PAH categories compared to a risk assessment that does not include a NT-proBNP measurement.

PASC advised that the assessment report should provide a summary of the NT-proBNP lab tests used in Australia, including the analytical performance of these tests.

Population 2: Patients with PAH (longitudinal accuracy)

The application referenced a *posthoc* analysis investigating the prognostic role of NT-proBNP in patients with RHC confirmed PAH (Chin et al., 2019). The study population was derived from the GRIPHON trial, an international, double-blind, randomised, placebo-controlled phase III trial investigating the safety and efficacy of a PAH-targeted drug, selexipag, in patients with PAH (Sitbon et al., 2015). Chin et al. evaluated the NT-proBNP concentration in selexipag (n=443) and placebo control (n=424) samples of patients treated

at various time points- baseline, weeks 4, 8, 16, and 26, and at 6-month intervals after that. The results showed that the baseline and follow-up NT-proBNP categories were highly prognostic for future morbidity/mortality events during the study (P<0.0001).

The association between enlarged right atrial area (RAA) or the right atrial area index (RAAI), as measured by TTE, and prognosis of PAH has been evaluated in a recent systematic review and meta-analysis (Liu et al., 2020).

Because RHC is the gold standard test to compare the diagnostic and prognostic performance of other tests and is usually carried out sequentially in symptomatic patients already assessed with other tests, the stand-alone performance for risk assessment is not applicable.

Risk assessment algorithms: The application has suggested that algorithms consisting of non-invasive variables, including NT-proBNP, are also utilised in prognosticating and risk stratifying the PAH patients (p37) (Benza et al., 2021). A detailed discussion of these algorithms is provided in the clinical management algorithms section below.

Safety

No adverse events associated with NT-proBNP testing are known in the literature. It is a simple blood test that does not require any preparation and complex procedure.

TTE is an established non-invasive test used frequently in the clinic and is generally considered a safe procedure. RHC, on the other hand, is an invasive procedure. However, it is generally considered a safe procedure when performed by an experienced medical team and is associated with a low risk of serious complications (Rosenkranz and Preston, 2015).

PASC noted that there are no significant risks to NT-proBNP testing, as it is a simple blood test. However, should the test lead to more false positives followed by more invasive interventions such as RHC, it may result in safety issues associated with invasive RHC.

Value of Knowing

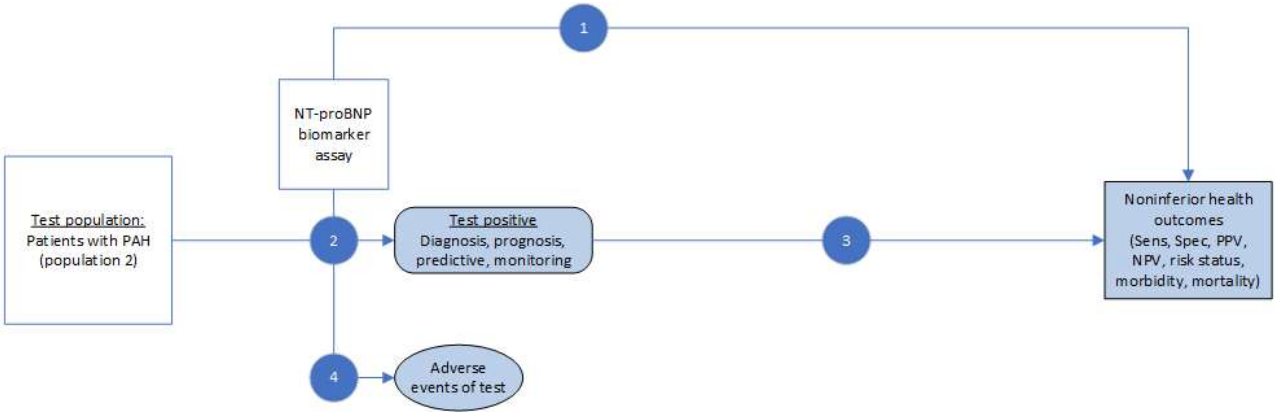
The application did not present any analysis of the value of knowing test results. Although no relevant value of knowing issues could be identified during the PICO preparation, the applicant should comment on any potential value of knowing issues in the assessment report.

Assessment framework

The clinical claim is of noninferiority in terms of comparing the diagnostic and prognostic performance of NT-proBNP with the comparators TTE/RHC (population 2). Given this, and that the proposed test claims to

replace the existing MBS tests (TTE and/or RHC), an assessment framework truncated at test accuracy seems appropriate (p82, TG 9.3, MSAC Technical Guidelines).

Figure 4 Assessment framework that has been truncated at test accuracy (concordance, test accuracy) with the inference that identical test accuracy will result in the same health outcomes



PAH= pulmonary arterial hypertension; Sens= sensitivity, Spec= specificity; PPV= positive predictive value; NPV= negative predictive value; NT-proBNP= N-terminal proB-type natriuretic peptide.
Figure notes: 1: direct from test to health outcomes evidence; 2: concordance of NT-proBNP testing with TTE and RHC in patients with PAH (population 2); 3: similar test results from both proposed test (NT-proBNP) and comparator/s (TTE and RHC) will result in the same management decisions, and noninferior health outcomes; 4: adverse events due to testing.
Source: Adapted from p82, Figure 9, MSAC Guidelines for preparing assessments for the Medical Services Advisory Committee 2021.

PASC noted that a truncated assessment framework at test accuracy seems appropriate.

Clinical management algorithms

Population 2: Patients previously diagnosed with PAH

ESC/ESR is the most adopted guideline for the risk assessment and monitoring of patients previously diagnosed with PAH. These guidelines strongly recommend regular assessment of patients with PAH in expert pulmonary hypertension centres and emphasise a comprehensive assessment due to the lack of a single variable that provides diagnostic and prognostic information. A multidimensional approach comprising of several variables has been suggested to answer questions regarding clinical deterioration since the last assessment, underlying cause of disease progression, right ventricular stability, and identification of low-risk patients. Table 13 shows the recommendations on the risk assessment and timing for the follow-up of patients with PAH. The application stated that the Australian clinical practice currently uses ESC/ESR guidelines to determine risk and prognosis (p29), which includes the NT-proBNP test (as part of the Basic lab variable in Table 13).

Table 13: Clinical management algorithm, including NT-proBNP, suggested in the application for population 2: Suggested assessment and timing for the follow-up of patients with pulmonary arterial hypertension

Variables	At baseline [a]	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 FC	+	+	+	+	+
ECG	+	+	+	+	+
6MWT/Borg dyspnoea score	+	+	+	+	+
CPET	+		+		+ [e]
Echo	+		+	+	+
Basic lab [b] (**including NT-proBNP**)	+	+	+	+	+
Extended lab [c]	+		+		+
Blood gas analysis[d]	+		+	+	+
RHC	+		+ [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: *Table compiled during the PICO preparation from Figure 6, p29 of the application and (Galiè et al., 2016)*

In addition to the ESC/ESR guidelines, different baseline and follow-up parameters have been utilised individually or combined with formulae or calculators for risk stratification (Galiè et al., 2019). These include the French Pulmonary Hypertension Network (FPHN) registry risk equation, the PH connection equation, the Scottish composite score, and the US Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) risk equation and score (Galiè et al., 2019). The REVEAL 2.0 risk score calculator (14 variables) was derived from the original REVEAL risk score calculator (Benza et al., 2012a) and has been widely used to risk-stratify PAH patients (Benza et al., 2019). The risk categories included: low risk = REVEAL score $\leq$ 6; intermediate risk = REVEAL score 7 and 8, and high risk=REVEAL score $\geq$9. Both original REVEAL and REVEAL 2.0 included BNP/NT-proBNP, TTE and RHC, among other variables (Benza et al., 2019).

Recently, a simplified version of the REVEAL 2.0 risk assessment calculator, REVEAL Lite 2, has been proposed for patients with PAH (Benza et al., 2021) (Figure 5). The simplified risk assessment calculator includes six non-invasive variables- FC, vital signs (systolic BP and heart rate), 6MWD, BNP/NT-proBNP, and renal insufficiency (by estimated glomerular filtration rate).

The application seems to have proposed REVEAL Lite 2.0 as the preferred clinical management algorithm, which includes the BNP/NT-proBNP test for routine risk stratification of PAH patients in the expert clinical centres. However, the proposed MBS item description does not include BNP.

As per the 2015 ESC/ESR guidelines, the overall treatment goal in patients with PAH is achieving a low-risk status, which is usually associated with good exercise capacity, good quality of life, good RV function and low mortality risk (Galiè et al., 2016). The therapeutic regimens also focus on bringing and/or maintaining the patients in WHO FC II whenever possible. The PBAC post-market review of PAH medicines acknowledged the PAH risk assessment criteria in the 2015 ESC/ERS guidelines and noted that the contemporary treatment goal is for patients to reach a low-risk status (para 5.11, p23, Agenda item 11.04, November 2019 PBAC Meeting). The PBAC also noted that patients not reaching the clinical goals aligned with low risk are considered to have an inadequate response to treatment, and recommended dual combination therapy as second line treatment for patients with WHO FC III symptoms and first line treatment for patients with WHO FC IV symptoms (para 2.10 and 5.36, pp 3 and 27, 11.04, November 2019 PBAC Meeting).

Figure 5: Variables included in the REVEAL 2.0 and REVEAL Lite 2 Risk Calculators and Associated Risk Scores, as provided in the application

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: Figure 7, p30 of the application and (Benza et al., 2021).
NOTE: **The dashes denote parameters not included in REVEAL Lite 2**. 6MWD =6-min walk distance; BNP =brain natriuretic peptide; bpm =beats per minute; DLCO =diffusing capacity of the lungs for carbon monoxide; eGFR =estimated glomerular filtration rate; FC =functional class; HR =heart rate; mRAP =mean right atrial pressure; NT-proBNP =N-terminal prohormone of brain natriuretic peptide; NYHA =New York Heart Association; PAH =pulmonary arterial hypertension; PVR =pulmonary vascular resistance; REVEAL =Registry to Evaluate Early and Long-Term PAH Disease Management; RHC =right heart catheterisation; SBP =systolic BP; WHO =World Health Organization.

Key differences in the REVEAL Lite 2.0 and other risk assessment algorithms include:

- REVEAL Lite 2.0 does not include TTE and RHC for the regular risk assessment, whereas the other risk calculators recommend these tests at regular intervals (every 6-12 months).
- The original REVEAL and the derivative risk calculators did not report the test frequency as the follow-up was limited to one year only. ESC/ESR guidelines provide recommendations for the timing for the follow-up of patients with PAH.

PASC acknowledged that a current clinical management algorithm in the absence of NT-proBNP testing was not included in the application. PASC also noted a lack of clarity in the proposed clinical management algorithm, including NT-proBNP testing. PASC considered the clinical management algorithms should reflect the use of NT-proBNP as a part of a risk assessment algorithm. PASC requested that updated clinical management algorithms to be provided to PASC for consideration out of session. PASC advised the assessment group, the Department, and the applicant to set up a meeting to finalise the current and proposed clinical management algorithms for population 2.

Clinical management algorithms for population 2 were developed post-PASC by the applicant and the Department and considered by PASC out of session.

PASC enquired about the screening frequency of NT-proBNP testing in patients with PAH. The applicant suggested that testing would be performed twice a year in most cases, but a maximum of 4 NT-proBNP tests per year were proposed to provide flexibility for clinical worsening or changing therapy. PASC advised to appropriately model the screening frequency in the assessment report.

Current clinical management algorithm

Figure 6 presents the current clinical management algorithm developed following the PASC meeting.

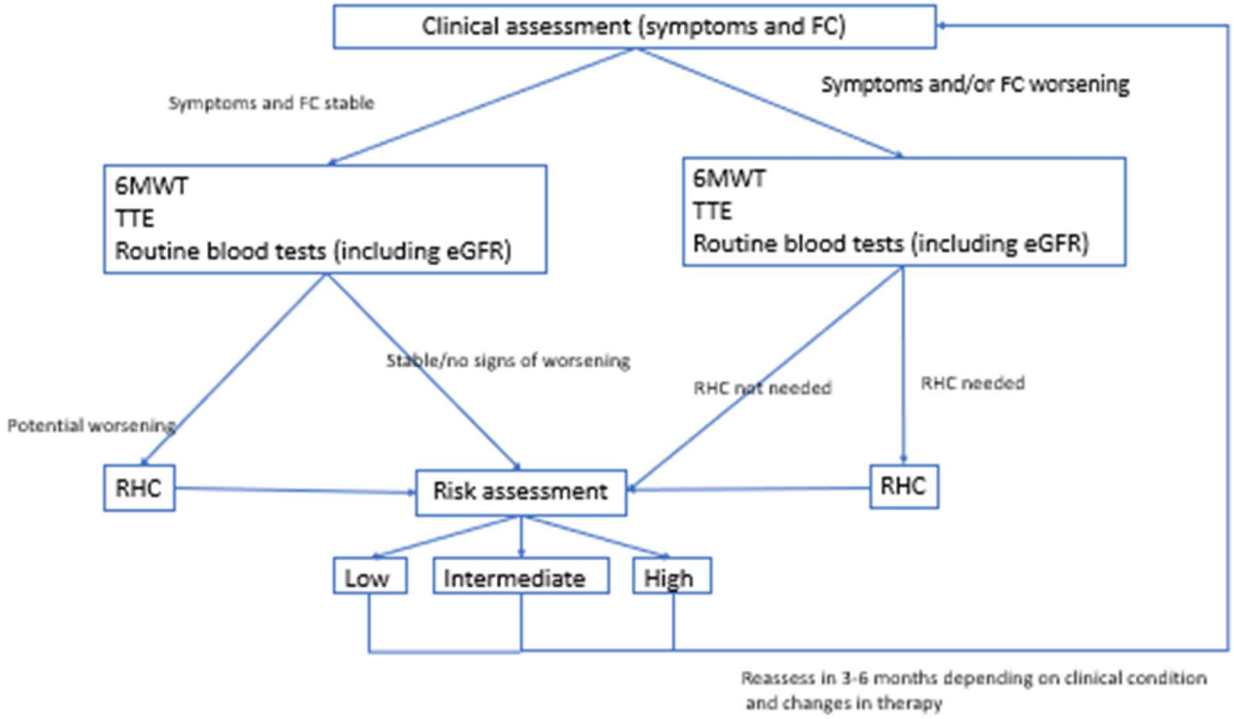


Figure 6 Current clinical management algorithm for risk assessment in pulmonary arterial hypertension
Note: Clinical assessment includes assessment of symptoms, functional class, heart rate and blood pressure. The applicant's clinical experts advised that pulomonary function tests are not a part of regular risk assessment for people with PAH.
6MWD =6-min walk distance; BNP =brain natriuretic peptide; eGFR =estimated glomerular filtration rate; FC =functional class; NT-proBNP =N-terminal prohormone of brain natriuretic peptide; PAH = pulmonary arterial hypertension; RHC = right heart catheterisation

Proposed clinical management algorithm

Figure 7 presents the proposed clinical management algorithm, including NT-proBNP testing developed post-PASC.

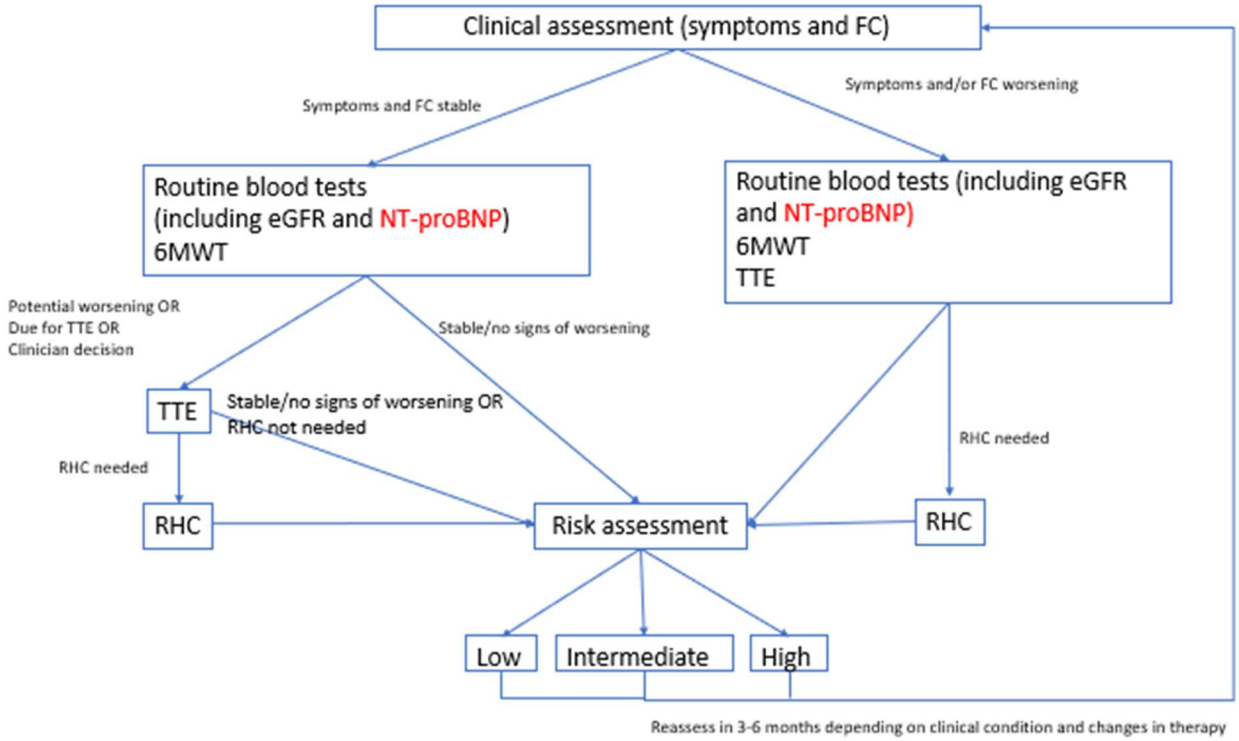


Figure 7 Proposed clinical management algorithm for risk assessment in pulmonary arterial hypertension
Note: Clinical assessment includes assessment of symptoms, functional class, heart rate and blood pressure. The applicant's clinical experts advised that pulomonary function tests are not a part of regular risk assessment for people with PAH.
6MWD =6-min walk distance; BNP =brain natriuretic peptide; eGFR =estimated glomerular filtration rate; FC =functional class; PAH = pulmonary arterial hypertension; RHC = right heart catheterisation

Proposed economic evaluation

The application has proposed a non-inferior clinical claim, implicitly suggesting the non-inferior safety and effectiveness for the NT-proBNP testing compared to TTE/RHC for population 2 (p37). Based on this claim, the appropriate type of economic evaluation would be cost minimisation analysis (Table 14).

Table 14: Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	**Uncertain[a]**	**Noninferior[b]**	**Superior**
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis

? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis

[a] 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations

[b] An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

PASC noted that the most appropriate approach for economic evaluation would be a cost minimisation analysis, given the claim of non-inferior safety and effectiveness.

Proposal for public funding

The applicant stated during the pre-PASC teleconference that NT-proBNP is exempt from the Therapeutic Goods Administration evaluation process. Table presents commercial tests registered on the Australian Register of Therapeutic Goods (ARTG). A list of additional laboratory-based assays were provided by the applicant post PASC and are presented in Table 1.

Table 15: NT-proBNP tests on the Australian Register of Therapeutic Goods

Test	Laboratory-based test
Roche Diagnostics (CARDIAC® NT-pro-BNP)	ARTG 200461, Class 2 IVD, Specific Protein IVDs
Siemens Healthineers (Stratus® CS Acute Care™)	ARTG 179719 includes NT-proBNP, it is on the Immulite platform. ARTG 175075 includes NT-proBNP on the ADVIA Centaur and the Atellica Immunoassay module.
BioMerieux (VIDAS NT-proBNP2)	Not supplied in Australia

Source: Provided to the Department by the Therapeutic Goods Administration
ARTG = Australian Register of Therapeutic Goods; IVD = in vitro diagnostic medical device

Population 2: Patients with previously diagnosed pulmonary arterial hypertension (PAH)

The proposed MBS item descriptor for Population 2, patients with PAH, is presented in Table 16. The fee and benefit are the same as for the current MBS Item 66830 (BNP/NT-proBNP) and also the proposed MBS Item Descriptor for Population 1. However, this proposed item descriptor does not include BNP, as does MBS Item 66830.

Table 15: Proposed MBS Item Descriptor for Population 2: Patients with previously diagnosed pulmonary arterial hypertension (PAH)

Category 6 - PATHOLOGY SERVICES – (proposed category description) Group P2 – Chemical (proposed group description)
Proposed item descriptor: Quantification of *laboratory-based* NT proBNP *testing* in patients with *previously* 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

Suggested changes to the item descriptor in italics

PASC enquired whether point of care NT-proBNP tests are included in this application. The applicant confirmed that these tests are not a part of this application and requested testing for laboratory-based tests of NT-proBNP only.

The applicant accepted the amendment in the proposed item descriptor reflecting laboratory-based NT proBNP testing only, which was acknowledged by the PASC.

PASC considered whether the proposed service should be amalgamated with existing MBS item 66830 or whether new items should be created, and was broadly supportive of a creation of a separate item. The need for requester restrictions and strengthening the frequency restrictors were also discussed, and is to be developed as part of the ESC and MSAC process.

Summary of public consultation input

Six (6) organisations and one (1) individual responded to the consultation process:

- Australian Scleroderma Interest Group (ASIG)
- Scleroderma Australia
- Thoracic Society of Australia and New Zealand (TSANZ)
- Australian Rheumatology Association (ARA)
- Public Pathology Australia (PPA)
- The Royal College of Pathologies of Australasia (RCPA)
- Individual - specialist

All responses were supportive of the application.

Benefits

Organisations considered that patients would benefit from a more accessible and convenient test compared to TTE or RHC, especially those located in rural and remote areas. ASIG advised that screening of patients with scleroderma for PAH is the standard of care but it is often is performed ad-hoc, or not at all. Similarly, due to poor access to TTE and the invasive nature of right heart catheterization (RHC), risk stratification of patients with PAH is not done consistently. Scleroderma Australia noted that TTE for screening of PAH is uncomfortable and can have limited accuracy where there is a lack of tricuspid regurgitation Doppler signal, whereas the NT-proBNP test would provide patients with a more convenient and accurate test.

Organisations noted that public funding would make NT-proBNP testing more equitable and accessible and lead to more regular and widespread screening for PAH in patients with SSc and risk stratification for patients with PAH. This could lead to earlier diagnosis of PAH in patients with SSC, resulting in improved

survival, quality of life and PAH WHO FC. For patients with PAH, regular risk stratification would inform treatment and improve survival, WHO FC, and quality of life for patients and carers.

ASIG considered that NT-proBNP testing would reduce the need for TTEs and RHCs and result in cost savings overall.

A specialist in cardiac-related biomarkers noted that NT-proBNP, a biomarker of myocardial stress, may be elevated in patients with PH and is an independent risk predictor in these patients, and noted that natriuretic peptides (including NT-proBNP) remain the only biomarkers that are widely used in the routine practice of PH centres as well as in clinical trials. The specialist noted that test levels correlate with myocardial dysfunction and provided prognostic information at the time of diagnosis and during follow-up assessments.

PPA considered that the test has good sensitivity with a strong negative predictive value and could be used in the initial screening to rule out the condition with normal/negative results.

Disadvantages

The specialist and PPA noted that natriuretic peptides are not specific for PH and can be elevated in almost any heart disease, and so they need to be considered in the overall clinical context of a patient's condition. PPA considered that other factors that should be considered and could affect results are gender (higher in women than men), an increase of levels with age and BMI (an inverse relationship with BMI).

PPA noted that public funding of the proposed has the potential to impact the continuity of care if patients choose other pathology providers who use different platforms and interpret results differently.

PASC noted the consultation feedback provided on the draft PICO. PASC noted that the consultation feedback was supportive of the application and considered that NT-proBNP testing would provide patients with a more convenient and easily accessible option due to poor access to TTE in some circumstances.

Next steps

PASC advised the assessment group, the Department, and the applicant o set up a meeting to finalise the current and proposed clinical management algorithms for population 2.

PASC requested that updated clinical management algorithms for population 2 should be provided for consideration out of session before the PICO Confirmation can be finalised.

Clinical management algorithms for population 2 were developed post-PASC by the applicant and the Department.

PASC noted that the applicant has elected to progress its application as an ADAR (applicant developed assessment report).

Applicant Comments on the Ratified PICO Confirmation

Nil.

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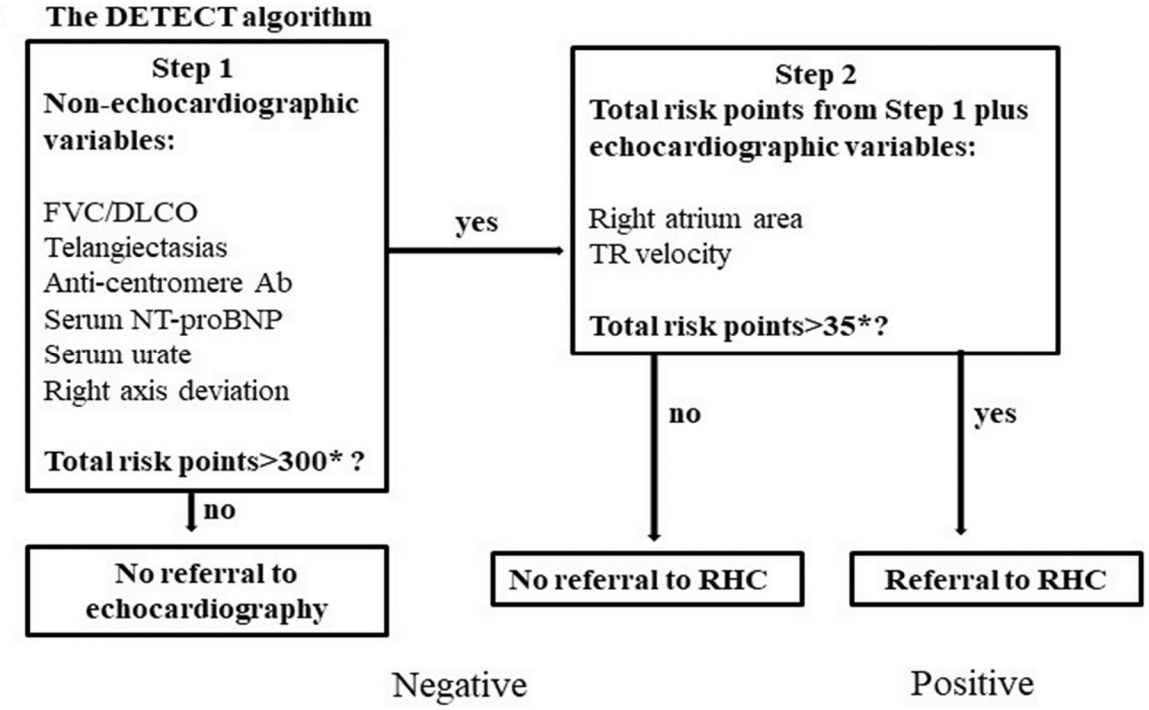
Appendix

Clinical management algorithms for population 1 (patients with SSc)

DETECTion (DETECT) of PAH in SSc algorithm

DETECT is a 2-step algorithm, which was based on the results of a prospective international multicentre study of 466 SSc patients considered at high risk of PAH (DLCO < 60%; duration of disease > 3 years) (Coghlan et al., 2014). Step 1 entails six simple assessments (FVC percent predicted/DLCO percent predicted, current/past telangiectasias, serum anticentromere antibody, serum NT-proBNP, serum urate, and right axis deviation on electrocardiogram) to determine continued evaluation with echocardiography. Step 2 uses the step 1 score and two echocardiographic measures (right atrium area and VTR) to determine whether the patient is suitable for RHC confirmation. Figure A1 presents an overview of the DETECT algorithm.

Figure A1: The DETECTion (DETECT) of PAH in SSc algorithm

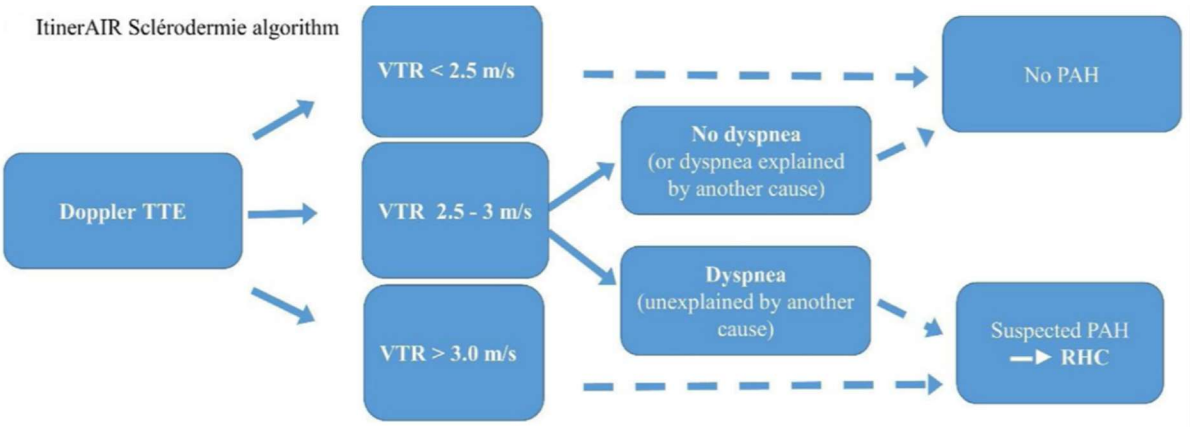


FVC= forced vital capacity; DLCO= diffusing capacity of lung for carbon monoxide; Ab= antibody; NT-proBNP= N-terminal pro-B-type natriuretic peptide. Source: (Coghlan et al., 2014)

ItinerAIR screening algorithm

Proposed by a multidisciplinary board of experts in France, the ItinerAIR algorithm aims to identify patients with SSc at high risk for PAH by considering the peak velocity of tricuspid regurgitation (VTR) on echocardiogram/TTE (Hachulla et al., 2004, Lechartier and Humbert, 2021). High-risk patients, defined by a VTR greater than 3 m/s or a VTR between 2.5 and 3 m/s with dyspnoea not explained by another cause, are recommended for RHC confirmation (Figure A2).

Figure A2: ItinerAIR scleroderma algorithm for patients with SSc

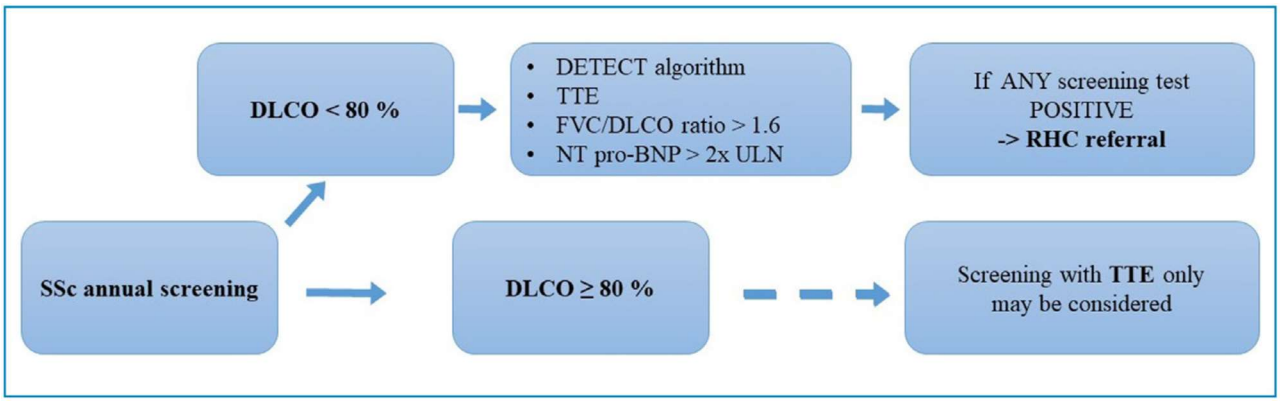


VTR=velocity of tricuspid regurgitation; PAH=pulmonary arterial hypertension; TTE= transthoracic echocardiography; RHC= right heart catheterisation. Source: (Lechartier and Humbert, 2021)

6th World Symposium on Pulmonary Hypertension guidelines

The 6th World Symposium on Pulmonary Hypertension proposed some fundamental changes to the hemodynamic and clinical classification of pulmonary hypertension, including the updated diagnostic workup for SSc-PAH (Frost et al., 2019). For SSc patients with uncorrected DLCO ≥ 80% of predicted, annual screening considered with TTE alone was recommended. A variety of screening tools were suggested for patients with uncorrected < 80% of predicted, as shown in Figure A3.

Figure A3: Sixth world symposium guidelines for screening patients with SSc: 6th World Symposium on PH diagnostic algorithm for SSc-PAH patients



NT-proBNP= N-terminal pro-B-type natriuretic peptide; DLCO= diffusing capacity of lung for carbon monoxide; FVC= forced vital capacity; TTE= transthoracic echocardiography; ULN= upper limit of normal; RHC= right heart catheterisation. Source: (Frost et al., 2019)

Table 16: NT-proBNP laboratory tests on the Australian Register of Therapeutic Goods

COMPANY	ASSAY NAME	ASSAY SYSTEM/PLATFORM	PLATFORM	MANUFACTURED AND SOLD UNDER LICENCE FROM
Roche Diagnostics	Elecsys® proBNP II STAT	Cobas e 411, e 601, e 602 and e 801	Electro-chemiluminescence immunoassay, ECLIA	Roche Diagnostics
Roche Diagnostics	Elecsys® proBNP II	Cobas e 411, e 601, e 602 and e 802	Electro-chemiluminescence immunoassay, ECLIA	Roche Diagnostics
BioMerieux	VIDAS NT-proBNP2	VIDAS System, VIDAS 3	Enzyme-linked Fluorescent Assay, ELFA	Roche Diagnostics
Siemens Healthineers	Atellica IM NT-proBNP	Atellica IM Analyser	Chemiluminescent sandwich immunoassay	-
Siemens Healthineers	Atellica IM NT-proBNP	Dimension EXL	Chemiluminescent sandwich immunoassay	-
Siemens Healthineers	Advia IM NT-proBNP	Advia Centaur XP, XPT, CP	Chemiluminescent sandwich immunoassay	-
Siemens Healthineers	Advia IM NT-proBNP	Dimension Vista 500 or 1500	Chemiluminescent sandwich immunoassay	-
Abbott	Alere NT-proBNP	Alinity i Assay	Chemiluminescent micropartcile immunoassay, CMIA	Roche Diagnostics
Abbott	Alere NT-proBNP	Alinity i Assay	Chemiluminescent micropartcile immunoassay, CMIA	Roche Diagnostics
Abbott	Alere NT-proBNP	ARCHITECT i1000SR System	Chemiluminescent micropartcile immunoassay, CMIA	Roche Diagnostics
Abbott	Alere NT-proBNP	ARCHITECT i1000SR System	Chemiluminescent micropartcile immunoassay, CMIA	Roche Diagnostics
Ortho-Clinical Diagnostics	VITROS NT-proBNP	VITROS 5600	-	-
Ortho-Clinical Diagnostics	VITROS NT-proBNP	VITROS XT 7600	-	-
Ortho-Clinical Diagnostics	VITROS NT-proBNP II	VITROS 5600	-	-
Ortho-Clinical Diagnostics	VITROS NT-proBNP II	VITROS XT 7600	-	-

Source: Provided by the applicant post PASC.