

MSAC Application 1689.1

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

Application for MBS eligible service or health technology

MSAC Application Number

1689.1

Application title:

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

Submitting organisation:

JANSSEN-CILAG PTY LTD

Submitting organisation ABN:

47000129975

Application contact details

Are you the applicant, or are you a consultant or lobbyist acting on behalf of the applicant?

Applicant

Are you applying on behalf of an organisation, or as an individual?

Organisation

Application description

Succinct description of the medical condition/s:

Pulmonary arterial hypertension is characterised by increased pulmonary vascular resistance (resistance against blood flow), and may be idiopathic (arising from an unknown cause), or due to other underlying factors or disease associations such as connective tissue disease.

Succinct description of the service or health technology:

Measurement of NT-proBNP (also known as N-terminal pro-brain natriuretic peptide, N-terminal pro-B-type natriuretic peptide or N-terminal prohormone of brain natriuretic peptide) through a blood test. The blood test is intended to be used as a regular assessment of pulmonary arterial hypertension disease progression.

Application details

Have you lodged an MSAC application for this service or health technology previously?

Yes

Please provide the previous application number, if known:

1689

Please provide details of the previous application:

Quantification of NT-proBNP in patients with diagnosed pulmonary arterial hypertension (PAH) for ongoing risk assessment AND in patients with systemic sclerosis (scleroderma).

Have you had a pre-application meeting with the Department?

No

Will a full assessment report be required for your application?

Yes

Does the implementation of your service or health technology rely on a new listing on the Pharmaceutical Benefits Scheme (PBS) and/or the Prostheses List?

No

Is the application for a new service or health technology, or an amendment to an existing listed service or health technology?

New

Relevant MBS items

Please select any relevant MBS items:

MBS item	Reason(type)	Reason
66830	Other	Note, this current application is similar, i.e. measurement of NT-proBNP but not identical to the service covered by item number 66830 on MBS. The MBS item number 66830 is for a different patient population (distinguishing between cardiac and respiratory causes of shortness of breath in patients presenting to an Emergency Department).

What is the type of service or health technology?

Investigative

Please select the type of investigative health technology:

Clinical and laboratory haematology

State the purpose(s) of the health technology for this application, and provide a rationale.

Purpose category	Purpose description	Rationale	Used in
Monitoring	To monitor a condition over time.	<p>The proposed medical service is a screening service of plasma level for NT-proBNP (also known as N-terminal pro-brain natriuretic peptide, N-terminal pro-B-type natriuretic peptide or N-terminal prohormone of brain natriuretic peptide). NT-proBNP is a non-invasive screening strategy (i.e. a blood test) for regular assessment of pulmonary arterial hypertension (PAH) disease progression.</p> <p>NT-proBNP levels correlate with myocardial dysfunction and provide prognostic information at the time of PAH diagnosis, during follow-up assessments to monitor for clinical deterioration caused by progression of PAH, and to stratify patients into low, intermediate, and high-risk categories (Galie et al., 2016, Benza et al., 2021, Humbert et al., 2022).</p>	PICO sets

What additional purpose(s) could the health technology be used for, other than the purposes listed above for this application?

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Applications for investigative health technologies require input from each of the requestor of the service, the provider of the service, and as necessary, the manufacturer of any device components.

Can you confirm that the application reflects their perspectives on the use of the proposed health technology or service?

Yes

Provide a summary of how you obtained and used this input in preparing this application:

Clinician expert opinion was sought in the preparation of this resubmission. Additional perspectives were incorporated in the preparation of the initial submission request (ADAR 1689). Furthermore, all the tests are listed on the ARTG. Note that the publication of updated ESC/ERS Guidelines 2022 (Humbert et al., 2022) reflects a revised clinical management algorithm for the use of NT-proBNP in patients with PAH.

PICO sets

Application PICO set:

Patients diagnosed with pulmonary arterial hypertension (PAH).

What is the relevant purpose for this PICO set?

Monitoring

Population

Describe the population in which the proposed health technology is intended to be used:

Patients who have received a diagnosis of pulmonary arterial hypertension (PAH) are proposed to be eligible for the proposed health technology at the time of follow-up assessments. PAH is characterised by increased pulmonary vascular resistance and may be idiopathic or due to other underlying factors or disease associations such as connective tissue disease (CTD), most commonly SSc within CTD-PAH. PAH is defined as an increase in mean pulmonary arterial pressure (mPAP) ≥ 20 mmHg at rest along with pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg and pulmonary vascular resistance (PVR) > 2 Wood units (WU), as assessed by right heart catheterisation (RHC) (Humbert et al., 2022). PAH is a rare, severe, intractable, and debilitating progressive clinical condition characterised by a sustained elevation of pulmonary vascular resistance (due to narrowing of the pulmonary arteries), which if left untreated ultimately leads to right heart failure and death (Studer et al., 2019).

PAH is a type of pulmonary hypertension (PH), which has been classified into five categories sharing similar pathological findings, haemodynamic characteristics, and management. PAH is Group 1 (Table 1) of PH and there are six subgroups of PAH by aetiology as follows (Humbert et al., 2022).

- 1- Idiopathic PAH (IPAH).
- 2- Heritable PAH.
- 3- Associated with drug and toxins.
- 4- PAH associated with connective tissue disease, HIV infection, portal hypertension, congenital heart diseases or schistosomiasis (a parasitic infection).
- 5- PAH with features of venous/capillary (POD/PCH) involvement
- 6- Persistent PH of the newborn

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

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

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

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

Patients who have received a diagnosis of pulmonary arterial hypertension (PAH) are proposed to be eligible for the proposed health technology at the time of follow-up assessments. N-terminal pro-brain natriuretic peptide (NT-proBNP) levels correlate with myocardial dysfunction and provide prognostic information at the time of diagnosis, and during follow-up assessments. These are commonly used in routine clinical practice and clinical trials.

The 2022 European Society of Cardiology and the European Respiratory Society (ESC/ERS) guidelines recommend a series of variables to stratify patients at follow up assessments into 4 strata: low, intermediate-low, intermediate-high and high-risk categories, which correspond to estimated one-year mortality rates of less than 3%, 2-7%, 9-19% and greater than 20% respectively and subsequently guides clinical management. Stratification of patients into these four strata during routine regular risk assessment is recommended at 3-6 monthly intervals, utilising 3 non-invasive variables: WHO FC, 6-minute walking distance (6MWD) and NT-proBNP (or BNP) (Tables 17 and 18 of Humbert et al., 2022 attached). The guidelines recommend that additional variables be considered as needed, especially right heart imaging and haemodynamics. In the previous iteration of the ESC/ERC guidelines, not all of these assessments were needed to be measured at each visit; however, the basic program should include determination of the WHO FC, at least one measurement of exercise capacity (6MWD or CPET), and information on RV function (either BNP/NT-proBNP or echocardiography, Galie et al., 2016).

These guidelines to determine risk and prognosis are used in Australian clinical practice, yet a lack of funding for NT-proBNP currently limits adoption of the specific recommendation for regular routine assessment using the three non-invasive variables only, with clinicians resorting to invasive TTE in order to assess risk status and RV function.

Disease severity classification and risk stratification

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

the REVEAL registry (n=982) has shown a significantly higher rate of survival for patients whose FC improved than those who remained unchanged, within subtypes of PAH and whether newly diagnosed or previously diagnosed (Barst et al., 2013 and Benza et al., 2021).

Provide a rationale for the specifics of the eligible population:

All patients who are diagnosed with PAH and are undergoing routine follow-up assessment will be eligible for the proposed service.

Are there any prerequisite tests?

No

Search and select the most applicable Medical condition terminology (SNOMED CT):

pulmonary arterial hypertension

Intervention

Name of the proposed health technology:

NT-proBNP biomarker assay

Describe the key components and clinical steps involved in delivering the proposed health technology:

Regular assessment is a key part of the evaluation of patients with PAH, as it provides valuable information for determining disease severity, improvement, deterioration, or stability.

NT- proBNP levels correlate with myocardial dysfunction and provide prognostic information at the time of diagnosis and during follow-up assessments. The medical service would occur up to a maximum of every 3 months (i.e. up to 4 times per year) according to patients needs and physician discretion (Tables 17 and 18 of Humbert et al., 2022 attached).

To expedite risk assessment in the clinic, where comprehensive data for all patients may be lacking and time constrained, it is thought that risk assessment tools using fewer variables are preferable (REVEAL Lite 2 risk calculator (Benza et al 2021). REVEAL Lite 2 uses six modifiable and non-invasive variables. The model indicated that the most highly predictive parameter included in REVEAL Lite 2 was BNP/NT- proBNP, followed by 6MWD and NYHA or WHO FC. The most recent iteration of the ESC/ERS guidelines for pulmonary hypertension also recommend a simplified risk assessment tool with three non-invasive variables: WHO FC, 6-minute walking distance and NT-proBNP (or BNP). (Table 18, Humbert et al., 2022 attached). Utilising NT-proBNP testing into non-invasive risk assessment algorithms obviates the needs to perform the invasive procedures of RHC and still discriminates among PAH risk groups.

Identify how the proposed technology achieves the intended patient outcomes:

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

NT-proBNP testing has the ability to stratify patients according to risk status when used with other non-invasive parameters (Benza et al., 2021). The most highly predictive parameter (REVEAL Lite 2) was BNP/NT-proBNP, followed by 6MWD and FC (indicating that TTE and invasive RHC variables were not needed). Including NT-proBNP in the non-invasive risk assessment (REVEAL Lite 2), provides a simplified method of risk assessment that can be implemented routinely in daily clinical practice and is a robust tool that provides discrimination among patients at low, intermediate, and high risk of 1-year mortality (Benza et al., 2021), or low, intermediate-low, intermediate-high and high risk of 1-year mortality in a 3-variable risk assessment tool as per the ESC/ERS guidelines (Humbert et al., 2022)

NT-proBNP is proposed to be non-inferior to current standard of care with respect to safety and clinical effectiveness. NT-proBNP is anticipated to reduce the number of TTEs and RHCs for routine risk assessment relative to current practice with a commensurate reduction in morbidity and mortality associated with this test.

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components?

Yes

Explain whether it is essential to have this trademark component or whether there would be other components that would be suitable:

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

- Roche Diagnostics (elecsys cobas®),
- Siemens Healthineers (ADVIA Centaur®, Atellica Advia®, Dimension® Vista®/XLTM),
- BioMerieux (VIDAS® NT-proBNP2)
- Abbott (Alere NT-proBNP for Alinity)
- Ortho Clinical Diagnostics (VITROS® NT-proBNP)

This application only applies to the NT-proBNP laboratory-based assays, not Point of Care Assays (PoC).

Are there any proposed limitations on the provision of the proposed health technology delivered to the patient (For example: accessibility, dosage, quantity, duration or frequency):

Yes

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

Will a select type of health professional be needed to provide the proposed health technology?

Yes

Select the types of health professional:

- Specialist cardiologist
- Specialist general pathologist
- Specialist immunologist
- Specialist respiratory and sleep medicine physician (specialist - Respiratory and Sleep Medicine)
- Specialist rheumatologist
- Other

Please provide details, if 'Other' has been selected as a health professional type:

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

Can delivery of the proposed health technology be delegated to another professional?

No

Are there any proposed limitations on who might provide a referral for the proposed health technology?

Yes

Select the types of health professional:

- Specialist cardiologist
- Specialist general pathologist
- Specialist immunologist
- Specialist respiratory and sleep medicine physician (specialist - Respiratory and Sleep Medicine)
- Specialist rheumatologist
- Other

Please provide details, if 'Other' has been selected as a health professional type: The assay would be performed by an accredited pathology service and only requested and evaluated by PAH specialist physicians involved in the management of patients with PAH.

Is there specific training or qualifications required to provide or deliver the proposed service, and/or any accreditation requirements to support delivery of the health technology?

Yes

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

Indicate the proposed setting(s) in which the proposed health technology will be delivered.

Setting	Rationale
Laboratory	The assay would be performed by a NATA accredited pathology service with appropriate facilities and likely under the supervision of a Fellow of the Royal College of Pathologist of Australasia (RCPA) (biochemistry).

Is the proposed health technology intended to be entirely rendered inside Australia?

Yes

Descriptor

Item	Category	Group
AAAAA	PATHOLOGY SERVICES	CHEMICAL

Please search and select the proposed category:

PATHOLOGY SERVICES

Please search and select the proposed group:

CHEMICAL

Please draft a proposed item descriptor to define the population and health technology usage characteristics that would define eligibility for funding:

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

Maximum of 4 tests per patient in any one year.

Rationale for descriptor: The descriptor reflects the intended use of the proposed test. The proposed descriptor is similar to what was approved by MSAC as part of ADAR 1689 for Population 1 - quantification of NT-proBNP in patients with systemic sclerosis.

Comparator

Comparator name	Comparator type
Note: the service only applies if the patient meets one or more of the following and the requirements of Note: IR.1.2 Frequent repetition serial real time transthoracic echocardiographic examination of the heart with real time colour flow mapping from at least 3 acoustic windows, with recordings on digital media, if the service: (a) is for the investigation of a patient who: (i) has an isolated pericardial effusion or pericarditis; or (ii) has a normal	MBS

Comparator name	Comparator type
baseline study, and has commenced medication for non?cardiac purposes that has cardiotoxic side effects and is a pharmaceutical benefit (within the meaning of PartVII of the National Health Act 1953) for the writing of a prescription for the supply of which under that Part an echocardiogram is required; and (b) is not associated with a service to which: (i) another item in this Subgroup applies (except items55137, 55141, 55143, 55145 and 55146); or (ii) an item in Subgroup 2 applies (except items55118 and 55130); or (iii) an item in Subgroup 3 applies (R)	
RIGHT HEART BALLOON CATHETER, insertion of, including pulmonary wedge pressure and cardiac output measurement (Anaes.)	MBS
RIGHT HEART BALLOON CATHETER, insertion of, including pulmonary wedge pressure and cardiac output measurement, when performed in association with the administration of anaesthesia (6 basic units)	MBS
Right heart catheterisation: (a) performed at the same time as a service to which item 38244, 38247, 38248, 38249, 38251, 38252, 38307, 38308, 38310, 38311, 38313 or 38314 applies; and (b) including any of the following (if performed): (i) fluoroscopy; (ii) oximetry; (iii) dye dilution curves; (iv) cardiac output measurement; (v) shunt detection; (vi) exercise stress test (Anaes.)	MBS

Comparator 1 - MBS

Type: MBS

MBS Item: 55133

MBS Item descriptor: Note: the service only applies if the patient meets one or more of the following and the requirements of Note: IR.1.2 Frequent repetition serial real time transthoracic echocardiographic examination of the heart with real time colour flow mapping from at least 3 acoustic windows, with recordings on digital media, if the service: (a) is for the investigation of a patient who: (i) has an isolated pericardial effusion or pericarditis; or (ii) has a normal baseline study, and has commenced medication for non?cardiac purposes that has cardiotoxic side effects and is a pharmaceutical benefit (within the meaning of PartVII of the National Health Act 1953) for the writing of a prescription for the supply of which under that Part an echocardiogram is required; and (b) is not associated with a service to which: (i) another item in this Subgroup applies (except items55137, 55141, 55143, 55145 and 55146); or (ii) an item in Subgroup 2 applies (except items55118 and 55130); or (iii) an item in Subgroup 3 applies (R)

Please provide a description of the comparator:

MBS item for transthoracic echocardiographic examination (TTE) of the heart.

Please provide a rationale for why this is a comparator:

The ongoing risk assessment in the PAH population requires a multi-dimensional approach. Not all of these assessments need to be measured at each visit; however, the basic program should include determination of the WHO FC, at least one measurement of exercise capacity (6MWD or CPET), and information on RV function (either BNP/NT- proBNP or echocardiography) (Galie et al., 2018). These guidelines to determine risk and prognosis in Australian clinical practice and non-invasive haemodynamic assessment (Figure 1) provides risk assessment for distinguishing

between low, intermediate, and high-risk patients. The most highly predictive parameter in REVEAL Lite 2 is BNP/NT-proBNP, followed by 6MWD and FC, thus obviating the need to include TTE or an invasive RHC test to assess risk in PAH patients. The updated ESC/ERS guidelines determine 4-strata risk at routine assessment based on WHO FC, 6-minute walking distance and NT-proBNP (or BNP) (Humbert et al., 2022)

The appropriate comparator for the proposed medical service in this population is a risk assessment algorithm that does not use NT-proBNP and instead uses TTE and RHC for risk assessment. This comparator was accepted by the MSAC in its consideration of the first submission in July 2022.

Pattern of substitution - Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator?

Partial – in some cases, the proposed technology will replace the use of the comparator, but not all cases

Please outline and explain the extent to which the current comparator is expected to be substituted:

The NT-proBNP assay, as part of a multiparametric validated non-invasive risk assessment or invasive risk assessment of PAH patients, will partially replace the use of TTE or RHC, respectively. This is because, there may be some clinical circumstances in which use of TTE or RHC may be required following an NT-proBNP test, e.g., after changes in therapy or in cases of clinical worsening (Table 17, Humbert et al., 2022 attached).

This critical component of the application, as discussed at the post-MSAC meeting, will be addressed as part of the ADAR and updated analyses. Preliminary analyses indicate that NT-proBNP will partially replace the comparator (base case) and fully replace the comparator (sensitivity analyses).

Comparator 2 - MBS

Type: MBS

MBS Item: 13818

MBS Item descriptor: RIGHT HEART BALLOON CATHETER, insertion of, including pulmonary wedge pressure and cardiac output measurement (Anaes.)

Please provide a description of the comparator:

MBS item for right heart catheterisation (RHC).

Please provide a rationale for why this is a comparator: Refer to rationale provided for Comparator 1.

Pattern of substitution - Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator?

Partial – in some cases, the proposed technology will replace the use of the comparator, but not all cases

Please outline and explain the extent to which the current comparator is expected to be substituted:

Refer to rationale provided for Comparator 1.

Comparator 3 - MBS

Type: MBS

MBS Item: 22015

MBS Item descriptor: RIGHT HEART BALLOON CATHETER, insertion of, including pulmonary wedge pressure and cardiac output measurement, when performed in association with the administration of anaesthesia (6 basic units)

Please provide a description of the comparator: MBS item for right heart catheterisation (RHC).

Please provide a rationale for why this is a comparator: Refer to rationale provided for Comparator 1.

Pattern of substitution - Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator?

Partial – in some cases, the proposed technology will replace the use of the comparator, but not all cases

Please outline and explain the extent to which the current comparator is expected to be substituted:

Refer to rationale provided for Comparator 1.

Comparator 4 - MBS

Type: MBS

MBS Item: 38254

MBS Item descriptor: Right heart catheterisation: (a) performed at the same time as a service to which item 38244, 38247, 38248, 38249, 38251, 38252, 38307, 38308, 38310, 38311, 38313 or 38314 applies; and (b) including any of the following (if performed): (i) fluoroscopy; (ii) oximetry; (iii) dye dilution curves; (iv) cardiac output measurement; (v) shunt detection; (vi) exercise stress test (Anaes.)

Please provide a description of the comparator:

MBS item for right heart catheterisation (RHC).

Please provide a rationale for why this is a comparator: Refer to rationale provided for Comparator 1.

Pattern of substitution - Will the proposed health technology wholly replace the proposed comparator, partially replace the proposed comparator, displace the proposed comparator or be used in combination with the proposed comparator?

Partial – in some cases, the proposed technology will replace the use of the comparator, but not all cases

Please outline and explain the extent to which the current comparator is expected to be substituted: Refer to rationale provided for Comparator 1.

Outcome

Outcome no.	Outcome type	Outcome name
1	Health benefits	Safety outcomes
2	Resources	Clinical effectiveness Outcomes

Outcome 1

Outcome type: Health benefits

Outcome name: Safety outcomes

Outcome description: Reduction of TTE and RHCs relative to current practice with a commensurate reduction in morbidity and mortality associated with these tests.

Outcome 2

Outcome type: Resources

Outcome name: Clinical effectiveness Outcomes

Outcome description: 1- Sensitivity, 2- Specificity, 3- Positive predictive value, 4- Negative predictive value

Algorithms

Preparation for using the health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, before patients would be eligible for the proposed health technology:

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

- (i) is there any evidence of clinical deterioration since the last assessment?
- (ii) if so, is clinical deterioration caused by progression of PH or by a concomitant illness?
- (iii) is RV function stable and sufficient? and
- (iv) is the current status compatible with a good long-term prognosis, i.e. does the patient meet the low-risk criteria.

In order to answer these questions, a multidimensional approach is needed.

Not all of these assessments need to be measured at each visit; however, the basic program should include determination of the WHO FC, at least one measurement of exercise capacity (6MWD or CPET), and information on RV function (either BNP/NT-proBNP or echocardiography, Galie et al., 2016). The updated ESC/ERS guidelines determine risk of mortality at one-year according to four-strata and based on the routine assessment of three variables; WHO FC, 6-minute walking distance and NT-proBNP (or BNP) (Humbert et al., 2022)

Table 17 of the ESC/ERS 2022 guidelines (Humbert et al., 2022) provides recommendations on the assessment, and timing for the follow-up of patients with PAH. These guidelines are used in Australian clinical practice to determine risk and prognosis of patients with PAH, but uptake of NT-proBNP is currently limited due to a lack of funding.

Additionally, in stable patients, risk assessment tools using fewer variables are preferable to expedite assessments and include those variables recommended by the new ESC/ERS guidelines and REVEAL Lite 2 (based on the recently developed and validated REVEAL 2.0 risk calculator; Benza et al 2012, Anderson 2020, Kanwar et al., 2020). REVEAL Lite 2 uses six modifiable and non-invasive variables (Figure 1). The model indicated that the most highly predictive parameter included in REVEAL Lite 2 (based on the c₂ value) was BNP/NT-proBNP, followed by 6MWD and NYHA or WHO FC. These risk assessment tools obviate the needs to perform the invasive procedures of RHC. This non-invasive risk assessment allows for NT-proBNP to be ordered prior to the patients visiting their specialist so results can be discussed at the consultation.

Is there any expectation that the clinical management algorithm before the health technology is used will change due to the introduction of the proposed health technology?

No

Use of the health technology

Explain what other healthcare resources are used in conjunction with delivering the proposed health technology:

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

Explain what other healthcare resources are used in conjunction with the comparator health technology:

Healthcare resources that are used in conjunction with the comparator health technology are as described earlier for NT-proBNP, as NT-proBNP is one of several variables measured to determine risk stratification of patients with PAH.

Describe and explain any differences in the healthcare resources used in conjunction with the proposed health technology vs. the comparator health technology:

Refer to details described earlier. This will be addressed in further detail in the ADAR.

Clinical management after the use of health technology

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, after the use of the proposed health technology:

After a risk assessment including NT-proBNP, results of all variables are combined to derive the PAH patient's 1-year mortality risk. Per the updated ESC/ERS 2022 guidelines, the observed 1-year mortality rates in the four-risk strata are 0-3%, 2-7%, 9-19% and greater than 20% for the low, intermediate-low, intermediate-high, and high risk groups, respectively. Therefore, the clinical management of patients after the use of NT-proBNP will vary according to the outcome of this risk assessment in terms of therapeutic decision-making, but as suggested in earlier sections, even in circumstances where no treatment changes are recommended, risk assessments will be repeated as part of routine clinical management of PAH patients at least every 3-6 months.

Define and summarise the clinical management algorithm, including any required tests or healthcare resources, after the use of the comparator health technology:

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

Describe and explain any differences in the healthcare resources used after the proposed health technology vs. the comparator health technology:

Refer to details described earlier. This will be addressed in further detail in the ADAR.

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?

Non-inferior

Provide a brief rationale for the claim:

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

NT-proBNP testing has the ability to stratify patients according to risk status when used with other non-invasive parameters (Benza et al., 2021). The most highly predictive parameter (REVEAL Lite 2) was BNP/NT-proBNP, followed by 6MWD and FC (the variables TTE and invasive RHC were

not needed). Including NT-proBNP in the non-invasive risk assessment (REVEAL Lite 2), provides a simplified method of risk assessment that can be implemented routinely in daily clinical practice and is a robust tool that provides discrimination among patients at low, intermediate, and high risk of 1-year mortality (Benza et al., 2021). The updated ESC/ERS guidelines determine 4-strata risk at routine assessment based on WHO FC, 6-minute walking distance and NT-proBNP (or BNP) (Humbert et al., 2022). In their review of the initial submission, MSAC considered that the clinical claim of non-inferior comparative clinical effectiveness was reasonable. MSAC noted that there was limited evidence to suggest that risk stratification calculators including NT-proBNP are at least as effective as those that do not include.

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?

In terms of safety outcomes, the proposed test is associated with a reduction of TTEs and RHCs relative to current practice with a commensurate reduction in morbidity and mortality associated with this test. In its consideration of the first submission, MSAC noted that, as a blood test, NT-proBNP testing has similar safety compared with the comparators.

In terms of clinical effectiveness, the proposed test is non-inferior to the comparator(s) as supported by the following:

- 1- Sensitivity
- 2- Specificity
- 3- Positive predictive value
- 4- Negative predictive value

As noted previously, MSAC considered the claim of non-inferior effectiveness in the first submission was reasonable.

For some people, compared with the comparator(s), does the test information result in:

- **A change in clinical management?** No
- **A change in health outcomes?** No
- **Other benefits?** Yes

Please provide a rationale, and information on other benefits if relevant:

As was acknowledged by the ESC as part of the initial submission evaluation, the value of knowing could be a relevant consideration as NT-proBNP provides prognostic information for patients in whom PAH is being managed. Additionally, NT-proBNP would be a more accessible test than TTE, particularly for people who live in rural and remote areas.

In terms of the immediate costs of the proposed technology (and immediate cost consequences, such as procedural costs, testing costs etc.), is the proposed technology claimed to be more costly, the same cost or less costly than the comparator?

Less costly

Provide a brief rationale for the claim: As was acknowledged by the ESC as part of the initial submission evaluation, NT-proBNP was considered cost saving in most clinically plausible sensitivity analyses because it is likely that NT-proBNP will replace at least some TTEs.

Summary of evidence

Evidence no.	Citation	Published?
1	<p>Marc Humbert, Gabor Kovacs, Marius M Hoeper, Roberto Badagliacca, Rolf M F Berger, Margarita Brida, Jørn Carlsen, Andrew J S Coats, Pilar Escribano-Subias, Pisana Ferrari, Diogenes S Ferreira, Hossein Ardeschir Ghofrani, George Giannakoulas, David G Kiely, Eckhard Mayer, Gergely Meszaros, Blin Nagavci, Karen M Olsson, Joanna Pepke-Zaba, Jennifer K Quint, Göran Rådegran, Gerald Simonneau, Olivier Sitbon, Thomy Tonia, Mark Toshner, Jean Luc Vachiery, Anton Vonk Noordegraaf, Marion Delcroix, Stephan Rosenkranz, ESC/ERS Scientific Document Group, 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: Developed by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Endorsed by the International Society for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG)., European Heart Journal, Volume 43, Issue 38, 7 October 2022, Pages 3618–3731, https://doi.org/10.1093/eurheartj/ehac237</p>	Published
2	<p>Marius M. Hoeper, Christine Pausch, Karen M. Olsson, Doerte Huscher, David Pittrow, Ekkehard Grünig, Gerd Staehler, Carmine Dario Vizza, Henning Gall, Oliver Distler, Christian Opitz, J. Simon R. Gibbs, Marion Delcroix, H. Ardeschir Ghofrani, Da-Hee Park, Ralf Ewert, Harald Kaemmerer, Hans-Joachim Kabitz, Dirk Skowasch, Juergen Behr, Katrin Milger, Michael Halank, Heinrike Wilkens, Hans-Jürgen Seyfarth, Matthias Held, Daniel Dumitrescu, Iraklis Tsangaris, Anton Vonk-Noordegraaf, Silvia Ulrich, Hans Klose, Martin Claussen, Tobias J. Lange, Stephan Rosenkranz European Respiratory Journal Jul 2022, 60 (1) 2102311; DOI: 10.1183/13993003.02311-2021</p>	Published
3	<p>Athénaïs Boucly, Jason Weatherald, Laurent Savale, Pascal de Groote, Vincent Cottin, Grégoire Prévot, Ari Chaouat, François Picard, Delphine Horeau-Langlard, Arnaud Bourdin, Etienne-Marie Jutant, Antoine Beurnier, Mitja Jevnikar, Xavier Jaïs, Gérald Simonneau, David Montani, Olivier Sitbon, Marc Humbert European Respiratory Journal Jun 2022, 59 (6) 2102419; DOI: 10.1183/13993003.02419-2021</p>	Published

Evidence 1

Evidence number: 1

Type of evidence/study design: ESC/ERS 2022 Guidelines for the diagnosis and treatment of pulmonary hypertension

Published? Published

Citation: Marc Humbert, Gabor Kovacs, Marius M Hoeper, Roberto Badagliacca, Rolf M F Berger, Margarita Brida, Jørn Carlsen, Andrew J S Coats, Pilar Escribano-Subias, Pisana Ferrari, Diogenes S Ferreira, Hossein Ardeschir Ghofrani, George Giannakoulas, David G Kiely, Eckhard Mayer, Gergely Meszaros, Blin Nagavci, Karen M Olsson, Joanna Pepke-Zaba, Jennifer K Quint, Göran Rådegran, Gerald Simonneau, Olivier Sitbon, Thomy Tonia, Mark Toshner, Jean Luc Vachieri, Anton Vonk Noordegraaf, Marion Delcroix, Stephan Rosenkranz, ESC/ERS Scientific Document Group, 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: Developed by the task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Endorsed by the International Society for Heart and Lung Transplantation (ISHLT) and the European Reference Network on rare respiratory diseases (ERN-LUNG)., *European Heart Journal*, Volume 43, Issue 38, 7 October 2022, Pages 3618–3731, <https://doi.org/10.1093/eurheartj/ehac237>

Description and relevance of citation: Regular assessment of mortality risk in patients with PAH in expert PH centres is strongly recommended; assessment should utilise 3 non-invasive variables: WHO FC, 6-minute walking distance and NT-proBNP (or BNP) with additional variables considered as needed (Tables 17 & 18).

Publication date/ estimated publication date: 07/10/2022

Website link: <https://doi.org/10.1093/eurheartj/ehac237>

Evidence 2

Evidence number: 2

Type of evidence/study design: Prospective registry analysis

Published? Published

Citation: Marius M. Hoeper, Christine Pausch, Karen M. Olsson, Doerte Huscher, David Pittrow, Ekkehard Grünig, Gerd Staehler, Carmine Dario Vizza, Henning Gall, Oliver Distler, Christian Opitz, J. Simon R. Gibbs, Marion Delcroix, H. Ardeschir Ghofrani, Da-Hee Park, Ralf Ewert, Harald Kaemmerer, Hans-Joachim Kabitzi, Dirk Skowasch, Juergen Behr, Katrin Milger, Michael Halank, Heinrike Wilkens, Hans-Jürgen Seyfarth, Matthias Held, Daniel Dumitrescu, Iraklis Tsangaris, Anton Vonk-Noordegraaf, Silvia Ulrich, Hans Klose, Martin Claussen, Tobias J. Lange, Stephan Rosenkranz

European Respiratory Journal Jul 2022, 60 (1) 2102311; DOI: 10.1183/13993003.02311-2021

Description and relevance of citation: Study validates thresholds for the four-strata risk assessment with three variables (WHO FC, 6MWD and NT-proBNP), and is referenced by the 2022 ESC/ERS Guidelines.

Publication date/ estimated publication date: 01/01/2022

Website link: <https://doi.org/10.1183/13993003.02311-2021>

Evidence 3

Evidence number: 3

Type of evidence/study design: Prospective registry analysis

Published? Published

Citation: Athénaïs Boucly, Jason Weatherald, Laurent Savale, Pascal de Groote, Vincent Cottin, Grégoire Prévot, Ari Chaouat, François Picard, Delphine Horeau-Langlard, Arnaud Bourdin, Etienne-Marie Jutant, Antoine Beurnier, Mitja Jevnikar, Xavier Jaïs, Gérald Simonneau, David Montani, Olivier Sitbon, Marc Humbert

European Respiratory Journal Jun 2022, 59 (6) 2102419; DOI: 10.1183/13993003.02419-2021

Description and relevance of citation: Study validates thresholds for the four-strata risk assessment with three variables (WHO FC, 6MWD and NT-proBNP), and is referenced by the 2022 ESC/ERS Guidelines.

Publication date/ estimated publication date: 01/01/2022

Website link: <https://doi.org/10.1183/13993003.02419-2021>

Estimated utilisation

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

The DUSC review of PAH treatments (DUSC, 2015), found that the prevalence and incidence rates of PAH are 87.6 and 18.6 per million population, respectively. Applying the prevalence and incidence to projected Australian population from 2022 to 2027 (ABS 3222.0 Series B data), the number of PAH patients in Australia (and therefore of the proposed population) is estimated to be 2,341 in year 1, and 3,055 in year 6.

Provide the percentage uptake of the proposed health technology by the proposed population:

Year 1 estimated uptake (%): 90.00

Year 2 estimated uptake (%): 90.00

Year 3 estimated uptake (%): 90.00

Year 4 estimated uptake (%): 90.00

Estimate the number of patients who will utilise the proposed technology for the first full year:

4530

Will the technology be needed more than once per patient?

Yes, multiple times

Over what duration will the health technology or service be provided for a patient?

NT-proBNP is a blood test.

What frequency will the health technology or service be required by the patient over the duration?

4 times per year

Cost information

Proposed item	Category	Group	Cost	Proposed fee
AAAAA	PATHOLOGY SERVICES	CHEMICAL	\$0.00	\$58.50

Indicate the overall cost per patient of providing the proposed health technology:

\$0.00

Please specify any anticipated out of pocket costs:

\$0.00

Provide details and explain:

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

How is the technology/service funded at present?

Self-funded by patients.

Consultation

Succinct description of the medical condition/s:

Pulmonary arterial hypertension is characterised by increased pulmonary vascular resistance (resistance against blood flow), and may be idiopathic (arising from an unknown cause), or due to other underlying factors or disease associations such as connective tissue disease.

Succinct description of the service or health technology:

Measurement of NT-proBNP (also known as N-terminal pro-brain natriuretic peptide, N-terminal pro-B-type natriuretic peptide or N-terminal prohormone of brain natriuretic peptide) through a blood test. The blood test is intended to be used as a regular assessment of pulmonary arterial hypertension disease progression.

List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the health technology/service:

Professional body name	Rationale
Cardiac Society of Australia and New Zealand (CSANZ)	The professional body for cardiologists and those working in cardiology across Australia and New Zealand.
Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ)	Professional society focused on facilitating research into pulmonary hypertension, helping to educate members on the diagnosis and treatment of the disease. Members include

Professional body name	Rationale
	cardiologists, respiratologists, immunologists, rheumatologists, nurses and allied health professionals.
Royal College of Pathologists of Australasia (RCPA)	The Royal College of Pathologists of Australasia, more commonly known by its acronym RCPA is a medical organization that promotes the science and practice of pathology. The RCPA is a leading organisation representing pathologists and other senior scientists in Australasia.
Thoracic Society of Australia and New Zealand (TSANZ)	This society is committed to serving the professional needs of its members by improving knowledge and understanding of lung disease, with the ultimate goals being to prevent respiratory illness through research and health promotion and to improve health care for people with respiratory illness.

List all appropriate professional bodies / organisations representing the group(s) of health professionals who request the health technology/service:

Professional body name	Rationale
Cardiac Society of Australia and New Zealand (CSANZ)	Refer rationale provided earlier.
Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ)	Refer rationale provided earlier.
Thoracic Society of Australia and New Zealand (TSANZ)	Refer rationale provided earlier.

List all appropriate professional bodies / organisations representing the group(s) of health professionals that may be impacted by the health technology/service:

Professional body name	Rationale
Cardiac Society of Australia and New Zealand (CSANZ)	Refer rationale provided earlier.
Pulmonary Hypertension Society of Australia and New Zealand (PHSANZ)	Refer rationale provided earlier.
Thoracic Society of Australia and New Zealand (TSANZ)	Refer rationale provided earlier.

List the patient and consumer advocacy organisations or individuals relevant to the proposed health technology:

Name	Type	Rationale
Lung Foundation Australia (LFA)	Organisation	The only charity and leading peak body of its kind in Australia that funds life-changing research and delivers support services that give hope to people living with lung disease or lung cancer.

Name	Type	Rationale
Pulmonary Hypertension Association of Australia Inc (PHAA)	Organisation	Provide online resources and support to patients and carers/families of those living with PAH in Australia.
Pulmonary Hypertension Network Australia (PHNA)	Organisation	Active patient-facing organisation for PAH patients and professionals based in Western Australia.

List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed service or health technology:

Professional body name	Rationale
Abbott	Abbott manufacture Alere NT-proBNP for Alinity.
BioMerieux	BioMerieux manufacture the VIDAS NT-proBNP2 immunoassay.
Ortho Clinical Diagnostics	Ortho Clinical Diagnostics manufacture VITROS® NT-proBNP.
Roche Diagnostics	Roche Diagnostics manufacture elecsys cobas®.
Siemens Healthineers	Siemens Healthineers manufacture ADVIA Centaur®, Atellica Advia®, Dimension® Vista®/EXLTM.

Nominate (at least) two experts who could be approached about the proposed service or health technology and the current clinical management of the service or health technology. Include justification of expertise for each expert:

Number of experts identified: 2

Regulatory information

Would the proposed health technology involve the use of a medical device, in-vitro diagnostic test, radioactive tracer or any other type of therapeutic good?

Yes

Has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

Yes

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

No

Please enter all relevant ARTG IDs:

ARTG ID	ARTG name
200461	Clinical chemistry-specific protein IVDs
300302	Clinical chemistry-specific protein IVDs
333340	Clinical chemistry-specific protein IVDs
369216	Clinical chemistry substrate IVDs
371578	Clinical chemistry substrate IVDs
376379	Clinical chemistry-specific protein IVDs

Is the intended purpose in this application the same as the intended purpose of the ARTG listing(s)?

Yes

Are there any single and/or multi-use consumables delivered as part of the service or health technology?

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