Cancer Council Australia

Clinical practice guidelines for hepatocellular carcinoma surveillance for people at high risk in Australia

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Contact

guidelines@cancer.org.au

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Summary of recommendations

1. Liver cancer in Australia

Aetiology of hepatocellular carcinoma

Aetiology of cirrhosis and hepatocellular carcinoma

Alcohol-related liver disease

Viral aetiologies (chronic hepatitis B and C)

Metabolic dysfunction-associated fatty liver disease

Non-cirrhotic hepatocellular carcinoma

The role of hepatocellular carcinoma surveillance

2. HCC surveillance in people with cirrhosis

Background

Recommendations

Strong recommendation against

2.1 Adapted evidence-based recommendation

Do not routinely offer surveillance for HCC for people who have limited projected life expectancy^ (NICE 2016 *[15]*)

^Does have significant comorbidities and therefore has a non-HCC-related life expectancy of less than 6 months.

Strong recommendation

2.2 Adapted evidence-based recommendation

In people with cirrhosis who are willing[(a)] and suitable[(b)] to receive HCC treatment, offer 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) (WHO 2015 *[16]*; NICE 2016 *[15]*; Omata et al 2017*[17]* ; EASL 2018 *[18]*; Marrero et al 2019 *[19]*; GESA 2020).*[20]*

(a) Willingness is defined as: 1. Willing to have an HCC diagnosis made AND 2. Considering HCC treatment if HCC is diagnosed. (b) Suitability is defined as: 1. Well enough to receive HCC treatment, including patients with Child-Pugh stage A or B cirrhosis or patients with Child-Pugh stage C awaiting liver transplantation AND 2. Does not have significant comorbidities and therefore has a non-HCC-related life expectancy of greater than 6 months.

3. HCC surveillance in people without liver cirrhosis

Background

Recommendations

Weak recommendation

Hepatitis C-related cirrhosis post sustained virologic response

3.1 Evidence-based recommendation

In people with HCV-related cirrhosis who achieve a sustained virologic response to treatment, offer 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) if they are willing[(a)] and suitable[(b)] to receive treatment (Uyei et al 2019 *[21]*; Farhang Zangneh et al 2019 *[22]*).

(a) Willingness is defined as: 1. Willing to have an HCC diagnosis made AND 2. Considering HCC treatment if HCC is diagnosed. (b) Suitability is defined as: 1. Well enough to receive HCC treatment, including patients with Child-Pugh stage A or B cirrhosis or patients with Child-Pugh stage C awaiting liver transplantation AND 2. Does not have significant comorbidities and therefore has a non-HCC-related life expectancy of greater than 6 months.

Weak recommendation

Non-cirrhotic liver disease in people with chronic HBV infection

3.2 Adapted evidence-based recommendation

In people with chronic HBV infection not part of a priority population[1], offer 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) if ALL of the following apply:

- age ≥ 40 years[2]
- family history of HCC[3]

(Sources: WHO 2015 *[16]*; NICE 2016 *[15]*; Omata et al 2017 *[17]*; EASL 2018 *[18]*; Marrero et al 2019 *[19]*; GESA 2020 *[20]*; GESA 2022 *[23]*; Robotin et al 2009 *[25]*; Sangmala et al 2014 *[30]*; Zhang et al 2004 *[110]*; Chen et al 2003 *[111]*; Chang et al 2011 *[112]*).

[1]Defined by the Expert Advisory Group as Aboriginal and Torres Strait Islander people, people of Asian or Pacific background, and people of sub-Saharan African background

[2]HCC surveillance of younger people may be indicated according to either: regional incidence of HCC in country of birth, or country of birth where HBV is endemic. This may include the impact of differences between regional, racial, and ethnic backgrounds.

[3]Family history of HCC is defined as one or more first degree relatives with HCC. Consider offering surveillance 10 years prior to earliest case in a family.

Weak recommendation against New

HCV-related advanced hepatic fibrosis post sustained virologic response

3.4 Evidence-based recommendation

In people with HCV and F3 fibrosis (non-cirrhotic)[#] who achieve a sustained virologic response to treatment, do not routinely offer surveillance for HCC (Farhang Zangneh et al 2019 *[22]*).

[#] Fibrosis stage should be based on the pre-treatment assessment.

Practice Points

Good practice statement New

Non-cirrhotic chronic HBV infection

3.3 Practice Point

In people with chronic HBV infection not part of a priority population[1], consider offering 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) based on an individual risk assessment[2] including family history of HCC[3].

[1] *Defined by the Expert Advisory Group as Aboriginal and Torres Strait Islander people, people of Asian or Pacific background, and people of sub-Saharan African background*

[2] *Refer to Chapter 3 for aspects to consider when assessing risk.*

[3] *Family history of HCC is defined as one or more first degree relatives with HCC. Consider offering surveillance 10 years prior to earliest case in a family.*

Good practice statement New

HCV-related advanced hepatic fibrosis post-sustained virologic response

3.5 Practice Point

People with HCV and F3 fibrosis (non-cirrhotic) [#] who achieve a sustained virologic response to treatment should be monitored* for progression to cirrhosis

[#] *Fibrosis stage should be based on the pre-treatment assessment.*

*** Based on elastography or other similar technology.*

Good practice statement New

F3 fibrosis (non-cirrhotic)

3.6 Practice point*

In people with F3 fibrosis (non-cirrhotic) [#], excepting people with HCV who achieve a sustained virologic response to treatment, consider offering 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) based on an individual risk assessment[1].

[*] *Adapted from EASL guidelines.*

[#] *Fibrosis stage should be based on the pre-treatment assessment.*

[1] *Refer to Chapter 3 for aspects to consider when assessing risk.*

Good practice statement New

F3 fibrosis (non-cirrhotic)

3.7 Practice point

People with F3 fibrosis (non-cirrhotic) [#] not considered high-risk for HCC based on the individual risk assessment[1] should be monitored* for progression to cirrhosis.

[#] *Fibrosis stage should be based on the pre-treatment assessment.*

[1] *Refer to Chapter 3 for aspects to consider when assessing risk.*

*** Based on elastography or other similar technology.*

Good practice statement New

Non-cirrhotic liver disease due to causes other than chronic HBV infection

3.8 Practice point

People with metabolic dysfunction-associated fatty liver disease/non-alcoholic fatty liver disease without cirrhosis should be monitored* for progression to cirrhosis.

**Based on elastography or other similar technology.*

Resource and other considerations

4. HCC surveillance in Aboriginal and Torres Strait Islander people

Background

Recommendations

Weak recommendation

4.1 Evidence-based recommendation

In Aboriginal and Torres Strait Islander people with chronic HBV infection, consider offering 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) if age ≥ 50 years (Carter et al *[24]*).

Weak recommendation New

4.2 Evidence-based recommendation

In Aboriginal and Torres Strait Islander people with chronic HBV infection, consider offering 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) if there is a family history of HCC[1] or if age ≥ 40 with a high-risk HBV genotype[2] individually confirmed (e.g.C4) or epidemiologically likely (Carter et al *[24]*).

For Aboriginal and Torres Strait Islander people without chronic HBV infection, follow recommendations in these guidelines based on their aetiology.

[1]*Family history of HCC is defined as one or more first degree relatives with HCC. Consider offering surveillance 10 years prior to earliest case in a family.*

[2]*It is noted that genotype testing is not routinely offered and not subsidised through the Medicare Benefits Schedule.*

Practice Points

Good practice statement

4.3 Practice point

Local access to culturally safe, preventive care, surveillance and treatment should be provided for Aboriginal and Torres Strait Islander people through primary care within communities and on-Country where possible.

Good practice statement New

4.4 Practice point

Health professionals and health system decision-makers must enable evidence-based recommended treatments for HCC to be offered to Aboriginal and Torres Strait Islander people in an equitable way. Aboriginal and Torres Strait Islander leadership in these decisions is crucial. Current evidence suggests that, when offered early, HCC treatment is accepted and effective irrespective of geographical location.

Limitations

Resource and other considerations

5. HCC surveillance in people of Asian or Pacific background

Background

Recommendations

Weak recommendation New

5.1 Evidence-based recommendation

In people of Asian or Pacific background with chronic HBV infection, consider offering 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) to:

- males ≥ 40 years of age
- females ≥ 50 years of age

For people of Asian or Pacific background without chronic HBV infection, follow recommendations in these guidelines based on their aetiology (Robotin et al 2009 *[25]*; Yu et al 2022 *[26]*; Waziry et al 2016 *[27]*)

Limitations

Other considerations

6. HCC surveillance in people of sub-Saharan African background

Background

Recommendations

Consensus recommendation New

6.1 Consensus-based recommendation

In people of sub-Saharan African background with chronic HBV infection, consider offering 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) to males and females ≥ 20 years of age.

Family history of HCC should be considered when determining the age at which to commence HCC surveillance[1].

For people of sub-Saharan African background without chronic HBV infection, follow recommendations in these guidelines based on their aetiology.

(Sources: EASL 2018 *[18]*; Marrero et al 2019 *[19]*; GESA 2020 *[20]*).

[1] *Family history of HCC is defined as one or more first degree relatives with HCC. Consider offering surveillance 10 years prior to earliest case in a family.*

Limitations

Resource and other considerations

7. HCC surveillance in Australia: Use of alpha-fetoprotein testing and HCC surveillance cost-effectiveness

Background

Recommendations

Weak recommendation New

7.1 Evidence-based recommendation

In people for whom HCC surveillance is recommended, consider offering 6-monthly alpha-fetoprotein testing in addition to ultrasound (Andersson et al 2008 *[28]*; Thompson Coon et al 2008 *[29]*; Sangmala et al 2014 *[30]*; Parikh et al 2020 *[31]*).

Practice Points

Good practice statement New

7.2 Practice point

The provision of 6-monthly ultrasound for HCC surveillance may be cost-effective compared to no surveillance for people with compensated cirrhosis in the Australian context.

Good practice statement New

7.3 Practice point

The provision of 6-monthly ultrasound with alpha-fetoprotein testing may be cost-effective compared to no surveillance and could be provided as part of HCC surveillance for people with compensated cirrhosis in the Australian context.

Limitations

Resource and other considerations

8. Implications and implementation of recommendations, evidence gaps and future research needs

Key recommendations

Key implementation considerations

Areas of major debate

Evidence gaps

Updating the guidelines

Appendices

Abbreviations

Acronym/abbreviation	Description
AASLD	American Association for the study of Liver Diseases
APASL	Asian Pacific Association for the Study of the Liver
AFP	Alpha-fetoprotein
ALT	Alanine aminotransferase
APRI	Aspartate aminotransferase-platelet ratio index
ARLD	Alcohol related liver disease
AST	Aspartate aminotransferase
CARPA	Central Australian Rural Practitioners Association
CER	Cost-effectiveness ratio
CI	Confidence interval
DAA	Direct-acting antiviral
DNA	Deoxyribonucleic acid
EASL	European Association for the Study of the Liver
EBR	Evidence-based recommendation
ECOG	Eastern Cooperative Oncology Group
F3	Advanced fibrosis
F4	Cirrhosis
FIB-4	Fibrosis-4 Index
GALAD	Gender, Age, Alpha-fetoprotein L3% (AFP-L3), AFP, Des-gamma-carboxy prothrombin52
GESA	Gastroenterological Society of Australia
GP	General practitioner
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
IRR	Incidence rate ratio
MAFLD	Metabolic dysfunction-associated fatty liver disease (also called metabolic-associated fatty liver disease)
MELD	Model for end-stage liver disease
MBS	Medicare Benefits Schedule
METAVIR	Meta-analysis of histological data in viral hepatitis

NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NICE	National Institute for Health and Care Excellence
PAST	Partnership Approach to Sustainably eliminating Chronic Hepatitis B in the Northern Territory
PICO	Population, intervention, comparator and outcome
PP	Practice point
QALY	Quality-adjusted life years
RCT	Randomised controlled trial
WHO	World Health Organization

Glossary

Term	Definition
AFP	A protein produced by the liver and can be a tumour biomarker for liver cancer.
APRI	An index of liver fibrosis and cirrhosis based on the ratio of aspartate aminotransferase to platelets in the body
ARLD	Refers to liver disease associated with excess alcohol consumption
CER	The ratio of the net cost of item(s) or health intervention to the health outcome, e.g., cost per diseases prevented
Child-Pugh	A 15-point scoring system used to assess the prognosis of liver disease
Cirrhosis	Late-stage scarring of liver tissue resulting in the formation of nodules
DAA	Medication used to treat chronic hepatitis C that targets the chronic hepatitis C replication life cycle
Fibrosis	The deposition of scar tissue in the liver
F1-3	Progressive scarring of the liver tissue, leading to the disruption of normal blood flow and impairment of liver function
FIB-4	A scoring test used to estimate liver scarring
Genotype testing	Genetic testing that compares DNA/RNA structure, variations, or changes
HBV	A vaccine-preventable liver infection caused by the hepatitis B virus which can lead to long-term liver damage
HCC	Most common type of primary liver cancer
HCV	A liver infection caused by the hepatitis C virus that causes inflammation and can lead to cirrhosis and cancer
MAFLD	The updated term for NAFLD to acknowledge its association with metabolic syndrome, excess adiposity and type 2 diabetes.
MELD	A scoring system to predict liver disease severity and is often used to determine a patient's urgency for liver transplantation
NAFLD	A condition resulting from a fat build up in the liver in the absence of excessive alcohol consumption.

Plain language summary

The purpose of these guidelines is to help doctors discover liver cancer as early as possible. It does not cover cancer treatment.

Liver cancer in Australia
Each year about 2,800 Australians are diagnosed with liver cancer, and around 2,400 die from liver cancer.

Liver cancer is becoming more common. It is usually diagnosed when it is too late to cure.

The most common type of liver cancer is called HCC (hepatocellular carcinoma).

Who gets HCC?
People have a higher chance of HCC if they have long-term hepatitis B, hepatitis C, fatty liver disease, or consume large amounts of alcohol.

HCC usually begins as scars on the liver in people with one of these long-term liver conditions.

Most people have liver cirrhosis (a severe type of liver scarring) before they develop HCC.

Medical tests can find some HCCs while they are still curable. This kind of repeated testing that looks for any new tumour spots in the liver over years is called HCC surveillance.

Who should have regular testing for HCC?
The risk of HCC is low so the need for testing depends on a person's age and the type of liver problem they have.

Testing for HCC is recommended for these groups of people:

- people with hepatitis B who are at higher risk (based on age and background)
- people with liver cirrhosis
- people with liver cirrhosis and hepatitis C (even if cured)
- people waiting for a liver transplant
- people with other long-term liver problems.

Testing may not be needed if someone is young or has no signs of liver scarring.

Testing is not worthwhile if the benefits are not greater than the possible harm and costs. For example, if someone is too unwell to have cancer treatment, or if someone is more likely to die of some other health problem in the short-term.

What does regular testing (surveillance) involve?
Testing for HCC (surveillance) involves having a liver ultrasound every 6 months. Ultrasound can detect tumours in the liver and show how big they are.

A blood test may also be done at the same time, every 6 months. This tests for alpha-fetoprotein (AFP), which may show when there might be a cancer.

If these tests show that a person may have HCC, they may need more tests.

More information about liver conditions
Hepatitis B
Hepatitis B is a liver condition caused by infection with hepatitis B virus.

It can lead to severe liver scarring (cirrhosis) and/or HCC.

Long-term hepatitis B infection is common in some regions, including Southeast Asia and Africa.

Vaccination prevents infection.

Treatment is available for people with hepatitis B and can lower liver cancer risk.

Untreated hepatitis B can lead to severe liver scarring (cirrhosis) and HCC.

Hepatitis C
Hepatitis C is a liver condition caused by infection with hepatitis C virus.

Hepatitis C can be cured with antiviral treatment.

Long-term hepatitis C infection is becoming less common in Australia.

Untreated hepatitis C can lead to severe liver scarring (cirrhosis), and then HCC.

People with other long-term liver problems
There are two main types of long-term liver problems: fatty liver disease and alcohol-related liver disease. These are the most common but there are also other types of long-term liver problems.

Fatty liver disease is related to type 2 diabetes and obesity.

This condition is also called 'non-alcoholic fatty liver disease' and 'metabolic-associated fatty liver disease'. It can also be related to excessive alcohol consumption.

In Australia, fatty liver disease is becoming a common cause of HCC.

Too much fat stored in the liver can lead to liver inflammation and scarring (cirrhosis), type 2 diabetes, and HCC.

Long-term heavy drinking leads to liver scarring (liver cirrhosis).

Where to find information about liver cancer and liver cancer treatment
Cancer Council

131120

www.cancer.org.au

Understanding Liver Cancer (A guide for people with cancer, their families and friends) - Booklet available from: https://www.cancer.org.au/cancer-information/downloadable-resources

Introduction

Primary liver cancer incidence and mortality are rapidly rising in Australia. Between 1982 and 2022, the age-standardised incidence rate rose from 1.8 to an estimated 8.8 per 100,000 people, and the age-standardised mortality rate rose from 2.3 to an estimated 7.3 per 100,000 people *[1]*.

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. HCC surveillance of people with risk factors such as chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), alcohol-related liver disease (ARLD), or metabolic dysfunction-associated fatty liver disease (MAFLD; or non-alcoholic fatty liver disease: NAFLD) aims to facilitate the early detection of HCC when curative treatments may be possible *[2]*.

Intended users

These guidelines are intended for health professionals caring for people at high risk of liver disease and liver cancer.

They may also be of use to policy makers and people with training in medicine or other health sciences.

They are not intended as health information for the general public.

Target populations

These guidelines cover a range of Australian populations:

- people at high risk of HCC:
  - people with liver cirrhosis
  - people with chronic infection with HBV or HCV
  - people with ARLD
  - people with NAFLD/MAFLD.
- people from priority populations that have a higher-than-average risk of HCC:
  - Aboriginal and Torres Strait Islander people
  - people of Asian or Pacific background
  - people of sub-Saharan African background.

Health care settings in which the guidelines will be applied

These guidelines apply to the range of public and private healthcare settings in which services are provided for the target populations.

These include, but are not limited to:

- hospitals
- specialist clinics
- imaging services
- pathology services
- allied health care services
- primary care services, including general practice, community health, and Aboriginal and Torres Strait Islander Community Controlled Health Organisations (ACCHOs)

- alcohol and other drug treatment services
- prison health services.

Purpose and scope

The *Clinical practice guidelines for HCC surveillance for people at high risk in Australia* aim to provide information and recommendations to guide surveillance for people at high risk of HCC. Evidence has shown it to be successful in detecting lesions and/or early-stage tumours, increasing the receipt of curative treatment and improving overall survival *[2][3]*. These guidelines do not cover HBV/HCV screening, testing and treatment, screening for advanced liver disease, surveillance for other types of liver cancer such as intrahepatic cholangiocarcinoma, or ongoing monitoring or surveillance of people with HCC for recurrence.

Publication Approval

Australian Government

National Health and Medical Research Council

The guideline recommendations were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on 14 April 2023 under section 14A of the *National Health and Medical Research Council Act 1992*. In approving the guideline recommendations, NHMRC considers that they meet the NHMRC standard for clinical practice guidelines. This approval is valid for a period of five years.

NHMRC is satisfied that the guideline recommendations are systematically derived, based on the identification and synthesis of the best available scientific evidence, and developed for health professionals practising in an Australian health care setting.

This publication reflects the views of the authors and not necessarily the views of the Australian Government.

The Royal Australian College of General Practitioners (RACGP) endorsement

Endorsed clinical guideline

RACGP

Funding

Cancer Council Australia was funded by the Department of Health and Aged Care to develop these guidelines as part of the Roadmap to Liver Cancer Control project. Cancer Council Australia sub-contracted The Daffodil Centre, a joint venture between Cancer Council NSW and the University of Sydney, to perform the systematic reviews and predictive modelling, and provide project co-ordination to support guideline development. The funding body did not influence the content of these guidelines.

Guidelines development process

An Expert Advisory Group was convened to determine the scope of the clinical practice guidelines for HCC surveillance for people at high risk in Australia (see Appendix A for complete guideline development process). The guidelines were developed by a multidisciplinary Working Group and Daffodil Centre staff, overseen by the Expert Advisory Group (full details of the multidisciplinary guideline development group can be found in Appendix H2 and Appendix I). The development was guided by the following clinical questions:

1. Does HCC surveillance improve health outcomes?
2. Which high-risk groups would benefit from HCC surveillance in the Australian context?
    1. by aetiology
    2. by priority population.
3. How would surveillance for HCC be provided to the target population in an effective, feasible, acceptable and cost-effective way?

The development of these questions was based on the evidence and current practice identified in Phase One of the Roadmap to Liver Cancer Control initiative funded by the Department of Health and Aged Care.

The priority populations were defined by the Expert Advisory Group as Aboriginal and Torres Strait Islander people, people of Asian or Pacific background, and people of sub-Saharan African background. While ethnocultural background is not a risk factor for HCC, region or country of birth correlates with the probability of developing HCC, such as for chronic hepatitis B. Therefore, we have used birth country or region as a surrogate marker of risk among people living in Australia. However, risk of HCC may be modulated by other factors, including belonging to more than one ethnocultural group. HCC risk factors also vary between Australian populations that are distinguished by ethnocultural features other than country of birth.

Although country of birth and similar factors are useful as strong proxy measures of HCC risk, and are straightforward to determine, it must be emphasised that these are non-causal risk factors and are merely indicative of the likelihood of an individual carrying a causal risk factor, such as a subtype of HBV with high risk of HCC progression.

Cultural determinants of health also impact health care provision as well as the ongoing effects of colonisation, systemic racism, stigma and social marginalisation. The provision of culturally sensitive and safe health care is central to HCC surveillance. Culturally sensitive and safe health services can be provided through an understanding, consideration and respectful accommodation of an individual's cultural, linguistic, religious, sexual and racial/ethnic characteristics to ensure that all are welcome, safe and protected.

In Australia, frameworks, manuals and guides have been developed to support health care providers to provide culturally sensitive and safe services, specific to Aboriginal and Torres Strait Islanders *[4][5]*, people living in remote communities *[6]*, refugees to Australia *[7][8][9]*, people impacted by the justice system *[10]* and to support inclusiveness of gender identities *[11]*. As an example, the Central Australian Rural Practitioners Association (CARPA) standard treatment manual includes guidance around providing culturally sensitive care in four broad categories: cultural beliefs, loss and grief, communication, and questioning a patient *[6]*.

For Aboriginal and Torres Strait Islanders, guidance from the National Aboriginal Community Controlled Health

Organisation, Royal Australian College of General Practitioners and Cancer Australia highlights the importance of patient-centred care in preventive health and cancer care *[12][13]*. These guides outline the principles of respect for patients and their families' cultural and religious beliefs, taking time to understand a patient's knowledge, values, and cultural needs throughout the decision-making process *[12][13]*. They also recommend providers use plain language and to ensure information is accessible and in culturally appropriate formats. Family involvement and support is also encouraged in discussions about outcomes and care plans *[12]*.

In the absence of Australian guidelines for HCC surveillance, health practitioners currently use existing international guidelines and consensus statements to support clinical decision making. After a review of current practice, the Expert Advisory Group determined that clinical question 1 was adequately covered by existing guidelines underpinned by systematic reviews, and that adapted evidence-based recommendations and/or practice points would be developed for the Australian context (Chapters 2 and 3). For clinical questions 2 and 3, specific clinical questions were developed by the Expert Advisory Group, PICO (population, intervention, comparator and outcome) questions were formulated by the Project Team in consultation with the Expert Advisory Group (Table 1), and systematic reviews were conducted (Chapters 4 to 8). For complete list of clinical questions and PICO questions see Appendix B.

Systematic literature reviews and cost-effectiveness modelling studies were completed, and the evidence was appraised using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology *[14]*. A summary of the systematic review questions is shown in Table 1.

Table 1. Summary of systematic review questions.

PICO	Systematic Review Question
PICO 1	Does HCC surveillance improve liver cancer outcomes for people with non-cirrhotic liver disease and for people with HCV-related cirrhosis who have been treated with direct-acting antiviral agents?
PICO 2	Is prior HCC surveillance associated with improved liver cancer outcomes for people with HCC with either (i) non-cirrhotic liver disease or (ii) HCV-related cirrhosis treated with direct-acting antiviral agents?
PICO 3	Does HCC surveillance improve liver cancer outcomes for Aboriginal and Torres Strait Islander people?
PICO 4	Does HCC surveillance improve liver cancer outcomes for Asian or Pacific-born people in Australia?
PICO 5	Does HCC surveillance improve liver cancer outcomes for sub-Saharan Africa-born people in Australia?
PICO 6	Does the addition of alpha-fetoprotein testing to 6-monthly ultrasound imaging for HCC surveillance improve liver cancer outcomes?

Based on the evidence reviews, the Working Groups formulated recommendations and practice points. Evidence-based recommendations were developed through a structured process, considering the body of evidence and its relevance to Australian clinical practice. Each recommendation was assigned a grade (either strong or weak) based on consideration of the balance between desirable and undesirable consequences of alternative management strategies, the certainty of evidence, values and preferences of people applying or affected by the recommendation, and implications for resource use. Where a systematic review was conducted but no evidence was identified, a consensus-based recommendation was developed. The choice of recommendation and wording reflects the certainty of evidence. Where there is clear and strong evidence of benefit, 'offer' or 'do not offer' is used. Where the benefit is less certain based on the evidence, the recommendation is worded as 'consider offering'.

Practice points were also developed or adapted to support the recommendations and provide guidance on areas not examined by a systematic review. Practice points were developed where there was a message regarding existing clinical practice or the implementation of HCC surveillance that needed to be included and considered to ensure equity of care and access. The wording used in the practice points reflects the urgency of the issue. In some cases, the practice points indicate the likelihood of a benefit as a way of highlighting the importance of an issue rather than its

urgency.

Table 2. Types of recommendations included in these guidelines.

Type	Process
Evidence-based recommendations (EBR)	Recommendations based on systematic review conducted for these guidelines
Adapted evidence-based recommendations (AEBR)	Recommendations adopted/adapted from existing evidence-based clinical practice guidelines
Consensus-based recommendations (CBR)	Recommendations based on systematic review conducted for these guidelines where no evidence was identified
Practice points (PP)	Guidance on topics for which systematic reviews were either not conducted, developed as the identified body of evidence was considered low quality, or no evidence was identified.

The Working Groups followed a structured process and consensus was reached in the Working Group through formal meetings and offline correspondence, where required. Any uncertainties were raised with the guidelines co-Chairs and discussed with the Working Group lead. Once drafted, the recommendations and practice points were circulated to the Working Group for comments. In this way, Working Group members were able to comment on recommendations and practice points across the guidelines. Comments and suggested changes were raised with the corresponding Working Group lead and any subsequent changes were circulated to the Working Group members for final confirmation.

The guidelines were reviewed by people with lived experience of liver cancer or precursor conditions, caregivers, research advocates, and representatives of consumer organisations (the Community Reference Group). The Community Reference Group included Aboriginal and Torres Strait Islander people and Aboriginal leadership, people from culturally and linguistically diverse communities, and people who live in rural/remote regions. The group advised on aspects of the guidelines affecting the target clinical population, including applicability, inclusivity and clarity. The group was asked to review the content and submit feedback which was then brought back to the Working Groups to discuss incorporation. The Working Group leads facilitated incorporation of the feedback and provided responses to comments from the Community Reference Group. Over the course of the guidelines, the Community Reference Group met three times and corresponded via email. At least one member of the Project Team was present at each meeting to support the Community Reference Group and, where possible, one of the co-Chairs was also in attendance.

The guidelines were released for targeted expert consultation and public consultation in October 2022. The Working Groups considered all submissions and agreed on appropriate amendments in response to comments and proposed changes. The final guidelines were published in July 2023.

Scheduled review of these guidelines

Newly published evidence relevant to each systematic review question will continue to be monitored. If there is strong evidence emerging in HCC surveillance, the Working Group will be reconvened to assess if this warrants a guideline update (full or partial). It is recommended that the guideline be updated within 5 years.

Acknowledgments

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A complete list of contributors can be found in Appendix Iand a register of competing interests in Appendix J.

Citation

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Summary of recommendations

This is a summary of the recommendations in the Clinical practice guidelines for hepatocellular carcinoma (HCC) surveillance for people at high risk in Australia. HCC surveillance is a well-established intervention to facilitate early detection through regular monitoring of populations at high risk. HCC surveillance typically targets people with cirrhosis as well as high-risk groups (e.g. those with hepatitis B virus (HBV)), using ultrasound and/or measurement of tumour biomarker(s) such as alpha-fetoprotein (AFP). Evidence has shown it to be successful in detecting lesions and/or early-stage tumours, increasing the receipt of curative treatment and improving overall survival *[2][3]*. These recommendations are intended to guide decision making in determining who should receive regular HCC surveillance and all should be considered for implementation in practice. They are presented in an order which reflects clinical judgement (see Appendix F for decision aid).

Principles of clinical judgement and shared decision-making using a culturally sensitive and safe approach apply when implementing the recommendations in these guidelines. In considering whether a person should receive regular HCC surveillance, a clinician needs to take into account individual factors including age, family history of HCC, individual risk factors, ethnocultural group/region of birth, any comorbidities, performance (ECOG status) and liver-related health status. This may be done through individual risk assessment (see Chapter 3) that considers all the potential benefits and risks. HCC surveillance should only be offered if the clinician and patient agree that the likely benefits outweigh the risks, and the patient is willing to participate in HCC surveillance and to undergo any subsequent HCC treatment that might be indicated.

These guidelines include adapted evidence-based recommendations (AEBR), evidence-based recommendations (EBR), consensus-based recommendations (CBR) and practice points (PP). Each EBR was assigned a grade by the expert Working Group, taking into account the volume, consistency, generalisability, applicability and clinical impact of the body of evidence using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology *[14]*. Recommendations and practice points were developed by Working Group members. The choice of recommendation and wording reflects the certainty of evidence. Where there is clear and strong evidence of benefit, 'offer' or ‘do not offer’ is used. Where the benefit is less certain based on the evidence, the recommendation is worded as 'consider offering'.

For each recommendation, the corresponding chapter in the guidelines provides more detailed information, including the evidence and rationale for the recommendation. The recommendations should be implemented with consideration of the evidence summaries provided.

Number	Type	Strength	Recommendation
HCC surveillance in people with liver cirrhosis			
2.1	**Adapted evidence-based recommendation**	Strong	Do not routinely offer surveillance for HCC for people who have limited projected life expectancy^ (NICE 2016 *[15]*). *^Does have significant comorbidities and therefore has a non-HCC-related life expectancy of less than 6 months*
2.2	**Adapted evidence-based recommendation**	Strong	In people with cirrhosis who are willing[(a)] and suitable[(b)] to receive HCC treatment, offer 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) (WHO 2015 *[16]*; NICE 2016 *[15]*; Omata et al 2017 *[17]*; EASL 2018 *[18]*; Marrero et al 2019 *[19]*; GESA 2020 *[20]*). *(a) Willingness is defined as: 1. Willing to have an HCC diagnosis made AND 2. Considering HCC treatment if HCC is diagnosed. (b) Suitability*

			is defined as: 1. Well enough to receive HCC treatment, including patients with Child-Pugh stage A or B cirrhosis or patients with Child-Pugh stage C awaiting liver transplantation AND 2. Does not have significant comorbidities and therefore has a non-HCC-related life expectancy of greater than 6 months
3.1	**Evidence-based recommendation**	Weak	In people with HCV-related cirrhosis who achieve a sustained virologic response to treatment, offer 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) if they are willing(a) and suitable(b) to receive HCC treatment (Uyei et al 2019 *[21]*; Farhang Zangneh et al 2019 *[22]*). *(a) Willingness is defined as: 1. Willing to have an HCC diagnosis made AND 2. Considering HCC treatment if HCC is diagnosed. (b) Suitability is defined as: 1. Well enough to receive HCC treatment, including patients with Child-Pugh stage A or B cirrhosis or patients with Child-Pugh stage C awaiting liver transplantation AND 2. Does not have significant comorbidities and therefore has a non-HCC-related life expectancy of greater than 6 months.*
HCC surveillance in people without liver cirrhosis			
3.2	**Adapted evidence-based recommendation**	Weak	In people with chronic HBV infection not part of a priority population[1], offer 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) if ALL of the following apply: • age ≥ 40 years[2] • family history of HCC[3] (Sources: WHO 2015 *[16]*; NICE 2016 *[15]*; Omata et al 2017 *[17]*; EASL 2018 *[18]*; Marrero et al 2019 *[19]*; GESA 2020 *[20]*; GESA 2022 *[23]*; Zhang et al 2004 *[110]*; Chen et al 2003 *[111]*; Sangmala et al 2014 *[30]*). *[1]Defined by the Expert Advisory Group as Aboriginal and Torres Strait Islander people, people of Asian or Pacific background, and people of sub-Saharan African background* *[2]HCC surveillance of younger people may be indicated according to either: regional incidence of HCC in country of birth, or country of birth where HBV is endemic. This may include the impact of differences between regional, racial, and ethnic backgrounds.* *[3]Family history of HCC is defined as one or more first degree relatives with HCC. Consider offering surveillance 10 years prior to earliest case in a family.*

3.3	**Practice Point**	NA	In people with chronic HBV infection not part of a priority population[1], consider offering 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) based on an individual risk assessment[2] including family history of HCC[3]. *[1]Defined by the Expert Advisory Group as Aboriginal and Torres Strait Islander people, people of Asian or Pacific background, and people of sub-Saharan African background* *[2]Refer to Chapter 3 for aspects to consider when assessing risk.* *[3]Family history of HCC is defined as one or more first degree relatives with HCC. Consider offering surveillance 10 years prior to earliest case in a family.*
3.4	**Evidence-based recommendation**	Weak	In people with HCV and F3 fibrosis (non-cirrhotic) [#] who achieve a sustained virologic response to treatment, do not routinely offer surveillance for HCC (Farhang Zangneh et al 2019 *[22]*). *[#] Fibrosis stage should be based on the pre-treatment assessment*
3.5	**Practice Point**	NA	People with HCV and F3 fibrosis (non-cirrhotic) [#] who achieve a sustained virologic response to treatment should be monitored* for progression to cirrhosis. *[#] Fibrosis stage should be based on the pre-treatment assessment.* ** Based on elastography or other similar technology.*
3.6	**Practice point***	NA	In people with F3 fibrosis (non-cirrhotic) [#], excepting people with HCV who achieve a sustained virologic response to treatment, consider offering 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) based on an individual risk assessment[1]. *[*] Adapted from EASL guidelines.* *[#] Fibrosis stage should be based on the pre-treatment assessment.* *[1] Refer to Chapter 3 for aspects to consider when assessing risk.*
3.7	**Practice point**	NA	People with F3 fibrosis (non-cirrhotic) [#] not considered high-risk for HCC based on the individual risk assessment[1] should be monitored* for progression to cirrhosis.

			[#] *Fibrosis stage should be based on the pre-treatment assessment.* [1] *Refer to Chapter 3 for aspects to consider when assessing risk.* * *Based on elastography or other similar technology.*
3.8	**Practice point**	NA	People with metabolic dysfunction-associated fatty liver disease/non-alcoholic fatty liver disease without cirrhosis should be monitored* for progression to cirrhosis. * *Based on elastography or other similar technology.*
HCC surveillance in Aboriginal and Torres Strait Islander people			
4.1	**Evidence-based recommendation**	Weak	In Aboriginal and Torres Strait Islander people with chronic HBV infection, consider offering 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) if age ≥ 50 years (Carter et al *[24]*).
4.2	**Evidence-based recommendation**	Weak	In Aboriginal and Torres Strait Islander people with chronic HBV infection, consider offering 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) if there is a family history of HCC[1] or if age ≥ 40 with a high-risk HBV genotype[2] individually confirmed (e.g. C4) or if the genotype is epidemiologically likely (Carter et al *[24]*). For Aboriginal and Torres Strait Islander people without chronic HBV infection, follow recommendations in these guidelines based on their aetiology. [1]*Family history of HCC is defined as one or more first degree relatives with HCC. Consider offering surveillance 10 years prior to earliest case in a family.* [2]*It is noted that genotype testing is not routinely offered and not subsidised through the Medicare Benefits Schedule.*
4.3	**Practice point**	NA	Local access to culturally safe, preventive care, surveillance and treatment should be provided for Aboriginal and Torres Strait Islander people through primary care within communities and on-Country where possible.
4.4	**Practice point**	NA	Health professionals and health system decision-makers must enable evidence-based recommended treatments for HCC to be offered to Aboriginal and Torres Strait Islander people in an equitable way. Aboriginal and Torres Strait Islander leadership in these decisions is crucial. Current evidence suggests that, when offered early, HCC treatment is accepted and effective irrespective of geographical location.
HCC surveillance in people of Asian or Pacific background			

5.1	**Evidence-based recommendation**	Weak	In people of Asian or Pacific background with chronic HBV infection, consider offering 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) to: • males ≥ 40 years of age • females ≥ 50 years of age For people of Asian or Pacific background without chronic HBV infection, follow recommendations in these guidelines based on their aetiology (Robotin et al 2009 *[25]*; Yu et al 2022 *[26]*; Waziry et al 2016 *[27]*)
HCC surveillance in people of sub-Saharan African background			
6.1	**Consensus-based recommendation**	NA	In people of sub-Saharan African background with chronic HBV infection, consider offering 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) to males and females ≥ 20 years of age. Family history of HCC should be considered when determining the age at which to commence HCC surveillance[1]. For people of sub-Saharan African background without chronic HBV infection, follow recommendations in these guidelines based on their aetiology. (Sources: EASL 2018 *[18]*; Marrero et al 2019 *[19]*; GESA 2020 *[20]*). [1] *Family history of HCC is defined as one or more first degree relatives with HCC. Consider offering surveillance 10 years prior to earliest case in a family.*
HCC surveillance in Australia: Effectiveness and cost-effectiveness			
7.1	**Evidence-based recommendation**	Weak	In people for whom HCC surveillance is recommended, consider offering 6-monthly alpha-fetoprotein testing in addition to ultrasound (Andersson et al 2008 *[28]*; Thompson Coon et al 2008 *[29]*; Sangmala et al 2014 *[30]*; Parikh et al 2020 *[31]*).
7.2	**Practice point**	NA	The provision of 6-monthly ultrasound for HCC surveillance may be cost-effective compared to no surveillance for people with compensated cirrhosis in the Australian context.
7.3	**Practice point**	NA	The provision of 6-monthly ultrasound with alpha-fetoprotein testing may be cost-effective compared to no surveillance and could be provided as part of HCC surveillance for people with compensated cirrhosis in the Australian context.

1. Liver cancer in Australia

Liver cancer in Australia was estimated to result in 2,905 new cancer cases and 2,492 cancer deaths in 2022, with liver cancer rates rapidly increasing. Between 1982 and 2022, the age-standardised incidence rate increased from 1.8 to an estimated 8.8 per 100,000 population and the mortality rate increased from 2.3 to an estimated 7.3 per 100,000 population *[1]*.

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, accounting for 80% of all primary liver cancers *[32]*. The incidence of HCC in Australia is highest among people aged 59 – 75 years *[33]*.

Survival rates for liver cancer are poor, with 5-year survival of 22% for the latest data period of 2014 – 2018 *[33]*. Many patients with liver cancer receive their diagnosis when the cancer is already at an incurable late stage *[34]*.

While the overall incidence and mortality rates for all cancers combined are expected to decline in Australia, based on current trends, incidence and mortality rates for liver cancer are projected to continue to increase to 2044 *[35]*.

The burden of disease due to liver cancer is disproportionately high among Aboriginal and Torres Strait Islander people, and migrants to Australia from countries where viral hepatitis is endemic *[26][34][36][37]*.

Given the growing burden of liver cancer and poor survival rates, it is important to look for opportunities to improve outcomes.

Aetiology of hepatocellular carcinoma

The strongest risk factor for HCC is liver cirrhosis, which is identified in more than 80% of those diagnosed with HCC *[19]*. Only 10–20% of HCC cases are diagnosed in the absence of cirrhosis *[38][39]*.

Chronic advanced liver disease generally begins with chronic liver injury, which leads to the formation of scar tissue in the liver (fibrosis) and may eventually progress to cirrhosis (see Box 1). In its early stages, liver disease is often asymptomatic or is associated with non-specific symptoms such as fatigue, weakness, loss of appetite, nausea, and weight loss. Early-stage liver fibrosis can be reversible *[40]*. In the asymptomatic phase (compensated cirrhosis), the liver is scarred but functional. In a cirrhotic liver, scar tissue increasingly disrupts blood flow and compromises the organ's functions. Progressive scarring of the liver eventually leads to severe impairment of liver function (decompensated cirrhosis), giving rise to clinical symptoms such as ascites, bleeding, jaundice, and encephalopathy.

In Australia in 2017 an estimated 24,150 people were living with decompensated cirrhosis and 157,920 people were living with compensated cirrhosis, representing 0.74% of the total population *[41]*. In over 90% of cases globally, HCC occurs in the setting of chronic liver disease *[42]*.

Chronic liver damage developing from inflammation provides an environment in which cancer can develop *[19]*. The risk of developing HCC is influenced by the underlying aetiology of liver disease and its treatment, the severity of liver disease, and individual characteristics including age, sex, genetics, and lifestyle and environmental factors *[43]*.

Box 1: Fibrosis and cirrhosis

Liver fibrosis refers to the deposition of scar tissue in the liver. Fibrosis causes architectural distortion, severe vascular alterations and impairs optimal liver function. Fibrosis severity can be staged using one of several proposed systems such as *METAVIR [44]* and the *Ishak* modified histologic activity index *[45]*. F0 refers to no fibrosis. F1, F2 and F3 refer to progressively more liver scarring. F4 refers to liver cirrhosis when the parenchyma is surrounded by fibrous tissue resulting in the formation of nodules.

Liver cirrhosis can be further sub-classified as **compensated cirrhosis**, which is typically asymptomatic and **decompensated cirrhosis** where liver function is significantly compromised, and survival is reduced. Scoring systems, such as METAVIR or *Ishak*, separately assess the degree of liver inflammation and other features including the extent of liver fat deposition. Fibrous tissue, including that in early cirrhosis, can reverse if the inciting cause is removed. Cancer development results from progressive molecular and cellular changes within chronically injured liver cells, which in most cases is closely associated with the extent of fibrosis. Most liver cancers arise in a liver with cirrhosis or advanced liver fibrosis.

Historically, liver fibrosis and cirrhosis were diagnosed by liver biopsy, but this is invasive and carries the risk of complications, patient discomfort and inconvenience. For these reasons, liver biopsies for the purpose of cirrhosis diagnosis and fibrosis staging are rarely used in favour of new, less invasive technologies. Elastography (including specialised technologies like transient elastography or shear wave elastography) is now used to determine the extent of liver stiffness, a surrogate of fibrosis. However, these technologies are not universally available or subsidised centrally through the Medicare Benefits Schedule in Australia. Cirrhosis progression can also be assessed using aspartate aminotransferase-platelet ratio index (APRI) and fibrosis score based on four factors (FIB-4), or coagulation studies to consider cirrhosis progression.

Several measures of the severity of liver dysfunction are in use, such as the *Child-Pugh* score. The Child-Pugh score uses a 15-point system to classify the liver disease as class A, B, or C, each of which has different prognostic implications. The *Model for End-Stage Liver Disease (MELD)* score is a similar measure of severity using routinely measured laboratory parameters.

Aetiology of cirrhosis and hepatocellular carcinoma

Worldwide, there is considerable regional variation in the aetiology of cirrhosis and HCC *[46]*. The most common aetiologies are alcohol-related liver disease (ARLD), chronic infection with HBV and/or HCV, and metabolic dysfunction-associated fatty liver disease (MAFLD; also classified as non-alcoholic fatty liver disease [NAFLD]) *[47]*. Other causes include haemochromatosis, primary biliary cholangitis, and autoimmune hepatitis.

Alcohol-related liver disease

ARLD is associated with long-term excess alcohol consumption and a common cause of liver cirrhosis globally *[48]*. An estimated 17% of Australians consume alcohol at levels that put them at lifetime risk of an alcohol-related disease or injury *[49]*. Australia has guidelines to support the reduction of health risks from drinking alcohol. These are not specific to liver disease and liver cancer but play an important role in reducing harm associated with excessive alcohol intake *[50]*.

The prevalence of ARLD in Australia is unknown. ARLD includes a spectrum from simple steatosis, when hepatocytes become distended with lipids but is benign and reversible, or the more severe alcohol-related hepatitis and liver cirrhosis *[51]*. Alcohol-related cirrhosis is another well-recognised risk factor for HCC *[52]*. The risk of HCC among patients with alcohol-related cirrhosis ranges from 1.3% to 3% annually. A retrospective cohort study of patients with cirrhosis in Queensland noted that a higher proportion of Aboriginal and Torres Strait Islander participants had alcohol-related cirrhosis, compared with non-Indigenous participants *[53]*.

Viral aetiologies (chronic hepatitis B and C)

In high-income countries, such as Australia and North American countries, the predominant viral aetiology is

hepatitis C virus (HCV) infection *[46][52]*. Individuals with HCV and cirrhosis are at high risk of developing HCC, with annual cancer risk estimated at 3–5% in this group *[19]*. However, these reported risk data predate the introduction of direct-acting antiviral (DAA) treatment for HCV, which can achieve a cure in greater than 95% of infected individuals *[54]*. Although HCV clearance reduces HCC risk *[55][56]*, individuals with advanced liver disease before treatment retain a residual risk of HCC *[57]*.

The prevalence of chronic HCV infection is declining in Australia. The number of people receiving treatment for HCV treatment was highest in 2016 and has declined steadily since then. Between March 2016 and December 2021, 99,735 people received treatment for HCV *[58]*.

Chronic infection with hepatitis B virus (HBV) is the predominant HCC aetiology in Southeast Asia and Africa. The annual incidence of HCC is 2–5% in patients with HBV-related cirrhosis *[19]*. In Australia, there are an estimated 200,385 people living with HBV in 2021 *[59]*. Of these, modelling suggests that 72.5% were diagnosed but only 12.7% were reported to receive treatment *[59]*. Of note, 2020 estimates indicated 68.4% of all people living with chronic hepatitis B in Australia were born overseas and 7.2% were Aboriginal and/or Torres Strait Islander *[60]*. Population linkage studies have shown that Asian-born Australian residents were 30 times more likely to have a diagnosis of HBV-associated HCC than with Australian-born residents *[61]* and that HCC incidence was higher in areas with greater Aboriginal and Torres Strait Islander people *[62]*.

HBV-associated HCC can also be seen in the absence of cirrhosis in individuals from endemic areas such as Eastern Asia and sub-Saharan Africa *[46]*. In contrast, non-cirrhotic HBV-associated HCC is rarely seen in low-prevalence regions such as Europe or North America *[63]*. Differences in the HBV genotype, onset and duration of infection, and environmental exposures may contribute to the higher frequency of HCC in patients with HBV without cirrhosis in HBV endemic areas *[46]*.

A coinfection of HBV and HCV can increase the risk of developing HCC *[64]*. Hepatitis delta virus is of even lower prevalence and occurs only in individuals with underlying or concomitant HBV *[65]*. Chronic infection carries a high risk of cirrhosis and HCC with poor outcomes. Additionally, the negative social impact of an infection with HBV can include stigma, discrimination and social marginalisation and may reduce the willingness to access health care services to treat the infection and undertake surveillance for HCC *[66]*. The management of HBV and HCV in Australia are guided by consensus statements developed by the Gastroenterological Society of Australia *[23][67]*.

Metabolic dysfunction-associated fatty liver disease

MAFLD (or NAFLD) is projected to be a rapidly growing cause of HCC in western countries, including Australia, largely due to rising obesity rates though high-quality data are not always available *[68][69]*. NAFLD can progress through stages from simple steatosis to non-alcoholic steatohepatitis (NASH), where the build-up of fat causes liver inflammation and scarring. NAFLD-related cirrhosis is a risk factor for HCC, with prevalent NAFLD cases projected to increase to 25% by 2030 in Australia *[68]*.

Based on available data, it has been estimated that in 2020 in Australia, 5,700,000 people were living with NAFLD, representing 22.2% of the total population. NAFLD-related liver cancer has been projected to increase 75% by 2030 in Australia *[68]*.

The prevalence of MAFLD in Australia has been estimated at 37.0%, based on the application of the new diagnostic criteria (see Box 2) in a large prospective cohort *[70]*.

Box 2: Note on MAFLD terminology

It has recently been proposed that non-alcoholic fatty liver disease (NAFLD) should be renamed metabolic-

associated fatty liver disease (MAFLD), to better reflect patient heterogeneity and allow for treatment stratification *[71][72]*. Where NAFLD was diagnosed based on detection of hepatic steatosis and exclusion of other causes (excessive alcohol consumption, HBV/HCV infection *[73]*), the diagnostic criteria for MAFLD are based on the presence of clinical features rather than on exclusion *[72]*. A diagnosis of MAFLD is based on detection of hepatic steatosis in addition to one of the following: obesity, type 2 diabetes mellitus, or two or more metabolic abnormalities *[72]*. Additionally, NASH, a sub-diagnosis of NAFLD with liver inflammation, is now instead typically classified as metabolic-associated steatohepatitis.

Though there is significant overlap, these terms are not interchangeable. These guidelines use both the established and new terminology according to evidence sources.

Non-cirrhotic hepatocellular carcinoma

Patients with non-cirrhotic HCC tend to have a more advanced tumour stage at time of diagnosis, partially due to lack of surveillance among people without known cirrhosis *[74]*. The overall and disease-free survival rates are generally better in patients without underlying cirrhosis, as they generally preserve liver function and can undergo a larger resection *[74]*.

Non-cirrhotic HBV-related HCC is thought be due to integration of HBV DNA into host cellular DNA, which disrupts gene regulation independent of cirrhosis *[75]*.

HCV, an RNA virus, cannot integrate into host cell genomes. Animal studies suggest that non-cirrhotic HCV-related HCC might occur due to altered cell regulation in response to the presence of HCV gene products *[74]*.

Several studies suggest that NAFLD-associated HCC also occurs in the absence of cirrhosis *[38][76][77]*. Diabetes mellitus is associated with a twofold to threefold increase in the risk of HCC *[78]*, but it is unclear whether this is mediated by NAFLD. NAFLD is an emerging cause of non-cirrhotic HCC and the prevalence is expected to increase with the growing obesity burden *[79]*. A 2021 systematic review with meta-analysis reported an absence of cirrhosis in 37% (96%CI 28 to 46) of patients with NAFLD-related HCC *[77]*. Prevalence estimates varied across different continents, with a higher prevalence reported in Asia (45%) compared to North America, Europe and South America (37%, 36% and 22%, respectively) *[77]*.

The role of hepatocellular carcinoma surveillance

The combination of recent advances in treatment of HBV, high cure rates for HCV, and the increasing prevalence of NAFLD and metabolic syndrome in Australia, is expected to alter the relative prevalence of the causal aetiologies of HCC *[43][68][69]*.

Although patterns of causal aetiologies are changing, improved ability to identify groups at high risk of developing HCC provides the potential to develop more effective strategies for the prevention, early detection and curative treatment of liver cancer in Australia.

HCC surveillance is a well-established intervention to facilitate early detection through regular monitoring of populations at high risk. HCC surveillance targets people with cirrhosis as well as high-risk groups with HBV, using ultrasound and/or measurement of tumour biomarker(s) such as alpha-fetoprotein (AFP). Evidence has shown it to be successful in detecting lesions and/or early-stage tumours, increasing the receipt of curative treatment and improving overall survival *[2][3]*. In Japan and South Korea, established national surveillance programs for those at high risk have been associated with improved survival *[80][81]*.

AFP is a glycoprotein produced by the foetal liver and yolk sac early in gestation. Blood levels normally show a

rapid decline after birth and remain low throughout life *[82]*. In the 1960s, AFP was identified in the serum of patients with HCC, and it became the first serologic assay used for the detection of HCC *[82]*. AFP cut-points proposed for surveillance strategies are much lower than those recommended for the diagnosis of HCC *[82][83]*. AFP elevation can also be due to chronic viral hepatitis or liver fibrosis in people without HCC and in other cancer types *[82][84]*. In HCC surveillance, the added benefit of AFP to ultrasound, compared with ultrasound alone, remains unclear *[83][85]*. In Australia there have been calls to assess evidence for the feasibility and effectiveness of screening and surveillance programs and to identify optimal strategies for reducing liver disease-related morbidity and mortality for specific Australian populations *[3][37]*. The Gastroenterological Society of Australia (GESA) commenced this work by developing a consensus statement on the management of HCC *[20]* and including consideration for HCC surveillance in the consensus statements for HBV and HCV *[23][67]*. Existing guidelines for HCC surveillance include those developed by the UK National Institute for Health and Care Excellence (NICE) *[15][86][87]*, the American Association for the Study of Liver Diseases (AASLD) *[19][88]*, the European Association for the Study of the Liver (EASL) *[18]*, the Asian Pacific Association for the Study of the Liver (APASL) *[17]*, and the World Health Organization (WHO) *[16]*.

2. HCC surveillance in people with cirrhosis

Background

People with cirrhosis (Chapter 1 Box 1) are at high risk of developing hepatocellular carcinoma (HCC), and regular monitoring in this group is an established mechanism for earlier diagnosis and improved survival *[2]*.

Regular surveillance for people with cirrhosis using ultrasound, with or without alpha-fetoprotein (AFP) testing, aims to detect a tumour at an early stage when curative treatment could potentially be offered. Cirrhosis is associated with a significant reduction in life expectancy *[89]*, which impacts on the potential health benefits and cost-effectiveness of HCC surveillance. Patients with cirrhosis typically have significant comorbidities, which can be caused by the same underlying issue that led to the development of liver cirrhosis *[90]*. While the most common comorbidities (arterial hypertension, diabetes and obesity) would not preclude suitability, these are important to consider in conjunction with other patient characteristics.

Available evidence has been reviewed and recommendations have been developed by several organisations, including the Gastroenterological Society of Australia (GESA) *[20][23]*, the American Association for the study of Liver Diseases (AASLD) *[19][88]*, the UK National Institute for Health and Care Excellence (NICE) *[15][87]*, the European Association for the Study of the Liver (EASL) *[18]*, the Asian Pacific Association for the Study of the Liver (APASL) *[17]*, and the World Health Organization (WHO) *[16]*. Evidence-based recommendations from these guidelines (shown in Appendix C) have been adapted for the Australian context.

Recommendations

Strong recommendation against

2.1 Adapted evidence-based recommendation

Do not routinely offer surveillance for HCC for people who have limited projected life expectancy^ (NICE 2016 *[15]*)

^Does have significant comorbidities and therefore has a non-HCC-related life expectancy of less than 6 months.

Rationale

This recommendation is based on recommendations made in other guidelines based on systematic reviews of evidence.

Clinical question/ PICO

Population: People with limited projected life expectancy
Intervention: Surveillance for HCC
Comparator: No surveillance for HCC

Strong recommendation

2.2 Adapted evidence-based recommendation

In people with cirrhosis who are willing[(a)] and suitable[(b)] to receive HCC treatment, offer 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) (WHO 2015 *[16]*; NICE 2016 *[15]*; Omata et al 2017*[17]* ; EASL 2018 *[18]*; Marrero et al 2019 *[19]*; GESA 2020).*[20]*

(a) Willingness is defined as: 1. Willing to have an HCC diagnosis made AND 2. Considering HCC treatment if HCC is diagnosed. (b) Suitability is defined as: 1. Well enough to receive HCC treatment, including patients with Child-Pugh stage A or B cirrhosis or patients with Child-Pugh stage C awaiting liver transplantation AND 2. Does not have significant comorbidities and therefore has a non-HCC-related life expectancy of greater than 6 months.

Rationale

This recommendation is based on recommendations made in other guidelines including guidelines based on systematic reviews of evidence.

Clinical question/ PICO

Population: People with cirrhosis who are willing and suitable to receive HCC treatment
Intervention: 6-monthly surveillance for HCC
Comparator: No surveillance for HCC

3. HCC surveillance in people without liver cirrhosis

Background

Patients with non-cirrhotic liver disease and non-cirrhotic HCC

Although hepatocellular carcinoma (HCC) predominantly develops in people with cirrhosis, approximately 20% of HCC in Western countries is diagnosed in patients without underlying liver cirrhosis *[79][93][91][92]*. In these cases, HCC can be asymptomatic and is typically detected at a later stage compared with patients with cirrhosis, in some cases with fewer available treatment options *[74][94][95]*.

Chronic hepatitis B describes a spectrum of disease that is usually characterised by the presence of detectable hepatitis B surface antigen (HBsAg) in the blood or serum for longer than 6-months. Although most people with chronic hepatitis B viral infection (HBV) do not have any physical symptoms, a proportion will require treatment. Regular monitoring is recommended for all those affected to monitor for disease progression. Individuals affected with chronic HBV are at risk of developing HCC in the absence of cirrhosis.

Comparatively less is known about the aetiology of non-cirrhotic HCC, but the underlying causes are similar to those of HCC associated with cirrhosis *[74][79][96]*. Metabolic dysfunction-associated fatty liver disease (MAFLD) is a growing cause of non-cirrhotic HCC *[95]* but there are no current estimates of prevalence. However, a global analysis estimated that 37% (95% confidence interval [CI] 28–46%) of non-alcoholic fatty liver disease (NAFLD)-associated HCCs occur in patients without cirrhosis *[77]*. Alcohol-related liver disease (ARLD) is also associated with non-cirrhotic HCC, as well as alcohol-related cirrhosis, but prevalence is difficult to estimate. There is increasing interest in understanding the impact of heavy alcohol consumption on liver disease, especially in non-cirrhotic HCC, but evidence is limited *[65][74]*.

Cohort studies of non-cirrhotic HCC have reported higher proportions of males than females, typically with a ratio of more than two to one. People diagnosed with non-cirrhotic liver disease-associated HCC are typically older than those with cirrhotic HCC, with cohort studies reporting a mean age at diagnosis of between 67.5 and 69 years, compared with 63–66 for those with cirrhotic HCC. The median age at diagnosis has been estimated at 71 years in males and 66 years in females *[95]*. A retrospective analysis of data from 54 Australian patients with non-alcoholic fatty liver disease (NAFLD)-associated HCC found that those without cirrhosis had a significantly larger median tumour diameter at diagnosis than those with cirrhosis *[97]*.

Risk assessment tools

Risk prediction tools that do not rely on a diagnosis of cirrhosis have been developed to help identify groups at high risk of HCC. These tools typically use serum biomarkers and patient characteristics (such as age and sex) to quantify short-, mid- and long-term term HCC risk and refer high-risk patients to additional diagnostic procedures and/or HCC surveillance *[98]*. Early tools were developed mainly using data from hepatitis B virus (HBV)-infected people from East Asia and include characteristics such as age, sex, family history of HCC (defined as one or more first degree relatives with HCC), alcohol consumption, virological factors (HBV e-antigen [HBeAg], HBV DNA, HBV genotype) and serum biomarkers *[99]*. As these early tools were developed based on data from people treated in tertiary care settings and in the absence of antiviral therapies, their accuracy may differ when applied to other populations *[99]*. Nevertheless, some tools have been shown to predict HCC well in cohorts of people with chronic HBV infection, regardless of cirrhosis status *[100][99]* with predictability improving in more recently developed tools, for people from both Asian and non-Asian backgrounds *[101]*.

Risk prediction tools have not been widely implemented in clinical practice for patients without cirrhosis with hepatitis C virus (HCV), alcohol-related liver disease (ARLD) or non-alcoholic fatty liver disease (NAFLD), but there is accumulating evidence for their utility in identifying people with HBV requiring HCC surveillance *[99][101]*. Recent evidence on risk assessment for people with suspected NAFLD used Fibrosis-4 Index (FIB-4) alongside a NAFLD Fibrosis Score that included age, body mass index (BMI), impaired fasting glucose/diabetes, AST, ALT, platelet count, and albumin levels *[102]*.

Emerging evidence suggests that incorporating ethnic or ethnocultural background and lifestyle risk factors may improve the clinical utility of risk prediction tools that are not based on the diagnosis of cirrhosis or HBV/HCV status *[103]*.

Lifestyle risk factors suggested for incorporation into risk prediction tools include alcohol consumption, physical activity, dietary intake of saturated fats, trans fatty acids, lean meat, eggs, vitamin B, and total healthy eating index score, in addition to other factors such as age, sex, BMI, height, diabetes, cholesterol level, and self-reported general health condition *[103]*.

HCV-related advanced liver disease post sustained virologic response

Direct-acting antiviral (DAA) treatment has been available in Australia since March 2016 *[104]* and can effectively cure HCV, reduce liver enzyme levels and reduce liver inflammation and fibrosis *[105]*. A reduction in the number of adult liver transplantations performed for HCV-related liver cirrhosis and HCC was found following the introduction of universal access to DAAs in New Zealand and Australia *[106]*. However, risk of HCC is not considered to be eliminated in people with HCV-related advanced liver disease who achieve a sustained virologic response *[107]*. Among those with treated HCV, there is the possibility of either fibrosis regression, and possible reclassification of cirrhotic to non-cirrhotic, or the initiation of carcinogenesis before regression resulting in sustained risk *[74]*. A recent meta-analysis found that HCC incidence in people treated for HCV with advanced fibrosis was 0.5 per 100 person–years and 2.1 per 100 person–years for those with cirrhosis, with declining risk over time *[108]*.

HCC Surveillance

While existing international guidelines include clear recommendations for surveillance in patients with cirrhosis, there have also been calls to improve access and availability of HCC surveillance services for patients with non-cirrhotic liver disease or HCV-related advanced liver disease post sustained virologic response *[79][91][94][96]*.

The Gastroenterological Society of Australia's 2020 consensus statement *[20]* made the following recommendations: (1) HCC surveillance should be undertaken in non-cirrhotic individuals with chronic hepatitis B infection who are at increased risk of HCC. (Evidence quality: Low; Grade of recommendation: Strong). (2) Patients with HCV-related cirrhosis who achieve sustained virological response and undergo curative therapy for their HCC require ongoing surveillance (Evidence quality: Moderate; Grade of recommendation: Strong).

Recommendations

Hepatitis C-related cirrhosis post sustained virologic response

Weak recommendation

3.1 Evidence-based recommendation

In people with HCV-related cirrhosis who achieve a sustained virologic response to treatment, offer 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) if they are willing[(a)] and suitable[(b)] to receive treatment (Uyei et al 2019 *[21]*; Farhang Zangneh et al 2019 *[22]*).

(a) Willingness is defined as: 1. Willing to have an HCC diagnosis made AND 2. Considering HCC treatment if HCC is diagnosed. (b) Suitability is defined as: 1. Well enough to receive HCC treatment, including patients with Child-Pugh stage A or B cirrhosis or patients with Child-Pugh stage C awaiting liver transplantation AND 2. Does not have significant comorbidities and therefore has a non-HCC-related life expectancy of greater than 6 months.

Practical info

Evidence statement

For patients with HCV who underwent DAA treatment who had cirrhosis before DAA treatment, HCC surveillance with 6-monthly ultrasound is cost-effective in the USA and Canada (*[21][22]*).

Evidence to decision

Benefits and harms

For patients with HCV who undergo DAA treatment with cirrhosis before DAA treatment or after a sustained virologic response to DAA treatment for HCV, HCC surveillance with 6-monthly ultrasound is cost-effective i.e. the costs per quality adjusted life year saved were below a specified willingness to pay threshold.

These findings may not be directly applicable to the current Australian context as the two studies providing this evidence were not based on treatments and costs in Australia; one was based on treatments and costs in the USA with a willingness to pay threshold of US$100,000 per quality adjusted life year gained and the other on treatments and costs in Canada.

Certainty of the Evidence

The certainty of the body of evidence is low to very low as the design of the two modelling studies raised serious to very serious concerns about the potential risk of bias.

Values and preferences

DAA treatment for HCV has been available in Australia for almost a decade. While treatment can be effective, uptake is low and treatment numbers continue to decline over time *[60]*. Generally treatment uptake is lower in areas of higher HCV prevalence and remote regions *[60]*, possibly exacerbating inequalities in outcomes.

Clinical question/ PICO

Population: People with direct acting antiviral treated cirrhotic chronic HCV
Intervention: HCC surveillance programs
Comparator: No surveillance; Usual or standard care

Summary

Evidence summary

A systematic review of intervention studies was undertaken to answer the clinical question- **Does HCC surveillance improve liver cancer outcomes for people with HCV-related cirrhosis who have been treated with direct-acting antiviral (DAA) therapies?** The search strategy, inclusion and exclusion criteria, and assessment of the certainty of evidence are described in detail in the technical report (Appendix D). Case-control studies were not included as they are subject to significant risk of potential confounding when assessing screening interventions *[108]* and thus their evidence is very uncertain.

The review identified two modelling studies conducted in the USA and Canada *[21][22]*.

Patient populations

The two studies explored outcomes in people with HCV-related cirrhosis either before DAA treatment or after DAA treatment [21, 22].

Surveillance strategies

The studies modelled surveillance with ultrasound alone compared with either no surveillance or no routine surveillance.

Study designs

The two Markov models evaluated the cost-effectiveness of various surveillance strategies.

- A US study compared ultrasound surveillance strategies with no routine HCC surveillance in patients with HCV-related compensated cirrhosis aged 60 years who have undergone DAA treatment [21].
- A Canadian study compared ultrasound surveillance strategies with no HCC surveillance in patients aged 50 years with compensated cirrhosis after a sustained virologic response to DAA treatment [22].

Additional evidence

The Working Group also considered the following relevant studies, which were published after the search period for the systematic review undertaken for this guideline (Appendix D2):

A retrospective cohort study conducted in Japan followed 567 patients with HCV infection and without history of HCC who achieved sustained virological response at 24 weeks after HCV eradication treatment *[115]*. At median follow-up of 50.2 months, HCC was diagnosed in 30 patients, with a cumulative incidence of 5.9% *[115]*. Multivariate analysis identified significant pre-treatment factors as age ≥ 71 years (hazard ratio [HR]: 3.402) and liver stiffness measurement ≥ 9.2 kPa (HR: 6.328) *[115]*.

A European cohort study followed 527 patients with HCV infection with pre-treatment advanced chronic liver disease who achieved a sustained virologic response to interferon-free therapy *[116]*. At median follow-up of 41 months, HCC was diagnosed in 4.6% of those with compensated advanced chronic liver disease and 23.1% of those with decompensated advanced liver disease (p <0.001). The investigators concluded that simple algorithms based on post-treatment age, albumin, liver stiffness measurement, with or without AFP, and alcohol consumption, accurately stratified patients with compensated advanced chronic liver disease according to risk of de novo HCC after sustained virologic response *[116]*. They proposed that those with advanced but asymptomatic liver disease assessed to be at very low risk (<1%/year) of HCC might not need to undergo 6-monthly ultrasound *[116]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** No surveillance; Usual or standard care	**Intervention** HCC surveillance programs	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Cost-effectiveness [1]	Based on data from participants in 2 studies.	Surveillance with 6-monthly and 12-monthly US is cost effective when compared with no surveillance (2 modelling studies) ***Anticipated absolute effect (95% CI):*** Not Applicable *US = ultrasound*		Very low Modelling studies with very serious concerns regarding risk of bias [2]	For people with DAA-treated cirrhotic chronic hepatitis C, we are uncertain whether 6-monthly HCC surveillance is cost-effective in Australia.

1. .
2. **Risk of Bias: very serious.** Data underpinning effect of surveillance not critically appraised plus an important medical treatment for intermediate stage disease was not included in the model in Farhang

Zangneh 2019. **Inconsistency: no serious.** No inconsistency. Results are consistent across studies. Both studies found that surveillance with either 6-monthly or 12-monthly US was cost effective when compared with no surveillance for HCV patients with cirrhosis and treated with DAAs. This was despite differences in the populations modelled ie. cirrhotic and treated with DAAs (Uyei 2019) versus cirrhotic following sustained DAA-induced virologic response (Farhang Zangneh 2019) . **Indirectness: no serious.** Both studies report proportion of cirrhosis that is compensated at baseline .

Clinical question/ PICO

Population: HCC patients with cirrhosis who have been treated for HCV with direct acting antivirals
Intervention: Previous HCC surveillance
Comparator: No previous surveillance

Summary

Summary

A systematic review of prognostic studies was undertaken to answer the clinical question- **Is prior HCC surveillance associated with improved liver cancer outcomes for people with HCC with hepatitis C-related cirrhosis treated with DAAs?** The search strategy, inclusion and exclusion criteria, and assessment of the certainty of evidence are described in detail in the technical report (Appendix D2).

Included studies

No studies were identified that assessed the effect of surveillance on prognosis in patients with HCV treated with DAA therapies and met the inclusion criteria.

Non-cirrhotic liver disease in people with chronic HBV infection

Weak recommendation

3.2 Adapted evidence-based recommendation

In people with chronic HBV infection not part of a priority population[1], offer 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) if ALL of the following apply:

- age ≥ 40 years[2]
- family history of HCC[3]

(Sources: WHO 2015 *[16]*; NICE 2016 *[15]*; Omata et al 2017 *[17]*; EASL 2018 *[18]*; Marrero et al 2019 *[19]*; GESA 2020 *[20]*; GESA 2022 *[23]*; Robotin et al 2009 *[25]*; Sangmala et al 2014 *[30]*; Zhang et al 2004 *[110]*; Chen et al 2003 *[111]*; Chang et al 2011 *[112]*).

[1] *Defined by the Expert Advisory Group as Aboriginal and Torres Strait Islander people, people of Asian or Pacific background, and people of sub-Saharan African background*

[2] *HCC surveillance of younger people may be indicated according to either: regional incidence of HCC in country of birth, or country of birth where HBV is endemic. This may include the impact of differences between regional, racial, and ethnic backgrounds.*

[3] *Family history of HCC is defined as one or more first degree relatives with HCC. Consider offering surveillance 10 years prior to earliest case in a family.*

Practical info

Evidence statement

For people with chronic HBV infection two early RCTs undertaken in China found that, compared with no surveillance, 6-monthly HCC surveillance reduced HCC-related and/or liver cancer-related mortality and also increased the proportion of patients with HCC diagnosed at an early stage of disease (*[110][111]*).

For people with chronic HBV infection a single cost-effectiveness analysis estimated that HCC surveillance using 6-monthly ultrasound and AFP or ultrasound alone, is cost-effective compared with no surveillance in Thailand *[30]*.

Evidence to decision

Benefits and harms

HCC surveillance in people with chronic HBV infection, using 6-monthly ultrasound and AFP or ultrasound alone, is cost-effective (cost per quality life year gained) compared with no surveillance in Thailand. This finding is not directly applicable to the current Australian context.

Existing tools and risk scores still cannot safely exclude patients with liver disease without cirrhosis from HCC surveillance *[101]*. However, individual risk assessments are commonly used in practice in the absence of formal tools and risk scores.

Certainty of the Evidence

Overall, the certainty of the body of evidence is low to very low as the design of the RCTs, the observational studies and the modelling studies raised serious to very serious concerns about the potential risk of bias and there were serious concerns about indirectness for the modelling study that provided cost-effectiveness results.

Both RCTs were assessed as having a high risk of bias due to application of cluster design, missing outcome data and outcome measurement. The modelling study that provided cost-effectiveness results was assessed as having serious concerns regarding indirectness and risk of bias. The certainty of the prognostic studies' evidence was low to very low as they were cohort studies rather than randomised controlled trials assessing the effect of an intervention.

The RCT and modelling evidence was primarily for people with HBV in Asia. The findings may not be directly applicable to the current Australian context, but applicable to high-risk populations in which HBV is endemic, co-infection with hepatitis D is prevalent, there is a family history of HCC (one or more first degree relatives with HCC) and/or HBV infection occurs around the time of birth, resulting in lifelong exposure.

Values and preferences

People with non-cirrhotic liver disease who are identified as being high-risk would be, generally, willing to undergo regular HCC surveillance. Adherence to the 6-monthly frequency can be challenging and would require clear communication of the need and ensuring the availability and access to the required health services.

Clinical question/ PICO

Population: People with non-cirrhotic liver disease
Intervention: HCC surveillance programs
Comparator: No surveillance; Usual or standard care

Summary

Evidence summary

A systematic review of intervention studies was undertaken to answer the clinical question - **Does HCC surveillance improve liver cancer outcomes for people with non-cirrhotic liver disease and for people with HCV-related cirrhosis who have been treated with direct-acting antiviral (DAA) therapies?** The search strategy, inclusion and exclusion criteria, and assessment of the certainty of evidence are described in detail in the technical report (Appendix D). Case-control studies were not included as they are subject to significant risk of potential confounding when assessing screening interventions *[108]* and thus their evidence is very uncertain.

The review identified five relevant studies:
two randomised controlled trials (RCTs) conducted in China *[110,111]*, and three Markov modelling studies conducted in Australia and Asia *[25][30][112]*.

Patient populations

RCT study populations included males and females, the majority of whom had HBV infection and of which almost 10% presented with a history of chronic hepatitis (with or without cirrhosis) *[110]*, and males with chronic HBV infection (with or without cirrhosis) *[111]*. The modelling studies
explored outcomes in people with chronic HBV infection without cirrhosis *[25][112] and* people with chronic HBV infection of unspecified cirrhosis status *[30]*.

Surveillance strategies

Screening/surveillance strategies included ultrasound plus alpha-fetoprotein (AFP), risk-stratified ultrasound plus AFP. ultrasound alone, computed

tomography (CT), magnetic resonance imaging (MRI), and the combination of AFP and ALT. Comparators included no surveillance (both RCTs and two modelling studies) and usual care (one modelling study *[25]*).

Study designs

Randomised controlled trials

A cluster RCT conducted at more than 300 sites
in urban Shanghai, China, compared 6-monthly surveillance (ultrasound and AFP) with no surveillance in males and females aged 35–59 years with HBV infection or chronic hepatitis (with or without cirrhosis) *[110]*. Reported outcomes included HCC-related mortality and HCC detected at early stage *[110]*.

Another RCT conducted in China compared 6-monthly surveillance (AFP and ALT) with no surveillance in males with chronic HBV infection with or without cirrhosis across 23 townships. Reported outcomes included overall mortality, and liver cancer-related mortality, and liver cancer detected at early stage *[111]*.

Modelling studies

The three Markov models mainly evaluated the cost per quality-adjusted life year or life year gained of various surveillance strategies but only one reported cost-effectiveness using a willingness to pay threshold [30].

An Australian modelling study included patients with non-cirrhotic chronic
HBV infection born in Asia and aged 35 years and over. The model compared risk-stratified 6-monthly surveillance (ultrasound and AFP) with usual care *[25]*.

A Thai modelling study compared a variety of surveillance strategies with no surveillance in patients with chronic HBV infection aged over 40 years *[30]*.

A modelling study in Taiwan compared ultrasound surveillance with no surveillance in patients aged over 50 with chronic HBV infection without cirrhosis *[112]*.

Additional evidence

The recommendation for people with chronic HBV infection not part of a priority population is based on those developed by other high-quality guidelines based on systematic reviews of evidence and cover the general population with HBV. Available evidence has been reviewed and recommendations developed by several organisations, including the Gastroenterological Society of Australia (GESA) *[20][23]*, the American Association for the study of Liver Diseases (AASLD) *[19][88]*, the UK National Institute for Health and Care Excellence (NICE) *[15][87]*, the European Association for the Study of the Liver (EASL) *[18]*, the Asian Pacific Association for the Study of the Liver (APASL) *[17]*, and the World Health Organization (WHO) *[16]*. Evidence-based recommendations from these guidelines (shown in Appendix C) have been adapted for the Australian context. Recommendations relating to priority population groups, including those with HBV, can be found in other sections of the Guidelines [see Chapters 4,5 and 6].

Outcome Timeframe	**Study results and measurements**	**Comparator** No surveillance; Usual or standard care	**Intervention** HCC surveillance programs	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Overall mortality	Based on data from 5,581 participants in 1 studies. (Randomized controlled)	**Rate ratio:** 0.97 (CI 95% 0.77 — 1.22) ***Anticipated absolute effects (95% CI)**: Not applicable as the reported*		Very low One study with very serious concerns regarding risk of	For people with non-cirrhotic HBV we are uncertain whether HCC surveillance programs improve or worsen

Outcome Timeframe	**Study results and measurements**	**Comparator** No surveillance; Usual or standard care	**Intervention** HCC surveillance programs	**Certainty of the Evidence** (Quality of evidence)	**Summary**
		outcome metric is events per person years.		bias and serious concerns regarding indirectness. [1]	overall mortality
Liver disease-related mortality	Based on data from 10,000 participants in 1 studies.	**Relative effect (95% CI):** Not calculable* ***Anticipated absolute effects*** **Metric:** % **Risk with no surveillance:** 33.8 **Risk with surveillance:** 33.6 (risk-stratified surveillance) **For the modelled outcome of liver disease-related mortality a risk ratio and 95% confidence interval were not calculated as the confidence intervals will be much narrower than those of real (non-modelled) outcome because of the modelling process which is designed to produce "stable" outcomes.*		Very low Modelling study with very serious concerns regarding risk of bias [2]	For people with non-cirrhotic HBV we are uncertain whether HCC surveillance programs improve or worsen liver disease-related mortality
HCC or liver-cancer related mortality [3]	Based on data from 24,397 participants in 2 studies.	**Relative effect (95% CI):** • *6 monthly US+AFP* - **Rate ratio** = 0.63 (0.41-0.98) • *6 monthly AFP+ALT* - **Rate ratio** = 0.86 (0.69-1.07) ***Anticipated absolute effects (95% CI):*** *Not applicable as the reported outcome metric is events per person years.* *AFP = alpha-fetoprotein; ALT = alanine transaminase; US = ultrasound*		Very low Very serious concerns regarding risk of bias and serious concerns regarding indirectness [4]	For people with non-cirrhotic HBV we are uncertain whether HCC surveillance programs improve or worsen HCC or liver-cancer related mortality
Liver cancer diagnosed at an early stage	Based on data from 24,397 participants in 2 studies.	**Relative effect (95% CI):** • *6 monthly US+AFP* - Risk ratio = Not calculable • *6 monthly AFP+ALT* - Risk ratio = 7.54 (2.82 -20.14) ***Anticipated absolute effects (95% CI)***		Very low Very serious concerns regarding risk of bias and serious concerns regarding indirectness [5]	For people with non-cirrhotic HBV we are uncertain whether HCC surveillance programs improve liver cancer diagnosed at an early stage

Outcome Timeframe	**Study results and measurements**	**Comparator** No surveillance; Usual or standard care	**Intervention** HCC surveillance programs	**Certainty of the Evidence** (Quality of evidence)	**Summary**
		Metric: % **Risk with no surveillance:** • *6 monthly US+AFP* = 0 • *6 monthly AFP+ALT* = 3.7 **Risk with surveillance:** • *6 monthly US+AFP* = 60.5 • *6 monthly AFP+ALT* = 27.9 (10.4-74.5)** ** *Calculated by review team by applying risk ratio or rate ratio and its 95% confidence interval to the risk with no surveillance* *AFP = alpha-fetoprotein; ALT = alanine transaminase; US = ultrasound*			
Cost effectiveness	Based on data from participants in 1 studies.	Surveillance (6-monthly US or US+-AFP) is cost effective for HBV patients when compared with no surveillance (1 study) ***Anticipated absolute effects (95% CI):*** Not applicable *AFP = alpha-fetoprotein; ALT = alanine transaminase; HBV = chronic hepatitis B; US = ultrasound*		Very low Modelling study with serious concerns regarding risk of bias and indirectness [6]	For people with non-cirrhotic HBV we are uncertain whether HCC surveillance programs are cost-effective in Australia

1. **Risk of Bias: very serious.** One study with high risk of bias due to measurement of the outcome. **Indirectness: serious.** For this PICO question the population of interest is people with non-cirrhotic liver disease or DAA-treated cirrhotic HCV. This study was in a HBV population and does not report the proportion with cirrhotic disease at baseline. It was assumed to be <20%. **Imprecision: serious.** Single study with rate ratio (95% CI) = 0.97 (0.77-1.22). 95% confidence crosses 1.0.
2. **Risk of Bias: very serious.** Data underpinning effect of surveillance not critically appraised plus some important medical treatments were not included in the model. **Indirectness: no serious.** This study was in a HBV population and reports % cirrhotic at baseline and rate of surveillance for comparator, usual care.
3. HCC = Hepatocellular carcinoma
4. **Risk of Bias: very serious.** Both studies high risk of bias. In Chen 2003 this was due to the measurement of the outcome. In Zhang 2004 this was due to the application of cluster design and missing outcome data. **Inconsistency: no serious.** The results from the two studies were not consistent. However, the inconsistency can be explained by differences in the length and mode of follow-up, possible treatments offered for stage disease, and the type of surveillance used with one study using ultrasound and AFP (Zhang 2004) and the other using AFP and ALT (Chen 2003). **Indirectness: serious.** For this PICO question the population of interest is people with non-cirrhotic liver disease or DAA-treated cirrhotic HCV. Both studies were in HBV populations and neither reported the proportion with cirrhotic disease at baseline. It was assumed to be <20%. **Imprecision: serious.** In Chen 2003 the 95% confidence interval

crossed 1.0 (rate ratio (95%CI) = 0.86 (0.69-1.07)). In Zhang 2004 the rate ratio (95%CI) was 0.63 (0.41-0.98) with the upper limit of the confidence interval only just below 1.0. It likely would have crossed 1.0 if the authors had adjusted for the cluster design. When these results were pooled the rate ratio (95%CI) was 0.81 (0.66-0.98). The extent of this 95% confidence interval is also likely an underestimate as it includes the results from the trial (Zhang 2004) that did not adjust for cluster design.
5. **Risk of Bias: very serious.** Both studies high risk of bias. In Chen 2003 this was due to a high risk of bias due to the measurement of the outcome. In Zhang 2004 this was due to a high risk of bias arising from the application of cluster design, missing outcome data, and measurement of the outcome . **Inconsistency: no serious.** Results of the two studies are consistent in showing an increase in the proportion of liver cancers diagnosed at an early stage despite differences in the length of follow-up, and the type of surveillance used. Zhang 2004 used ultrasound and AFP while Chen 2003 used AFP and ALT. **Indirectness: serious.** For this question the population of interest is people with non-cirrhotic liver disease or DAA-treated cirrhotic HCV. Both studies were in HBV populations and neither reported the proportion with cirrhotic disease at baseline. It was assumed to be <20%. **Imprecision: serious.** In both studies the proportion of cancer diagnosed at early stage increased. In Zhang 2004 there was an increase of 60.5 percentage points however, confidence intervals were not calculable as none of the HCC patients in the control arm were diagnosed at an early stage. In Chen 2003 the risk ratio (95%CI) = 7.45 (2.82-20.14). Given this 95%CI and the proportion of HCC early-stage at diagnosis for the comparator was 3.7%; then the 95% confidence interval for the outcome for the intervention was 10.4%-75.5% HCC early-stage at diagnosis. This is an increase of 6.7 percentage points when compared with the comparator which is above the threshold of 5 percentage points considered clinically important. However, the effect is large and the ratio of the upper limit of the CI to the lower limit of the CI is >3.0.
6. **Risk of Bias: very serious.** Authors do not critically appraise sources of data underpinning effect of surveillance and medical treatment for intermediate stage disease not included in model. **Inconsistency: no serious.** Probabilistic sensitivity analysis undertaken. **Indirectness: no serious.** Reports % cirrhosis compensated at baseline.

Clinical question/ PICO

Population: HCC patients with non-cirrhotic liver disease
Intervention: Previous HCC surveillance
Comparator: No previous surveillance

Summary

Evidence summary

A systematic review of prognostic studies was undertaken to answer the clinical question - **Is prior HCC surveillance associated with improved liver cancer outcomes for people with HCC with either (i) non-cirrhotic liver disease or (ii) hepatitis C-related cirrhosis treated with DAAs?** The search strategy, inclusion and exclusion criteria, and assessment of the certainty of evidence are described in detail in the technical report (Appendix D2).

Included studies
The review identified two relevant studies that met inclusion criteria *[113][114]*. Both were retrospective cohort studies conducted in Taiwan comparing ultrasound surveillance in the 3-9 months prior to HCC diagnosis with no regular surveillance (previous surveillance 28-39 months prior to diagnosis). A study designed to identify optimal intervals for ultrasound screening for early

diagnosis of HCC in Taiwan analysed data from a cohort of 114,022 patients with HCC diagnosed between 2003 and 2015 and followed to 2017. It included more than 2,000 patients with non-cirrhotic HCV and reported the percentage of HCC detected at an early stage in this group *[113]*. An earlier study assessed HCC mortality in a cohort of approximately 7,400 patients with non-cirrhotic liver disease of mixed aetiology diagnosed with HCC between 2002 and 2007 *[114]*.

Evidence sources

Kuo SC, Lin CN, Lin YJ, Chen WY, Hwang JS, Wang JD. Optimal intervals of ultrasonography screening for early diagnosis of Hepatocellular Carcinoma in Taiwan. JAMA Netw. 2021 Jun 24;4(6):e2114680.

Wu CY, Hsu YC, Ho HJ, Chen YJ, Lee TY, Lin JT. Association between ultrasonography screening and mortality in patients with hepatocellular carcinoma: a nationwide cohort study. Gut. 2016 Apr;65(4):693–701.

Outcome Timeframe	**Study results and measurements**	**Comparator** No previous surveillance	**Intervention** Previous HCC surveillance	**Certainty of the Evidence** (Quality of evidence)	**Summary**
5-year overall mortality [1]	Hazard ratio 0.8 (CI 95% 0.75 — 0.85) Based on data from 7,425 participants in 1 studies.	73 per 100 Difference:	58 per 100 **15 fewer per 100** 11 fewer — 18 fewer	Very low One large cohort study using Taiwanese national data with a moderate risk of bias [2]	For people diagnosed with HCC we are uncertain whether previous HCC surveillance improves overall mortality
Proportion of HCC early stage at diagnosis† [3]	Relative risk 1.63 (CI 95% 1.44 — 1.84) Based on data from 2,223 participants in 1 studies.	46 per 100 Difference:	76 per 100 **29 more per 100** 20 more — 39 more	Low One cohort study using Taiwanese national data with a low risk of bias [4]	For people diagnosed with HCC previous HCC surveillance may increase the proportion of HCC early stage (Barcelona Clinic Liver Cancer stage 0/A at diagnosis)

1. Risk with regular surveillance: Calculated by review team by applying risk ratio or hazard ratio and its 95% confidence interval to the risk with no regular surveillance. Risk with no regular surveillance reported in included study.
2. **Risk of Bias: serious.** Moderate risk of bias due to ascertainment of surveillance status. Confounding well adjusted for. **Indirectness: serious.** Regular surveillance (US in 3-9 months prior to diagnosis) and no regular surveillance (last US prior to diagnosis (28-39 months prior to diagnosis) considered a reasonable approximation of surveillance vs no surveillance, however studies relied on ICD coding for diagnosis of cirrhosis which is unreliable. **Imprecision: no serious.** HR (95%CI) = 0.80 (0.75-0.85) and the effect is moderate.
3. †Early stage includes Barcelona Clinic Liver Cancer stage 0/A, meeting Milan criteria, or China Liver Cancer Study group stage I (see Appendix D2). Risk with regular surveillance: Calculated by review team by applying risk ratio or hazard ratio and its 95% confidence interval to the risk with no regular surveillance. Risk with no regular surveillance reported in included study.
4. **Risk of Bias: serious.** Moderate risk of bias. Potential important confounders age, comorbidities and

DAA status not adjusted for. **Indirectness: serious.** Regular surveillance (US in 3-9 months prior to diagnosis) and no regular surveillance (last US 28-39 months prior to diagnosis) considered a reasonable approximation of surveillance vs no surveillance however studies relied on ICD coding for diagnosis of cirrhosis which is unreliable. **Imprecision: no serious.** Risk ratio (95%CI) = 1.63 (1.44-1.84) and proportion of HCC early-stage at diagnosis for the comparator is 46.4% so the 95% confidence interval for the outcome for the intervention will be 66.8%-85.4% HCC early-stage at diagnosis with the lowest increase being 66.8% which equals an increase of 20.4 percentage points when compared with the comparator. The effect is large however the ratio of the upper to limit of the confidence interval is less than 3.0. 1588 early-stage diagnoses > 400 events.

HCV-related advanced hepatic fibrosis post sustained virologic response

Weak recommendation against

New

3.4 Evidence-based recommendation

In people with HCV and F3 fibrosis (non-cirrhotic)[#] who achieve a sustained virologic response to treatment, do not routinely offer surveillance for HCC (Farhang Zangneh et al 2019 *[22]*).

[#] *Fibrosis stage should be based on the pre-treatment assessment.*

Practical info

Evidence statement

For people with advanced hepatic fibrosis after a sustained virologic response to DAA treatment for HCV a single cost-effectiveness analysis estimated that, surveillance with 6-monthly or 12-monthly liver is not cost-effective; it was not estimated to increase quality-adjusted life years in the patient population and jurisdiction studied *[22]*.

Evidence to decision

Benefits and harms

HCC surveillance with 6-monthly or 12-monthly ultrasound for people with HCV with advanced hepatic fibrosis after a sustained virologic response to DAA treatment was not cost effective in the modelled patient populations and jurisdictions studied.

Certainty of the Evidence

The certainty of the body of evidence is low to very low.

Clinical question/ PICO

Population: People with HCV and F3 fibrosis (non-cirrhotic) who achieve a sustained virologic response to treatment

Intervention: Surveillance

Comparator: No surveillance

Summary

Evidence summary

A Canadian modelling study found that surveillance with 6-monthly or 12-monthly ultrasound for people with HCV with advanced hepatic fibrosis after a sustained virologic response to DAA treatment for HCV is not cost-effective *[22]*.

Additional evidence

Cost-effectiveness evidence for HCC surveillance for patients with DAA-treated HCV is emerging, with at least one relevant study *[117]* published after the literature search period for this systematic review. This study conducted under US health system conditions concluded that 6-monthly surveillance for HCC in patients with sustained virologic response to antiviral treatment for HCV was cost-effective until age 60 years for patients with stable advanced fibrosis (compared with age 70 for patients with cirrhosis).

Evidence for risk factors for HCC among patients with DAA-treated HCV is also emerging. A retrospective cohort study conducted in Japan *[115]* followed 567 patients with HCV infection and without history of HCC who achieved sustained virological response at 24 weeks after HCV eradication treatment. At median follow-up of 50.2 months, HCC was diagnosed in 30 patients, with a cumulative incidence of 5.9%. Multivariate analysis identified significant pre-treatment factors as age ≥ 71 years (hazard ratio [HR]: 3.402) and liver stiffness measurement ≥ 9.2 kPa (HR: 6.328) *[115]*.

A European cohort study *[116]* followed 527 patients with HCV infection with pre-treatment advanced chronic liver disease who achieved a sustained virologic response to interferon-free therapy. At median follow-up of 41 months, HCC was diagnosed in 4.6% of those with compensated advanced chronic liver disease and 23.1% of those with decompensated advanced liver disease ($p < 0.001$). The investigators concluded that simple algorithms based on post-treatment age, albumin, liver stiffness measurement, with or without AFP, and alcohol consumption, accurately stratified patients with compensated advanced chronic liver disease according to risk of de novo HCC after sustained virologic response. They proposed that those with advanced but asymptomatic liver disease assessed to be at very low risk (<1% per year) of HCC might not need to undergo 6-monthly ultrasound.

Outcome Timeframe	**Study results and measurements**	**Comparator** No surveillance	**Intervention** Surveillance	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Cost effectiveness	Based on data from participants in 1 studies.	Surveillance (6-monthly or 12-monthly US) is **not** cost effective for DAA-treated HCV patients with advanced fibrosis following sustained virologic response when compared with no surveillance (1 study) **Anticipated absolute effect:** Not applicable *DAA = direct acting antiviral; HCV = chronic hepatitis C; US = ultrasound*		Very low Modelling study with very serious concerns regarding risk of bias [1]	For people with HCV and F3 fibrosis (non-cirrhotic) who achieve a sustained virologic response to treatment, we are uncertain whether HCC surveillance is or is not cost-effective in Australia

1. **Risk of Bias: very serious.** Authors do not critically appraise sources of data underpinning effect of surveillance and medical treatment for intermediate stage disease not included in model. **Inconsistency: no serious.** Probabilistic Sensitivity Analysis undertaken. **Indirectness: no serious.** Reports % cirrhosis compensated at baseline.

Practice Points

Non-cirrhotic chronic HBV infection

Good practice statement

New

3.3 Practice Point

In people with chronic HBV infection not part of a priority population[1], consider offering 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) based on an individual risk assessment[2] including family history of HCC[3].

[1]*Defined by the Expert Advisory Group as Aboriginal and Torres Strait Islander people, people of Asian or Pacific background, and people of sub-Saharan African background*

[2]*Refer to Chapter 3 for aspects to consider when assessing risk.*

[3]*Family history of HCC is defined as one or more first degree relatives with HCC. Consider offering surveillance 10 years prior to earliest case in a family.*

HCV-related advanced hepatic fibrosis post-sustained virologic response

Good practice statement

New

3.5 Practice Point

People with HCV and F3 fibrosis (non-cirrhotic) [#] who achieve a sustained virologic response to treatment should be monitored* for progression to cirrhosis

[#] Fibrosis stage should be based on the pre-treatment assessment.
** Based on elastography or other similar technology.*

F3 fibrosis (non-cirrhotic)

Good practice statement

New

3.6 Practice point*

In people with F3 fibrosis (non-cirrhotic) [#], excepting people with HCV who achieve a sustained virologic response to treatment, consider offering 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) based on an individual risk assessment[1].

[*] Adapted from EASL guidelines.
[#] Fibrosis stage should be based on the pre-treatment assessment.
[1] Refer to Chapter 3 for aspects to consider when assessing risk.

Rationale

There was negligible evidence on which to base recommendations for surveillance in people with non-cirrhotic liver disease due to causes other than chronic HBV infection. Regular surveillance is associated with improved HCC survival for patients with mixed-aetiology HCC. Thus, the benefits of HCC surveillance are unclear.

F3 fibrosis (non-cirrhotic)

Good practice statement

New

3.7 Practice point

People with F3 fibrosis (non-cirrhotic) [#] not considered high-risk for HCC based on the individual risk assessment[1] should be monitored* for progression to cirrhosis.

[#] Fibrosis stage should be based on the pre-treatment assessment.
[1] Refer to Chapter 3 for aspects to consider when assessing risk.
** Based on elastography or other similar technology.*

Rationale

There was negligible evidence on which to base recommendations for surveillance in people with non-cirrhotic liver disease due to causes other than chronic HBV infection. Regular surveillance is associated with improved HCC survival for patients with mixed-aetiology HCC. Thus, the benefits of HCC surveillance are unclear.

Non-cirrhotic liver disease due to causes other than chronic HBV infection

Good practice statement

New

3.8 Practice point

People with metabolic dysfunction-associated fatty liver disease/non-alcoholic fatty liver disease without cirrhosis should be monitored* for progression to cirrhosis.

**Based on elastography or other similar technology.*

Rationale

People with non-cirrhotic MAFLD/NAFLD, particularly those with advanced liver fibrosis, are at increased risk of HCC. Risk factors for the development of cirrhosis in people with MAFLD and/or HCC in people with NAFLD include type 2 diabetes and obesity *[118]*. For those with NAFLD-related HCC, risk factors include not only type 2 diabetes and obesity, but also smoking and advanced fibrosis or cirrhosis *[119]*. Additional risk factors commonly cited are excess alcohol consumption, iron overload, age > 65 and sex (male). HCC incidence in people without cirrhosis is 0.03 per 100 person–years for those with NAFLD *[120]*. Thus, the benefits of HCC surveillance are unclear.

Resource and other considerations

Resource considerations

Practice points include the use of individual risk assessment. Although there is no specific tool or risk score recommended for use in Australia, individual risk assessments are often used in clinical practice. It is noted that there is a lack of evidence to guide best-practice and it is an ongoing area of research. Nonetheless, individual risk assessments have been included to reflect current practice.

Implementation considerations

In implementing these recommendations, clinicians should recognise that many patients have multiple causes of liver disease. In primary care it may be challenging to identify patients with compensated advanced chronic liver disease/advanced fibrosis, manage risk for fibrosis progression (alcohol, obesity, diabetes) and monitor annually for progression to cirrhosis. Moreover, in this group ultrasound may be inadequate due to obesity (reported as 'limited due to body habitus'). In addition to challenges posed by body habitus, patients with significant liver steatosis may have poor visualisation scores, making HCC surveillance with ultrasound difficult or insensitive. Clinical consideration should be made for this possibility when monitoring and/or providing HCC surveillance.

Future evidence considerations

The recommendations included in these guidelines do not explicitly nominate people with ARLD. This is a growing area of interest and a possible cause of non-cirrhotic HCC, however there is currently limited evidence to support its separate inclusion. The evidence should be revisited when updating these guidelines.

People with chronic HBV infection can achieve seroclearance, though HCC risk may remain. However, seroclearance before the age of 50 years is associated with a very low risk of HCC and in those over 50 years of age the risk can be higher *[121]*. Although out of scope for these guidelines, emerging evidence suggests that this group may also benefit from HCC surveillance, based on their individual risk. In HBsAg-cleared patients, HCC risk estimation based on age at seroclearance, cirrhosis, family history of HCC, and alcohol consumption could help identify those at high risk who would benefit from HCC surveillance *[122]*.

4. HCC surveillance in Aboriginal and Torres Strait Islander people

Background

Aboriginal and Torres Strait Islander people represent approximately 3.8% of the Australian population and experience poorer health outcomes than non-Indigenous Australians *[123]*. In 2012-2016, cancer incidence was 14% higher for Aboriginal and Torres Strait Islander people than non-Indigenous Australians *[34]*. In 2015–2019, the age-standardised mortality rate for all cancers combined was 45% higher for Aboriginal and Torres Strait Islander people than non-Indigenous Australians *[34]*.

Aboriginal and Torres Strait Islander people are impacted more by liver disease and liver cancer than non-Indigenous Australians. Liver disease is the third most significant contributor to the gap in life expectancy between Aboriginal and Torres Strait Islander people and non-Indigenous Australians *[124]* and liver cancer is the fourth most common cause of cancer incidence and second most common cause of cancer death in Aboriginal and Torres Strait Islander people *[34]*. In the Torres Strait Islands and Northern Peninsular Area of Cape York (where 90% of the population identify as a Torres Strait Islander), liver cancer (with HCC the highest contributor) is the 7th most common cancer by incidence (lung, urological, gynaecological, breast, colorectal and upper gastrointestinal cancers are more common) *[125]*.

We recognise that within Aboriginal and Torres Strait Islander peoples there are many distinct nations, cultures and languages and that the approach to optimal delivery of HCC surveillance should be locally adapted to meeting differing needs. For example, research conducted in Torres Strait Islander communities identified a series of clinical and non-clinical issues affecting health service delivery. Clinical barriers to effective health management included resource constraints, variable health knowledge and health system inadequacies *[126][127]*. Non-clinical barriers included the reality and logistics of small island living, lack of employment opportunities and inadequate income, costly healthy food options and dental problems *[126]*. Whilst the basic principles of Aboriginal health management and service delivery are critical, they are not necessarily transferrable to Torres Strait Islander communities and those living in non-remote communities without additional consultation with the specific communities and appropriate adaptation.

Incidence, mortality and survival

Age-standardised incidence and mortality rates for hepatocellular carcinoma (HCC) are 2.4 times higher among Aboriginal and Torres Strait Islander people than non-Indigenous Australians *[128]*. The mortality rate difference between Aboriginal and Torres Strait Islander people and non-Indigenous Australians is more pronounced for HCC than for any other cancer except for cervical cancer *[36][128]*. Five-year HCC survival rates are also lower among Aboriginal and Torres Strait Islander people than non-Indigenous Australians: 14% versus 20% based on Australian Institute of Health Welfare data for 2012–2016 *[34]* and 10% versus 17.3%, based on linked cancer registry data from Queensland, South Australia and the Northern Territory *[128]*.

Age profile for HCC

On average, HCC is diagnosed at a younger age in Aboriginal and Torres Strait Islander people than in non-Indigenous Australians (59.9 versus 65.4 years) *[128]*, and is associated with lower life expectancy. Data from the Top End region of the Northern Territory show that rates of HCC incidence rise steeply from age 50 among Aboriginal and Torres Strait Islander people, compared with a much smaller gradual increase among non-Indigenous Australians *[129]*.

Comparative incidence of HCC by region

In the Northern Territory, the incidence of HCC is six times higher among Aboriginal and Torres Strait Islander people than among non-Indigenous people *[130][131]*. In Queensland, HCC incidence rates are higher in areas with greater proportions of Aboriginal and Torres Strait Islander people *[62]*.

A retrospective cohort study of data from Queensland, South Australia and the Northern Territory found that approximately 50% of Aboriginal and Torres Strait Islander people with HCC were living in remote and very remote areas *[128]*.

Prevalence of risk factors

Aboriginal and Torres Strait Islander people are likely to have comorbidities that contribute to their risk of HCC and potentially decrease survival rates *[128]*. Prevalence of risk factors for HCC among Aboriginal and Torres Strait Islander people and the overall Australian population are presented in Table 6. The prevalence of all risk factors for HCC are higher among Aboriginal and Torres Strait Islander people than in the overall Australian population *[132][133][134][135][136]*. These health disparities are exacerbated not only by differences in individual risk factors but also differences in socio-economic, education and employment levels and health service accessibility and availability challenges *[137]*. The effects of colonisation and ongoing systemic racism impact on all aspects of healthcare including HCC surveillance and should be considered in the provision of culturally safe and sensitive care.

Of note, Aboriginal people living in the Northern Territory have been found to have the unique C4 sub-genotype of hepatitis B virus (HBV). This sub-genotype has molecular features that suggest aggressive disease including faster progression to cirrhosis and increased risk of HCC *[138][139][140]*. In Far North Queensland over 80% of Aboriginal people have a D genotype (D2 and D4). Genotype D (D2 and D3) have not been found to be significantly associated with a higher risk of HCC *[141]*. Additionally, emerging evidence has identified the different genotypes of Hepatitis B (C14, C13 and C3 rather than C4) in Torres Strait Islander people [personal communication]. In Australia, genotype testing is not routinely performed in clinical practice nor subsidised through the Medicare Benefits Schedule (MBS), making it difficult to implement as part of standard practice. Genotyping can be epidemiologically likely based on existing evidence and geographic location and the presence, or lack thereof, of a high-risk genotype can inform the surveillance approach.

Table 6. Prevalence of risk factors for HCC in overall population and in Aboriginal and Torres Strait Islander people.

Risk factor	Prevalence in overall Australian population [source data period]	Prevalence in Aboriginal and Torres Strait Islander people [source data period]
HBV	0.86% [2020] *[132]*	2.0% [2020]*[132]*
HCV	0.78% [2016] *[132]*	3.7% [2016] *[142]*
Smoking	11% [2018–2019] *[143]*	37% [2014–2015] *[136]*
Hazardous alcohol consumption[a]	16.1% [2017–2018] *[133]*	20.0% [2018–2019*[136]*
Overweight/obesity[b]	67.0% [2018–2018] *[134]*	74.2% [2018–2019] *[136]*
Diabetes[c]	4.9% [2017–2018] *[135]*	8.0% [2018–2019] *[136]*

[a] *Proportion of persons who exceeded the lifetime risk guidelines for alcohol consumption defined as consuming more than 2 standard drinks per day where a standard drink contained approximately 10 grams of pure alcohol.*

[b] *Proportion of persons whose body mass index was equal to or greater than 25.00.*

[c] *Based on self-reported data, includes type 1 and type 2 diabetes, and type unknown.*

HCC Surveillance

In conjunction with strategies to control infections with HBV or hepatitis C virus, HCC surveillance is an important intervention for improving liver cancer outcomes in high-risk populations like Aboriginal and Torres Strait Islander people. Researchers have called for improved access to HCC surveillance services for this population *[20][128][144]*.

The Gastroenterological Society of Australia 2020 consensus statement *[20]* recommended that *HCC surveillance should be performed in Aboriginal and Torres Strait Islander people older than 50 years with chronic hepatitis B, in the absence of cirrhosis, as well as in all people with cirrhosis.*

Recommendations

Weak recommendation

4.1 Evidence-based recommendation

In Aboriginal and Torres Strait Islander people with chronic HBV infection, consider offering 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) if age ≥ 50 years (Carter et al *[24]*).

Practical info

Evidence Statement

One cost-effectiveness study estimated that for Aboriginal and Torres Strait Islander people with cirrhosis, surveillance and risk-based surveillance with 6-monthly ultrasound were cost-effective when compared to usual care *[24]*.

Evidence to decision

Benefits and harms

The provision of 6-monthly HCC surveillance to Aboriginal and Torres Strait Islander people (especially those living in remote regions) could improve outcomes.

Certainty of the Evidence

The certainty of the evidence was rated low to very low, based on the GRADE assessment.

Values and preferences

Culturally respectful HCC surveillance for Aboriginal and Torres Strait Islanders should be provided, through demonstrating an understanding, consideration and respectful accommodation of an individual's cultural, linguistic, religious, sexual and racial/ethnic characteristics to ensure that all are welcome, safe and protected.

Clinical question/ PICO

Population: Aboriginal and Torres Strait Islander peoples
Intervention: HCC surveillance programs
Comparator: No surveillance; Usual or standard care

Summary

Evidence summary

A systematic review of intervention studies was undertaken to compare outcomes for HCC surveillance programs versus no surveillance or usual care in Aboriginal and Torres Strait Islander people. The search strategy, inclusion and exclusion criteria, and assessment of the certainty of evidence are described in detail in the technical report (Appendix D3).

One relevant study was identified *[24]*, providing evidence of low to very low certainty based on the GRADE assessment. This Australian cost-effectiveness study *[24]* developed a Markov cohort model to

evaluate several HCC surveillance scenarios for people with cirrhosis. Compared with no formal surveillance, both HCC surveillance in people selected on the basis of a biomarker test, and HCC surveillance in all people with cirrhosis were cost-effective *[24]*. This finding was strengthened in the subgroup of Aboriginal and Torres Strait Islander people, where cost-effectiveness of HCC surveillance increased as relative risk of HCC increased *[24]*.

Preliminary data from an unpublished study investigating the implementation of two surveillance and management interventions in the Northern Territory indicate improvements in HCC outcomes among Aboriginal and Torres Strait Islander people *[145]*. The first intervention was a program of early on-Country surveillance and diagnosis, delivered systematically with a core clinical care group including Aboriginal Health Practitioners *[147][148][149]*. The second was implementation of a model of interstate multidisciplinary team meetings enabling a greater range of treatments for HCC to be offered *[145]*.

The study observed an increase of treatment uptake among Aboriginal and Torres Strait Islander participants, including:

- a trend towards an increase in the uptake of treatment with curative intent
- a significant increase in uptake of transarterial chemoembolisation treatment
- a reduction in the proportion of people who received only palliative and supportive care measures but no active treatment for HCC.

The results suggest that rates of HCC diagnosis and access to a range of treatment options for Aboriginal and Torres Strait Islander people (especially those living in remote regions) would be improved by 6-monthly surveillance as per the recommendations for people with cirrhosis, HBV or non-cirrhotic liver disease.

Outcome Timeframe	**Study results and measurements**	**Comparator** No surveillance; Usual or standard care	**Intervention** HCC surveillance programs	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Cost effectiveness [1]	Based on data from participants in 1 studies.	**Surveillance** AU$21,874 per QALY gained*^ Surveillance cost effective using a willingness to pay threshold AU$50,000 per QALY gained **Risk-stratified surveillance** AU$34,665 per QALY gained*^ Risk stratified surveillance cost effective using a willingness to pay threshold of AU$50,000 per QALY gained ***Anticipated absolute effect (95% CI):*** Not applicable **If Aboriginal and Torres Strait Islander peoples have relative risk*		Low Very serious concerns regarding risk of bias [2]	For Aboriginal and Torres Strait Islander peoples with cirrhosis, we are uncertain whether HCC surveillance programs are cost-effective

Outcome Timeframe	**Study results and measurements**	**Comparator** No surveillance; Usual or standard care	**Intervention** HCC surveillance programs	**Certainty of the Evidence** (Quality of evidence)	**Summary**
		of 1.2 of presenting with advanced-stage HCC when compared with the general Australian population not undergoing formal screening – the cost effectiveness ratio decreases with increasing risk of presenting with advanced-stage HCC *^ Costs for surveillance include AFP testing* *QALY = quality-adjusted life year; AFP = alpha-fetoprotein*			

1. .
2. **Risk of Bias: very serious.** Credibility of model: the structural assumptions and the validation methods of the model not properly reported. Certainty of evidence for each model input: Authors do not critically appraise sources of data underpinning effect of surveillance. **Indirectness: no serious.** Does not report sex, % aetiologies or treated for viral hepatitis for population of interest although not a serious concern for indirectness.

Weak recommendation

New

4.2 Evidence-based recommendation

In Aboriginal and Torres Strait Islander people with chronic HBV infection, consider offering 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) if there is a family history of HCC[1] or if age ≥ 40 with a high-risk HBV genotype[2] individually confirmed (e.g.C4) or epidemiologically likely (Carter et al *[24]*).

For Aboriginal and Torres Strait Islander people without chronic HBV infection, follow recommendations in these guidelines based on their aetiology.

[1]*Family history of HCC is defined as one or more first degree relatives with HCC. Consider offering surveillance 10 years prior to earliest case in a family.*

[2]*It is noted that genotype testing is not routinely offered and not subsidised through the Medicare Benefits Schedule.*

Practical info

Evidence Statement

One cost-effectiveness study estimated that for Aboriginal and Torres Strait Islander people with cirrhosis, surveillance and risk-based surveillance with 6-monthly ultrasound were cost-effective when compared to usual care *[24]*.

Evidence to decision

Benefits and harms

The provision of 6-monthly HCC surveillance to Aboriginal and Torres Strait Islander people (especially those living in remote regions) could improve outcomes.

Certainty of the Evidence

The certainty of the evidence was rated low to very low, based on the GRADE assessment.

Values and preferences

Culturally respectful HCC surveillance for Aboriginal and Torres Strait Islanders should be provided, through demonstrating an understanding, consideration and respectful accommodation of an individual's cultural, linguistic, religious, sexual and racial/ethnic characteristics to ensure that all are welcome, safe and protected.

Clinical question/ PICO

Population: Aboriginal and Torres Strait Islander peoples
Intervention: HCC surveillance programs
Comparator: No surveillance; Usual or standard care

Summary

Evidence summary

A systematic review of intervention studies was undertaken to compare outcomes for HCC surveillance programs versus no surveillance or usual care in Aboriginal and Torres Strait Islander people. The search strategy, inclusion and exclusion criteria, and assessment of the certainty of evidence are described in detail in the technical report (Appendix D3).

One relevant study was identified *[24]*, providing evidence of low to very low certainty based on the GRADE assessment. This Australian cost-effectiveness study *[24]* developed a Markov cohort model to evaluate several HCC surveillance scenarios for people with cirrhosis. Compared with no formal surveillance, both HCC surveillance in people selected on the basis of a biomarker test, and HCC surveillance in all people with cirrhosis were cost-effective *[24]*. This finding was strengthened in the subgroup of Aboriginal and Torres Strait Islander people, where cost-effectiveness of HCC surveillance increased as relative risk of HCC increased *[24]*.

Preliminary data from an unpublished study investigating the implementation of two surveillance and management interventions in the Northern Territory indicate improvements in HCC outcomes among Aboriginal and Torres Strait Islander people *[145]*. The first intervention was a program of early on-Country surveillance and diagnosis, delivered systematically with a core clinical care group including Aboriginal Health Practitioners *[147][148][149]*. The second was implementation of a model of interstate multidisciplinary team meetings enabling a greater range of treatments for HCC to be offered *[145]*.

The study observed an increase of treatment uptake among Aboriginal and Torres Strait Islander participants, including:

- a trend towards an increase in the uptake of treatment with curative intent
- a significant increase in uptake of transarterial chemoembolisation treatment
- a reduction in the proportion of people who received only palliative and supportive care measures but no active treatment for HCC.

The results suggest that rates of HCC diagnosis and access to a range of treatment options for Aboriginal and Torres Strait Islander people (especially those living in remote regions) would be improved by 6-monthly surveillance as per the recommendations for people with cirrhosis, HBV or non-cirrhotic liver disease.

Outcome Timeframe	**Study results and measurements**	**Comparator** No surveillance; Usual or standard care	**Intervention** HCC surveillance programs	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Cost effectiveness [1]	Based on data from participants in 1 studies.	**Surveillance** AU$21,874 per QALY gained*^ Surveillance cost effective using a willingness to pay threshold AU$50,000 per QALY gained **Risk-stratified surveillance** AU$34,665 per QALY gained*^ Risk stratified surveillance cost effective using a willingness to pay threshold of AU$50,000 per QALY gained ***Anticipated absolute effect (95% CI):*** Not applicable **If Aboriginal and Torres Strait Islander peoples have relative risk of 1.2 of presenting with advanced-stage HCC when compared with the general Australian population not undergoing formal screening – the cost effectiveness ratio decreases with increasing risk of presenting with advanced-stage HCC* *^ Costs for surveillance include AFP testing* *QALY = quality-adjusted life year; AFP = alpha-fetoprotein*		Low Very serious concerns regarding risk of bias [2]	For Aboriginal and Torres Strait Islander peoples with cirrhosis, we are uncertain whether HCC surveillance programs are cost-effective

1. .
2. **Risk of Bias: very serious.** Credibility of model: the structural assumptions and the validation methods of the model not properly reported. Certainty of evidence for each model input: Authors do not

critically appraise sources of data underpinning effect of surveillance. **Indirectness: no serious.** Does not report sex, % aetiologies or treated for viral hepatitis for population of interest although not a serious concern for indirectness.

Practice Points

Good practice statement

4.3 Practice point

Local access to culturally safe, preventive care, surveillance and treatment should be provided for Aboriginal and Torres Strait Islander people through primary care within communities and on-Country where possible.

Rationale

This advice is based on limited empirical evidence but supported by expert advice. Cultural commitments, distance, time, uncertainty, and systemic racism may prevent patients travelling to major tertiary care centres. People may be more likely to undergo recommended ultrasound assessments if these are available at their community-controlled health centre or local clinic. Aboriginal and Torres Strait Islander health workers and health practitioners play a vital role in facilitating culturally safe care. Providing them with adequate educational resources that are co-designed with Aboriginal and Torres Strait Islander people, plus equipment, financial, and human resources, is a priority to support these recommendations.

Culturally respectful care involves offering the involvement of Aboriginal and Torres Strait Islander health workers or interpreters in consultations. Delivering education in a patient's first language, or in simple English with minimal use of medical jargon. Being mindful of kinship when having these discussions and being aware some health topics can only be delivered female to female and male to male. Involving significant family members in decision making processes if required.

Good practice statement

New

4.4 Practice point

Health professionals and health system decision-makers must enable evidence-based recommended treatments for HCC to be offered to Aboriginal and Torres Strait Islander people in an equitable way. Aboriginal and Torres Strait Islander leadership in these decisions is crucial. Current evidence suggests that, when offered early, HCC treatment is accepted and effective irrespective of geographical location.

Rationale

This advice is based on limited empirical evidence but supported by expert advice. Cultural commitments, distance, time, uncertainty, and systemic racism may prevent patients travelling to major tertiary care centres. People may be more likely to undergo recommended ultrasound assessments if these are available at their community-controlled health centre or local clinic. Aboriginal and Torres Strait Islander health workers and health practitioners play a vital role in facilitating culturally safe care. Providing them with adequate educational resources that are co-designed with Aboriginal and Torres Strait Islander people, plus equipment, financial, and human resources, is a priority to support these recommendations.

Culturally respectful care involves offering the involvement of Aboriginal and Torres Strait Islander health

workers or interpreters in consultations. Delivering education in a patient's first language, or in simple English with minimal use of medical jargon. Being mindful of kinship when having these discussions and being aware some health topics can only be delivered female to female and male to male. Involving significant family members in decision making processes if required.

Limitations

The systematic review sought to identify evidence on the impact of HCC surveillance in Aboriginal and Torres Strait Islander people, regardless of aetiology. Few studies have evaluated the clinical, epidemiological, social, or economic impact of HCC surveillance in Aboriginal and Torres Strait Islander people. Recommendations were formulated based on the limited available evidence alongside existing guidelines and expert advice. Purpose-designed studies are needed to fill the evidence gaps for Aboriginal and Torres Strait Islander people, especially for those with non-HBV aetiologies.

Resource and other considerations

Resource considerations

Notably, recommendations in these guidelines include the consideration of a high-risk genotype in Aboriginal and Torres Strait Islander populations. It is noted that genotype testing is not routinely offered, widely available nor currently subsidised through MBS. Routine genotyping is not part of standard practice and may not be universally appropriate across Australia. However, it is an important factor to consider. Genotyping can be epidemiologically likely based on existing evidence and geographic location and could indicate the need for HCC surveillance. There is ongoing work exploring the geographical reach of this sub-genotype across northern Australia and supports the role of genotype in the risk assessment needed for HCC surveillance decisions in Aboriginal and Torres Strait Islander people without cirrhosis. The evolving evidence on HCC risk based on the HBV C4 sub-genotype in people living with chronic HBV infection who do not have cirrhosis may inform future risk assessment tools that can be used. Future risk assessment may also include consideration of family history of HCC *[140]*.

Future evidence considerations

Further evidence is needed on Aboriginal and Torres Strait Islander populations and this must be co-designed with Aboriginal and Torres Strait Islander people and conducted in an ethical and culturally safe manner.
Evidence is needed to support the design and delivery of HCC surveillance among Aboriginal and Torres Strait Islander people including:

- analysis of barriers to screening for advanced liver disease, HCC surveillance, and subsequent treatment
- assessment of the effectiveness of early detection of cirrhosis (therefore entry into HCC surveillance programs) for Aboriginal and Torres Strait Islander people with MAFLD
- evaluation of strategies for increasing participation in HCC surveillance programs
- further evaluation of on-Country delivery models such as the 'one stop liver shop' *[149]* and the mobile liver clinic approaches delivered in several Australian states and territories *[150]*
- development of co-designed and culturally safe educational resources to support HCC surveillance and treatment, translated into Aboriginal languages for patients
- development and evaluation of early surveillance tests that are easier to conduct in a remote setting, such as urine metabolomics, therefore enabling prioritisation of patients requiring further investigations at a tertiary centre.

Research currently underway includes:

- the Partnership Approach to Sustainably eliminating chronic hepatitis B in the Northern Territory (Hep B PAST) project, with the objective of eliminating chronic hepatitis B among Aboriginal and Torres Strait Islander people in the Northern Territory *[151]*. This project uses a holistic hub and spoke model of care grounded in primary care. Systematic data-driven continuous quality improvement approaches alongside Aboriginal Health Practitioners are at the centre of this care delivery, and preliminary results from the model show significant improvements in the cascade of care for chronic HBV infection in this setting *[132][148]*
- the Prevention of Liver Fibrosis and Cancer Australia study in the Northern Territory (PROLIFICA NT *[152]*)
- Characterising HBV in northern Australia through molecular epidemiology (the CHARM study) *[140]*
- HCC in the Northern Territory pre- and post-implementation of on-Country care and a multidisciplinary management meeting *[221]*.

5. HCC surveillance in people of Asian or Pacific background

Background

People born in Asian or Pacific countries where chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection is endemic are considered to be at increased risk of liver cancer. There is high incidence of liver cancer in some Asian countries, particularly in East and South-East Asia *[32]*.

Note: Country of birth was used in the systematic review as a proxy for identifying people living in Australia who may be at higher risk of HCC due to known geographical differences in chronic HBV/HCV infection prevalence. However, risk factors may vary between Australian populations that are distinguished by ethnocultural features other than simply country of birth. In addition, a person may belong to more than one ethnocultural group.

In this section, Asian-born and Pacific-born status as well as people with an Asian or Pacific background are surrogate measures of ethnicity that may affect risk. The practice points may reasonably be applied to selected individuals born in Australia who belong to one of these ethnocultural groups, according to clinical judgement.

Regional liver cancer and viral hepatitis rates

Among World Health Organization (WHO) regions, in 2020 the Western Pacific Region showed the highest age-standardised liver cancer incidence (17.5 per 100.000 population) and mortality (15.9 per 100.000 population) *[153]*. This region includes China, Mongolia, Japan, Vietnam, Laos, Cambodia, Singapore, The Philippines, Malaysia, Papua New Guinea, and the Pacific Islands (as well as Australia and New Zealand). Liver cancer incidence and mortality rates are 4.9 per 100,000 population and 4.8 per 100,000 population, respectively, in the WHO South-East Asian Region (Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, Timor-Leste) *[153]*. Over 100 million people were living with chronic HBV infection in 2016 and over 12 million people were living with chronic HCV infection in 2020 in the Western Pacific Region. Approximately 68 million people were living with chronic HBV infection in 2016 and 9.5 million people were living with chronic HCV infection in 2020 in the South-East Asian Region *[154]*.

Global analyses of data published up to 2014 have reported that chronic HBV infection accounts for 69% (95% confidence interval [CI] 63–74%) of hepatocellular carcinoma (HCC) cases in Eastern Asia, while chronic HCV infection accounts for 11% of cases (95% CI 9–14%) *[155]*. The true burden of HCC may be underestimated due to the limited availability of accurate data from countries that do not have central cancer registries *[32]*.

In 2021, there were an estimated 3,832,890 Australian residents born in Asian or Pacific countries, representing approximately 15% of the total population *[156]*. People born in Asia or the Pacific comprise nearly one-third (32%) of all chronic HBV infection cases in Australia, with higher HBV prevalence among people born in Asia or the Pacific region excluding Australia, compared with those born in Australia (Table 7) *[132]*. There are no representative data available from which to estimate the prevalence of HCV infection by country of origin in Australia *[132]*.

Table 7. Prevalence of HBV in 2020 in Asian and Pacific-born Australian residents

Population	HBV prevalence
Overall Australian population	0.86%
Born in North-East Asia	6.2%
Born in South-East Asia	4.8%
Born in Oceania (excluding Australia and New Zealand)	3%

Data from the Viral Hepatitis Mapping Project national Report 2020 [132]

A study of Australian national incidence data for liver cancer from 2005 to 2014 reported a higher incidence among those born in Asia or Pacific regions compared with people born in Australia: incidence rate ratio (IRR) ranged from 1.06 to 3.38 *[26]*. The incidence among Vietnamese-born people was more than 5-fold higher than among Australian-born people: IRR 5.44 (95% CI 4.77–6.21) *[26]*. These results support findings from a NSW linkage study analysing 2000–2014 data from people with HBV and HCV infection, which found that the risk of HCC was 3.4 times higher in those born in Asia, and 4.3 times higher in those born in the Pacific region (excluding Australia), than in those born in Australia *[27]*.

Analysis of NSW cancer data showed that the age-standardised mortality rate due to liver cancer per 100,000 among NSW residents from 2004 to 2008 was 7.4 (95% CI 6.1–8.9) in those born in South-East Asia, 6.9 (95% CI 4.1–10.9) in those born in high-income Asia-Pacific countries, 6.4 (95% CI 4.0–9.6) in those born in Oceania, and 6.4 (95% CI 5.1–7.9) in those born in East Asia *[157]*.

In several other high-income countries including Canada, the UK, Sweden, France, and the Netherlands, higher liver cancer incidence and mortality rates have been reported in migrants from Asia and the Pacific region *[158][159]*. A US study of veterans with chronic hepatitis B found that those born in the Asia-Pacific region had a higher HCC incidence than Caucasian and African American participants *[160]*.

A recent nation-wide study in Sweden calculated the HCC incidence in people with non-cirrhotic chronic hepatitis B. It found that Asian-born males had an incidence rate of 0.6 (0.3–1.1) per 100 person–years, exceeding the 0.2% annual incidence threshold for recommended HCC surveillance *[161]*. The incidence of HCC was comparatively rare in Asian-born females with non-cirrhotic chronic HBV infection, only exceeding the 0.2% threshold in females aged over 60 years *[161]*. A recent cohort study of people with HBV in the USA and Spain found that there was no difference between Asian and non-Asian subgroups in rates of 5 year survival (47.5% versus 51.9%, p=0.47) or 10-year survival (31.8% versus 38.2%, p=0.27) *[162]*. The authors suggested this could be attributed to improved HBV awareness and disease monitoring *[162]*.

In Australia, a 2008 study found no significant association between survival rates in people with HBV-related HCC or HCV-related HCC and their region of birth *[163]*. However, another Australian analysis of HCC cases during 1982–2014 indicated that Asian-born Australians with HCC had a median survival of 13.0 months (95% CI 11.3–14.7), which was higher when compared with European-born people (6.2 months, 95% CI 5.6–6.7) and those born in Oceania (5.0 months, 95% CI 4.8–5.3) *[33]*. Another study in NSW also reported 32% lower risk of death among people with HCV-related HCC born in Asia-Pacific countries, compared with those born in Australia (adjusted hazard ratio 0.7, 95% CI 0.5–0.8) *[164]*.

Projected effect of HBV vaccination

The WHO target of universal HBV vaccination will support reduction in the rate of new HBV infections and associated HCC *[165]*. During the period 2005–2017, rates of HBV vaccination coverage increased in WHO Western Pacific Region countries from 63% to 85% for birth dose and from 76% to 93% for third dose, cutting HBV infection prevalence to less than 1% of children, down from 8% *[166]*.

Given the relatively long latency period of development of HCC, and the fact that vaccine programs in many countries only commenced in the 1990s, it will take time for vaccine coverage to affect rates of HBV-related HCC *[165]*. A decreasing trend in HCC rate has been reported in countries like Taiwan, where high-coverage universal HBV vaccination started in 1984 *[167][168][169]*. Australian projections suggest that HBV vaccination programs will have limited impact on HBV-related HCC through to 2025 *[163]*. Data on vaccination rates by country of birth are not available in Australia. Although catch-up vaccination provided after arrival in Australia will reduce new infections, migrants to Australia may have undiagnosed chronic HBV/HCV infection, putting them at higher risk of liver disease and cancer.

Other aetiologies

While chronic HBV infection is still the leading cause of HCC in the Asia-Pacific region and among Australian residents born in this region, the prevalence of metabolic dysfunction-associated fatty liver disease (MALFD) is

thought to have increased in the region. For example, the overall prevalence of metabolic syndrome in Malaysia is 27.5% *[170]*.

HCC Surveillance

In conjunction with strategies to control HBV/HCV infection, HCC surveillance is an important intervention for improving liver cancer outcomes in high-risk populations, such as Asian and Pacific immigrant populations and those with an Asian and Pacific background. Researchers have called for improved access to HCC surveillance services for this population *[20][171]*.

The Gastroenterological Society of Australia's 2020 consensus statement *[20]* recommended HCC surveillance for all people with cirrhosis and for those with non-cirrhotic chronic hepatitis B at increased risk of HCC. This statement included consideration of HCC surveillance in people born in Asian countries as a population at increased risk of HCC and recommended that *HCC surveillance should be performed in Asian males older than 40 years and Asian females older than 50 years diagnosed with chronic hepatitis B*. Similar recommendations were made in the Asia–Pacific clinical practice guidelines on the management of HCC in 2017 *[17]*.

Recommendations

Weak recommendation

New

5.1 Evidence-based recommendation

In people of Asian or Pacific background with chronic HBV infection, consider offering 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) to:

- males ≥ 40 years of age
- females ≥ 50 years of age

For people of Asian or Pacific background without chronic HBV infection, follow recommendations in these guidelines based on their aetiology (Robotin et al 2009 *[25]*; Yu et al 2022 *[26]*; Waziry et al 2016 *[27]*)

Practical info

Evidence Statement

No studies were identified that evaluated the effects of HCC surveillance on liver cancer outcomes specifically in Pacific-born people living in Australia.

One early modelling study estimated that for Asian born people with chronic HBV living in Australia, risk-stratified HCC surveillance may lead to a slight decrease in the rate of liver-related mortality with a gain of 0.014 quality-adjusted life years (QALY) per person when compared with usual care *[25]*.

Given the absence of evidence to support a recommendation for or against HCC surveillance in Asian and Pacific-born people living in Australia, this guidance is based on available evidence demonstrating a high prevalence of HCC among Asian-born and Pacific-born people in Australia *[26][27]*.

Evidence to decision

Benefits and harms

HCC surveillance in Asian and Pacific-born people living in Australia is intended to provide more vigorous surveillance for people at high-risk of HCC based on their country of birth. Use of risk-stratified HCC

surveillance may lead to a slight decrease in the rate of liver-related mortality with a gain of 0.014 quality-adjusted life years (QALY) (Robotin et al. 2009 *[25]*).

Certainty of the Evidence

The certainty of the evidence was rated low to very low, based on the GRADE assessment.

Values and preferences

Culturally safe and sensitive HCC surveillance should be provided to Asian-born and Pacific-born people in Australia, through demonstrating an understanding, consideration and respectful accommodation of an individual's cultural, linguistic, religious, sexual and racial/ethnic characteristics to ensure that all are welcome, safe and protected.

Clinical question/ PICO

Population: Asian or Pacific-born people in Australia
Intervention: HCC surveillance programs
Comparator: No surveillance; Usual or standard care

Summary

A systematic review of intervention studies was undertaken to identify studies reporting outcomes of HCC surveillance in people living in Australia who were born in Asian or other Pacific countries. The search strategy, inclusion and exclusion criteria, and assessment of the certainty of evidence are described in detail in the technical report (Appendix D4).

Evidence Summary

One early modelling study estimated that for Asian born people with chronic HBV living in Australia, risk-stratified HCC surveillance may lead to a slight decrease in the rate of liver-related mortality with a gain of 0.014 quality-adjusted life years (QALY) per person when compared with usual care *[25]*.

Two cohort studies reported outcomes of HCC surveillance in Australian patient populations that included substantial proportions of Asian-born people *[92][172]*.

In a 12-month prospective cohort study conducted in Melbourne in 2012–2013, 22% of 272 individuals diagnosed with incident HCC during the study were of Asian ethnicity (mainly East and South-East Asia) *[92]*. The investigators reported that HCC surveillance based on 6-monthly ultrasound, with or without alpha-fetoprotein (AFP), was associated with a 40% reduction in the risk of death (adjusted HR: 0.60, 95% CI 0.38–0.93) *[92]*. Data were not analysed separately according to ethnicity.

In a retrospective cohort of 151 patients with HCC admitted to two hospitals in Sydney (1993–2003), 41% were Asian born. Among the full cohort, small tumour size (one <5 cm or three <3 cm) at diagnosis was observed in a larger proportion of those diagnosed through HCC surveillance (44%) than those diagnosed through incidental finding or symptomatic presentation (20%) *[172]*. In this study, HCC surveillance included ultrasound with or without AFP assessments, but no details about the frequency of assessments were provided.

Another Australian study *[25]* modelled the impact of different management strategies for chronic HBV infection in Asian-born adults aged 35 years and over. Participants were stratified according to age, HBV DNA level and ALT level:

- Group 1 included people with low HBV DNA (i.e. <2000 IU/ml if age ≥50 years, or <20,000 IU/mL if age <50 years)
- Group 2 included people with high HBV DNA (i.e. ≥2000 IU/mL if age ≥50 years, or ≥20,000 IU/ml if age<50 years) and normal ALT
- Group 3 included people with both high HBV DNA and high ALT.

Interventions evaluated included HBV monitoring in group 1, HBV monitoring and HCC surveillance (i.e. 6-monthly ultrasound and AFP) in group 2 (enhanced HCC surveillance), and HCC surveillance and HBV treatment in group 3 (HCC prevention) *[25]*. The investigators used a Markov model to compare these two surveillance strategies with 'current practice' which included limited HBV treatment and HCC surveillance based on existing low uptake.

The model showed that risk-stratified HCC surveillance may lead to a slight decrease in the rate of liver-related mortality compared with usual care (cumulative rate of 33.6 versus 33.8 per 100 participants), with a gain of 0.014 quality-adjusted life years (QALY) per person *[25]*. The findings demonstrated AU$401,516 per QALY gained using enhanced HCC surveillance strategy and AU$12,956 per QALY gained using HCC prevention strategy. The investigators recommended HCC prevention as a cost-effective strategy.

Outcome Timeframe	**Study results and measurements**	**Comparator** No surveillance; Usual or standard care	**Intervention** HCC surveillance programs	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Liver disease-related mortality	Based on data from 10,000 participants in 1 studies.	**Relative effect (95% CI):** Not calculable* **Modelled rates** **Metric:** Cumulative per 100 patients **Usual Care:** 33.8 **Risk-stratified surveillance:** 33.6 *For the modelled outcome of liver disease-related mortality risk ratios and 95% confidence intervals were not calculated as the confidence intervals will be much narrower than those of real (non-modelled) outcome because of the modelling process which is designed to produce "stable" outcomes		Very low Very serious concerns regarding the risk of bias [1]	For Asian born people in Australia with HBV we are uncertain whether HCC surveillance programs improve or worsen liver disease-related mortality
QALYs gained [2]	Based on data from 10,000 participants in 1 studies.	**Relative effect:** 0.014 QALY gained per person *QALY = quality-adjusted life years*		Very low Very serious concerns regarding the risk of bias [3]	For Asian born people in Australia with HBV we are uncertain whether HCC surveillance programs result in a gain in QALYs

Outcome Timeframe	**Study results and measurements**	**Comparator** No surveillance; Usual or standard care	**Intervention** HCC surveillance programs	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Cost-effectiveness	Based on data from 10,000 participants in 1 studies.	AU$401,516 per QALY gained **Anticipated absolute effect (95% CI):** Not applicable *QALY = quality-adjusted life years*		Very low Very serious concerns regarding the risk of bias [4]	For Asian born people in Australia with HBV we are uncertain whether HCC surveillance programs are or are not cost-effective

1. **Risk of Bias: very serious.** Certainty of evidence for each model input: Authors do not critically appraise sources of data underpinning effect of surveillance. Authors do not include relevant costs of transplantation, chemotherapy, SIRT/TARE, palliative care or HCC follow-up. **Indirectness: no serious.** Although does not report AFP threshold, this is not a serious concern.
2. QALY = Quality adjusted life years
3. **Risk of Bias: very serious.** Certainty of evidence for each model input: Authors do not critically appraise sources of data underpinning effect of surveillance. Authors do not include relevant costs of transplantation, chemotherapy, SIRT/TARE, palliative care or HCC follow-up. **Indirectness: no serious.** Although does not report AFP threshold, this is not a serious concern.
4. **Risk of Bias: very serious.** Certainty of evidence for each model input: Authors do not critically appraise sources of data underpinning effect of surveillance. Authors do not include relevant costs of transplantation, chemotherapy, SIRT/TARE, palliative care or HCC follow-up. **Indirectness: no serious.** Although does not report AFP threshold, this is not a serious concern.

Limitations

The systematic review sought to identify evidence on the impact of HCC surveillance in Asian-born and Pacific-born people in Australia, regardless of aetiology. Few studies have evaluated the clinical, epidemiological, social, or economic impact of HCC surveillance in Asian-born and Pacific-born people in Australia. Recommendations were formulated based on the limited available evidence alongside existing guidelines and expert advice. Purpose-designed studies are needed to fill the evidence gaps for Asian-born and Pacific-born people in Australia, especially for those with non-HBV aetiologies.

A key study for Asian-born and Pacific-born people in Australia (Robotin et al 2009) has limitations of note in its application to current practice. The study was conducted in 2009 making several study assumptions no longer applicable *[25]*. For example, routine pre-treatment liver biopsy is no longer recommended and newer HBV antiviral treatments with improved viral suppression and higher barriers to resistance, such as entecavir and tenofovir, are now available. Additionally, the eligibility criteria for HBV treatment have changed and factors other than HBV DNA and ALT levels are now considered for treatment decision-making, including HBV e-antigen (HBeAg) status and liver fibrosis *[23]*. Finally, raised serum AFP is not specific for progressive liver disease.

Other considerations

Future evidence considerations

Current ongoing projects in Australia aim to explore the state of HCC surveillance in a culturally and linguistically diverse population including adherence and barriers in people who meet criteria for HCC surveillance. Other aspects to be investigated include outcomes of people undergoing HCC surveillance, including HCC detection and surveillance related harm. Novel models and strategies to improve HCC surveillance are also under evaluation that will also be applicable to Asian-born and Pacific-born people in Australia.

6. HCC surveillance in people of sub-Saharan African background

Background

Note: Country of birth was used in the systematic review as a proxy for identifying people living in Australia who may be at higher risk of hepatocellular carcinoma (HCC) due to known geographical differences in the prevalence of chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection. However, risk factors may vary between Australian populations that are distinguished by ethnocultural features other than simply country of birth. In addition, a person may belong to more than one ethnocultural group.

In this section, sub-Saharan African-born status is a surrogate measure of ethnicity that may affect risk. The practice points may reasonably be applied to selected individuals born in Australia who belong to one of these ethnocultural groups, according to clinical judgement.

Hepatitis and HCC rates in sub-Saharan Africa

HBV infection is endemic in sub-Saharan Africa and there is very limited access to testing and treatment in some regions *[173]*. HCC is the second leading cause of cancer-related deaths among males and the fourth among females in sub-Saharan Africa, though data are not available from all countries in the region, which may result in underreporting of other cancer types *[174]*. HCC in sub-Saharan Africa occurs among younger people than in other regions *[175][176]*.

The World Health Organization (WHO)'s International Agency for Research on Cancer estimates that the age-standardised incidence of liver cancer in sub-Saharan Africa is 6.3 per 100,000, compared with the global average of 9.5, based on 2020 data *[177]*. However, HCC rates for the region may underestimate the true burden of HCC due to the lack of accurate cancer registry data in some sub-Saharan African countries *[174]*.

Recent global analyses have shown that chronic HBV infection accounts for 50% (95% confidence interval [CI] 39–60%) of HCC cases in sub-Saharan Africa, while chronic HCV infection accounts for 21% of cases (95% CI 13–32%) *[155]*.

Sub-Saharan African-born people living in Australia

In 2021 there were an estimated 412,680 sub-Saharan African-born residents living in Australia, representing 1.6% of the total population *[156]*. Of these, nearly half (49%) were born in South Africa *[156]*. Census data for 2021 showed that, among African migrants to Australia, the most common countries of origin were South Africa (201,930 people), Zimbabwe (45,420 people), Mauritius (29,700 people), Kenya (26,020 people), and Ethiopia (16,660 people) *[156]*.

People born in sub-Saharan Africa comprise 3.4% of all chronic hepatitis B cases in Australia. Approximately 2.4% of Australian residents born in sub-Saharan African are living with chronic HBV infection, compared with the overall national prevalence of 0.86%, based on 2020 data from the National Viral Hepatitis Mapping Project *[60]*. There are no HCV prevalence data available for sub-Saharan African-born people in Australia.

Patterns of liver cancer incidence in Australia from 2005 to 2014 showed no difference among immigrants born in Southern and Eastern Africa compared with the Australia-born population: adjusted incidence rate ratio (IRR) 0.99 (95% CI 0.82–1.20) *[26]*. While this study did not report liver cancer rates by type, HCC is known to account for 80% of primary liver cancers in Australia *[32]*. However, the region of sub-Saharan Africa is highly diverse, and includes over 50 countries with wide variation in the ethnic, cultural and linguistic diversity, migration experiences, and HBV, HCV and HCC risk. Therefore, data for the entire region of sub-Saharan Africa may not be effective in identifying those at risk of HCC. [**Note.** The findings of this study also indicated that other groups of African immigrants may require special consideration for HCC surveillance; those born in North Africa had liver cancer rates more than three times higher than those of the Australian-born population (IRR= 3.32 (95% CI 2.85-3.88)) *[26]*.

There are no data available on the liver cancer mortality or survival rates among Australian residents born in sub-Saharan Africa. However, analysis of unpublished data suggests potentially higher rates and a high proportion of HCC cases attributable to HBV and HCV, for specific countries of birth within this region (Appendix E).

HCC rates among sub-Saharan African-born subgroups in other populations

In other western countries, including the UK, France and Sweden, higher rates of liver cancer incidence and mortality have been reported among migrants from sub-Saharan Africa *[159]*. A recent nation-wide registry study in Sweden found that the incidence rate of HCC among sub-Saharan African-born people with chronic HBV ranged from 0.02 to 0.27 per 100 person–years for males and 0.04 to 0.15 per 100 person–years for females *[161]*.

Other African migrant groups in Australia

A high proportion of African migrants to Australia are from Sudan and South Sudan, which are outside the sub-Saharan African region according to classification used by the Australian Bureau of Statistics. The prevalence of HBV infection has been estimated at approximately 12% in Sudan (with wide variation between regions) and 22% in South Sudan, and unpublished data indicate a higher-than-average HCC risk in those born in these countries.

Other factors affecting HBV-associated HCC risk

Data from other populations suggest that some HBV genotypes carry a higher risk of HCC than others. Genotype C HBV is associated with a higher risk of HCC than other major HBV genotypes *[178][179]*. Subgenotype Aa HBV is the predominant genotype identified in Africa *[179]*. The implications of genotype for risk level and optimal surveillance among HBV-positive Australians born in sub-Saharan Africa are not known.

Coinfection with human immunodeficiency virus (HIV) and chronic HBV or HCV is associated with more rapid progression to liver fibrosis and a higher incidence of HCC than chronic hepatitis alone *[180][181][182]*. In sub-Saharan Africa, the overlap between high HIV and HBV prevalence may increase the incidence of HCC *[181]*. However, the implications for surveillance among sub-Saharan African-born Australian residents with chronic HBV infection are unclear.

Higher viral loads have been associated with greater HCC risk among Asian populations with chronic hepatitis B *[183][184][185]*, but data on viral loads among HBV-positive people in sub-Saharan Africa are limited *[174]*. The implications for HCC surveillance are unclear.

Environmental exposures such as ingestion of aflatoxin and dietary iron overload are contributors to HCC burden and have a strong synergistic effect with HBV, which may disproportionately affect rural sub-Saharan African populations *[186][187]*. Aflatoxin contributes to the risk of HCC in people with HBV from the sub-Saharan African region and West Africa *[188][189]*.

Projected effect of HBV vaccination

The WHO target of universal HBV vaccination will support reduction in the rate of new HBV infections and associated HCC *[165]*. Over the last 40 years there has been a slight decrease in the incidence of HBV-related HCC in Africa, estimated at a percentage change of –0.50% (95% CI –0.74% to –0.25%) per decade in the prevalence of HBV among HCC cases from 1980 to 2014. This reduction has been attributed to childhood HBV immunisation programs that commenced in the 1980s and 1990s *[190]*. Despite this remarkable achievement, in 2020 there was only a 6% coverage of HBV birth-dose vaccination in the African region, compared with global coverage rate of 42% *[191]*.

Due to the relatively long latency period from infection with HBV at childhood to development of HCC, it will take time for HBV vaccine coverage to take effect *[169]*. Australian data on vaccination rates by country of birth are not available. Although catch-up vaccination provided after arrival in Australia will help reduce new infections, migrants to Australia may have undiagnosed chronic HBV and/or HCV infection, putting them at

higher risk of liver disease and cancer.

HCC Surveillance

Existing recommendations for sub-Saharan African-born subgroups

The Gastroenterological Society of Australia *[20]* has recommended HCC surveillance should be performed in sub-Saharan Africans older than 20 years.

Other international guidelines *[18][19]* recognise an increased risk of HCC among those of African ethnicity, but do not provide a specific age-based HCC surveillance recommendation due to lack of robust evidence.

Recommendations

Consensus recommendation

New

6.1 Consensus-based recommendation

In people of sub-Saharan African background with chronic HBV infection, consider offering 6-monthly surveillance for HCC (using ultrasound, with or without alpha-fetoprotein testing) to males and females ≥ 20 years of age.

Family history of HCC should be considered when determining the age at which to commence HCC surveillance[1].

For people of sub-Saharan African background without chronic HBV infection, follow recommendations in these guidelines based on their aetiology.

(Sources: EASL 2018 *[18]*; Marrero et al 2019 *[19]*; GESA 2020 *[20]*).

[1] *Family history of HCC is defined as one or more first degree relatives with HCC. Consider offering surveillance 10 years prior to earliest case in a family.*

Practical info

Evidence Statement

No relevant studies that met inclusion criteria were identified. Existing guidelines based on consensus were used to inform the recommendation.

Evidence to decision

Benefits and harms

In conjunction with strategies to control HBV/HCV infection, HCC surveillance is an important intervention for improving liver cancer outcomes in high-risk populations, such as people of sub-Saharan African background. Researchers have called for improved access to HCC surveillance services for this population *[20][171]*.

Certainty of the Evidence

The certainty of evidence is not applicable given no studies were identified in this systematic review.

Values and preferences

Culturally safe and sensitive HCC surveillance should be provided to Australian residents born in sub-Saharan Africa, through demonstrating an understanding, consideration and respectful accommodation

of an individual's cultural, linguistic, religious, sexual and racial/ethnic characteristics to ensure that all are welcome, safe and protected.

Clinical question/ PICO

Population: sub-Saharan African-born people in Australia
Intervention: HCC surveillance programs
Comparator: No surveillance; Usual or standard care

Summary

A systematic review of intervention studies was undertaken to identify studies reporting outcomes of HCC surveillance in people living in Australia who were born in sub-Saharan Africa. The search strategy, inclusion and exclusion criteria, and assessment of the certainty of evidence are described in detail in the technical report (Appendix D5).

Evidence summary

Given the absence of evidence to support a recommendation for or against HCC surveillance in sub-Saharan African-born people living in Australia, this guidance is based on available clinical experience indicating a higher prevalence of HCC among sub-Saharan African-born people in Australia.

Limitations

The systematic review sought to identify evidence on the impact of HCC surveillance among Australian residents born in sub-Saharan Africa, regardless of aetiology. No studies were identified to have evaluated the clinical, epidemiological, social, or economic impact of HCC surveillance in Australian residents born in sub-Saharan Africa. Recommendations were formulated based on existing guidelines and expert advice. Purpose-designed studies are needed to fill the evidence gaps for Australian residents born in sub-Saharan Africa.

Resource and other considerations

Resource considerations

A recent Australian single-centre hospital-based cohort study with 775 at-risk patients undergoing HCC surveillance identified African ethnicity, and a culturally and linguistically diverse background, as risk factors for not receiving full HCC surveillance according to the recommended strategy (significantly associated with a lower percentage of time up-to-date with HCC surveillance) *[171]*. A retrospective analysis of data from the Victorian Integrated Hepatitis B Service, set up to support chronic hepatitis B care in general practice, documented multiple barriers to adherence to HCC surveillance among a cohort of eligible patients of whom 64% were born in a country in the sub-Saharan African region *[192]*. Other authors have reported that access to chronic hepatitis B services among sub-Saharan African migrants in Australia is limited by competing resettlement priorities, inconsistent information from providers and public health authorities, and other social and cultural barriers *[193][194][195][196]*. These issues have sparked calls to improve access to HCC surveillance services, especially for people from a culturally and linguistically diverse background *[128][171]*.

Future evidence considerations

More evidence is needed on HCC incidence and risk factors among Australian residents born in sub-Saharan Africa, including variation in risk according to age group, HBV prevalence among subgroups, and variation in risk according to country of origin. This includes further research on the determinants of health specific to this priority population. These determinants include behavioural and social determinants, health literacy and willingness to engage in HCC surveillance, disruption of care during migration, and other factors which may modify the risk and/or impact of liver disease and HCC. A key aspect of this would be determining the differences in HCC presentation among this group, including the stage at which HCC is diagnosed and the pathway to diagnosis.

Further studies are also required to understand the potential psychological burden of HCC surveillance among sub-Saharan African-born people, particularly among younger people for whom surveillance may be recommended.

Recommendations for HCC surveillance of Australians born in sub-Saharan Africa should be informed by a better understanding the risks and challenges affecting this group and weighing the potential benefits against costs and potential harms. Additional analysis could extend these recommendations to people born in Northern Africa, including people born in countries with a high prevalence of chronic HCV infection, such as Egypt.

7. HCC surveillance in Australia: Use of alpha-fetoprotein testing and HCC surveillance cost-effectiveness

Background

Alpha-fetoprotein testing in combination with ultrasound in HCC surveillance among patients with chronic liver disease

Alpha-fetoprotein

The use of alpha-fetoprotein testing (AFP) in surveillance has been limited due to its low sensitivity (especially for detecting small hepatocellular cancers (HCCs)) and suboptimal specificity *[20][82][83]*; AFP elevation can also be due to chronic viral hepatitis in people without HCC and/or the presence of other cancer types *[82][84]*. However, antiviral therapy is now known to reduce AFP baseline levels, which may improve the diagnostic accuracy of AFP in patients with chronic hepatitis B *[82]*. In HCC surveillance, the added benefit of AFP to ultrasound, compared with ultrasound alone, remains unclear *[83][85]*. Some meta-analyses have reported no statistically significant improvement in the sensitivity of surveillance to detect early-stage HCC when AFP was added to 6-monthly ultrasound *[2][197]*.

The AFP test is subsidised through the Medicare Benefits Schedule (MBS) item 66650 for the detection or monitoring of hepatic tumours *[198]*.

Other AFP-based tests

The GALAD score is a serum biomarker-based model using sex ('gender' in the acronym), age, alpha-fetoprotein L3% (AFP-L3), AFP, and des-gamma-carboxy prothrombin (DCP) to predict the probability of HCC in patients with chronic liver disease (cirrhosis or chronic hepatitis B). It has been reported to increase early detection of HCC compared with ultrasound alone *[199]*. GALAD score is rarely used in Australia and is not subsidised by MBS. Globally, it is not as widely used as ultrasound plus AFP.

Existing guidelines and surveillance programs

The 2020 Gastroenterological Society of Australia consensus statement on the management of HCC advises that clinicians planning surveillance can consider combining AFP testing with ultrasound every 4–8 months *[20]*.

Recommendations

Weak recommendation

New

7.1 Evidence-based recommendation

In people for whom HCC surveillance is recommended, consider offering 6-monthly alpha-fetoprotein testing in addition to ultrasound (Andersson et al 2008 *[28]*; Thompson Coon et al 2008 *[29]*; Sangmala et al 2014 *[30]*; Parikh et al 2020 *[31]*).

Practical info

Evidence Statement

A modelling study based on US data found that, among people with compensated cirrhosis who develop HCC, the proportion of those diagnosed at an early stage was likely to be higher using a surveillance strategy based on AFP and ultrasound than with ultrasound alone *[31]*.

For individuals with cirrhosis, three cost-effectiveness modelling studies reported conflicting findings on the cost-effectiveness of surveillance using AFP and ultrasound when compared with surveillance using ultrasound only *[28][29][31]*.

For individuals with chronic HBV in Thailand, a single cost-effectiveness modelling study estimated that surveillance with AFP and ultrasound was cost effective when compared with ultrasound only *[30]*.

Evidence to decision

Benefits and harms

In HCC surveillance, the added benefit of AFP to ultrasound, compared with ultrasound alone, remains unclear. The use of AFP in surveillance has been limited due to its low sensitivity (especially for detecting small hepatocellular cancers) and suboptimal specificity. US guidelines note that it is not possible to determine from current evidence whether surveillance with ultrasound alone, or the combination of ultrasound plus AFP, leads to a greater improvement in survival in patients with cirrhosis *[19]*.

Certainty of the Evidence

The certainty of the evidence was rated low to very low for cirrhotic populations. Modelling studies with low to very low certainty of evidence reported conflicting findings on cost-effectiveness *[28][29][30]*. The certainty of the evidence was rated moderate to low for a single Thai study modelling a chronic HBV population.

Values and preferences

Internationally, strategies favour 6-monthly ultrasound but the inclusion of AFP varies by stage and aetiology based on the AFP interpretation criteria (Appendix C). In Australia, the AFP test is subsidised through the Medicare Benefits Schedule (MBS) item 66650 for the detection or monitoring of hepatic tumours *[198]*.

Clinical question/ PICO

Population: Adults with cirrhotic liver disease undergoing HCC surveillance
Intervention: HCC surveillance with 6-monthly ultrasound + AFP
Comparator: HCC surveillance with 6-monthly ultrasound only

Summary

A systematic review of intervention and modelling studies was undertaken to compare surveillance using ultrasound plus AFP with ultrasound alone in patients with cirrhotic or non-cirrhotic chronic liver disease. The systematic review did not include studies evaluating other, less widely used surveillance strategies such as GALAD and liquid biopsy biomarkers (85). The search strategy, inclusion and exclusion criteria, and assessment of the certainty of evidence are described in detail in the technical report (Appendix D6).

Evidence summary
Overall, ten studies were identified that met the inclusion criteria: four comparative modelling studies and six non-comparative Australian studies. Most were studies designed to assess cost-effectiveness of surveillance rather than clinical efficacy of AFP.

Comparative modelling studies
Three studies used Markov models (not validated) to compare surveillance strategies of 6-monthly ultrasound plus AFP and 6-monthly ultrasound only in cirrhotic populations:

- A study conducted under US conditions analysing cost-effectiveness, benefits and harms of HCC surveillance, which compared surveillance strategies of ultrasound alone, ultrasound plus AFP (unspecified cut-point), and no surveillance in 1 million simulated patients with compensated cirrhosis (age not specified), reported that the addition of AFP to ultrasound was cost-effective *[31]*. However, this model assumed a higher willingness-to-pay threshold (incremental cost-effectiveness ratio approximately $100,000 US) than might apply in Australia.
- An earlier cost-effectiveness study conducted in the USA compared a policy of no surveillance with six surveillance strategies in patients with compensated cirrhosis aged over 50 years *[28]*. This study reported that AFP plus ultrasound was not cost-effective compared with ultrasound alone, and that cost-effectiveness depended on the sensitivity of ultrasound *[28]*.
- A UK cost-utility analysis modelled surveillance strategies in patients with compensated cirrhosis divided into aetiology subgroups: alcohol-related liver disease (ARLD), chronic HBV infection and chronic HVC infection *[29]*. The investigators reported that the combination of AFP and ultrasound was cost-effective, compared with ultrasound alone, for the HBV population only *[29]*.

Overall, the evidence for cost-effectiveness of AFP testing plus ultrasound, compared with ultrasound alone, is weak and not readily generalisable to the Australian population.

Australian non-comparative surveillance studies

Of six non-comparative studies conducted in Australia, three evaluated surveillance with 6-monthly ultrasound plus AFP:

- A retrospective case-series assessing the acceptability and effectiveness of a nurse-led HCC surveillance program analysed outcomes in health records of a small (n=76) cohort of patients with cirrhosis or advanced fibrosis referred to a Western Australian HCC clinic between 2009 and 2015 *[200]*.
- A retrospective case-series reported HCC detection rates and outcomes in a series (n=268) of patients with cirrhosis, and male non-cirrhotic patients with HBV aged over 40 years, who underwent HCC surveillance between 1998 and 2004 in a Melbourne hospital, with follow-up to 2007 *[201]*.
- A study designed to audit and then optimise an HCC surveillance program reported outcomes over 3 years for a cohort (n=114) of patients with chronic hepatitis B or C attending a South Australian hospital *[202]*.

Another three non-comparative studies evaluated surveillance with 6-monthly ultrasound alone:

- A cost-effectiveness study assessing ultrasound screening informed by serum biomarkers in Queensland patients with compensated cirrhosis aged over 50 years used a single-arm analysis Markov model to compare three scenarios: risk-stratified screening for high-risk patients, all-inclusive screening, and no formal screening *[24]*.
- A retrospective case series of 100 patients with non-alcoholic fatty liver disease (NAFLD)-related cirrhosis in Western Australia between 2009 and 2015 assessed outcomes among those in whom the diagnosis of cirrhosis was incidental (previously undiagnosed, discovered unintentionally, and was unrelated to the medical condition being treated or investigated; n=49) or by intent (staging investigation used for the purpose of assessing fibrosis severity; n=14) *[203]*.
- A Western Australian retrospective analysis of hospital records from patients diagnosed with HCC reported outcomes in 128 patients who underwent 6-monthly ultrasound surveillance before HCC diagnosis *[93]*.

Outcome Timeframe	**Study results and measurements**	**Comparator** HCC surveillance with 6-monthly ultrasound only	**Intervention** HCC surveillance with 6-monthly ultrasound + AFP	**Certainty of the Evidence** (Quality of evidence)	**Summary**
% HCC that are early stage† [1]	Based on data from 1,000,000 participants in 1 studies.	**Relative effect (95% CI):** Not calculable* **Anticipated absolute effects (95% CI):** **Metric:** % total HCC **Risk with 6-monthly US only surveillance:** 83% **Risk with 6-monthly US + AFP surveillance:** 91% **For the modelled outcome of percentage HCC diagnosed at early stage, risk ratios and 95% confidence intervals were not calculated as the confidence intervals will be much narrower than those of real (non-modelled) outcomes as a consequence of the modelling process which is designed to produce "stable" outcomes. (For detailed information in the technical report see Appendix D6)* *AFP = alpha-fetoprotein; HCC = hepatocellular carcinoma; US =ultrasound*		Very low Serious concerns regarding the risk of bias and indirectness [2]	For adults with cirrhotic liver disease undergoing 6-monthly HCC surveillance, we are uncertain as to whether the addition of AFP testing to ultrasound increases or decreases % HCC that are early stage†
Overall mortality	Based on data from 1,000,000 participants in 1 studies.	**Relative effect (95% CI):** Not calculable* **Anticipated absolute effects (95% CI):** **Metric:** Mean survival **Risk with 6-monthly US only surveillance:** 10.8 years **Risk with 6-monthly US + AFP surveillance:** 10.9 years *For the modelled outcome of overall mortality risk ratios and 95% confidence intervals were not calculated as the confidence intervals will be much narrower than those of real (non-modelled) outcomes as a consequence of the modelling process which is designed to produce "stable" outcomes. (For detailed information in the technical report see Appendix D6)		Very low Serious concerns regarding the risk of bias and indirectness [3]	For adults with cirrhotic liver disease undergoing 6-monthly HCC surveillance, we are uncertain as to whether the addition of AFP testing to ultrasound surveillance improves or worsens overall mortality

Outcome Timeframe	**Study results and measurements**	**Comparator** HCC surveillance with 6-monthly ultrasound only	**Intervention** HCC surveillance with 6-monthly ultrasound + AFP	**Certainty of the Evidence** (Quality of evidence)	**Summary**
		AFP = alpha-fetoprotein; US =ultrasound			
Cost-effectiveness	Based on data from participants in 3 studies.	AFP + US is not cost-effective when compared with US only (1 modelling study). AFP + US is more effective and has lower costs than US alone (1 modelling study). AFP + US is cost-effective when compared with US only for HBV patients (1 modelling study). ***Anticipated absolute effects (95% CI):*** Not applicable		Very low Very serious concerns regarding the risk of bias [4]	For adults with cirrhotic liver disease undergoing 6-monthly HCC surveillance, we are uncertain whether the addition of AFP testing to ultrasound surveillance is cost-effective

1. HCC = hepatocellular carcinoma. †Early stage includes Barcelona Clinic Liver Cancer stage 0/A, meeting Milan criteria, or China Liver Cancer Study group stage I.
2. **Risk of Bias: serious.** Data underpinning effect of surveillance not critically appraised. **Indirectness: serious.** Single study which did not report an AFP threshold.
3. **Risk of Bias: serious.** Data underpinning effect of surveillance not critically appraised. **Indirectness: serious.** Single study which did not report an AFP threshold.
4. **Risk of Bias: very serious.** Data underpinning effect of surveillance not critically appraised plus some important medical treatments were not included in the model in two of the three studies (Andersson 2008; Thompson Coon 2008). **Inconsistency: no serious.** Inconsistency present. Does not appear to be explained by differences in QALYs gained for populations of mixed aetiology which ranged from 0.017 to 0.03 with the study with highest estimate of benefit the one study that found that the addition of AFP was not cost effective (Andersson 2008). The inconsistency can be explained by the costs of the type and mix of treatments offered for early-stage and more advanced-stage HCC. For example, studies differed as to whether ablation was offered as a treatment for early-stage disease, the use of TACE and whether advanced disease was treated i.e. they can be explained by the different times and settings of the studies. **Indirectness: no serious.** Only one of the three studies (Parikh 2020) did not report an AFP threshold.

Clinical question/ PICO

Population: Adults with chronic HBV undergoing HCC surveillance
Intervention: HCC surveillance with 6-monthly ultrasound + AFP
Comparator: HCC surveillance with 6-monthly ultrasound only

Summary

A systematic review of intervention and modelling studies was undertaken to compare surveillance using ultrasound

plus alpha-fetoprotein (AFP) with ultrasound alone in patients with cirrhotic or non-cirrhotic chronic liver disease. The systematic review did not include studies evaluating other, less widely used surveillance strategies such as GALAD and liquid biopsy biomarkers (85). The search strategy, inclusion and exclusion criteria, and assessment of the certainty of evidence are described in detail in the technical report (Appendix D6).

Evidence summary

Overall ten studies were identified that met the inclusion criteria: four comparative modelling studies and six non-comparative Australian studies. Most were studies designed to assess cost-effectiveness of surveillance rather than clinical efficacy of AFP.

Comparative modelling studies

One study used a Markov model (not validated) to compare surveillance strategies of 6-monthly ultrasound plus AFP and 6-monthly ultrasound only in a chronic HBV population:

- A Thai study evaluating the potential economic impact of a national HCC surveillance program for patients with chronic HBV infection aged 40–60 years compared lifetime costs and outcomes for no surveillance program with alternative surveillance strategies including ultrasound alone and ultrasound plus AFP (cut-point > 20 ng/mL) *[30]*. This study provides very limited evidence directly relevant to Australia due to dissimilarities in patient population, costs, treatment practices and willingness-to-pay thresholds.

Outcome Timeframe	**Study results and measurements**	**Comparator** HCC surveillance with 6-monthly ultrasound only	**Intervention** HCC surveillance with 6-monthly ultrasound + AFP	**Certainty of the Evidence** (Quality of evidence)	**Summary**
Cost-effectiveness	Based on data from participants in 1 studies.	AFP + US cost effective when compared with US only ***Anticipated absolute effects (95% CI):*** Not applicable AFP = alpha-fetoprotein; US = ultrasound		Low Serious concerns regarding the risk of bias [1]	For adults with chronic HBV undergoing 6-monthly HCC surveillance, the addition of AFP testing to ultrasound surveillance may be cost-effective

1. **Risk of Bias: serious.** Data underpinning effect of surveillance not critically appraised. **Indirectness: no serious.** Single study which reports AFP threshold.

Practice Points

Good practice statement

New

7.2 Practice point

The provision of 6-monthly ultrasound for HCC surveillance may be cost-effective compared to no surveillance for people with compensated cirrhosis in the Australian context.

Rationale

Cost-effectiveness of HCC surveillance

A scoping review identified 26 studies that assessed the cost-effectiveness of HCC surveillance. Surveillance based on 6- or 12-monthly ultrasound with or without AFP testing was generally found to be cost-effective, with 6-monthly ultrasound typically favourable for people with chronic HBV infection and 12-monthly ultrasound typically favourable for people with chronic HCV infection *[204]*. Model-generated cost-effectiveness analyses are often used to guide cancer control, especially for managing cancers like HCC that can take time to develop and be diagnosed. Predictive modelling has been used in the development of Australian guidelines for cervical and colorectal cancers to support recommendations relating to organised screening programs *[205][206]*. Existing models for HCC surveillance in Australia are Markov-type models tailored specifically to priority populations *[201][207]*. Full descriptions and summaries of additional studies are included in Appendix D7, Tables 50 to 58.

Australian cost-effectiveness modelling

To support these guidelines, a new model of cirrhosis, HCC and surveillance in the Australian setting was developed: *Policy1-Liver*. *Policy1-Liver* is a mathematical model that simulates the distribution of expected time-to-event for relevant health state transitions (compensated cirrhosis to decompensated cirrhosis, cirrhosis to HCC, early-stage HCC to late-stage HCC, etc), and combines this with locally relevant economic data to generate relevant health economic outputs. Additional information on *Policy1-Liver* can be found in Appendix D7.

The modelling estimates generated by *Policy1-Liver* indicated that 6-monthly HCC surveillance by ultrasound in people with compensated cirrhosis could reduce the chance of HCC death by 14–15% over their lifetime. Each individual was expected to experience 13 surveillance events (ultrasound with or without AFP testing) over their lifetime. The lifetime overall cost, including HCC surveillance (ultrasound with or without AFP), diagnostic, and treatment costs was estimated to be up to $140,000 per person with compensated cirrhosis, compared to lifetime HCC diagnostic and treatment costs of $131,000 for people not undergoing surveillance. Both 6-monthly ultrasound and 6-monthly ultrasound with AFP were found to be cost-effective, with cost-effectiveness ratios of $26,122 and $28,140 per quality-adjusted life year (QALY) saved (with 5% annual discounting), respectively, compared with no surveillance.

The incremental cost-effectiveness (ICER) for HCC surveillance with 6-monthly ultrasound was $62,856 per QALY saved, compared with HCC surveillance with 6-monthly ultrasound and AFP, slightly above the indicative willingness-to-pay threshold of $50,000/QALY often used in Australia (208). This finding indicates that the addition of AFP to ultrasound surveillance may not be cost-effective. Note that this is not the same as the cost-effectiveness ratio (CER) of HCC surveillance compared with no surveillance, where HCC surveillance was found to be cost-effective both with and without AFP.

Good practice statement

New

7.3 Practice point

The provision of 6-monthly ultrasound with alpha-fetoprotein testing may be cost-effective compared to no surveillance and could be provided as part of HCC surveillance for people with compensated cirrhosis in the Australian context.

Rationale

Cost-effectiveness of HCC surveillance

A scoping review identified 26 studies that assessed the cost-effectiveness of HCC surveillance. Surveillance based on 6- or 12-monthly ultrasound with or without AFP testing was generally found to be cost-effective, with 6-monthly ultrasound typically favourable for people with chronic HBV infection and 12-monthly ultrasound typically favourable for people with chronic HCV infection *[204]*. Model-generated cost-effectiveness analyses are often used to guide cancer control, especially for managing cancers like HCC that

can take time to develop and be diagnosed. Predictive modelling has been used in the development of Australian guidelines for cervical and colorectal cancers to support recommendations relating to organised screening programs *[205][206]*. Existing models for HCC surveillance in Australia are Markov-type models tailored specifically to priority populations *[201][207]*. Full descriptions and summaries of additional studies are included in Appendix D7, Tables 50 to 58.

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Limitations

Tumour biomarker tests other than AFP have not been considered as part of these guidelines. Though other tumour biomarker tests were not formally included in the systematic review, evidence in this area is currently limited and, at times, funded through industry resulting in possible bias.

Resource and other considerations

Resource considerations

The AFP test is widely available in Australia and subsidised through the Medicare Benefits Schedule (MBS) item 66650 for the detection or monitoring of hepatic tumours.

Implementation considerations

Implementation of this recommendation may result in little to no change in out-of-pocket healthcare costs to patients as all tests required are subsidised by the MBS. There may be a change in the costs to the health system based on the HCC surveillance costs and the impact on downstream treatment costs.

8. Implications and implementation of recommendations, evidence gaps and future research needs

In these guidelines, implications of the recommendations for clinical practice and the health system, implementation considerations, evidence gaps and areas of future research are noted within each section. They are summarised below to inform guideline dissemination and implementation.

Key recommendations

The guidelines build on existing international guidelines, national consensus statements and current practice. They broadly align with current practice and consolidate guidance for the Australian context. A comparison of existing recommendations and guidelines for clinicians has been developed (Appendix G) to outline similarities and differences with recommendations from these guidelines. The recommendations reinforce the necessity for hepatocellular carcinoma (HCC) surveillance in high-risk patients and differ from other guidance and current clinical practice in three key areas:

1. People for whom HCC surveillance should not routinely be offered are clearly identified;
2. Monitoring for progression to cirrhosis is highlighted as an alternative strategy in the place of 6-monthly HCC surveillance;
3. Consideration of an individual's risk (and health status) should be used to inform HCC surveillance recommendations in people with advanced liver fibrosis.

Key implementation considerations

Adoption of these guideline recommendations will depend on:

1. Engaging health care providers and patients: Awareness and understanding of liver health, the risks of liver disease and cancer, and willingness to engage in preventive, secondary and/or tertiary care;
2. Clinical identification of high-risk patients, especially in primary care;
3. Providing culturally safe and sensitive health services for high-risk patients;
4. Equitable implementation of HCC surveillance especially through the availability and accessibility of required infrastructure and resources;
5. Building capacity and supporting education needs; and
6. Supporting delivery models of care for HCC surveillance.

Engaging health care providers and patients

While these guidelines have been developed for use in clinical practice, recommendations are conditional on the presumption that they can be implemented and delivered appropriately by health care providers, and that they are accepted by patients. This requires that health care providers and people who would be suitable for HCC surveillance have a basic understanding of liver health and associated risk factors. Given the utility of ethnocultural background and country or region of birth as surrogate markers in assessing liver cancer, health care providers need to engage with patients to appropriately determine and record any individual characteristics that may help in identifying people requiring surveillance for HCC (see Appendix F for a decision aid). Ideally, this would occur at an initial consultation and be recorded in the electronic medical records.

Engaging people at high risk in services to improve the awareness of risk factors could aid risk assessment activities that may be employed by clinicians and identify key barriers early. Patients must also accurately recall and recount the presence of risk factors or symptoms of relevance and be willing to undertake surveillance and any potential treatment required if a diagnosis is made. Improving patient engagement could also contribute to their improved understanding of liver health, HCC surveillance, and support informed decision making. Patient

adherence to HCC surveillance, reportedly hampered by difficulties in scheduling clinical visits and transport *[209]*, presents an additional challenge to its successful implementation.

Clinical identification of high-risk patients

Recent developments and trends are changing the make-up of the high-risk population in Australia, including improvements in the treatment of chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV), and the growing prevalence of metabolic dysfunction-associated fatty liver disease (MAFLD). These changes reinforce the need to better identify people at high risk of cirrhosis and HCC in primary care *[210]*, which will be challenging but represents a critical step in the HCC surveillance pathway.

Clinical identification of high-risk patients can be facilitated by the implementation of validated risk prediction tools *[98]*. Such tools have been shown to be clinically useful, especially in people with chronic HBV infection. Where employed, these tools can ensure that people with chronic HBV infection are diagnosed, assessed for treatment, and offered HCC surveillance where appropriate *[99][100]*. While these guidelines did not specifically review risk prediction tools, it will be critical to validate them and determine their usefulness in the Australian context. Future consideration should also be given to the impact of a patient's family history of HCC and the appropriate reporting and recording of country or region of birth as a part of risk prediction, which was also out of scope for detailed review and analyses.

There is emerging evidence that risk prediction tools can also facilitate the identification of people with advanced liver disease. Where patients are identified, the clinical management of risk factors for fibrosis progression (alcohol, excess adiposity, diabetes) and annual monitoring for progression to cirrhosis is critical.

Providing culturally safe and sensitive health services for high-risk patients

Individual uptake of HCC surveillance may be affected by sociodemographic and/or cultural factors and commitments, including stigma associated with chronic viral hepatitis, language, knowledge, financial means, systemic racism, travel limitations and misinformation *[211][212]*. Culturally sensitive and safe health systems and health services demonstrate respect to an individual’s cultural, linguistic, religious, sexual and racial/ethnic characteristics and values. They also address racism and inequity to ensure that all are welcome, safe and protected. Overcoming these issues requires major systemic reform to the make-up and culture of the health system. The guidelines encourage and support the provision of HCC surveillance in a culturally safe and sensitive manner based on existing frameworks, guides and manuals in Australia *[4][5][6][7][8][9][10][11]* and best practice in working with marginalised communities.

Equitable implementation of surveillance

Improving patient identification and stratification for HCC surveillance would improve survival but, if not done appropriately and systematically, could exacerbate disparities in care and increase demand for specialist services beyond their existing current capacity *[213]*. In regional and remote areas there is limited access to ultrasound services and lack of infrastructure to provide follow-up services equitably, if required. This is especially evident for Aboriginal and/or Torres Strait Islander communities, where efforts should be made to provide culturally safe local access to preventive care, HCC surveillance and treatment through primary care within communities, and on Country where possible.

Evidence-based recommended HCC treatments must be offered equitably and in a culturally safe manner to Aboriginal and Torres Strait Islander people, including those living in remote communities. Available evidence suggests that, when offered early, HCC treatment is accepted and effective, irrespective of geographical location. Aboriginal Community Controlled Health Organisations and local clinics play an important role in providing comprehensive, high quality, and culturally appropriate care for Aboriginal and Torres Strait Islander people.

Additionally, incarcerated people and people accessing addiction services have higher prevalence of HCV and, although not explicitly included in these guidelines, present important considerations for the accessibility and availability of HCC surveillance in these contexts. Significant barriers exist to accessing HCC surveillance and

related treatment and the intersectionality between this group and the priority populations covered in the guidelines requires further consideration to ensure inequities are not further exacerbated.

Some technologies noted in these guidelines, such as elastography, are not widely available in Australia and, when available, are unsubsidised for investigative purposes and costly. The feasibility of the widespread use of elastography for monitoring of HCC is not feasible within the current health care system. Its implementation would need to be carefully considered to ensure health inequalities were not exacerbated. Emerging technologies such as portable ultrasound, and serum biomarkers for diagnosis, could assist with health service and treatment delivery for the identified and other high-risk populations, especially outside of larger urban areas and on Country. Their availability and associated costs would also need to be carefully considered before implementation.

Building capacity and supporting education needs

Implementation of these recommendations in clinical practice needs to be supported by building capacity and providing targeted education in liver health and liver diseases, especially for primary care health professionals and Aboriginal Health Workers and Aboriginal Health Practitioners. Building capacity requires additional infrastructure, personnel and financial resourcing to support the provision of HCC surveillance, as well as education.

The Liver Foundation has recently developed training modules for general practice on liver disease in an effort to improve understanding of the rising burden in the Australian community. In implementing these recommendations, clinicians need to recognise that many patients have multiple causes of liver disease. The Liver Foundation modules could be complemented by focused HCC surveillance training to guide decision-making. Culturally appropriate educational resources should be developed, using co-design approaches including community leaders as a priority, and customised to represent the relevant culture and language. For example, Hep B Story was created and translated by community members and health workers across the Northern Territory as a visual, interactive application designed to outline HBV and treatment for patients living with chronic HBV and their families *[214]*. Targets included in the forthcoming Fourth National Hepatitis B Strategy will also emphasise the importance of access to information in language. In addition, culturally safe care for Aboriginal and Torres Strait Islander people and culturally and linguistically diverse communities is important to provide, and its delivery should be led by a culturally safe workforce.

Ultrasound is the fundamental basis for the provision of HCC surveillance and the success of surveillance is dependent on the quality of ultrasound. Various factors may result in inadequate ultrasound including patient characteristics, lesion characteristics, quality of machinery etc., requiring alternative modalities of surveillance *[215][216]*. Further consideration should be given to the need for high quality ultrasounds in Australia and appropriate support and training for health care professionals providing these services.

Supporting delivery models of care for HCC surveillance

Little is known about the implementation of HCC surveillance. Previous work scoped the existing evidence base for the feasibility and effectiveness of HCC surveillance *[204]*. We identified five high-level HCC surveillance pathways being used in different settings and populations across Australia, including GP-led and nurse-led delivery models *[217]*. However, there is no direct evidence of effectiveness for clinical and patient-reported outcomes or for efficiencies of the different HCC surveillance pathways.

There is little direct evidence on HCC surveillance implementation and uptake in people at high risk in Australia. Randomised studies that would be required to investigate this are not feasible, given that informed patients prefer surveillance *[218]*. In the absence of data, predictive modelling is becoming a commonly used surrogate for guiding policy decision-makers. The modelling supporting these guidelines indicated that HCC surveillance using 6-monthly ultrasound in people with cirrhosis could reduce the chance of HCC death by 14–15% over their lifetime, demonstrating the health benefit. The cost-effectiveness results were below the indicative willingness-to-pay threshold when ultrasound was used with or without alpha-fetoprotein (AFP). However, the cultural sensitivity and safety aspects of HCC surveillance provision should be further investigated to ensure

delivery models are feasible and acceptable in the community.

Areas of major debate

There was robust discussion within the Working Group and/or subcommittee members on the following chapters and/or points:

- Family history of HCC is not clearly defined in the literature in the context of consideration for HCC surveillance. The definition included in these guidelines, based on expert advice, is one or more first degree relatives with HCC. In some cases, HCC surveillance is recommended if there is any family history of HCC. In consultation with the Working Group, a qualification has been included here to consider offering surveillance 10 years prior to earliest case in a family. This approach is in line with other Australian cancer guidelines where family history is considered (e.g., colorectal cancer *[205]*). This was decided to reduce the likelihood that a person with a family history of HCC in a first degree relative at age 70 is subject to HCC surveillance from a very early age.
- Does HCC surveillance improve liver cancer outcomes for Aboriginal and Torres Strait Islander people? Recommendations in these guidelines include the consideration of a high-risk genotype which is not routinely offered, widely available nor currently subsidised through MBS. Despite this, the Working Group regard this qualification important to consider in Aboriginal people as it would inform the approach to HCC surveillance. In the absence of routine, subsidised genotype testing, genotyping can be epidemiologically likely based on existing evidence and geographic location. There was considerable discussion on this point and the decision was made to include the high-risk genotype to highlight that it can be considered as part of an assessment.
- Does HCC surveillance improve liver cancer outcomes for sub-Saharan Africa-born people in Australia? In the absence of evidence and after consultation with the Working Group members, the decision was made to adopt a conservative approach by retaining rules generally applied in clinical practice by referencing a sex-age statement.
- Does the addition of alpha-fetoprotein testing to 6-monthly ultrasound imaging for HCC surveillance improve liver cancer outcomes? There was some discussion around the evidence relating to the use of AFP in specific groups of people at high risk. It was concluded that the evidence was insufficient to nominate any such groups thus it would be prudent to recommend AFP as part of HCC surveillance.

In each instance, the guideline development Working Group was able to reach a decision about the content and recommendations.

Evidence gaps

The systematic reviews that underpin these guidelines highlighted the paucity of literature in key areas. This was particularly true for evidence relating to at-risk patients without cirrhosis, and for priority population groups.

Additional evidence is required to inform appropriate HCC surveillance recommendations for people with MAFLD, especially given the shifting burden of disease and increasing presence of comorbidities.

The ongoing impact of existing interventions such as HBV vaccination and direct-acting antiviral (DAA) therapies must also be considered and accounted for in any recommendations for HCC surveillance, especially in cases where prevention may reduce the benefit of surveillance. Assessment of people who decline or fail treatment with DAA was out of scope but are an important group to assess to ensure HCC surveillance is offered, where appropriate.

Outcome measures of quality of life and overall morbidity and mortality could be included in future assessments to assess broader benefits. These outcome measures could be supported by the reporting and quantification of

patient report outcomes and the impact of risk factor management on risk for liver disease progression and HCC. Advancements in risk assessment tools that can be used in clinical practice, such as GALAD scores or other biomarkers, could improve the identification and stratification of high-risk patients without cirrhosis and improve the effectiveness and efficiency of HCC surveillance recommendations.

In the priority populations identified for the guidelines, further research is needed to assess the impact of social determinants of health on HCC surveillance uptake and liver cancer outcomes. This includes the investigation of settlement impact and the family environment, particularly in relation to HBV. Research in priority populations should uphold ethical and culturally safe standards and facilitate a co-design approach, where appliable. Future work could also address HCC surveillance and recommendations specific to people who are incarcerated and people who require addiction services. Future work could also extend recommendations to incorporate lifestyle prevention guidance and hepatitis-specific recommendations (e.g., early detection of hepatitis reinfection) alongside HCC surveillance.

There is mounting evidence for provision of early appropriate palliative care to improve the quality and duration of life of people with advanced liver disease and HCC *[219][220]*.

Future work should ensure that the HCC management pathway incorporates active decision-making about specialist referral and consideration of appropriate involvement of palliative care services. These considerations would optimise clinical and psychosocial outcomes for patients in whom curative treatment is not viable, such as those with decompensated cirrhosis.

Updating the guidelines

As more evidence (including from modelling studies) emerges, there may be a need to modify and update the recommendations. Ongoing assessment of the clinical and cost-effectiveness of targeted screening for advanced liver disease and HCC surveillance is warranted and will build the case for supporting the most effective and cost-effective interventions to improve liver cancer outcomes, based on the best available evidence.

The key aim of these guidelines is to support decision-making by clinicians providing HCC surveillance. However, there is also the need to understand the barriers and facilitators for people participating in HCC surveillance, to enable its uptake by those at greatest need.

These guidelines are part of a Department of Health and Aged Care-funded Roadmap to Liver Cancer Control initiative. The Roadmap will look at strategic priority areas for action to improve liver cancer outcomes in Australia and to support the implementation of HCC surveillance.

Appendices

Click on the link below to access an Appendix:

Appendix A

Appendix B

Appendix C

Appendix D

Appendix E

Appendix F

Appendix G

Appendix H

Appendix I

Appendix J

References

1. Australian Institute of Health and Welfare : Cancer data in Australia. (null) 2022; Website

2. Singal AG, Zhang E, Narasimman M, Rich NE, Waljee AK, Hoshida Y, et al. : HCC surveillance improves early detection, curative treatment receipt, and survival in patients with cirrhosis: A meta-analysis. J Hepatol 2022;77(1):128-139 Journal

3. Jeffrey GP, Gordon L., Ramm G. : Hepatocellular carcinoma surveillance in Australia: time to improve the diagnosis of cirrhosis and use liver ultrasound. Med J Aust 2020;212(7):297-299 Journal

4. ACOSAQIHC : User Guide for Aboriginal and Torres Strait Islander Health. Website

5. Australian Institute of Health and Welfare : Cultural safety in health care for Indigenous Australians: monitoring framework, Summary. Website

6. Remote Primary Health Care Manuals : CARPA Standard Treatment Manual 7th Edition. 2017; Website

7. Culturally Responsive Clinical Practice: Working with People from Migrant and Refugee Backgrounds. 2019; Website

8. Rural and Regional Health and Aged Care Services : Cultural responsiveness framework: Guidelines for Victorian health services. 2009; Website

9. National Safety and Quality Health Service Standards : User Guide for Health Service Organisations Providing Care for Patients from Migrant and Refugee Backgrounds. 2021; Website

10. The Royal Australian College of General Practitioners : Standard for Health Services in Australian prisons. 2011; Website

11. Teller M, Tollit M, Pace C, Pang K : Australian Standards of Care and Treatment Guidelines: For trans and gender diverse children and adolescents. 2020; Website

12. CA : A guide to implementing the optimal care pathway for Aboriginal and Torres Strait Islander people with cancer. Website

13. National Aboriginal Community Controlled Health Organisation, The Royal Australian College of General Practitioners : National guide to a preventive health assessment for Aboriginal and Torres Strait Islander people. null: 2018;3rd Edition

14. Holger Schünemann JBGGAO : GRADE Handbook - Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. null: (null) 2013; Website

15. National Institute for Health and Care Excellence : Cirrhosis in Over 16s: Assessment and Management. NICE guideline [NG50]. (null) 2016; Website

16. World Health Organization : Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. (null) 2015;

17. Omata M, Cheng A-L, Kokudo N, Kudo M, Lee JM, Jia J, et al. : Asia–Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int 2017;11(4):317-370 Journal

18. European Association for the Study of the Liver : Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69(1):182-236 Journal

19. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. : Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. Clin Liver Dis (Hoboken) 2019;13(1):1-1 Journal

20. Gastroenterological Society of Australia : Hepatocellular Carcinoma Consensus Statement Working Group. Australian recommendations for the management of hepatocellular carcinoma: a consensus statement. (null) 2020; Website

21. Uyei J, Taddei TH, Kaplan DE, Chapko M, Stevens ER, Braithwaite RS : Setting ambitious targets for surveillance and treatment rates among patients with hepatitis C related cirrhosis impacts the cost-effectiveness of hepatocellular cancer surveillance and substantially increases life expectancy: A modeling study. PloS one 2019;14(8):e0221614

22. Farhang Zangneh H, Wong WW, Sander B, Bell CM, Mumtaz K, Kowgier M, et al. : Cost effectiveness of hepatocellular carcinoma surveillance after a sustained virologic response to therapy in patients with hepatitis C virus infection and advanced fibrosis. Clin Gastroenterol Hepatol 2019;17(9):1840-1849e.16 Journal

23. Gastroenterological Society of Australia : Australian consensus recommendations for the management of hepatitis B infection. (null) 2022;

24. Carter HE, Jeffrey GP, Ramm GA, Gordon LG : Cost-Effectiveness of a serum biomarker test for risk-stratified liver ultrasound screening for Hepatocellular Carcinoma. Value in Health 2021;24(10):1454-1462 Journal

25. Robotin MC, Kansil M., Howard K., George J., Tipper S., Dore GJ, et al. : Antiviral therapy for hepatitis B-related liver cancer prevention is more cost-effective than cancer screening. J Hepatol 2009;50(5):990-998 Journal

26. Yu XQ, Feletto E, Smith MA, Yuill S, Baade PD : Cancer incidence in migrants in Australia: patterns of three infection-related cancers. Cancer Epidemiol Biomarkers Prev 2022; OF1-8 Journal

27. Waziry R, Grebely J, Amin J, Alavi M, Hajarizadeh B, George J, et al. : Trends in hepatocellular carcinoma among people with HBV or HCV notification in Australia (2000-2014). J Hepatol 2016;65(6):1086-1093 Journal

28. Andersson KL, Salomon JA, Goldie SJ, Chung RT : Cost effectiveness of alternative surveillance strategies for hepatocellular carcinoma in patients with cirrhosis. Clin Gastroenterol Hepatol 2008;6(12):1418-1424

29. Thompson Coon J., Rogers G., Hewson P., Wright D., Anderson R., Jackson S., et al. : Surveillance of cirrhosis for hepatocellular carcinoma: a cost-utility analysis. Br J Cancer 2008;98(7):1166-75 Journal

30. Sangmala P, Chaikledkaew U, Tanwandee T, Pongchareonsuk P : Economic Evaluation and Budget Impact Analysis of the Surveillance Program for Hepatocellular Carcinoma in Thai Chronic Hepatitis B Patients. Asia Pacific J Cancer Prev 2014;15(20):8993-9004 Journal

31. Parikh ND, Singal AG, Hutton DW, Tapper EB : Cost-Effectiveness of Hepatocellular Carcinoma Surveillance: An Assessment of Benefits and Harms. Am J Gastroenterol 2020;115(10):1642-1649 Journal

32. Rumgay H, Ferlay J, de Martel C, Georges D, Ibrahim AS, Zheng R, et al. : Global, regional and national burden of primary liver cancer by subtype. Eur J Cancer 2022;161 108-118 Journal

33. Wallace MC, Preen DB, Short MW, Adams LA, Jeffrey GP : Hepatocellular carcinoma in Australia 1982-2014: Increasing incidence and improving survival. Liver Int 2019;39(3):522-530 Journal

34. Australian Institute of Health and Welfare : Cancer in Australia 2021. (null) 2021; Website

35. Luo Q, O'Connell DL, Yu XQ, Kahn C, Caruana M, Pesola F, et al. : Cancer incidence and mortality in Australia from 2020 to 2044 and an exploratory analysis of the potential effect of treatment delays during the COVID-19 pandemic: a statistical modelling study. Lancet Public Health 2022;7(6):e537-e548 Journal

36. Australian Institute of Health and Welfare : Cancer in Aboriginal & Torres Strait Islander people of Australia. 2018; Website

37. Cocker F, Yee KC, Palmer AJ, Graaff DB : Increasing incidence and mortality related to liver cancer in Australia: time to turn the tide. Aust N Z J Public Health 2019;43(3):267-273 Journal

38. Mittal S, El-Serag HB, Sada YH, Kanwal F, Duan Z, Temple S, et al. : Hepatocellular Carcinoma in the Absence of Cirrhosis in United States Veterans is Associated With Nonalcoholic Fatty Liver Disease. Clin Gastroenterol Hepatol 2016;14(1):124-131.e1 Journal

39. El-Serag HB : Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 2012;142(6):1264-1273.e1 Journal

40. Campana L, Iredale JP : Regression of Liver Fibrosis. Semin Liver Dis 2017;37(1):1-10 Journal

41. Sepanlou SG, Safiri S, Bisignano C, Ikuta KS, Merat S, Saberifiroozi M, et al. : The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol 2020;5(3):245-266 Journal

42. Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, et al. : Hepatocellular carcinoma. Nat Rev Dis Primers 2021;7(1):6 Journal

43. Fujiwara N, Friedman SL, Goossens N, Hoshida Y : Risk factors and prevention of hepatocellular carcinoma in the era of precision medicine. J Hepatol 2018;68(3):526-549 Journal

44. Bedossa P., Poynard T. : An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology 1996;24(2):289-293 Journal

45. Ishak K., Baptista A., Bianchi L., Callea F., De Groote J., Gudat F., et al. : Histological grading and staging of chronic hepatitis. J Hepatol 1995;22(6):696-699 Journal

46. Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR : A global view of hepatocellular carcinoma: trends, risk, prevention and management. Nat Rev Gastroenterol Hepatol 2019;16(10):589-604 Journal

47. Moon AM, Singal AG, Tapper EB : Contemporary Epidemiology of Chronic Liver Disease and Cirrhosis. Clin Gastroenterol Hepatol 2020;18(12):2650-2666 Journal

48. Ganne-Carrié N, Nahon P : Hepatocellular carcinoma in the setting of alcohol-related liver disease. J Hepatol 2019;70(2):284-293 Journal

49. Australian Government Department of Health and Aged Care : National Alcohol Strategy 2019-2028. (null) 2019; Website

50. National Health and Medical Research Council : Australian guidelines to reduce health risks from drinking alcohol. 2020; Website

51. Osna NA, Donohue TM, Kharbanda KK : Alcoholic Liver Disease: Pathogenesis and Current Management. Alcohol Res 2017;38(2):147-161

52. Melaku YA, Appleton SL, Gill TK, Ogbo FA, Buckley E, Shi Z, et al. : Incidence, prevalence, mortality, disability-adjusted life years and risk factors of cancer in Australia and comparison with OECD countries, 1990–2015: findings from the Global Burden of Disease Study 2015. Cancer Epidemiol 2018;52 43-54 Journal

53. Valery PC, Clark PJ, Pratt G, Bernardes CM, Hartel G, Toombs M, et al. : Hospitalisation for cirrhosis in Australia: disparities in presentation and outcomes for Indigenous Australians. Int J Equity Health 2020;19(1):27 Journal

54. Holmes JA, Rutledge SM, Chung RT : Direct-acting antiviral treatment for hepatitis C. Lancet 2019;393(10179):1392-1394 Journal

55. Kanwal F, Kramer J, Asch SM, Chayanupatkul M, Cao Y, El-Serag HB : Risk of Hepatocellular Cancer in HCV Patients Treated With Direct-Acting Antiviral Agents. Gastroenterol 2017;153(4):996-1005.e1 Journal

56. Ioannou GN, Green PK, Berry K : HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. J Hepatol 2018;68(1):25-32 Journal

57. Ioannou GN, Green P, Kerr KF, Berry K : Models estimating risk of hepatocellular carcinoma in patients with alcohol or NAFLD-related cirrhosis for risk stratification. J Hepatol 2019;71(3):523-533 Journal

58. Kirby Institute : Monitoring hepatitis C treatment uptake in Australia (Issue 12). (null) 2022; Website

59. Romero N, Nguyen A, Maclachlan J, Cowie B : Hepatitis B Modelling Technical Briefing. 2023;

60. MacLachlan J, Stewart S., Cowie BC : Viral Hepatitis Mapping Project: National Report 2020. (null) 2021;

61. Amin J, O'Connell D, Bartlett M, Tracey E, Kaldor J, Law M, et al. : Liver cancer and hepatitis B and C in New South Wales, 1990-2002: a linkage study. Aust N Z J Public Health 2007;31(5):475-482 Journal

62. Clark PJ, Stuart KA, Leggett BA, Crawford DH, Boyd P., Fawcett J., et al. : Remoteness, race and social disadvantage: disparities in hepatocellular carcinoma incidence and survival in Queensland, Australia. Liver Int 2015;35(12):2584-94 Journal

63. Chayanupatkul M, Omino R, Mittal S, Kramer JR, Richardson P, Thrift AP, et al. : Hepatocellular carcinoma in the absence of cirrhosis in patients with chronic hepatitis B virus infection. J Hepatol 2017;66(2):355-362 Journal

64. Zhu RX, Seto W-K, Lai C-L, Yuen M-F : Epidemiology of Hepatocellular Carcinoma in the Asia-Pacific Region. Gut Liver 2016;10(3):332-339 Journal

65. Asrani SK, Devarbhavi H, Eaton J, Kamath PS : Burden of liver diseases in the world. Journal of Hepatology 2019;70(1):151-171 Journal

66. Wallace J., Pitts M., Liu C., Lin V., Hajarizadeh B., Richmond J., et al. : More than a virus: a qualitative study of the social implications of hepatitis B infection in China. Int J Equity Health 2017;16 137 Journal

67. Gastroenterological Society of Australia : Australian consensus recommendations for the management of hepatitis C infection. (null) 2016;

68. Adams LA, Roberts SK, Strasser SI, Mahady SE, Powell E, Estes C, et al. : Nonalcoholic fatty liver disease burden: Australia, 2019-2030. J Gastroenterol Hepatol 2020;35(9):1628-1635 Journal

69. Younossi ZM, Marchesini G, Pinto-Cortez H, Petta S : Epidemiology of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis: Implications for Liver Transplantation. Transplantation 2019;103(1):22-27 Journal

70. Farrell AM, Magliano DJ, Shaw JE, Thompson AJ, Croagh C, Ryan MC, et al. : A problem of proportions: estimates of metabolic associated fatty liver disease and liver fibrosis in Australian adults in the nationwide 2012 AusDiab Study. Sci Rep 2022;12(1):1956 Journal

71. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. : A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol 2020;73(1):202-209 Journal

72. Eslam M, Sanyal AJ, George J, Sanyal A, Neuschwander-Tetri B, Tiribelli C, et al. : MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. Gastroenterol 2020;158(7):1999-2014.e1 Journal

73. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. : The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. J Hepatol 2018;67(1):328-357 Journal

74. Trevisani F, Frigerio M, Santi V, Grignaschi A, Bernardi M : Hepatocellular carcinoma in non-cirrhotic liver: A reappraisal. Dig Liver Dis 2010;42(5):341-347 Journal

75. Bréchot C : Pathogenesis of hepatitis B virus—related hepatocellular carcinoma: Old and new paradigms. Gastroenterol 2004;127(5, Supplement 1):S56-S61 Journal

76. Perumpail RB, Wong RJ, Ahmed A, Harrison SA : Hepatocellular Carcinoma in the Setting of Non-cirrhotic Nonalcoholic Fatty Liver Disease and the Metabolic Syndrome: US Experience. Dig Dis Sci 2015;60(10):3142-3148 Journal

77. Castellana M, Donghia R, Lampignano L, Castellana F, Zupo R, Sardone R, et al. : Prevalence of the Absence of Cirrhosis in Subjects with NAFLD-Associated Hepatocellular Carcinoma. J Clin Med 2021;10(20): Journal

78. El-Serag HB, Hampel H, Javadi F : The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. Clin Gastroenterol Hepatol 2006;4(3):369-380 Journal

79. Desai A, Sandhu S, Lai J-P, Sandhu DS : Hepatocellular carcinoma in non-cirrhotic liver: A comprehensive review. World J Hepatol 2019;11(1):1-18 Journal

80. Kwon JW, Tchoe HJ, Lee J., Suh JK, Lee JH, Shin S. : The Impact of National Surveillance for Liver Cancer: Results from Real-World Setting in Korea. Gut Liver 2020;14(1):108-116 Journal

81. Kudo M. : Surveillance, diagnosis, treatment, and outcome of liver cancer in Japan. Liver Cancer 2015;4(1):39-50 Journal

82. Galle PR, Foerster F, Kudo M, Chan SL, Llovet JM, Qin S, et al. : Biology and significance of alpha-fetoprotein in hepatocellular carcinoma. Liver Int 2019;39(12):2214-2229 Journal

83. Zhang J, Chen G, Zhang P, Zhang J, Li X, Gan D, et al. : The threshold of alpha-fetoprotein (AFP) for the diagnosis of hepatocellular carcinoma: A systematic review and meta-analysis. PLOS ONE 2020;15(2):e0228857 Journal

84. He Y, Lu H, Zhang L : Serum AFP levels in patients suffering from 47 different types of cancers and noncancer diseases. Progress in Molecular Biology and Translational Science, null, null 2019;162 199-212 Website

85. Adeniji N, Dhanasekaran R : Current and Emerging Tools for Hepatocellular Carcinoma Surveillance. Hepatology Communications 2021;5(12):1972-1986 Journal

86. National Institute for Health and Care Excellence : Non-Alcoholic Fatty Liver Disease (NAFLD): Assessment and Management. NICE guideline [NG49]. (null) 2016; Website

87. National Institute for Health and Care Excellence : Hepatitis B (chronic); diagnosis and management. Clinical guideline [CG165] Last updated October 2017. (null) 2013; Website

88. Terrault NA, Lok AS, McMahon BJ, Chang K-M, Hwang JP, Jonas MM, et al. : Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatol 2018;67(4):1560-1599 Journal

89. D'Amico G, Garcia-Tsao G, Pagliaro L : Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006;44(1):217-231 Journal

90. Vaz J, Eriksson B, Strömberg U, Buchebner D, Midlöv P : Incidence, aetiology and related comorbidities of cirrhosis: a Swedish population-based cohort study. BMC Gastroenterol 2020;20(1):84 Journal

91. Schütte K, Schulz C, Poranzke J, Antweiler K, Bornschein J, Bretschneider T, et al. : Characterization and prognosis of patients with hepatocellular carcinoma (HCC) in the non-cirrhotic liver. BMC Gastroenterol 2014;14(1):117 Journal

92. Hong TP, Gow PJ, Fink M, Dev A, Roberts SK, Nicoll A, et al. : Surveillance improves survival of patients with hepatocellular carcinoma: a prospective population-based study. Med J Aust 2018;209(8):348-354 Journal

93. Huang Y., Wallace MC, Adams LA, MacQuillan G., Garas G., Ferguson J., et al. : Rate of Nonsurveillance and Advanced Hepatocellular Carcinoma at Diagnosis in Chronic Liver Disease. J Clin Gastroenterol 2018;52(6):551-556 Journal

94. Jamwal R, Krishnan V, Kushwaha DS, Khurana R : Hepatocellular carcinoma in non-cirrhotic versus cirrhotic liver: a clinico-radiological comparative analysis. Abdom Radiol 2020;45(8):2378-2387 Journal

95. Liu Y, Li H, Ye N, Luo C-J, Hu Y-Y, Wu H, et al. : Non-Cirrhotic Liver is Associated with Poor Prognosis of Hepatocellular Carcinoma: A Literature Review. Med Sci Monit 2019;25 6615-6623 Journal

96. Stine JG, Wentworth BJ, Zimmet A, Rinella ME, Loomba R, Caldwell SH, et al. : Systematic review with meta-analysis: risk of hepatocellular carcinoma in non-alcoholic steatohepatitis without cirrhosis compared to other liver diseases. Aliment Pharmacol Ther 2018;48(7):696-703 Journal

97. Leung C, Yeoh SW, Patrick D, Ket S, Marion K, Gow P, et al. : Characteristics of hepatocellular carcinoma in cirrhotic and non-cirrhotic non-alcoholic fatty liver disease. World J Gastroenterol 2015;21(4):1189-1196 Journal

98. Abeysekera KWM, Macpherson I, Glyn-Owen K, McPherson S, Parker R, Harris R, et al. : Community pathways for the early detection and risk stratification of chronic liver disease: a narrative systematic review. The Lancet Gastroenterology & Hepatology 2022;In Press Journal Website

99. Ma X, Yang Y, Tu H, Gao J, Tan Y-T, Zheng J-L, et al. : Risk prediction models for hepatocellular carcinoma in different populations. Chin J Cancer Res 2016;28(2):150 Journal

100. Roberts SK, Majeed A, Kemp W : Controversies in the Management of Hepatitis B: Hepatocellular Carcinoma. Clin Liver Dis 2021;25(4):785-803 Journal

101. Voulgaris T, Papatheodoridi M, Lampertico P, Papatheodoridis GV : Clinical utility of hepatocellular carcinoma risk scores in chronic hepatitis B. Liver Int 2020;40(3):484-495 Journal

102. Hayward KL, McKillen BJ, Horsfall LU, McIvor C, Liew K, Sexton JO, et al. : Towards collaborative management of non-alcoholic fatty liver disease: a 'real-world' pathway for fibrosis risk assessment in primary care. Intern Med J 2021;52(10):1749-1758 Journal

103. Thomas J, Liao LM, Sinha R, Patel T, Antwi SO : Hepatocellular Carcinoma Risk Prediction in the NIH-AARP Diet and Health Study Cohort: A Machine Learning Approach. JHC 2022;9 69-81 Journal

104. Hajarizadeh B., Grebely J., Matthews GV, Martinello M., Dore GJ : Uptake of direct-acting antiviral treatment for chronic hepatitis C in Australia. J Viral Hepat 2018;25(6):640-648 Journal

105. Zeng H, Li L, Hou Z, Zhang Y, Tang Z, Liu S : Direct-acting Antiviral in the Treatment of Chronic Hepatitis C: Bonuses and Challenges. Int. J. Med. Sci. 2020;17(7):892-902 Journal

106. Howell J, Majumdar A, Fink MA, Byrne M, McCaughan G, Strasser SI, et al. : Turning the Tide on Hepatitis C Virus–Related Liver Transplantation: The Return on Investment in Hepatitis C Virus Treatment in Australia and New Zealand. Liver Transplant 2022;28(2):236-246 Journal

107. Lee T-P, Bernstein D : The impact of direct-acting antivirals on hepatitis C associated hepatocellular carcinoma. Hepatoma Res 2020;6(21): Journal

108. Lockart I, Yeo MGH, Hajarizadeh B, Dore G, Danta M, Abe K, et al. : HCC incidence after hepatitis C cure among patients with advanced fibrosis or cirrhosis: A meta-analysis. Hepatology 2022;76(1):139-154 Journal

109. Cronin KA, Connor RJ, Prorok PC, Weed DL : Case-Control Studies of Cancer Screening: Theory and Practice. J Natl Cancer Inst 1998;90(7):498-504 Journal

110. Zhang BH, Yang BH, Tang ZY : Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol 2004;130(7):417-422 Journal

111. Chen JG, Parkin DM, Chen QG, Lu JH, Shen QJ, Zhang BC, et al. : Screening for liver cancer: Results of a randomised controlled trial in Qidong, China. J. Med. Screen. 2003;10(4):204-209 Journal

112. Chang Y, Lairson DR, Chan W, Lu S-N, Aoki N : Cost-effectiveness of screening for hepatocellular carcinoma among subjects at different levels of risk: Cost-effectiveness of screening for HCC. J Evaluation Clin Pract 2011;17(2):261-267 Journal

113. Kuo S-C, Lin C-N, Lin Y-J, Chen W-Y, Hwang J-S, Wang J-D : Optimal intervals of ultrasonography screening for early diagnosis of Hepatocellular Carcinoma in Taiwan. JAMA Netw 2021;4(6):e2114680 Journal

114. Wu C-Y, Hsu Y-C, Ho HJ, Chen Y-J, Lee T-Y, Lin J-T : Association between ultrasonography screening and mortality in patients with hepatocellular carcinoma: a nationwide cohort study. Gut 2016;65(4):693-701 Journal

115. Nakai M, Yamamoto Y, Baba M, Suda G, Kubo A, Tokuchi Y, et al. : Prediction of hepatocellular carcinoma using age and liver stiffness on transient elastography after hepatitis C virus eradication. Sci Rep 2022;12(1):1449 Journal

116. Semmler G, Meyer EL, Kozbial K, Schwabl P, Hametner-Schreil S, Zanetto A, et al. : HCC risk stratification after cure of hepatitis C in patients with compensated advanced chronic liver disease. J Hepatol 2022;76(4):812-821 Journal

117. Mueller PP, Chen Q, Ayer T, Nemutlu GS, Hajjar A, Bethea ED, et al. : Duration and cost-effectiveness of hepatocellular carcinoma surveillance in hepatitis C patients after viral eradication. J Hepatol 2022;77(1):55-62 Journal

118. Jarvis H, Craig D, Barker R, Spiers G, Stow D, Anstee QM, et al. : Metabolic risk factors and incident advanced liver disease in non-alcoholic fatty liver disease (NAFLD): A systematic review and meta-analysis of population-based observational studies. PLOS Med 2020;17(4):e1003100 Journal

119. Huang DQ, El-Serag HB, Loomba R : Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2021;18(4):223-238 Journal

120. Orci LA, Sanduzzi-Zamparelli M, Caballol B, Sapena V, Colucci N, Torres F, et al. : Incidence of Hepatocellular Carcinoma in patients with nonalcoholic fatty liver disease: A Systematic Review, Meta-analysis, and Meta-regression. Clin Gastroenterol Hepatol 2022;20(2):283-292.e10 Journal

121. Yip TC-F, Chan HL-Y, Wong VW-S, Tse Y-K, Lam KL-Y, Wong GL-H : Impact of age and gender on risk of hepatocellular carcinoma after hepatitis B surface antigen seroclearance. J Hepatol 2017;67(5):902-908 Journal

122. Yang H, Bae SH, Nam H, Lee HL, Lee SW, Yoo SH, et al. : A risk prediction model for hepatocellular carcinoma after hepatitis B surface antigen seroclearance. J Hepatol 2022;77(3):632-641 Journal

123. Australian Bureau of Statistics : Estimates of Aboriginal and Torres Strait Islander Austraians. Reference Period June 2021. 2022; Website

124. Australian Institute of Health and Welfare : Contribution of chronic disease to the gap in adult mortality between Aboriginal and Torres Strait Islander and other Australians. (null) 2011; Website

125. Queensland Health : Cancer Data Explorer. 2022; Website

126. Wallace J, Pitts M, Ward J, McNally S : Management of chronic hepatitis B in the Torres Strait Islands: an identified need for a comprehensive public health approach to chronic hepatitis B in remote Australian Indigenous communities. Aust J Prim Health 2014;20(3):273-277 Journal

127. Anderson E, Ellard J, Wallace J : Torres Strait Islanders' understandings of chronic hepatitis B and attitudes to treatment. Aust J Prim Health 2016;22(4):316-319 Journal

128. Wigg AJ, Narayana SK, Hartel G, Medlin L, Pratt G, Powell EE, et al. : Hepatocellular carcinoma amongst Aboriginal and Torres Strait Islander peoples of Australia. EClinMed 2021;36 100919 Journal

129. Parker C., Tong SYC, Dempsey K., Condon J., Sharma SK, Chen JWC, et al. : Hepatocellular carcinoma in Australia's Northern Territory: High incidence and poor outcome. Med J Aust 2014;201(8):470-474 Journal

130. Condon JR, Cunningham J, Barnes T, Armstrong BK : Long-term trends in cancer mortality for Indigenous Australians in the Northern Territory. Med J Aust 2004;180(10):504-507 Journal

131. Condon JR, Zhang X, Dempsey K, Garling L, Guthridge S : Trends in cancer incidence and survival for Indigenous and non-Indigenous people in the Northern Territory. Med J Aust 2016;205(10):454-458 Journal

132. MacLachlan JH, Smith C, Towell V, Cowle BC : Viral Hepatitis Mapping Project: National Report 2018–19. (null) 2020;

133. Australian Bureau of Statistics : National Health Survey, alcohol consumption 2017-18. (null) 2018; Website

134. Australian Bureau of Statistics : National Health Survey, Body Mass Index, waist circumference, height and weight 2017-18. null: (null) 2018; Website

135. Australian Bureau of Statistics : National Health Survey, long-term health conditions, 2017-18. null: (null) 2018; Website

136. Australian Bureau of Statistics : National Aboriginal and Torres Strait Islander Health Survey. 2019; Website

137. Australian Bureau of Statistics : National Aboriginal and Torres Strait Islander Social Survey, 2014-15. Australian Bureau of Statistics 2016; Website

138. Davies J, Littlejohn M, Locarnini SA, Whiting S, Hajkowicz K, Cowie BC, et al. : The molecular epidemiology of hepatitis B in the Indigenous people of northern Australia: Hepatitis B genotypes in Australia. J Gastroenterol Hepatol 2013;28(7):1234-1241 Journal

139. Littlejohn M., Davies J., Yuen L., Edwards R., Sozzi T., Jackson K., et al. : Molecular virology of hepatitis B virus, sub-genotype C4 in northern Australian Indigenous populations. J Med Virol 2014;86(4):695-706 Journal

140. Davies J, Smith EL, Littlejohn M, Edwards R, Sozzi V, Jackson K, et al. : Towards genotype-specific care for chronic Hepatitis B: The first 6 years follow up from the CHARM cohort study. Open Forum Infect Dis 2019;6(11):ofz469 Journal

141. McMahon BJ, Nolen LD, Snowball M, Homan C, Negus S, Roik E, et al. : HBV Genotype: A Significant Risk Factor in Determining Which Patients With Chronic HBV Infection Should Undergo Surveillance for HCC: The Hepatitis B Alaska Study. Hepatology 2021;74(6):2965-2973 Journal

142. Kirby Institute : Progress towards hepatitis C elimination among Aboriginal and Torres Strait Islander people in Australia: monitoring and evaluation report, 2021. (null) 2021;

143. Australian Institute of Health and Welfare : National Drug Strategy Household Survey 2019. Website

144. Howell J, Ward JS, Davies J, Clark PJ, Davis JS : Hepatocellular carcinoma in Indigenous Australians: a call to action. Med J Aust 2021;214(5):201 Journal

145. Carroll M, Binks P, Campbell K, Tse E, Maddison M, Veysey M, et al. : Care on Country Improves uptake of Treatment for HCC in Indigenous Australians. J Hepatol 2021;74(S1):372A-373 Journal

146. Thel K. Hla, Sarah Bukulatjpi, Paula Binks, et al. : A “one stop liver shop” approach improves the cascade-of-care for Aboriginal and Torres Strait Islander Australians living with chronic hepatitis B in the Northern Territory of Australia. Int J Equity Health 2020;

147. Hosking K, Stewart G, Mobsby M, Skov S, Zhao Y, Su J-Y, et al. : Data linkage and computerised algorithmic coding to enhance individual clinical care for Aboriginal people living with chronic hepatitis B in the Northern Territory of Australia - Is it feasible?. PLoS One 2020;15(4):e0232207 Journal

148. Davies J, Davis JS, Hosking K, Binks P, Gargan C, Greenwood-Smith B, et al. : Eliminating chronic hepatitis B in the northern territory of Australia through a holistic care package delivered in partnership with the community. J Hepatol 2022;77(S1):s239-40

149. Hla TK, Bukulatjpi SM, Binks P, Gurruwiwi GG, Dhurrkay RG, Davies J : A “one stop liver shop” approach improves the cascade-of-care for Aboriginal and Torres Strait Islander Australians living with chronic hepatitis B in the Northern Territory of Australia: results of a novel care delivery model. Int J Equity Health 2020;19(1):64 Journal

150. Tashkent K, Olynyk J, Wigg AJ : Liver disease in Aboriginal and Torres Strait Islander peoples. J Aust Indigenous HealthInfoNet 2022;3(4): Journal

151. Menzies School of Health Research : Hep B PAST. 2022; Website

152. Menzies School of Health Research : PROLIFICA-NT. 2022; Website

153. International Agency for Research on Cancer : GLOBOCAN 2020 Cancer Today, Estimated number of new cases in 2020, liver, both sexes, all ages. 2020; Website

154. CDA Foundation : Countries Dashboard - Polaris. 2022; Website

155. Maucort-Boulch D, de Martel C, Franceschi S, Plummer M : Fraction and incidence of liver cancer attributable to hepatitis B and C viruses worldwide. Int J Cancer 2018;142(12):2471-2477 Journal

156. Australian Bureau of Statistics : Australia's Population by Country of Birth 2020-21. 2021; Website

157. Feletto E, Sitas F : Quantifying disparities in cancer incidence and mortality of Australian residents of New South Wales (NSW) by place of birth: an ecological study. BMC Public Health 2015;15(1):823 Journal

158. McDermott S, DesMeules M, Lewis R, Gold J, Payne J, Lafrance B, et al. : Cancer Incidence Among Canadian Immigrants, 1980–1998: Results from a National Cohort Study. J Immigr Minor Health 2011;13(1):15-26 Journal

159. Arnold M, Razum O, Coebergh J-W : Cancer risk diversity in non-western migrants to Europe: An overview of the literature. Eur J Cancer 2010;46(14):2647-2659 Journal

160. Mittal S, Kramer JR, Omino R, Chayanupatkul M, Richardson PA, El-Serag HB, et al. : Role of age and race in the risk of Hepatocellular Carcinoma in veterans with Hepatitis B Virus infection. Clin Gastroenterol Hepatol 2018;16(2):252-259 Journal

161. Duberg A-S, Lybeck C, Fält A, Montgomery S, Aleman S : Chronic hepatitis B virus infection and the risk of hepatocellular carcinoma by age and country of origin in people living in Sweden: A national register study. Hepatol Commun 2022;6(9):2418-2430 Journal

162. Huang DQ, Hoang JK, Leong J, Riveiro-Barciela M, Maeda M, Yang JD, et al. : Differential characteristics and outcomes of Asian and non-Asian patients with HBV-related hepatocellular carcinoma. Liver Int 2021;41(8):1922-1932 Journal

163. Nguyen VTT, Razali K, Amin J, Law MG, Dore GJ : Estimates and projections of hepatitis B-related hepatocellular carcinoma in Australia among people born in Asia-Pacific countries. J Gastroenterol Hepatol 2008;23(6):922-929 Journal

164. Waziry R, Grebely J, Amin J, Alavi M, Hajarizadeh B, George J, et al. : Survival following hospitalization with hepatocellular carcinoma among people notified with hepatitis B or C virus in Australia (2000-2014). Hepatol Commun 2017;1(8):736-747 Journal

165. Akbar SM, Al Mahtab M, Begum F, Hossain SAS, Sarker S, Shrestha A, et al. : Implications of birth-dose vaccination against Hepatitis B Virus in Southeast Asia. Vaccines 2021;9(4):374 Journal

166. Woodring J, Pastore R, Brinke A, Ishikawa N, Takashima Y, Tohme R : Progress toward Hepatitis B control and elimination of mother-to-child transmission of Hepatitis B Virus — Western Pacific Region, 2005–2017. MMWR Morb Mortal Wkly Rep 2019;68(8):195-200 Journal

167. Chang M-H : Hepatitis B vaccination and Hepatocellular Carcinoma rates in boys and girls. JAMA 2000;284(23):3040 Journal

168. Chang M-H, You S-L, Chen C-J, Liu C-J, Lai M-W, Wu T-C, et al. : Long-term Effects of Hepatitis B Immunization of Infants in Preventing Liver Cancer. Gastroenterol 2016;151(3):472-480.e1 Journal

169. Flores JE, Thompson AJ, Ryan M, Howell J : The Global Impact of Hepatitis B Vaccination on Hepatocellular Carcinoma. Vaccines 2022;10(5):793 Journal

170. Rampal S, Mahadeva S, Guallar E, Bulgiba A, Mohamed R, Rahmat R, et al. : Ethnic differences in the prevalence of Metabolic Syndrome: Results from a multi-ethnic population-based survey in Malaysia. PLOS ONE 2012;7(9):e46365 Journal

171. Low E, Apostolov R, Wong D, Lin S, Kutaiba N, Grade J, et al. : Hepatocellular carcinoma surveillance and quantile regression for determinants of underutilisation in at-risk Australian patients. World J Gastroenterol 2021;13(12):2149-2160 Journal

172. Gellert L., Jalaludin B., Levy M. : Hepatocellular carcinoma in Sydney South West: late symptomatic presentation and poor outcome for most. Int Med J 2007;37(8):516-522 Journal

173. World Health Organization Regional Office for Africa : Hepatitis. 2022; Website

174. Mak D, Kramvis A : Epidemiology and aetiology of hepatocellular carcinoma in Sub-Saharan Africa. Hepatoma Res 2021;7 39 Journal

175. Kew MC : Epidemiology of hepatocellular carcinoma in sub-Saharan Africa. Ann Hepatol 2013;12(2):173-182 Journal

176. Sharma R, Aashima, Nanda M, Fronterre C, Sewagudde P, Ssentongo AE, et al. : Mapping Cancer in Africa: A Comprehensive and Comparable Characterization of 34 Cancer Types Using Estimates From GLOBOCAN 2020. Front. Public Health 2022;10 839835 Journal

177. World Health Organization International Agency for Research on Cancer : Global Cancer Observatory. 2022; Website

178. Pujol FH, Navas M-C, Hainaut P, Chemin I : Worldwide genetic diversity of HBV genotypes and risk of hepatocellular carcinoma. Cancer Lett 2009;286(1):80-88 Journal

179. Wong GL-H, Chan HL-Y, Yiu KK-L, Lai JW-Y, Chan VK-K, Cheung KK-C, et al. : Meta-analysis: The association of hepatitis B virus genotypes and hepatocellular carcinoma. Aliment Pharmacol Ther 2013;37(5):517-526 Journal

180. Dika IE, Harding JJ, Abou-Alfa GK : Hepatocellular carcinoma in patients with HIV. Curr Opin HIV AIDS 2017;12(1):20-25 Journal

181. Maponga TG, Glashoff RH, Vermeulen H, Robertson B, Burmeister S, Bernon M, et al. : Hepatitis B virus-associated hepatocellular carcinoma in South Africa in the era of HIV. BMC Gastroenterol 2020;20(1):226 Journal

182. Saud LRC, Chagas AL, Maccali C, Pinto PVA, Horvat N, Alencar RSSM, et al. : Hepatocellular carcinoma in patients coinfected with hepatitis B or C and HIV: more aggressive tumor behavior?. Eur J Gastroenterol Hepatol 2021;33(4):583-588 Journal

183. Tang B, Kruger WD, Chen G, Shen F, Lin WY, Mboup S, et al. : Hepatitis B viremia is associated with increased risk of hepatocellular carcinoma in chronic carriers. J Med Virol 2004;72(1):35-40 Journal

184. Chen G, Lin W, Shen F, Iloeje UH, London WT, Evans AA : Past HBV viral load as predictor of mortality and morbidity from HCC and chronic liver disease in a prospective study. Am J Gastroenterol 2006;101(8):1797-1803 Journal

185. Liu T-T, Fang Y, Xiong H, Chen T-Y, Ni Z-P, Luo J-F, et al. : A case-control study of the relationship between hepatitis B virus DNA level and risk of hepatocellular carcinoma in Qidong, China. World J Gastroenterol 2008;14(19):3059-3063 Journal

186. Liu Yan, Wu Felicia : Global Burden of Aflatoxin-Induced Hepatocellular Carcinoma: A Risk Assessment. Environ Health Perspect 2010;118(6):818-824 Journal

187. Kew M.C. : Hepatic Iron Overload and Hepatocellular Carcinoma. Liver Cancer 2014;3(1):31-40 Journal

188. Petrick JL, McGlynn KA : The changing epidemiology of primary liver cancer. Curr Epidemiol Rep 2019;6(2):104-111 Journal

189. Shimakawa Y, Lemoine M, Njai HF, Bottomley C, Ndow G, Goldin RD, et al. : Natural history of chronic HBV infection in West Africa: a longitudinal population-based study from The Gambia. Gut 2016;65(12):2007-2016 Journal

190. Dakurah OB, Tamandjou CRT, Zunza M, Preiser W, Maponga TG : Viral hepatitis associated hepatocellular carcinoma on the African continent, the past, present, and future: a systematic review. BMC Cancer 2021;21(1):715 Journal

191. World Health Organization : Hepatitis B vaccination coverage. 2021; Website

192. Allard N, Cabrie T, Wheeler E, Richmond J, MacLachlan J, Emery J, et al. : The challenge of liver cancer surveillance in general practice: Do recall and reminder systems hold the answer?. Aust Fam Physician 2017;46(11):859-864

193. Wallace J, McNally S, Richmond J, Hajarizadeh B, Pitts M : Challenges to the effective delivery of health care to people with chronic hepatitis B in Australia. Sex Health 2012;9(2):131-137 Journal

194. Wallace J, Hajarizadeh B, Richmond J, McNally S : Challenges in managing patients in Australia with chronic hepatitis B: the General Practitioners' perspective. Aust N Z J Public Health 2013;37(5):405-410 Journal

195. Sievert K, O'Neill P, Koh Y, Lee J-H, Dev A, Le S : Barriers to Accessing Testing and Treatment for Chronic Hepatitis B in Afghan, Rohingyan, and South Sudanese Populations in Australia. J Immigr Minor Health 2018;20(1):140-146 Journal

196. Mude W, Fisher C, Richmond J, Wallace J, Le Gautier R : A qualitative investigation of barriers, support-seeking and coping among South Sudanese people with chronic hepatitis B in Australia. Aust J Prim Health 2019; Journal

197. Singal A., Volk ML, Waljee A., Salgia R., Higgins P., Rogers MAM, et al. : Meta-analysis: Surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. Aliment Pharmacol Ther 2009;30(1):37-47 Journal

198. Australian Government Department of Health and Aged Care : MBS Online. 2022; Website

199. Yang JD, Addissie BD, Mara KC, Harmsen WS, Dai J, Zhang N, et al. : GALAD Score for Hepatocellular Carcinoma Detection in Comparison with Liver Ultrasound and Proposal of GALADUS Score. Cancer Epidemiol Biomarkers Prev 2019;28(3):531-538 Journal

200. Nazareth S, Leembruggen N, Tuma R, Chen S-L, Rao S, Kontorinis N, et al. : Nurse-led hepatocellular carcinoma surveillance clinic provides an effective method of monitoring patients with cirrhosis. Int J Nurse Pract 2016;22(S2):3-11 Journal

201. Qian MY, Yuwei JR, Angus P., Schelleman T., Johnson L., Gow P. : Efficacy and cost of a hepatocellular carcinoma screening program at an Australian teaching hospital. J Gastroenterol Hepatol 2010;25(5):951-6 Journal

202. Kennedy NA, Rodgers A., Altus R., McCormick R., Wundke R., Wigg AJ : Optimisation of hepatocellular carcinoma surveillance in patients with viral hepatitis: A quality improvement study. Int Med J 2013;43(7):772-777 Journal

203. Bertot LC, Jeffrey GP, Wallace M, MacQuillan G, Garas G, Ching HL, et al. : Nonalcoholic fatty liver disease-related cirrhosis is commonly unrecognized and associated with hepatocellular carcinoma. Hepatol Commun 2017;1(1):53-60 Journal

204. Freeman V, Hughes S, Worthington J, He E, Feletto E : Roadmap to Liver Cancer Control: Scoping Review. Prepared for Cancer Council Australia and the Department of Health. (null) 2021;

205. Cancer Council Australia Colorectal Cancer Guidelines Working Party : Clinical practice guidelines for the prevention, early detection and management of colorectal cancer. (null) 2017; Website

206. Cancer Council Australia Cervical Cancer Screening Guidelines Working Party : National Cervical Screening Program: Guidelines for the management of screen-detected abnormalities, screening in specific populations and investigation of abnormal vaginal bleeding. Clinical Guidelines 2018; Website

207. Robotin M., Patton Y., Kansil M., Penman A., George J. : Cost of treating chronic hepatitis B: Comparison of current treatment guidelines. World J Gastroenterol 2012;18(42):6106-6113 Journal

208. Wang S, Gum D, Merlin T : Comparing the ICERs in Medicine Reimbursement Submissions to NICE and PBAC—Does the Presence of an Explicit Threshold Affect the ICER Proposed?. Value Health 2018;21(8):938-943 Journal

209. Singal AG, Lok AS, Feng Z, Kanwal F, Parikh ND : Conceptual Model for the Hepatocellular Carcinoma Screening Continuum: Current Status and Research Agenda. Clin Gastroenterol Hepatol 2020; Journal

210. Chandran V, Rajandran A, Loo KF, Bate J, Wigg AJ, Chinnaratha MA : The Face of Hepatocellular Carcinoma (HCC) is Changing: Analysis of the temporal trends in aetiology and clinical patterns of HCC in South Australia. Int Med J 2022;In Press Journal

211. Jin D, Brener L, Treloar C : Knowledge and beliefs about hepatitis B virus infection and associated factors among Chinese migrants in Australia: The result of a quantitative study. Health Social Care Comm 2022;30(3):918-925 Journal

212. Guirgis M., Nusair F., Bu YM, Yan K., Zekry AT : Barriers faced by migrants in accessing healthcare for viral hepatitis infection: Barriers faced by migrants. Int Med J 2012;42(5):491-496 Journal

213. Robotin MC, Kansil MQ, George J, Howard K, Tipper S, Levy M, et al. : Using a population-based approach to prevent hepatocellular cancer in New South Wales, Australia: effects on health services utilisation. BMC Health Services Research 2010;10(1):215 Journal

214. Menzies School of Health Research : Hep B Story. 2022; Website

215. Hong SB, Kim DH, Choi SH, Kim SY, Lee JS, Lee NK, et al. : Inadequate Ultrasound Examination in Hepatocellular Carcinoma Surveillance: A Systematic Review and Meta-Analysis. J Clin Med 2021;10(16):3535 Journal

216. Sparchez Z, Craciun R, Caraiani C, Horhat A, Nenu I, Procopet B, et al. : Ultrasound or Sectional Imaging Techniques as Screening Tools for Hepatocellular Carcinoma: Fall Forward or Move Forward?. J Clin Med 2021;10(5):903 Journal

217. Cancer Council Australia : Roadmap for Liver Cancer Control in Australia project: Environmental Scan Draft Report. (null) 2021;

218. Poustchi H, Farrell GC, Strasser SI, Lee AU, McCaughan GW, George J : Feasibility of conducting a randomized

control trial for liver cancer screening: is a randomized controlled trial for liver cancer screening feasible or still needed?. Hepatology 2011;54(6):1998-2004 Journal

219. Patel AA, Walling AM, Ricks-Oddie J, May FP, Saab S, Wenger N : Palliative Care and Health Care Utilization for Patients With End-Stage Liver Disease at the End of Life. Clin Gastroenterol Hepatol 2017;15(10):1612-1619.e4 Journal

220. Gofton C, Agar M, George J : Early Implementation of Palliative and Supportive Care in Hepatocellular Carcinoma. Semin Liver Dis 2022; Journal

221. Hepatology Clinical. Journal of Gastroenterology and Hepatology 2022;37(S1):41-102 Journal Website