MSAC Application 1797

Vibration-Controlled Transient Elastography (VCTE™) for identifying advanced fibrosis in patients with metabolic dysfunction-associated fatty liver disease

PICO Set 1

VCTE™ for identifying advanced fibrosis in patients with metabolic dysfunction-associated fatty liver disease in primary care

Population

Describe the population in which the proposed health technology is intended to be used:
The population in which the investigative technology is intended to be used is patients with metabolic dysfunction-associated fatty liver disease (MAFLD), in order to identify patients with advanced fibrosis (AF) in general practice or primary care. MAFLD is a prevalent condition characterised by excessive fat accumulation, called hepatic steatosis, in the liver due to metabolic dysregulation (Pipitone, Ciccioli et al. 2023). The presence of ≥ 5% hepatosteatosis is a sine qua non for diagnosis irrespective of detection modality (Vaz, Clayton-Chubb et al. 2023).

MAFLD was proposed as a new name for non-alcoholic fatty liver disease (NAFLD) in 2020 by Australian researchers. (Vaz, Clayton-Chubb et al. 2023) (Gofton, Upendran et al. 2023). This change allows for:

1. Multiple overlapping causes and drivers of this disease (Vaz, Clayton-Chubb et al. 2023)
2. Inclusion of patients with some alcohol consumption (Vaz, Clayton-Chubb et al. 2023)
3. Reduced stigma associated with alcoholic liver disease (ALD) (Gofton, Upendran et al. 2023)

Diagnosis of MAFLD requires at least one of the following to be present: (1) overweight according to body mass index (BMI) (specific threshold for those of Asian ethnicity versus other ethnicities); (2) type 2 diabetes mellitus (T2DM) as per standard diagnostic criteria; or (3) metabolic 'dysfunction' defined by presence of at least two of seven clinical and biochemical criteria. The differences between MAFLD and NAFLD are further detailed in Table 1.

Table 1 Differences in diagnostic criteria between MAFLD and NAFLD and rationale for each

MAFLD	NAFLD	Rationale
≥ 5% hepatosteatosis with; 1. Overweight— BMI ≥ 23 kg/m^2 (Asian population) or ≥ 25 kg/m^2 (all other ethnicities) 2. T2DM—per standard diagnostic criteria 3. Metabolic dysfunction—any ≥ 2 of; (i) Elevated waist circumference: ≥ 90 cm/80 cm (males/females) among Asian population or ≥ 102 cm/88 cm (males/females) among all other ethnicities (ii) Blood pressure ≥ 130/85 mmHg or need for antihypertensive therapy (iii) Plasma triglycerides ≥ 1.70 mmol/L or need for specific lipid-lowering therapy (iv) Plasma HDL-cholesterol < 1.0 mmol/L for males or < 1.3 mmol/L for females or need for specific therapy (v) Prediabetes according to standardised criteria (vi) HOMA-IR score ≥ 2.5	≥ 5% hepatosteatosis without any other aetiology of liver disease	For MAFLD; • Name change and diagnostic criteria better encapsulate pathogenesis of disease, namely metabolic dysregulation and insulin-resistance • Inclusive criteria allowing for recognition of co-factors for liver disease which may impact additively or synergistically on natural history and clinical outcomes. This better reflects heterogeneity seen in clinical practice and can positively impact drug trial recruitment • Cut-off for alcohol consumption to discriminate 'safe' from 'excessive' with regard to steatogenic and fibrogenic potential not well established • Removes potentially stigmatising and trivial terms (i.e., 'alcoholic' and 'non-') • May lead to greater disease recognition among health professionals beyond hepatology For NAFLD; • Concern around impact on stakeholder acceptance, especially industry and regulatory bodies with impact on drug and biomarker discovery, development and acceptance (particularly with currently accepted histologic outcome measures for drug-development) • Uncertainty around what entails 'metabolic health' and hence around criterion three (metabolic dysfunction) of proposed diagnostic criteria

(vii) Plasma HS-CRP > 2 mg/L	• Lack of consensus among major hepatological societies

Abbreviations: MAFLD, metabolic-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; HS-CRP, high-sensitivity C-reactive protein
Source: (Vaz, Clayton-Chubb et al. 2023)

Given that most people with NAFLD (>80%) also fulfil diagnostic criteria for MAFLD, and levels of non-invasive liver fibrosis test results are similar between the two definitions, it is likely that literature using the NAFLD definition is applicable to the population defined as having MAFLD (Kemp, Clayton-Chubb et al. 2022, Lim, Tang et al. 2023).

A further nomenclature change, to metabolic-associated Steatotic liver disease (MASLD), has recently been proposed because of the concern that the use of "fatty" in the title may be stigmatising (Younossi, Alqahtani et al. 2024). Notably, the definition of MASLD requires exclusion of excessive alcohol consumption (defined as ≥20 g/day for women and ≥30 g/day for men) and alternative forms of liver disease.

Key differences between the three include (Ciardullo, Carbone et al. 2023):

1. NAFLD and MASLD exclude alcohol or hepatitis-related liver disease
2. MAFLD can coexist with hepatitis B or C

Carduiollo et al. show MAFLD and MASLD have higher prevalence rates than NAFLD (Ciardullo, Carbone et al. 2023).

For this application and for consistency, MAFLD is the preferred diagnostic criteria and term as it is more encompassing and aligns with current clinical consensus accepted by the Australian Liver Association and as part the Gastroenterological Society of Australia (GESA) MAFLD consensus statement (MAFLD Consensus Statement Working Group 2024).

Progression of metabolic associated fatty liver disease to advanced fibrosis

As fat continues to accumulate, MAFLD can progress from simple steatosis (fatty liver) to steatohepatitis, characterised by inflammation and liver cell damage. Persistent inflammation and liver cell damage can lead to the activation of hepatic stellate cells, which produce excess extracellular matrix proteins, resulting in fibrosis (Vancells Lujan, Viñas Esmel et al. 2021). Liver fibrosis is typically quantified from a liver biopsy using a staging score that categorises its severity on a graded scale from F0 (no fibrosis) to F1 (mild fibrosis), F2 (significant fibrosis), F3 (advanced fibrosis, AF) and F4 (equivalent to cirrhosis) (Bedossa 2014).

If not adequately treated, approximately one in 5 to 10 people will develop liver fibrosis over time, which can progress to cirrhosis, liver failure or liver cancer (Gofton and George 2021). Fibrosis progression in MAFLD is slow, progressing at a rate of around 0.12 stages per year (Gofton and George 2021). However, MAFLD progression is influenced by stage of liver fibrosis.

Complications of metabolic associated fatty liver disease

High fibrosis stages are associated with increased liver-related morbidity and all-cause mortality (Vilar-Gomez, Calzadilla-Bertot et al. 2018). Patients with AF are at a higher risk of liver-related

events, including cirrhosis and hepatocellular carcinoma (HCC), compared to those with lower fibrosis stages (F0-F2).

MAFLD is not only a hepatic condition but also a multisystem disease (Pipitone, Ciccioli et al. 2023). It is associated with a higher risk of extrahepatic complications, including cardiovascular disease (CVD), T2DM, and various cancers (Pipitone, Ciccioli et al. 2023). These associations are due to the proinflammatory, profibrogenic, and procoagulant systemic environment created by MAFLD (Pipitone, Ciccioli et al. 2023). CVD remains the leading cause of death in MAFLD patients without AF, highlighting the systemic impact of the disease (Hassen, Singh et al. 2022) (Rinella, Neuschwander-Tetri et al. 2023). Death from liver disease predominates in patients with advanced fibrosis. A strong association exists between NAFLD and atherosclerotic heart disease, heart failure, and arrhythmias, particularly atrial fibrillation (Rinella, Neuschwander-Tetri et al. 2023).

Risk factors of metabolic associated fatty liver disease

In the Australian population, there are three prominent health issues that have been identified as significant predictors for the progression to AF: obesity, diabetes, and metabolic syndrome. These conditions, along with advanced age, are becoming increasingly prevalent in the Australian population (Adams, Roberts et al. 2020). Specifically, people over 50 years who have had longstanding overweight or obesity (interview with Prof Jacob George, 2024). The major metabolic risk factors are hypertension, T2DM and hyperlipidaemia. Additionally, in woman, a major risk factor is menopause.

Prevalence of MAFLD in specific population groups in Australia

A 2022 cross-sectional analysis in regional Victoria estimated the age- and sex-standardised prevalence of MAFLD at 47.2%. The higher prevalence in rural and regional areas may be attributed to people having 1.18 ($p<0.001$) times greater odds of being overweight and 1.31 ($p=0.01$) times greater odds of being obese compared to those in metropolitan areas (Roberts, Majeed et al. 2021, Kemp, Clayton-Chubb et al. 2022).

Currently, there is limited data available on the prevalence of MAFLD within individual Australian States and Territories; and the available data are from white/Caucasian populations and therefore cannot be generalised to other groups, including Aboriginal and Torres Strait Islander peoples. Another study examining HCC in Aboriginal and Torres Strait Islander peoples found that 6.1% had MAFLD. However, similar to the general population, these results are likely to be substantially underestimated in Aboriginal and Torres Strait Islander peoples, especially with the prevalence of the related comorbidities of T2D and obesity being up to 48% and 45%, respectively, in this group (Dick, Wheeler et al. 2024).

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

The proposed investigative technology under evaluation in this document is Vibration Controlled Transient Elastography (VCTE™), a non-invasive diagnostic tool that assesses the extent of liver fibrosis. VCTE™ works by generating a mechanical pulse that creates a shear wave through the

liver tissue. VCTE™ measures the speed of a mechanically induced shear wave using pulse-echo ultrasonic acquisitions in a much larger portion of the tissue, approximately 100 times more than a liver biopsy core. The speed of the wave correlates directly with liver stiffness - faster speeds indicate stiffer tissue and more advanced fibrosis. This measurement is converted into a numerical value expressed in kilopascals (kPa), known as the Liver Stiffness Measurement (LSM).

Patients that have been assessed and diagnosed with MAFLD show evidence of the presence of hepatic steatosis in addition to one of the following three criteria: overweight/obesity, T2DM, or evidence of metabolic dysregulation (Table 1) (Sangro, de la Torre Aláez et al. 2023).

Currently in Australia, risk stratification of patients with MAFLD is complicated by the lack of reimbursed non-invasive tests (NITs). While the definitive diagnosis of MAFLD requires a liver biopsy which is an invasive procedure that is no longer routinely performed in clinical practice, clinicians rely on sequential non-invasive testing pathways to manage patients appropriately. Use of sequential non-invasive testing pathways have been examined in the GESA MAFLD consensus statement (MAFLD Consensus Statement Working Group 2024). The current standard clinical practice in Australia involves first line test in primary care, followed by referral to a liver specialist for further testing and management of all patients with MAFLD.

Initial test in the primary care setting typically involves reimbursed blood tests like fibrosis-4 (FIB-4) or aspartate aminotransferase-to-platelet ratio index (APRI) which are scores calculated based on liver function tests (LFTs) and patient characteristics. LFTs such as FIB-4 serve as a rule out test due to their high negative predictive value, low cost and accessibility. Patients with low FIB-4 scores (<1.3) generally don't require additional testing, while those with intermediate or high scores (i.e. FIB-4 between 1.3-2.7) undergo further evaluation by a specialist. This is due to the limited positive predictive value of these blood-based tests. Usually, patients are referred for a further second-line test in either an outpatient centre or a private hepatology clinic for a more comprehensive evaluation. The results of these second-line tests, when conducted, take precedence in guiding treatment decisions (interview with Prof James O'beirne, 2024). Once a patient is referred to either a hepatologist or outpatient liver clinic, the proposed health technology would be considered for use by a liver specialist (relevant to PICO Set 2 instead).

Given limited availability of VCTE™ devices in outpatient clinics, Table 2 outlines in detail the criteria for accessing public outpatient services where VCTE™ tests are performed based on time urgency and severity.

Table 2 Criteria to access public outpatient services

Category	**Criteria**
Category 1 Recommended to be seen within 30 calendar days.	Abnormal LFTs if any of the following: bilirubin > 34 albumin < 35 INR > 1.7 and/or platelets are outside normal range in setting of known or suspected liver disease (excluding unconjugated hyperbilirubinemia). Abnormal LFTs associated with new symptoms (e.g. nausea, anorexia) or ≥ 5% unexplained weight loss in past 1 month or ≥ 10% unexplained weight loss in past 6 months. Persisting liver inflammation with ALT > 200 for more than a month. New, abnormal liver function in a pregnant patient.
Category 2	Liver disease treatment required where outside the scope of the referrer scope of practice.

Recommended to be seen within 90 calendar days.	Metabolic syndrome or alcohol dependence suspected and non-invasive serological algorithm (FIB 4) suggestive of cirrhosis (FIB 4 score above 3.5; a threshold where cirrhosis is likely), or elastography or radiologic evidence of cirrhosis.
Category 3 Recommended to be seen within 365 calendar days.	Metabolic syndrome associated LFTs derangement suspected MAFLD and fibrosis indeterminate (FIB 4 score 1.3 - 3.5) where significant fibrosis and even cirrhosis is possible. Abnormal LFTs and negative liver screen regardless of aetiology, severity or degree of work-up performed. Fibrosis assessment requested (FibroScan referral) when FIB 4 score above 1.3 (indeterminate) or known risk factors for chronic liver disease requiring monitoring (e.g. methotrexate, metabolic-associated steatohepatitis, Hepatitis B).

Abbreviations: ALT, alanine transaminase; INR, international normalised ratio; LFT, liver function test; FIB 4, fibrosis 4
Source: (NSW Health 2024)

As show in Table 2, There are a variety of tests that can be used to assess liver fibrosis. Liver ultrasound or radiology is commonly recommended when liver disease is suspected in Australia and can detect the presence of steatosis and cirrhosis (Sangro, de la Torre Aláez et al. 2023). Magnetic resonance imaging (MRI) is the most sensitive imaging test for steatosis, and is highly accurate even in mild steatosis, although is not commonly used due to its costs (interview with Prof James O'beirne, 2024). Acoustic radiation force impulse (ARFI) and point or 2D shear wave elastography (SWE) are alternative transient elastography (TE) tools to VCTE™ and are used in public hospital and radiology clinics but are not as well validated (interview with Dr Jess Howell, 2024). VCTE™ is different to alternate TE tools as VCTE™ specifically uses a mechanical pulse to generate shear waves whereas SWE uses focused ultrasound beams to generate shear waves.

Overall, the management of MAFLD focuses on routine blood tests, lifestyle interventions, control of diabetes, and treatment of metabolic risk factors. Patients undergo sequential testing mainly using blood-based serum tests and radiology prior to accessing the proposed health technology. Specific criteria required to access VCTE™ is for patients with a FIB-4 greater than 1.3. There is no Therapeutic Goods Administration (TGA) approved therapy specifically for MAFLD, so the emphasis is on managing the underlying metabolic dysfunction and preventing progression through lifestyle changes and testing (Sangro, de la Torre Aláez et al. 2023). Repeat testing is recommended every 3 years patients classified as low-risk, or a FIB-4 score between 1.3 to 2.7.

Provide a rationale for the specifics of the eligible population:

The absence of early symptoms and limited awareness among both the general public and wider healthcare profession can result in MAFLD going undetected for prolonged periods. Concerningly, incident cases of advanced liver disease and liver-related deaths due to MAFLD are estimated to increase by 85% in Australia between 2019 and 2030 (Adams, Roberts et al. 2020). Due to the asymptomatic nature of MAFLD, and current low surveillance due to a lack of awareness amongst non-specialised physicians of the disease's progression and associated complications, efforts to reduce and monitor disease burden are crucial to minimising future healthcare impacts. Hence, there is major concern regarding the management of these patients and implementing appropriate preventative measures, especially as morbidity and mortality associated with chronic liver disease is increasing in Australia and worldwide (Adams, Roberts et al. 2020).

Currently, up to 30% of people with MAFLD assessed in primary care have a FIB-4 score greater than 1.3 and require further assessment. However, the prevalence of AF in general practice is only 5%–10% (Gofton and George 2021). In the majority of MAFLD cases, progression of fibrosis stages is generally slow. Hence, primary care physicians can manage most of these patients by implementing lifestyle modifications and optimising metabolic risk factors. However, select groups of MAFLD patients, such as those with advanced liver fibrosis or cirrhosis, should be referred to specialist care (Ngu, Goh et al. 2016). Therefore, risk stratification using VCTE™ in primary care for patients with elevated FIB-4 scores (>1.3) will lead to better targeting of high-risk patients resulting in fewer patients that require referral to liver specialists. This approach improves healthcare system efficiency and reduces unnecessary specialist visits.

However, the use of VCTE in primary care faces obstacles due to limited device availability and lack of a MBS rebate, which poses financial challenges for both patients and providers.

- **Device Availability**: VCTE™ devices are scarce in general practice settings, with most located in major metropolitan hospitals or outpatient specialist clinics.
- **Financial Barriers**: Without appropriate MBS rebates, implementing VCTE™ in primary care becomes less feasible due to the associated costs.

Due to challenges in widespread VCTE™ implementation across Australian general practices and the potential for inequitable access, this MBS listing will prioritise targeted services in high need areas/cases. The focus will be on general practices with specialised liver services, especially in rural and underserved areas, where unique needs exist. That is, areas with limited specialist access and where general practitioners (GPs) manage a broader range of conditions. This bridge in the care gap can provide more certain access to essential liver services in communities that face substantial barriers to care, especially specialist care.

Incorporating VCTE in primary care addresses several systemic issues:

- **Reduced specialist burden**: Enabling primary care providers to perform initial fibrosis assessments relieves pressure on liver specialists, especially beneficials for patients in rural and regional settings
- **Improved equity of access**: Expanding access to VCTE™ beyond major metropolitan centres would benefit patients in a variety of geographic areas.
- **Improved health outcomes**: Early detection and identification of high-risk patients can identify individuals at high-risk of progressing to more severe liver diseases and liver cancer.

Overall, incorporating VCTE™ in primary care for MAFLD assessment offers a valuable tool for early detection, efficient risk stratification, and ongoing monitoring of low-risk patients. This approach will improve patient outcomes and healthcare system efficiency in managing the growing burden of MAFLD. Especially in regional areas of where healthcare resources are already strained and as the demand is likely to exceed the capacity of specialist liver services in the future.

Are there any prerequisite tests? (please highlight your response)

Yes No

Are the prerequisite tests MBS funded? (please highlight your response)

Yes No

Intervention

Name of the proposed health technology:
The proposed investigative technology is VCTE™ which is exclusively performed by FibroScan® devices.

Previously, VCTE™ was used interchangeably with TE or with the broader term liver elastography in literature.

However, concerns about misuse of VCTE™-based data to strengthen the validity and accuracy of other TE technologies led to exclusive use of VCTE™. Most studies start referring to FibroScan® as VCTE™ from 2014 onwards.

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

Patients are required to fast for at least 2 hours before taking the test. Once fasting is complete, patients are placed in a supine position with their right arm positioned behind their head. The test requires a minimum of ten valid readings per patient, with at least a 60% success rate and an interquartile range of ≤30% of the median value being taken (Kemp 2013). LSM is the median of the successful stiffness measurements (target ≥10). The LSM ranges from 2.5 (lowest stiffness) to 75 kPa (highest stiffness).

These devices are designed for use in a medical practice by an operator trained health care professional to measure LSM in patients with MAFLD. Prior to a VCTE™ test, a FIB-4 score greater than 1.3 is required and is outlined in the GESA MAFLD consensus statement (MAFLD Consensus Statement Working Group 2024).

Identify how the proposed technology achieves the intended patient outcomes:

VTCE™ is included in the GESA MAFLD consensus statement, which aligns best practice with evidence (MAFLD Consensus Statement Working Group 2024). Securing MBS funding for VCTE™ will ensure that patients can receive evidence-based and effective care for liver disease management. Lack of appropriate reimbursement and the resultant cost of liver fibrosis diagnostic pathways is a major determinant of uptake by doctors and patients. MSAC considered in Application No. 1366 (Transient Elastography at 50Hz for the diagnosis of liver fibrosis in patients with confirmed Hepatitis B or C, March 2016) that a consequence of any MBS listing would be to extend the use of VCTE™ beyond the public hospital sector where it is already available, to include GP settings, especially rural and regional communities that lack access to specialist hepatology services but have a high prevalence of MAFLD.

This application represents an initial step towards making VCTE™ more accessible to patients in specialist (PICO set 2) and primary care settings. Greater adoption of VCTE™ will improve patient outcomes by enabling earlier intervention and better management of patients with MAFLD. The prognostic ability of diagnostic tests such as VCTE™ has been proven and will risk stratify patients and their risk for future liver-related outcomes.

By facilitating these improvements in liver disease diagnosis and management, VCTE™ ultimately aims to reduce the incidence of advanced liver disease, related complications, and mortality in patients with MAFLD.

Does the proposed health technology include a registered trademark component with characteristics that distinguishes it from other similar health components? (please highlight your response)

Yes No

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

VCTE™ is a proprietary technology trademarked by Echosens and is unique only to the FibroScan device. The controlled vibration aspect of the technology distinguishes it from other elastography methods such as SWE which is not as well validated as FibroScan VCTE™ and does not provide comparable benefits.

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): (please highlight your response)

Yes No

Provide details and explain:
Once every three years

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

- GPs
- Primary care nurses

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

N/A

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

VCTE™ is currently available in a small number of privately owned hepatology clinics in metro cities in Australia. It is also mainly in public hospitals and community clinics for drug, alcohol and infectious related diseases (Matthews, MacGilchrist et al. 2019). However, referrals for VCTE™ is primarily constrained by device availability due to capital costs. Public hospitals often face significant wait times for VCTE™, sometimes extending beyond three months, which can impact patient management.

Hence, this application proposes a practice change in management of liver disease in Australia brought about by wider availability of VCTE™ in primary care setting, especially in rural and regional Australia where specialist hepatology services are not available.

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? (please highlight your response)

Yes No

Provide details and explain:

Examinations with VCTE™ is performed by an operator who has been certified by the manufacturer or its approved local representative. In Australia, this is defined as completing a three-hour manufacturer training and 10 conducting supervised scans before a health care professional is trained to do it independently (Armstrong, Corbett et al. 2013).

The process for formal training and quality assurance program is currently under discussion with appropriate clinical bodies to ensure consistent quality and training of healthcare providers The provider aims to finalise this before the MBS item becomes available.

Indicate the proposed setting(s) in which the proposed health technology will be delivered: (select all relevant settings)

☐ 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)

The proposed setting for VCTE™ at point of care in primary care health settings that do not require a referral.

Is the proposed health technology intended to be entirely rendered inside Australia? (please highlight your response)

Yes No

Please provide additional details on the proposed health technology to be rendered outside of Australia:
N/A

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 health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service:

The clinical utility comparator for VCTE™ in primary care is the referral to a liver specialist and ultrasound service.

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

1. For abdominal ultrasound, MBS item 55036 is used.

Please provide a rationale for why this is a comparator:

The rationale for ultrasound as a clinical comparator is based on the clinical landscape of liver disease in Australia, the current access issues to VCTE, GESA MAFLD consensus statement and past MSAC liver test applications made to the Department (MAFLD Consensus Statement Working Group 2024).

Ultrasound is widely accessible and routinely used for liver assessment in Australia in radiology clinics. Ultrasound and VCTE will be assessed across different settings since ultrasound services are not provided in primary care and are only available in radiology clinics. It serves as a first-line imaging modality for evaluating liver disease due to its non-invasive nature, it is freely available and a relatively inexpensive imaging modality to detect hepatic steatosis. However, liver ultrasound has its limitations, including a degree of operator dependency in test performance and reduced sensitivity in certain populations, including those with obesity or with mild hepatic steatosis (Hernaez, Lazo et al. 2011).

While VCTE™ are preferred by clinicians in the current clinical landscape, their availability is often limited, especially in rural and remote areas. Currently, there are 200 VCTE™ machines mainly in metropolitan cities in Australia, with some sites owning multiple devices (Personal communications with Medical Technologies Australia, 2024). VCTE™ is also limited outside of hospitals and infectious diseases group clinics. Ultrasound is more broadly available across different healthcare settings. Assessing VCTE™ in primary care versus specialist care was considered but based on precedence from the Hepascore MSAC application 1446, PASC did not consider it an appropriate comparator due to it not being MBS listed.

Previous MSAC considerations for Hepascore (Application No. 1446) also noted that VCTE is limited in access outside public hospitals and that patients receive services via other subsidy arrangements or pay privately.

"MSAC noted the pre-MSAC response disagreed on the use of confirmatory testing. MSAC noted the pre-MSAC response considered that transient elastography (FibroScan®) has limited access, however MSAC noted that it is routinely used in public hospitals…

PASC did not consider FibroScan® (transient elastography) an appropriate comparator, as it is not listed on the MBS. Liver biopsy is the reference standard however it is less frequently performed in the current era and it was not considered appropriate as the initial comparator. The Pre-ESC Response (p3) claimed that ultrasound elastography is performed by radiological providers using a liver ultrasound machine and is rebated as a liver ultrasound…

The pre-ESC response considered that the clinical assessment of patients with Chronic Hepatitis C and Chronic Hepatitis B includes Hepascore, transient elastography (FibroScan®) or ultrasound elastography where patients receive these services funded through other subsidy arrangements or pay privately."

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? (please select your response)

☐ 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 in all cases
☐ Full – subjects who receive the proposed intervention will not receive the comparator

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

VCTE™ is anticipated to become the primary tool for assessing AF and accurately staging liver fibrosis in MAFLD patients within high need primary care settings. However, ultrasound will not be fully replaced by VCTE™ but used as an additional tool following VCTE™ where needed. This aligns with the findings in MSAC application no. 1366 which stated that VCTE™ is unlikely to fully substitute conventional ultrasound due to yielding limited information (p. 11) (Medical Services Advisory Committee 2016).

This is because most NITs have been developed to diagnose AF or cirrhosis at point of care despite its setting. Each non-invasive test has specific advantages and limitations, with no single test being perfect (European Association for the Study of the Liver 2021). Similarly, ultrasound is inaccurate for determining AF and lacks sensitivity for determining cirrhosis (Hetland, Kronborg et al. 2023).

Thus, specific diagnostic NITs such as VCTE™ are required for accurate staging of liver fibrosis in people with MAFLD. Although ultrasound has clinical utility in determining hepatic steatosis and assessing the anatomy of the liver, therefore it is partially displaced in the continuum of care for patients with MAFLD.

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): (please select your response)

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

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

The outcomes of interest in this application include test accuracy compared to liver biopsy (reference standard) (Eddowes, Sasso et al. 2019), concordance with ultrasound (Kamali, Adibi et al. 2019) and prognostic accuracy (Ciardullo, Muraca et al. 2023). It is important to note that the NAFLD-based literature is likely applicable to those with MAFLD given the 80% overlap of diagnostic criteria and similar test results (Kemp, Clayton-Chubb et al. 2022).

The major expected patient-relevant outcomes associated with using VCTE™ are its superior accuracy compared to clinical assessment. In relation to the current SOC, VCTE™ is anticipated to improve risk stratification of patients with mild disease and AF, thereby providing better opportunities for lifestyle intervention and initiate surveillance for hepatocellular carcinoma (HCC) to reduce mortality.

Additionally, incorporating VCTE™ in primary care will lead to a change in management. Therefore, reduced referrals to secondary care are another key outcome. Two Australian studies by Hayward et al. (2021) and Brain et al. (LOCATE-NAFLD) investigate the feasibility of VCTE™ in primary care and its associated benefits of reduced referrals and better patient care (Hayward, McKillen et al. 2022) (Brain, O'Beirne et al. 2020). Data for LOCATE-NAFLD is currently being analysed with results to be soon published.

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): (please select your response)

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

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

It is anticipated that use of VCTE™ outside of specialist care will reduce unnecessary referral rates of patients with non-advanced disease and the decrease the cost to detect AF.

While there is limited evidence supporting the use of the FIB-4 index as an inexpensive initial first line test followed by VCTE™ for patients with indeterminate scores, this two-tier approach is recommended by most guidelines. These include the GESA MAFLD consensus statement, the American Association for the Study of Liver Diseases (AASLD) 2023 guidelines, the National Institute for Health and Care Excellence (NICE) 2023 guidelines, and the European Association for the Study of the Liver (EASL) 2021 update. These guidelines all outline this 2-step management approach in order to risk stratify patients at a primary care level and reduce unnecessary referrals to secondary care.

Hayward et al. (2021) outlined a collaborative two-step pathway between primary care physicians and specialists to assess fibrosis risk in NAFLD patients in line with EASL guidelines (Hayward, McKillen et al. 2022). By developing a real-world, implementable pathway for primary care, the study aimed to improve early detection and management of at-risk patients, potentially reducing the burden on specialist services through more effective triage and management at the primary care level. Out of 153 completed patient assessments, 139 (90.8%) were not considered to have clinically significant fibrosis. Most patients without clinically significant fibrosis (122 out of 139, or 87.8%) avoided referral to secondary care (Hayward, McKillen et al. 2022). The findings support a larger UK study where a primary care triage pathway (FIB-4 followed by the serum ELF™ test) reduced unnecessary NAFLD referrals by 81% and improved the detection of patients with AF fivefold (Srivastava, Gailer et al. 2019).

Additionally, a UK study by Srivastav et al. modelled a two-tier approach using a cost-effectiveness model (Srivastava, Jong et al. 2019). Their analysis showed that using the SOC versus a combination of FIB-4 and VCTE™ resulted in reduced healthcare spending by £151,816 per 1,000 patients over one year. The cost utility, measured as the cost per case of AF detected, saved £9,083, and cost savings from reduced specialist referrals amounted to £26,216, given that 234 referrals were avoided compared to SOC (Srivastava, Jong et al. 2019).

Proposed MBS items

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

State-based funding in public hospitals and mobile tests performed in rural and regional areas are funded through local health services.

Self-funded by patients.

Please provide at least one proposed item with their descriptor and associated costs, for each population/Intervention: (please copy the below questions and complete for each proposed item)

Proposed item details

MBS item number (where used as a template for the proposed item)	MBS item 699 used as a template
Category number	Category 1 - to be confirmed
Category description	Professional attendance
Proposed item descriptor	Vibration Controlled Transient Elastography at 50 Hz performed by a suitably trained health professional in primary care for the assessment of liver fibrosis in patients with metabolic dysfunction-associated fatty liver disease in addition to: a. collection of relevant information, including taking a patient history; and b. initiating interventions and referrals as indicated; and c. implementing a management plan; and d. providing the patient with preventative health care advice and information. Used on the liver – 1 service only every 3 year - including interpretation and report
Proposed MBS fee	Fee: $101.70
Indicate the overall cost per patient of providing the proposed health technology	Fee: $101.70
Please specify any anticipated out of pocket expenses	N/A
Provide any further details and explain	The proposed fee includes: - Conducting VTCE™ scan - Collect relevant information - Initiating interventions and referrals as indicated - Implementing a management plan - Providing the patient with preventative health care advice and information - Item descriptor comparable to preventative MBS item 699 for a heart health assessment - Reference fee taken from MBS item 82210 and 23

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:

As outlined in the GESA MAFLD consensus statement for the assessment of patients in primary care, sequential testing and use of a NITs, such as FIB-4, is required to be offered as an initial test to help "rule out" the risk of AF among patients with MAFLD (MAFLD Consensus Statement Working Group 2024).

Depending on first line test results, patients would be eligible for VCTE™. That is, patients with a FIB-4 score between 1.3 and 2.7 would then be eligible for a second-line test with VCTE™ in primary care.

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? (please highlight your response)

Yes No

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

A first-line FIB-4 score is typically needed before referring patients with MAFLD for a second-line test (Ultrasound or VCTE™). Therefore, no differences in clinical management are expected before using VCTE™ or its comparator.

Use of the health technology

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

No additional healthcare resources are used in conjunction with delivering the VCTE™ service.

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

Referral to a radiology centre that provides liver ultrasound is necessary. Based, on ultrasound findings, referral to a liver specialist may be needed. Due to the lack of second-line tests in more rural and remote areas, and lack of awareness of MAFLD, the disease is underdiagnosed in Australia.

Additional healthcare resources will be required to accurately identify patients with advanced disease stages who were not correctly diagnosed due to limited access to accurate quantitative tests for determining liver fibrosis stages. In some cases, especially for patients that live in rural

and remote areas, patients would need to travel to metro cities to access hepatology and VCTE™ services.

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

Equipment costs and availability
Abdominal ultrasound uses standard ultrasound machines that are widely available in most healthcare facilities. Whereas VCTE™ requires the specialised device and is therefore limited by accessibility. If VCTE™ is not available locally, patients might need to travel to access the test.

Time and procedure
An abdominal ultrasound exam roughly takes 30 minutes to perform versus 10 to 20 minutes for a VCTE™ test.

Operator dependence
Ultrasound requires a degree of radiological expertise, with variability in accuracy noted among less experienced operators (Losurdo, Ditonno et al. 2024). Moreover, ultrasound need to be conducted by radiologists, sonographers or other HCPs with training in ultrasound techniques. VCTE™ is less operator-dependent and easier to use compared to ultrasound, making it a more standardised and reproducible method. Generally, VCTE™ can be operated by trained technicians or nurses with specific training on the device.

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:

Depending on LSM score derived from VCTE™ test. Patients would be either managed in primary care for low-risk patients or require further specialist monitoring for high-risk patients. Most patients with MAFLD do not require specialist hepatology referral and are best managed holistically in primary care. This is defined in the GESA MAFLD consensus statement by an LSM ≥ 8 kPa for high-risk patients and an LSM < 8 kPa for low-risk patients (MAFLD Consensus Statement Working Group 2024).

Patients diagnosed with MAFLD will usually undergo further assessment to identify and address underlying causes in primary care such as viral hepatitis, alcohol use, or metabolic factors. There is no approved pharmacotherapy for MAFLD. Hence, current management involves reducing the burden of metabolic dysregulation to reduce both liver injury and adverse extrahepatic outcomes. The cornerstone of current therapy remains lifestyle modification including dietary change, weight loss and structured exercise intervention (Gofton and George 2021).

Additionally, patients are counselled on lifestyle changes to help slow disease progression, including weight loss, exercise, and reducing alcohol intake if applicable. Patients with MAFLD are recommended to undergo testing every three years with FIB-4 and VCTE™ testing.

Patients with AF are managed on a case-by-case basis by specialists. Additionally, patients with AF (LSM ≥ 8 kPa) and cirrhosis (LSM ≥ 10 kPa) are screened for complications such as liver cancer and portal hypertension.

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

After an ultrasound, the use of VCTE™ may be required to further risk stratify patients in specialist care presenting with abnormal liver ultrasound. Especially where there are inconclusive findings.

Similarly, after the comparator health technology, clinicians will focus on lifestyle modifications and addressing associated metabolic conditions. The management strategy typically includes testing every 3 years with a FIB-4 and subsequent ultrasound and/or VCTE™ test where available.

Additionally, patients with AF (LSM ≥ 8 kPa) and cirrhosis (LSM ≥ 10 kPa) are screened for complications such as liver cancer and portal hypertension. However, use of comparator technology has limited accuracy in detecting cirrhosis and AF.

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

A higher proportion of patients with MAFLD would be managed in primary care without having to enter secondary care with the proposed increased availability of reimbursed VCTE™ in targeted primary care centres vs the comparator technology.

Table 3 Differences in healthcare resources after use of VCTE™ versus ultrasound

	VCTE™ in primary care	**Ultrasound**
Frequency of follow-up:	Recommended every 3 years for patients with MAFLD	Variable (every 1 to 3 years)
Additional testing	N/A	Ultrasound pathway may require subsequent VCTE™ testing, potentially increasing overall resource utilisation
Specialist referrals and risk stratification	VCTE™ pathway likely results in more targeted specialist referrals due to better risk stratification. Most patients that are managed in primary care with MAFLD will not be referred to a hepatologist, High-risk (LSM ≥ 8 kPa): Continued specialist monitoring and care	Ultrasound does not provide risk stratification of patients with MAFLD
Additional management	VCTE™ pathway may lead to more accurate identification of patients requiring screening for liver cancer and portal hypertension	Similar screening for complications in high-risk patients, but with limited accuracy in detecting advanced fibrosis and cirrhosis

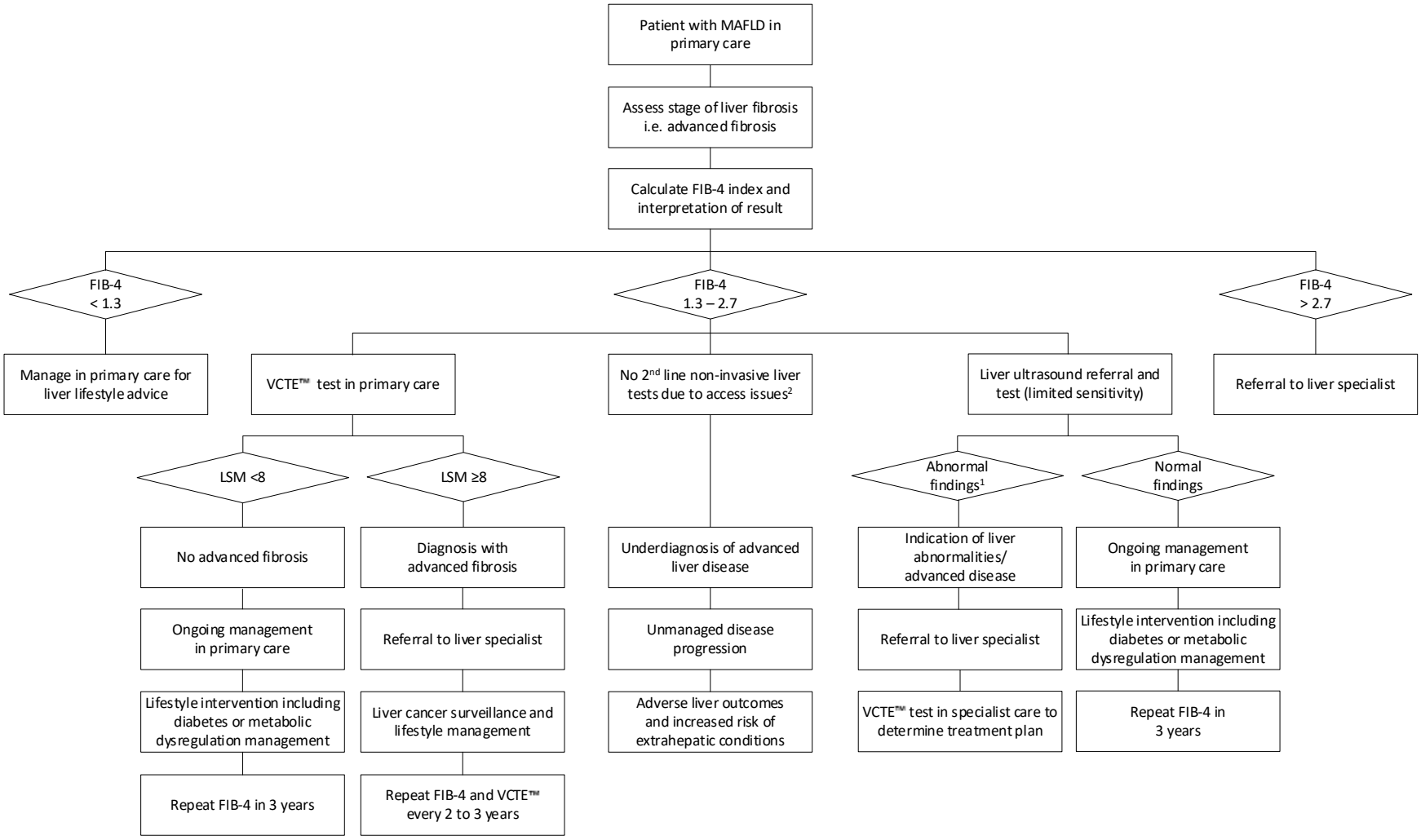
Abbreviation: LSM, liver stiffness measurement; MAFLD, metabolic dysfunction-associated fatty liver disease; VCTE™, vibration-controlled transient elastography

Algorithms

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

Note: Please ensure that the diagrams provided do not contain information under copyright.

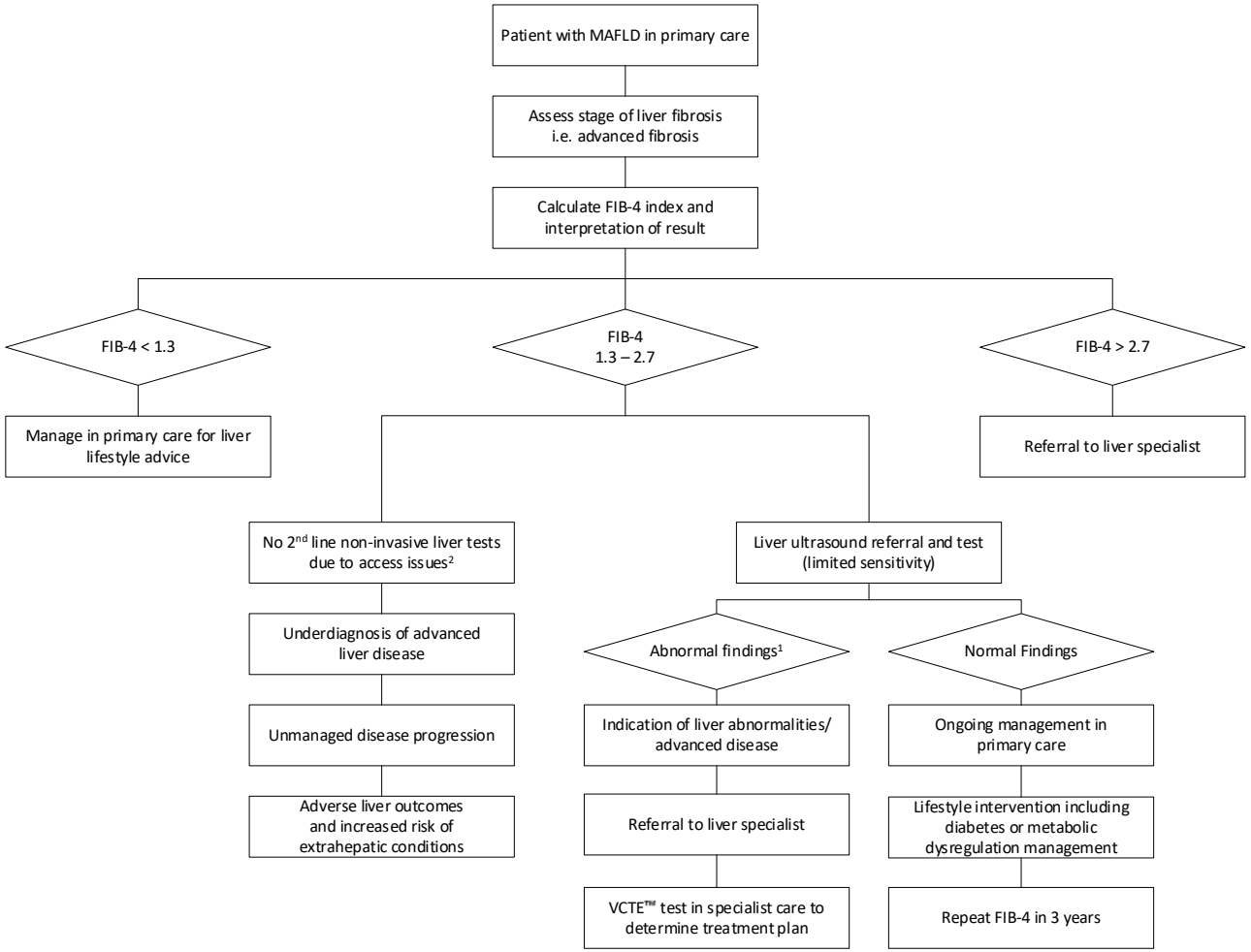
Clinical management algorithm with VCTE™



[1]Abnormal Ultrasound findings refer to aspects related to fibrosis deposition, namely irregularity of liver profile and heterogeneity of its echotexture.

[2]Patients that cannot travel for a second line test due to their primary care provider not offering VCTE™

Clinical management algorithm without VCTE™



[1] Abnormal Ultrasound findings refer to aspects related to fibrosis deposition, namely irregularity of liver profile and heterogeneity of its echotexture.

[2]Patients that cannot travel for a second line test or do not have access to hepatology services in remote areas

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)? (please select your response)

☒ Superior
☐ Non-inferior
☐ Inferior

Please state what the overall claim is, and provide a rationale:
VCTE™ is superior to ultrasound for the detection and risk stratification of intermediate (F2) to AF (F3-F4).

VCTE™ provides quantitative measures of liver stiffness (measured in kPa), which correlates strongly with the degree of liver fibrosis and is highly accurate in identifying advanced fibrosis (F3) and cirrhosis (F4) with validated cut-off values. Ultrasound is qualitative, assessing liver texture, echogenicity, and vascular changes and therefore has poor sensitivity in determining presence of advanced fibrosis.

Additionally, VCTE™ provides valuable prognostic information about the risk of future LREs, including HCC and mortality. Therefore, helping GPs in timely identification of those at-risk of disease progression and plan appropriate patient management.

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

When available, clinicians and GPs use VCTE™ rather than ultrasound as a second-line test for assessing liver fibrosis. VCTE™ is more extensively validated and provides superior accuracy, especially for risk stratifying patients with intermediate (F2) to AF (F3-F4) (MAFLD Consensus Statement Working Group 2024). VCTE™ provides numerical values for liver stiffness, allowing for more objective and precise testing of disease progression or regression over time. Unlike ultrasound imaging, which relies heavily on operator interpretation, VCTE™ offers more standardised results.

Similarly, ultrasound is inaccurate for determining AF and lacks sensitivity for determining cirrhosis (Hetland, Kronborg et al. 2023). In contrast, VCTE™ can detect fibrosis more accurately at earlier stages and differentiate between more mild and advanced disease, allowing clinicians to implement treatment and lifestyle modifications to slow or reverse the advancement of advanced chronic liver disease.

Ultrasound as a second-line test would be used as an additional tool in overall management where VCTE™ is not currently available and where patients require assessment of the structural integrity of the liver (Kemp 2013).

Identify how the proposed technology achieves the intended patient outcomes:

VCTE™ can assist health care professionals assess the severity of their liver fibrosis and risk of complications through early identification, risk stratification and testing of disease progression. This informs more appropriate management, better referral pathways and treatment decisions to avoid future adverse outcomes.

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

A change in clinical management?	Yes	No
A change in health outcome?	Yes	No
Other benefits?	Yes	No

Please provide a rationale, and information on other benefits if relevant:
VCTE™, as a non-invasive and accessible tool for assessing liver fibrosis, can play a crucial role in the early detection and risk stratification of MAFLD patients in primary care.

If VCTE™ is made more widely available outside of specialised hepatology practices, it could help reduce the number of patients with MAFLD that require investigation and management in secondary care settings with non-advanced disease. The prevalence of MAFLD in the Australian population is expected to increase by 25% from the current burden by the year 2030, with one third of the adult population expected to have the disease (Adams, Roberts et al. 2020). Therefore, with the rising burden it is crucial to risk stratify and prevent disease progression early on to relieve strain on hepatology clinics and healthcare resources.

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? (please select your response)

☐ More costly
☐ Same cost
☒ Less costly

Provide a brief rationale for the claim:
VCTE™ in primary care is anticipated to be less costly than ultrasound requires a referral and a higher degree of operator expertise and training to perform and interpret results. Additional tests are also required when using ultrasound to determine AF. In most cases, patients will still often require VCTE™ testing alongside ultrasound findings which results in resource inefficiency.

Summary of Evidence

Provide one or more recent (published) high quality clinical studies that support use of the proposed health service/technology

	Type of study design*	**Title of journal article or research project (including any trial identifier or study lead if relevant)**	**Short description of research (max 50 words)****	**Website link to journal article or research (if available)**	**Date of publication*****
1.	Multicentre cross-sectional Prospective study Diagnostic accuracy	NCT01985009 Accuracy of FibroScan Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients with Non-alcoholic Fatty Liver Disease	Diagnostic accuracy of CAP and LSM against liver histology in patients with NAFLD (n=450).	10.1053/j.gastro.2019.01.042	25 Jan 2019
2.	Multicentre Cohort study Diagnostic accuracy	Validation of the accuracy of the FAST™ score for detecting patients with at-risk non-alcoholic steatohepatitis (NASH) in a North American cohort and comparison to other non-invasive algorithms	Assessed FibroScan-AST (FAST™) diagnostic accuracy across different patient populations and compared performance to other NITs for identifying at-risk NASH (n=585).	10.1371/journal.pone.0266859	15 Apr 2022
3.	Observational cohort study Prognostic accuracy	Using liver stiffness to predict and monitor the risk of decompensation and mortality in patients with alcohol-related liver disease	Evaluated if LSM, using TE, and LSM changes predict decompensation and mortality in patients with alcohol-related liver disease (n = 536).	https://doi.org/10.1016/j.jhep.2024.02.019	27 Feb 2024
4.	Multicentre, retrospective analysis Prognostic accuracy	Monitoring occurrence of liver-related events and survival by transient elastography in patients with non-alcoholic fatty liver disease and compensated advanced chronic liver disease	Investigated in a large cohort of patients with NAFLD and compensated advanced chronic liver disease (n=1039), baseline LSMs and their changes can be used to identify patients at-risk for liver-related and extrahepatic events.	10.1016/j.cgh.2020.06.045	2 Jul 2020

	Type of study design*	**Title of journal article or research project (including any trial identifier or study lead if relevant)**	**Short description of research (max 50 words)****	**Website link to journal article or research (if available)**	**Date of publication*****
5.	Systematic review and meta-analysis Prognostic accuracy	Liver stiffness is associated with all-cause mortality in patients with NAFLD: A systematic review and meta-analysis	Several studies reported an association between LSM obtained through VCTE and all-cause mortality in patients with NAFLD. The objective of this systematic review and meta-analysis was to summarise available evidence on the nature and magnitude of this association.	10.1111/liv.15742	19 Sep 2023
6.	Retrospective cohort study Prognostic accuracy	CAP and LSM as determined by VCTE are independent predictors of all-cause mortality in the US adult population	Study on CAP and LSM to predict mortality in a prospective US cohort at a population level (n=4192).	10.1097/HEP.0000000000000023	April 2023
7.	Prospective, cluster RCT feasibility Pathway management study	Local care and treatment of liver disease (LOCATE) – A cluster-randomised feasibility study to discover, assess and manage early liver disease in primary care	Feasibility trial (n=2082 / TE=910) in the UK hypothesised that setting up nurse-led primary care-based liver clinics using additional non-invasive testing would increase the number of new diagnoses of liver disease compared to usual care.	https://doi.org/10.1371/journal.pone.0208798	21 Dec 2018
8.	Interventional, parallel randomised trial Pathway management study	ACTRN12620000158965 LOCal assessment and triage evaluation of non-alcoholic fatty liver disease (LOCATE-NAFLD) Protocol	It is anticipated that the results of this study will provide valuable new information regarding the management of NAFLD in the Australian setting.	https://dx.doi.org/10.1186/s12913-020-05233-2	Data is currently being analysed with final results to be published.

	Type of study design*	**Title of journal article or research project (including any trial identifier or study lead if relevant)**	**Short description of research (max 50 words)****	**Website link to journal article or research (if available)**	**Date of publication*****
9.	Feasibility study of 2-step pathway Pathway management study	Towards collaborative management of non-alcoholic fatty liver disease: a 'real-world' pathway for fibrosis risk assessment in primary care	Feasibility trial (n=162) examining a 2-step pathway that combined simple scores (NFS and FIB-4 Index) with FibroScan to streamline NAFLD referrals from a 'routine' primary care population to specialist hepatology management clinics (HMC).	10.1111/imj.15422	7 June 2022
10.	Cost-effectiveness analysis model	Cost-comparison analysis of FIB-4, ELF and FibroScan in community pathways for non-alcoholic fatty liver disease	A probabilistic model compared standard care with four alternative scenarios using FIB-4, Enhanced Liver Fibrosis test, and FibroScan in various combinations for 1000 NAFLD patients over one year. The study aimed to determine the most cost-effective approach for detecting AF from a healthcare payer perspective.	10.1186/s12876-019-1039-4	11 July 2019

** Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes. For yet to be published research, provide high level information including population numbers and whether patients are being recruited or in post-recruitment.*

**** If the publication is a follow-up to an initial publication, please advise. For yet to be published research, include the date of when results will be made available (to the best of your knowledge).*

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