

Medical Services Advisory Committee (MSAC) Public Summary Document

Application No. 1740 – N-Terminal-pro Brain Natriuretic Peptide (NT-proBNP) to aid in the diagnosis of patients with suspected heart failure in a non-hospital setting

Applicant: Roche Diagnostics Australia Pty Limited

Date of MSAC consideration: 23-24 November 2023

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of N-terminal (NT)-pro hormone brain natriuretic peptide (NT-proBNP) assays for diagnosis of heart failure (HF) in patients where the diagnosis is suspected but uncertain was received from Roche Diagnostics Australia Pty Limited by the Department of Health and Aged Care.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC supported the creation of a new Medicare Benefits Schedule (MBS) item for Brain Natriuretic Peptide (BNP) and N-Terminal-pro Brain Natriuretic Peptide (NT-proBNP) testing to aid in the diagnosis of patients with suspected but uncertain heart failure (HF) in a non-hospital setting. The evidence demonstrated that BNP and NT-proBNP testing had superior test accuracy, but did not show that testing improved health outcomes. However, despite the substantial limitations of the published evidence for change in management and health outcomes, MSAC considered that use of BNP/NT-proBNP testing as a triage test for echocardiography was likely to have superior effectiveness as it is widely recommended for this purpose in Australian and international clinical practice guidelines. MSAC's previous assessment of non-inferior safety in the non-hospital setting remained reasonable. MSAC considered there was a compelling argument that publicly funding this testing would improve equity of access for First Nations people and people in rural and remote areas.

While the cost-effectiveness and total financial impact of the service were somewhat uncertain, listing was likely to be cost-effective and result in a net financial saving to the MBS because it was reasonable to assume echocardiography is currently performed in a high proportion of suspected HF patients. MSAC considered that the main value of this testing arose from avoiding echocardiography after a rule out diagnosis, and was concerned that there was a risk of widespread inappropriate use outside this purpose, including clinical situations when echocardiography will be used anyway. The risk of leakage should be reduced through a practice note describing that the test purpose is as a decision aid for determining whether to conduct echocardiography, restricting the frequency to once per year, and requesting the relevant professional organisations develop education programs for health professionals. Utilisation should also be monitored through a utilisation review after two years.

Table 1 MSAC's supported MBS item descriptor

Category 6 – Pathology services Group P2 Chemical
<p>MBS item CCCC</p> <p>Quantitation of BNP or NT-proBNP for the exclusion of a diagnosis of heart failure in patients presenting to a non-hospital setting to assist in decision-making regarding the clinical necessity of an echocardiogram, where heart failure is suspected based on signs and symptoms but diagnosis is uncertain.</p> <p>Applicable not more than once in a 12-month period</p>
<p>Fee: \$58.50 Benefit: 75% = \$43.90 85% = \$49.75</p>
<p>New practice note PN.XX: BNP or NT-proBNP testing under MBS item CCCC is intended as a decision aid regarding the clinical necessity of an echocardiogram. Where a patient presents with symptoms of suspected but uncertain heart failure, a BNP or NT-proBNP test under MBS item CCCC can be requested by the treating medical practitioner where clinically appropriate, in line with guidelines from the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand.</p>

Consumer summary

This was an application from Roche Diagnostics Australia requesting Medicare Benefits Schedule (MBS) listing of a test to measure the levels of a protein called N-terminal-pro hormone brain natriuretic peptide (NT-proBNP) in a blood sample, to diagnose heart failure in patients who have uncertain but suspected heart failure. MSAC previously considered an application for this testing in a non-hospital setting in 2007, but did not support it then because there was not enough evidence that it was good value for money.

Heart failure occurs when the heart does not pump blood as well as it should, which can lead to fluid building up in the lungs, causing shortness of breath. Other symptoms of heart failure include swelling of the ankles, dizziness and fatigue. Because these symptoms can be caused by several other conditions too, heart failure can be difficult to diagnose.

People who have an uncertain but suspected diagnosis of heart failure are usually sent to have a test called an echocardiogram to help work out the diagnosis. This is a test that uses ultrasound waves to give a picture of the heart and look at how well the heart is pumping. However, echocardiograms are not easily available to some people (such as those living in rural and remote areas), and some people pay high out-of-pocket costs for an echocardiogram.

As pressure in the heart increases, the heart muscles are stretched and overloaded, and they release a protein called B-type natriuretic peptide (BNP) into the blood stream. The levels of BNP and NT-proBNP can be measured with a blood test for BNP or NT-proBNP. Higher levels of BNP and NT-proBNP in the bloodstream may mean problems with the heart, such as heart failure. This is then confirmed using more tests, including an ultrasound assessment of the heart (an echocardiogram). But if a patient's BNP and NT-proBNP levels are low enough to rule out heart failure, then those patients may not need an echocardiogram. This can help prevent patients from having unnecessary echocardiograms and so reduce costs to both patients and the healthcare system.

Testing for BNP and NT-proBNP is already publicly funded in the hospital emergency setting. This application proposed also funding the test in a non-hospital setting, such as in a general practitioner's (GP's) or specialist's office.

The evidence showed that compared to clinical care without BNP and NT-proBNP testing, adding this testing is more accurate at ruling out a diagnosis of heart failure. However, there was limited evidence that adding this testing would improve patients' health outcomes. But despite the lack of strong evidence, MSAC considered that national and international clinical

Consumer summary

guidelines recommend the use of BNP/NT-proBNP in non-hospital settings, so it already has an established role in the diagnostic pathway for heart failure. MSAC considered that some patients may already be doing this testing by paying privately for it, and publicly funding it would improve equity of access to BNP/NT-proBNP testing in the community, especially for people in rural and remote areas and First Nations people. First Nations people are disproportionately burdened by heart failure. Heart failure is 1.7 times more common in First Nations people than non-indigenous Australians, and heart failure occurs 10-20 years earlier among First Nations people than non-indigenous Australians.

MSAC considered the best evidence that was presented on how many people would be able to avoid an echocardiogram after BNP/NT-proBNP testing was no longer relevant. MSAC considered that probably many people who currently get an echocardiogram will have heart failure ruled out by BNP/NT-proBNP testing when it is available. This will save money for patients and the healthcare system, and also makes this testing good value for money. While it was hard to know exactly how many echocardiograms will be avoided in practice, MSAC considered this testing was likely to overall save the MBS money.

MSAC did not have any concerns about the safety of BNP/NT-proBNP testing.

The applicant proposed only NT-proBNP testing, but MSAC supported funding both the NT-proBNP and BNP tests. This is in line with MSAC's previous support for funding of testing that measures either BNP or NT-proBNP for patients in other settings, and is supported by clinical practice guidelines.

MSAC considered the value of this testing comes from helping make decisions about whether or not to do an echocardiogram, so testing is not needed when a decision has already been made to do an echocardiogram. To ensure doctors understand when to use this testing and help avoid inappropriate use of the test, MSAC advised the test should be described as a decision aid for echocardiography, limited to once per year, and relevant professional organisations should be asked to develop education programs for doctors. A review should also be undertaken after 2 years to ensure this testing is being used appropriately.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC supported MBS funding of BNP and NT-proBNP to rule out a diagnosis of heart failure in patients who have uncertain but suspected heart failure in the non-hospital setting. MSAC considered the testing to be safe and effective in helping some patients avoid unnecessary echocardiography. MSAC also considered the test to be good value for money, and that financially it would likely be a net cost saving for the MBS from echocardiograms avoided.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this application from Roche Diagnostics Australia Pty Ltd requested Medicare Benefits Schedule (MBS) funding of N-terminal-pro hormone brain natriuretic peptide (NT-proBNP) assays for the diagnosis of heart failure in patients in the non-hospital setting, whose diagnosis is suspected but uncertain.

MSAC noted that heart failure (HF) is a highly prevalent condition. The two main types of HF are HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). HFpEF has previously been difficult to detect and diagnose but recently has become increasingly recognised by clinicians. HF is becoming increasingly treatable with medical therapy that improves prognosis. However, heart failure is often hard to diagnose because its symptoms, such as exertional shortness of breath, are non-specific. MSAC noted that the National Heart

Foundation of Australia (NHFA) and Cardiac Society of Australia and New Zealand (CSANZ) guidelines¹ recommend BNP or NT-proBNP testing in primary care for patients with suspected heart failure when the diagnosis is uncertain.

MSAC recalled there had been two previous MSAC applications for BNP and NT-proBNP testing for the diagnosis of heart failure. At its November 2006 meeting, MSAC supported funding of BNP assays (i.e., including both BNP and NT-proBNP) in the diagnosis of heart failure in the hospital emergency setting only (Part A of MSAC application 1087², implemented as MBS item 66830). Then at its May 2007 meeting, MSAC considered the use of the assay in the non-hospital setting (Part B of MSAC application 1087), but did not support public funding. This was primarily due to highly uncertain cost-effectiveness, arising mainly from the overestimation of the echocardiography referral rate in the comparator arm relative to the best available real-world evidence on the echocardiography referral rate.

MSAC noted the applicant had proposed only NT-proBNP, and not also BNP, in this application. To align with both national and international guidelines and previous MSAC advice (for applications 1087 (part A) and 1689.1³), MSAC advised this testing should include BNP assays in addition to the proposed NT-proBNP assays.

MSAC noted the application had originally proposed one item to be restricted to cardiologists only, but also incorrectly described cardiology as being part of primary care. PASC had considered that cardiologists were not regarded as primary care providers in Australia, and that the test would likely be of more value in primary care (such as the general practitioner (GP) setting) rather than in specialist settings. MSAC noted PASC had considered that the test was less likely to be cost-effective if requested by cardiologists because it was more likely that cardiologists would still perform an echocardiogram even if the BNP or NT-proBNP test ruled out heart failure. PASC had therefore advised that the primary care and specialist populations should be assessed separately, and the PICO contained two separate PICO sets and item descriptors: one for the primary care setting in which NT-proBNP testing was proposed to triage access to echocardiography (MBS item AAAA), and another for the specialist setting in which NT-proBNP testing would be used in addition to echocardiography (MBS item BBBB). However, the ADAR did not present evidence for PICO set 2, so ESC proposed the populations should be combined (MBS item CCCC).

MSAC noted the NHFA/CSANZ guidelines position BNP/NT-proBNP testing not purely as a triage test but as an option alongside direct referral to echocardiography, or in addition to echocardiography. When used before echocardiography, MSAC noted a rule-out threshold of 300 pg/mL NT-proBNP is a “pragmatic guide” and the current national recommendation, although the NHFA/CSANZ guidelines acknowledge there are different cut-offs in other international guidelines depending on the balance sought in the trade-off between over-diagnosis and under-diagnosis. Additional age-based rule-in thresholds are also provided by the NHFA/CSANZ guidelines.

MSAC noted that consultation feedback was supportive of public funding for NT-proBNP to aid in the diagnosis of patients with suspected heart failure in the non-hospital setting. MSAC agreed

¹ Atherton JJ, Sindone A, et al. (2018). "National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018." *Heart Lung Circ* 27(10): 1123-1208.

² MSAC application 1087 – Brain natriuretic peptide assays in the diagnosis and monitoring of heart failure. Available at: <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1087-public>

³ MSAC application 1689.1 – Quantification of NT-proBNP in patients with diagnosed pulmonary arterial hypertension for ongoing risk assessment. Available at: <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1689.1-public>

with the applicant's pre-MSAC response that, despite not being publicly reimbursed in the non-hospital setting, the strong recommendation for NT-proBNP in Australian guidelines could create a significant equity issue for people who cannot afford the test in the primary care setting. MSAC also agreed with feedback from the Heart Foundation that access to NT-proBNP would provide a significant health benefit for people who are disproportionately burdened by heart failure (such as those in rural and remote areas, and First Nations people), which is compounded by limited access to echocardiography.

MSAC noted that in the clinical management algorithm, NT-proBNP testing was proposed to occur after the initial clinical assessment and when there was an uncertain but suspected diagnosis of HF. MSAC considered this was appropriate and in accordance with the NHFA/CSANZ guidelines. MSAC noted the comparator in the primary care setting was no NT-proBNP, while the comparator in the specialist and consultant physician setting was echocardiography.

MSAC noted that no evidence was presented in the applicant-developed assessment report (ADAR) for PICO set 2 (NT-proBNP as an additional test to echocardiography in the specialist requestor setting). This included no evidence being presented for the use of NT-proBNP as an additional test to echocardiography, which was advised by PASC. MSAC considered that clinical evidence that would have supported the use of the test in this setting and pathway could have included prognostic studies and diagnostic studies that specifically addressed the role of NT-proBNP in HFpEF.

MSAC considered that the effectiveness evidence presented for PICO set 1 (BNP/NT-proBNP as a triage test to access echocardiography in the primary care setting) was of very poor quality. However, MSAC considered that without the sharing of linked datasets across the health system, it was unlikely that better quality evidence would be obtained soon. MSAC noted that there were very few studies reporting on the value of BNP/NT-proBNP for determining prognosis, but considered this reasonable as BNP/NT-proBNP testing is not generally used as a prognostic tool.

MSAC noted that three of the included studies (Burri et al 2012⁴, Verdu et al 2012⁵, Taylor et al 2017⁶) examined point-of-care BNP or NT-proBNP testing (PoCT). MSAC considered that BNP/NT-proBNP testing in the non-hospital setting should appropriately be performed in a laboratory, and noted policy advice that legislation would restrict this testing to that provided in a laboratory (ie. excluding PoCT) by default, therefore MSAC considered the evidence from PoCT studies was not relevant. MSAC therefore also advised that it was not necessary to specify in the item descriptor that this was for laboratory-based testing only.

MSAC noted that the ADAR did not address the comparative safety of the test. MSAC considered that, although the test is a standard venepuncture blood test that is unlikely to cause direct harm to the patient, false positive or false negative test results could consequently cause harm, which were not addressed in the ADAR. However, MSAC recalled that in its consideration of application 1087 in 2007, it had accepted that "*as the population of interest in the non-hospital setting is not acutely ill, delayed treatment associated with (the very low likelihood of) a false negative test result is unlikely to be harmful*" (p2 part B May 2007 MSAC 1087 PSD), and had advised that BNP/NT-proBNP testing for the diagnosis of heart failure in patients presenting with

⁴ Burri EK, et al. (2012). "B-type natriuretic peptide in the evaluation and management of dyspnoea in primary care." *J Intern Med* 272(5): 504-513.

⁵ Verdu JM, et al. (2012). "Rapid point-of-care NT-proBNP optimal cut-off point for heart failure diagnosis in primary care. [Spanish]." *Rev Esp Cardiol (Engl Ed)* 65(7): 613-619.

⁶ Taylor CJ, et al. (2017). "Primary care REFerral for Echocardiogram (REFER) in heart failure: A diagnostic accuracy study." *Br J Gen Pract* 67(655): e94-e102

dyspnoea in a non-hospital setting was comparatively safe. In line with its previous advice, MSAC advised the comparative safety of BNP/NT-proBNP testing was likely non-inferior.

MSAC considered that the evidence supported a clinical claim of superior effectiveness in terms of test accuracy. MSAC noted that the Danish pragmatic cluster-RCT presented did not appear to show benefit in terms of HF diagnosis⁷, which MSAC considered was a result that lacked face validity and could not be relied upon for decision-making. MSAC considered the main evidence for diagnostic accuracy was therefore Zaphiriou et al. 2005⁸, which reported consistently high sensitivity but lower specificity across a range of thresholds.

MSAC considered that BNP and NT-proBNP are not perfect biomarkers for HF, and there is the potential for a false negative result (i.e. falsely ruling out HF) when using this testing to detect HFpEF, because 20-35% of patients with HFpEF (which account for more than 50% of HF patients in the community) have low BNP/NT-proBNP levels despite evidence of increased pulmonary capillary wedge pressure⁹. This can be due to genetics, obesity and insulin resistance, lack of increased wall stress, increased androgens, and being of African descent.

While the evidence supported improved test accuracy, MSAC considered the evidence from the literature did not show that testing would improve health outcomes, and noted the evidence base for health outcomes was small and of low certainty. The evidence suggested improved health outcomes were more likely in patients correctly excluded from heart failure than those diagnosed with heart failure, which aligned with MSAC's advice for application 1087 but was not modelled in the economic analyses. NT-proBNP testing also appeared to have little effect on the downstream utilisation of echocardiography. However, MSAC considered that BNP/NT-proBNP testing is widely recommended in Australian and international guidelines, and is being increasingly used as a diagnostic tool for patients with suspected heart failure. MSAC considered that this testing has a well-established role as a triage test before echocardiography, and that despite the substantial limitations of the published evidence, BNP/NT-proBNP testing was likely to have superior effectiveness as a triage test for echocardiography because it is widely recommended for this purpose in clinical practice guidelines in Australia and internationally.

MSAC noted the application was predicated on the assertion that NT-proBNP testing would be able to rule out HF in some patients, allowing them to avoid echocardiography. MSAC noted that the assumption of 100% echocardiography uptake in the absence of BNP/NT-proBNP testing aligned with guidelines from the National Institute for Health and Care Excellence (NICE), but PASC and ESC were concerned that assuming perfect uptake did not align with real-world evidence. MSAC had previously reviewed evidence that stated the echocardiography uptake was more likely to be 3.8-17.7% in the comparator arm. In its pre-ESC response the applicant revised the assumed echocardiography uptake from 100% to 64%, citing real-world evidence from Krum et al. 2001¹⁰ showing >64% of people with suspected HF would be referred for echocardiography. However MSAC considered this was an incorrect interpretation and Krum et al. had in fact reported echocardiography utilisation was 17.7% amongst the proposed population of patients with suspected HF, as per its previous advice on the results of this study

⁷ Najbjerg AG, et al. (2019). NT-proBNP to exclude heart failure in primary care - a pragmatic, cluster-randomized study. *Scand J Clin Lab Invest*, 79(5), 334–340.

⁸ Zaphiriou A, et al. (2005). "The diagnostic accuracy of plasma BNP and NTproBNP in patients referred from primary care with suspected heart failure: Results of the UK natriuretic peptide study." *Eur J Heart Fail* 7(4): 537-541

⁹ Sanjiv J Shah, BNP: Biomarker Not Perfect in heart failure with preserved ejection fraction, *Eur Heart J.*, Volume 43, Issue 20, 21 May 2022, Pages 1952–1954, <https://doi.org/10.1093/eurheartj/ehac121>

¹⁰ Krum H. et al (2001). Guidelines for management of patients with chronic heart failure in Australia, *Med J Aust*, 174, 459-466.

under application 1087. However, MSAC considered the results from Krum et al. were now out of date and no longer relevant as clinical practice has changed over time. MSAC noted that current clinical practice guidelines recommend that echocardiography is performed if HF is uncertain but suspected and BNP/NT-proBNP testing is not available. MSAC considered clinical feedback also showed that echocardiography is considered in the standard workup for confirming a diagnosis of HF. Therefore, given changes in clinical practice that have been reflected in management guidelines, MSAC considered it likely that echocardiography uptake for suspected HF was probably greater than 50%. MSAC considered that although it was erroneous, the applicant's 64% echocardiography uptake may well be closer to the truth than the outdated real-world evidence of 17.7%.

MSAC considered the appropriate clinical place for BNP/NT-proBNP testing was as a triage test for echocardiography (and it would also allow some unnecessary cardiologist referrals to be avoided), but there was a risk that it would be used inappropriately (e.g., used when an echocardiogram will be done anyway, or to assess HF severity). MSAC considered the item descriptor should specify in the practice notes that this test is to be used as a "decision aid" in determining whether an echocardiogram is needed. MSAC considered that the addition of a reference to the NHFA/CSANZ guidelines in the practice note would also support appropriate requesting practices. MSAC considered the proposed frequency restriction of maximum once in a 12-month period was reasonable and would help mitigate the risk of inappropriate use. MSAC considered that while the test would likely be used mostly in primary care, the item descriptor should not exclude specialist or consultant physician requestors, as it would not be appropriate to exclude them from being able to request the test.

MSAC noted that the ADAR's economic model results showed NT-proBNP testing ± echocardiography was cost saving over echocardiography alone (\$68 saved per patient), and the commentary's respecified base case found the intervention was still dominant over echocardiography (\$25 saved per patient). Additionally, the time to diagnosis or exclusion of HF was reduced when NT-proBNP testing was used. MSAC noted that the pre-MSAC response also revised the base case to apply a 3-month (rather than 2-month) delay to echocardiography, in response to ESC feedback. This resulted in a greater reduction in time to diagnosis for NT-proBNP ± echocardiography (1.43 months) than echocardiography alone (1.92 months). The pre-MSAC response also presented an additional scenario that considered out-of-pocket costs (gap payment and travel). This resulted in a greater incremental cost-saving per patient (\$42.60) than the revised base case saving (\$9.59).

MSAC noted that the economic model was sensitive to the percentage of echocardiography referrals, that affected both costs and the number of correct diagnoses of HF. The ADAR's economic model assumed that 100% of patients in the comparator arm would receive echocardiography, which was assumed to have a higher cost, perfect accuracy and slower access than the intervention. MSAC noted that, when the model assumed 64% of patients would be referred for echocardiography in the comparator arm, the intervention would still be cost saving. MSAC noted that the commentary considered several different echocardiography uptake rates, and that uptake at or below 80% changed the intervention from being cost saving to cost positive (Table 17).

MSAC noted that similar findings were seen with the financial impacts. The ADAR (assuming 100% echocardiography referrals in the comparator arm) estimated net cost savings to the MBS of \$6,473,083 in year 1 to \$9,675,089 in year 6. The commentary revised the financial impacts by updating the MBS fees (from July 2023), using the test accuracy results from Zaphiriou et al. 2005, including additional GP visits to receive results, assuming that all patients were treated in primary care, and correcting errors. This resulted in reduced net cost savings of \$2,050,786 in year 1 to \$3,749,889 in year 6. Sensitivity analyses showed that NT-proBNP testing was cost-

saving to the MBS when used as an add-on to echocardiography in up to 50% of cases. However, MSAC agreed with ESC that an increased cost to the MBS did not necessarily equate to poor value for money.

MSAC considered there was a risk of widespread inappropriate use (in particular, where an echocardiogram will be done anyway), so advised on safeguards around BNP/NT-proBNP testing to rule out heart failure. As above, the MBS item descriptor should clarify that this testing is to be used specifically as a decision aid for referral to echocardiography. MSAC also advised that requestors should be provided guidance on the correct use and interpretation of the tests. MSAC requested the Department write to various colleges to request their support to develop education programs for health professionals, such as the Royal Australian College of General Practitioners (RACGP), the Cardiac Society of Australia and New Zealand (CSANZ), the Australian College of Rural and Remote Medicine (ACRRM), and the Royal College of Pathologists of Australasia (RCPA) in their role as stewards of the Choosing Wisely initiative¹¹. MSAC considered that healthcare provider education around this testing should include that some people with HFpEF will have a low BNP/NT-proBNP result (false negative result), as detailed above. MSAC also advised that an analysis of predicted versus actual utilisation be undertaken 2 years post-implementation.

4. Background

MSAC has previously considered NT-proBNP testing for the diagnosis of HF, under MSAC application 1087 in November 2006 and May 2007 (Table 2). MBS item 66830 (quantitation of BNP or NT-proBNP for the diagnosis of HF in patients presenting with dyspnoea to a hospital emergency department) was introduced on the MBS from 1 July 2008. At the time, MSAC did not support public funding in the non-hospital setting.

MSAC has also previously considered NT-proBNP testing in patients with systemic sclerosis, and in patients with diagnosed pulmonary arterial hypertension (PAH), under MSAC applications 1689 and 1689.1.

Table 2 Prior MSAC applications for BNP and NT-proBNP testing for the diagnosis of heart failure

MSAC meeting	Application number and name Setting	MSAC advice
15 November 2006	MSAC application 1087 - B-type natriuretic peptide assays in the diagnosis of heart failure Part A – in the hospital emergency setting	MSAC found there was sufficient evidence that B-type natriuretic peptide assays, when used in the hospital emergency setting for the diagnosis of heart failure in patients presenting with dyspnoea, were safe, effective (diagnostically accurate), cost-effective and had an acceptable financial cost. MSAC did not support public funding for their use in monitoring the progress of patients with heart failure.
May 2007	MSAC application 1087 - B-type natriuretic peptide assays in the diagnosis of heart failure Part B – in the non-hospital setting	MSAC found there was major uncertainty around the cost effectiveness in the non-hospital setting. MSAC advised that public funding was not supported for the use of assays of B-type natriuretic peptides in the diagnosis of heart failure in patients presenting with dyspnoea in the non-hospital setting at this time. MSAC advised further research should be conducted on the use of BNP in the general practice setting to identify appropriate usage and the patient group most likely to benefit in the non-hospital setting.

¹¹ Choosing Wisely Australia, an initiative of NPS MedicineWise. Available at: <https://www.choosingwisely.org.au/>

MSAC meeting	Application number and name Setting	MSAC advice
6-7 April 2017	Report to MSAC on real world outcomes of application 1087: Brain natriuretic peptide assays in the diagnosis and monitoring of heart failure Hospital emergency department setting	After considering the real-world utilisation of the outcomes of MSAC application 1087, MSAC noted there was significant under-utilisation of MBS item 66830 post-implementation and advised no further action.

Source: Adapted from Commentary Table 1 of MSAC 1740 ADAR+ in-line commentary

Previous observations made by MSAC in its May 2007 consideration of B-type natriuretic peptides for diagnosing HF in the non-hospital setting (MSAC application 1087, part B) are summarised in Table 3, based on the key matters of concern described in Appendix A of the 1740 PICO Confirmation.

Table 3 Summary of key matters of concern from MSAC application 1087 – part B, non-hospital setting

Component	Matters of concern from application 1087, and updated evidence required	How the commentary considered current assessment report addresses the matter of concern
Patient population	MSAC advised further research on the use of BNP in the general practice setting to identify appropriate usage and the patient group most likely to benefit in the non-hospital setting (PSD, p.3).	Not addressed. The patient population specified in the PICO was 'people with signs and/or symptoms consistent with HF in whom a HF diagnosis is suspected but uncertain.' The extent to which these patients are appropriately treated currently, and how broadly the test is likely to be used in practice, were not addressed.
Test performance	MSAC found there was sufficient evidence that BNP assays, when used in the diagnosis of HF, are effective and safe. However, the assessment report identified that it is unlikely that the use of the NT-proBNP test would result in earlier identification of HF than currently for patients due to the low positive predictive value of the test and thus the need for further testing. MSAC advised the assessment report should provide updated evidence on the test performance and the resulting change in management (time to appropriate diagnosis and treatment) to support the clinical claim in this application (PSD, p.3).	Not adequately addressed. The ADAR included one study on change in management (Burri, 2012). The study used a BNP point-of-care test, which limited the applicability regarding time to appropriate treatment (which was initiated on-the-day in 66% of patients in the BNP group in the study). This outcome was assessed as very low certainty evidence according to GRADE. Additional direct and change in management outcomes were not reported in the ADAR. Those reported by the commentary did not support improved HF outcomes. If there is a clinical benefit, it is likely to be in patients with alternative diagnoses in which HF can be more rapidly excluded. The ADAR did not provide clinical evidence to support this, nor model these outcomes in the economic analysis.

Component	Matters of concern from application 1087, and updated evidence required	How the commentary considered current assessment report addresses the matter of concern
Health outcomes	<p>Clinical impact of the test (i.e., on health outcomes) was unknown in non-hospital settings.</p> <p>MSAC advised that if there is a change in diagnosis, timing of diagnosis or treatment, or patient behaviour resulting from the use of NT-proBNP, the assessment report should assess whether this change in management leads to better health outcomes (PSD, p.3).</p>	<p>Not adequately addressed.</p> <p>The commentary added health outcomes reported in Burri (2012) and Najbjerg (2019). These outcomes did not show a benefit of NT-proBNP testing.</p> <p>The ADAR relied on assumed perfect adherence to clinical practice guidelines to assess the benefit of the testing strategy, however published evidence showed that such guidelines are poorly adhered to in this patient population (Sindone, 2021¹²; Hayhoe, 2018¹³).</p>
Cost-effectiveness	<p>MSAC found there was major uncertainty around the cost-effectiveness of NT-proBNP testing in the non-hospital setting.</p> <p>MSAC noted that cost-effectiveness usually depended on referral propensity. This was explored, though the three referral pattern scenarios all assumed that 100% of patients would currently receive an echocardiogram as per guidelines, and MSAC was concerned that available data suggested that actual echocardiogram referral rates may range from 3.8% to 17.7% for patients with new symptoms suggestive of HF. Results of a one-way sensitivity analysis suggested that BNP testing would not be cost-saving if GPs currently refer this patient group to echocardiography at a rate of 60% or lower.</p>	<p>Not adequately addressed.</p> <p>Although rates of echocardiography referral may have increased in Australia since 2007, it does not follow that all patients with a suspected but uncertain diagnosis of HF are currently referred for echocardiography. Echocardiography referral rates vary across Australia¹⁴. No data were presented on the actual rate of referral for echocardiography for the proposed patient population.</p>

Abbreviations: ADAR, Applicant Developed Assessment Report; BNP, B-type natriuretic peptide; GP, general practitioner; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; HF, heart failure; MSAC, Medical Services Advisory Committee; NT-proBNP, N-terminal-pro brain natriuretic peptide; PICO, population intervention comparator outcome; PSD, Public Summary Document. **Source:** Adapted from Table 3 of MSAC 1740 ADAR+ in-line commentary, which was based on 1740 PICO Appendix A.

5. Prerequisites to implementation of any funding advice

The proposed technology is laboratory NT-proBNP immunoassay. There are multiple commercially available assays. The Elecsys® proBNP II and proBNP II STAT assays are manufactured by Roche Diagnostics. Other commercially available laboratory-based assays include Siemens Healthineers (Stratus® CS Acute Care™), BioMerieux (VIDAS NT-proBNP2), Abbott Alere NT-proBNP, Ortho VITROS® NT-proBNP II, and Radiometer AQT90 FLEX NT-proBNP.

The Elecsys® proBNP II and proBNP II STAT assay is included in the Australian Register of Therapeutic Goods (ARTG) under identification number 200275. The registered intended

¹² Sindone AP, et al. (2021). "Clinical characteristics of people with heart failure in Australian general practice: results from a retrospective cohort study." *ESC Heart Fail* 8(6): 4497-4505.

¹³ Hayhoe B, et al. (2019). Adherence to guidelines in management of symptoms suggestive of heart failure in primary care. *Heart*, 105(9), 678–685.

¹⁴ Australian Commission on Safety and Quality in Healthcare (ACSQH), 2018 Third atlas of variation. Available at: <https://www.safetyandquality.gov.au/sites/default/files/migrated/4.4-Text-Standard-echocardiography-18-years-and-over.pdf>

purpose is for the qualitative/quantitative determination of specific proteins in biological samples, with no conditions specified.

The Royal College of Pathologists Australasia (RCPA) has Quality Assurance Programs for NT-proBNP testing.

6. Proposal for public funding

The proposed MBS item descriptor for patients with suspected but uncertain HF in a non-hospital setting is presented in Table 4. The proposed fee and benefit are the same as MBS item 66830 (quantitation of BNP or NT-proBNP for the diagnosis of HF in patients presenting with dyspnoea to a hospital emergency department). The proposed item descriptor differed from item 66830 in that it did not include BNP and was only for patients presenting in a non-hospital setting.

MSAC considered the appropriate biomarker or biomarkers. PASC considered it was probably reasonable to restrict the intervention to NT-proBNP testing based on the shorter half-life of BNP and the applicant's intention to expand the use of the Roche NT-proBNP assay, however the ADAR's evidence base included both biomarkers. In July 2022, MSAC supported testing of NT-proBNP alone rather than of BNP or NT-proBNP, although for a different patient population (MSAC application 1689). Australian clinical practice guidelines recommend either NT-proBNP or BNP testing but do not specify the setting.

PASC advised that NT-proBNP testing in primary care should be assessed separately from where the request is made by a cardiologist, and advised on PICO sets 1 and 2 for different requestor settings. Separate MBS items were therefore proposed for each setting, to facilitate MSAC advising separately on each (Table 4). If MSAC advised that NT-proBNP should be available without reference to a particular requesting practitioner (i.e., in both primary care setting and specialist physician setting), then only one MBS item would be required.

At time of preparation of the commentary, the Pathology Policy Section was seeking advice as to whether and how, an MBS item can be restricted to general practitioners (GPs) and nurse practitioners only, at the exclusion of specialists and consultant physicians. Policy was also seeking advice on how such an item descriptor might be worded to prevent leakage to the specialist setting.

PASC considered that while proposed item BBBB was intended primarily for use by cardiologists, there will be times when a patient presents to a different type of specialist or consultant physician with signs and/or symptoms of HF, so requestors should not exclude other specialists. PASC therefore advised that requestors for proposed item BBBB should be expanded to all specialists or consultant physicians.

The proposed item descriptor included a restriction to 'once in a 12-month period' to mitigate non-diagnostic use of the test.

Table 4 Proposed MBS items

Category 6 – Pathology services Group P2 Chemical
<p>MBS item AAAA</p> <p>Quantitation of NT-proBNP for the exclusion of a diagnosis of heart failure in patients presenting to a non-hospital setting, where all of the following apply:</p> <p>(a) Heart failure is may be suspected based on signs and symptoms but diagnosis is uncertain based on initial assessment</p> <p>(b) The service is requested by a general practitioner or appropriate nurse practitioners</p> <p>Applicable not more than once in a 12-month period</p>
<p>Fee: \$58.50 Benefit: 75% = \$43.90 85% = \$49.75</p>
<p>MBS item BBBB</p> <p>Quantitation of NT-proBNP for the exclusion of a diagnosis of heart failure in patients presenting to a non-hospital setting, where all of the following apply:</p> <p>(a) Heart failure is suspected but diagnosis is uncertain based on initial assessment</p> <p>(b) The service is requested by a specialist or consultant physician</p> <p>Applicable not more than once in a 12-month period</p>
<p>Fee: \$58.50 Benefit: 75% = \$43.90 85% = \$49.75</p>

Note: Strikethrough and underline indicate deletions and additions from/to the item descriptors from the ratified PICO Confirmation.
Source: Table 9 of MSAC 1740 ADAR+ in-line commentary and Table 11 of Ratified PICO

7. Population

The Ratified PICO Confirmation specified two PICO sets, one for each requestor setting.

PICO Set 1

The population specified in the PICO Confirmation for PICO set 1 was patients presenting to the primary care setting with signs and symptoms of HF, where the diagnosis of HF is suspected but uncertain.

PASC advised that in this setting, NT-proBNP testing would be used as a triage test before echocardiography.

PICO Set 2

The population specified in the PICO Confirmation for PICO set 2 was all patients who are referred to a specialist or consultant physician with a suspected but uncertain HF diagnosis.

PASC advised that in this setting, NT-proBNP testing would be used as an additional test alongside echocardiography.

The applicant disagreed that NT-proBNP would be used as an additional test and proposed NT-proBNP be used as a triage test in both settings.

8. Comparator

PICO Set 1

For PICO set 1, the Ratified PICO Confirmation advised that the comparator to NT-proBNP testing as part of the initial investigations in a primary care setting was no NT-proBNP testing (i.e., initial investigations without NT-proBNP testing). In this comparator scenario, if patients are still suspected of HF after the initial investigations (i.e., without NT-proBNP testing) but the diagnosis is uncertain, they may then be referred for a specialist clinical assessment (by a cardiologist and/or echocardiogram) for confirmation or exclusion of the HF diagnosis. If the initial investigations determined HF was unlikely, patients may then be investigated for an alternative diagnosis, or referred to a different type of specialist, such as a respiratory physician. PASC considered this was appropriate.

PASC further commented that if the echocardiogram were regarded as part of the intervention and comparator rather than subsequent, then an alternative approach to use a weighted comparator (comprising an evidence-based proportion of patients receiving echocardiogram, and the remainder receiving only initial assessment) appeared reasonable.

The ADAR has taken the second approach of including echocardiogram as part of both the intervention and the comparator rather than subsequent. The commentary considered this was an appropriate approach for the assessment of a triage test (and it aligned with PASC advice); however, this necessitated consideration of whether the decision threshold for clinicians for requesting a NT-proBNP test was different to that for referral for an echocardiogram (Question 1 of the Assessment Framework, page 18 of Ratified PICO Confirmation). This 'weighted comparator' approach was not taken by the ADAR: instead, it assumed 100% echocardiography uptake in the comparator, and identical referral propensities for NT-proBNP and echocardiography.

The ADAR proposed that implementation of NT-proBNP testing would reduce the number of echocardiograms (MBS item 55126) as patients without HF can be excluded from echocardiogram referral based on the NT-proBNP test result.

PICO Set 2

For PICO set 2, the Ratified PICO Confirmation advised that the comparator to the NT-proBNP assay + echocardiogram, requested in a specialist setting, was echocardiogram alone (MBS item 55126).

The applicant disagreed that NT-proBNP would be an additional test to echocardiography in this setting. The applicant considered that NT-proBNP testing will be used as a triage test prior to echocardiography in both settings.

The ADAR stated that the use of NT-proBNP as a triage test is consistent with Australian clinical practice guidelines from the National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand (NHFA/CSANZ; Atherton et al, (2018)). The guidelines do not specifically position NT-proBNP as a triage test for echocardiography; they state:

'The single most useful investigation in patients with suspected or confirmed heart failure is the echocardiogram. However, if the diagnosis is unclear and an echocardiogram cannot be arranged in a timely fashion, measurement of plasma BNP and NT-proBNP has been shown to improve diagnostic accuracy.'

The 2018 NHFA/CSANZ guidelines additionally include age-based rule-in thresholds for NT-proBNP and BNP, which were not discussed in the ADAR.

Summary

The commentary considered that the ADAR did not align with the Ratified PICO Confirmation, in particular the ADAR:

- (1) did not consider differential rates of uptake of echocardiography for PICO set 1 (primary care setting) but assumed 100% uptake in the comparator (no NT-proBNP testing) and identical referral propensities for NT-proBNP and echocardiography in primary care
- (2) did not address PICO set 2 (specialist requestor setting) as specified by PASC.

9. Summary of public consultation input

Consultation feedback was received from four organisations:

- Lung Foundation Australia (LFA)
- National Heart Foundation of Australia (The Heart Foundation)
- Royal Australian College of General Practitioners (RACGP)
- Royal College of Pathologists of Australasia (RCPA)

The consultation feedback received was all supportive of public funding for NT-proBNP to aid in the diagnosis of patients with suspected HF in the non-hospital setting.

Clinical need and public health significance

The main benefits of public funding received in the consultation feedback related to early diagnosis of lung conditions and HF leading to early treatment and better health and financial outcomes. A further benefit identified was complying with international guidelines from the UK, US, and Europe; that all recommend the use of NT-proBNP to diagnose or rule out HF in primary care/ambulatory settings.

The Department sought feedback from several general practice organisations on whether this test should be used in the primary care setting. The RACGP proposed that testing should be available for GPs to conduct in their practices.

The main disadvantages of public funding received in the consultation feedback were limitations to accessing specialist and laboratory services, particularly for those in rural and remote areas.

The proposed population, clinical claim, service description and fee

The consultation agreed with the proposed population and clinical claims. Neither organisation commented on the proposed comparator, service descriptor or fee.

Additional comments

The Heart Foundation stated that First Nation people are 1.4 times more likely to die from HF than non-indigenous Australians. They added that hospitalisation rates for people with HF are substantially higher in remote areas compared with major cities.

The RACGP refer to a B-type natriuretic peptide (BNP) test and not specifically NT-proBNP testing.

Targeted consultation was received from the RCPA regarding the usage of BNP versus NT-proBNP. The RCPA considered BNP and NT-pro-BNP both clinically perform well and should yield similar results, noting that NT-proBNP has a longer half-life and is more stable.

PASC noted the consultation feedback from the five professional medical organisations and considered the consensus was that:

- There was support for the use of NT-proBNP testing in the diagnosis of HF as a good rule-out test as it can shorten the time to diagnosis and appropriate treatment.
- NT-proBNP testing may be better placed in primary care due to difficulty in accessing cardiology services and echocardiography.
- In some cases, NT-proBNP testing may also provide prognostic information.

10. Characteristics of the evidence base

PICO Set 1

The key evidence included for PICO set 1 is summarised in Table 5. There were three randomised controlled trials (RCTs); two provided direct evidence of health outcomes and of change in management, and one provided evidence of diagnostic accuracy and concordance with the comparator. Two used laboratory-based NT-proBNP testing and one used rapid point-of-care BNP testing. The ADAR included the RCT that used the BNP biomarker to increase the volume of evidence providing change in management outcomes, implying it considered the two biomarkers interchangeable. The commentary considered this an appropriate approach.

The remaining studies were cross-sectional diagnostic accuracy studies. The commentary and the ADAR selected different sets of studies on diagnostic accuracy.

Diagnostic accuracy was the only outcome applied to the economic evaluation. The diagnostic accuracy studies used in the ADAR's economic evaluation included point-of-care NT-proBNP studies that were excluded from the ADAR's clinical evaluation. Given the limited evidence base on test performance at the threshold specified in the Australian guidelines, the commentary considered that point-of-care tests, and studies using alternative thresholds, were appropriate to include in the clinical evaluation.

Table 5 Key features of the included evidence

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base
Accuracy and performance of the test (cross-sectional accuracy)	ADAR: 2 studies using an NT-proBNP threshold of 300 pg/mL (± 25 pg/mL), 9 additional studies Commentary: 7 studies across a range of thresholds (6 cross-sectional accuracy, 1 RCT)	k=7 n=157,278 ^a	Low risk
Prognostic evidence (longitudinal accuracy)	None provided in the ADAR. Commentary included a brief summary of a recent systematic review and meta-analysis.	N/A	N/A
Change in patient management	RCTs (1 reported in the ADAR, 1 identified by the commentary)	k=2 n=323 patients (1 study), 69 GP practices (1 study)	Some concerns
Health outcomes	RCTs (not reported in the ADAR, added by the commentary)	k=2 n=323 patients (1 study), 69 GP practices (1 study)	Some concerns
Predictive effect (treatment effect variation)	Not reported	N/A	N/A

Abbreviations: ADAR, Applicant Developed Assessment Report; GP, general practitioner; k, number of studies; NT-proBNP, N-terminal-pro brain natriuretic peptide; n, number of patients; N/A, not applicable, pg/mL, picograms per millilitre; RCT, randomised controlled trial.
^a One diagnostic accuracy study was from a large database and included 155,347 patients.

Source: Compiled for the commentary from MSAC 1740 ADAR+ in-line commentary

PICO Set 2

The commentary noted that the ADAR did not present any evidence to address PICO set 2.

11. Comparative safety

The commentary noted that the ADAR did not address the comparative safety of the test. The test is a standard venepuncture blood test that is unlikely to cause direct harm to the patient; however, false positive or false negative test results could cause consequent harm, and this was not addressed.

MSAC previously accepted that *"as the population of interest in the non-hospital setting is not acutely ill, delayed treatment associated with (the very low likelihood of) a false negative test result is unlikely to be harmful"* and advised that BNP/NT-proBNP testing for the diagnosis of HF in patients presenting with dyspnoea in a non-hospital setting was comparatively safe (MSAC application 1087, part B (May 2007), Public Summary Document, page 2).

12. Comparative effectiveness

Health outcomes

The ADAR did not present any direct from test to health outcomes evidence. The commentary presented direct from test to health outcomes evidence from two RCTs; one identified in the

ADAR (Burri, 2012 – used for change of management outcomes only in the ADAR) and one identified by the commentary (Najbjerg et al, 2019). The characteristics of these studies are summarised in Table 6.

One study (Burri et al, 2012) used point-of-care BNP testing rather than laboratory-based NT-proBNP testing. The tests are likely to have similar performance, however the different test approaches may limit applicability for some outcomes such as time to appropriate treatment. This study included patients with dyspnoea as their primary presenting symptom, rather than suspected but uncertain HF as per the PICO confirmation. As dyspnoea is the most common symptom of HF, the commentary did not consider this to appreciably reduce applicability.

The second study (Najbjerg et al, 2019) was a pragmatic cluster RCT. Randomisation occurred at the level of the GP practice. Intervention GP practices received a standardised educational visit and had NT-proBNP testing available. The control GP practices received no information regarding the project and did not have NT-proBNP testing available. The denominator for the outcomes was the number of registered patients across the GP practices.

Table 6 Study characteristics of RCTs providing direct to health outcomes evidence

Study Country	N	Study design Risk of bias	Population	Intervention	Comparator	Key outcomes(s)
Burri, 2012 Switzerland and Germany	323 patients BNP: 163 Control: 160	Single-blind RCT Some concerns (ADAR assessment)	Adults with dyspnoea (new onset or clearly worsening) as their primary symptom at presentation Exclusions: obvious traumatic cause of dyspnoea, severe renal disease, sepsis	Evaluation using diagnostic strategy that included rapid point-of-care measurement of BNP levels at initial presentation	Evaluation using conventional diagnostic strategy without measurement of BNP	<u>Direct</u> All-cause mortality All-cause hospitalisation <u>Change in management</u> Echocardiograms received Time to appropriate treatment
Najbjerg, 2019 Denmark	69 GP practices Intervention: 34 Control: 35	Pragmatic cluster-RCT Some concerns (commentary assessment)	Data collected on adults referred from a GP to outpatient echocardiography and examined at a regional hospital heart clinic on suspicion of HF	NT-proBNP testing ^a available plus educational visit	No NT-proBNP testing and no information regarding project	<u>Direct</u> Number of HF diagnoses <u>Change in management</u> Echocardiograms received

Abbreviations: BNP, B-type natriuretic peptide; ESC, European Society of Cardiology; GP, general practitioner; HF, heart failure; ITT, intention to treat; NT-proBNP, N-terminal-pro brain natriuretic peptide; RCT, randomised controlled trial

^a Test result interpretation based on Danish Health Board Guidance and ESC guidelines (<125 ng/L HF unlikely).

Source: Adapted from Commentary Table 5 from MSAC 1740 ADAR+ in-line commentary

Burri et al. 2012 reported no difference in mortality between the BNP testing strategy and the conventional testing strategy in primary care at 3 or 12 months (Table 7). The number of hospitalisations and the number of days in hospital were similar in both groups at 3 and 12 months (Table 7 and Table 8, respectively).

Table 7 Mortality and hospitalisation with and without BNP testing in primary care (Burri et al, 2012)

Outcomes	Intervention (n=163)	Comparator (n=160)	Absolute difference (95% CI)	Relative risk (95% CI)
Mortality (after 3 months)	4 (2.5%)	3 (1.9%)	6 more deaths per 1000 (13 fewer to 89 more)	RR 1.31 (0.30 to 5.76)
Mortality (after 12 months)	9 (5.5%)	11 (6.9%)	14 fewer deaths per 1000 (45 fewer to 61 more)	RR 0.80 (0.34 to 1.89)
Hospitalisations (3-months)	28 (17.2%)	20 (12.5%)	46 more hospitalisations per 1000 (24 fewer to 168 more)	RR 1.37 (0.81 to 2.34)
Hospitalisations (12-months)	50 (30.7%)	42 (26.3%)	45 more hospitalisations per 1000 (45 fewer to 171 more)	RR 1.17 (0.83 to 1.65)

Abbreviations: CI, confidence interval; n, number of patients; RR, relative risk.

Source: Adapted from Commentary Table 6 from MSAC 1740 ADAR+ in-line commentary

Table 8 Days in hospital with and without BNP testing in primary care (Burri et al, 2012)

Outcomes	Intervention (n=163)	Comparator (n=160)	p-value
Days in hospital (3 months), median (IQR)	12.1 (5–18)	9.5 (4–14)	0.31
Days in hospital (12 months), median (IQR)	14.3 (4–20)	14.9 (4–16)	0.76

Abbreviations: IQR, interquartile range.

Source: Commentary Table 7 from MSAC 1740 ADAR+ in-line commentary

There was no difference between the groups in the number per 1000 of HF patients diagnosed among those referred to echocardiography from intervention GPs with access to NT-proBNP testing compared to control GPs without access (Table 9) (Najbjerg et al, 2019).

Table 9 Patients diagnosed with heart failure from Najbjerg (2019)

Outcome	Intervention (35 GP practices)	Comparator (34 GP practices)	p-value
Patient base, n	75,025	11,3027	-
Patients diagnosed with HF, n	7	16	-
Patients diagnosed with HF per 1,000 patients, x (95% CI)	0.09 (0.02-0.16)	0.14 (0.07-0.21)	0.35

Abbreviations: CI, confidence interval; GP, general practice; HF, heart failure; n, number of patients; x, estimate.

Source: Commentary Table 8 from MSAC 1740 ADAR+ in-line commentary

The commentary concluded that the direct evidence showed no statistically significant difference between BNP/NT-proBNP testing compared to no testing in primary care, although the evidence base was very small, and outcomes were rated as very low certainty using GRADE.

The commentary considered that the search strategy in the ADAR may have failed to detect all relevant studies presenting evidence on direct health outcomes, safety and change of management because the search terms included a filter for diagnostic accuracy studies.

Test accuracy

The ADAR and the commentary differed regarding the inclusion of diagnostic test accuracy studies. The ADAR's inclusion and exclusion criteria were not clearly specified, and studies were included in the ADAR that did not match the PICO criteria. As per MSAC Guidelines, the

commentary included only those diagnostic studies in which a 2-by-2 table (showing the proportion of patients who test positive and negative for the test) could be reconstructed.

The ADAR placed greater weight on studies at, or close to, the rule-out threshold recommended in Australian guidelines of 300 pg/mL. The commentary noted that the guidelines also include rule-in thresholds, and that the proposed MBS item descriptor did not specify a threshold. Furthermore, international guidelines use different rule-out thresholds: 125 pg/mL recommended by the European Society of Cardiology (ESC; McDonagh, 2021¹⁵) and the American College of Cardiology/American Heart Association (ACC/AHA; Heidenreich, 2022¹⁶) or 400 pg/mL by the National Institute for Health and Care Excellence (NICE, 2018¹⁷). Moreover, reference ranges vary depending on age, gender, comorbidities and body mass index. Therefore, the commentary considered that all diagnostic studies in the relevant population should be appraised equally over a range of thresholds given the lack of evidence for the threshold specified in the Australian guidelines and the likelihood that additional patient factors may be considered in practice.

The characteristics of the diagnostic accuracy studies included by the commentary are presented in Table 10. Wright et al. 2003¹⁸ was an RCT; all other studies were non-randomised diagnostic accuracy studies.

¹⁵ McDonagh TA et al. (2021). "2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC." *Eur Heart J*42(36): 3599-3726.

¹⁶ Heidenreich PA, et al. (2022). "2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines." *Circulation* 145(18): e895-e1032.

¹⁷ National Institute for Health and Care Excellence (2018). Chronic heart failure in adults: diagnosis and management.

¹⁸ Wright SP, et al. (2003). "Plasma amino-terminal pro-brain natriuretic peptide and accuracy of heart-failure diagnosis in primary care: A randomized, controlled trial." *J Am Coll Cardiol* 42(10): 1793-1800.

Table 10 Study characteristics of diagnostic accuracy studies providing sensitivity and specificity of NT-proBNP testing compared to the reference standard

Study N	Study design Risk of bias	Population	Intervention NT-proBNP thresholds reported	Reference standard	Used in economic model
Hobbs, 2002 ¹⁹ 607 total 103 with clinical diagnosis	Prospective cohort High risk Applicability concerns regarding the population	Patients (aged >45 years) randomly selected from a primary care population Four population cohorts: <ul style="list-style-type: none"> • >45 years (general population screen) • clinical diagnostic label of HF • prescribed diuretic drugs • at high risk of HF (history of MI, angina, hypertension, or diabetes) 	NT-proBNP immunoassay 305 pg/mL (not pre-specified – based on optimising diagnostic outcomes)	ESC criteria for HF diagnosis (including echocardiography)	No
Wright, 2003 NT-proBNP arm: 153	Randomised single-blind controlled trial Low risk	Patients presenting to a GP with symptoms of dyspnoea and/or oedema of recent onset	Clinical diagnosis plus NT-proBNP No explicit threshold – GP interpretive aid stated < 50 pmol/L (~434 pg/mL) is normal range and >150 pmol/L (~1,271 pg/mL) strongly suggests HF	Clinical diagnosis of HF made by a panel of 4 experts (3 cardiologists and 1 GP) using rigorous application of pre-defined criteria	No
Neilsen, 2004 ²⁰ 363 (18 excluded from analysis [<50 years], 345 analysed)	Cross-sectional diagnostic accuracy High risk	Patients presenting to a GP complaining of dyspnoea of at least 2 weeks duration	NT-proBNP assay Men: <ul style="list-style-type: none"> • 76 pg/mL • 93 pg/mL • 153 pg/mL Women: <ul style="list-style-type: none"> • 68 pg/mL • 144 pg/mL • 220 pg/mL (Thresholds not prespecified – picked from ROC curve)	ESC criteria for HF diagnosis Diagnosis made at a hospital dyspnoea clinic	No
Zaphiriou, 2005 306 (NT-proBNP available in	Cross sectional diagnostic accuracy	Consecutive patients referred by a GP to rapid access HF clinic	NT-proBNP	Cardiologist diagnosis of HF based on ESC criteria (blind to	Yes – for ADAR (pooled analysis)

¹⁹ Hobbs FDR, et al. (2002). "Reliability of N-terminal pro-brain natriuretic peptide assay in diagnosis of heart failure: Cohort study in representative and high risk community populations." *BMJ* 324(7352): 1498-1500.

²⁰ Nielsen LS, et al. (2004). "N-terminal pro-brain natriuretic peptide for discriminating between cardiac and non-cardiac dyspnoea." *Eur J Heart Fail* 6(1): 63-70.

Study N	Study design Risk of bias	Population	Intervention NT-proBNP thresholds reported	Reference standard	Used in economic model
302 participants)	Low risk		<ul style="list-style-type: none"> • 125 pg/mL • 166 pg/mL • 280 pg/mL (NICE) • 400 pg/mL (NICE) 	BNP and NT-proBNP results)	Yes – for commentary analysis
Taylor 2023 ²¹ 155,347 (NT-proBNP)	Diagnostic accuracy Some concerns	Patients aged ≥45 years in the two clinical practice research data link databases with a BNP or NT-proBNP test result in their primary care record between 1 Jan 2004 and 31 Dec 2018	NT-proBNP assay: <ul style="list-style-type: none"> • 125 pg/mL • 400 pg/mL • 2000 pg/mL 	HF diagnosis within 6 months of most recent NT-proBNP test, obtained from diagnostic code in CPRD database or HES Admitted Patient Care data based on hospital admission because of HF or echocardiography findings consistent with HF	No
Verdu 2012 (point-of-care) 220	Cross sectional diagnostic accuracy Low risk	Consecutive patients in whom echocardiography was requested by a primary care physician to investigate suspected HF, regardless of comorbidities or current medical treatment	NT-proBNP assay <ul style="list-style-type: none"> • 125 pg/mL • 280 pg/mL • 400 pg/mL 	ESC criteria for HF (single cardiologist)	Yes – for ADAR (pooled analysis)
Taylor 2017 (point-of-care) 304	Cross sectional diagnostic accuracy Low risk	Primary care patients aged >55 years presenting with recent new onset shortness of breath, lethargy or peripheral ankle oedema of >48 hours duration for which there was no other obvious cause	NT-proBNP assay <ul style="list-style-type: none"> • 125 pg/mL • 280 pg/mL (NICE) • 400 pg/mL 	ESC criteria for HF by an expert consensus panel of 3 cardiology specialists (blinded to assessments by other panel members)	Yes – for ADAR (pooled analysis)

Abbreviations: ADAR, Applicant Developed Assessment Report; BNP, B-type natriuretic peptide; CPRD, Clinical Practice Research Datalink; ESC, European Society of Cardiology; GP, general practitioner; HES, Hospital Episodes Statistics; HF, heart failure; MI, myocardial infarction; N, number of patients; NICE, National Institute for Health and Care Excellence; NR, not reported; NT-proBNP, N-terminal-pro brain natriuretic peptide; ROC, receiver operating curve.

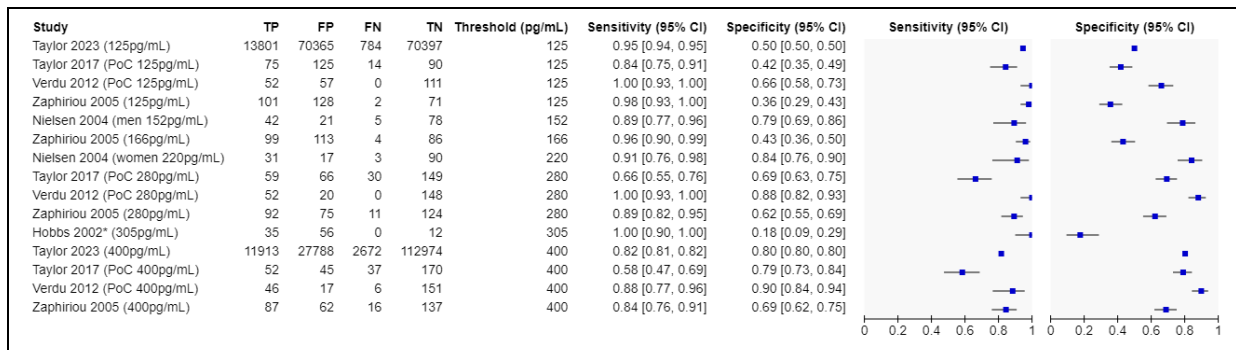
Note: Thresholds obtained from the NICE Guidelines rather than the primary study are noted.

Source: Adapted from Commentary Table 9 from MSAC 1740 ADAR+ in-line commentary

²¹ Taylor CJ, et al. (2023). "Natriuretic peptide testing and heart failure diagnosis in primary care: diagnostic accuracy study." *Br J Gen Pract* 73(726): E1-E8.

A summary of the diagnostic accuracy data is presented in Figure 1. Across a range of thresholds, NT-proBNP (laboratory and point-of-care) demonstrated a high sensitivity (range 0.58 to 1.0). This evidence was rated of moderate certainty using GRADE by both the ADAR and the commentary despite including different studies. For specificity, the ADAR and commentary rated the outcome as low certainty due to the heterogeneity in point estimates (range 0.18 to 0.90) and associated confidence intervals. However, a high sensitivity is appropriate for a triage test, ensuring a low rate of false negatives (missed HF diagnoses).

Figure 1 Results of NT-proBNP diagnostic accuracy studies at thresholds from 125 to 400 pg/mL



Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; NT-proBNP, N-terminal-pro brain natriuretic peptide; PoC, point-of-care; TN, true negative; TP, true positive.

* Data were presented from the group of patients with an existing clinical diagnosis of HF in Hobbs (2002)

Source: Commentary Figure 7 from MSAC 1740 ADAR+ in-line commentary

Wright et al (2003) is an RCT that provided key diagnostic accuracy and change in management evidence in MSAC assessment 1087 (May 2007). The study presented diagnostic outcomes for the intervention arm, and also included diagnostic concordance between the intervention and comparator. Correct diagnosis by the GP with and without NT-proBNP results was the primary outcome. Correct diagnoses increased by 21% at the follow-up visit with NT-proBNP testing and by 8% without. The between group difference of 13% was statistically significant (95% CI 5.5 to 21.0%, p=0.002). The authors noted the main impact of the intervention was allowing GPs to accurately rule out a diagnosis of HF.

Diagnostic accuracy from the intervention arm of Wright et al (2003) was reported in MSAC application 1087 (May 2007). NT-proBNP plus customary clinical assessment correctly ruled out 44.1% of patients and incorrectly ruled out 2.6% (false negatives). The sensitivity was 90.7% and the specificity 61.5%. Note that these outcomes were not reported at a specific NT-proBNP threshold but based on the GP's diagnosis compared to that of the reference standard (clinical diagnosis of HF made by a panel of 4 clinical experts according to pre-defined criteria).

It is notable that the sources of key evidence on diagnostic accuracy (Wright et al, 2003; Hobbs et al, 2002; Zaphiriou et al, 2005), particularly at the proposed threshold, has not changed since MSAC application 1087 (May 2007). Based on the evidence presented for diagnostic accuracy under application 1087, MSAC was satisfied that BNP/NT-proBNP testing was comparatively effective (diagnostically accurate).

As international guidelines use alternate NT-proBNP thresholds to the Australian guidelines, diagnostic accuracy outcomes in more recent studies are more commonly reported with the NT-proBNP threshold designated as 125 pg/mL (ESC threshold) or 400 pg/mL (NICE threshold). No studies used the NHFA/CSANZ threshold of 300 pg/mL.

Change in management

The two RCTs that reported health outcomes (Table 6) also reported change of management outcomes. Both studies reported echocardiograms received; however, due to differences in the study designs, the outcomes cannot be combined (Table 11). No statistical difference in echocardiograms received was found between patients who did and did not receive BNP testing in Burri et al (2012). In Najbjerg et al (2019), significantly more patients in the intervention group, where NT-proBNP testing was available, were referred to echocardiography, although the difference was unlikely to be clinically significant. The commentary concluded that overall, these studies did not show a reduction in echocardiography when BNP or NT-proBNP testing was used in primary care to diagnose HF in patients with suspected but uncertain HF.

Table 11 Number of echocardiograms with and without BNP/NT-proBNP testing in primary care (Burri et al, 2012; Najbjerg et al, 2019)

Outcome	Intervention n/N (%)	Comparator n/N (%)	Risk difference (95% CI)	Relative risk (95% CI)	Certainty
Echocardiograms received (3 months follow-up) Burri, 2012	18/163 (11)	12/160 (7.5)	35 more echocardiograms per 1,000 (from 20 fewer to 147 more)	1.47 (0.73 to 2.96)	Very low
Echocardiogram referrals (follow up not specified) Najbjerg, 2019	131/113,027 (0.12)	53/75,025 (0.07)	2 more echocardiograms per 10,000 (from 1 more to 9 more)	1.34 (1.19 to 2.26)	Moderate

Abbreviations: CI, confidence interval; n = number of participants who received an echocardiogram; N = total number of participants in the intervention or comparator arm

Source: Commentary Table 14 and Commentary Table 23 from MSAC 1740 ADAR+ in-line commentary

A significant decrease in time to initiate appropriate treatment and the need for further diagnostic work up was reported in Burri et al (2012) (Table 12). Appropriate treatment was initiated on the day of initial presentation in 98 patients (66%) in the BNP group. As a point-of-care test was used, however, this is not likely to reflect the anticipated time to appropriate therapy for a laboratory-based test as assessed in the ADAR. The authors note the benefit in reduced diagnostic workup and time to appropriate treatment seemed to be mainly in avoiding long treatment delays as both the intervention and control groups had similar median values, but large differences in the 75th percentile values.

Table 12 Change in management outcomes with and without BNP testing in primary care (Burri, 2012)

Outcomes	Intervention (n=163)	Comparator (n=160)	p-value	Certainty
Time to appropriate therapy (days)	Mean 12.8 (95% CI 8.0, 17.6) Median 0.04 (IQR 0.04, 8)	Mean 24.7 (95% CI 18.3, 31.1) Median 0.04 (IQR 0.04, 34)	0.01 ^a	Very low
Need for further diagnostic work up	33%	45%	0.02	Not assessed

Abbreviations: CI, confidence interval; IQR, interquartile range; n, number.

^a It is suspected that reporting of the p-value with the median and IQR is an error in the table in the Burri 2012 publication, and the p-value should be reported with the mean. Text in the publication indicates that this is the case.

Source: Table 23 (including commentary additions) and Commentary Table 23 from MSAC 1740 ADAR+ in-line commentary

Based on Wright et al. (2003), MSAC application 1087 concluded that there was a clinically important improvement in the proportion of correct diagnoses of HF with the addition of NT-proBNP testing. The main impact occurred by enabling GPs to correctly 'rule out' HF, with use of the test unlikely to lead to earlier identification of HF but more likely to lead to earlier

identification of alternative diagnoses. The commentary considered the additional evidence presented aligned with this conclusion but did not support a reduced rate of echocardiography referral as claimed in the ADAR.

Clinical claim

PICO Set 1

The ADAR stated that the use of NT-proBNP testing \pm echocardiography in primary care (GPs) for the diagnosis of HF resulted in at least **non-inferior** effectiveness and **non-inferior** safety compared with echocardiography alone.

The commentary considered that the use of NT-proBNP testing as part of the initial clinical assessment compared to clinical assessment without NT-proBNP testing for the diagnosis of HF resulted in **superior** test accuracy and **non-inferior** safety.

The commentary considered that the use of NT-proBNP testing as part of the initial clinical assessment compared to clinical assessment alone to triage patients to echocardiography may not result in superior health outcomes, but there was significant uncertainty regarding the use and value of the test when implemented in primary care.

PICO Set 2

The ADAR stated that the use of NT-proBNP testing \pm echocardiography by specialist physicians (cardiologists) for the diagnosis of HF results in at least **non-inferior** effectiveness and **non-inferior** safety compared with echocardiography alone.

The clinical claim requested by PASC was for NT-proBNP + echocardiogram compared to echocardiogram alone. No evidence was presented to assess this clinical claim in the specialist setting. Instead, the ADAR relied on the transferability of the primary care findings, but the commentary considered insufficient evidence was provided to support this.

13. Economic evaluation

A cost-effectiveness analysis was conducted to assess the economic implications of NT-proBNP \pm echocardiography compared to echocardiography alone, for people with a suspected but uncertain diagnosis of HF in the non-hospital setting.

The structure of the model is summarised in Table 13. A decision tree was developed, and the model compared the costs and outcomes of two pathways.

PASC requested a cost-utility analysis or a cost-effectiveness analysis for both PICO sets, based on the clinical claims of superior effectiveness and non-inferior safety. The ADAR considered there was insufficient evidence to present a cost-utility analysis and described the cost-utility analysis undertaken by NICE (2018) as 'overly complex.' The NICE model had a slightly different focus, in trying to find the threshold cut-off with the highest net monetary benefit, while ensuring cost-utility (in terms of incremental cost per quality-adjusted life year [QALY] gained) compared to a strategy in which everyone suspected of HF received an echocardiogram. However, the commentary considered it informative. The model presented in the ADAR was very simple and the commentary did not consider it sufficient for the assessment, nor did it align with the advice of PASC. In particular, the model did not incorporate different referral propensities for NT-proBNP testing compared to echocardiography (i.e. a weighted comparator) and instead assumed perfect

alignment with their interpretation of clinical practice guidelines (i.e., to triage patients for echocardiography).

A separate economic analysis of PICO set 2 was not undertaken.

Table 13 Summary of the economic evaluation

Component	Description
Perspective	Australian healthcare system perspective
Population	Patients who have a suspected but uncertain diagnosis of HF in the non-hospital setting (primary care or cardiologists) Nb. No separate analysis was undertaken for PICO set 2 (specialist requestor setting) in which PASC requested NT-proBNP be considered an additional test to echocardiography
Prior testing	Cardiorespiratory physical examination and assessment (MBS item 110) Blood chemistry (electrolytes, urea/creatinine, glucose) assessment (MBS item 66509) Thyroid function tests (MBS item 66719) Full blood count (MBS item 65070) Electrocardiogram (ECG) (MBS item 11704) and chest X-ray (MBS item 58500)
Intervention	NT-proBNP ± echocardiography
Comparator	Echocardiography (MBS item 55126) NB: PASC requested that if echocardiography was regarded as part of the intervention and comparator rather than subsequent, that this be weighted such that a portion of patients received echocardiography and a portion receive clinical assessment only
Type of analysis	Cost-effectiveness analysis
Outcomes	Total cost Echocardiograms delivered Correct initial diagnosis (of HF only) Correct final diagnosis (of HF only) Time to correct final diagnosis (of HF only) Incremental cost per echocardiogram delivered Incremental cost per time to correct final diagnosis (of HF only)
Time horizon	Only immediate implications of testing were considered
Computational method	Expected value decision tree analysis
Generation of the base case	Trial-based
Health states	N/A
Cycle length	N/A
Transition probabilities	Test accuracy
Discount rate	N/A
Software	Excel

Abbreviations: HF, heart failure; MBS, Medicare Benefits Schedule; N/A, not applicable; Nb, note; NT-proBNP, N-terminal-pro brain natriuretic peptide; PASC, PICO Advisory Sub-Committee; PICO, population, intervention, comparator, outcome.

Source: Table 26 from MSAC 1740 ADAR+ in-line commentary

The key inputs were the prevalence of HF, test accuracy, time to diagnosis, and healthcare resource costs.

The test accuracy used in the ADAR's base case was derived from a meta-analysis (NICE, 2018) that NICE did not use for its own economic evaluation due to heterogeneity. Two of the three

studies in the meta-analysis were point-of-care studies that the ADAR excluded from the clinical evaluation.

The model assumed that all patients with suspected but uncertain HF currently undergo echocardiography. However, PASC advised in the PICO Confirmation that the ADAR would need to assess the uptake of echocardiography in both the intervention and comparator arms, informed by real world evidence if possible. This assessment was not undertaken and the assumption that, in the absence of NT-proBNP testing, all patients suspected of HF are referred to echocardiography was considered unlikely to occur in practice by the commentary.

The model assumed all patients with an NT-proBNP result above the rule-out threshold would receive an echocardiogram and all those below the rule-out threshold would avoid one, with the exception of patients with suspect false negative test results. No evidence was provided in the ADAR to support this assumption and therefore the commentary considered this was uncertain.

It was assumed that patients with a false negative test result would require an additional GP visit after one month and then an additional two-month wait for an echocardiogram. The commentary considered this was uncertain, and that the six-month delay used by NICE (2018) was more appropriate.

The ADAR's base case results are presented in Table 14. NT-proBNP saved \$68 per patient, led to faster HF diagnosis or exclusion by 0.93 months, and resulted in 0.53 fewer echocardiograms per patient. This was based on the assumptions noted above, most notably that all patients in whom HF is suspected but uncertain were, in the absence of NT-proBNP testing, referred to echocardiogram and, with the addition of NT-proBNP testing, there was complete alignment with the proposed triage pathway based on the NT-proBNP result. The diagnoses in the model related to HF only (HF or exclusion of HF), and so whether there was a more rapid diagnosis for those in whom HF is excluded was not modelled. Under application 1087, MSAC considered that effectiveness arose primarily from ruling out HF and assisting in earlier identification of an alternative diagnosis in these patients. Cost reductions and QALY benefits in the NICE model were driven by diagnosing conditions other than HF earlier.

Table 14 Results of the ADAR base case economic evaluation (per patient)

Parameter	NT-proBNP ± echocardiography	Echocardiography alone	Increment
Costs	\$172.05	\$240.05	-\$68.00
Time to diagnosis or exclusion of HF (months)	1.07	2.00	-0.93
Echocardiography delivered	0.47	1.00	-0.53

Abbreviations: HF, heart failure; NT-proBNP, N-terminal-pro brain natriuretic peptide.

Source: Table 32 and Table 33 from MSAC 1740 ADAR+ in-line commentary

The commentary considered several of the inputs in the model to be inappropriate and provided a revised model using:

- sensitivity and specificity from Zaphiriou et al (2005) rather than from the NICE 2018 meta-analysis – this study was dated and may not have reflected current practice but was deemed a more suitable base case
- current MBS fees (at 01 July 2023)
- an additional follow-up appointment after both a NT-proBNP test and echocardiogram (follow up appointments and screening for those ruled out of HF were not considered in the model)

- extended time to diagnosis to 0.5 month (from 0.1) for NT-proBNP testing and six months for a false negative NT-proBNP result (from one month).

The commentary's revised economic analysis showed smaller differences between the intervention and comparator, particularly for time to diagnosis (Table 15). It did not, however, overcome the structural weaknesses of the ADAR's model or alter its underlying assumptions.

Table 15 Results of the commentary revised base case economic evaluation (per patient)

Parameter	NT-proBNP ± echocardiography	Echocardiography alone	Increment
Costs	\$264.58	\$289.90	-\$25.32
Time to diagnosis or exclusion of HF (months)	1.81	2.00	-0.19
Echocardiography delivered	0.56	1.00	-0.44

Abbreviations: HF, heart failure; NT-proBNP, N-terminal-pro brain natriuretic peptide.

Source: Adapted from commentary Table 18 from MSAC 1740 ADAR+ in-line commentary

Key drivers of the results are summarised in Table 16.

Table 16 Key drivers of the model

Description	Method/Value	Impact
Uptake rate of echocardiography	Model assumes 100% in comparator (patients with suspected but uncertain HF) and 100% in intervention test positive population and 0% in intervention test true negative population (i.e. perfect adherence to test results/clinical practice guidelines).	High Favours NT-proBNP
Wait times for echocardiogram and for test results (NT-proBNP and echocardiogram)	Values in model are assumptions Model did not include wait times for echocardiography results	Moderate Shorter wait times for NT-proBNP test results favour NT-proBNP
Wait time for re-presentation following false negative NT-proBNP test	Value in model based on assumption	Moderate Shorter wait times for re-presentation favour NT-proBNP
Test specificity	Varies across primary studies Pooled data from NICE (2018) used	High Higher specificity favours NT-proBNP

Abbreviations: HF, heart failure; NICE, National Institute for Health and Care Excellence; NT-proBNP, N-terminal-pro brain natriuretic peptide.

Source: Derived from Section 3.2 of MSAC 1740 ADAR+ in-line commentary

The ADAR's sensitivity analyses reported that NT-proBNP ± echocardiography was highly cost effective, and dominant, in all plausible scenarios. The sensitivity analyses undertaken by the commentary, using the revised base case, did not replicate this finding and is reported here.

As there was no diagnostic accuracy study at low risk of bias that aligned with the PICO criteria, a sensitivity analysis was undertaken using data from the most applicable studies. This included the three studies that were pooled in the NICE analysis (Zaphiriou et al, 2005; Verdu et al, 2012; Taylor et al, 2017) and the patients with diagnosed but not confirmed HF from Hobbs et al (2002). Additionally, Taylor et al (2023) was included at a NT-proBNP threshold of 125 pg/mL

due to having a mid-range specificity. The analysis aligned with the findings of NICE (2018) that outcomes were most sensitive to test specificity. Although there was generally a high sensitivity of the test across the diagnostic studies, specificity varied and at low specificities the test was no longer cost saving, even in a model in which perfect guideline adherence was assumed (Table 17).

Table 17 Commentary sensitivity analysis

Scenario	Incremental cost	Incremental number of correct HF diagnoses	Incremental echocardiograms	Incremental time to correct diagnosis of HF (months)
ADAR base case	-\$68.00	Equal	-0.53	-0.93
Commentary revised base case	-\$25.32	Equal	-0.44	-0.19
Diagnostic accuracy (ADAR base case, NICE (2018) pooled analysis 280 ng/mL, Sens 89/ Spec 75) Zaphiriou (2005) (280 pg/mL) (Commentary base case) Sens 89/ Spec 62	-\$25.32	Equal	-0.44	-0.19
Verdu (2012) (280 pg/mL) Sens 100/ Spec 88	-\$81.35	Equal	-0.62	-0.75
Taylor (2017) (280pg/mL) Sens 66/ Spec 69	-\$34.40	Equal	-0.49	0.11
Taylor (2023) (125 pg/mL) Sens 81/ Spec 50	\$1.22	Equal	-0.35	0.12
Hobbs (2002) (305 pg/mL) Diagnosed but not confirmed HF Sens 100/ Spec 18	\$62.67	Equal	-0.13	0.24
Rate of echo referral (base case) 100%	-\$25.32	Equal (100%)	-0.44	-0.19
90%	-\$12.56	0.07	-0.40	-0.10
80%	\$0.20	0.14	-0.35	-0.01
70%	\$12.95	0.21	-0.31	0.08
60%	\$25.71	0.28	-0.26	0.16
50%	\$38.46	0.35	-0.22	0.25

Abbreviations: ADAR, Applicant Developed Assessment Report; echo, echocardiography; HF, heart failure; NICE, National Institute for Health and Care Excellence; sens, sensitivity; spec, specificity.

Source: Commentary Table 19 and Commentary Table 20 from MSAC 1740 ADAR+ in-line commentary

A significant uncertainty in the model, and the clinical evidence, was the extent to which guideline recommendations are currently followed in clinical practice. The PICO included PASC’s consideration that “in clinical practice, guidelines are a reference tool and are deviated from for a plethora of reasons” and stated that “it would not be appropriate for the assessment to assume strict alignment with guideline practices in place of evidence-based estimates”.

The ADAR undertook a sensitivity analysis in which 50% of patients were referred to echocardiography. This was extended based on the commentary’s preferred inputs (Table 17). This analysis assumed that the same rate of referral to echocardiography applied at all points in

the model (i.e., all patients in the echocardiography arm, and all positive and false negative NT-proBNP tests in the NT-proBNP arm). Although this was a simplified analysis, it demonstrated that at lower rates of referral to echocardiography in both the intervention and comparator arm, there were more correct diagnoses of HF with NT-proBNP ± echocardiography than echocardiography alone but there were also higher costs.

The model presented in the ADAR assumed that GPs currently refer all patients with suspected but uncertain HF for echocardiography. MSAC application 1087 cited studies demonstrating this rate could range from 3.8 per cent (BEACH data, AIHW 2001²²) to 17.7 per cent (CASE study, Krum 2001) for patients with new symptoms suggestive of HF. Furthermore, two included clinical studies demonstrated no reductions in echocardiography referral with the use of NT-proBNP/BNP testing (Table 11). The MSAC application 1087 public summary document stated that NT-proBNP testing may not be cost saving if GPs refer to echocardiography at a rate of 60% or lower; the sensitivity analysis using the commentary revised base case found this threshold to be 80% or lower.

PASC also commented that it would appear reasonable for the ADAR to use a weighted analysis such that, of the initial eligible population, a portion of patients receive echocardiography and a portion receive clinical assessment only. PASC advised the echocardiography uptake rates in intervention and comparator arms should be informed by real world evidence if possible. The model presented was overly simple and not aligned with PASC's request.

The commentary considered the ADAR did not present an appropriate economic analysis of PICO set 2, the use of NT-proBNP testing in specialist requestor settings.

14. Financial/budgetary impacts

An epidemiological approach was adopted to inform the utilisation and financial estimates.

The financial implications to the MBS resulting from the proposed listing of NT-proBNP in primary care, as presented in the ADAR, are summarised in Table 18. The commentary considered that the use of NT-proBNP in practice would be unlikely to reflect the idealised scenario that was modelled in the ADAR. Furthermore, the modelling of NT-proBNP as a triage test in specialist setting (not shown) did not align with the PICO as advised by PASC.

²² AIHW (2001). A general practice view of cardiovascular disease and diabetes in Australia. AIHW cat. No. CVD 17 (Cardiovascular Disease Series No. 18), Canberra, AIHW.

Table 18 ADAR net financial implications to the MBS of NT-proBNP testing in primary care#

Parameter	Year 2024	Year 2025	Year 2026	Year 2027	Year 2028	Year 2029
Estimated use and cost of the proposed health technology						
Number of people eligible for NT-proBNP in primary care	103,411	105,018	106,605	108,150	109,701	111,228
Number of people who receive NT-proBNP in primary care	51,706	78,763	90,614	91,928	93,246	94,544
Cost to the MBS	\$2,571,057	\$3,916,500	\$4,505,801	\$4,571,098	\$4,636,640	\$4,701,210
Change in use and cost of other health technologies						
Change in use of echocardiography	-27,522	-41,924	-48,232	-48,931	-49,633	-50,324
Change in use of GP visits	1,651	2,515	2,894	2,935	2,978	3,019
Net change in costs to the MBS	-\$5,549,976	-\$8,454,299	-\$9,726,385	-\$9,867,338	-\$10,008,818	-\$10,148,203
Net financial impact to the MBS	-\$2,978,919	-\$4,537,799	-\$5,220,584	-\$5,296,240	-\$5,372,179	-\$5,446,992

Abbreviations: ADAR, Applicant Developed Assessment Report; GP, general practitioner; MBS, Medicare Benefits Schedule; NT-proBNP, N-terminal-pro brain natriuretic peptide.

Source: Table 50 from MSAC 1740 ADAR+ in-line commentary

Note that these costings are only for the patient population initially presenting to the primary care setting, which applies only to proposed MBS item AAAA. The ADAR did not provide a clinical evaluation or economic analysis of the population seen by the specialist care setting, which relates to proposed MBS item BBBB. Therefore, the commentary has not included the financial analysis for item BBBB in this section.

The commentary provided an updated analysis using sensitivity and specificity from Zaphiriou et al (2005), updated MBS fees, including an additional GP visit to receive NT-proBNP test results, an additional GP visit to receive echocardiography results and assuming all patients were treated in primary care. In this revised analysis, net cost savings to the MBS were smaller, increasing from \$2,050,786 in 2024 to \$3,749,889 in 2029. The reduced net cost savings were driven by the assumption of a second GP visit to receive NT-proBNP test results and plan follow-up (echocardiography or alternative tests or referrals). Follow-up tests for HF negative patients were not included in the analysis and may negate some savings.

Although the financial analysis demonstrated a theoretical net cost-saving to the MBS due to reduced use of echocardiography, the commentary considered that actual savings were highly uncertain due to uncertain referral patterns, low adherence to guidelines (Sindone et al, 2021; Hayhoe et al, 2018, and clinical evidence that showed no change in service use (Table 11). This was the same conclusion as for the economic analysis.

GP consultations and echocardiography can both incur out-of-pocket costs to patients. The average out-of-pocket cost for echocardiography was \$102 in 2014 (ACSQH, 2018). If out-of-pocket costs were driven by echocardiography referral, then the overall impact on out-of-pocket costs will depend on the frequency of echocardiography referral.

The impact on other health budgets was uncertain. The SHAPE study of the management of HF in Australian primary care reported limited use of guideline recommended therapies for HF and frequent use of medications that may worsen HF (Sindone et al, 2021). It was therefore unclear,

on its own, whether the implementation of NT-proBNP would have a significant impact on the Pharmaceutical Benefits Scheme (PBS) budget.

Two studies were identified by the commentary that report NT-proBNP uptake rates in primary care in the Netherlands (Valk et al, 2020²³) and the UK (Roalfe et al, 2022²⁴). In the Netherlands, there were 2.5 requests per 1000 person years (PY) in 2005, increasing to 15.6 requests per 1000 PY in 2009 after which the rate stabilised. The study period ended in 2013 with 14.0 requests per 1000 PY. In the UK, there were 0.24 requests per 1000 PY in 2004, which increased each year to 16.88 requests per 1000 PY in 2018. Both studies concluded that NT-proBNP testing was underutilised in primary care. These studies may provide an alternative estimate of potential utilisation, and uptake, of NT-proBNP testing in primary care in Australia. The underutilisation of NT-proBNP testing in primary care overseas may also take place in Australia, given actual NT-proBNP testing in the emergency department was found in 2017 to be used less than had been estimated in the assessment.

The commentary considered that the financial/budgetary impact of PICO set 2 was not appropriately addressed.

15. Other relevant information

Considerations raised in the Ratified PICO Confirmation and the ADAR, but that were not explored in the ADAR included:

- equity of access to existing diagnostic services for HF and the proposed NT-proBNP test (e.g., rural and remote populations)
- HF in Aboriginal and/or Torres Strait Islander people
- geographic and socioeconomic considerations.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

- The commentary identified point-of-care (POC) measurement of BNP studies that were not presented in the ADAR. However, it would be more appropriate to not add these studies to the evidence base, as this application proposed laboratory-based testing only.
- Specificity results from early studies may be unreliable, as they likely under-appreciated the potential for heart failure with preserved left ventricular ejection fraction. In addition, up to 30% of heart failure with preserved ejection fraction patients have BNP levels below the diagnostic threshold due to a lack of BNP release.
- The ADAR mainly considered BNP testing as a triage test for referral for echocardiography, which ESC considered was more appropriate than the separation into triage testing in primary care versus additional testing in specialist care as recommended in the PICO.

²³ Valk M, et al. (2020). Time trends in the use and appropriateness of natriuretic peptide testing in primary care: an observational study. *B J GP open*, 4(4).

²⁴ Roalfe AK, et al. (2021). Long term trends in natriuretic peptide testing for heart failure in UK primary care: a cohort study. *Eur Heart J*, 43(9), 881–891.

- The clinical claim that the use of NT-proBNP testing ± echocardiography by specialist physicians for the diagnosis of heart failure resulted in at least non-inferior effectiveness and safety compared with echocardiography alone was reasonably justified.
- It is not practical to restrict the test to the primary care setting (GPs/nurse practitioners) or non-GP medical specialists only. The test would likely be mainly used in primary care as a filter for referral to echocardiography and/or cardiology review.
- The service should include BNP testing in addition to NT-proBNP testing, to be consistent with MSAC's advice on biomarkers under application 1689.1.

Economic issues:

- The economic model used a decision tree and a simple structure with minimal assumptions. MSAC should consider whether this is sufficient for decision-making, or whether it is necessary to include a more complex model that requires assumptions that link testing outcomes to downstream consequences (albeit introducing uncertainty and weak or absent data on patient outcomes).
- No evidence was provided to support the assumption in the economic model that 100% of patients in the comparator arm would receive echocardiography. Previously, MSAC did not support similar application 1087 primarily due to uncertain cost-effectiveness from the assumption of 100% echocardiography uptake in the comparator arm. MSAC considered the assumption of 100% uptake, while in line with clinical practice guideline recommendations, was unrealistic given real-world evidence suggested uptake was only 3.8-17.7%.
- The applicant departed from the PICO by performing a CEA rather than a CUA, arguing that the need for assumptions and a lack of data to support a full CUA precluded such an analysis. The CUA performed by NICE found that NT-proBNP testing for the diagnosis of heart failure was cost-effective, supporting the simpler model used in the application.

Financial issues:

- There were uncertain estimates in the financials, including the prevalence of heart failure, the use of echocardiography regardless of NT-proBNP test outcomes, and the use of NT-proBNP where echocardiography is not normally used. In the commentary's revised estimates, most scenarios remained cost saving.

ESC discussion

ESC noted that this application from Roche Diagnostics Australia Pty Ltd. requested Medicare Benefits Schedule (MBS) funding of N-terminal (NT)-pro hormone brain natriuretic peptide (NT-proBNP) assays for the diagnosis of heart failure in patients where the diagnosis is suspected but uncertain.

ESC noted heart failure is a syndrome with non-specific symptoms, including dyspnoea.

ESC noted that there have been two previous MSAC applications for B-type natriuretic peptide (BNP) and NT-proBNP testing for the diagnosis of heart failure. At its November 2006 meeting, MSAC considered [application 1087](#) for funding of BNP assays (i.e. including both BNP and NT-proBNP) in the diagnosis of heart failure and supported its use in the hospital emergency setting only (Part A of MSAC application 1087 implemented as MBS item 66830). At its May 2007 meeting, MSAC considered an application for the use of the assay in the non-hospital setting (Part B of MSAC application 1087), but did not support it primarily due to uncertainty over the cost-effectiveness, arising mainly from the overestimation of the echocardiography referral rate in the comparator.

ESC noted that the application form had proposed one MBS item only and this should be restricted to cardiologists, yet had also described the setting as primary care. PASC had noted that cardiologists are not considered primary care physicians in Australia, and had considered

the main value of the test would likely be in the primary care setting, because in the cardiology setting the test would more likely be requested in addition to (rather than triaging access to) echocardiography. PASC had therefore recommended the requesting populations to be split to allow MSAC to consider the value in each setting separately. Therefore the PICO contained two separate PICO sets and item descriptors: one for the primary care setting in which NT-proBNP testing was proposed to triage access to echocardiography (MBS item AAAA) and another for the specialist and consultant physician setting in which NT-proBNP testing was proposed to be used in addition to echocardiography (MBS item BBBB). ESC agreed that the main use for the test would likely be allowing GPs to discriminate between a diagnosis of heart failure versus other conditions with similar presentations. However, ESC considered that it was impractical to restrict the test to primary care requestors only. ESC noted that GPs are considered specialists by the Australian Health Practitioner Regulation Agency (AHPRA), however there is currently no provision in the Pathology Services Table of the MBS for tests to be restricted to requestors in the primary care setting only. ESC considered it would be more appropriate to have one MBS item descriptor not referring to specific requestors. ESC noted the policy proposal to replace the requestor with the intent that NT-proBNP testing be done in situations where it may triage to referral for echocardiography, and considered this was reasonable (new item CCCC, Table 19, to replace PICO items AAAA and BBBB).

ESC considered the frequency restriction of maximum once in a 12-month period was reasonable.

ESC noted that for [MSAC application 1689.1](#), MSAC had in July 2023 supported including both BNP and NT-proBNP biomarkers in testing for patients with previously diagnosed pulmonary arterial hypertension. ESC considered that it would be similarly appropriate to include BNP as well as NT-proBNP in the MSAC application 1740 intervention.

ESC considered the proposed schedule fee of \$58.50 to be appropriate as it aligned with MBS items 66830 and 66585 for quantitation of BNP or NT-proBNP.

Table 19 ESC's revised and combined item descriptor

Category 6 – Pathology services Group P2 Chemical
MBS item CCCC Quantitation of BNP or NT-proBNP for the exclusion of a diagnosis of heart failure in patients presenting to a non-hospital setting to assist in decision-making regarding the clinical necessity of an echocardiogram, where heart failure is suspected based on signs and symptoms but diagnosis is uncertain.
Applicable not more than once in a 12-month period
Fee: \$58.50 Benefit: 75% = \$43.90 85% = \$49.75
New practice note PN.XX: BNP or NT-proBNP testing under MBS item CCCC is intended to assist treating medical practitioners in making a decision regarding the clinical necessity of an echocardiogram. Where a patient presents with symptoms of suspected heart failure, a BNP or NT-proBNP test under MBS item CCCC can be requested by the treating medical practitioner where clinically appropriate.

Source: ESC

ESC also noted that in response to the applicant's comments on the PICO, PASC had advised some changes to the PICO after the applicant-developed assessment report (ADAR) had been lodged.

ESC noted that the National Heart Foundation of Australia (NHFA) and Cardiac Society of Australia and New Zealand (CSANZ) guidelines for the prevention, detection and management of

heart failure in Australia 2018 (Atherton et al. 2018) strongly recommend BNP or NT-proBNP testing in primary care for patients with suspected heart failure when the diagnosis is uncertain. ESC noted that the clinical management algorithm for PICO set 1 (primary care setting) reflected the NHFA/CSANZ guidelines that BNP and NT-proBNP are best used as an additional test to echocardiography, to improve diagnostic accuracy, rather than as a triage test prior to echocardiography. ESC noted that the NHFA/CSANZ guidelines include a rule-out threshold of 300 pg/mL (when the test is used before echocardiography) and additional age-based rule-in thresholds are provided. ESC noted variable rule-out thresholds for NT-proBNP tests are used in different international guidelines (ranging from 125 pg/mL to 400 pg/mL), and considered this somewhat reduced the applicability of the evidence. ESC noted that at the proposed lower NT-proBNP threshold of 300 pg/mL, the advantages of the test - as a triage to echocardiography - were to reduce overdiagnosis with reasonable specificity, and to reduce underdiagnosis with a reasonably high sensitivity.

ESC noted that in the NHFA/CSANZ guidelines the BNP or NT-proBNP test was not positioned purely as a triage test, but as an option alongside direct referral to echocardiography or used in addition to echocardiography. ESC noted that BNP and NT-proBNP testing are widely recommended to assist with the diagnosis of heart failure in ambulatory settings in clinical practice guidelines, both in Australia and internationally, with many countries now requiring BNP or NT-proBNP to be a part of the investigational work-up for a heart failure diagnosis.

ESC noted that the comparator for the PICO set 1 (triage testing in the primary care setting) was no NT-proBNP testing, while the comparator for the PICO set 2 (additional testing in the specialist setting) was echocardiography.

ESC noted that no evidence was presented in the ADAR for PICO set 2, regarding NT-proBNP as an additional test to echocardiography in the specialist setting. ESC considered that clinical evidence that could have supported the use of the test in this setting and pathway included prognostic studies and diagnostic studies that specifically address the role of NT-proBNP in heart failure with preserved ejection fraction (the most common presentation), but these were not presented in the ADAR. ESC noted the pre-ESC response stated the ADAR had focused on the use of NT-proBNP as a triage test, based on the availability of clinical evidence and circumstances of use proposed by the applicant prior to PASC consideration. ESC agreed with the applicant's comment in the pre-ESC response that the use of the test by cardiologists is expected to be in accordance with the CSANZ diagnostic algorithm (where NT-proBNP testing is positioned for use as an option in addition to echocardiography) and expert clinical judgement.

The clinical data presented consisted of 11 studies for accuracy and test performance (including one cohort study and a cross-sectional exploratory study using an NT-proBNP threshold of 300 pg/mL or within ± 25 pg/mL), which were considered to have a low risk of bias, and one randomised controlled trial (RCT) for change in patient management, which had a higher risk of bias. ESC considered the studies included a range of settings and indications, and had not been sufficiently focussed. ESC noted that the commentary added several more studies for POC testing, however considered that in its experience POC results did not correlate well with the laboratory-based results, and also that testing must be laboratory-based to be MBS-funded, therefore ESC did not consider the POC studies to be relevant. The commentary also provided a brief summary of a recent systematic review and meta-analysis for prognostic evidence, one RCT for change in patient management and two RCTs for health outcomes, but these were either not very informative or had some risk of bias. ESC noted that there was no evidence provided for predictive effect.

ESC noted that the ADAR did not address the comparative safety of the test. ESC considered that although the test is a standard venepuncture blood test that is unlikely to cause direct harm to

the patient, false positive or false negative test results could consequently cause harm, which was not addressed in the ADAR. However, ESC noted that in MSAC's consideration of application 1087 in 2007 it had considered that *"as the population of interest in the non-hospital setting is not acutely ill, delayed treatment associated with (the very low likelihood of) a false negative test result is unlikely to be harmful"* and had advised that BNP and NT-proBNP testing for the diagnosis of heart failure in patients presenting with dyspnoea in a non-hospital setting was safe. On balance, ESC considered that the comparative safety of BNP/NT-proBNP testing was likely non-inferior.

Regarding comparative effectiveness, ESC noted that, for PICO set 1, the evidence supported a clinical claim of superior effectiveness in terms of test accuracy but did not show that testing would improve health outcomes. ESC noted there was a paucity of evidence to inform the effect of BNP/NT-proBNP testing on the health outcomes of patients in both a primary care and specialist setting. ESC noted that the evidence showed BNP testing made no significant difference to the proportion of patients diagnosed with heart failure (Najbjerg et al 2019), rates of echocardiograms referred (Najbjerg et al 2019) or received (Burri et al 2012), or mortality or hospitalisations (at 3 months or 12 months; Burri et al 2012). ESC noted that, while BNP appeared to reduce the time to appropriate therapy (from 24.7 to 12.8 days, $p=0.01$, Burri et al 2012), ESC considered this was based on a study that used a POC test so was not likely to reflect the anticipated time to appropriate therapy for a laboratory-based test.

ESC considered the change of management outcomes suggested improved health outcomes were more likely in patients correctly excluded from heart failure than those identified as having heart failure, which aligned with MSAC's previous advice on application 1087, however was not modelled in the economic analyses. ESC noted that the pre-ESC response stated that BNP/NT-proBNP testing was likely to facilitate more appropriate management of patients with chronic heart failure in primary care, and considered it is likely that an earlier diagnosis of heart failure would lead to health benefits, particularly because GPs could prescribe medications to manage heart failure – however considered that the ADAR had not presented evidence for this. Overall, ESC considered that although the evidence presented did not clearly illustrate a change in management with improved health outcomes resulting from BNP/NT-proBNP testing, the claim of non-inferior effectiveness may be reasonable.

ESC noted that the pre-ESC response stated that NT-proBNP carried a strong recommendation for use in the diagnosis of heart failure in both national and international guidelines due to the reduction in both time to diagnosis and unnecessary echocardiography. However, ESC considered no evidence had been presented to support these outcomes in the ADAR.

ESC noted that the included diagnostic accuracy studies showed that the assay had relatively high sensitivity when using lower thresholds, but that this sensitivity decreased for thresholds greater than 400 pg/mL. ESC considered that countries using thresholds of 400 pg/mL were focused on avoiding overdiagnosis, so were more concerned with test specificity; on the other hand countries focused on avoiding underdiagnosis use lower thresholds. ESC considered this somewhat reduced the applicability of the international evidence to the Australian context.

ESC noted that early studies for specificity of BNP/NT-proBNP tests may have under-appreciated the potential for heart failure in patients with preserved left ventricular ejection fraction. ESC also noted that up to 30% of heart failure with preserved ejection fraction patients have BNP/NT-proBNP levels below the diagnostic threshold due to a lack of BNP release (clinical expert advice).

ESC considered that the ADAR's clinical claim – that the use of NT-proBNP testing \pm echocardiography by specialist physicians for the diagnosis of heart failure results in at least non-

inferior effectiveness and non-inferior safety compared with echocardiography alone – was reasonably justified.

ESC noted that feedback from Lung Foundation Australia (LFA) was supportive of the application, with LFA noting that symptoms of heart failure can be similar to certain lung conditions and the test would allow heart failure to be ruled out and other diagnoses to be explored. The National Heart Foundation of Australia and the CSANZ were supportive of the test. The Heart Foundation stated that making the test available to all specialists may assist with access issues in areas that have variable access to cardiologists, and that pathologists would need to be appropriately qualified to analyse the test. Additionally, funding the use of the test in primary care would reduce out-of-pocket costs, lead to appropriate referral to rehabilitation services for patients and avoid hospitalisations. Feedback also noted the value of the test for First Nations people who have a higher rate of hospitalisations due to heart failure. The Royal Australian College of General Practitioners (RACGP) noted that cardiovascular disease is a complex condition and patients are often managed entirely by GPs.

For the economic evaluation, ESC noted that the PICO stated that based on the clinical claim a cost-effectiveness analysis (CEA) or a cost-utility analysis (CUA) should be used. The ADAR stated that the CUA performed by the National Institute for Health and Care Excellence (NICE) to inform its guidelines for chronic heart failure in adults was overly complex, made too many assumptions, and used heterogeneous and low-quality evidence. Therefore, the ADAR presented a CEA. ESC noted that the commentary stated this may have been inappropriate as it would not allow exploration of uncertainty in the evidence base, however ESC considered that a CEA was reasonable as there was evidence for test accuracy but no evidence for health outcomes, so a CUA would have been based on many assumptions. ESC also considered that a CUA may have underestimated the full value of NT-proBNP relating to the diagnosis of other (for example, respiratory) illnesses. Therefore, ESC considered that the decision tree used by the applicant was appropriate and better aligned with the evidence base. ESC also noted that the NICE CUA found the intervention to be cost-effective in the UK setting, which it considered supported the economic results. ESC noted the NICE model was driven by specificity and gains in quality-adjusted life years (QALYs) from the early diagnosis of other diseases.

Based on the discussion around the choice of economic model, ESC raised the broader issue of when it was appropriate to do CUA modelling of a medical test technology given an absence of health outcomes and the inevitable high degree of uncertainty in model structure and modelled outcomes.

ESC noted that the comparator in the model assumed that 100% of patients would receive echocardiography, which was assumed to have a higher cost, perfect accuracy and slower access than the intervention. However, ESC considered that this was not reasonable and there were reasons why not everyone in the comparator arm would have echocardiography. ESC recalled that MSAC had not supported application 1087 primarily due to uncertain cost-effectiveness, which had been mainly due to the assumption of 100% echocardiography uptake in the comparator arm whereas real world evidence suggested only 3.8-17.7% echocardiography uptake, resulting in the cost-offset from echocardiography averted having been overestimated. ESC noted that while echocardiography uptake may be higher now than in 2007 due to improved clinician education regarding heart failure investigations, no updated real-world evidence on this had been provided. This was despite PASC advising that *“the assessment will need to include the uptake rate of echocardiogram in both intervention and comparator arms, informed by real world evidence if possible”* (PICO pg 13), which was not done in the ADAR’s economic model.

ESC considered that there were applicability issues with the economic model. ESC noted the NICE model used a pooled estimate from three studies that was not well aligned with the

Australian population. Additionally, two studies used POC testing, although these reported similar accuracy to the laboratory-based tests. ESC also noted that a rule-out threshold of 280 pg/mL was used, which was lower than the threshold recommended in the Australian guidelines. However, ESC noted that no single study aligned with the PICO, so considered that testing multiple parameters was appropriate. ESC did not identify any extrapolation or transformation issues with the model.

Regarding the model structure, ESC noted that the ADAR estimated 29% of patients indicated for echocardiography in the absence of BNP/NT-proBNP testing would have heart failure, which the commentary agreed with. For the comparator, it was assumed that all patients would receive echocardiography regardless of their heart failure diagnosis following initial clinical assessment. For the intervention, only those patients who were above the rule-out threshold for NT pro-BNP would receive echocardiography, so the model proposed there would be cost offsets associated with echocardiography avoided in patients who have a BNP/NT-proBNP result below the diagnostic threshold. ESC noted that the model assumed a 2-month delay for receiving an echocardiogram, but ESC considered that this may not be reasonable as patients may find it difficult to access echocardiograms due to long wait times. Regarding the time for patients to re-present to their GP for results, ESC considered that a 1-month delay was reasonable because it was likely that many of the eligible patients would typically see their GP regularly. ESC considered that patients with false negative results returning to their GP after 1-6 months with ongoing symptoms could potentially be associated with a small risk of survival decrement, but that this was not addressed by the model as it was not a CUA. ESC considered that given the long wait for cardiology appointments, integrated care may be an appropriate model of care to mitigate delays: in integrated care the GP and cardiologist work together to manage the patient's therapy, including via telehealth.

ESC noted that ADAR's economic model results showed NT-proBNP testing \pm echocardiography was cost saving over echocardiography alone (incremental cost of -\$68, i.e., \$68 saved per patient), and the commentary's respecified base case found the intervention was still dominant over echocardiography (incremental cost of -\$25).

ESC noted that the model was sensitive to the percentage of echocardiography referrals, which affected both costs and the number of correct diagnoses of heart failure. Based on a CASE study (Krum et al 2001²⁵) cited by the commentary, the pre-ESC response claimed that no less than 64% of people with suspected heart failure would be referred for echocardiography, and that at 64% the intervention would still be cost-saving. ESC considered this to be uncertain because there was insufficient evidence available on the use of echocardiography nationally. ESC noted that the commentary considered several different uptake scenarios (ranging from 50–100% of patients receiving echocardiography appropriately), which changed the intervention from being cost saving to cost positive. The sensitivity analysis using the commentary revised base case found that NT-proBNP testing may not be cost saving if GPs refer patients above the threshold to echocardiography at a rate of 80% or lower.

ESC also considered that the use of BNP/NT-proBNP testing could reduce the number of echocardiography referrals because it would allow a diagnosis of heart failure to be ruled out earlier. However, it was difficult to establish an accurate offset of echocardiography referrals, as there were reasons other than suspected heart failure for requesting echocardiography. ESC considered that the number of echocardiography referrals may not be affected by BNP/NT-proBNP testing where referrals are appropriately made for investigating other diseases.

²⁵ H. Krum, et al. (2001) Chronic heart failure in Australian general practice: The Cardiac Awareness Survey and Evaluation (CASE) Study. *Med J Aust* **174**, 439-444 (2001).

ESC noted that the uncertainty in the economic model affected the financial impacts. The ADAR estimated net cost savings to the MBS of \$6,473,083 in year 1 to \$9,675,089 in year 6. The commentary revised the financial impacts by updating the MBS fees (from July 2023), using the test accuracy results from Zaphiriou et al. 2005, including additional GP visits to receive results, assuming that all patients were treated in primary care, and correcting errors. This resulted in reduced net cost savings of \$2,050,786 in year 1 to \$3,749,889 in year 6. However, ESC considered that these figures could be underestimated as there were cost offsets not captured, including through reduced emergency department visits, and opportunity costs resulting from long wait times for echocardiograms. ESC considered that increased costs from more GP visits may be preferable to greatly increased costs from emergency department and cardiologist visits.

ESC noted the commentary included sensitivity analyses of BNP/NT-proBNP uptake rates of 50%, 75% and 85% in the primary care setting and higher uptake rates in the specialist setting. ESC noted that the commentary's sensitivity analyses of the financial cost accounted for the add-on use of NT-proBNP when echocardiography was not replaced (for example, in rural and regional areas). The results showed that add-on use of NT-proBNP above 50% would result in a net cost to the MBS – although ESC considered that increased cost to the MBS does not necessarily indicate poor value-for-money. However, in the commentary's revised estimates, most sensitivity analyses remained cost-saving. Overall, ESC considered the extent of cost-savings remained uncertain for the financials due to uncertainty in assumptions in prevalence of heart failure, use of echocardiography regardless of BNP/NT-proBNP testing outcome and use of BNP/NT-proBNP in clinical situations when echocardiography would not usually be considered.

ESC considered there were also other significant factors that may influence MSAC's consideration of this application. ESC considered that the use of BNP/NT-proBNP testing when echocardiography was not available may mitigate equity of access for rural/remote and low-socioeconomic populations, and for First Nations people. ESC considered that the overall impact on the out-of-pocket costs for patients as a result of BNP/NT-proBNP testing remained unclear. However, ESC noted the commentary considered that out-of-pocket costs may increase for patients due to the costs of echocardiography and additional GP consultations that may be required.

17. Applicant comments on MSAC's Public Summary Document

The applicant had no comment.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)