MSAC Application 1797

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

Applicant: Medical Technologies Australia Pty Ltd

PICO Confirmation

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with metabolic dysfunction-associated fatty liver disease (MAFLD)

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

Table 1 **PICO for Vibration-Controlled Transient Elastography (VCTE™) in primary care for identifying advanced fibrosis in patients with metabolic dysfunction-associated fatty liver disease (MAFLD): PICO Set 1**

Component	Description
Population	Presenting to primary care, patients diagnosed with metabolic dysfunction-associated fatty liver disease (MAFLD) and who have a fibrosis-4 (FIB-4) index score 1.3 to 2.7.
Prior tests	• Diagnosis of MAFLD (≥5% hepatosteatosis, and at least one of the following: (1) overweight; (2) type 2 diabetes mellitus [T2DM]; or (3) metabolic dysfunction[a]). • Fibrosis-4 (FIB-4) score (requiring assessment of aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels and platelet count).
Intervention	Vibration-Controlled Transient Elastography (VCTE™) administered in primary care with or without abdominal ultrasound with subsequent: (i) management in primary care if liver stiffness measurement (LSM) <8 kilopascals (kPa) by VCTE™; OR (ii) referral to specialist care if LSM ≥8 kPa by VCTE™. Additionally includes a consultation to (i) collect relevant information, including taking a patient history; (ii) initiate interventions and referrals as indicated; (iii) implement a management plan; and (iv) provide the patient with preventative health care advice and information. The item is proposed as 1 service only every 3 years.
Comparator/s	For VCTE™: Standard of care (which may include referral for liver ultrasound, referral to a specialist, or ongoing management in primary care without referral or further testing. It could also include other non-funded tests for the diagnosis of advanced fibrosis). For consultation: standard GP attendance items (e.g., items 036, 044 or 123) which include taking a detailed patient history, clinical examination, arranging investigations, implementing a management plan and providing appropriate preventive health care).
Reference standard	Liver biopsy

Component	Description
Outcomes	• Safety (including any potential risk of harm to the patient). • Accuracy (sensitivity, specificity, positive and negative predictive values) compared with the reference standard liver biopsy. • Change in patient management – change in proportion who remain in primary care, change in proportion who are referred to specialists. • Patient impacts – inequity in the system where VCTE™ for MAFLD is funded differently to other causes of AF, negative impact resulting from VCTE™ being the only funded option for determination of AF. • Efficacy/effectiveness (including, but not limited to, patient-relevant outcomes such as advanced fibrosis, progression of fibrosis, compensated and decompensated cirrhosis, health-related quality of life, mortality) – of VCTE™ itself and of subsequent management. • Health care resources. • Cost-effectiveness. • Total Australian Government health care costs.
Assessment questions	What is the safety, effectiveness and cost-effectiveness of VCTE™ versus standard of care in patients in primary care with a diagnosis of MAFLD and a FIB-4 score of 1.3 to 2.7 for the detection and risk stratification of intermediate to advanced liver fibrosis?

a (i) Elevated waist circumference: ≥90 centimetres (cm) in males or ≥80 cm in females among the Asian population or ≥102 cm in males or ≥88 cm in females among all other ethnicities. (ii) Blood pressure ≥130/85 millimetres of mercury (mmHg) or need for antihypertensive therapy. (iii) Plasma triglycerides ≥1.70 millimole per litre (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) Homeostatic model assessment for insulin resistance (HOMA-IR) score ≥2.5. (vii) Plasma high-sensitivity C-reactive protein (HS-CRP) >2 mg/L.

Table 2 PICO for Vibration-Controlled Transient Elastography (VCTE™) in specialist care for identifying advanced fibrosis in patients with metabolic dysfunction-associated fatty liver disease (MAFLD): PICO Set 2

Component	Description
Population	Presenting to specialist care, patients diagnosed with metabolic dysfunction-associated fatty liver disease (MAFLD) with either: (i) A FIB-4 test score of 1.3 to 2.7 where VCTE™ has not been performed in primary care (e.g., due to lack of access). (ii) A FIB-4 score >2.7. Although not specified in the application, the applicant's clinical expert indicated that conduct of VCTE™ in these patients would provide valuable prognostic information.
Prior tests	• Diagnosis of MAFLD (≥5% hepatosteatosis; and at least one of the following (1) overweight; (2) type 2 diabetes mellitus [T2DM]; or (3) metabolic dysfunctionᵃ). • Fibrosis-4 (FIB-4) score (requiring assessment of aspartate aminotransferase [AST], alanine aminotransferase [ALT] and platelet count).
Intervention	VCTE™ with or without abdominal ultrasound and management in specialist care. Additionally includes a consultation to (i) collect relevant information, including taking a patient history; (ii) initiate interventions and referrals as indicated; (iii) implement a management plan; and (iv) provide the patient with preventative health care advice and information. The item is proposed as 1 service only every 3 years.
Comparator/s	For VCTE™: Standard of care (which may include liver ultrasound, other non-funded tests for the diagnosis of advanced fibrosis, and ongoing management in specialist care). For consultation: standard attendance items (e.g., items 110 and 116) for initial and subsequent attendances by a consultant physician.
Reference standard	Liver biopsy
Outcomes	• Safety (including any potential risk of harm to the patient). • Accuracy (sensitivity, specificity, positive and negative predictive values) compared with the reference standard liver biopsy. • Change in patient management – change in proportion who remain in primary care, change in proportion who are referred to specialists. • Patient impacts – inequity in the system where VCTE™ for MAFLD is funded differently to other causes of AF, negative impact resulting from VCTE™ being the only funded option for determination of AF. • Efficacy/effectiveness (including, but not limited to, patient-relevant outcomes such as advanced fibrosis, progression of fibrosis, compensated and decompensated cirrhosis, health-related quality of life, mortality) – of VCTE™ itself and of and of subsequent management. • Health care resources. • Cost-effectiveness. • Total Australian Government health care costs.

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Component	Description
Assessment questions	What is the safety, effectiveness and cost-effectiveness of VCTE™ versus standard of care in patients in specialist care with a diagnosis of (i) MAFLD, a FIB-4 score of 1.3 to 2.7 and LSM ≥8 kPa and (ii) MAFLD and a FIB-4 score of ≥1.3 for the detection and risk stratification of intermediate to advanced liver fibrosis?

^a (i) Elevated waist circumference: ≥90 centimetres (cm) in males or ≥80 cm in females among the Asian population or ≥102 cm in males or ≥88 cm in females among all other ethnicities. (ii) Blood pressure ≥130/85 millimetres of mercury (mmHg) or need for antihypertensive therapy. (iii) Plasma triglycerides ≥1.70 millimole per litre (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) Homeostatic model assessment for insulin resistance (HOMA-IR) score ≥2.5. (vii) Plasma high-sensitivity C-reactive protein (HS-CRP) >2 mg/L

Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of Vibration-Controlled Transient Elastography (VCTE™) for identifying advanced fibrosis (AF) in patients with metabolic dysfunction-associated fatty liver disease (MAFLD) was received from Health Technology Analysts Pty Ltd by the Department of Health and Aged Care. The application identified two settings for the proposed technology: primary care (PICO set 1) and specialist care (PICO set 2). The application claimed that VCTE™ is superior to ultrasound alone for the detection and risk stratification of intermediate (F2 [significant fibrosis]) to AF (F3 [AF] to F4 [equivalent to cirrhosis]) in the MAFLD population.

PICO criteria

Population

The proposed populations in PICO sets 1 and 2 are limited to patients with a diagnosis of MAFLD, who are further categorised using specific Fibrosis-4 index (FIB-4) test thresholds. The prerequisite (FIB-4) scores are intended to:

(i) Stratify patients according to risk of AF.
(ii) Determine eligibility for VCTE™ (either in primary or specialist care).
(iii) Determine whether subsequent management of the patient should occur in primary or specialist care.

The application proposed the FIB-4 cut-offs presented in Table 3 to stratify the different populations, with details of the associated risk of AF, eligibility for VCTE™ (in the primary care or specialist setting) and recommended subsequent management of the patient (in the primary care or specialist setting). Management of patients, according to the requested item descriptors, includes (i) collecting relevant information, including taking a patient history; (ii) initiating interventions and referrals as indicated; (iii) implementing a management plan; and (iv) providing the patient with preventative health care advice and information.

Table 3   FIB-4 Index score and associated AF risk

FIB-4 Index score	AF risk	Eligible for VCTE™	Management	PICO Set
<1.3	Low	No	Primary care	-
1.3-2.7	Indeterminate	Yes, primary care or specialist care[a]	Primary or specialist care	PICO Set 1 & 2
>2.7	High	Yes, specialist care	Specialist care	PICO Set 2

[a]   VCTE™ conducted in specialist care if no access to VCTE™ in primary care setting

AF = advanced fibrosis; VCTE™ = vibration controlled transient elastography

Patients with a FIB-4 score below 1.3 are considered to be at low risk for AF and are out of scope of this application.

Patients with a FIB-4 test result of 1.3-2.7 are considered at indeterminate risk of AF, and VCTE™ would be conducted (typically in primary care) to determine if AF was present. These patients would be directed to management in primary care or under specialist care based on the result of VCTE™:

- PICO set 1: Patients with liver stiffness measurement (LSM) of <8 kilopascals (kPa) by VCTE™ performed in primary care are considered low risk of AF and would continue to be managed in primary care. Patients with LSM of ≥8 kPa by VCTE™ performed in primary care are considered at high risk of AF and would be escalated to specialist care for management. It is not clear whether these patients would all continue under specialist care as the applicant's clinical expert noted that liver stiffness is not a definitive diagnosis of fibrosis, although it correlates with fibrosis stage and referral for a secondary assessment with a specialist is advised.

- PICO set 2: VCTE™ may be undertaken in specialist care, should a primary care practitioner not have access to VCTE™. If undergoing VCTE™ in specialist care, based on the clinical algorithm (see 5) those with LSM <8 kPa would return to primary care for management and those with LSM ≥8 kPa would be managed under specialist care (if AF was present).

Patients with a FIB-4 score >2.7 are considered to be at high risk of AF, and are included within PICO set 2.

The applicant has clarified that the proposed items are focused solely on initial risk stratification and identification of AF for clinical decision making, rather than ongoing monitoring of fibrosis. Repeat testing is for the purpose of identifying AF in patients in whom it was not present at earlier tests. Although this is the stated intention, the item descriptors allow for repeat testing every 3 years and do not preclude the use of VCTE™ to monitor progression of fibrosis (see discussion under 'Proposal for public funding').

Metabolic dysfunction-associated fatty liver disease (MAFLD) – PICO sets 1 and 2

MAFLD is characterised by excessive fat accumulation in the liver (called hepatic steatosis). Individuals with MAFLD have ≥5% hepatosteatosis and at least one of the following:

1. Overweight according to body mass index (BMI), i.e., BMI ≥23 kilograms per metre squared (kg/m^2) (Asian population) or BMI ≥25 kg/m^2 (all other ethnicities).
2. Type 2 diabetes mellitus (T2DM) as per standard diagnostic criteria.
3. Metabolic 'dysfunction' defined by presence of at least 2 of 7 clinical and biochemical criteria:
   (i)   Elevated waist circumference: ≥90 centimetres (cm) in males or ≥80 cm in females among the Asian population or ≥102 cm in males or ≥88 cm in females among all other ethnicities.

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(ii)   Blood pressure ≥130/85 millimetres of mercury (mmHg) or need for antihypertensive therapy.

(iii)   Plasma triglycerides ≥1.70 millimole per litre (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)   Homeostatic model assessment for insulin resistance (HOMA-IR) score ≥2.5.

(vii)   Plasma high-sensitivity C-reactive protein (HS-CRP) >2 mg/L.

The predecessor term for MAFLD was non-alcoholic fatty liver disease (NAFLD). NAFLD is defined as the presence of ≥5% hepatosteatosis in the absence of significant ongoing or recent alcohol consumption and other known causes of liver disease. MAFLD is a relatively new term designed to better reflect the aetiology of liver disease with 'positive' inclusion criteria compared with NAFLD. Eslam (2020a) described that MAFLD can be diagnosed irrespective of alcohol consumption and can coexist with concomitant liver diseases such as hepatitis B or C infection. The key difference between NAFLD and MAFLD is the inclusion of concomitant causes of liver disease under the definition of MAFLD. The application stated 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 (Kemp 2022, Lim 2023). It is implied that the evidence in the NAFLD population is likely to be applicable to the MAFLD population. One study (Vaz 2023a) found that the change in diagnostic criteria has impacted the understanding of the epidemiology and natural history of fatty liver disease; substitution of NAFLD for MAFLD has led to an increased prevalence of fatty liver disease, with a heightened risk for overall mortality. Importantly, there is an apparent difference in predictors of overall mortality between these fatty liver conditions.

Throughout this PICO Confirmation document, references are made to both MAFLD and NAFLD. Where studies have referred to the population as NAFLD, they are described as such below; however, the evidence presented by these studies has been taken to be relevant to or representative of the MAFLD population. For consistency and simplicity, the Gastroenterological Society of Australia (GESA) MAFLD consensus statement (GESA 2024) uses only the term MAFLD throughout, but does acknowledge that the consensus statement will need to be updated as new data emerge in the context of the newer term MAFLD and its updated definition (rather than relying only on older NAFLD data).

PASC noted that, while the proposed populations for both PICO set 1 and 2 consist of patients diagnosed with MAFLD, there are references to NAFLD throughout the PICO confirmation. In terms of its preference regarding terminology, PASC considered it appropriate to refer to either MAFLD or NAFLD in the PICO confirmation, depending on what was used in the relevant literature, and to make clear any potential differences in patient definitions between the proposed population and the evidence base. However, PASC considered that for simplicity and ease of reading, the assessment report could use the term 'MAFLD' only, provided the difference between these terms and their usage is appropriately explained.

The application used the term MAFLD and its diagnostic criteria to align with current clinical consensus accepted by the Australian Liver Association and reflected in GESA (2024).

The application also differentiated MAFLD from metabolic dysfunction-associated steatotic liver disease (MASLD). MASLD, similar to NAFLD, requires exclusion of excessive alcohol consumption (defined as ≥20

grams (g)/day for women and ≥30 g/day for men) and alternative (e.g., hemochromatosis, hepatitis-related) liver diseases.

By definition, MAFLD is associated with several metabolic conditions, including obesity, T2DM, dyslipidaemia and hypertension. The relationship between MAFLD and these metabolic conditions is bidirectional: the presence of these conditions increases the risk of MAFLD development, as well as progression to advanced liver disease, but, conversely, the presence of MAFLD is associated with an increased likelihood of developing coexisting metabolic conditions. Due to shared risk factors and pathogenic mechanisms, MAFLD is also associated with increased risk of cardiovascular disease (CVD), chronic kidney disease (CKD) and obstructive sleep apnoea (OSA). Given the increased prevalence and incidence of these conditions and their impact on MAFLD severity, it is recommended that patients with MAFLD are routinely screened for these comorbidities. Furthermore, it is important to recognise that quality of life and disease-related morbidity in people with MAFLD may be dominated by coexisting metabolic conditions, rather than by MAFLD itself, emphasising the need to assess and manage these conditions according to Australian condition-specific management algorithms (e.g., the Australian Obesity Management Algorithm and the Australian Type 2 Diabetes Risk Assessment Tool (GESA 2024)).

Figure 1 depicts GESA's assessment algorithm for patients presenting with MAFLD, including metabolic conditions associated with MAFLD.
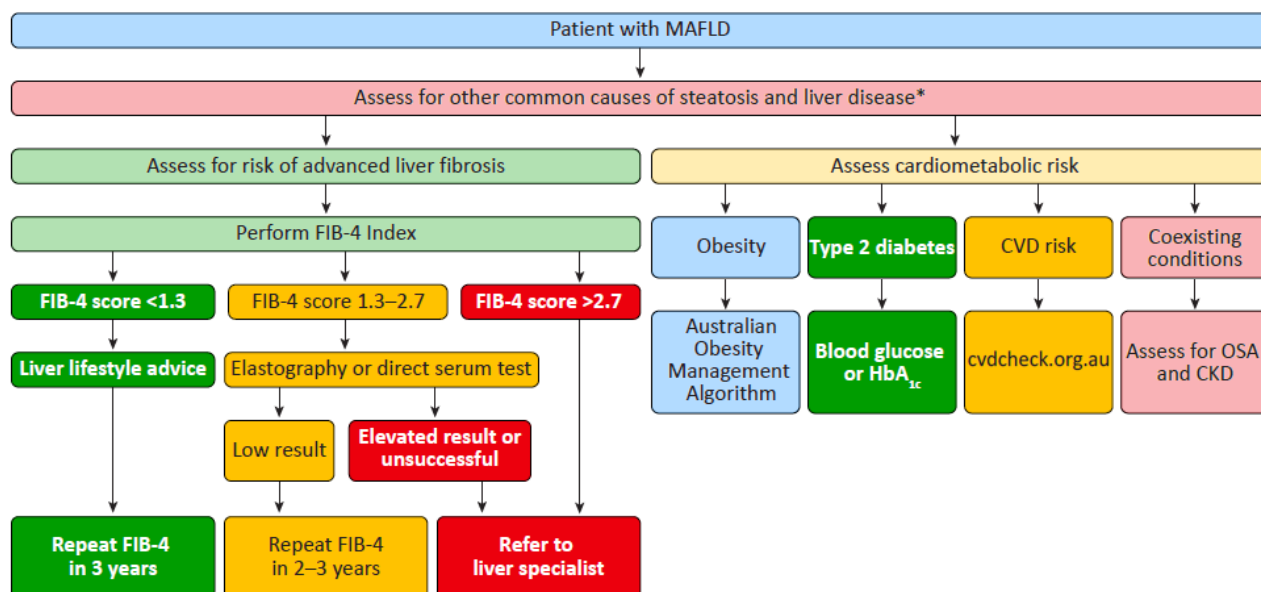

Figure 1 Assessment algorithm for a patient presenting with MAFLD
Source: Figure 2, p25 GESA 2024

Diagnosis of MAFLD and determination of ≥5% hepatosteatosis

The applicant's clinical expert advised that very few general practitioners (GPs) currently screen for MAFLD. However, those who do would administer a liver function test (LFT) in the first instance. While there may be little direct screening for MAFLD, LFTs are routinely used in clinical practice during the assessment and management of CVD and T2DM, such that there may be incidental assessment/diagnoses.

Standard LFTs include measurement of bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) and albumin levels. Other relevant tests include high-density lipoprotein,

triglycerides and platelets. In particular, elevated ALT and AST (both ≥2 times the upper limit of normal), lower platelets, low high-density lipoprotein and triglycerides ≥1.7mmol/L are statistically significant risk factors of fatty liver disease (Hossain 2009; Noureddin 2013). The applicant's clinical expert suggested that if a LFT is abnormal, then abdominal ultrasound is typically requested by a GP.

Liver ultrasound is used to establish the presence of ≥5% hepatosteatosis, which is a requirement for the diagnosis of MAFLD. GESA (2024) stated that ultrasound has consistently demonstrated good to very good accuracy in the detection of fatty liver, and is both inexpensive and readily available in the community. In a moderate-quality updated systematic review and meta-analysis, the area under the curve (AUC), sensitivity and specificity of ultrasound compared with histology for the detection of hepatic steatosis of ≥5% were 0.87, 82% and 87%, respectively, and for the detection of hepatic steatosis ≥30% were 0.92, 85% and 85%, respectively (Ballestri 2021). However, liver ultrasound has its limitations with reduced sensitivity in certain populations, including those with obesity (GESA 2024).

Alternatively, hepatic steatosis can be detected with controlled attenuation parameter (CAP) using VCTE™. However, there are limited available data on the accuracy of CAP as a screening tool in the primary care setting (GESA 2024). CAP demonstrated good accuracy in detecting any hepatic steatosis (i.e., grade S0 vs grades S1–3) in patients with MAFLD, with an AUC of 0.81 and summary sensitivity and specificity of 79% and 73%, respectively. In addition, patients' characteristics such as BMI and diabetes increase CAP readings independently of steatosis grade and should be considered when interpreting CAP results in patients with MAFLD (Petroff 2021). The possibility of using VCTE™ for detecting hepatic steatosis was discussed at the pre-PASC teleconference; however, the applicant's clinical expert opined it would not be used this way, and it is not the intent of the current application. Nevertheless, the implication of the CAP method using VCTE™ for MAFLD diagnosis may need to be considered as potential use beyond the intent of the item descriptor.

Other diagnostic methods include magnetic resonance imaging (MRI), which has the best diagnostic accuracy, with an AUC of 0.95 (95% confidence interval [CI]: 0.93; 0.97), sensitivity of 91% and specificity of 90% (Wang 2018). However, MRI is expensive to perform and not readily accessible nor eligible for an MBS rebate for this indication (GESA 2024).

GESA (2024) indicated that there are several non-commercial biomarkers that have been evaluated to identify or detect MAFLD at a population level; these include the Fatty Liver Index (FLI), hepatic steatosis index, MAFLD liver fat score, visceral adiposity index and triglyceride 9 glucose index. GESA (2024; p12) stated that "these biomarkers are typically composed of a mixture of clinical and laboratory parameters that reflect underlying obesity and metabolic dysfunction. All appear to be confounded by fibrosis and inflammation, and do not accurately quantify steatosis, which may limit their clinical utility".

Prevalence of MAFLD
MAFLD (previously known as NAFLD) is the most prevalent condition affecting the liver, with a global prevalence of NAFLD estimated to be approximately 30% in adults (Younossi 2023; Le 2022). In Australia, there is a paucity of high-quality epidemiological and prevalence data on MAFLD. A disease burden of NAFLD and non-alcoholic steatohepatitis (NASH; or liver inflammation) in Australia was estimated by Adams (2020). A Markov model was used to estimate fibrosis progression, primary liver cancer, and liver deaths among the Australian NAFLD population, with changes in incident NAFLD cases based on long-term trends for changes in the prevalence of obesity. The model forecast the prevalence of NAFLD in Australia

to increase by 25% over the decade to 2030 (from 5,551,000 cases in 2019 to 7,024,000 cases in 2030) or from 22.0% (18.8%–25.0%) in 2019 to 23.6% (19.6%–26.5%) by 2030. The model was reliant on imputed prevalence data extrapolated from studies conducted outside Australia (GESA 2024). The model parameters are considered to be populated with statistics characterised with a high degree of uncertainty. The application cited the same publication with the projected increase in NAFLD significant fibrosis (F2) stage cases by 50% from 2019 to 2030, while AF (F3) stage cases would increase by 70% over the same period.

Two population-based cross-sectional studies have evaluated prevalence in Australia using the validated FLI to identify people with MAFLD. The first of these studies, performed in regional Victoria in 2018 (N=722), reported a high prevalence of 47.2% among a predominantly older White population (Kemp 2022). In another 2012 survey, an analysis of the data from 4747 Australian adults (aged 34-97 years) from the Australian Diabetes, Obesity and Lifestyle (AusDiab) study reported a high MAFLD prevalence of 37% defined as FLI >60 alongside metabolic risk factors; the risk of AF in this MAFLD population was estimated at 61% (Farrell 2022).

MSAC application 1446 for Hepascore was considered at the November 2020 MSAC meeting and included the following estimate: more than 6 million people in Australia have chronic liver disease, including 300,000 with chronic hepatitis C, 200,000 with chronic hepatitis B, 5.5 million with NAFLD and 4.5 million at-risk of alcoholic liver disease (MSAC 1446 PSD p2). NAFLD diagnosis is reliant on excluding alternate causes of liver disease (i.e., alcohol-related fatty liver, viral hepatitis, and drug-induced steatosis). The applicant's clinical expert advised that MAFLD is very common, occurring in ~1 in 4 Australians (i.e., ~7 million people are affected with MAFLD in Australia). Increase in MAFLD is largely driven by increasing prevalence of T2DM. A high-quality meta-analysis of 80 quantitative studies involving 49,419 patients with T2DM found the overall prevalence of MAFLD was 55.5%, which was more than two-fold higher than in the general population (GESA 2024).

Prevalence of liver fibrosis in the MAFLD population

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 liver fibrosis (Vancells Lujan 2021) (PICO Set 1, p2; PICO Set 2, p2). Using liver biopsy as a gold diagnostic standard, liver fibrosis is typically quantified in its severity on a graded scale from F0 (no fibrosis) to F1 (mild fibrosis), F2 (significant fibrosis), F3 (AF) and F4 (equivalent to cirrhosis) (Bedossa 2014). High fibrosis stages are associated with increased liver-related morbidity and all-cause mortality (Vilar-Gomez 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) (PICO Set 1, p3; PICO Set 2, p3). However, reflecting a complex aetiology of MAFLD, while high-risk for fibrosis was the greatest influence over liver-related mortality (hazard ratio [HR] 17.15, 95% confidence interval [CI]: 4.55, 64.65), the other covariates with most influence on overall mortality were alcohol-related liver disease (HR 4.50, 95% CI: 1.89, 10.75) and chronic kidney disease (HR 2.92, 95% CI: 1.21, 7.01) (Vaz 2023a).

The prevalence of AF (i.e., stages F3 and F4) among people with MAFLD in general population studies from overseas ranges from 3.0% to 7.4% (GESA 2024), with a prevalence of 7.6% seen in the UK primary care population (Armstrong 2012). In studies targeting people at risk of NAFLD, the prevalence of AF ranged

from 3.7% to 30% (Caballeria 2018). The variability in these estimates likely resulted from the use of different criteria to determine "being at risk of liver disease" and differences in both the methods of AF diagnosis and the criteria used for risk assessment. No Australian studies estimating prevalence of AF in the MAFLD population were identified; all published data relates to earlier studies conducted in the NAFLD population.

In one Australian study, prevalence of AF in a NAFLD population was estimated using repeated comparative cross-sectional studies in four towns in regional Victoria (Vaz 2023b). Fatty liver in the absence of excess alcohol and viral hepatitis was diagnosed according to FLI score ≥60, calculated from body mass index (BMI), waist circumference, gamma-glutamyl transferase (GGT), and fasting triglycerides. Over 15 years, crude prevalence of NAFLD increased from 32.7% to 38.8% (P <0.01), while age-standardised/sex-standardised prevalence increased from 32.4% to 35.4% (P <0.01).

Assessment of liver fibrosis

In addition to a diagnosis of MAFLD, patients considered in this application must have a FIB-4 Index test result. GESA recommends a non-invasive 'first-line' test such as FIB-4 to help rule out the risk of advanced liver fibrosis in people with MAFLD (see Attachment 1).

PASC noted that the definition of the eligible population, based on the non-invasive FIB-4 index, was not entirely consistent with the GESA guidelines, where non-invasive tests such as (i.e., not limited to) FIB-4 were recommended.

The FIB-4 Index is a non-commercial, low-cost, non-invasive test (NIT) using common laboratory test results that are widely available in clinical practice (AST, ALT and platelet count). FIB-4 can be easily performed using online calculators and is calculated as:

$$\text{(age [years]} \times \text{AST [units per litre or U/L])/(platelet count [}10^9\text{/L]} \times \sqrt{\text{ALT [U/L])}}$$

FIB-4 has been broadly validated as an accurate predictor of AF. Mozes (2022) reported on an individual patient data meta-analysis of 37 studies involving 5735 patients, resulting in a summary AUC statistic of 0.76 (95% CI: 0.74, 0.77) for FIB-4. GESA (2024, p23) states 'interpretation of FIB-4 is aided by lower and upper cut-offs, which translate to low and high risk, respectively, of advanced liver fibrosis. A lower FIB-4 score cut-off of 1.3 is 74% (95% CI: 72%, 76%) sensitive for the diagnosis of AF, whereas a cut-off of 2.67 is 94% (95% CI: 93%, 94%) specific. Results between these cut-offs are indeterminate'. The prevalence of AF is relatively low (between 5% and 10%) in a primary care population (relevant to PICO set 1), and the negative predictive value (NPV) of a FIB-4 score <1.3 is 95%–97%, highlighting its ability to exclude patients with AF; however, the positive predictive value (PPV) of a FIB-4 score >2.67 is only 24%–40% in primary care settings, indicating a need for further confirmatory testing (GESA 2024). In fact, due to the low PPV of the FIB-4 Index for AF, GESA notes that further investigation for AF is required for patients with a score ≥1.3 (GESA 2024). No data were available for the specialist setting, relevant to PICO set 2.

The applicant's clinical expert advised on the medical decision algorithm: if FIB-4 <1.3, there is 98% certainty that the patient does not have AF and these patients are not eligible for VCTE™. If FIB-4 >2.7, liver fibrosis is still not certain, but the patient probably has advanced liver disease and should be referred directly to specialist care.

PASC noted that patients with a FIB-4 score >2.7 were considered at high risk of MAFLD, rather than indeterminate risk. While this application focused on risk stratification of patients (where risk could not be determined from FIB-4 scoring alone), PASC considered it reasonable to include these patients in the proposed population.

The disadvantages of FIB-4 include age as a factor affecting FIB-4 performance. It is inaccurate in people younger than 35 years and should not be used in this population. An indeterminate score of 2.0 to 2.7[1] (rather than 1.3 to 2.7) is recommended for people older than 65 years, because of the reduced specificity of FIB-4 in this age category. FIB-4 scores may be falsely elevated in patients with thrombocytopenia of non-hepatic aetiology (e.g., immune thrombocytopenic purpura or harmful alcohol use) or in those with acute hepatitis, so its use in these clinical scenarios should be avoided.

Although not raised in the GESA Consensus Statement, there is some literature suggesting the accuracy of FIB-4 is compromised in patients with T2DM.

A number of studies report the prevalence of T2DM in the MAFLD population, which ranges from 19% to 28% (Cao 2024, Lim 2023, Farell 2022, Liu 2022, Younossi 2016). GESA (2024) also notes that the prevalence of T2DM increases with severity of underlying liver histology, with prevalences of 22.5% and 43.6% reported in patients with MAFLD and metabolic steatohepatitis (MASH), respectively.

Gracen 2022 reported that FIB-4 had low accuracy in identifying patients with T2DM at low risk of AF, noting that among patients with T2DM who had a VCTE™ LSM of ≥8 kPa (indicative of fibrosis), FIB-4 was <1.3 in 50 of 97 (51.5%) patients. The authors noted this supported the contention that FIB-4 has low sensitivity and resulted in a high number of "false negatives" in those with T2DM, which was particularly concerning given current guidelines indicate that all patients with FIB-4 <1.3 should not be referred to a liver specialist. Gracen 2022 suggested that in people with T2DM, VCTE™ or a patented serum test may be a preferable initial step in fibrosis risk stratification rather than FIB-4.

This issue was discussed at the pre-PASC meeting, with the applicant's clinical expert advising that in the general population attending a GP, the prevalence of advanced liver fibrosis (LF) is <5%, but in the T2DM subgroup it is up to 20%. The expert continued that if pre-test probability is altered, it alters reliability of the <1.3 cut-off, so for this population there is no barrier to FIB-4 being tested more often i.e., annually, such that accuracy of capturing patients with fibrosis will improve over time as testing is repeated to improve its prognostic power. However, this claim may not be justified given multiple factors impact the FIB-4 result. Testing more frequently in situations where parameters included in the algorithm are persistently abnormal will not necessarily lead to a different test result at an individual patient level, meaning a patient may continually experience a "false negative" FIB-4 <1.3. The applicant's clinical expert continued that this is not an issue if FIB-4 >1.3 (since they will be eligible for VCTE™). In relation to 51.5% of T2DM patients with liver stiffness having FIB-4 <1.3, the applicant's expert noted that liver stiffness is not necessarily equivalent to liver fibrosis. However, if the cut-off FIB-4 score for VCTE™ eligibility is set at ≥1.3, there will be a risk that required specialist care is delayed for T2DM patients.

PASC noted that some issues with FIB-4 index thresholds have been reported among those with T2DM, and those aged <35 and ≥65 years old. PASC also noted that the potential alternative FIB-4 score range for

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[1] https://liver.org.au/health-professionals/fib-4-calculator/

indeterminate risk for those aged ≥65 years (2.0 to 2.7) is higher than that in the general population (1.3 to 2.7), meaning that no patients at indeterminate risk would be missed, but rather that some patients at low risk may be screened unnecessarily. PASC acknowledged that these thresholds are less reliable in the T2DM population and those <35 years old. However, PASC considered that the use of standard validated cutoffs for the eligible population was preferable and there was no need to use different cutoffs for different subgroups. PASC noted that the thresholds proposed in the application align with the GESA consensus statement, and considered these to be appropriate.

Other simple serum-based scores, including the NAFLD Fibrosis Score (NFS) and the AST to platelet ratio index (APRI), have been validated in patients with MAFLD but are less favoured due to lower accuracy (GESA 2024).

More complex serum scores, which include direct markers of fibrogenesis or fibrinolysis, include the Enhanced Liver Fibrosis (ELF) score and Hepascore. These direct serum fibrosis tests have limited availability in Australia but have been shown in Australian and international studies to have greater accuracy than the FIB-4 Index for predicting advanced liver fibrosis, with Hepascore also being more accurate for predicting future hepatic decompensation, hepatocellular carcinoma (HCC) and liver-related death (Bertot 2023, Vali 2023, Adams 2011). ELF has been evaluated in an independent meta-analysis (n = 11 studies in 4,452 patients) with an AUROC of 0.83 for detecting AF (Vali 2020). Overall, diagnostic accuracy of patented serum fibrosis tests for staging fibrosis is at least similar to (Anstee 2019), if not higher (Guillaume 2019) than, that of FIB-4 and NFS, but their widespread application in clinical practice is limited by cost and availability (EASL 2021).

PASC considered that the diagnosis of ≥5% hepatosteatosis (required in the population definition) should not be restricted to being determined by ultrasound, noting the potential to use other imaging tests.

PASC noted that Hepascore was considered by MSAC in November 2020 (application 1446[2]) for the diagnosis and monitoring of fibrosis in patients with chronic hepatitis B or C, but was not supported for MBS funding due to limited clinical utility over existing tests and it was considered unlikely to improve clinical management or health outcomes for the intended population.

There are recent studies that have demonstrated an improvement in diagnostic accuracy of individual NITs by combining ELF and FIB-4 in the general population (Kjaergaard 2023) and in the NAFLD population (Younossi 2023). Younossi (2023) determined the cut-off scores of two individual NITs and their combination to rule in and rule out significant fibrosis among NAFLD patients. The authors had liver biopsy results in 463 NAFLD patients of 48 ± 13 years of age, 31% male, 35% T2DM; and 39% of whom had significant fibrosis. The mean ELF score was 9.0 ± 1.2, and mean FIB-4 score was 1.22 ± 1.05 (validated cut-offs for significant fibrosis [F2 - F4] are ≥9.8 and ≥1.3 for ELF and FIB-4, respectively). The performance of the two NITs in identifying significant fibrosis was: AUC= 0.78 (95% CI: 0.74, 0.82) for ELF, and 0.79 (95% CI: 0.75, 0.83) for FIB-4. The combination of ELF score ≥9.8 and FIB-4 ≥1.96 returned a PPV of 95% which can reliably rule in significant fibrosis (sensitivity 22%, specificity >99%), while an ELF score ≤7.7 or FIB-4 ≤0.30 had a NPV of 95% ruling out significant fibrosis (sensitivity 98%, specificity 22%).

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[2] https://www.msac.gov.au/applications/1446

Prevalence of indeterminate and high FIB-4 Index test results

In the Vaz (2023b) study described above, applying the FIB-4 cut-off point of >2.67 to the 2001–2003 cohort of 1040 NAFLD participants, there were 4.6% people at a high risk of AF, while 30.4% fell into the indeterminate risk category (FIB-4 between 1.3 and 2.67). The study was repeated in 2016–2018 recruiting 704 people and, using the same criteria, found that 3.6% were at a high risk of AF and 38.7% were in the indeterminate risk subgroup.

In a NAFLD population of 571 people from a primary care clinic in Brisbane, 3.9% were assessed at high risk of AF based on the FIB-4 cut-off point of 2.67 (Patel 2018b; Supplementary Table 1), while a larger proportion of patients (31%) fell into an indeterminate range.

The applicant's clinical expert stated that the grey area constituting up to the third of patients (supported by estimates in the literature of approximately 30% reported in Patel (2018b) and Vaz (2023b)) is when the FIB-4 score is between 1.3 and 2.7, indicating uncertainty of whether the patient has prognostically significant liver disease.

Utilisation

The application provided an estimate of the number of VCTE™ scans in the first year of listing for both primary care in rural and regional areas and specialist care, see Table 4.

Table 4   Utilisation of VCTE™ in primary care (rural and regional areas) and specialist care in the first year

	Primary care (PICO Set 1)	Specialist care (PICO Set 2)	Source
Proportion Australians living in rural or remote regions	28%	-	Australian Institute of Health and Welfare (AIHW) 2024
Proportion Australians who live in major cities accessing specialist hepatology private clinics	-	72%	Vaz 2023
Proportion of NAFLD patients requiring second-line test	Up to 60%	Up to 60%	Vaz 2023
Number of patients with NAFLD	287,500	287,500	Adams 2020
GP uptake	60%	-	
Specialist uptake	-	70%	
Estimated utilisation in first year	28,980	86,940	

Source: 'Estimated utilisation.xlsx' provided with the application

It is not clear why the estimates for utilisation in primary care were restricted to 'rural and remote areas', as although this is a likely under-serviced population, the item descriptor does not restrict use of VCTE™ in the primary care setting to those in rural and remote areas. The applicant stated that the initial utilisation estimates in primary care were focused on rural and remote areas to reflect the current limited availability of VCTE™ devices in primary care and the intent to prioritise early access in under-serviced, high-need populations. The applicant stated the item descriptor is not geographically restricted and future uptake is expected to expand to all eligible high-risk and indeterminate-risk groups regardless of location. Utilisation estimates should relate to the estimated number of patients in the high risk and indeterminate risk groups.

The applicant has advised that clinician uptake is influenced primarily by device availability, as hepatologists mostly agree on the clinical utility of VCTE™ within their practices and VCTE™ is part of all major clinical guidelines. The applicant noted that utilisation will be elaborated further in the applicant-developed assessment report (ADAR) and was selected as an initial estimate.

Along with VCTE™ there may also be increased utilisation of LFTs and ultrasound, along with assessment of insulin resistance (HOMA-IR) and plasma HS-CRP for the diagnosis of MAFLD as a result of increasing awareness among primary care providers regarding diagnosis, management and referral of MAFLD patients (see 'Intervention' below). These should be estimated in the assessment report.

VCTE™ has the potential to be used in broader populations that are not considered in the application, such as those needing assessment for liver fibrosis due to alcoholic fatty liver disease and/or viral hepatitis B or C infection.

PASC acknowledged that VCTE™ has applications in patient groups other than MAFLD, such as those with alcoholic fatty liver disease and/or viral hepatitis B or C infection. PASC noted the applicant's comments that MAFLD was the focus of this application because it is a leading and major cause of liver cirrhosis and cancer, with a significant healthcare burden. The applicant also stated that VCTE™ is well validated in the MAFLD population, and that other causes of liver disease have different care pathways. PASC considered that there may be an issue of inequity for patients with other forms of liver disease, and this may be considered as part of the patient outcomes for this application.

In 2016, MSAC did not support public funding for VCTE™ for chronic hepatitis B and C patients (MSAC 1366). At the time, while MSAC accepted that transient elastography (TE) was being used by hepatologists as part of routine practice, the evidence that it improved patient outcomes by changing treatment decisions for either hepatitis B or C patients was negligible. MSAC also remained unconvinced by the economic modelling and was concerned about the potential for use in other liver conditions, and for monitoring of treatment responses in hepatitis B and C patients, resulting in substantial additional costs and no clear health gains (MSAC 1366 PSD, p1).

Intervention

The proposed investigative technology for both PICO set 1 and 2 is VCTE™, which is exclusively performed using FibroScan® devices.

In addition to VCTE™, based on the wording of the proposed item descriptors, the intervention includes consultation with either a GP (PICO set 1) or specialist (PICO set 2) to:

a) Collect relevant information, including taking a patient history.
b) Initiate interventions and referrals as indicated.
c) Implement a management plan.
d) Provide the patient with preventative health care advice and information.

While the applicant stated that the clinical utility of VCTE™ relies on the consultation part of the item descriptor, there may be a rationale for separating the VCTE™ scan from the consultation (particularly in the primary care setting) (see 'Proposal for public funding' for further discussion).

PASC noted that the proposed intervention consists of a test component and a consultation component. PASC noted advice from the department that there is a preference to avoid consultation items for specific medical conditions. PASC considered that existing MBS items could be used for the consultation component, either general attendance items or those specific to chronic diseases. Therefore, PASC advised that the consultation component of the proposed item should be removed, and that the intervention itself should be

focussed on the test alone. PASC advised that only the test should be included in the item descriptor, which would also simplify the application (requiring only a single PICO set) and its assessment. PASC advised that if either a bundled item descriptor or a standalone disease-specific attendance item is pursued by the applicant, this would need to be supported by evidence to justify the benefits of the consultation element, as well as the test.

The application (PICO Set 1, p8; PICO Set 2, p7) noted that VCTE™ has been used interchangeably with transient elastography or with the broader term liver elastography in the literature. The application noted that due to concerns about the misuse of VCTE™-based data to strengthen the validity and accuracy of other transient elastography technologies, the term VCTE™ is now exclusively used with reference to FibroScan®, with most studies referring to FibroScan® as VCTE™ from 2014 onwards.

The application is specifically seeking use of VCTE™, rather than an agnostic listing for 'transient elastography' or 'elastography'. Multiple ultrasound elastography variants are available commercially, including VCTE™, Real Time Elastography (RTE), Acoustic Radiation Force Impulse (ARFI) Elastography, Shear Wave Elastography (SWE) and Sound Touch Elastography (STE); all of which (except RTE) provide a quantitative LSM (Gatos 2022). A more recent additional variant is Visual Transient Elastography (ViTE) which is similar to VCTE™ and allows guidance through B-Mode visualisation (Gatos 2022). Gatos (2022) compared VCTE™, ViTE, SWE and STE in chronic liver disease patients using liver biopsy as the gold standard. Patients (n=152) with varying stages of liver disease were included: 30% F0, 20% F1, 9% F2, 18% F3 and 22% F4. The authors concluded that '[t]he results indicate that all methods analyzed in this study perform similarly and can well differentiate fibrosis stage groups, as all balanced accuracies are higher than 0.875 and corresponding AUCs are also higher than 0.945'.

PASC noted that the proposed intervention is specifically limited to branded VCTE™, rather than using broader terms such as 'transient elastography' or 'elastography' to encompass the use of other branded technologies. However, PASC noted that MSAC has a preference for an agnostic approach, rather than branded device- or method-specific tests and interventions, where appropriate. PASC noted the applicant's reasoning, which stated that VCTE™ is accepted by specialists, has validated cutoffs, is reproducible and is more reliable than other methods. PASC advised that these claims would need to be supported by evidence within the assessment report to justify the proposed brand-specific item descriptor, which specifies VCTE™. This would include evidence demonstrating that alternative methods, such as SWE, are inferior for the detection and risk stratification of liver fibrosis in the proposed populations. If this evidence is not available, PASC advised that the proposed intervention and corresponding item descriptor should be agnostic and instead use a broader term such as 'transient elastography'.

The application (PICO Set 1, p4; PICO Set 2, pp3-4) describes VCTE™ as 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.

The VCTE™ measurement is converted into a numerical value expressed in kPa, known as the Liver Stiffness Measurement (LSM). LSM is the median of the successful stiffness measurements (target ≥10).

The LSM ranges from 2.5 (lowest stiffness) to 75 kPa (highest stiffness). The Memorial Sloan Kettering Cancer Center[3] provide the following interpretations for LSM:

- 2 to 7 kPa: F0 to F1, normal.
- 7.5 to 10 kPa: F2, moderate scarring.
- 10 to 14 kPa: F3, severe scarring.
- >14 kPa: F4, cirrhosis.

The applicant stated the proposed LSM threshold of ≥8 kPa for referral to specialist care aligns with their interpretation and clinical intent. The applicant further stated the 8 kPa threshold for FibroScan® is aligned with international guidelines, including those from the European Association for the Study of the Liver (EASL 2021), the American Association for the Study of Liver Diseases (AASLD; Rinella 2023), and the Asian Pacific Association for the Study of the Liver (APASL; Eslam 2025) where these guidelines recognise 8 kPa as a key low cut-off value that provides high confidence in ruling out significant fibrosis. The applicant further stated that in NSW, the eHealth pathways also adopt an 8 kPa threshold, reinforcing its clinical relevance in local practice functioning as a reliable exclusion criterion - if a patient's LSM is below this value, clinicians can be confident that significant fibrosis is unlikely to be missed, ensuring appropriate triage and resource allocation. Of note, liver stiffness is a physical property of the tissue, which depends not only on the amount of liver fibrosis but also on several other factors. LSM results can overestimate fibrosis in cases of inflammation, obstructive cholestasis, food ingestion, exercise, or venous congestion. These should be carefully excluded to avoid misdiagnosis (EASL 2021).

The application (PICO Set 1, p8; PICO Set 2, p7) states that 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. An ultrasound-like probe is placed on the skin over the liver area, typically in the right mid-axillary line. The test requires a minimum of 10 valid readings per patient, with at least a 60% success rate and an interquartile range (IQR) of ≤30% of the median value being taken (Kemp & Roberts 2013). The applicant advised that the machine indicates to the operator performing VCTE™ if there is an invalid result, and validity of the results can be assessed by the operator.

Among patients with NAFLD in an Australian primary care setting, the prevalence of overweight and obesity were reported as 27% and 67%, respectively (Patel 2018b). GESA (2024) reported that 'VCTE™ scans are less accurate with increasing BMI and are invalid in up to 20% of patients with morbid obesity (BMI >35 kg/m^2)'. The applicant clarified that the term 'invalid' does not mean the whole test is invalid, but that a particular shear wave reading has not worked. The applicant explained that this may mean the test may take longer (as more shear wave readings are taken). The applicant further advised there have been technological advancements to improve performance in obese patients.

In recognition that VCTE™ assessment with a medium (M) probe is difficult to perform in obese and overweight patients, an advancement in the technology has been the development of the extra-large (XL) probe. The M probe has an ultrasound frequency of 3.5 MHz for measurement at a depth from 2.5 to 6.5 cm from the skin, while the XL probe, with an ultrasound frequency of 2.5 MHz for measurement from 3.5 to 7.5 cm, is used when the skin-to-liver capsule distance is >2.5 cm (Vuppalanchi 2018). The applicant has

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[3] https://www.mskcc.org/cancer-care/patient-education/understanding-your-fibroscan-results

also advised there are further developments with SmartExam (2021), and guided-VCTE™ (2024), which have also improved performance in the obese. Bastard (2025) provided the following information: "Guided-VCTE relies on the use of shear waves not only to measure liver stiffness, but also to help the operator locate the liver. In addition to the ultrasound images and ultrasound-based indicators, a real-time predictive indicator of shear wave propagation is displayed to the operator during the Guided- VCTE procedure. To improve stiffness measurement in patients with high BMI, this new technique also takes advantage of continuous shear wave propagation to implement shear wave map (SWMP) averaging, thereby improving signal-to-noise ratio". Bastard (2025) reported that the success rate of individual measurements and the time required for localisation of the liver was improved with guided- VCTE™ examination, especially in patients with BMI ≥35 kg/m². The applicant's clinical expert also advised that very few VCTE™ are unable to be performed in obese patients, except for the patients who are morbidly obese, which is rare.

VCTE™ can stratify risk of future liver-related events in patients within the indeterminate FIB-4 score range (1.3–2.7); patients with a FIB-4 score ≥1.3 and LSM <8.0 kPa are at low risk of AF and liver-related morbidity, similar to those with a FIB-4 score of <1.3, whereas those with a FIB-4 score ≥1.3 and LSM ≥8.0 kPa are at an increased risk of liver-related events (Boursier 2022).

PICO Set 1
The application proposed a two-step non-invasive testing pathway with the first step – diagnosis of MAFLD and a FIB-4 test result as a pre-requisite to establish eligibility for the second step – VCTE™ (and consultation) conducted in primary care, which would assist a GP in making a decision to refer a patient to a specialist:

- Patients with MAFLD, a FIB-4 score of 1.3 to 2.7 and LSM of <8 kPa would be managed in primary care.
- Patients with MAFLD, a FIB-4 score of 1.3 to 2.7 and LSM ≥8.0 kPa are referred to specialist care.

Although this is generally consistent with the GESA Consensus Statement (GESA 2024), it should be noted that GESA (2024) recommendations are broader than the proposed intervention, where second-line assessment (second step) could be any of VCTE™, SWE or one of several serum fibrosis tests (including ELF score and Hepascore).

PICO Set 2
The proposed intervention for PICO set 2 is VCTE™ (and consultation) conducted in specialist care. As for PICO set 1, this is broadly consistent with the GESA Consensus Statement (GESA 2024), although it should be noted that other second-line assessment options may also be available and appropriate.

The applicant considered that, in both the primary and specialist care settings (i.e., PICO set 1 and 2), VCTE™ may be performed by (i) practice staff (e.g., nurses or technicians), considered the most likely clinical practice scenario or (ii) a billing practitioner (either a GP or specialist). That is, the two proposed components of the intervention (VCTE™ and consultation) may be performed by different people.

While there is currently no dedicated MBS item for VCTE™, the proposed intervention is currently performed in a number of scenarios and may be fully or partially publicly funded:

- Primary care consultation item with VCTE™ in rooms (with potential patient out-of-pocket costs).

- Primary care consultation item with the patient referred to a private radiology practice (covered with MBS billed primary consultation item and MBS billed abdominal ultrasound with element of private billing for elastography) for elastography (which may be VCTE™ or another method).
- Primary care consultation item with referral to liver specialist for VCTE™ .

Current VCTE™ providers include public hospitals and community health facilities, where 41% of FibroScan® devices are located, where services may be funded under the National Health Reform Agreement, meaning the service is Medicare ineligible. The submission received from GESA also indicated that many local VCTE™ services are funded through research programs rather than local health services (e.g., Northern Territory and South Australia remote services including for Aboriginal Community Controlled Health Organisations [ACCHOs]), and Medicare ineligible outreach services such as prisons, safe injecting rooms and, community correction facilities.

Uptake of the technology
The applicant has advised that as of February 2025, REDACTED VCTE™ machines are currently split across specialist centres (in hospitals and clinics), community health facilities and other locations. A detailed description of the split is shown below:

- REDACTED hepatology specialist care:
  - REDACTED public hospitals
  - REDACTED in private hospitals

- REDACTED community health facilities:
  - REDACTED infectious diseases
  - REDACTED drug and alcohol care

- REDACTED (REDACTED) in other locations, including
  - REDACTED in Aboriginal health clinics
  - REDACTED in prison for viral hepatitis
  - REDACTED in diabetes units
  - REDACTED owned by a private GP
  - REDACTED in research or radiology

Further, the applicant has advised there are REDACTED VCTE™ machines in New South Wales, REDACTED in Victoria, REDACTED in Queensland, REDACTED in Western Australia (further devices have since been purchased), REDACTED in South Australia, REDACTED in Tasmania, REDACTED in the Australian Capital Territory and REDACTED in the Northern Territory. It was not clear where the remaining REDACTED machines (of the REDACTED in Australia) are located.

PICO Set 1
The application claimed that increasing accessibility of VCTE™ to primary care patients and risk stratification using VCTE™ in primary care for patients with indeterminate FIB-4 scores (1.3-2.7) would lead to better targeting of high-risk patients resulting in fewer low risk patients being referred to liver specialists. This application stated that this would improve healthcare system efficiency and reduce unnecessary specialist visits (PICO Set 1, p6).

Based on the current distribution of VCTE™ machines, if public funding of VCTE™ in the primary care setting was supported, this would need to be accompanied with investment in the technology in the primary care setting. The applicant anticipated that there would be investment in the technology if it were to be MBS listed, with a particular focus on expanding access in community clinics located in high-need areas, which would likely involve device-sharing agreements to optimise resource distribution and accessibility. In general, Medicare benefits are not payable for professional services (such as those provided in hospitals, multipurpose services and community clinics) where other government funding is already provided for that service.

At the pre-PASC teleconference, the applicant suggested REDACTED.

PASC noted the applicant's intent to expand the availability of VCTE™ in the primary care setting, which requires investment in both equipment and training, and potentially 'hub' and/or device sharing arrangements. PASC noted that although the application discussed the test as mainly being rolled out in areas of high need, no implementation plan to address this was proposed, other than the expectation that an MBS item would lead to clinics investing in the technology.

PASC also queried the training required to perform VCTE™, in particular for the GP workforce, and noted consultation feedback that VCTE™ may be best conducted by specialists. The applicant clarified that training was not onerous – the company provides a standardised 3-hour course covering both the conduct and interpretation of the scan; there is also an expectation of ongoing practice.

Creating awareness among primary care providers regarding diagnosis, management and referral of MAFLD patients would also be needed. A cross-sectional survey of primary care clinicians' approach to diagnosis, management and referral of NAFLD patients (defined by demonstration of hepatic steatosis by liver ultrasound in the presence of metabolic risk factors and the exclusion of significant alcohol consumption [≥20 g/day] or other chronic liver diseases, including a prior history of alcohol-related liver disease) with liver fibrosis was conducted in Queensland between August 2016 and March 2017 (Patel 2018a). 51% of respondents considered the prevalence of NAFLD in the general population to be ≤10%, and 24% of respondents felt that liver enzymes were sufficiently sensitive to detect underlying NAFLD. Most respondents were unsure whether the FIB-4 score (62.7% unsure) or ELF score (63.7% unsure) could help to identify AF or cirrhosis. Although 47% of respondents said they would refer a patient to a gastroenterologist/ hepatologist if they suspected the patient had NAFLD, 44.1% do not make any referrals. The authors concluded that these findings demonstrate that many primary care clinicians underestimate the prevalence of NAFLD and under-recognise the clinical spectrum of NAFLD and how this is assessed. It is noted the GESA (2024) consensus statement is available on the Royal Australian College of General Practitioners website.[4]

PICO Set 2

While the applicant has advised that REDACTED of VCTE™ machines are currently in hepatology specialist care, this does not indicate how widely accessible VCTE™ is for those referred to specialists (i.e., what proportion of specialist hepatology centres have VCTE™). This represents a potential equity of access issue.

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[4] https://www.racgp.org.au/search?q=mafld#gsc.tab=0&gsc.q=mafld&gsc.page=1

Comparator(s)

The application states 'The clinical utility comparator for VCTE™ in primary care is the referral to a liver specialist and ultrasound service' (PICO Set 1, p11). For abdominal ultrasound, MBS item 55036[5] is used.

For the consultation component of the intervention, standard GP attendance items (e.g., items 023[6], 036[7], 044[8] and 123[9]) may be relevant.

The application states the 'The clinical utility comparator for VCTE™ in specialist care is ultrasound' (PICO Set 2, p10). For abdominal ultrasound, MBS item 55036 is used (as in PICO set 1).

For the consultation component of the intervention, consultant physician attendance items 110[10] and 116[11] may be applicable:

The overall consensus is that further tests are required for people with indeterminate (e.g., FIB-4 test scores of 1.3-2.7; GESA 2024) or indeterminate to high-risk scores (e.g., FIB-4 test score ≥1.3; EASL 2021) to confirm the diagnosis of AF or cirrhosis. Liver elastography (including VCTE™ and shear wave elastography [SWE]) or a direct serum fibrosis test (including Hepascore and ELF) are typically recommended for second-line evaluation of a patient with an indeterminate FIB-4 result, owing to the higher accuracy of these tests (GESA 2024; EASL 2021).

PASC did not consider the proposed test comparator, ultrasound, to be appropriate, since ultrasound is not able to accurately assess liver fibrosis. PASC noted that the GESA guidelines included alternative tests for the diagnosis of fibrosis, namely SWE and direct serum fibrosis tests, neither of which are currently MBS-listed.

The MSAC guidelines indicate that public funding is an indicator of established cost-effectiveness. Non-publicly funded comparators may be used, but "where the comparator is funded under a different source, and the cost-effectiveness of the comparator is unknown, the cost-effectiveness of both the comparator and the intervention may need to be established" (Guidelines for preparing assessments for the Medical Services Advisory Committee, p36)[12].

PASC noted that SWE was available as an add-on to standard ultrasound equipment and available in public and private radiology clinics. PASC noted the applicant's comments that the method was less well-validated than VCTE™. With respect to direct fibrosis serum tests, PASC noted there are 2 available in Australia – ELF and Hepascore.

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[5] https://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=55036&qt=item&criteria=55036
[6] https://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&qt=ItemID&q=23
[7] https://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&qt=ItemID&q=36
[8] https://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&qt=ItemID&q=44
[9] https://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&qt=ItemID&q=123
[10] https://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&qt=ItemID&q=110
[11] https://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&qt=ItemID&q=116
[12] https://www.msac.gov.au/sites/default/files/2024-10/guidelines-for-preparing-assessments-for-msac.pdf

In MSAC application 1366 for transient elastography (TE) for patients with chronic hepatitis B or chronic hepatitis C, MSAC considered that the most appropriate comparator for TE was clinical assessment rather than liver biopsy (MSAC 1366 PSD, p2). Alternative comparators were not presented. Although liver biopsy is an appropriate reference standard for the assessment of analytical validity (see below), it is invasive, associated with a risk of complications and is not routinely done. Clinical assessment is inherently complex and involves all the clinical and laboratory tests (used in combination) routinely performed in patients with liver disease (MSAC 1366 PSD, p2). In the context of the Hepascore application (MSAC 1446), MSAC stated that the proposed comparator for both populations is usual clinical assessment that includes medical history, physical examination, LFTs, full blood count, international normalised ratio (INR), aspartate aminotransferase-to-platelet ratio index (APRI) and liver ultrasound where available (MSAC 1446 PSD, p9).

The applicant's expert stated that the first step in general practice is LFT, then ultrasound and more tests to exclude hemochromatosis and hepatitis, followed by referral to a specialty clinic for thorough evaluation if needed, including fibrosis assessment using transient elastography—VCTE™. The applicant advised that they do not advocate using VCTE™ for screening (e.g., with CAP) in the primary care population for fatty liver disease or fibrosis, but they ask GPs to look at risk groups (T2DM and obese) and think about fatty liver disease. Elsewhere, the applicant's expert suggested that, in the absence of VCTE™, ultrasound should be done at least annually (presumably in the MAFLD population, with uncertain FIB-4 scores ranging from 1.3 to 2.7). Current practice (although this is not protocolised) is GPs conducting LFTs and monitoring ultrasounds and then referring patients to specialists if results are abnormal.

The application stated that the 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 (PICO, Set 1 p12). Similarly, PICO Set 2 (p11) stated that VCTE™ is expected to partially displace ultrasound to determine extent of AF and accurate staging of liver fibrosis in people with MAFLD. The application further stated that 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, it appears that it will be partially displaced by VCTE™ in the continuum of care for patients with MAFLD (PICO Set 1, p13; PICO Set 2, p11).

MSAC Application 1446 (MSAC 1446 PSD p2 and 19) noted that FibroScan® is routinely used in public hospitals, and that FibroScan® and the ELF test are routinely performed for patients in rural and remote areas and are usually paid for by local health services. MSAC also considered liver ultrasound may include SWE, but noted that this is considered less effective than TE in detecting fibrosis. MSAC acknowledged that Hepascore may be of value in rural and remote areas where transient elastography is less accessible.

The department also noted that clinical assessment, the provision of management advice and VCTE™, when performed by a medical practitioner, can already be rebated via MBS attendance items (as discussed in the Intervention section).

PASC advised that 'standard of care' is the most appropriate comparator since there are no MBS-listed alternative fibrosis tests. According to the current clinical management algorithm, for patients in primary care, this may include a referral to a specialist, or ongoing management in primary care without referral or further testing. It could also include other non-funded tests. In the specialist setting, standard of care may

include liver ultrasound, other non-funded tests for the diagnosis of advanced fibrosis, and ongoing management.

Reference standard (for investigative technologies only)

According to GESA (2024), liver biopsy remains the reference standard for assessment of liver fibrosis, although the accuracy of the result is influenced by the size of the tissue sample and the experience of the liver pathologist. However, liver biopsy is also invasive, costly and not scalable; hence, it is not a suitable screening test for fibrosis and has limited use in monitoring disease progression.

Similarly, liver biopsy was accepted as the reference standard for the MSAC 1446 application (MSAC 1446 PSD, p9). For MSAC 1366, MSAC considered that although liver biopsy is an appropriate reference standard for the assessment of analytical validity, it is invasive, associated with a risk of complications and is not routinely done (MSAC 1366 PSD, p2).

PASC considered liver biopsy to be the appropriate reference standard for the assessment of the analytical validity of VCTE™, while also noting that the procedure is invasive and not suitable for widespread use in the primary care setting.

Outcomes

For both PICO sets (1 and 2), the application proposed the following key health outcomes (health benefits) for assessing the clinical claim for VCTE™ versus the comparator:

- Test accuracy compared to liver biopsy (reference standard).
- Concordance with ultrasound.
- Prognostic accuracy compared to clinical assessment.

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, for PICO set 1 (primary care), the application proposed the resource-related health outcome of reduced referrals to specialist care (Hayward 2022; Brain 2020). The application claimed that incorporating VCTE™ in primary care will lead to a change in clinical management, reducing unnecessary referral of patients with non-advanced disease, thereby decreasing the cost to detect AF.

The application (PICO Set 1, p6) stated that incorporating VCTE™ into primary care will address several systemic issues:

- Reduced specialist burden: enabling primary care providers to perform initial fibrosis assessments would relieve pressure on liver specialists, which may be especially beneficial for patients in rural and regional settings. As GPs would have access to VCTE™ results, they need only refer patients with AF to a liver specialist.
- Improved equity of access: expanding access to VCTE™ beyond major metropolitan centres would benefit patients in a variety of geographic areas. Note that this would be dependent on increased

availability of VCTE™, which would in turn depend on investment in the primary care sector (see 'Intervention' for discussion).

- Improved health outcomes: Early detection and identification of high-risk patients would identify individuals at high-risk of progressing to more severe liver diseases and liver cancer.

The application made no claims regarding health harms or the value of knowing.

Notably, the application has limited the outcomes under assessment to those of diagnostic accuracy and change in clinical management rather than extending out to health outcomes such as morbidity, mortality and health-related quality of life. The applicant has stated that the ADAR will work towards assessing the following patient-relevant outcomes, providing the availability of clinical evidence:

- Progression of liver fibrosis: VCTE™ is validated as a non-invasive tool for liver fibrosis staging, particularly for patients with MAFLD. The diagnostic accuracy of LSM by VCTE™ has been confirmed in multiple studies, showing high sensitivity for detecting AF (F≥3) and cirrhosis (F4). VTCE is able to rule out cirrhosis, suggesting its effectiveness in early-stage fibrosis detection.
- Compensated versus decompensated cirrhosis: VCTE™ is an effective diagnostic tool for assessing compensated cirrhosis (F4). LSM by VCTE™ has been validated as an independent predictor of liver-related events, including the transition from compensated to decompensated cirrhosis.
- Further outcomes will be specified given the available studies and data on progression and QALYs.

Total Australian Government health care costs are also considered relevant.

The following provides examples of the types of outcomes reported in published trials and previous HTA assessments, for reference.

Published trials/studies

A brief scan of the literature identified a study reported by Hayward (2022) which replicated the same sequential testing approach as proposed in this application (i.e., FIB-4 (or NFS) followed by FibroScan®). Hayward (2022) reported on a study where 220 patients (n=162 analysed) with a primary care diagnosis of NAFLD were referred to a two-step pathway between June 2019 and December 2020 in Brisbane, Queensland. Patients were classified as 'low risk' if both FIB-4 (<1.3, or <2.0 if aged ≥65 years) and NFS (<- 1.455) were low (n=55; notably, 56 and 131 patients had low NFS and FIB-4 results, respectively, with only 55 patients having concordant 'low' results); and classified as 'high risk' if FIB-4 (>2.67) or NFS (>0.676) were high (n=17). Patients considered low risk were returned to the care of their primary care physician and those at high risk were referred to a hepatology management clinic for further assessment. Those with indeterminate FIB-4 (1.3 [or 2.0 for those aged ≥65 years] to 2.67) and/or NFS (- 1.455 to 0.676) results (n=90) proceeded to a second step of VCTE™; those with LSM <8.0 kPa were returned to their primary care provider and those with ≥8.0 kPa were referred to a hepatology management clinic for further assessment.

Hayward (2022) reported that VCTE™ was performed in primary care in 88 of 90 'indeterminate risk' patients, with 73 having LSM <8.0 kPa, consistent with no clinically significant fibrosis; 69 (94.5%) of these 73 patients remained under the care of their primary care physician and 4 were referred to a hepatology management clinic for other clinical concerns. Of the 15 remaining patients, 10 patients had LSM ≥8.0 kPa and 5 had invalid results and were referred to a hepatology management clinic. Ultimately, from these 19

'indeterminate' patients, once referred to a hepatology management clinic, 4 had LSM <8.0 kPa, 8 had LSM ≥8.0 kPa and 7 had no VCTE™ results (1 failed to attend, 5 awaiting assessment and 1, although not having VCTE™ had a liver biopsy ≥F3). Interestingly, of the 17 'high risk' patients according to FIB-4 or NFS, 11 had LSM <8.0 kPa.

Further relevant published trials/studies are discussed below.

The LOCal Assessment and Triage Evaluation of Non-Alcoholic Fatty Liver Disease (LOCATE-NAFLD; Tulleners 2024; Brain 2020) is an Australian randomised controlled trial (RCT) that investigated community-based fibrosis assessment service using FibroScan®. Patients with diagnosed or suspected NAFLD were randomised (1:1) to either usual care, whereby patients remained on the wait list to see a hepatologist at a hospital hepatology clinic, or to the LOCal Assessment and Triage Evaluation (LOCATE) model of care, where a FibroScan® appointment was arranged for the patient. The primary outcome of LOCATE-NAFLD was time to diagnosis of high-risk NAFLD, based on the number of participants in each arm of the study who received a diagnosis of clinically significant fibrosis (defined as VCTE™ ≥8.0 kPa). Patient-relevant secondary clinical outcomes included reduction in hospital admissions, reduction in emergency department presentations, improved health-related quality of life using the EQ-5D-3L (measured at study recruitment and at 12 months), reduced HCC detected outside specific surveillance, increased referrals to a specialist other than a hepatologist (e.g., to a dietician or exercise physiologist) and reduced mortality.

Pearson 2024 reported the results of a study that investigated the impact of adding the ELF score as a second-line test (subsequent to an indeterminate or high FIB-4 and/or non-alcoholic fatty liver disease fibrosis score) in order to guide referral and prognostication in 1,327 patients with indeterminate fibrosis scores (NFS or FIB-4 index). The clinical primary endpoints reported by Pearson (2024) were diagnosis of cirrhosis (documented by a hepatology specialist based on all available evidence, including signs, symptoms, biochemistry, stiffness measurements and/or imaging), and liver-related morbidity, defined as an admission to hospital with an episode of decompensated liver disease (ascites, variceal bleeding, hepatic encephalopathy), or diagnosis of hepatocellular carcinoma (HCC). Secondary endpoints included liver-related mortality and all-cause mortality. The study also investigated change in rate of hepatology referrals.

Previous MSAC applications

The MSAC 1446 application considered by MSAC in November 2020 sought MBS listing of the Hepascore test (a serum fibrosis panel test) to diagnose and monitor liver fibrosis severity in patients diagnosed with hepatitis B and C infection. The application proposed that the test could be requested by GPs or specialists. The outcomes included in the ratified PICO were:

- Safety — false negatives or false positives;
- Analytical validity, including coefficient of variability (within individual (biological) variability) of each of the tests;
- Diagnostic accuracy – false positives (FP), false negatives (FN), true positive (TP), true negative (TN) as absolute counts, according to the different cut offs (AF (F3) and cirrhosis (F4)), sensitivity, specificity and receiver operating characteristic (ROC) for each cut off;
- PPV and NPV;
- Efficacy / effectiveness including, but not limited to, patient-relevant outcomes, predictive of long-term liver related outcomes; and

- Healthcare resources: cost of the additional test, surveillance of patients diagnosed with cirrhosis; costs associated with liver disease.

International HTA evaluations

National Institute for Health and Care Excellence (NICE)

NICE has conducted an evaluation of FibroScan® for assessing liver fibrosis and cirrhosis in primary or community care, which included the treatment of patients with NAFLD. The project scope (p8, NICE, Medical technology guidance scope, FibroScan® for assessing liver fibrosis and cirrhosis in primary or community care) listed the outcome measures to be considered included:

- Test accuracy;
- Agreement between measurement made by FibroScan® done in primary and secondary/tertiary care;
- Comparative performance between different FibroScan® models;
- Test failure;
- Uptake of offered FibroScan® test;
- Uptake of behaviour/ lifestyle change intervention;
- Number of referrals to secondary care;
- Number of people referred to alcohol or weight management services;
- Severity of liver fibrosis;
- Device-related AEs;
- Use of NHS services (for example, GP or outpatient appointments);
- Mortality; and
- Morbidity (such as liver cirrhosis, liver related complications, cardiovascular complications).

The comparator was FibroScan® used in the same way as the intervention, but in secondary or specialist care only (i.e., as in PICO set 2).

In June 2023, NICE recommended FibroScan® as an option for assessing liver fibrosis or cirrhosis outside secondary and specialist care (in primary or community care) if:

- each FibroScan® device is expected to be used for at least 500 scans per year, typically requiring use in locations which cover larger populations, such as community diagnostic hubs;
- this is likely to improve access to testing for underserved groups;
- it is used in accordance with national guidelines;
- a clear care pathway with guidance for healthcare professionals doing the test on what to do based on a FibroScan® result is established locally through collaboration between primary or community care and secondary or specialist care providers; and
- there are training and supportive materials available for healthcare professionals.

Canada's Drug Agency (CDA), formerly the Canadian Agency for Drugs and Technologies in Health (CADTH)

In 2012, CADTH produced a Rapid Response Report for the Diagnosis and Monitoring of Liver Fibrosis in Patients with Chronic Hepatitis C: A Review of the Clinical Evidence and Cost Effectiveness. The aim of the review was to evaluate the available evidence regarding the validity of non-invasive methods and their cost effectiveness compared with liver biopsy in the diagnosis and monitoring of liver fibrosis in patients with chronic hepatitis C viral infection. The commonly reported non-invasive methods for detecting

hepatic fibrosis identified in the report included transient elastography (TE, or FibroScan®) as well as other biomarker methods such APRI and Fibrotest (uses the results of 6 blood serum tests (alpha-2-macroglobulin, haptoglobin, apolipoprotein A1, GGT, total bilirubin, and ALT) to generate a score that is correlated with the degree of liver damage[13]). The main outcomes investigated were the accuracy and validity of the tests to detect and grade liver fibrosis such as area under receiver operating characteristic curve (AUROC), sensitivity, specificity, PPV and NPV. The report noted that AUROC is an estimate of the probability of a true diagnosis, with an AUROC of 1.0 (100%) indicating a test can classify a patient with perfect accuracy, while an AUROC of 0.5 indicates that a test has a 50% chance of correct classification. Cost-effectiveness (ICER, $/QALY) was also investigated.

PASC advised that the applicant's proposed outcome of harms from "false-negative FIB-4 scores" should be excluded from both PICO sets, as this is not an outcome of the proposed intervention, VCTE™, but rather occurs earlier in the clinical pathway.

PASC advised that test accuracy measures should be compared to the reference standard of liver biopsy.

PASC advised that, when considering the outcome of change in patient management, 'what proportion continue to be referred to specialist care due to comorbid reasons for AF or due to low accuracy of FIB-4 (due to T2DM or age)' should be excluded. This is because these patients would already be captured in the other change in management outcomes, specifically the 'change in proportion [of patients] who are no longer referred to specialists'.

PASC noted that patient impact outcomes had not been captured in the applicant's proposed outcomes. PASC considered that there was potential for inequities. If implemented as proposed in this application, VCTE™ for MAFLD would be funded differently to tests for other causes of AF, and there may be a negative impact from VCTE™ being the only funded option for determination of AF. PASC acknowledged that these impacts would be difficult to capture and likely would not be supported by data.

PASC noted that cost-effectiveness of VCTE™ would depend on the effectiveness of lifestyle and dietary modification. PASC advised that effectiveness for the purposes of cost-effectiveness determination would be ideally measured with health outcomes, rather than test outcomes. PASC considered that a cost-utility analysis would be desirable, but noted that a cost-effectiveness analysis (CEA) was acceptable based on the clinical claim. One example of a health outcome measurable in a CEA would be cost per case of cirrhosis or liver cancer averted.

The relevant outcomes for both PICO set 1 and PICO set 2, incorporating PASC's advice, are outlined below:

- Safety (including any potential risk of harm to the patient).
- Accuracy (sensitivity, specificity, positive and negative predictive values) compared to the reference standard of liver biopsy.
- Change in patient management – change in proportion who remain in primary care, change in proportion who are no longer referred to specialists).
- Patient impacts – inequity in the system where VCTE™ for MAFLD is funded differently to other causes of AF, negative impact resulting from VCTE™ being the only funded option for determination of AF.

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[13] https://www.sciencedirect.com/topics/medicine-and-dentistry/fibrotest

- Efficacy/effectiveness (including, but not limited to, patient-relevant outcomes such as AF, progression of fibrosis, compensated and decompensated cirrhosis, health-related quality of life, mortality) – of VCTE™ itself and of the elements related to the consultation.
- Health care resources.
- Cost-effectiveness.
- Total Australian Government health care costs.

Assessment framework (for investigative technologies)

A linked evidence approach is the most appropriate as there is unlikely to be direct evidence of the impact of VCTE™ testing on health outcomes. An assessment framework linking VCTE™ testing to relevant health outcomes is presented in Figure 2.

PASC noted that the impact of treatment and management is an important part of the linked evidence approach, and that the assessment framework did not specifically indicate a "change in management". PASC advised that this should be included at point '5' in figure 3. This has since been amended. *PASC noted that this was relevant to Question 4 below.*
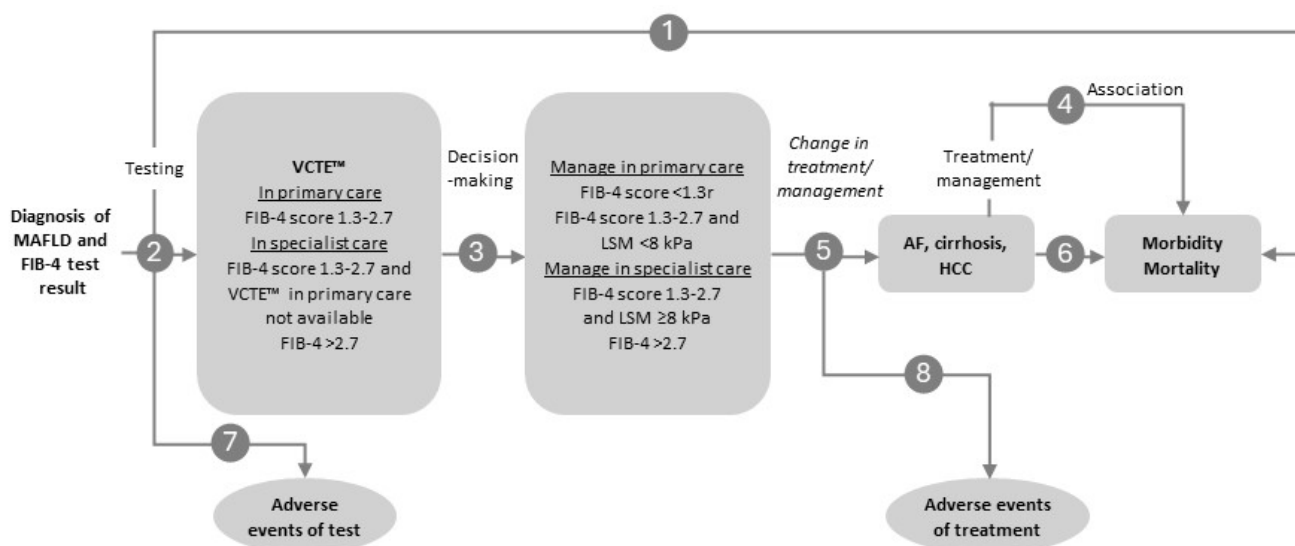

Figure 2 VCTE™ assessment framework showing the links from the test population to health outcomes

Figure notes: 1: direct from test to health outcomes evidence; 2: test accuracy; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: influence of the change in management on intermediate outcomes; 6: association of intermediate outcomes with health outcomes; 7: adverse events due to testing; 8: adverse events due to treatment
AF = advanced fibrosis; FIB-4 = fibrosis-4; HCC = hepatocellular carcinoma; kPa = kilopascals; LSM = liver stiffness measurement; MALFD = metabolic dysfunction-associated fatty liver disease

Questions relevant to this assessment framework are as follows:

1. What is the accuracy of VCTE™ compared with liver biopsy?
2. Does the availability of new information (LSM status) from VCTE™ testing in primary care lead to a change in management of the patient?
3. Does the use of VCTE™ in place of standard of care result in the claimed superior health outcomes?
4. Do the differences in patient management derived from VCTE™ result in the claimed superior health outcomes (OS, HRQoL)?

5. Are any adverse events associated with VCTE™?
6. Are any adverse events associated with changes in clinical management?

PASC advised that, if the comparator was revised to be standard of care as opposed to ultrasound, Question 3 would need to also be revised, for example to read: 'Does the use of VCTE™ in place of standard of care result in the claimed superior health outcomes?'

Clinical management algorithms

The current clinical management algorithm provided by the applicant *and amended according to PASC advice* is presented in Figure 4. *PASC considered that for the 'no second-line non-invasive liver test' arm in the current clinical management algorithm, that (i) other tests could be conducted at this stage, although they are not MBS-listed, and could be included within the algorithm; and (ii) the subsequent events in this pathway of the algorithm, as proposed by the applicant, represented a subset of outcomes rather than being part of the clinical management pathway.*

An updated proposed clinical management algorithm provided by the applicant (and amended for the PICO Confirmation) is presented in Figure 5 for the primary care (PICO set 1) and specialist (PICO set 2) settings.

PASC noted that the use of repeat VCTE™ for the purposes of monitoring known fibrosis every 2-3 years (included in the applicant's proposed treatment algorithm following referral to specialist care) was out of scope for the application.
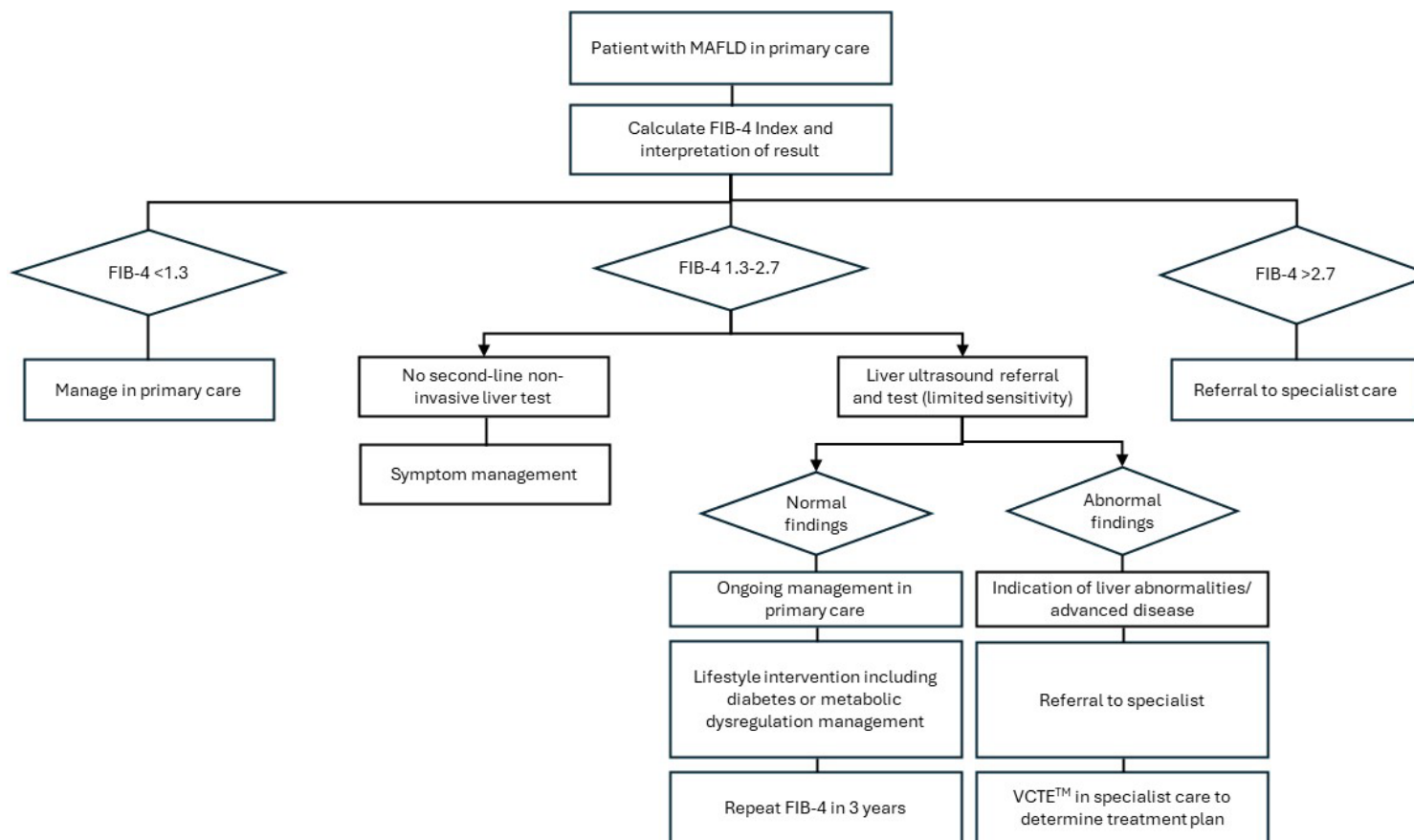
Figure 3 Current algorithm without VCTE™ funding

Source: Application documents, amended for the PICO Confirmation
[1] Abnormal ultrasound findings refer to aspects related to fibrosis deposition, namely irregularity of liver profile and heterogeneity of its echotexture.
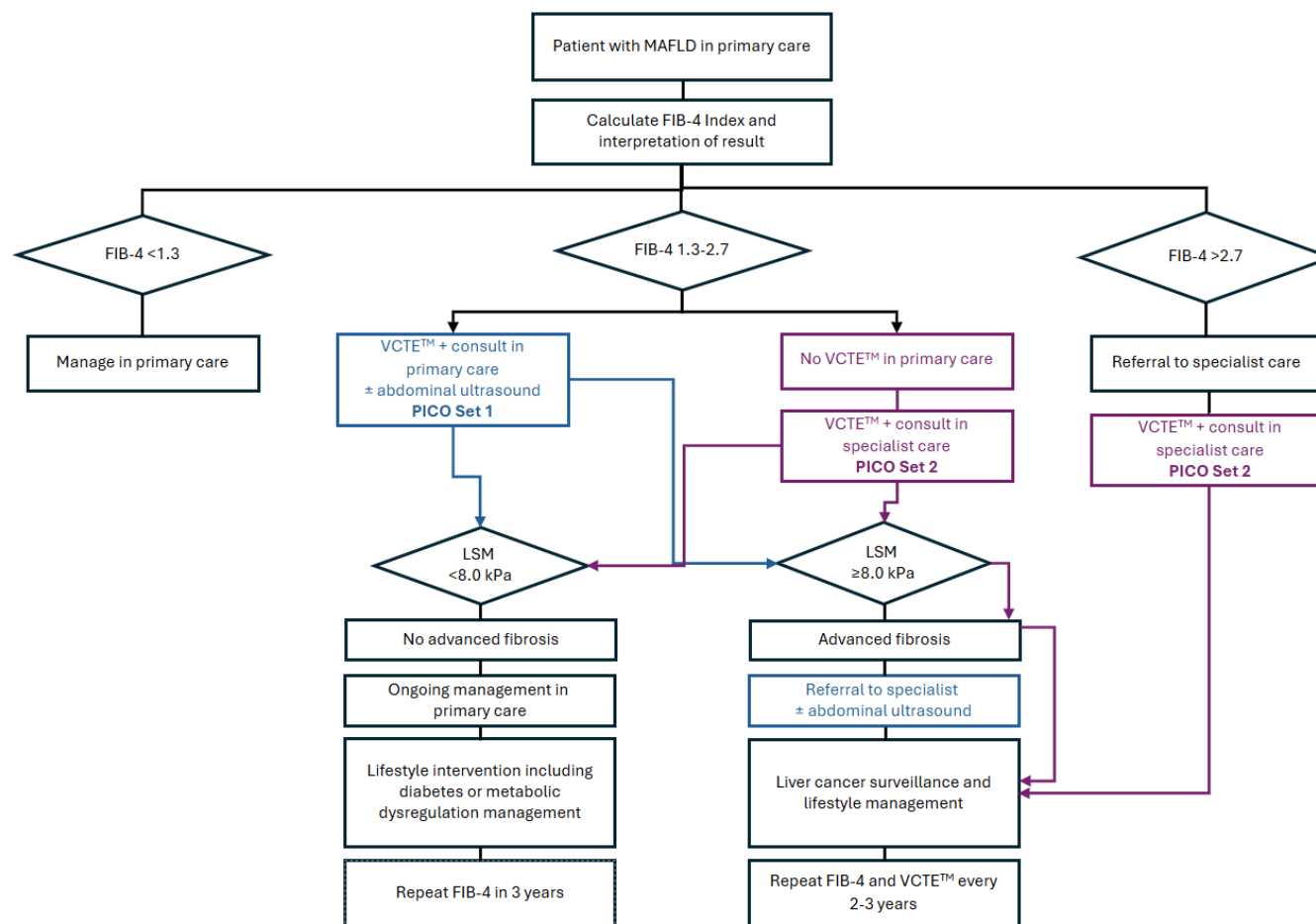
Figure 4 Proposed treatment algorithm with VCTE™

Source: Applicant, amended for the PICO Confirmation
Black font represents pathways that are the same between PICO Sets 1 & 2, blue font represents PICO Set 1 pathway and purple font represents PICO Set 2 pathway.

The applicant has clarified that VCTE™ complements ultrasound, as both tests assess different aspects of liver health. Ultrasound detects liver fat, while VCTE™ measures liver stiffness. The applicant stated that stiffness correlates with fibrosis severity, the key predictor of adverse liver outcomes. Ultrasound cannot assess liver stiffness, making VCTE™ essential for risk stratification.

Their complementary roles are reflected in GESA guidelines, ensuring a comprehensive liver assessment.

For the current treatment algorithm, in the absence of VCTE™ in the primary care setting, it is possible that all patients with MAFLD and FIB-4 score 1.3-2.7 may be referred to specialist care. If this is the case, the proposed inclusion of VCTE™ as in PICO set 1 may aid in stratifying high risk (LSM ≥8 kPa) patients for referral, while low risk (LSM <8 kPa) patients can remain in primary care. This will, however, be dependent on the availability of VCTE™ in the primary care setting.

There are several scenarios clinically that could arise and are already in practice including:

- The primary care clinician follows the pathway proposed in the application (which the application indicates may not be common due to the lack of machines in primary care settings).
- The primary care clinician does not have access to VCTE™, thus refers patients to another clinician (primary care or specialist) for VCTE™.
- The primary care clinician does not have access to VCTE™, thus refers the patient to a radiology practice for a 'fibrosis scan' which may be VCTE™, but may also be an alternative assessment such as SWE.
- VCTE™ or an alternate elastography method is conducted at the point of initial ultrasound (at the prior test phase). The primary care clinician has the results and refers/manages for MALFD from this point and does not require a repeat subsequent VCTE™.
- VCTE™ is conducted for another clinical reason (i.e., VCTE™/another method is conducted in the setting of a diagnosis such as hepatitis) which then needs investigation to exclude other causes of fibrosis meaning the prior tests become the subsequent tests.

While the current application is limited to VCTE™, GESA (2024) has nominated the following broader list of non-invasive tests (NITs) for identifying liver fibrosis:

- <u>Indirect blood-based tests</u> (serum markers of fibrosis; laboratory variables). This includes ALT, AST, alkaline phosphatase, gamma-glutamyl transferase, bilirubin, albumin, and total protein. Results of individual LFTs could be combined to identify patterns of liver damage (e.g., alcoholic liver disease or hepatitis) and improve diagnostic accuracy.

  A range of validated simple scores are used in practice and may include routinely available laboratory variables with or without clinical variables (e.g., AST/ALT ratio; APRI). FIB-4 (based on age, AST levels, ALT levels and the platelet count) and NFS fall into this category. NFS is calculated by adding BMI and the presence of diabetes to the four parameters used in the FIB-4 index. NFS is considered more specific to NAFLD, making it potentially more accurate for diagnosing AF in NAFLD patients; however, given the majority of these patients also fit MAFLD criteria, it may still be relevant to MAFLD.

  Despite their potential to act as 'gate-keeping tests' in primary care liver fibrosis screening pathways, the simple fibrosis scores only include indirect markers of liver damage (AST, ALT), risk factors (age, BMI, diabetes) or liver function and portal hypertension (platelet count, cholesterol), and are not direct markers of liver fibrosis (EASL 2021).

- Direct blood markers of liver damage. These involve more complex serum scores, which include direct markers of fibrogenesis or fibrinolysis. Direct blood markers are products of activated hepatic stellate cells (myofibroblasts): the cells responsible for generating fibrosis in the liver. Examples include the ELF score and Hepascore.

  MSAC application 1446 for MBS listing for Hepascore in hepatitis C and B populations (to diagnose cirrhosis) was considered at MSAC meeting in November 2020. MSAC considered that there was limited clinical need for an additional test to diagnose and monitor liver fibrosis given the variety of alternative tests available. MSAC agreed with the Evaluation Sub-Committee (ESC) that Hepascore would be an additional test (not a replacement test) to assess liver fibrosis. MSAC also noted that the AST to platelet ratio index (APRI) is calculated from routine monitoring tests and has similar specificity to Hepascore at a threshold of 2, meaning it can rule out cirrhosis as effectively as Hepascore. There was no application for ELF test listing on MBS.

- Elastography methods assessing physical properties of the liver (e.g., liver stiffness). LSM can be obtained by different methods including VCTE™ (sometimes is referred to by the shorter abbreviation – TE); techniques integrated in ultrasound devices such as point-shear wave elastography (pSWE) and bidimensional shear wave elastography (2D-SWE), both of which can be performed in combination with regular ultrasound if the device is provided with adequate software; and magnetic resonance elastography (MRE), which can be implemented on a regular MRI machine. Unlike VCTE™, pSWE and 2D-SWE I can be used in patients with obesity and/or ascites (EASL 2021).

- Imaging methods routinely used in chronic liver disease include ultrasound-based techniques, computed tomography (CT)-based techniques and magnetic resonance (MR)-based techniques.

Each NIT has specific advantages and limitations, with no single test being perfect. GESA (2024) commented that the above testing strategies are complementary, and all available data need to be considered together to reach an accurate assessment of fibrosis severity. For example, standard liver function tests are not accurate in detecting AF and may even give normal results in the presence of cirrhosis. Confidence in FIB-4 result is uncertain in alcoholic and genetic liver diseases, and viral, autoimmune or drug-induced conditions. Similarly, ultrasound is inaccurate for determining AF and lacks sensitivity for determining cirrhosis (GESA 2024). The applicant's expert also commented on a low sensitivity of ultrasound for detecting liver fibrosis.

Proposed economic evaluation

For both PICO set 1 and 2, based on a claim of superiority versus the appropriate comparator(s) for the detection and risk stratification of intermediate (F2) to AF (F3-F4), a cost-effectiveness/cost-utility analysis would be relevant.

PASC considered that on the basis of a claim of superiority, a cost-effectiveness/cost-utility analysis would be appropriate.

PASC noted that a cost-utility analysis would best capture the spectrum of impacts from testing. However, if a cost-effectiveness analysis was pursued, effectiveness should be measured as a health outcome (e.g.,

cost per case of cirrhosis prevented) which is more informative than a test outcome (e.g., cost per case of fibrosis detected).

PASC also considered that any changes to the number of referrals to specialists based on risk stratification in the primary care setting should be captured in the economic evaluation.

Table 5 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

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

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis
? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis
[a] 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations
[b] An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

Proposal for public funding

The item descriptors proposed by the applicant are presented in Table 6 and Table 7, for primary (PICO set 1) and specialist (PICO set 2) care, respectively.

Table 6 Proposed item descriptor for VCTE™ in the primary care setting (PICO set 1)

Category 1 – Professional attendances
MBS item XXXX Vibration-Controlled Transient Elastography at 50 Hz performed in primary care by a suitably trained medical practitioner or by practice staff on behalf of the medical practitioner, following an indeterminate (1.3–2.7) FIB-4 test, for the assessment of liver fibrosis in patients with metabolic dysfunction-associated fatty liver disease. Additionally: 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 years - including interpretation and report.
Fee: $101.70

Table 7   Proposed item descriptor for VCTE™ in the specialist care setting (PICO set 2)

Category 1 – Professional attendances
MBS item XXXX Vibration-Controlled Transient Elastography at 50 Hz performed in specialist care by a suitably trained medical practitioner or by practice staff on behalf of the medical practitioner, following an indeterminate or high (1.3 or higher) FIB-4 test, for the assessment of liver fibrosis in patients with metabolic dysfunction-associated fatty liver disease. Additionally: 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 years - including interpretation and report.
Fee: $141.75

In MSAC application 1366, the item was proposed to be Category 5 – Diagnostic Imaging Services (MSAC 1366 PSD, p5). Although VCTE™ is a type of ultrasound, the department has advised that an MBS item would not sit in the Diagnostic Imaging Services Table as the scan generates a measurement rather than a diagnostic image, and would be better placed under Category 2 (Diagnostic Procedures and Investigations) of the General Medical Services Table.

Inclusion of the trade marked terminology Vibration-Controlled Transient Elastography™ in the item descriptor restricts the use of this item solely to the FibroScan® device. This wording will legislatively prohibit the public funding of any other forms of elastography.

PASC considered the appropriateness of the item descriptor specifying VCTE™ as opposed to alternative forms of elastography. PASC advised that there is a preference for device/method agnostic descriptors for MBS items, and therefore suggested that the term 'transient elastography' may be more appropriate than 'VCTE™'. PASC reiterated that the pursual of an item descriptor specifying a specific device would need to be substantiated with evidence to justify limiting testing to a particular method (e.g., superior outcomes compared to alternative methods).

PASC advised that if proceeding with a bundled item, the item descriptor should more clearly specify who can undertake each component of the proposed bundled item (e.g., practice staff may perform the scan, but cannot carry out consultation points (a)-(d) on behalf of the medical practitioner).

The applicant clarified that the proposed service is intended solely for initial risk stratification and identification of AF for clinical decision making, rather than ongoing monitoring of established fibrosis.

In addition, patients who undergo VCTE™ in primary care generally would not require an immediate repeat scan upon referral to specialist care (this would be relevant to those with MAFLD, a FIB-4 score 1.3 to 2.7 and LSM ≥8 kPa when VCTE™ is conducted in primary care). The purpose of VCTE™ in primary care is to serve as an initial risk stratification tool, identifying individuals at risk of AF who may require further specialist evaluation and management. The applicant stated the initial VCTE™ results would remain clinically valid for interpretation by hepatologists or other specialists.

PASC considered that the wording of the proposed test and consultation bundled item descriptor may not adequately restrict its use to the initial identification of fibrosis, nor sufficiently prevent its use for monitoring or immediate repeat scans by a specialist following referral from primary care.

PASC questioned whether 1 scan every 3 years was appropriate for initial diagnosis of AF but noted that it was consistent with recommendations in the GESA guidelines.

The proposed fees are based on combining nurse practitioner attendance item 82210 ($58.85) (compensating the VCTE™ component) with a GP ($42.85, Item 23 level B) or specialist ($98.95, Item 104) attendance item. The specialist fee was then adjusted downward (from $157.80 to $141.75) based on earlier feedback from the department. The department noted that for specialist attendances, items 110 or 116 may be more relevant as gastroenterologists and hepatologists are recognised by Medicare as consultant physicians. This may further increase the fee for the proposed specialist item.

> **Item 82210**
> Professional attendance by a participating nurse practitioner lasting at least 20 minutes and including any of the following:
> a) taking a detailed history;
> b) undertaking clinical examination;
> c) arranging any necessary investigation;
> d) implementing a management plan;
> e) providing appropriate preventive health care;
> for 1 or more health related issues, with appropriate documentation

The applicant clarified that Item 82210 was used to determine the VCTE™ scan fee as VCTE™ could be performed by a nurse practitioner on behalf of the billing practitioner. However, VCTE™ takes less than 20 minutes, suggesting that Item 82205 – Professional attendance by a participating nurse practitioner lasting at least 6 minutes and less than 20 minutes and including all of the above elements, with a fee of $31.05 may be a more appropriate starting point. In addition, the applicant stated that the scan could be performed by less qualified staff (practice nurses or technicians), and both the nurse practitioner items include multiple consultation elements that are not required when doing the scan and duplicate elements of the medical practitioner's consultation with the patient.

In MSAC application 1366, the proposed fee for transient elastography (TE) was claimed to be in line with other point-of-care testing services at $55.65, and could be performed by 'a suitably trained health professional' (MSAC 1366 PSD, p5), i.e. was similar to the proposed fee and justification in the current application. However, MSAC considered that the proposed fee for was high and that, while the fee of $55.56 was linked to the cost of MBS item 55014 for abdominal ultrasound, MSAC felt that this was inappropriate given that the delivery of a TE service is much less complex than of an abdominal ultrasound service and does not require a skilled operator (MSAC 1366 PSD, p4). Note that item 55014 was removed from the MBS in 2020. The current MBS item for abdominal ultrasound involving morphological assessment is 55036, with a fee of $124.70.

PASC noted the proposed fees, and particularly that the scan component was based on Item 82210. PASC considered that the scan fee may be more appropriately aligned with Item 82205, given that VCTE™ takes less than 20 minutes. PASC considered that, as operators less qualified than a nurse practitioner could undertake the scan, a fee lower than that based on Item 82205 may also be reasonable.

The applicant stated that the higher MBS fee for the proposed specialist item was justified by the greater expertise, clinical decision-making and resource intensity required in specialist care. The applicant stated that, in primary care, patients typically have less complex pathophysiology, requiring more straightforward

management pathways, such as lifestyle interventions, diabetes control, targeted risk factor management, or referral to a specialist (Gofton & George 2021). In specialist settings, patients often present with more comorbidities, advanced liver disease, and complex treatment needs. This may involve fibrosis and cirrhosis management, off-label pharmacological treatments and more intensive monitoring (GESA 2024).

PASC noted that the applicant's rationale for different fees for the proposed items when conducted by GPs versus specialists was based on complexity, expertise and patient management. PASC also noted that consultation feedback raised concerns about differential fees when the proposed item descriptors require the same service be delivered. PASC questioned whether the fee difference was sufficiently justified. PASC considered that this would be resolved if the item were limited to the scan only. In that case, the item would be used in both primary and specialist care, and a single fee would apply to the scan, regardless of the care pathway. For the consultation element of the proposed service, existing consultation items would be used, which are specific to the care pathway, and have appropriate associated fees. The differences in complexity and expertise would therefore be accounted for, as is already the case for consultations.

At the pre-PASC meeting there was a discussion about splitting the proposed MBS items into:

(1)   VCTE™ scan (for diagnostic investigation); and

(2)   A consultation covering assessment of results, management plans, referrals.

The applicant considered that splitting the items would create unnecessary fragmentation and undermine VCTE™'s key advantage as a point of care tool. The applicant further stated 'Unlike traditional diagnostics such as ultrasound, which require separate reporting and follow-up, VCTE™ provides immediate results, enabling clinicians to interpret findings, discuss management options and initiate referrals within the same consultation. Introducing separate item numbers would disrupt workflow, reduce efficiency and be particularly counterproductive in primary care, where timely decision-making is essential for effective patient management'. It should be noted that separating the item into its component parts would not prevent the use of VCTE™ as a point of care tool as the scan and consultation could still be performed at the same time.

An advantage of splitting the items is that where two health care practitioners perform the service, they could claim for the delivery of their respective services. This may be particularly relevant if large GP clinics become 'VCTE™ hubs' (see 'Intervention' section) as a patient could undergo VCTE™ at the hub (attracting the fee for the scan), with consultation, management, advice and any relevant referrals provided by the patient's 'regular' GP (attracting the fee for a consultation). It would also avoid complications where a provider is unable to meet the full descriptor of the bundled service and thus ineligible to bill for the scan. For example, a patient who receives VCTE™ in primary care and has a LSM ≥8.0 kPa is likely to be referred to a specialist for advice and implementation of a management plan, rather receiving these from the GP.

The other advantage in splitting the items is that it addresses the potential, especially in the primary care space, for financial disadvantage to the patient. Currently both VCTE™ and consultation services could be provided by a primary care clinician under longer consultation items than item 023 proposed as the fee basis in this application. Clinicians currently providing the service using items such as 036, 044 or 123 will no longer be able to provide such services to MAFLD patients using these items should the current application be supported. This may financially disincentivise these practitioners from continuing to provide such a service or alternatively result in patients bearing the cost differential between the proposed item and what can currently be accessed. Patients with alternative diagnoses such as hepatitis, who require

VCTE™ as part of their management would continue to be able to access VCTE™ through longer consultation items in the primary care setting.

All primary care and consultant physician attendance items could be used, in addition to the 'health assessment' items nominated in the application. In primary care, this includes the longer consultation items (036, 044 and 123) and the chronic disease care plan items. In specialist care it includes standard attendance items and A4 items such as 132 and 133, where applicable.

Assuming that separating the proposed MBS item into its components is accepted, a single VCTE™ item could be proposed and used by any appropriate service provider. The above existing attendance items could be used for the consultation component of the service.

PASC advised that it would be more appropriate to have a single new item for the scan only, with existing consultation items used for the consultation component. This would simplify the application and only one PICO set would be needed. PASC reiterated a preference to avoid condition-specific consultation items. However, if the proposed bundled item were to be pursued, PASC advised that justification and evidence would need to be provided to support a bundled condition-specific consultation item, rather than using existing MBS items.

A standalone item descriptor for the VCTE™ scan, in line with PASC's advice, is presented in Table 8.

Table 8   Potential MBS item descriptor for the VCTE™ scan only

Category 1 – Professional attendances
MBS item XXXX Vibration-Controlled Transient Elastography (VCTE™) of the liver at 50 Hz, including interpretation and report, performed by a medical practitioner or by appropriately trained practice staff under the supervision of the medical practitioner, following an indeterminate or high FIB-4 test score (≥1.3), for the assessment of liver fibrosis in patients with metabolic dysfunction-associated fatty liver disease (MAFLD). Available once per patient in a 36 month period, provided no prior Liver Stiffness Measurement (LSM) obtained by VCTE™ for that patient is ≥8 kPa.
Fee: to be determined

Summary of public consultation input

PASC noted and welcomed consultation input from 4 organisations and 7 individuals, 3 of whom were consumers and 4 health professionals. The 4 organisations that submitted input were:

- LiverWELL
- Gastroenterological Society of Australia Liver Faculty (GESA)
- The Royal Australian and New Zealand College of Radiologists (RANZCR)
- The Royal Australian College of General Practitioners (RACGP)

The consultation input received was mostly supportive of public funding for VCTE™ for identifying advanced fibrosis in patients with MAFLD. The consultation input raised a number of concerns, predominately in relation to the population being too restricted and the delivery of VCTE™.

Benefits and Disadvantages

The main benefit of public funding received in the consultation input included that VCTE™ can provide additional information about liver health compared to ultrasound, while being less invasive than liver biopsy. It was noted that access to VCTE™ might reduce the need for liver biopsies in some cases, could improve access to liver health assessments in remote regions of Australia, and reduce the burden on specialists.

The main disadvantages of public funding received in the consultation input included the cost of the device and the concentration of VCTE™ devices in specialist centres, imposing significant travel, financial, and logistical burdens on patients.

Population, Comparator (current management) and Delivery

The consultation input largely agreed with the proposed populations, although a number of health professionals and GESA noted that patients other than those specified in the application could benefit from VCTE™, including those with type 1 diabetes and viral hepatitis. Input from GESA stated that the population should include people with MAFLD and a FIB-4 greater than 1.3 (not just between 1.3-2.7) to confirm advanced liver fibrosis and cirrhosis diagnosis.

The consultation broadly agreed with the proposed comparator. The feedback from GESA stated that liver ultrasound lacks sensitivity and specificity for liver cirrhosis diagnosis.

Consultation input was provided in relation to service delivery, stating that an increased number of VCTE™ machines would be required to support equitable access across Australia and training in the correct use of VCTE™ would need to be provided for specialists and nurses. GESA stated that portable VCTE™ mobile outreach regional services may be suitable and that these services have been used in Australia for the outreach viral hepatitis liver assessment program.

MBS Item Descriptor and Fee

The consultation input from health professionals and professional organisations varied from agreeing to disagreeing with the proposed item descriptor. One health professional stated the item should be restricted to specialist hepatologists and gastroenterologists as the results require specialist interpretation. RACGP stated that GPs are well placed to prevent, diagnose and manage MAFLD. RANZCR advocated for an item for non-invasive assessment of liver fibrosis that allows the use of multiple technologies including SWE and MRE. GESA disagreed with the frequency restriction stating it is not in line with the Australian GESA MAFLD consensus statement which recommends repeat assessment every 1-3 years depending on risk.

The consultation input from health professionals and professional organisations ranged from agreeing to disagreeing with the proposed service fee, with some consultation input stating it should be higher to support the cost of VCTE™ machines and support small rural services. RACGP stated that the fee for GPs should be in line with other specialists as they are undertaking the same tasks.

Additional Comments

GESA noted that VCTE™ in combination with platelet count (blood test) has the additional benefit of triaging the need for invasive and expensive gastroscopy to diagnose portal hypertension in people with MAFLD.

PASC noted the consultation feedback.

Next steps

The applicant indicated the intent to proceed to an applicant-developed assessment report (ADAR).

Based on PASC's advice, the assessment report should focus on the test alone as the intervention, with existing consultation items used for the consultation component of the proposed service. PASC advised that only a single PICO set would then be required.

A summary of the potential single PICO set that could be explored in the ADAR is outlined in Table 9, below*.* This incorporates PASC's advice that the intervention should only include the test, and should exclude the consultation component. Corresponding changes have been made to the other PICO components; for example, the comparator no longer includes a consultation component. PASC's advice on other PICO elements, including appropriate outcomes, has also been incorporated.

Note that changes to the PICO set should be consistently reflected throughout the ADAR, for example with appropriate changes made to the clinical management algorithm.

Table 9: PASC-advised PICO for Vibration-Controlled Transient Elastography (VCTE™) for identifying advanced fibrosis in patients with metabolic dysfunction-associated fatty liver disease (MAFLD)

Component	Description
Population	Patients diagnosed with metabolic dysfunction-associated fatty liver disease (MAFLD) who have a FIB-4 test score of >1.3[a].
Prior tests	• Diagnosis of MAFLD (≥5% hepatosteatosis; and at least one of the following (1) overweight; (2) type 2 diabetes mellitus [T2DM]; or (3) metabolic dysfunction[a]). • Fibrosis-4 (FIB-4) score (requiring assessment of aspartate aminotransferase [AST], alanine aminotransferase [ALT] and platelet count).
Intervention	VCTE™ with or without abdominal ultrasound for the diagnosis of advanced liver fibrosis. The item is proposed as 1 service only every 3 years.
Comparator/s	Standard of care (which may include liver ultrasound, other non-funded tests for the diagnosis of advanced fibrosis, and/or referral to specialist care (where appropriate)).
Reference standard	Liver biopsy

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Outcomes	• Safety (including any potential risk of harm to the patient). • Accuracy (sensitivity, specificity, positive and negative predictive values) compared with the reference standard liver biopsy. • Change in patient management – change in proportion who remain in primary care, change in proportion who are referred to specialists. • Patient impacts – inequity in the system where VCTE™ for MAFLD is funded differently to other causes of AF, negative impact resulting from VCTE™ being the only funded option for determination of AF. • Efficacy/effectiveness (including, but not limited to, patient-relevant outcomes such as advanced fibrosis, progression of fibrosis, compensated and decompensated cirrhosis, health-related quality of life, mortality) – of VCTE™ itself and of and of subsequent management. • Health care resources. • Cost-effectiveness. • Total Australian Government health care costs.
Assessment questions	What is the safety, effectiveness and cost-effectiveness of VCTE™ versus standard of care in patients with a diagnosis of MAFLD and a FIB-4 score of ≥1.3 for the detection and risk stratification of intermediate to advanced liver fibrosis?

[a] Noting that this includes those with a FIB-4 score > 2.7, in line with PASC advice that it is reasonable to include this group of patients in the proposed population.

Applicant Comments on Ratified PICO

The applicant notes PASC have recognised the importance of improving diagnostic pathways for patients with MAFLD given the high disease burden in Australia. The applicant reiterates that this application is specifically for the use of VCTE, which does not include other ultrasound-based transient elastography technologies, due to the gap in clinical evidence and lower diagnostic accuracy for the other devices. Overall, this limits the ability to evaluate all liver fibrosis technologies concurrently and prevents generalisation of findings related to test accuracy and impact on clinical management.

The applicant also recognises that there are other important conditions that lead to liver fibrosis. However, given its burden and prevalence, MAFLD remains the primary focus of this application. The true value of the diagnostic capabilities of VCTE, including its impact on patient outcomes and healthcare efficiency, will be demonstrated in the assessment report. The applicant agrees with PASC on the separation of test, as the focus of the application, and consultation. However, the applicant notes that use of VCTE in primary care and specialist care are distinctive based on variations in the financial and clinical evidence, and this will be covered in the assessment report.

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Attachment 1

Table 10 GESA recommendations for the assessment of MAFLD in primary care

No	Recommendation
	Who should be assessed for MAFLD?
1	Adults with obesity and/or type 2 diabetes mellitus, or two or more metabolic risk factors* should be assessed for MAFLD (Evidence quality: Low; Grade of recommendation: Strong)
	How should MAFLD be diagnosed?
2	Liver ultrasound should be the first-line test to diagnose hepatic steatosis in people at high risk of MAFLD. (Evidence quality: Moderate; Grade of recommendation: Strong)
	What co-morbid conditions should be assessed in people with MAFLD?
3	People with obesity and MAFLD should be assessed in accordance with the Australian Obesity Management Algorithm. (Evidence quality: Low; Grade of recommendation: Strong)
4	People with MAFLD should be assessed for undiagnosed type 2 diabetes using measurement of fasting blood glucose or HbA1c levels. (Evidence quality: Moderate; Grade of recommendation: Strong)
5	People with MAFLD should be assessed and monitored for the presence and risk of future cardiovascular disease according to current Australian guidelines. (Evidence quality: High; Grade of recommendation: Strong)
6	Baseline assessment for potential comorbid conditions of obstructive sleep apnoea and chronic kidney disease should be considered for people with MAFLD. (Evidence quality: Moderate; Grade of recommendation: Weak)
	How should other aetiologies of liver disease be assessed in people with MAFLD?
7	People with MAFLD should be assessed for other common causes of fatty liver and liver disease. (Evidence quality: Low; Grade of recommendation: Strong)
8	People with MAFLD should undergo screening for harmful alcohol use. (Evidence quality: Moderate; Grade of recommendation: Strong)
9	People with MAFLD and elevated serum aminotransferase levels should undergo baseline evaluation for hepatitis B and C infection. (Evidence quality: Moderate. Grade of recommendation Strong)
10	People with MAFLD and elevated serum aminotransferase levels should undergo evaluation for iron overload. (Evidence quality: Moderate. Grade of recommendation Strong)
	How should the severity of liver disease be assessed in people with MAFLD?
11	Non-invasive testing should be offered to people with MAFLD to assess their risk of liver fibrosis. (Evidence quality: Moderate; Grade of recommendation: Strong)
12	A non-invasive test such as FIB-4, should be offered as an initial test to help "rule out" the risk of advanced liver fibrosis among people with MAFLD. (Evidence quality: Moderate; Grade of recommendation: Strong)
13	A second-line assessment with liver elastography or a direct liver fibrosis serum test should be performed in people with MAFLD and a FIB-4 score between 1.3 and 2.7. If these are unavailable, referral to a clinician with expertise in liver disease should be considered. (Evidence quality: Low; Grade of recommendation: Strong)
14	People with MAFLD and a FIB-4 > 2.7 or elevated results of a direct liver fibrosis serum test or liver elastogram, should be referred to a clinician with expertise in liver disease. (Evidence quality: Low; Grade of recommendation: Strong)
15	People with MAFLD and clinical, laboratory or imaging evidence of cirrhosis should be referred to a clinician with expertise in liver disease. (Evidence quality: High; Grade of recommendation: Strong)
	How should liver fibrosis in people with MAFLD be monitored over time?
16	People with MAFLD who have an initial non-invasive fibrosis test showing a low risk of advanced fibrosis are recommended to undergo repeat non-invasive fibrosis testing in 3 years. (Evidence quality: Low; Grade of recommendation: Strong)
17	People with MAFLD and a FIB-4 score between 1.3 and 2.7 who undergo elastography or a direct liver fibrosis serum test that shows a low risk of advanced liver fibrosis should be offered repeat testing with a FIB-4 at least every 3 years. (Evidence quality: Low; Grade of recommendation: Weak)

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No	Recommendation
18	For people who are 75 years or older and have MAFLD, routine monitoring for fibrosis progression should be performed on a case-by-case basis, depending on their comorbid conditions and life expectancy. (Evidence quality: Low; Grade of recommendation: Strong)
19	People with cirrhosis who would be willing and suitable for HCC therapy should be undergoing 6-monthly surveillance for hepatocellular carcinoma using appropriate imaging with or without serum AFP testing. (Evidence quality: Low; Grade of recommendation: Strong)
	How should co-morbid conditions be monitored over time in people with MAFLD?
20	Weight, BMI and/or waist circumference should be monitored at least annually in people with MAFLD to guide management. (Evidence quality: Low; Grade of recommendation: Strong)
21	People with MAFLD should be monitored for the development of type 2 diabetes according to current Australian guidelines. (Evidence quality: Moderate; Grade of recommendation: Strong)

Source: GESA 2024, pp7-8