MSAC Application 1825

Transcranial Doppler bubble test for patent foramen ovale

PICO Set

Population

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

The test is performed in patients with cryptogenic ischaemic stroke i.e. patients in whom no cause of stroke was demonstrated despite thorough investigation. Cryptogenic stroke accounts for 15-40% or ischaemic strokes. In many patients with cryptogenic stroke, the underlying cause is patent foramen ovale (PFO). Overall, PFO accounts for ischaemic stroke in 30% of people aged ≤50 years and 10% of people aged >50 years.

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

Mostly the test will be performed in patients ≤60 years of age. They will have suspected embolic ischaemic stroke. They will most likely have already had an MRI brain scan, vascular imaging to exclude extracranial and intracranial arterial stenosis, ECG monitoring to exclude atrial fibrillation, blood tests to exclude vasculitis and thrombophilia, and other tests if appropriate in selected cases. Older persons may also be considered for testing, for example, if they have embolic strokes, no vascular risk factors, and prolonged ECG monitoring fails to demonstrate atrial fibrillation.

Provide a rationale for the specifics of the eligible population:

Up to 40% of patients ≤60 years of age with ischaemic stroke have PFO-associated stroke. Up to 10% of persons >60 have PFO-associated stroke. Many of these patients with PFO have high-risk features for stroke recurrence and should undergo PFO closure to reduce their risk of stroke recurrence.

The foramen ovale is a communication between the right and left atria of the heart present in all foetuses. It exists to divert blood directly from right to left sides of the heart, bypassing the lungs, since foetuses do not breathe until born. In newborn babies the foramen ovale closes over but in about 25% there is a remnant communication, referred to as a PFO, which persists throughout life.

In some cases, PFO-associated stroke is due to passage of a thrombus (clot) through the PFO from right to left sides of the heart and into the arteries feeding the brain. This is known as paradoxical embolism because normally thrombus originating in deep veins in the legs or pelvis (deep vein thrombosis DVT) embolises to the lungs (pulmonary embolism PE). This is more likely to occur when a person does something which increases pressure in the vena cava, the vein that returns blood to the right side of the heart, such as straining on the toilet. We can simulate this

by asking the patient to try and force air out of their lungs whilst deliberately keeping their airway closed, the Valsalva manoeuvre.

In other cases, thrombus forms within the PFO, which is more like a tunnel than a hole.

A large PFO, high flow from right to atria with Valsalva (large shunt), spontaneous flow of blood from the right to left atria, and an associated atrial septal aneurysm (ASA) are all factors that increase the risk of stroke.

Are there any prerequisite tests?

Yes, as summarised above.

Are the prerequisite tests MBS funded?

Yes

Provide details to fund the prerequisite tests:

Not applicable

Intervention

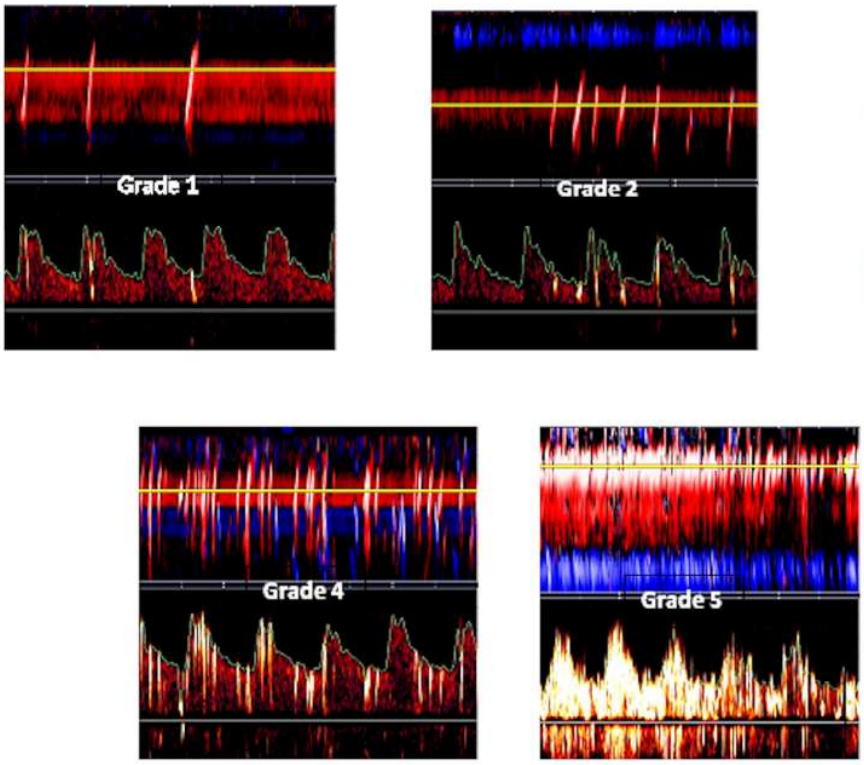
Name of the proposed health technology:

Transcranial Doppler (TCD) bubble test

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

The TCD bubble test involves monitoring blood flow in the middle cerebral artery (MCA) using a TCD device. A cannula is inserted in an arm vein to draw blood and to inject a small volume of agitated saline contrast. The contrast is a mixture of normal saline, a small amount of blood and a small amount of room air agitated with a syringe plunger. The agitated saline contrast contains microbubbles and if those microbubbles find their way into the MCA, they are detected as high intensity transient signals (HITS). The detection of HITS indicates the presence of shunting of blood from right to left sides of the heart. The degree of shunting is graded according to the number of HITS counted in one minute after injection of the saline contrast (see Figure). A grade 5 response indicates a large shunt.

Figure: TCD monitoring of MCA after injection of agitated saline contrast into an arm vein, showing varying grades of positivity. In each example, the bottom half shows the standard TCD spectral display over successive heart beats, and the top half shows the power M-mode display. A grade 5 response is commonly referred to as a curtain response since the HITS are too numerous to count. (*Spencer et al. J Neuroimaging. 2004;14:342-9*)



The test involves monitoring for HITS in the resting state before injection of agitated saline contrast, in the resting state after injection of agitated saline contrast, and again after injection of agitated saline contrast with Valsalva. Often, a test run is repeated to ensure the best possible Valsalva is obtained, to maximise the test sensitivity.

The TCD bubble test is usually performed using a dedicated TCD machine operated by an accredited vascular sonographer. A medical practitioner or certified health professional must also be present to consent the patient, canulate the arm vein, draw blood, prepare agitated saline contrast, inject the contrast, and instruct the patient to perform the Valsalva manoeuvre. The test generally takes 30-45 minutes to complete. TCD bubble test can also be done with a general vascular ultrasound machine with a transcranial ultrasound probe. This technique is known as transcranial colour duplex (TCCD).

Identify how the proposed technology achieves the intended patient outcomes:

Three highly specialised tertiary stroke units, the Austin Hospital in Melbourne, Royal Adelaide Hospital, and John Hunter Hospital in Newcastle have validated, in an Australian context, the TCD

bubble test over the past 4-5 years to detect PFO in patients with cryptogenic stroke. Patients with a positive TCD bubble test are referred for transoesophageal echocardiography (TOE) and review in the structural heart clinic. A positive study can negate the need for a transthoracic echocardiogram (TTE) in many patients, and a negative study can eliminate the need for a TOE. In patients with PFO-associated stroke, who have high risk for stroke recurrence features, the preferred treatment option is percutaneous endovascular PFO closure. A device, which looks like a double disc, is deployed across the PFO to seal it. Patients without high-risk PFO features may be treated medically.

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

No.

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

Not applicable.

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

Yes.

Provide details and explain:

At present the most significant limitation is access to TCD. Only 3 centres in Australia can offer this service.

Another limitation is that approximately 10% of the population have poor temporal bone insonation windows. The alternative diagnostic pathway for these patients is a transthoracic echocardiograph (TTE) with bubble test. However, the sensitivity is not as high as a TCD bubble test.

If applicable, advise which health professionals will be needed to provide the proposed health technology:

The TCD machine is operated by an accredited vascular sonographer. A medical practitioner or certified health professional must also be present to consent the patient, canulate the arm vein, draw blood, prepare agitated saline contrast, inject the contrast, and instruct the patient to perform the Valsalva manoeuvre.

If applicable, advise whether delivery of the proposed health technology can be delegated to another health professional:

A certified health professional could be trained to operate the TCD device. However, under existing rules, a Medicare claim for an ultrasound procedure can only be made if the operator is registered with the Australian Sonographer Accreditation Register (ASAR), at a site that is registered under the Diagnostic Imaging Accreditation Scheme (DIAS). The name of the accredited sonographer must be documented in the report. The ASAR and DIAS requirements would need to be relaxed if the device is to be operated by a certified health professional outside of a registered diagnostic imaging practice.

If applicable, advise if there are any limitations on which health professionals might provide a referral for the proposed health technology:

Not applicable.

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

Yes

Provide details and explain:

As described above.
The Austin Hospital Stroke Unit conducts 2-day training workshops each year.

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

☐ Consulting rooms
☐ Day surgery centre
☐ Emergency Department
☒ Inpatient private hospital
☒ Inpatient public hospital
☒ Laboratory
☒ Outpatient clinic
☐ Patient's home
☐ Point of care testing
☐ Residential aged care facility
☐ Other (please specify)

Specify further details here

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

Yes

Provide additional details on the proposed health technology to be rendered outside of Australia:

Not applicable

Comparator

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

The alternative diagnostic pathway is TTE with bubble test. There can be a delay of a couple of months. Sometimes the TTE is not performed with a bubble test and it might need to be repeated. Often, a TOE must be performed as well, as TTE with bubble test Is less sensitive than a TCD bubble test. In the public hospital system, the wait time for a TTE, then outpatient review, then TOE, then another outpatient review, can result in a delay of up to a year before a patient with PFO-associated stroke receives targeted treatment. Not only is this stressful for patients, but some patients will also have an interim stroke, which can be extremely costly to society, especially as those with PFO-associated stroke are often of working age.

List any existing MBS item numbers that are relevant for the nominated comparators:

Test	Item #	Schedule fee
TCD	11614	$86.20
TCCD	55280	$190.10

The MBS schedule fee for TTE, using the same device as for TCCD, is currently $258.70 (item number 55126 or 55129).

The MBS schedule fee for TOE, using the same device as for TCCD, is currently $308.90 (item number 55118).

Provide a rationale for why this is a comparator:

A TTE bubble test is a cardiac ultrasound imaging test which utilises the same agitated saline contrast solution as a TCD bubble test. It also involves the patient performing a Valsalva manoeuvre, which can be more difficult for a patient to do given the position of the patient whilst undergoing the TTE examination. This is probably the main reason why the TTE bubble test is not as sensitive as the TCD bubble test.

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

☐ None (used with the comparator)
☐ Displaced (comparator will likely be used following the proposed technology in some patients)
☒ Partial (in some cases, the proposed technology will replace the use of the comparator, but not all)
☐ Full (subjects who receive the proposed intervention will not receive the comparator)

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

The new test will replace TTE where the TCD bubble test is available and where there is a good temporal bone window i.e. 90% patients. A negative TCD bubble test will in most cases eliminate the need for a TTE and TOE, allowing referral for these tests only in the most clinically appropriate cases. For example, a patient with a positive TCD bubble test requires referral for TOE to confirm the PFO diagnosis, assess for high risk features, and determine appropriate sizing for a PFO closure device.

Outcomes

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

☒ Health benefits
☐ Health harms
☐ Resources
☐ Value of knowing

Outcome description – include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

More timely diagnosis. Targeted treatment. Fewer strokes.

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

☐ Health benefits
☐ Health harms
☒ Resources
☐ Value of knowing

Outcome description – include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

Using the TCD bubble test as a screening test will result in fewer referrals for TTE with bubble test and TOE with bubble test, freeing up these tests for more deserving indications, thereby reducing wait times.

List the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be measured in assessing the clinical claim for the proposed medical service/technology (versus the comparator):

☐ Health benefits
☐ Health harms
☐ Resources
☒ Value of knowing

Outcome description – include information about whether a change in patient management, or prognosis, occurs as a result of the test information:

Many patients are anxious if they have a stroke that remains unexplained after thorough testing. Demonstration that a stroke is PFO-associated is reassuring and will lead to appropriate medical and/or surgical treatment.

Proposed MBS items

How is the technology/service funded at present? (e.g., research funding; State-based funding; self-funded by patients; no funding or payments):

The TCD bubble test is currently funded using existing Medicare item numbers for standard diagnostic TCD tests. This is inadequate considering cost of device, personnel necessary to do test, and time taken. The currently available item numbers are:

Test	Item #	Schedule fee
TCD	11614	$86.20
TCCD	55280	$190.10

Provide at least one proposed item with their descriptor and associated costs, for each Population/Intervention:

MBS item number (where used as a template for the proposed item)	Pending
Category number	Insert category number here
Category description	Insert category description here
Proposed item descriptor	Bubble study for detection of patent foramen ovale in patient with previous ischaemic stroke. Must be performed by an accredited sonographer, in an accredited practice, using a registered TCD or TCCD device, with an attending medical practitioner or accredited health professional.
Proposed MBS fee	$250
Indicate the overall cost per patient of providing the proposed health technology	$250
Please specify any anticipated out of pocket expenses	Not applicable
Provide any further details and explain	

Algorithms

PREPARATION FOR USING THE HEALTH TECHNOLOGY

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

Patients ≤60 years of age who have suffered an ischaemic stroke undergo brain imaging (CT ± MRI) to confirm the diagnosis, and if a large artery stroke is diagnosed they then usually undergo vascular imaging (ultrasound, CTA, or MRA) to exclude extracranial or intracranial arterial occlusive disease, and ECG monitoring to exclude atrial fibrillation. If no underlying cause is found they will then usually undergo screening for vasculitis or thrombophilia. Some form of cardiac imaging will also be performed (usually TTE or TOE). Those patients in whom these tests are negative are deemed to have had a cryptogenic stroke and would then be referred for a TCD bubble test to diagnose PFO.

In patients >60 years of age a similar approach is followed except that a TCD bubble test is only indicated it brain imaging abnormalities are highly suggestive of a proximal source of embolism, and there only minor chronic small vessel ischaemic change evident on imaging, and more prolonged monitoring (28-day HeartBug, loop recorder) excludes atrial fibrillation. These patients are deemed to have embolic stroke unknown source (ESUS) and are considered for a TCD bubble test.

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

Yes. Fewer patients will be referred for TTE with bubble test or TOE with bubble test.

Describe and explain any differences in the clinical management algorithm prior to the use of the proposed health technology vs. the comparator health technology:

The TCD bubble test is more sensitive at detecting right to left shunt (most common cause being PFO) compared to TTE bubble test and TOE bubble test.

In those public hospitals offering the TCD bubble test it can usually be performed more rapidly than the TTE bubble test and TOE bubble test. TTE and TOE bubble tests may take several months to perform. If a TCD bubble test performed during the patients inpatient stay reveals PFO, the patient can be discharged from hospital confident that the explanation for their stroke has been diagnosed and with a clear treatment plan. Usually, they will undergo TOE to confirm the presence of the PFO and to assess for high risk for stroke recurrence features. If there are no high risk features then antiplatelet therapy is usually sufficient but if there are high risk features

they will benefit from endovascular PFO closure. A positive TCD bubble test will enable the patient to be prioritised for the TOE and review by the Heart-Brain multidisciplinary team.

In those hospitals not offering the TCD bubble test the alternative pathway is TTE with bubble test. There is usually a significant delay causing anxiety for the patient and increasing the risk of stroke recurrence before appropriate treatment can be implemented.

USE OF THE HEALTH TECHNOLOGY

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

As described above the TCD bubble test requires an ultrasound device, sonographer or accredited health care professional to operate the device, and an accredited health care professional to prepare and inject the agitated saline contrast. No additional resources are required.

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

No additional resource required.

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

Not applicable.

CLINICAL MANAGEMENT AFTER THE USE OF HEALTH TECHNOLOGY

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

If the TCD bubble test detects right-to-left shunt, patients are usually referred for a TOE to confirm the diagnosis of PFO and to assess for high risk features such as size of the PFO, large physiological shunt, atrial septal aneurysm, hypermobile interatrial septum, right atrial Chiari web and Eustachian valve. Note that spontaneous right-to-left shunt (i.e. without Valsalva) and grade 5 shunt detected by the TCD bubble study are also high risk for stroke. If there are no high risk features patients are usually treated with antiplatelet medication. Patients with high risk features are considered for endovascular PFO closure.

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

If a patient has a positive TTE with bubble test they are also usually referred for a TOE, following the same clinical algorithm as for the TCD bubble test above.

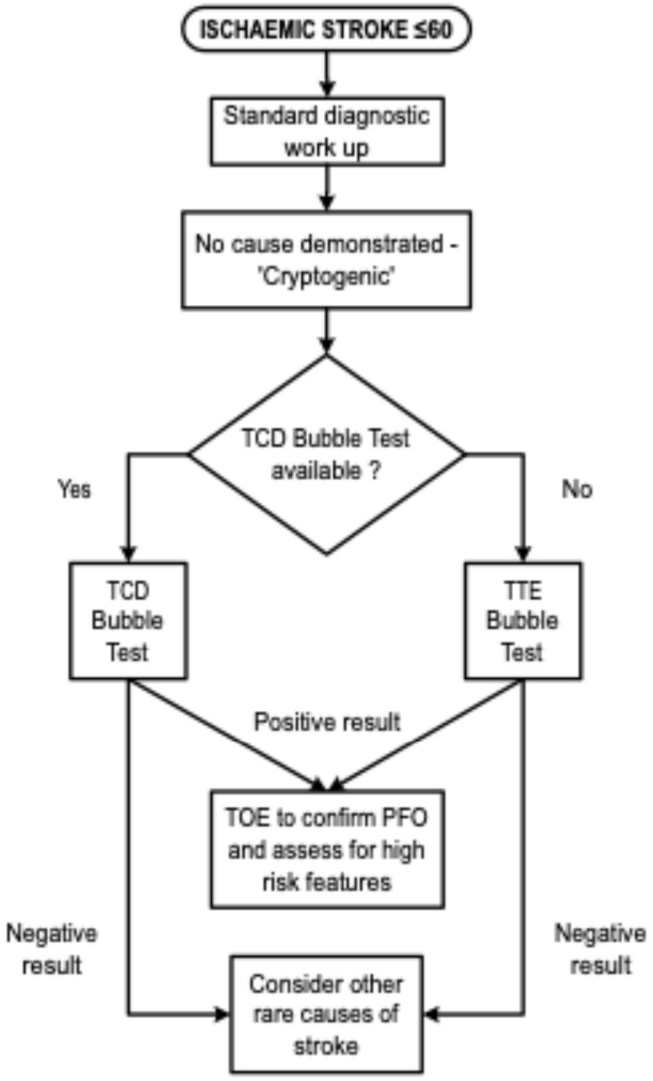
If a patient has a negative TTE with bubble test they are often referred for a TOE in any case, as TTE with bubble test is not as sensitive.

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

As indicated in the previous response, the TCD bubble test results in fewer requests for TOE, compared with the TTE bubble test.

More timely diagnosis and treatment of PFO-associated stroke will result in fewer cases of recurrent stroke, and savings in terms of healthcare resources.

Insert diagrams demonstrating the clinical management algorithm with and without the proposed health technology:



Claims

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

☒ Superior
☐ Non-inferior
☐ Inferior

Please state what the overall claim is, and provide a rationale:
Higher sensitivity for diagnosis of right-to-left shunt.

Why would the requestor seek to use the proposed investigative technology rather than the comparator(s)?
More timely diagnosis of PFO. Higher sensitivity

Identify how the proposed technology achieves the intended patient outcomes:
In hospitals where the TCD bubble test is offered it is more readily available than the TTE bubble test.

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

A change in clinical management? Yes

A change in health outcome? Yes

Other benefits? Yes

Please provide a rationale, and information on other benefits if relevant:
The psychological impact of uncertain causation of stroke cannot be underestimated.

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

☐ More costly
☐ Same cost
☒ Less costly

Provide a brief rationale for the claim:
The proposed fee for TCD bubble test is less than for TTE with bubble test. Further savings would be achieved by more targeted selection of patients for TOE.

If your application is in relation to a specific radiopharmaceutical(s) or a set of radiopharmaceuticals, identify whether your clinical claim is dependent on the evidence base of the radiopharmaceutical(s) for which MBS funding is being requested. If your clinical claim is dependent on the evidence base of another radiopharmaceutical product(s), a claim of clinical noninferiority between the radiopharmaceutical products is also required.

Not applicable.

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology. At 'Application Form lodgement',

	Type of study design*	Title of journal article or research project	Short description of research	Website link to journal article or research	Date of publication
1.	Systematic review	Transcranial Doppler versus transthoracic echocardiography for the detection of patent foramen ovale in patients with cryptogenic cerebral ischemia: a systematic review and diagnostic test accuracy meta-analysis	35 studies. 3067 patients. Comparison of TCD or TTE with TOE as gold standard. Sensitivity and overall diagnostic yield of TCD superior to TTE.	Ann Neurol 2016; 79: 625-635 DOI: 10.1002/ana.24609	2016
2.	Retrospective study of diagnostic accuracy	Transcranial Doppler as a screening tool for high-risk patent foramen ovale in cryptogenic stroke	461 patients with cryptogenic stroke who underwent TOE and TCD. TCD shunt grade correlates with presence of high-risk PFO features on TOE.	J Neuroimaging 2021; 31: 165-170 DOI: 10.111/jon.12783	2021

Identify yet-to-be-published research that may have results available in the near future (that could be relevant to your application).

Chambers B, Sanders L, Gilligan A, et al. Diagnosis and management of patent foramen ovale for stroke prevention: An Australian and New Zealand consensus statement developed by a modified nominal group approach. Submitted to Med J Australia. Copy uploaded Large Files section.