

Recommendations for the assessment of metabolic dysfunction-associated fatty liver disease (MAFLD) in primary care: a consensus statement

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Abstract

Metabolic dysfunction-associated fatty liver disease (MAFLD) is the most common liver condition in Australia and worldwide and is often encountered in general practice. The incidence of cirrhosis and hepatocellular carcinoma (HCC) related to MAFLD is increasing, and a standardised evidence-based approach is required for the identification and assessment of patients with MAFLD.

This consensus statement details 21 evidence-based recommendations to aid primary health care professionals in the diagnosis and assessment of liver disease and coexisting conditions in patients with MAFLD. The development of this document was led by

experts in hepatology, general practice, endocrinology, cardiometabolic disease, clinical biochemistry, nursing, implementation science and public health, with review by consumer representatives. The document was supported by a systematic literature search and appraisal, and a modified Delphi approach was used to reach consensus.

The application of these recommendations will aid in the determination of liver disease severity and assessment of underlying coexisting conditions in patients with MAFLD, thereby guiding appropriate referral pathways for specialist care and monitoring strategies.

Executive summary

Metabolic dysfunction-associated fatty liver disease (MAFLD) is common among people attending primary care and should be assessed in adults with type 2 diabetes, obesity or two or more metabolic risk factors (including hypertension, dyslipidaemia and prediabetes). Hepatic steatosis should be evaluated using ultrasound, whereas metabolic dysfunction, including the presence and complications of type 2 diabetes and obesity, should be assessed according to current Australian guidelines.

Cardiovascular disease, chronic kidney disease and obstructive sleep apnoea are common in people with MAFLD and should be considered as part of a holistic health assessment. Alternative causes of hepatic steatosis, including excessive alcohol use, must be considered, and hepatitis B and C infection and iron overload should be evaluated in patients with elevated serum aminotransferase levels.

The risk of advanced liver fibrosis requires assessment using the non-invasive serum-based Fibrosis-4 (FIB-4)

Index; a low score (<1.3) is associated with a $>95\%$ negative predictive value for advanced liver fibrosis. People with an indeterminate FIB-4 score (in the range of 1.3–2.7) should undergo second-line assessment with liver elastography or a direct liver fibrosis serum test or, if these tests are unavailable, should be referred to a clinician with expertise in liver disease. People with MAFLD and a high FIB-4 score (>2.7), elevated results of a direct liver fibrosis serum test or elastography or with clinical, laboratory or imaging evidence of cirrhosis should be referred for further evaluation. People with MAFLD and a low FIB-4 score (<1.3) or low elastography or direct liver fibrosis serum test results should have their metabolic risk factors actively managed and be monitored with a repeat FIB-4 Index performed at least every 3 years.

Weight, body mass index and/or waist circumference should be monitored at least annually, and the emergence of incident type 2 diabetes should be monitored over time in those without type 2 diabetes initially.

1 Introduction

1.1 Background and rationale

Metabolic dysfunction-associated fatty liver disease (MAFLD), formerly known as non-alcoholic fatty liver disease (NAFLD), is estimated to affect one in three Australian adults and is an increasingly frequent cause of cirrhosis and hepatocellular carcinoma (HCC).^{1,2} MAFLD is defined by the documented presence of hepatic steatosis on imaging, biomarkers or liver histology, in association with metabolic risk factors, including overweight or obesity, type 2 diabetes or features of the metabolic syndrome.³ Concerningly, incident cases of advanced liver disease and liver-related deaths due to MAFLD are estimated to increase by 85% in Australia between 2019 and 2030.⁴

Most people with MAFLD have their initial and ongoing health care interactions with general practitioners. An underappreciation of the prevalence of MAFLD in general practice, coupled with a lack of awareness of, and access to, methods to assess the severity of liver disease hamper the evaluation of patients with MAFLD.⁵ A lack of clinical guidelines in the Australian context has also been identified as a significant barrier to implementing care pathways for patients with MAFLD and type 2 diabetes.⁶

The development of evidence-based recommendations and a standardised clinical pathway provides the opportunity for case-finding and assessment of alternative causes of fatty liver and liver disease, as well as consideration of coexisting cardiometabolic conditions. Assessment of the severity of liver disease and coexisting conditions allows for management of risk factors for progressive liver and cardiometabolic disease and efficient identification of those patients who would benefit from specialist referral. Ultimately, this will improve the care of patients with MAFLD and reduce health care costs.

1.2 Purpose

This consensus statement provides an evidence-based document for GPs regarding the assessment and appropriate referral of adults with MAFLD. It provides

guidance on screening and diagnostic strategies, assessment of coexisting conditions, assessment of liver disease severity and alternative causes of liver disease, and monitoring strategies.

1.3 Target audience

The target audience of this document is health professionals working in primary care. It is recognised, however, that other specialists and allied health professionals, including endocrinologists, encounter and care for people with MAFLD. The recommendations are also applicable in these other settings.

1.4 Nomenclature

The nomenclature of MAFLD arose from a need to refine the historical definition of NAFLD, which did not reflect the underlying disease pathogenesis, was defined by exclusionary criteria and was potentially stigmatising.⁷ In contrast, MAFLD has positive diagnostic criteria, requiring the presence of metabolic dysfunction, defined as the presence of type 2 diabetes, overweight or obesity, or two metabolic risk factors (Figure 1).³ A key difference is the allowance for other coexisting causes of liver disease, such as excessive alcohol consumption, which was not previously possible with the NAFLD definition. This recognises the common clinical presentation in primary care of dual (or multiple) aetiologies of liver disease being present in the one individual.

Figure 1. Diagnostic criteria for metabolic dysfunction-associated fatty liver disease

Fatty liver	
+ One of:	Overweight or obesity
	Type 2 diabetes
	Two or more metabolic risk factors*

* Central obesity, hypertension, hypertriglyceridaemia, low level of high-density lipoprotein cholesterol, and prediabetes.

Although the definition of MAFLD arose in 2020, much of the literature regarding the assessment of fatty liver and use of biomarkers is derived from populations identified by the older NAFLD definition. Given that most people with NAFLD (>80%) also fulfil diagnostic criteria for MAFLD, and levels of non-invasive liver fibrosis test results are similar between the two definitions,^{8,9} it is likely that literature using the NAFLD definition is applicable to the population defined as having MAFLD. For consistency and simplicity, we use the term MAFLD throughout this consensus statement. This document will be updated as new data emerge in the context of the newer definition.

A further nomenclature change, to metabolic-associated steatotic liver disease (MASLD), has recently been proposed because of the concern that the use of “fatty” may be stigmatising.¹⁰ Notably, the definition of MASLD requires exclusion of excessive alcohol consumption (defined as ≥ 20 g/day for women and ≥ 30 g/day for men) and alternative forms of liver disease. However, the term MAFLD has received widespread support and endorsement from patient groups, stakeholders, societies and associations.^{11,12} As the presentation of patients with fatty liver in primary care is typically undifferentiated, the use of MAFLD is appropriate, with the approach to diagnosis and assessment incorporating screening for coexisting causes of liver disease.

2 Methods

This consensus statement was developed by applying the principles outlined in the Appraisal of Guidelines for Research & Evaluation (AGREE II) instrument.¹³

2.1 Steering Committee

A chair and co-chair were initially selected from the Gastroenterological Society of Australia (GESA) Liver Faculty Executive to form a Steering Committee (SC), with representation from specialty areas including hepatology, general practice, endocrinology, obesity medicine, cardiometabolic medicine, chemical pathology, implementation science and nursing. SC members are outlined in the [Acknowledgement of participation](#). Competing interest statements were sought from each member and are provided in the [Author disclosures](#) section. The SC provided oversight and governance for the development of the consensus statement and is responsible for the final publication.

2.2 Key clinical questions

The SC developed key clinical questions representing clinical dilemmas faced by practising GPs. These questions covered four main areas: screening, assessment of extrahepatic coexisting conditions, assessment of underlying liver disease, and monitoring patients over time (see [Appendix 1](#)). The key clinical questions were translated into a PICO framework, if appropriate, to assist in a subsequent literature search.

2.3 Literature review and appraisal

A member of the SC (LCB) undertook a literature review for each key clinical question using a hierarchical search approach for published systematic reviews, meta-analyses, primary literature and high-quality evidence-based guidelines up to January 2022 (see [Appendix 2](#)). This was supplemented with new publications as relevant. The MEDLINE, EMBASE and Guideline Central (<https://www.guidelinecentral.com>) databases were searched. Systematic reviews were assessed using A Measurement Tool to Assess Systematic Reviews (AMSTAR).¹⁴ The AMSTAR online platform (<https://amstar.ca/index.php>) was used to

assess systematic review quality. Guideline quality was assessed by two SC members (LA and LCB) using the online AGREE II tool (<https://www.agreetrust.org/my-agree/>).¹³ In the absence of appropriate systematic reviews, guidelines or meta-analyses, a literature review targeted to the Australian context was performed where appropriate.

Existing guideline recommendations relevant to the key clinical questions were tabulated, along with the quality of the guideline according to AGREE II (see [Appendix 3](#)). The methodological quality and outcome measures or summary statistics of systematic reviews were summarised in tabulated and text form. Primary literature, where needed, was described according to methods, data items, outcomes and measures. An interpretation of the evidence and an assessment of limitations were performed.

2.4 Statement development and consensus method

Four working groups comprising clinicians and experts were established and led by section chairs derived from the SC. Each working group covered one of the four main areas of key clinical questions and examined the literature summarised by the literature review, with the opportunity to add additional literature if appropriate. Recommendation statements tailored to the Australian context were then developed from this evidence base. Recommendations were forwarded to the SC for review before circulation to the broad group for reaching consensus using a modified Delphi approach.¹⁵ Two online questionnaires were circulated before a hybrid meeting was held on 13 June 2023. A third online questionnaire consisting of one recommendation followed the hybrid meeting. A total of 33 experts in liver disease management were invited to participate in the modified Delphi process, with online completion rates of 97% (32/33), 100% (33/33) and 100% (33/33) in Rounds 1, 2 and 3, respectively. The level of agreement with each recommendation was assessed using a five-point Likert scale (strongly disagree, disagree, neutral, agree, strongly agree). A decision rule with a supermajority of

≥80% (summative agree and strongly agree responses) was determined *a priori* as the determinant for consensus, as previously described.¹⁶ Participants had the opportunity to provide additional comments regarding the recommendation for refinement in the subsequent round.

2.5 Grading of evidence and strength of recommendations

Levels of evidence for the recommendations were assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, as recommended by the National Health and

Medical Research Council Guidelines for Guidelines.^{17,18} The quality or certainty of evidence was classified as high, moderate, low or very low, and the strength of recommendations was classified as strong or weak (Table 1). Quality of evidence was rated using the domains of risk of bias/study limitations, imprecision, inconsistency, indirectness and publication bias. The strength of recommendations was determined based on review of the quality of the evidence, certainty regarding the balance of desirable and undesirable effects, certainty or variability in patient values and preferences, and cost.¹⁷ Factors determining the strength of recommendations were adapted for diagnostic studies where appropriate.

Table 1. Grading of evidence and recommendations (adapted from GRADE)

Quality of evidence	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain
Strength of recommendation	Definition
Strong	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost
Weak	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted Recommendation is made with less certainty; higher cost or resource consumption

GRADE, Grading of Recommendations Assessment, Development and Evaluation.

3 Summary of recommendations

No.	Recommendation	Quality of evidence	Strength of 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.	Low	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.	Moderate	Strong
What coexisting 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.	Low	Strong
4	People with MAFLD should be assessed for undiagnosed type 2 diabetes using measurement of fasting blood glucose or HbA _{1c} levels.	Moderate	Strong
5	People with MAFLD should be assessed and monitored for the presence and risk of future cardiovascular disease according to current Australian guidelines.	High	Strong
6	Baseline assessment for potential coexisting conditions of chronic kidney disease and obstructive sleep apnoea should be considered for people with MAFLD.	Moderate	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.	Low	Strong
8	People with MAFLD should undergo screening for harmful alcohol use.	Moderate	Strong
9	People with MAFLD and elevated serum aminotransferase levels should undergo baseline evaluation for hepatitis B and C infection.	Moderate	Strong
10	People with MAFLD and elevated serum aminotransferase levels should undergo evaluation for iron overload.	Moderate	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.	Moderate	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.	Moderate	Strong

No.	Recommendation	Quality of evidence	Strength of recommendation
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.	Low	Strong
14	People with MAFLD and a FIB-4 score >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.	Low	Strong
15	People with MAFLD and clinical, laboratory or imaging evidence of cirrhosis should be referred to a clinician with expertise in liver disease.	High	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 result showing a low risk of advanced fibrosis are recommended to undergo repeat non-invasive fibrosis testing in 3 years.	Low	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 FIB-4 at least every 3 years.	Low	Weak
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 coexisting conditions and life expectancy.	Low	Strong
19	People with cirrhosis who would be willing and suitable for HCC therapy should be undergoing 6-monthly surveillance for HCC using appropriate imaging with or without serum AFP testing.	Low	Strong
How should coexisting 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.	Low	Strong
21	People with MAFLD should be monitored for the development of type 2 diabetes according to current Australian guidelines.	Moderate	Strong

AFP = alpha-fetoprotein; BMI = body mass index; FIB-4 = Fibrosis-4; HbA_{1c} = glycated haemoglobin; HCC = hepatocellular carcinoma; MAFLD = metabolic dysfunction-associated fatty liver disease.

* Metabolic risk factors: waist circumference ≥102 cm for White men and ≥88 cm for White women (or, for First Nations Australians and Asians, ≥90 cm for men and ≥80 cm for women); systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or drug treatment for high blood pressure; plasma triglyceride levels ≥1.7 mmol/L or drug treatment for elevated triglyceride levels; plasma high-density lipoprotein (HDL) cholesterol levels <1.0 mmol/L for men and <1.3 mmol/L for women or drug treatment for reduced HDL cholesterol levels; and prediabetes (i.e. fasting glucose levels of 6.1 to 6.9 mmol/L, or 2-h post-load glucose levels of 7.8 to 11.0 mmol, or HbA_{1c} level of 6.0% to 6.4%).

4 Screening and diagnosis of MAFLD

4.1 Prevalence and incidence in Australia and globally

MAFLD is the most prevalent condition affecting the liver, with an estimated global prevalence of 25%–30% in adults.^{19,20} It is rapidly emerging as the foremost indication for liver transplantation.^{21,22}

Most epidemiological studies using the MAFLD definition have been conducted in Asia, where the prevalence varies between and within countries; in China, it is 21%–47%, in Hong Kong 26%, in South Korea 34%–38%, in Japan 35% and in Sri Lanka 33%.²³ In comparison, studies from North America report prevalences between 20% and 38%, while there are limited data in Europe, with a study from the Netherlands in an older adult population reporting a MAFLD prevalence of 34%.²³

In Australia, there is a paucity of high-quality epidemiological and prevalence data on MAFLD. Although a Markov-based model forecast the prevalence of MAFLD in Australia to increase by 25% over the decade to 2030, the model was reliant on imputed prevalence data extrapolated from studies conducted outside Australia.⁴ More recently, two population-based cross-sectional studies have evaluated prevalence using the validated Fatty Liver Index (FLI) to identify people with MAFLD. The first of these studies, performed in regional Victoria in 2018, reported a high prevalence of 47% among a predominantly older White population.⁹ Similarly, an analysis of the 2012 survey of the Australian Diabetes, Obesity and Lifestyle (AusDiab) study reported a high MAFLD prevalence of 37%.² Importantly, the prevalence of MAFLD is on the rise in Australia, with crude and age- and sex-standardised prevalence rates reported to have increased significantly over the past 15 years, particularly among women, in association with a parallel increase in obesity.²⁴

4.2 Prevalence in people with high-risk conditions

High-risk conditions for MAFLD are type 2 diabetes, obesity (including central obesity) and a combination of two or more metabolic risk factors. Cardiometabolic risk factors include: waist circumference ≥ 102 cm for White men and ≥ 88 cm for White women (or, for First Nations Australians and Asians, ≥ 90 cm for men and ≥ 80 cm for women); systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or drug treatment for high blood pressure; plasma triglyceride levels ≥ 1.7 mmol/L or drug treatment for elevated triglyceride levels; plasma high-density lipoprotein (HDL) cholesterol levels < 1.0 mmol/L for men and < 1.3 mmol/L for women or drug treatment for reduced HDL cholesterol levels; and prediabetes (i.e. fasting glucose levels of 6.1 to 6.9 mmol/L, or 2-h post-load glucose levels of 7.8 to 11.0 mmol, or a glycated haemoglobin [HbA_{1c}] level of 6.0% to 6.4%).³

4.2.1 Type 2 diabetes

Type 2 diabetes is a significant risk factor for the development of MAFLD, with systematic reviews, meta-analyses and population-based studies showing a high pooled prevalence of MAFLD in people with diabetes (55%–60%). In an early low-quality meta-analysis that included 17 quantitative studies and involved 10,897 people with type 2 diabetes, the overall prevalence of MAFLD was 54% (95% CI, 45%–64%). However, there was significant heterogeneity across studies ($P < 0.01$).²⁵ A further low-quality meta-analysis, in which most of the 24 studies included patients recruited from diabetes clinics or at the time of hospitalisation, found the pooled prevalence of MAFLD among 35,599 patients with type 2 diabetes was 59.7%.²⁶ More recently, a comprehensive, high-quality meta-analysis of 80 quantitative studies involving 49,419 patients with type 2 diabetes found the overall prevalence of MAFLD among patients with type 2 diabetes was 55.5%, which was more than twofold higher than in the general population.²⁷ These data are consistent with the limited population data available from Australia.^{2,28} A prospective

population-based study in regional Victoria found that the overall prevalence of MAFLD among people with type 2 diabetes was 58% (95% CI, 45%–70%), with an adjusted prevalence ratio of MAFLD in people with diabetes of 1.6 (95% CI, 1.3–2.0).²⁸ Similarly, the cross-sectional analysis of the 2012 survey of the AusDiab study reported a high adjusted odds ratio for MAFLD of 3.39 (95% CI, 2.61–4.39) in patients with type 2 diabetes.²

4.2.2 Obesity

Obesity is a major risk factor for developing MAFLD. The prevalence of MAFLD in people with obesity is between 55% and 75%, depending on the geographic location of the study.^{28,29} A low-quality meta-analysis that included 21 quantitative cohort studies involving 381,655 people reported an overall 3.53-fold (95% CI, 2.48–5.03) increased risk of developing MAFLD among people with obesity, compared with those with normal body weight.³⁰ The relative risk (RR) of MAFLD among White people with obesity was slightly lower, at 2.67 (95% CI, 1.58–4.52).³⁰ Data from a retrospective population-based longitudinal cohort study from The Health Improvement Network (THIN) in the United Kingdom, in which 12,867 incident cases of MAFLD were diagnosed, showed a high 6.92 (95% CI, 6.40–7.48) incident risk of MAFLD among individuals with obesity compared with those with normal weight.³¹ Limited population data from Australia support these findings, with the prevalence of MAFLD in people with obesity from the CrossRoads study in regional Victoria being 76% (95% CI, 68%–83%); people with obesity had a 32-fold (95% CI, 12–86) increased risk of MAFLD compared with those with normal weight.²⁸

4.2.3 Multiple metabolic risk factors

Metabolic dysregulation, defined by the presence of at least two cardiometabolic risk factors (Table 2), independently influences the risk of developing MAFLD, as well as adverse cardiometabolic outcomes and progressive liver disease.^{3,32} Notably, the risk of developing MAFLD appears to significantly increase with worsening metabolic health, including in those with normal body weight.³¹ Among more than four million “healthy” people without MAFLD from THIN in the UK who participated in a longitudinal follow-up study, those who had normal body weight or were overweight but who had two or more metabolic

Table 2. Major metabolic risk factors for MAFLD

Risk factor	Prevalence of MAFLD ^{28,33}
Overweight	30%
Obesity	55%–75%
Type 2 diabetes	55%–60%
Dyslipidaemia	55%
Hypertension	50%
Metabolic syndrome	70%

MAFLD = metabolic dysfunction-associated fatty liver disease.

abnormalities had a 2.4- and 9.6-fold increased risk of incident MAFLD, respectively, compared with metabolically healthy people of normal weight.³¹

4.4 Does screening for MAFLD meet Wilson and Jungner criteria?

Screening for MAFLD in primary care meets most of the Wilson and Jungner criteria for screening (see [Appendix 1](#)). MAFLD is an important public health problem (criterion 1)⁴ that has a well understood natural history (criterion 7),³⁴ including timelines to progression (criterion 4), as well as prognostic factors in relation to who is most at risk of an adverse outcome and hence suitable for treatment (criterion 8).³⁵ The diagnosis can be made safely, inexpensively and readily using imaging, particularly liver ultrasound (criteria 3, 5 and 6) (see [section 4.6.1](#)). Accepted treatment involving lifestyle and dietary modification is available for patients with recognised disease, with effective pharmacotherapy likely to be approved in Australia in the near future (criteria 2 and 3).³⁶ In addition, there are limited data, albeit from overseas, to suggest screening for MAFLD is cost-effective, particularly if treatment is offered to those at risk of worsening disease (criterion 9).

4.5 Cost-effectiveness of screening for MAFLD

There are limited studies evaluating the cost-effectiveness of screening for MAFLD, with few specifically addressing primary care and all being reliant on Markov modelling or decision tree analysis. Moreover, most studies evaluating the cost-effectiveness of screening have focused on those

at higher risk of MAFLD, including patients with type 2 diabetes or metabolic syndrome, and have predominantly used liver ultrasound as the screening tool, typically followed by transient elastography using FibroScan®. Limited evidence from overseas suggests that screening for MAFLD could be cost-effective, provided there is treatment (including lifestyle intervention) available to those at risk of advanced liver disease.

Two modelling studies assessed screening approaches for MAFLD in people with type 2 diabetes and found that screening had either limited cost-effectiveness in certain scenarios or was not cost-effective.^{37,38} The first study was a cost utility analysis in a modelled population of patients with type 2 diabetes where nearly a third had F2 fibrosis or greater at baseline. This model assumed patients underwent a 1-year intensive lifestyle modification or pioglitazone treatment that led to fibrosis regression or resolution. It found that screening with ultrasound and liver enzyme tests was cost-effective, assuming that liver biopsy was not done. Other approaches using liver biopsy to assess non-alcoholic steatohepatitis (NASH) or fibrosis were found to be less effective and more costly than no screening.³⁷ A second modelling study from the United States of screening with liver ultrasound versus no screening in people with type 2 diabetes did not show cost-effectiveness of screening. Lack of cost-effectiveness was partly due to the side effects of liver biopsy and intolerance of the recommended therapy of pioglitazone.³⁸ A further modelling study from Thailand assessed the cost-effectiveness of ultrasound screening for MAFLD using local data of MAFLD prevalence in a population with metabolic syndrome.³⁹ Screening with ultrasound, coupled with an intensive weight management program, was found to be cost-effective compared with no screening and reduced progression to advanced liver disease, with an attendant reduction in costs.³⁹ However, this study has low generalisability to the Australian context, given the different population, varying health care utilisation and significantly lower willingness-to-pay threshold.

A more recent study used modelling to evaluate the cost-effectiveness of various non-invasive strategies to correctly identify high-risk patients among those with MAFLD at a community or primary care level.⁴⁰ The investigators found that shear wave elastography

(SWE)-based strategies were the most cost-effective for diagnosing $\geq$ F2 fibrosis. For $\geq$ F3 fibrosis, the FIB-4 Index, followed by SWE, was the most effective and least costly strategy.⁴⁰ Similarly, a modelling analysis to assess the cost-effectiveness of different non-invasive strategies for detecting cirrhosis among patients with MAFLD found that the FIB-4 Index, followed by vibration-controlled transient elastography (VCTE) using FibroScan®, magnetic resonance elastography (MRE) or liver biopsy, detected cirrhosis in patients with MAFLD with a high level of accuracy and low cost.⁴¹

Hence, there is a lack of data on which to base recommendations on the cost-effectiveness of screening for MAFLD in an Australian primary care population. Further studies using local populations, costs and therapies are needed to better understand the effectiveness and cost-effectiveness, benefits and possible harms of screening, as well as which high-risk subgroups should be targeted.

Practice points:

- Assessment for MAFLD among people with obesity, type 2 diabetes or at least two metabolic risk factors, regardless of body weight, should be performed based on the high prevalence rates in these populations, known natural history, acceptable diagnostic tests and opportunity to intervene to alter the natural history.

Implementation considerations:

- Data on the cost-effectiveness of screening for MAFLD in the Australian context are limited, and modelling studies in an Australian primary care population are needed.

Recommendation 1

Adults with obesity and/or type 2 diabetes mellitus or two or more metabolic risk factors should be assessed for MAFLD.*

* See [section 4.2](#).

Quality of evidence: Low

Strength of recommendation: Strong

4.6 Diagnostic methods for MAFLD

The detection and diagnosis of hepatic steatosis (i.e. fatty liver) in at-risk populations can be made by several different screening modalities, including imaging and non-commercial or commercial biomarker tests.

4.6.1 Imaging modalities

4.6.1.1 Liver ultrasound

Liver ultrasound is a widely studied, freely available and relatively inexpensive imaging modality to detect hepatic steatosis in primary care. It has consistently demonstrated good to very good accuracy in the detection of fatty liver. In a moderate-quality updated systematic review and meta-analysis, the area under the curve (AUC), sensitivity and specificity of ultrasound were 0.87, 82% and 87%, respectively, for the detection of hepatic steatosis of $\geq 5\%$, and 0.92, 85% and 85%, respectively, for hepatic steatosis $\geq 30\%$.⁴² Similar good to very good performance characteristics of liver ultrasound for the detection of fatty liver were obtained in an earlier meta-analysis that included more studies and patients but was of low quality overall.⁴³ However, liver ultrasound has its limitations, including a degree of operator dependency in test performance and reduced sensitivity in certain populations, including those with obesity or with mild hepatic steatosis.

4.6.1.2 Controlled attenuation parameter

Controlled attenuation parameter (CAP) using FibroScan[®] is a relatively new and accurate ultrasound-based modality to detect hepatic steatosis. In a recent high-quality meta-analysis using individual patient data from 13 quantitative studies involving 2346 patients, 95% of whom had obesity, 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.⁴⁴ However, CAP was less able to differentiate between degrees of steatosis (i.e. grades S0–1 vs S2–3) in patients with MAFLD, with the AUC, sensitivity and specificity being 0.75, 78% and 62%, respectively. Similar results were obtained in an earlier high-quality meta-analysis of individual patient data involving 19 studies and 2735 patients,

in which the diagnostic performance of CAP to detect any (S1–3), moderate to severe (S2–3) or severe (S3) hepatic steatosis, as measured by AUC, was 0.82, 0.86 and 0.88, respectively.⁴⁵ Although these performance characteristics are promising, there are limited available data on the accuracy of CAP as a screening tool in the primary care setting. Furthermore, important covariates, such as body mass index (BMI) and diabetes, increase CAP readings independently of steatosis grade and should be considered when interpreting CAP results in patients with MAFLD.⁴⁴ Finally, CAP is only available as part of a FibroScan[®] assessment and thus is not freely available in the community and has no specific Medicare Benefits Schedule (MBS) rebate.

4.6.1.3 Magnetic resonance imaging

Magnetic resonance imaging (MRI) appears to be the best of the available imaging modalities to detect and quantify hepatic steatosis. In a meta-analysis involving 21 studies and 1658 patients, the diagnostic accuracy of MRI using any technique (i.e. MRI, MRE or magnetic resonance spectroscopy) was high, with pooled AUC, sensitivity and specificity of 0.90, 82% and 86%, respectively.⁴⁶ Of the three techniques studied, MRI had the best diagnostic accuracy, with an AUC of 0.95 (95% CI, 0.93–0.97), sensitivity of 91% and specificity of 90%. In comparison, the pooled AUC, sensitivity and specificity were 0.88, 91%, and 82%, respectively, for magnetic resonance spectroscopy, and 0.89, 77% and 86%, respectively, for MRE. However, MRI is expensive to perform and not readily accessible nor eligible for an MBS rebate for this indication.

4.6.2 Biomarkers

Several non-commercial biomarkers have been evaluated to identify or detect MAFLD at a population level, including the FLI, hepatic steatosis index, MAFLD liver fat score, visceral adiposity index and triglyceride 9 glucose index. 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, typically have a proportion of patients who fall into an “indeterminate range” and do not accurately quantify steatosis, which may limit their clinical utility. Validation studies have demonstrated variable

accuracy, with an AUC for detection of fatty liver between 0.70 and 0.90.^{47,48} Of these biomarkers, the FLI — consisting of waist circumference, BMI and serum triglyceride and gamma-glutamyl transferase levels — has been most studied and validated, particularly at a population or community level, with an AUC between 0.79 and 0.83.⁴⁹ In a moderate-quality systematic review and meta-analysis involving 10 studies and 27,221 patients, an FLI cut-off <30 had a sensitivity of 81%, specificity of 65% and negative predictive value (NPV) of 84% to *rule out* MAFLD, whereas an FLI cut-off >60 had sensitivity, specificity and positive predictive value (PPV) of 44%, 90% and 67%, respectively, to *rule in* MAFLD.⁴⁹ Although non-commercial and inexpensive biomarkers, such as the FLI, are suited to population-based studies of MAFLD, they are not well suited to screening for MAFLD in primary care because of the multiple components required (including anthropometric and laboratory variables) and lack of automation of their complex algorithms.

In comparison, there are few commercial biomarkers to detect hepatic steatosis. The SteatoTest and next-generation SteatoTest 2 blood biomarker tests have been evaluated to detect MAFLD.^{50,51} Most studies of these two commercial biomarkers have been of low quality, but both tests appear to have suboptimal accuracy for fatty liver disease, with AUCs ranging from 0.63 to 0.82 in patients with MAFLD, 0.73 in people with type 2 diabetes and 0.78 in people with obesity. Furthermore, these tests are expensive and not readily available in Australia.

Practice points:

- Liver ultrasound has very good diagnostic performance to detect hepatic steatosis and is both inexpensive and readily available in the community.
- Clinicians should be aware of the lower sensitivity of ultrasound in patients with obesity or a low degree of hepatic steatosis.

Implementation considerations:

- CAP and MRI are not readily accessible in the community and do not attract an MBS rebate for diagnosis of hepatic steatosis.
- Non-commercial biomarkers are not well suited to screening for MAFLD in primary care because of the multiple components required and the complex algorithms involved.
- Commercial biomarker tests for hepatic steatosis are expensive and not readily available in Australia.

Recommendation 2

Liver ultrasound should be the first-line test to diagnose hepatic steatosis in people at high risk of MAFLD.

Quality of evidence: Moderate

Strength of recommendation: Strong

5 Assessment of coexisting conditions in MAFLD

5.1 Role of metabolic dysfunction in pathogenesis of MAFLD

MAFLD has a complex and incompletely understood pathogenesis, mediated by environmental and genetic factors, as well as the gut microbiome, but a key underlying mechanism is the presence of metabolic dysfunction and insulin resistance. Overnutrition, where energy intake exceeds metabolic needs, leads to expansion of visceral adipose tissue. Subsequent inflammation of adipose tissue, due to cellular stress from excess fats, leads to insulin resistance and systemic inflammation, causing increased circulating free fatty acids (FFAs). Increased delivery of FFAs to the liver and de novo hepatic lipogenesis then occur, with toxic lipid formation activating the inflammasome, causing oxidative stress and ultimately hepatocyte damage and activation of fibrogenesis.⁵²

5.2 Coexisting metabolic conditions in people with MAFLD

By definition, MAFLD is associated with several metabolic conditions, including obesity, type 2 diabetes, 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), as well as polycystic ovary syndrome. 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.

MAFLD may also be associated with other coexisting conditions, such as mental health disorders and an increased risk of extrahepatic malignancies.⁵³ At this time, there are insufficient data to make specific recommendations to screen for these conditions in patients with MAFLD outside of the recommendations applicable to the general population.

5.3 Obesity in people with MAFLD

Obesity is common in people with MAFLD and is associated with disease progression and other metabolic complications. Prevalence estimates for obesity range from 51% in patients diagnosed with MAFLD to 82% in patients with metabolic steatohepatitis (MASH), which is the inflammatory form of MAFLD and is defined by the presence of lobular inflammation and hepatocyte ballooning.¹⁹ In an Australian cohort of 705 patients, 69% of patients with MAFLD had obesity.²⁸

The Australian Obesity Management Algorithm (<https://www.sciencedirect.com/science/article/pii/S1871403X22000709>) is recommended for the assessment and management of obesity.⁵⁴ This algorithm uses BMI and waist circumference as measures of obesity (Table 3). It recognises that BMI has limitations and that the presence of abdominal obesity is more strongly associated with metabolic risk. Population-specific cut-offs for Asian and Australian First Nations peoples are provided in the algorithm.

The algorithm also offers guidance for assessment of obesity-related complications and recommends that these assessments be repeated regularly, given the chronic nature of obesity. In addition to MAFLD, the algorithm recommends assessment for type 2 diabetes, CVD, gastro-oesophageal reflux disease, OSA, asthma, idiopathic intracranial hypertension, arthralgia, lymphoedema, reproductive hormonal dysfunction, disordered eating and depression.

Table 3. Classification of weight by BMI and waist circumference*

Classification	General population BMI (kg/m ²)	Population-specific BMI (kg/m ²)†	General population waist circumference (cm)	Population-specific waist circumference (cm)†
Normal range	18.5–24.9	18.5–22.9	Female <80 Male <94	
Overweight	25.0–29.9	23.0–27.4	Female 80–88 Male 94–102	
Class I obesity	30.0–34.9	27.5–32.4	Female >88 Male >102	Female >80 Male >90
Class II obesity	35.0–39.9	32.5–37.4		
Class III obesity	≥40	≥37.5		

BMI = body mass index.

* Adapted from Markovic et al.⁵⁴

† Cut-offs apply to Asian populations and recommended for Australian First Nations populations.

Recommendation 3

People with obesity and MAFLD should be assessed in accordance with the Australian Obesity Management Algorithm.

Quality of evidence: Low

Strength of recommendation: Strong

5.4 Type 2 diabetes in people with MAFLD

5.4.1 Prevalence of type 2 diabetes in people with MAFLD

Up to a quarter of patients with MAFLD have type 2 diabetes. In a large meta-analysis of more than 2.6 million individuals with MAFLD, the prevalence of type 2 diabetes was 19.7%,⁵⁵ whereas a meta-analysis of 21 studies reported a prevalence of 24.7%.⁸ Both meta-analyses reported high heterogeneity in type 2 diabetes prevalence across the included studies. In regional Western Australia and Victoria, the prevalence of type 2 diabetes in people with MAFLD (diagnosed by the FLI) was 11% and 19%, respectively.^{28,56} A prevalence of 19% was found in the AusDiab study.² Notably, the prevalence of type 2 diabetes increases with severity of underlying liver histology, with a prevalence of 22.5% reported in patients with MAFLD and 43.6% in patients with MASH.¹⁹

In contrast to type 2 diabetes, MAFLD presence and severity are less well defined in people with type 1 diabetes or other forms of diabetes mellitus, such as gestational diabetes or type 3 diabetes (according to

the World Health Organization diabetes classification). Thus, recommendations pertaining to type 2 diabetes and MAFLD assessment for presence and severity do not apply to other forms of diabetes.

5.4.2 Significance of type 2 diabetes in people with MAFLD

The relationship between MAFLD and type 2 diabetes appears to be bidirectional. MAFLD may precede and increase the risk of incident type 2 diabetes by at least twofold, with greater risk in those with more advanced fibrosis.^{57–59} Conversely, type 2 diabetes is a strong risk factor for the development of MAFLD and progression of hepatic fibrosis in people with MAFLD. A cross-sectional study of more than 1000 patients with MAFLD found that a diagnosis of type 2 diabetes was associated with hepatic fibrosis (adjusted odds ratio, 2.57).⁶⁰ In a study of 447 patients with paired liver biopsies, patients with advanced fibrosis at both index and follow-up biopsy were more likely to have type 2 diabetes, and type 2 diabetes was an independent predictor of fibrosis progression (odds ratio, 1.69).⁶¹

Additionally, type 2 diabetes is associated with a higher risk of liver decompensation and HCC developing in patients with MAFLD. A meta-analysis of individual patient-level data for 2016 people with MAFLD found that those with type 2 diabetes had significantly higher 5-year cumulative incidence of liver decompensation than did those without type 2 diabetes (13.85% vs 3.95%), with type 2 diabetes and HbA_{1c} level being independently associated with a 2.1-fold and 1.3-fold higher risk, respectively, of hepatic

decompensation.⁶² Confirmatory data from Australia found type 2 diabetes to be associated with a 4.7-fold higher risk of liver decompensation and a 2.9-fold higher risk of HCC in a hospital-based cohort of 284 patients who were followed for 51 months.⁶³ A larger data-linked cohort of 8006 patients in Queensland also found type 2 diabetes to be a risk factor for decompensation (adjusted hazard ratio, 2.8) over a median 4.6 years of follow-up.⁶⁴ A similar magnitude of risk was found in a retrospective cohort of 271,906 patients with MAFLD in the US, which found that type 2 diabetes was independently associated with a 2.77-fold higher risk of HCC compared with patients without type 2 diabetes.⁶⁵ Type 2 diabetes has been associated with an increased risk of HCC across other liver disease aetiologies,⁶⁶ but the risk appears to be strongest in those with MAFLD.^{65,67} Notably, the risk of HCC related to type 2 diabetes also increases with each additional metabolic comorbidity (dyslipidaemia, obesity, hypertension), highlighting the risk of severe metabolic dysfunction for liver-related outcomes.^{65,68}

Practice points:

- People with MAFLD have a high prevalence of underlying type 2 diabetes, which is associated with a higher risk of liver fibrosis, liver decompensation and HCC in this population.
- Screening for type 2 diabetes using fasting blood glucose or HbA_{1c} levels should be performed according to the Australian Type 2 Diabetes Risk Assessment Tool (<https://www.health.gov.au/resources/apps-and-tools/the-australian-type-2-diabetes-risk-assessment-tool-ausdrisk>).

Recommendation 4

People with MAFLD should be assessed for undiagnosed type 2 diabetes using measurement of fasting blood glucose or HbA_{1c} levels.

Quality of evidence: Moderate

Strength of recommendation: Strong

5.5 Cardiovascular disease risk in people with MAFLD

5.5.1 Prevalence of other cardiovascular risk factors in people with MAFLD

Hypertension and dyslipidaemia characterised by hypertriglyceridaemia and low HDL cholesterol levels are also common metabolic conditions in people with MAFLD. In large meta-analyses, both hypertension and dyslipidaemia were present in 40%–50% of patients with MAFLD, although results across studies appear to be heterogeneous.^{8,19,55} A meta-analysis of 116 studies involving 2.6 million individuals in the general population found the prevalence of hypertension, hypertriglyceridaemia and low HDL cholesterol levels to be 42%, 46% and 54%, respectively, in people with MAFLD who had obesity or were overweight.⁵⁵ In the Australian context, the prevalence of hypertension was 37% among 626 patients with MAFLD referred from primary care to a tertiary hepatology clinic.⁶⁹ Cross-sectional data from rural Victoria found prevalences of hypertension and dyslipidaemia of 66% and 63%, respectively, in people with MAFLD, compared with 48% and 43%, respectively, in those without MAFLD.²⁸

5.5.2 Risk of cardiovascular morbidity and mortality in people with MAFLD

Among people with MAFLD, CVD is the most common cause of death, being responsible for a quarter of all deaths.⁷⁰ MAFLD is associated with an increased risk of CVD-related morbidity and mortality, in part due to its association with established cardiovascular risk factors. However, it has also been proposed that MAFLD may confer increased CVD risk independently of these other factors.⁷¹ Notably, in a meta-analysis of seven cohort studies comprising more than 13 million individuals, MAFLD was associated with a 50% higher risk of fatal or non-fatal CVD events, independently of age, sex, smoking and other traditional CVD risk factors.⁷² MAFLD has also been specifically associated with an increased risk of non-atherosclerotic CVD, including cardiac arrhythmias, structural heart disease and heart failure.^{73–76}

Practice points:

- CVD is a major cause of morbidity and mortality in people with MAFLD, with evidence suggesting an excess risk compared with individuals without MAFLD.
- Assessment and monitoring of CVD risk should be performed according to recent Australian guidelines (<https://www.cvdcheck.org.au/>).
- Statins are safe for patients with MAFLD, including those with compensated cirrhosis, and should not be avoided in people with MAFLD and elevated cardiovascular risk.⁷⁷

Recommendation 5

People with MAFLD should be assessed and monitored for the presence and risk of future cardiovascular disease according to current Australian guidelines.

Quality of evidence: High

Strength of recommendation: Strong

5.6 Chronic kidney disease in people with MAFLD

5.6.1 Prevalence of chronic kidney disease in people with MAFLD

CKD is another common coexisting condition in patients with MAFLD. A meta-analysis involving 10,925 patients across 21 studies found a prevalence of CKD in patients with MAFLD of 24%.⁸ In an updated meta-analysis of more than 1.2 million individuals, there was a 43% increased risk of incident CKD over a median follow-up period of 10 years.⁷⁸ Furthermore, a study from the UK Biobank has shown MAFLD to be associated with a doubling of the risk of end-stage kidney disease (defined as renal replacement therapy in the absence of acute kidney injury), with the risk increasing further as fibrosis status worsened.⁷⁹

5.6.2 Hypothesised pathogenic link of chronic kidney disease to MAFLD

CVD, CKD and metabolic dysfunction (which includes MAFLD) share a close pathophysiological interrelatedness, which can be conceptualised as

the cardiovascular–kidney–metabolic syndrome.⁸⁰ Specifically, MAFLD and CKD share common cardiometabolic risk factors, such as type 2 diabetes and hypertension. However, in addition to these shared risk factors, it has been proposed that the chronic inflammatory state of visceral obesity and intestinal dysbiosis, with associated increases in gut permeability, gram-negative organisms, lipopolysaccharide levels, secondary bile acids and renal toxins, contributes to renal and hepatic injury via inflammatory and fibrotic pathways.⁸¹ Other proposed links between MAFLD and CKD include dietary fructose consumption and platelet activation. It has also been found that the *PNPLA3* polymorphism, found to be a common genetic variant associated with a predisposition to steatohepatitis, is associated with renal dysfunction.⁸²

5.7 Obstructive sleep apnoea in people with MAFLD

5.7.1 Prevalence of obstructive sleep apnoea in people with MAFLD

OSA impairs quality of life and is associated with an increased risk of cardiometabolic disease.⁸³ Not surprisingly, OSA is common among people with MAFLD, particularly in the presence of obesity. A meta-analysis found MAFLD to be associated with a 6.8-fold increased risk of OSA, which is in part mediated by obesity.⁸⁴ The prevalence of OSA in a prospective cohort of patients with MAFLD in the US was 29% in those with obesity, compared with 9% in those without obesity.⁸⁵ A study from Australia of 95 patients with type 2 diabetes and MAFLD, who were recruited from primary care and endocrinology clinics, found a high occurrence of coexisting metabolic conditions, including a 32% prevalence of OSA.⁸⁶

5.7.2 Hypothesised pathogenic link of obstructive sleep apnoea to MAFLD

OSA, through collapse of the pharyngeal airway during sleep, causes intermittent hypoxia, which in turn causes systemic oxidative stress and an increased sympathetic response. Additionally, intermittent hypoxia triggers lipolysis and alters FFA metabolism. It has also been proposed that alterations in the gut–liver axis via the effect of OSA on the gut barrier and

microbiota play a role.⁸⁷ OSA has been shown to be an independent risk factor for the development of insulin resistance,⁸⁸ most likely through the effect of sympathetic activation and inflammation on lipolysis and circulating FFAs.

It is proposed that these mechanisms contribute to the pathogenesis and progression of MAFLD in people with OSA. In patients with MAFLD, the presence of OSA is associated with increased severity of steatohepatitis and a 2.5-fold increased risk of fibrosis.⁸⁹⁻⁹¹ However, clinical trials have not yet demonstrated that treatment of OSA with continuous positive airway pressure therapy improves hepatic steatosis levels or serum liver enzyme levels.⁹² Nonetheless, the high prevalence of OSA, coupled with its impairments to quality of life and the availability of a defined treatment strategy, warrants assessment for OSA in people with MAFLD.

Practice points:

- Screening for CKD should be performed as directed by Kidney Health Australia guidelines (<https://assets.kidney.org.au/resources/KHA-CKD-Handbook-5th-Ed-July2024.pdf>).
- Screening for symptoms of OSA should be considered in patients with MAFLD, particularly those with other conditions associated with a high prevalence of OSA, such as obesity, type 2 diabetes and treatment-resistant hypertension.
- Screening tools such as the STOP-BANG questionnaire can be used to screen for OSA.⁹³

Recommendation 6

Baseline assessment for potential coexisting conditions of chronic kidney disease and obstructive sleep apnoea should be considered for people with MAFLD.

Quality of evidence: Moderate

Strength of recommendation: Weak

6 Assessment of underlying liver disease

6.1. Assessment of other causes of fatty liver

6.1.1. Other causes of fatty liver

Although metabolic dysfunction related to excess adiposity and type 2 diabetes is the major cause of fatty liver, other causes (outlined in Box 1) should be considered because they will have different prognoses and treatments. Excess alcohol consumption (see section 6.1.2) and use of medications that can result in hepatic steatosis are relatively common in patients presenting to a GP. Corticosteroids, including prednisolone, cause metabolic dysfunction through weight gain and generation of insulin resistance, with resultant hepatic steatosis and steatohepatitis. Advanced fibrosis or cirrhosis due to corticosteroids appears to be rare, and the dose and duration required to cause fatty liver are unknown. In contrast, chronic methotrexate and amiodarone use has been associated with steatohepatitis and progressive liver injury, resulting in cirrhosis, and should be carefully evaluated in patients with fatty liver.⁹⁴ Genotype 3 hepatitis C virus (HCV) infection interferes with hepatic lipid metabolism and export and may cause fatty liver. People at risk of HCV infection include those with a history of injecting drugs, people in custodial settings, sexual partners of HCV-positive individuals and migrants from high-prevalence regions (Egypt, Pakistan, the Mediterranean, Eastern Europe, Africa and Asia).⁹⁵

Box 1. Common causes of fatty liver

- Overweight and obesity
- Type 2 diabetes
- Alcohol
- Medications (including corticosteroids, methotrexate, antipsychotics, valproate, amiodarone and tamoxifen)
- Hepatitis C (genotype 3)

Practice points:

- People with MAFLD should be assessed for additional causes of fatty liver and liver disease, including alcohol, medications, drug-induced liver injury and viral hepatitis, by taking a thorough medical history and using targeted serological testing if appropriate.

Recommendation 7

People with MAFLD should be assessed for other common causes of fatty liver and liver disease.

Quality of evidence: Low

Strength of recommendation: Strong

6.1.2 Epidemiology of alcohol use and alcohol-related liver disease in Australia

Harmful alcohol use is common among patients managed in primary care and is responsible for about a third of all deaths due to liver disease.⁹⁶ About 5% of Australians drink alcohol on a daily basis, and 27% consume an average of more than 10 standard drinks a week or consumed more than five drinks in any day at least monthly in the past 12 months.⁹⁷ In Australia in 2016, the prevalence of alcohol use disorder (defined as including harmful use of alcohol and alcohol dependence, according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*) was estimated at 4.4% (6.1% in men, 2.7% in women).⁹⁸ The 2018 Australian Burden of Disease Study found alcohol use contributed to 40% of the burden related to liver cancer and 19% of the burden of chronic liver disease.⁹⁷ Correspondingly, alcohol consumption accounted for 39% of all deaths due to liver cancer in Australia in 2018.⁹⁹

6.1.3 Impact of alcohol use on outcomes in people with MAFLD

Alcohol ingestion may result in hepatic steatosis, with alcohol-related fatty liver disease developing in 90% of people who drink more than 40 g of alcohol (or

four standard drinks) a day over a sustained period (months or years), of whom 8%–20% will develop alcohol-related liver cirrhosis.¹⁰⁰ Alcohol-related fatty liver disease combined with MAFLD related to excess adiposity and/or type 2 diabetes increases the risk of acute alcoholic hepatitis and cirrhosis, and both conditions should therefore be assessed in people presenting with fatty liver.^{101,102} Moderate alcohol consumption (average of 10–30 g/day), which may not be sufficient to cause fatty liver, has been associated in some studies with an increased risk of advanced liver fibrosis in patients with MAFLD.¹⁰³

Practice points:

- The Alcohol Use Disorders Identification Test (AUDIT-C) is a short three-question tool that can be used to screen for alcohol use disorder, but it may miss potentially harmful lower levels of consumption.
- Australian National Health and Medical Research Council guidelines (<https://www.nhmrc.gov.au/health-advice/alcohol>) recommend that healthy men and women should drink no more than 10 standard drinks a week and no more than four standard drinks on any one day, although it is recognised that the risk of harm is lower when less alcohol is consumed.⁹⁸
- Patients with cirrhosis should completely abstain from alcohol because of the increased risk of HCC and decompensation.¹⁰⁴

Recommendation 8

People with MAFLD should undergo screening for harmful alcohol use.

Quality of evidence: Moderate

Strength of recommendation: Strong

6.2. Assessment of alternative causes of liver disease

6.2.1 Assessment of chronic viral hepatitis in people with MAFLD

Infection with viral hepatitis B or C is a common cause of chronic liver disease in Australia and should

be assessed as a potential cause of elevated serum aminotransferase levels among people with MAFLD.

An estimated 74,400 people were living with chronic hepatitis C (CHC) infection in Australia at the end of 2022, with 9500 having cirrhosis.¹⁰⁵ The prevalence of CHC infection is higher in at-risk groups, being 12% among people who inject drugs and attend needle and syringe programs.

Chronic hepatitis B (CHB) is also relatively common in Australia and is present in 0.8% of the general population, with an estimated 200,385 people living with the infection at the end of 2021.¹⁰⁶ The prevalence of CHB infection is higher in certain populations in Australia, being 5% among people who were born in north-east Asia, 4% among those born in south-east Asia, 2% among Aboriginal and Torres Strait Islander peoples and 4% among gay and bisexual men.¹⁰⁶

In addition to screening people with MAFLD who have elevated serum aminotransferase levels, consideration should be given to screening people at higher risk of having CHB or CHC infection, including those born in endemic areas (central, south-east and north-east Asia; Pacific islands; north, central and sub-Saharan Africa; and southern and eastern Europe), people who inject drugs, men who have sex with men, people who have ever been incarcerated and those who have close contacts with CHB or CHC infection.^{95,107} Antiviral treatment is well tolerated and universally recommended for CHC infection; of the 5210 people who received HCV treatment in 2022, 94% were cured.¹⁰⁵ Treatment for CHB infection is recommended for people with an elevated hepatitis B viral load and elevated alanine aminotransferase (ALT) level or those who have advanced liver disease. Importantly, appropriate treatment reduces the risk of development of HCC and cirrhosis.^{95,107,108}

Over the past few years, there has been a change in the recommended upper reference limits of ALT level due to modification of the analytical methods in chemical pathology and recognition that “healthy control” populations may have included people with metabolic risk factors and fatty liver.¹⁰⁹ Harmonisation of reference ranges for serum ALT levels in Australia has been recommended by the Australasian Association for Clinical Biochemistry

and Laboratory Medicine and endorsed by the Royal College of Pathologists of Australasia, with the upper limits for men and women being 40 U/L and 35 U/L, respectively.¹¹⁰

Practice points:

- An elevated serum ALT level of >40 U/L for men and >35 U/L for women¹¹⁰ should trigger assessment of risk factors for CHB and CHC infection, noting that acute intercurrent illness and comorbidities may affect liver enzyme levels.
- Screening for viral hepatitis C and B should be performed with HCV antibody testing (and reflex testing for HCV RNA) and hepatitis B serological testing, respectively.

Recommendation 9

People with MAFLD and elevated serum aminotransferase levels should undergo baseline evaluation for hepatitis B and C infection.

Quality of evidence: Moderate

Strength of recommendation: Strong

6.2.2 Assessment of iron overload in people with MAFLD

Hyperferritinaemia is common among people with MAFLD, with studies from tertiary centres finding that up to a third of patients with MAFLD have elevated serum ferritin levels (>200 ng/mL in women and >300 ng/mL in men), but less than 10% have

an elevated transferrin saturation (>45%).¹¹¹⁻¹¹³ An elevated transferrin saturation value should precipitate testing for genetic haemochromatosis. Elevated serum ferritin levels usually reflect the systemic inflammatory state and metabolic dysfunction, rather than significant iron load, and are correlated with liver steatosis, insulin resistance and male sex.^{111,112,114} Hepatic iron content may be mildly increased in up to half of these patients; however, phlebotomy is not indicated as it does not reduce the underlying metabolic dysfunction or liver injury.^{115,116}

Hereditary haemochromatosis, caused by homozygous C282Y mutations in the *HFE* gene, occurs in about one in 200 Australians and thus may coexist in people with MAFLD. Liver disease is one of the most common manifestations of hereditary haemochromatosis, and screening is therefore recommended among individuals with elevated aminotransferase levels.¹¹⁷ Individuals with an elevated serum ferritin level and transferrin saturation should go on to have genetic testing for *HFE* gene mutations.

Recommendation 10

People with MAFLD and elevated serum aminotransferase levels should undergo evaluation for iron overload.

Quality of evidence: Moderate

Strength of recommendation: Strong

7 Assessment of liver fibrosis

7.1 Prevalence and significance of liver fibrosis in people with MAFLD

People with MAFLD may develop liver injury and inflammation (known as steatohepatitis), which can lead to liver fibrosis. Liver fibrosis is typically quantified from a liver biopsy using a staging score that categorises its severity on a graded scale from zero (no fibrosis) to one (mild fibrosis), two (significant fibrosis), three (advanced fibrosis) and four (equivalent to cirrhosis).^{118,119} The prevalence of advanced fibrosis (i.e. stages 3 and 4) among people with MAFLD in general population studies from overseas ranges from 3.0% to 7.4%,^{120–122} with a prevalence of 7.6% seen in a primary care population.¹²³ In Australia, a study of 704 people from rural Victoria found a 3.3% prevalence of advanced fibrosis among those with MAFLD, and a similar prevalence of 3.9% was found in 504 people from a primary care clinic in Brisbane.^{24,124}

A small but not insignificant proportion (up to 10%) of people with MAFLD develop liver decompensation or HCC over 10 to 20 years.^{125,126} The onset of these complications heralds significant morbidity, impaired quality of life and reduced life expectancy. A key prognostic factor for liver decompensation, HCC, liver-related mortality and overall mortality is the presence of fibrosis, with the risk particularly increasing with advanced fibrosis (stages 3 and 4).^{125,127,128} A meta-analysis of 13 studies involving 4428 patients with MAFLD showed that, compared with those without fibrosis, patients with stage 3 fibrosis had higher all-cause mortality (RR, 2.1; 95% CI, 1.7–2.7) and liver-related mortality (RR, 6.6; 95% CI, 2.0–22.2).¹²⁸ A more recent meta-analysis of more than 17,000 patients consolidated these findings, showing a 7.6-fold (95% CI, 2.8–20.5) increase in risk of liver-related mortality among patients with advanced fibrosis.³⁵

Recently, it has been highlighted that advanced fibrosis (stage 3) and cirrhosis (stage 4) exist as a spectrum of disease severity that heralds an increased risk of developing clinically significant portal hypertension and, thus, complications such as ascites, variceal bleeding and hepatic encephalopathy. This overlapping

of advanced fibrosis and cirrhosis is termed compensated advanced chronic liver disease (cACLD) and is interchangeable with advanced liver fibrosis (stages 3 and 4).¹²⁹ Non-invasive tests have been optimised for the detection of this endpoint, and their results may be reported as probability or risk of having advanced liver fibrosis or cACLD.

7.2 Rationale for non-invasive staging of liver fibrosis

Early identification of people at higher risk of adverse liver-related outcomes provides an opportunity for intervention to reduce disease progression and enable referral for specialist hepatology care before liver-related complications develop. 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.^{119,130,131} 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.

Non-invasive tests are increasingly used to predict the likelihood of advanced fibrosis or cirrhosis. They allow rapid point-of-care prognostication and can assist in determining clinical management priorities and the need for specialist referral or additional investigations. Data from a meta-analysis of individual patient data from 2518 patients with biopsy-proven MAFLD in 25 studies highlighted that simple non-invasive tests performed as well as histological assessment of fibrosis (using liver biopsy) in predicting clinical outcomes in patients with MAFLD.¹³²

7.3 Types and use of non-invasive tests for liver fibrosis

Non-invasive tests for liver fibrosis can be classified into three broad groups:

- blood tests, including simple scores using routinely available laboratory variables with or

without clinical variables, and “direct” serum tests that typically incorporate serum markers of fibrogenesis or fibrinolysis

- elastography methods assessing physical properties of the liver (e.g. liver stiffness)
- imaging methods, such as standard ultrasound or computed tomography (CT), which assess the anatomy of the liver and features of portal hypertension.

These strategies are complementary, and all available data need to be considered together to reach an accurate assessment of fibrosis severity. Importantly, standard liver function tests, including measurement of bilirubin, aminotransferase and albumin levels, are not accurate in detecting advanced liver fibrosis and may even give normal results in the presence of cirrhosis.^{133,134} Similarly, ultrasound and CT are inaccurate for determining advanced fibrosis and lack sensitivity for determining cirrhosis.¹³⁵ Thus, specific diagnostic non-invasive tests for liver fibrosis are required for accurate staging in people with MAFLD.

Most non-invasive tests have been developed to diagnose advanced liver fibrosis or cirrhosis. They are not accurate for diagnosing mild to moderate fibrosis and cannot discriminate between contiguous fibrosis stages. Each non-invasive test has specific advantages and limitations, with no single test being perfect.¹³⁶

The diagnostic performance of a non-invasive test depends on the prevalence of advanced fibrosis in the population under evaluation.¹³⁷ In populations with a low prevalence of advanced fibrosis, such as in primary care, the pre-test probability of a negative test result is high, whereas the pre-test probability of a positive result is low. Thus, non-invasive tests tend to have high NPVs and low PPVs when used in primary care. Non-invasive test thresholds may be chosen to have lower sensitivity (probability that a patient with advanced fibrosis tests positive) and higher specificity (probability that a patient without advanced fibrosis tests negative).¹³⁶ Therefore, in an unselected general population where the prevalence of MAFLD with advanced fibrosis is <5%, non-invasive tests have a greater utility to “rule out” advanced fibrosis using low-risk scores. Further tests are required for people with indeterminate or high-risk scores to confirm the diagnosis of advanced fibrosis or cirrhosis. Given

their utility in accurately risk-stratifying patients with MAFLD, the use of non-invasive tests in the assessment of MAFLD is supported by the practice guidelines of key international societies and expert opinion.¹³⁸⁻¹⁴³

Recommendation 11

Non-invasive testing should be offered to people with MAFLD to assess their risk of liver fibrosis.

Quality of evidence: Moderate

Strength of recommendation: Strong

7.4 First-line testing for liver fibrosis

The FIB-4 Index is a non-commercial, low-cost, non-invasive test using common laboratory test results that are widely available in clinical practice (aspartate aminotransferase [AST], ALT and platelet count). The algorithm of age [years] × AST [U/L]/(platelet count [10⁹/L] × √ALT [U/L]) can be easily performed using online calculators. FIB-4 has been broadly validated as an accurate predictor of advanced fibrosis in people with MAFLD, with a meta-analysis of 37 studies involving 5735 individuals finding a summary AUC statistic of 0.76.¹⁴⁴ It is useful even in patients with normal-range liver enzyme levels and has been validated in many different centres and in ethnically different populations with MAFLD.¹⁴⁵⁻¹⁴⁷

The 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 advanced fibrosis, whereas a cut-off of 2.67 is 94% (95% CI, 93%–94%) specific.¹⁴⁴ Results between these cut-offs are indeterminate. In a primary care population where the prevalence of advanced fibrosis is relatively low, at between 5% and 10%, the NPV of a FIB-4 score <1.3 is 95%–97%, highlighting its utility in excluding patients with advanced fibrosis. In contrast, the PPV of a FIB-4 score >2.67 is only 24%–40% in primary care settings, showing the need for further confirmatory testing.¹⁴⁴

The utility of FIB-4 as a first-line test for fibrosis assessment is confirmed by its prognostic ability,

which stratifies the risk of adverse liver outcomes in people with MAFLD. In an Australian cohort of 628 patients with MAFLD referred from primary care, the likelihood of those with a low FIB-4 score (<1.3) developing HCC or hepatic decompensation was 1% or lower over a median follow-up of 5 years.⁶⁹ Similarly, a meta-analysis of 25 studies involving 2518 patients with MAFLD followed for a median of 57 months found that 1% of individuals with a FIB-4 score <1.3 died or developed liver decompensation or HCC, whereas 20.8% with a FIB-4 score >2.67 reached the composite endpoint.¹³² The significantly increased risk of adverse outcomes in people with MAFLD and a FIB-4 score greater than 2.67 supports the recommendation that these patients should be referred for further assessment by a specialist in liver disease. It should also be noted that the cut-offs of 1.3 and 2.67 are specific for MAFLD, and other cut-offs are typically recommended for patients with chronic viral hepatitis.

Similar to all other biochemical assays, the FIB-4 Index has analytical variation between laboratories. Testing of AST and ALT measurements in more than 160 Australian laboratories by the Royal College of Pathologists of Australasia Quality Assurance Program has shown the average analytical coefficient of variation for FIB-4 to be between 8% and 11% when age and platelet values are fixed (personal communication, Graham Jones, SydPath, St Vincent's Hospital Sydney, 9 September 2022). Thus, for simplicity, it is reasonable in clinical practice to round the upper threshold of the FIB-4 score from 2.67 to 2.7.

Age affects the accuracy of the FIB-4 Index. FIB-4 is inaccurate in people younger than 35 years,¹⁴⁸ although the risk of advanced liver fibrosis in young adults is very low. The specificity of FIB-4 also reduces with increasing age, such that an upper cut-off score of 2.0 is recommended for patients older than 65 years.¹⁴⁸

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.^{149,150} More complex serum scores, which include direct markers of fibrogenesis or fibrinolysis, include the Enhanced Liver Fibrosis (ELF) score and Hepascore (see [section 7.5.3](#)).

Practice points:

- FIB-4 should not be used in people younger than 35 years of age, and an upper cut-off score of 2.0 is recommended for people older than 65 years.
- 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.
- The FIB-4 Index has a low PPV for advanced fibrosis, such that patients with a score ≥ 1.3 require further investigation for advanced fibrosis.

Recommendation 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.

Quality of evidence: Moderate

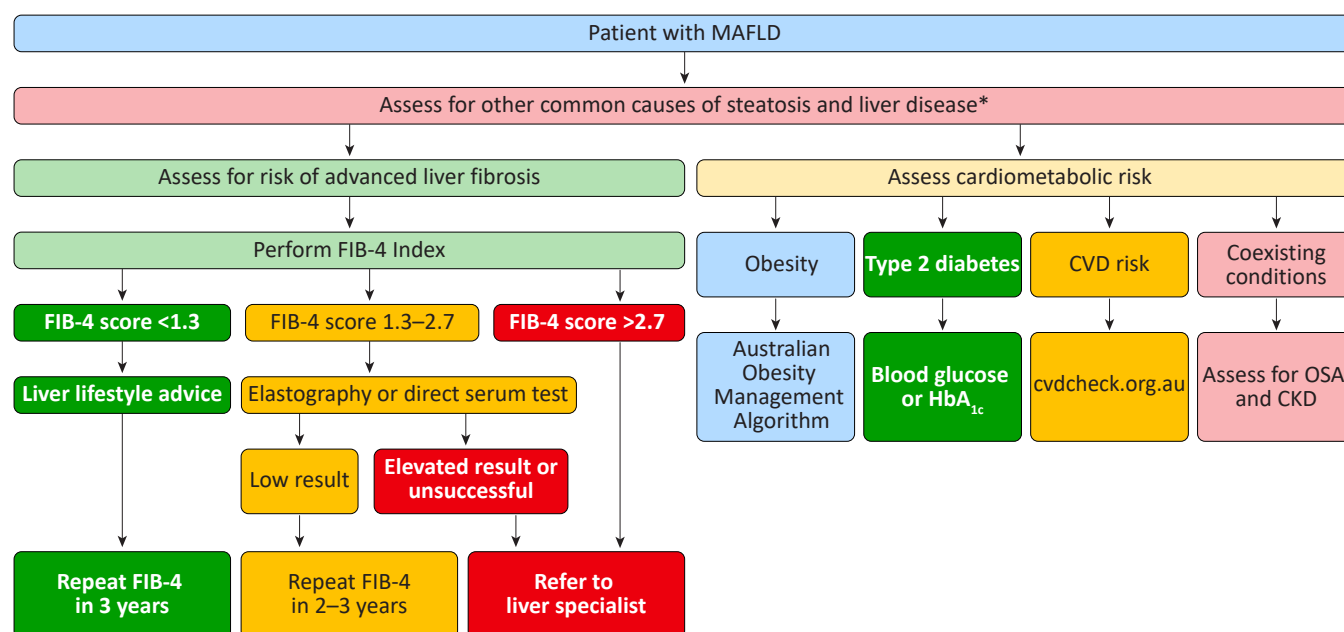
Strength of recommendation: Strong

7.5 Second-line testing for liver fibrosis

Up to a third of individuals tested with FIB-4 will have an indeterminate score in the range of 1.3–2.7,^{69,151} which requires a second-line test to determine the risk of advanced fibrosis and future liver-related morbidity and mortality (Figure 2). The sequential use of non-invasive tests has similar or improved accuracy for the diagnosis of advanced fibrosis compared with a single test, and it significantly reduces the proportion of patients with indeterminate results who would otherwise require a liver biopsy for definitive fibrosis staging.^{144,152,153}

Liver elastography (including VCTE, or FibroScan[®], and SWE) or a direct serum fibrosis test (including Hepascore and ELF) is typically recommended for second-line evaluation of a patient with an indeterminate FIB-4 result, owing to the higher accuracy of these tests. The selection of a second-line test should take into account local availability and referral pathways, the potential for false positive results and cost.

Figure 2. Assessment algorithm for a patient presenting with MAFLD



* Evaluate alcohol intake, medications, risk factors for viral hepatitis, and iron overload.

CKD = chronic kidney disease; CVD = cardiovascular disease; FIB-4 = Fibrosis 4; HbA_{1c} = glycated haemoglobin; MAFLD = metabolic dysfunction-associated fatty liver disease; OSA = obstructive sleep apnoea.

Recommendations are likely to be updated frequently as advances are made in the diagnosis, staging and management of MAFLD. Where possible, low-risk second-line non-invasive tests should be performed in the community to reduce unnecessary referrals to secondary care.

7.5.1 Second-line test: vibration-controlled transient elastography

VCTE, or FibroScan®, quantifies the elasticity of the liver parenchyma by sonographically measuring the velocity of an impulse induced by a mechanical driver held next to the patient's abdominal wall. Liver stiffness measurement (LSM) is quantified in kilopascals (kPa), positively correlates with liver fibrosis and allows prediction of the likelihood of advanced liver fibrosis.¹⁵⁴ VCTE has been extensively validated in Australia and internationally and is more accurate than the FIB-4 Index for predicting advanced liver fibrosis in people with MAFLD (AUC, 0.85; 95% CI, 0.84–0.86 vs 0.76; 95% CI, 0.74–0.77). An LSM cut-off of <8.0 kPa has 86% sensitivity for advanced fibrosis, whereas a cut-off of ≥15 kPa is 95% specific.¹⁴⁴ In a primary care population with a 5%–10% prevalence of advanced fibrosis, the NPV of an LSM <8.0 kPa is 98%–99%,

whereas the PPV of an LSM ≥15 kPa is 34%–54%.¹⁴⁴ VCTE also provides prognostic information, with the risk of liver-related death increasing 5% per 1 kPa in an Australian cohort of 6341 individuals with MAFLD.¹⁵⁵ VCTE can also 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 have an excellent prognosis, 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.¹⁵⁶ Thus, patients with MAFLD and a FIB-4 score of 1.3–2.7 and an LSM <8.0 kPa are at low risk of advanced liver fibrosis and liver-related morbidity and can be managed in primary care.

Practice points:

- LSM may be falsely elevated in patients with conditions of acute hepatitis, cholestasis (e.g. biliary obstruction), liver congestion (e.g. right heart failure) or focal liver lesions (e.g. tumours).¹⁵⁷
- VCTE scans are less accurate with increasing BMI and are invalid in up to 20% of patients with morbid obesity (BMI >35 kg/m²).^{158–160}

Implementation considerations:

- There is limited availability of VCTE devices for GPs in Australia, with most being located in major metropolitan hospital centres.
- The lack of MBS rebate for VCTE provides a disincentive for implementation due to the cost to the patient or provider.

7.5.2 Second-line test: shear wave elastography

SWE also assesses the stiffness of the liver by quantifying “shear wave” velocity or tissue displacement generated by an ultrasonic impulse, instead of a physical impulse as in VCTE. There are two main types of SWE: point SWE (pSWE), which measures the shear wave generated from one sonographic frequency, typically in one fixed region of interest; and two-dimensional SWE (2D-SWE), which measures sonographic waves in multiple frequencies, often in real time.¹⁵⁴ They are available via “add-on” equipment for standard ultrasound machines and thus can be incorporated into a standard ultrasound assessment. pSWE equipment is available from different manufacturers and includes the Siemens Acuson Virtual Touch Quantification (VTQ) platform and the Philips ElastPQ platform, whereas most validation of 2D-SWE has been performed with SuperSonic Imagine’s Aixplorer® platform.

SWE is less well validated in patients with MAFLD, compared with VCTE, and 2D-SWE in particular requires a degree of radiological expertise, with variability in accuracy noted among less experienced operators.¹⁶¹ A meta-analysis of pSWE (limited to the Siemens VTQ platform), involving 11 studies of 1209 patients, found excellent accuracy (summary AUC, 0.89; sensitivity, 80%; and specificity, 86%) for predicting advanced fibrosis in patients with MAFLD.¹⁶² A meta-analysis of four studies involving 488 patients found lower accuracy for 2D-SWE (limited to the Aixplorer® platform), with a summary AUC of 0.72, sensitivity of 72% and specificity of 72%.¹⁶² In contrast, a prospective study directly comparing VCTE (FibroScan®), pSWE (VTQ) and 2D-SWE (Aixplorer®) found equivalent accuracy (AUCs of 0.86, 0.84 and 0.89, respectively) for diagnosing advanced liver fibrosis in 291 patients with MAFLD.¹⁶³ Additional smaller studies have shown similar or slightly lower accuracy of the Philips ElastPQ pSWE platform when

compared with VCTE for the diagnosis of advanced liver fibrosis in patients with MAFLD.¹⁶⁴⁻¹⁶⁶

The cut-offs across most SWE platforms are not directly comparable due to technical and methodological differences. Furthermore, cut-offs for advanced fibrosis using SWE are not as widely validated as those for VCTE.¹⁶²⁻¹⁶⁴

There are limited data evaluating the use of SWE in sequential stepwise non-invasive test pathways; however, one study of 577 people with suspected MAFLD found the sequential use of the FIB-4 Index followed by 2D-SWE (Aixplorer®) had the same accuracy as the sequential use of FIB-4 followed by VCTE (accuracy of 84% and 81%, respectively).¹⁶⁷ Importantly, the same LSM cut-off of 8 kPa was used for both VCTE and 2D-SWE (Aixplorer®), suggesting that this is a reasonable threshold to stratify risk of advanced liver fibrosis and hence the need for referral from primary care to a specialist for further assessment.

LSM performed by SWE may also be increased because of the same confounding factors that are outlined above for VCTE (i.e. acute hepatitis, cholestasis, liver congestion or focal liver lesions), so interpretation of results in patients with these conditions needs to be done with caution. The reliability of pSWE also falls with increasing patient skin-to-liver capsule distance, being unreliable in half of patients with a distance of more than 30 mm.¹⁶⁸ A limitation of 2D-SWE is that it may be unreliable in up to a third of patients due to high variance in measures (determined by standard deviation or coefficient of variation).^{169,170} Unreliable LSM by SWE (2D-SWE or pSWE) should prompt assessment with an alternative second-line non-invasive test (VCTE, ELF test or Hepascore) or referral to a clinician with expertise in liver disease.

Implementation considerations:

- SWE is increasingly available in Australia through public and private radiology facilities.
- Rigorous attention to operator training and quality control is vital to ensure valid interpretation of SWE scan results.
- Reliability criteria should be included in SWE reports.

7.5.3 Second-line test: direct serum fibrosis tests

Direct serum fibrosis tests incorporate serum markers of fibrogenesis or fibrinolysis and thus may directly reflect the degree of liver fibrosis in patients with chronic liver disease. It is important to note that these tests are not specific to liver fibrosis and can also reflect other chronic fibrotic diseases.¹⁷¹ Direct serum fibrosis tests have the advantage of being accessible and relatively inexpensive, although they are not rebated by the MBS.

Two direct serum fibrosis tests have limited availability in Australia: the ELF test and Hepascore. These 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, HCC and liver-related death.^{149,150,172} Australian data examining the risk of future liver-related events (including liver failure, liver-related complications or HCC) in patients with MAFLD referred from primary care further confirm the ability of non-invasive tests such as FIB-4 (but also others, including Hepascore and NFS) to predict liver-related morbidity and mortality.⁶⁹ Patients with a Hepascore <0.6, FIB-4 score <1.3 and NFS < -1.455 have excellent outcomes, indicating that people not meeting these thresholds could be safely managed in primary care.

7.5.3.1 Enhanced Liver Fibrosis (ELF) test

The ELF test is an algorithm developed from serum levels of enzymes involved in fibrogenesis and fibrinolysis; namely, hyaluronic acid, procollagen III amino-terminal peptide and tissue inhibitor of matrix metalloproteinase-1. The ELF test has been widely validated and is accurate in predicting advanced liver fibrosis in patients with MAFLD, with a meta-analysis of 11 studies involving 4452 patients demonstrating a summary AUC of 0.83 (95% CI, 0.71–0.90).¹⁷³ Comparative multicentre studies have shown that the accuracy of the ELF test is higher than that of FIB-4 (AUC, 0.80 vs 0.77).¹⁴⁹ When using a cut-off of 9.8, the sensitivity and specificity of the ELF test for advanced liver fibrosis are 65% and 86%, respectively.¹⁷³ In primary care, where the prevalence of advanced fibrosis is up to 10%, scores above and below 9.8 have a PPV of 34% and NPV of 96%. This highlights the

need to use the ELF test in combination with other assessments for risk-stratifying patients.

An ELF score cut-off of 9.8 is recommended as the threshold for referral for specialist review when using this as a second-line test in those with an indeterminate FIB-4 score (i.e. in the range of 1.3–2.7). This strategy is associated with a relatively low proportion of patients with an ELF score >9.8 (14%) who are recommended for subsequent specialist referral, and it has a low false negative rate (8%) for predicting an elevated LSM (>8 kPa).¹⁵¹ When instituted into a series of primary care practices in the UK, sequential use of FIB-4 followed by the ELF test led to a fourfold increase in the diagnosis of advanced fibrosis and cirrhosis and an 81% reduction in unnecessary referrals.¹⁷⁴

7.5.3.2 Hepascore

Hepascore is an algorithm developed in Australia based on serum levels of alpha-2-macroglobulin, hyaluronic acid, bilirubin and gamma-glutamyl transferase, in combination with age and sex. It has routinely been performed in Western Australia by PathWest for patients with chronic liver disease since 2004 and predicts long-term risk of liver-related death, decompensation and HCC in patients with MAFLD.^{69,175} In an Australian cohort of 271 patients with MAFLD who had undergone liver biopsy, Hepascore had similar accuracy to FibroScan® for predicting advanced fibrosis (AUC, 0.88 vs 0.80), with a threshold of 0.6 having a sensitivity of 64% and specificity of 93%.¹⁷² The sequential use of FIB-4 Index followed by Hepascore for patients with indeterminate FIB-4 scores provided 80% diagnostic accuracy and 100% specificity, but only 50% sensitivity for the diagnosis of advanced fibrosis in a study of 938 patients with MAFLD.¹⁵² People with MAFLD referred from primary care for specialist review who have a Hepascore <0.6 have an NPV of 97%–100% for future liver decompensation or HCC in the next 10 years, suggesting that individuals below this cut-off can be monitored in primary care.⁶⁹

7.5.3.2 Alternative direct serum fibrosis tests

Other direct serum fibrosis tests are available and have been validated internationally but are not currently available in Australia. It is anticipated that further validation and refinement of existing tests, as well as

the addition of more novel non-invasive fibrosis tests, will enhance the ability to risk-stratify people with MAFLD and thus lead to updated recommendations.

Practice points:

- Hepascore includes bilirubin as an analyte and thus may be falsely elevated in patients with haemolysis or Gilbert syndrome.
- Serum hyaluronic acid is a component of both the ELF test and Hepascore, and its level increases with food intake, suggesting that fasting tests may be preferable.¹⁷⁶

Implementation considerations:

- Direct serum fibrosis tests are potentially more accessible to patients across diverse metropolitan, regional and remote settings than elastography.
- The costs of direct serum fibrosis tests are not reimbursed by Medicare, and thus the financial cost to the patient remains a barrier to widespread adoption.

Recommendation 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.

Quality of evidence: Low

Strength of recommendation: Strong

Recommendation 14

People with MAFLD and a FIB-4 score >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.

Quality of evidence: Low

Strength of recommendation: Strong

7.6 People with MAFLD-related cirrhosis

People with MAFLD can silently progress to cirrhosis in the absence of significant symptoms or clinical signs.¹⁷⁷ The development of jaundice, ascites, hepatic encephalopathy or gastro-oesophageal varices indicates significant liver dysfunction or portal hypertension and heralds a significantly shortened life expectancy.¹⁰⁴ Laboratory signs of advanced liver disease (hyperbilirubinaemia), synthetic dysfunction (hypoalbuminaemia, elevated international normalised ratio) and portal hypertension (thrombocytopenia) may precede clinical deterioration and should initiate prompt referral to a specialist in liver disease. Imaging features of cirrhosis (nodular liver surface), in association with portal hypertension (splenomegaly, portosystemic collaterals, ascites), have >90% specificity for a diagnosis of cirrhosis and should also prompt referral.¹³⁵

Recommendation 15

People with MAFLD and clinical, laboratory or imaging evidence of cirrhosis should be referred to a clinician with expertise in liver disease.

Quality of evidence: High

Strength of recommendation: Strong

8. Monitoring for progression of liver disease

8.1 Fibrosis progression in people with MAFLD

The rationale for monitoring patients with low non-invasive test scores is to detect those who develop progressive liver fibrosis, which is associated with an increased risk of future liver-related morbidity and mortality.¹⁷⁸ Overall, the progression of liver fibrosis among people with MAFLD is relatively slow, with a meta-analysis of 54 observational studies and clinical trials involving 26,738 people showing that the average time to progress one fibrosis stage in those with no or minimal fibrosis (F0–1) is 10 years.³⁴ Nonetheless, some patients will progress faster, with 6%–15% of people with F0–1 fibrosis progressing to advanced fibrosis or cirrhosis (F3–4) within 5 years.³⁴

8.2 Using non-invasive tests to monitor liver fibrosis progression

Serial FIB-4 scores tend to rise in association with progressive liver fibrosis; however, small increases may not be significant.^{179,180} An increase in FIB-4 score from low-risk to above indeterminate- or high-risk thresholds over a 3-year period is associated with an increased risk of incident cirrhosis, HCC and liver-related death.^{181,182} A large population cohort from Sweden showed that people with MAFLD who remain in a low-risk category (FIB-4 score <1.3) or transition from indeterminate to low risk (from a FIB-4 score of 1.3–2.67 to <1.3) over a median of 2.5 years have a low rate of future liver events (1%) after follow-up of 16 years.¹⁸² The highest event rate (13.2%) was seen in those who remained in the high-risk group (FIB-4 score >2.67), highlighting the need for these patients to be referred for liver specialist assessment. Among a cohort of 202,319 patients with MAFLD from the US, 20% of patients with a low FIB-4 score progressed to an indeterminate or high FIB-4 score after 3 years, which signalled an increased risk of future cirrhosis or HCC. The incidence of cirrhosis or HCC in patients with a persistently low FIB-4 score was 0.4/1000 person-years, which increased to 1.3/1000 person-years in those transitioning from low to indeterminate scores,

and was highest in patients transitioning from low to high scores, at 8.6/1000 person-years.¹⁸¹

Fibrosis progression is more likely with increasing liver enzyme levels and type 2 diabetes, especially when glycaemic control is not at target levels. A 10-unit increase in AST (but not ALT) is associated with a 30% increased risk of fibrosis progression, whereas a 1% increase in HbA_{1c} is associated with 15% higher odds of an increase in fibrosis stage.^{183,184} Patients with type 2 diabetes are 69% more likely to have progressive fibrosis compared with those without type 2 diabetes.⁶¹ Thus, repeat FIB-4 testing may be considered at shorter intervals (e.g. 1–2-yearly) for patients with type 2 diabetes or rising AST or HbA_{1c} levels.

Implementation considerations:

- Embedding repeat fibrosis testing in routine clinical practice, by including the FIB-4 Index in annual diabetes checks,⁶¹ and keeping registers of patients with MAFLD are likely to aid implementation of these recommendations.

Recommendation 16

People with MAFLD who have an initial non-invasive fibrosis test result showing a low risk of advanced fibrosis are recommended to undergo repeat non-invasive fibrosis testing in 3 years.

Quality of evidence: Low

Strength of recommendation: Strong

Recommendation 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 FIB-4 at least every 3 years.

Quality of evidence: Low

Strength of recommendation: Weak

8.3 Monitoring people aged over 75 years with MAFLD

The prevalence of MAFLD tends to reduce with increasing age, with an Australian study of more than 9000 participants showing that the prevalence fell from 34% in those aged between 70 and 75 years to 21% in those older than 85 years.¹⁸⁵

Overall, fatty liver in the absence of advanced liver fibrosis does not appear to be associated with excess mortality in older populations.^{186,187} A study of 4093 community-dwelling adults found that fatty liver in people over the age of 65 years was not associated with excess mortality.¹⁸⁶ Furthermore, a US population-based study found that MAFLD is associated with increased risk of mortality for 60–74-year-old individuals, but that this risk was not increased in those older than 74 years.¹⁸⁷

Nonetheless, the presence of advanced liver fibrosis, as defined by non-invasive tests, was associated with an increase in mortality in patients aged 60–74 years and 75 years or older. Similarly, patients aged over 80 years with cirrhosis have a significantly increased risk of incident HCC and liver-related death compared with patients of the same age without cirrhosis.¹⁸⁸

Although there are limited data in the Australian setting, a recent analysis of the large ASPREE (Aspirin in Reducing Events in the Elderly) cohort of Australians aged 70 years or older showed that the presence of MAFLD was not associated with overall mortality but was independently associated with disability-free survival, poorer metabolic health and frailty (unpublished data).

Thus, older patients with MAFLD but without advanced fibrosis are at low risk of future liver-related events and are likely to have competing risks for mortality related to other comorbid conditions. Given the wide spectrum of functional abilities and comorbidities among older Australians, the decision of whether to screen and monitor for fibrosis progression needs to be individualised.

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 coexisting conditions and life expectancy.

Quality of evidence: Low

Strength of recommendation: Strong

8.4 Surveillance for hepatocellular carcinoma in people with MAFLD

MAFLD is a recognised risk factor for the development of HCC, with most HCCs (70%–80%) that develop in the setting of MAFLD occurring in people with cirrhosis. Therefore, identifying people with MAFLD who have cirrhosis is paramount. A meta-analysis of 18 observational studies involving 470,404 patients indicated that the annual rate of HCC development in patients with cirrhotic MAFLD was over 3.5%,¹⁸⁹ exceeding the 1.5% annual risk threshold that is widely accepted for recommending regular HCC surveillance.¹⁹⁰ It is important to recognise that a significant minority of HCCs develop in patients with non-cirrhotic MAFLD; however, the annual risk of HCC development in this setting is <0.05%, and the large number of people with non-cirrhotic MAFLD makes HCC surveillance in this group impractical.^{189,191} Australian HCC clinical practice guidelines (<https://www.cancer.org.au/clinical-guidelines/liver-cancer/hepatocellular-carcinoma>) support the practice of surveillance for HCC among people with cirrhosis due to MAFLD.¹⁹² Despite this, people with MAFLD-related cirrhosis have significantly lower rates of surveillance compared with people with other aetiologies of liver disease.¹⁹³

HCC surveillance is performed with liver-directed ultrasound, with or without measurement of serum alpha-fetoprotein (AFP) levels, every 6 months and should be coordinated in conjunction with a specialist with expertise in liver disease. Patients with small nodules <10 mm in size should have a repeat ultrasound performed in 3 months to monitor for growth. Any patient with a previously uncharacterised liver nodule of 10 mm or greater in size, or with an elevated AFP level, should be imaged with multiphase

contrast-enhanced CT or MRI, with review by a liver specialist.

The benefit of HCC surveillance is the early detection of small HCCs that are more amenable to curative therapies. Data from Australian cohorts show that HCC surveillance is associated with improved survival (79% vs 49% at 12 months), and people participating in surveillance programs are more likely to have their HCC detected at an early stage and receive curative therapy (60% vs 30%).^{193,194} This is supported by a large meta-analysis of 59 studies with 145,396 patients with HCC, which showed surveillance to be associated with early-stage detection (RR, 1.86; 95% CI, 1.73–1.98), curative treatment (RR, 1.83; 95% CI, 1.69–1.97) and overall survival (hazard ratio, 0.67; 95% CI, 0.61–0.72; $I^2 = 78\%$), even after adjusting for lead-time bias.¹⁹⁵

The benefit of surveillance in people with MAFLD-related cirrhosis is likely limited to those whose future mortality risk is not primarily related to progressive decompensated liver disease or other comorbid conditions.¹⁶ We recommend that HCC surveillance be limited to people with Child–Pugh A or B cirrhosis, those with Child–Pugh C cirrhosis who are potential liver transplantation candidates and those without life-limiting comorbidities and reasonable functional status.¹⁹⁶

Recommendation 19

People with cirrhosis who would be willing and suitable for HCC therapy should be undergoing 6-monthly surveillance for HCC using appropriate imaging with or without serum AFP testing.

Quality of evidence: Low

Strength of recommendation: Strong

9. Monitoring of coexisting conditions

9.1 Impact of weight change on liver histology and outcomes in MAFLD

Obesity is intimately associated with the development of MAFLD; in particular, abdominal obesity carries a higher risk of insulin resistance, steatohepatitis and liver fibrosis.¹⁹⁷ Although not all studies have shown adiposity to be a risk factor for progressive disease, it is clear that weight loss and the attendant reduction in metabolic dysfunction is associated with clinical benefit. Patients who achieve weight loss have improvement in histological parameters (steatohepatitis, NAFLD Activity Score and fibrosis), with the degree of weight loss independently associated with benefit.³⁶ Relatively small amounts of weight loss can improve liver histology, with a 5 kg reduction in weight associated with a 39% probability of NASH resolution and 31% probability of improvement in liver fibrosis over 1.5–2 years.¹⁹⁸ Furthermore, weight loss related to bariatric surgery in patients with MAFLD and obesity is associated with a reduction in major adverse cardiovascular and liver-related events (including development of cirrhosis, HCC and liver-related death).¹⁹⁹ Conversely, weight gain is associated with lower odds of improvement in NASH and fibrosis.¹⁹⁸ Hence, weight loss is recommended for patients with MAFLD and overweight or obesity, with the greatest benefit seen in those who achieve >10% weight loss.^{36,200} Monitoring of weight, BMI or waist circumference provides an insight into the likelihood of disease progression or regression and should also precipitate further assessment and management according to the Australian Obesity Management Algorithm in the presence of ongoing weight gain.⁵⁴

Recommendation 20

Weight, BMI and/or waist circumference should be monitored at least annually in people with MAFLD to guide management.

Quality of evidence: Low

Strength of recommendation: Strong

9.2 Incidence of type 2 diabetes in people with MAFLD

A diagnosis of MAFLD often precedes the development of type 2 diabetes, and the presence of MAFLD is associated with an increased risk of incident type 2 diabetes. MAFLD may promote the development of type 2 diabetes, with hepatic steatosis promoting hepatic insulin resistance and increased gluconeogenesis.²⁰¹ In a large meta-analysis of more than 500,000 individuals, MAFLD was associated with a 2.2-fold increased risk of diabetes.²⁰² In patients with lean MAFLD, a 2.7-fold increased risk of incident type 2 diabetes has been seen, with the risk increasing with advanced fibrosis.²⁰³ The overall annual incidence rate of type 2 diabetes in people with underlying MAFLD is estimated at 2.7% (95% CI, 0.7%–4.4%), with hypertriglyceridaemia, prediabetes and low levels of physical activity increasing the risk.^{204,205} The onset of type 2 diabetes in people with MAFLD heralds an increased likelihood of liver-related complications, with a twofold higher risk of hepatic decompensation and a fivefold increased risk of future HCC.⁶²

Due to the increased risk of incident type 2 diabetes and associated ramifications for patient outcomes, it is recommended that people with MAFLD be periodically screened for the development of type 2 diabetes as per current Australian guidelines (<https://www.health.gov.au/resources/apps-and-tools/the-australian-type-2-diabetes-risk-assessment-tool-ausdrisk>).

Recommendation 21

People with MAFLD should be monitored for the development of type 2 diabetes according to current Australian guidelines.

Quality of evidence: Moderate

Strength of recommendation: Strong

10. Future developments and unmet needs

Intensive research in key areas is underway to try to improve the assessment and risk-stratification of people with MAFLD. Large consortia from Europe (Liver Investigation: Testing Marker Utility in Steatohepatitis [LITMUS]) and the US (Non-Invasive Biomarkers of Metabolic Liver Disease [NIMBLE]) have been formed to develop and validate novel diagnostic tools to assess the severity of liver disease. Novel diagnostic algorithms offer the promise of greater accuracy, simpler assessment pathways, minimisation of inappropriate referrals of patients with no or mild fibrosis and identification of those with silent advanced disease. Currently, up to 30% of people with MAFLD assessed in primary care have a FIB-4 score greater than 1.3 and require further assessment, whereas the prevalence of advanced fibrosis in general practice is only 5%–10%. More accurate first-line diagnostic tests with better risk-stratification will lead to less second-line testing and fewer referrals to liver specialists, leading to increased cost savings.

The cost of liver fibrosis diagnostic pathways is a major determinant of government reimbursement and thus uptake by doctors and patients. Cost-effectiveness studies specific to the Australian context are needed, with an emphasis on the impact of pathways on patient care and outcomes. These data will aid health policy and reimbursement strategies. Although data examining the implementation considerations of MAFLD-specific clinical pathways in primary care are emerging,⁶ it is clear that further work is needed in this area to understand the contextual factors that may limit widespread uptake and allow for examination of different implementation strategies.

Optimal methods to manage MAFLD, including more severe forms such as MASH, continue to be refined. This document focuses on assessment for MAFLD, and it is envisaged that subsequent consensus statements will incorporate management, as the evidence base consolidates. Numerous Phase III clinical trials are underway, raising the likelihood that effective pharmacotherapy will be available for people with MAFLD in the short to medium term. Notably, resmetirom received approval from the US Food and Drug Administration in March 2024 for the treatment of MASH, but it is not yet approved in Australia.²⁰⁶ The inclusion criteria for these trials are typically limited to people with steatohepatitis and significant (F2+) fibrosis, also termed “at-risk NASH”. Identification of this population for clinical trials has been challenging, with high screen failure rates reported.²⁰⁷ Current non-invasive tests are optimised for detecting advanced (F3+) fibrosis, with the FIB-4 Index having modest accuracy (AUC <0.8) for predicting at-risk NASH.²⁰⁸ Diagnostic non-invasive tests for at-risk NASH are being developed but are not yet widely validated or accessible.^{209,210} The eligibility criteria for drug therapy required by the Pharmaceutical Benefits Scheme will have a major impact on future assessment pathways, with the focus likely to shift to identifying eligible patients.

Finally, the objectives of this consensus statement will only be met if the recommendations are widely adopted in clinical practice. This will be aided by an education, dissemination and implementation strategy that includes all key stakeholders and identifies and overcomes barriers to cementing these recommendations into clinical practice.

11. Conclusion

The prevalence of MAFLD and associated end-stage liver disease is predicted to increase significantly in Australia in coming years.⁴ To assist in the assessment and management of people with MAFLD, this consensus statement has been developed based on a systematic literature review and broad input from a diverse range of stakeholders and experts. It provides a structured evidence-based framework to aid health professionals working in primary care to identify and assess MAFLD and to guide appropriate referral pathways, further investigation and management. Ideally, this will improve efficiency and workflow for GPs when reviewing people with MAFLD. Ultimately, implementation of the recommendations in this consensus statement aims to improve quality of life and reduce the burden of disease for our patients.

Abbreviations

2D-SWE	two-dimensional shear wave elastography
AFP	alpha-fetoprotein
AGREE	Appraisal of Guidelines for Research & Evaluation
ALT	alanine aminotransferase
APRI	aspartate aminotransferase to platelet ratio index
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
cACLD	compensated advanced chronic liver disease
CAP	controlled attenuation parameter
CHB	chronic hepatitis B
CHC	chronic hepatitis C
CKD	chronic kidney disease
CT	computed tomography
CVD	cardiovascular disease
ELF	Enhanced Liver Fibrosis
FFA	free fatty acid
FIB-4	Fibrosis-4
FLI	Fatty Liver Index
GESA	Gastroenterological Society of Australia
GP	general practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
MAFLD	metabolic dysfunction-associated fatty liver disease

MASH	metabolic steatohepatitis
MASLD	metabolic-associated steatotic liver disease
MRE	magnetic resonance elastography
MRI	magnetic resonance imaging
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NFS	NAFLD Fibrosis Score
NPV	negative predictive value
OSA	obstructive sleep apnoea
PPV	positive predictive value
pSWE	point shear wave elastography
RR	relative risk
SC	Steering Committee
SWE	shear wave elastography
VCTE	vibration-controlled transient elastography
VTQ	Virtual Touch Quantification
WG	Working Group

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SC = Steering Committee; WG = Working Group.

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Leon Adams has received honoraria for participating on advisory boards and speaker fees during development of the MAFLD consensus statement from Pfizer, Gilead, Roche Diagnostics and Novartis.

Gary Deed is a member of the Royal Australian College of General Practitioners (RACGP) and the Australian Diabetes Society.

Mohammed Eslam has received personal fees from Pfizer and honoraria from Sanofi outside his participation in development of the MAFLD consensus statement.

Jacob George was previously a GESA Board Director (2021–2023) and is on advisory boards and receives honoraria for talks from Novo Nordisk, AstraZeneca, Roche, BMS, Pfizer, Cincera, Pharmaxis and Boehringer Mannheim.

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Samantha Hocking has received honoraria from or participated on advisory boards for Eli Lilly, Novo Nordisk, iNova, Sanofi, AstraZeneca, Servier, Amgen, Nestle Health Sciences, Seqirus, Pfizer and Johnson & Johnson. She is President of the National Association of Clinical Obesity Services.

John Lubel is a GESA Board Director (2021–ongoing), serves on the advisory board (unpaid) for CSL, has received speaker fees from Norgine and Gilead, has presented at sponsored GP dinners (no personal fees) for Norgine and Dr Falk Pharma, has received sponsorship for a GP educational event (no speaker fee) from Viatris Pty Ltd, was invited by the Australian Gastrointestinal Trials Group to the Mentor to Preceptorship event (no personal fees) with flights and accommodation provided, is an IPSEN advisory consultant and has received speaker fees for internal staff education, and received sponsorship from IPSEN to attend the EASL 2024 meeting in Milan, Italy. Norgine partially supported his PhD student to travel to an international conference.

Graeme Macdonald is a Board Member of Hepatitis Queensland.

Kate Muller has received honoraria for participating on advisory boards and speaker fees during development of the MAFLD consensus statement from Chiesi, Eisai, AstraZeneca and Novo Nordisk.

John Olynyk is a member of the Overseas Trained Physicians Committee of the Royal Australasian College of Physicians and a member of the Scientific Advisory Committee at the Lions Eye Institute.

Milan Piya has received honoraria from Novo Nordisk, Eli Lilly, Takeda, Ethicon and iNova for speaking engagements and participation on advisory boards and support to attend conferences. He is on the Council of the Australian and New Zealand Obesity Society.

Elizabeth Powell has received honoraria for advisory board participation and support for an educational event from Novo Nordisk and has had access to the ELF test provided by Siemens Healthineers.

Simone Strasser has received honoraria for participating on advisory boards and speaker fees during development of the MAFLD consensus statement from Chiesi, Eisai, Sirtex, Norgine, Roche Products, Roche Diagnostics, AstraZeneca, Otsuka and Pfizer. She is a Board Director of the Liver Foundation.

Stephen Twigg is Chair of the Australian Diabetes Society Working Group for Diabetes and Liver Disease (in commissioning, with a national Diabetes Centre focus) and a member of the Abbott Diabetes Care Freestyle Libre Advisory Board, AstraZeneca Dapagliflozin Advisory Board and Nevro Spinal Stimulators for Painful Diabetes-Related Neuropathy Advisory Board.

Gerald Watts has received research grants and has been on the advisory boards of Arrowhead Pharma and CSL, both relevant to agents that lower triglyceride levels and could affect MAFLD.

Alan Wigg received AstraZeneca speaker and chairman fees in 2023.

Amany Zekry is a GESA Board Director (2023–ongoing).

Results of Delphi rounds

Colour coding	D1: First Delphi round
Agreement level $\geq 80\%$	D2: Second Delphi round
Agreement level $< 80\%$ and $> 70\%$	D3: Third Delphi round
Agreement level $\leq 70\%$	Agree: A <i>priori</i> threshold for agreement is $\geq 80\%$ summation of “agree” or “strongly agree” responses

No.	Recommendation	D1 Agree	D2 Agree	D3 Agree
1	Screening of adults for MAFLD in primary care should be offered to those at high risk, including those with obesity, type 2 diabetes mellitus, or two or more metabolic risk factors.	97%	91%	—
2	Liver ultrasound should be the first-line test to diagnose hepatic steatosis in people at high risk of MAFLD.	87%	85%	—
3	People with MAFLD should be assessed for other common causes of fatty liver and liver disease.	94%	88%	—
4	People with MAFLD should undergo screening for harmful alcohol use.	97%	100%	—
5	People with MAFLD should have a review of prescribed and non-prescribed medications.	90%	97%*	—
6	People with MAFLD and elevated serum aminotransaminase levels should undergo evaluation for hepatitis B and C infection.	93%	100%	—
7	People with MAFLD and elevated serum aminotransaminase levels should undergo screening for iron overload using measurement of serum transferrin and ferritin levels.	81%	85%	—
8	People with MAFLD should be offered non-invasive testing to assess their risk of liver fibrosis.	90%	97%	—
9	A non-invasive test, such as FIB-4, should be offered as an initial test to help “rule out” the risk of severe liver fibrosis among people with MAFLD.	87%	91%	—
10	In people with MAFLD and type 2 diabetes, a direct liver fibrosis serum test or liver elastography could be considered as an initial test if available.	74%	79%	—
11	People with MAFLD and a FIB-4 score between 1.3 and 2.7 should undergo a second-line assessment with liver elastography or a direct liver fibrosis serum test or, if these are unavailable, be considered for referral to a gastroenterologist or hepatologist.	90%	85%	—
12	People with MAFLD and a FIB-4 score > 2.7 or elevated direct liver fibrosis serum test or liver elastography should be referred for gastroenterologist or hepatologist assessment.	100%	94%	—

No.	Recommendation	D1 Agree	D2 Agree	D3 Agree
13	People with MAFLD who have an initial non-invasive fibrosis test result showing a low risk of advanced fibrosis are recommended to undergo repeat non-invasive fibrosis testing in 3 years.	77%	82%	—
14	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 elastography or a direct liver fibrosis serum test in 3 years.	—	85%	—
15	People with MAFLD and clinical, laboratory or imaging evidence of cirrhosis should be referred for gastroenterologist or hepatologist assessment.	100%	91%	—
16	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 coexisting conditions and life expectancy.	52%	97%	—
17	People with cirrhosis should undergo 6-monthly screening for hepatocellular carcinoma using appropriate imaging with or without serum AFP testing.	90%	94%	—
18	People with obesity and MAFLD should be assessed in accordance with the Australian Obesity Management Algorithm.	94%	91%	—
19	Weight and BMI should be monitored at least annually in people with MAFLD.	90%	91%	—
20	People with MAFLD should be assessed for type 2 diabetes using measurement of fasting blood glucose or HbA _{1c} levels.	90%	94%	—
21	People with MAFLD should be monitored for incident type 2 diabetes according to current Australian guidelines.	83%	91%	—
22	People with MAFLD should be assessed for the presence or risk of cardiovascular disease according to current Australian guidelines.	87%	91%	—
23	People with MAFLD should be assessed for thyroid dysfunction.	64%	64%	—
24	Assessment for the coexisting conditions of obstructive sleep apnoea, chronic kidney disease and polycystic ovary syndrome (in women of reproductive age) should be considered for people with MAFLD.	87%	85%*	—
25	Assessment for mental illness should be considered for people with MAFLD.	65%	61%	—
26	Assessment for chronic kidney disease could be considered at least annually in people with MAFLD.	74%	76%	75%

AFP = alpha-fetoprotein; BMI = body mass index; FIB-4 = Fibrosis-4; HbA_{1c} = glycated haemoglobin; HCC = hepatocellular carcinoma; MAFLD = metabolic dysfunction-associated fatty liver disease.

* Although ≥80% of participants agreed or strongly agreed with the recommendation, only 79% of participants agreed or strongly agreed to include the recommendation in the consensus statement.

Endorsing organisations

Organisation	Committee representative
Australian Diabetes Society (ADS)	Stephen Twigg
Australasian Hepatology Association (AHA)	Sinead Sheils
Australian and New Zealand Obesity Society (ANZOS)	Milan Piya
Liver Foundation	Simone Strasser
National Association of Clinical Obesity Services (NACOS)	Samantha Hocking
Royal Australian College of General Practitioners (RACGP)*	Gary Deed

* The MAFLD Consensus Statement has been officially recognised as an Accepted Clinical Resource by the Royal Australian College of General Practitioners.

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