Version for NHRMC Council

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

Preferred citation for the guideline publication: Cancer Council Australia Hepatocellular Carcinoma Surveillance Working Group. Clinical practice guidelines for hepatocellular carcinoma surveillance for people at high risk in Australia. Summary of Recommendations [Month] 2023. Sydney: Cancer Council Australia.

February 2023

Contents

Appendix A. Guideline development process 3
Appendix B. Clinical question list 11
Appendix C. Existing guidelines 14
Appendix D1. Technical report for question 1 23
Appendix D2. Technical report for question 2 54
Appendix D3. Technical report for question 3 78
Appendix D4. Technical report for question 4 100
Appendix D5. Technical report for question 5 120
Appendix D6. Technical report for question 6 134
Appendix D7. Modelling results 164
Appendix E. Data on Sub-Saharan African-born population in Australia 186
Appendix F. Decision aid 192
Appendix G. Guideline Recommendations Comparison 193
Appendix H1. NHMRC requirements 205
Appendix H2. Administrative report 214
Appendix H3. Dissemination plan 221
Appendix I. Working group members and contributors 222
Appendix J. Conflict of interest register 227

Appendix A. Guideline development process

Introduction

These clinical practice guidelines were developed as part of a project entitled “Roadmap to Liver Cancer Control”. The guidelines were developed after identifying a need for evidence-based hepatocellular carcinoma (HCC) surveillance guidelines for the Australian context that considered risk categorisation and priority populations at a national level.

The development of the guidelines was commissioned and funded by the Department of Health and Aged Care.

Guideline development, in line with NHMRC standards, commenced in November 2021.

Guidelines Development Group

Cancer Council Australia (CCA) approached respected experts in liver cancer control to establish an Expert Advisory Group (EAG). The EAG included specialists from various disciplines as well as consumers and was formed at the start of the Roadmap project in order to provide guidance on the research questions, evidence reviews and interpretation of the findings. The EAG co-Chairs also jointly chaired the Working Group responsible for developing the guidelines.

Execution of the overall project (i.e. management and strategic leadership) was conducted by the Project Team under the guidance of the EAG.

For the purpose of the guideline development, additional experts were invited to join in the Working Group which was responsible for translating the evidence into practical recommendations that are applicable to Australian healthcare settings.

The Working Group was divided into smaller groups that worked on specific aspects of the guidelines, with each group guided by a group lead. In addition to the smaller Working Groups, a Community Reference Group (CRG), including people with lived experience of liver cancer or precursor conditions a, reviewed the guidelines from a patient perspective. Members of the CRG were recruited through contacts across the Cancer Council and EAG networks. We also used a snowballing method to identify and invite additional members for the CRG.

Prospective members of the Working Group or CRG were invited to a meeting with members of the Project Team who explained the purpose of the guidelines, the expectations of their potential involvement and answered any questions. Once they agreed to participate, each individual was asked to declare any conflicts of interest and formalise their participation. An information session was held (and recorded) for all members and then each smaller group held an introductory meeting so all members could meet each other and discuss their personal or clinical experience as related to liver disease and liver cancer. Support for all members, including the CRG, was available through the Project Team as required.

Guideline 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. Based on evidence from a prior scoping review the EAG formulated the following clinical questions for the guidelines:

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

These guidelines do not cover hepatitis B/hepatitis C 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.

Steps in preparing clinical practice guidelines to NHMRC criteria

The Project Team, based at the Daffodil Centre, conducted the systematic reviews, comprising literature searches, screening against pre-determined inclusion and exclusion criteria, and critical evaluation, data extraction and GRADE (Grading of Recommendations, Assessment, Development and Evaluations) assessment of the included literature. The Project Team was responsible for liaising with the EAG and Working Group members regarding content development, content review and compiling the document. The clinical practice guidelines were developed according to the procedures and requirements for meeting the 2016 NHMRC Guideline Standards described in the 2018 NHMRC Guidelines for Guidelines following the steps outlined below.

Developing a structured clinical question

The focus for the guidelines required careful consideration of the clinical questions (described above in Guideline scope) to determine the key areas. PICOs were developed by each Working Group, under the guidance from the group leads and EAG, to guide the systematic reviews, with each Working Group focusing on one PICO question (see Appendix B). The PICO question focuses on the Population, Intervention, Comparison and Outcomes of relevant published literature and is used to define the scope and identify the key components of clinical evidence. Each PICO question was addressed by a systematic review.

Searching for existing relevant guidelines and systematic reviews

Relevant recent (2015 onwards) guidelines were identified by scanning the citations identified by the literature search and by Working Group members. To be considered for adoption by the Working Group, guidelines had to be evidence-based and meet the pre-specified criteria of scores of greater or equal to 70% for the following domains: rigour of development, clarity of presentation and editorial independence of the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/). Guidelines were not considered for adoption if they were not based on systematic reviews of the evidence i.e. did not report using systematic methods to search for evidence, did not clearly describe the criteria for selecting the evidence or did not assess the risk of bias or where this is not possible, appraise the quality of the evidence.

Conducting the systematic literature searches

Systematic search strategies were developed by the Project Team for each PICO question (see Appendix D for full details on search strategy). Medline (including MEDLINE Epub Ahead of Print, I-Process & Other Non-Indexed Citations) and Embase databases were

searched on 1 February 2022. Searches were limited to articles published in English from 1 January 2000 onwards. Complete lists of the terms used for each PICO question are included as Appendix D. The Cochrane Database of Systematic Reviews was searched on 31 March 2022 combining the search terms “liver cancer” and “screen”. Reference lists of included articles, recent relevant guidelines and systematic reviews were checked for potential additional articles. The process of identifying relevant articles for each systematic review, as well as a table of the retrieved articles that were not included and the reason for their exclusion, are documented in Appendix D. Most articles were excluded because the population was not relevant, the publication type was not relevant, or the study type or design was not relevant. The characteristics of all included studies, the results, risk of bias and/or quality appraisal assessments, and GRADE assessments for each outcome of interest were summarised and described in evidence tables (see Appendix D).

Screening of literature results against pre-defined inclusion and exclusion criteria

As part of the systematic review process all retrieved literature results were screened against the pre-defined inclusion and exclusion criteria in two stages.

a) First screen

During the first screening round, the titles and abstracts of all retrieved literature were screened by one or two reviewers. Clearly irrelevant and duplicate articles were removed.

b) Second screen

Full texts of the remaining articles were assessed for inclusion by one or two reviewers. Articles that met the inclusion criteria were forwarded for critical appraisal and data extraction.

Critical appraisal and data extraction of each included article

Two assessors independently assessed the risk of bias or quality of each of the included studies using a study design and type specific assessment tool (see Appendix D for all quality assessment tools). Any disagreements were adjudicated by a third reviewer. For all included articles, the relevant data were extracted and summarised in study characteristics and evidence tables. Extracted data were checked by a second assessor. These tables are included in the technical report for each question (see Appendix D).

Assessing the body of evidence and formulating recommendations

Two reviewers assessed the certainty of the extracted body of evidence for each outcome using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach which classifies the certainty of the evidence as high, moderate, low or very low (Table 1). The reviewers presented the evidence with GRADE assessments and interpretations for each outcome in evidence summary tables. The GRADE assessments and evidence summary tables are included in the technical report for each systematic review question and PICO (see Appendix D) The Project Team drafted an outline for each PICO incorporating existing data and main findings from the technical report. The Working Groups reviewed and discussed the technical report for their specific question. Any queries and concerns were passed on to the Project Team.

Table 1. Grading of the certainty of the evidence.

Grade	Certainty of evidence	Description

A	High	We are very confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
D	Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

After reviewing the technical report, the Working Groups developed recommendations in short form (i.e. dot points), ensuring each point translated into an action, and added these to the draft PICO outline. Based on these, the medical writer produced draft recommendations which the Working Groups reviewed and commented on. Each recommendation needed to address the specific clinical question and was ideally written as an action statement.

The Working Group leads, in collaboration with their Working Group members and Project Team assessed the body of evidence and evidence statements and assigned an overall grade to each recommendation (Table 2). The strength of recommendations was determined by the balance between desirable and undesirable consequences of alternative management strategies, quality of evidence, variability in values and preferences, and resource use. Where a systematic review was conducted but no evidence was identified, a consensus-based recommendation was developed.

Table 2. Overall recommendation grades.

Grade	Description
1	*Strong*: Recommendation is made with strong certainty. Most informed patients would choose the recommended management and clinicians can structure their interactions with patients accordingly.
2	*Weak*: Patients' choices will vary according to their values and preferences, and clinicians must ensure that patients' care is in keeping with their values and preferences.

In addition to developing evidence-based recommendations authors could also draft practice points when a matter was outside the scope of the search strategy for the systematic review. The leads were asked to draw on high-level evidence, particularly international guidelines, consensus statements and key literature considered to be relevant to Australian practice, to develop information and practice points. The Working Groups also outlined where evidence was lacking.

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 types of recommendations included in these guidelines are shown in Table 3.

Table 3. Types of recommendations.

Type	Description
Evidence-based recommendation	Recommendations based on systematic review conducted for these guidelines
Adapted evidence-based recommendation	Recommendations adopted/adapted from existing evidence-based clinical practice guidelines
Consensus-based recommendation	Recommendations based on systematic review conducted for these guidelines where no evidence was identified
Practice point	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.

Similar to the NICE and other guidelines, the choice of recommendation 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 important of an issue rather than its urgency.

Writing the content

For each clinical question, the Working Group leads in collaboration with the Project Team and medical writer produced a guideline chapter incorporating the evidence statement, narrative and recommendations using the following format:

- general introduction to the clinical question
- background to the clinical question, including its clinical importance and historical evidence, where relevant
- review of the evidence, including the number, quality and findings of studies identified by the systematic review
- evidence summary in tabular form including evidence statements, levels of evidence of included studies, and reference citations
- recommendation(s) and corresponding grade(s), and practice points
- implications for implementation of the recommendations, including possible effects on usual care, organisation of care, and any resource implications
- discussion, including unresolved issues, relevant studies currently underway, and future research priorities
- references.

Each group assessed the evidence and developed a group outline, with each draft often undergoing several iterations.

Review of the draft chapters

Draft guideline sections were circulated to the CRG for their input and the EAG for review. The groups were asked to review the content and submit feedback which was then brought back to the Working Groups and medical writer to discuss incorporation. The Working Group leads facilitated incorporation of the feedback before the draft guidelines were posted on CCA's website for external / public consultation.

Public consultation

A complete draft of the guideline was posted on CCA's website for external/public consultation, as well as, sent to specific organisations and individuals to provide feedback in October 2022.

All feedback received during the consultation period was summarised and disseminated to the relevant Working Group leads for review. They updated the guidelines in consultation with their Working Group members as appropriate.

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 as considered 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 (204) 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 an aggressive approach 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 subsidised through MBS. Despite this, the Working Group consider 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 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.

Organisations formally endorsing the guidelines

Endorsement of the guidelines will be sought from the following organisations:

- Royal Australian and New Zealand College of Radiologists (RANZCR)
- Royal Australian College of General Practitioners (RACGP)
- Royal Australasian College of Surgeons (RACS)
- Royal Australasian College of Physicians (RACP)
- Royal College of Pathologists of Australasia (RCPA)
- Gastroenterological Society of Australia (GESA)
- The Liver Foundation
- Hepatitis Australia
- Hepatitis Queensland
- LiverWell
- Australasian Hepatology Association (AHA)
- Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM)
- The Transplantation Society of Australia and New Zealand (TSANZ)
- Clinical Oncology Society of Australia (COSA)

[This is a placeholder for organisations that we will request endorsement from once the guidelines are NHMRC approved]

Dissemination and implementation

CCA will be responsible for and lead the implementation of the final guidelines, with guidance from the Project Team and the Working Group.

CCA is following a multi-strategy approach for the dissemination and implementation of the guidelines.

The guidelines will be published online via the CCA website, alongside the suite of Clinical Guidelines, making them a web-based global resource. A short-form PDF version may be available on request for reference, including all recommendations. The online guideline version increases availability as well as accessibility, and usage will be tracked and analysed with a web analytics solution.

CCA will undertake media and PR activity including, press releases to appropriate medical media contacts and PR activity in trade and clinical publications. In addition, the final guideline will be launched via email alert to professional organisations, interested groups and clinical experts in the field, directing them via URL link to the wiki guidelines and all associated resources. Australian health websites, such as EviQ will be approached to link to the online guidelines.

Promotion and dissemination will also be conducted through publication of papers in peer-reviewed journals, promotion at scientific meetings, national and international conferences and other continuing medical education events. Working Group members, and other identified local opinion leaders may be identified and approached to facilitate dissemination and act as champions for the guidelines.

The guidelines will be included in an education module being developed by the Liver Foundation with GPs. Further implementation options are explored as part of the Roadmap project.

Journal articles developed out of the guideline

The Project Team and lead authors of the guidelines aim to develop and submit articles out of their sections to promote usage of the guideline.

Future updates

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 10 years.

Appendix B. Clinical question list

The development of the HCC guidelines 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?*
   a. *by aetiology*
   b. *by priority population.*
3. *How would surveillance for HCC be provided to the target population in an effective, feasible, acceptable, and cost-effective way?*

Each of the systematic reviews conducted were registered in PROSPERO (International prospective register of systematic reviews).

PICO question 1 (section lead: Professor Stuart Roberts):

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? A systematic review of interventional studies. [CRD42022323067]

Population	***Intervention***	***Comparator***	***Outcomes***	***Study design***
People with: non-cirrhotic liver disease or Cirrhotic patients who have been treated for HCV with direct acting antivirals	HCC surveillance	No surveillance Usual or standard care	Overall mortality Liver disease-related mortality Liver cancer mortality Proportion of liver cancers that are early-stage Cost-effectiveness	Randomised controlled trials Cohort studies Modelling studies

HCC = Hepatocellular carcinoma; HCV = hepatitis C virus

PICO question 2 (section lead: Professor Leon Adams):

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? A systematic review of prognostic studies. [CRD42022323310]

Population	***Intervention***	***Comparator***	***Outcomes***	***Study design***
HCC patients with non-cirrhotic liver disease or Cirrhotic patients with HCC who have been treated for HCV with direct acting antivirals	Previous HCC surveillance	No previous surveillance	Survival Proportion of liver cancers that are early stage at diagnosis Cost-effectiveness	Observational cohort studies

HCC = Hepatocellular carcinoma; HCV = hepatitis C virus

PICO question 3 (section lead: Dr. Jane Davies):

Does HCC surveillance improve liver cancer outcomes for Aboriginal and Torres Strait Islander people? A systematic review of interventional studies. [CRD42022323316]

Population	***Intervention***	***Comparator***	***Outcomes***	***Study design***
Aboriginal and Torres Strait Islander peoples	HCC surveillance programs	No surveillance Usual or standard care	Overall mortality Liver disease-related mortality Liver cancer mortality Proportion of liver cancers that are early-stage Cost-effectiveness	Randomised controlled trials Cohort or case-control studies Modelling studies

HCC = Hepatocellular carcinoma

PICO question 4 (section lead: Associate Professor Behzad Hajarizadeh):

Does HCC surveillance improve liver cancer outcomes for Asian or Pacific-born people in Australia? A systematic review of interventional studies. [CRD42022323332]

Population	***Intervention***	***Comparator***	***Outcomes***	***Study design***
Asian or Pacific-born people in Australia	HCC surveillance programs	No surveillance Usual or standard care	Overall mortality Liver disease-related mortality Liver cancer mortality Proportion of liver cancers that are early stage Cost-effectiveness	Randomised controlled trials Cohort or case-control studies Modelling studies

HCC = Hepatocellular carcinoma

PICO question 5 (section lead: Dr Jennifer MacLachlan):

Does HCC surveillance improve liver cancer outcomes for sub-Saharan Africa-born people in Australia? A systematic review of interventional studies. [CRD42022323344]

Population	***Intervention***	***Comparator***	***Outcomes***	***Study design***
Sub-Saharan Africa-born people in Australia	HCC surveillance programs	No surveillance Usual or standard care	Overall mortality Liver disease-related mortality Liver cancer mortality Proportion of liver cancers that are early stage Cost-effectiveness	Randomised controlled trials Cohort or case-control studies Modelling studies

HCC = Hepatocellular carcinoma

PICO question 6 (section lead: Associate Professor Suzanne Mahady):

Does the addition of alpha-fetoprotein (AFP) testing to 6-monthly ultrasound imaging for HCC surveillance improve liver cancer outcomes? A systematic review of interventional studies. [CRD42022323358]

Population	***Intervention***	***Comparator***	***Outcomes***	***Study design***
Adults with cirrhotic or non-cirrhotic liver disease undergoing HCC surveillance	HCC surveillance with 6-monthly ultrasound + AFP	HCC surveillance with 6-monthly ultrasound only	Overall mortality Liver disease-related mortality Liver cancer mortality Proportion of liver cancers that are early stage Cost-effectiveness	Randomised controlled trials Interventional cohort studies Modelling studies Australian non-comparative studies - case series or above study designs with single arm analysis of intervention **or** comparator

AFP = alpha-fetoprotein; HCC = Hepatocellular carcinoma

Appendix C. Existing guidelines

Table 1: Existing guidelines from which adapted recommendations and practice points were sourced.

Organisation	**Guideline**
World Health Organization (WHO)	Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection 2015 (1)
National Institute for Health and Care excellence (NICE)	Hepatitis B (chronic): diagnosis and management 2013 updated 2017 (2)
National Institute for Health and Care excellence (NICE)	Cirrhosis in over 16s: assessment and management 2016 (3)
American Association for the Study of Liver Diseases (AASLD)	Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases (4)
American Association for the Study of Liver Diseases (AASLD)	Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance (5)
Gastroenterological Society of Australia (GESA)	Australian recommendations for the management of hepatocellular carcinoma: a consensus statement 2020 (6)
European Association for the Study of the Liver (EASL)	Clinical Practice Guidelines: Management of hepatocellular carcinoma 2018 (7)
Gastroenterological Society of Australia (GESA)	Australian consensus recommendations for the management of hepatitis B infection 2022 (8)

Asian Pacific Association for the Study of the Liver (APASL)	Asia–Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update (10)
Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM)	Decision making in Hepatitis B 2021 (9)

Table 2. Overview of international and national clinical recommendations for HCC surveillance

Guideline	Recommendation
NICE (2)	Patients with chronic hepatitis B (recommendations 17.1–17.3): 1. Perform 6-monthly surveillance for HCC by hepatic ultrasound and alpha-fetoprotein testing in people with significant fibrosis (METAVIR stage greater than or equal to F2 or Ishak stage greater than or equal to 3) or cirrhosis. 2. In people without significant fibrosis or cirrhosis (METAVIR stage less than F2 or Ishak stage less than 3), consider 6-monthly surveillance for HCC if the person is older than 40 years and has a family history of HCC and HBV DNA greater than or equal to 20,000 IU/ml. 3. Do not offer surveillance for HCC in people without significant fibrosis or cirrhosis (METAVIR stage less than F2 or Ishak stage less than 3) who have HBV DNA less than 20,000 IU/ml and are younger than 40 years.
NICE (3)	Patients with cirrhosis (recommendations 1.2.4–1.2.6): 1. Offer ultrasound (with or without measurement of serum alpha-fetoprotein) every 6 months as surveillance for hepatocellular carcinoma (HCC) for people with cirrhosis who do not have hepatitis B virus infection. 2. For people with cirrhosis and hepatitis B virus infection, see the surveillance testing for hepatocellular carcinoma in adults with chronic hepatitis B section in NICE's hepatitis B (chronic) guideline. 3. Do not offer surveillance for HCC for people who are receiving end of life care.
WHO (1)	Patients with chronic hepatitis B 1. Routine surveillance for HCC with abdominal ultrasound and alpha-fetoprotein testing every six months is recommended for: • persons with cirrhosis, regardless of age or other risk factors *(Strong recommendation, low quality of evidence)* • persons with a family history of HCC

	(Strong recommendation, low quality of evidence) • persons aged over 40 years (lower age may apply according to regional incidence of HCC), without clinical evidence of cirrhosis (or based on aspartate aminotransferase to platelet ratio index (APRI) score ≤2), and with HBV DNA level >2000 IU/mL (where HBV DNA testing is available). *(Conditional recommendation, low quality of evidence)*
AASLD (4)	Patients with cirrhosis (recommendations 1A-1C) 1A. The AASLD recommends surveillance of adults with cirrhosis because it improves overall survival. *Quality/Certainty of Evidence: Moderate Strength of Recommendation: Strong* 1B. The AASLD recommends surveillance using ultrasound, with or without AFP, every 6 months. *Quality/Certainty of Evidence: Low* *Strength of Recommendation: Conditional* 1C. The AASLD recommends not performing surveillance of patients with cirrhosis with Child's class C unless they are on the transplant waiting list, given the low anticipated survival for patients with Child's C cirrhosis. *Quality/Certainty of the Evidence: Low* *Strength of Recommendation: Conditional*
AASLD (5)	Guidance Statements for HCC Screening in Hepatitis B surface antigen (HBsAg)-Positive Persons: 1. All HBsAg-positive patients with cirrhosis should be screened with ultrasound examination with or without AFP every 6 months. 2. HBsAg-positive adults at high risk for HCC (including Asian or black men over 40 years and Asian women over 50 years of age), persons with a first-degree family member with a history of HCC, or persons with HDV should be screened with ultrasound examination with or without AFP every 6 months. 3. There are insufficient data to identify high-risk groups for HCC in children. However, it is reasonable to screen HBsAg-positive children and adolescents with advanced fibrosis (F3)

	or cirrhosis and those with a first-degree family member with HCC using ultrasound examination with or without AFP every 6 months. 4. For HBsAg-positive persons at high risk for HCC who are living in areas where ultrasound is not readily available, screening with AFP every 6 months should be performed.
APASL (10)	Surveillance recommendations 1. Surveillance for HCC should be undertaken in high-risk groups of patients and is recommended (B2). The high-risk groups of patients for whom a surveillance strategy is recommended are: o Cirrhotic hepatitis patients o HBV o HCV o Noncirrhotic (HBsAg positive) o Asian females >50 years o Asian males >40 years o Africans aged >20 years o History of HCC in the family 2. Measurement of AFP alone is not recommended for routine surveillance of HCC (A1). 3. The combination of US and serum AFP measurement performed biannually should be used as a surveillance strategy for HCC (B2).
GESA Hepatitis B Consensus recommendations (8)	Populations with chronic hepatitis B in whom surveillance for HCC should be performed: • People with cirrhosis • People without cirrhosis: o Asian men older than 40 years o Asian women older than 50 years o Sub-Saharan Africans older than 20 years* o Aboriginal and Torres Strait Islander people older than 50 years† o With coinfection with hepatitis delta virus o With family history of HCC (first-degree relative)

	○ Observed HBsAg loss with prior indications for HCC surveillance • Other high-risk groups in whom surveillance can be considered: ○ People from other racial groups, according to risk scores (e.g. PAGE-B) ○ Māori and Pacific Islander men older than 40 years and women older than 50 years* HBsAg = hepatitis B surface antigen; HCC = hepatocellular carcinoma; PAGE-B = HCC predictive score based on age, sex and platelet count * Reliable data not available, but HCC incidence is likely to be increased. † Based on Northern Territory linkage data Modified with permission from the Hepatocellular Carcinoma Consensus Statement Steering Committee, Australian recommendations for the management of hepatocellular carcinoma: a consensus statement
ASHM (9)	Hepatocellular carcinoma surveillance 6-monthly ultrasound with or without AFP is recommended for patients with CHB in these groups: • People with cirrhosis • Asian males > 40 years • Sub-Saharan African people > 20 years • Aboriginal and Torres Strait Islander people > 50 years • Anyone with observed HBsAg loss with prior indications of HCC • Māori and Pacific Islander males > 40 years • Māori and Pacific Islander females > 50 years • Asian females > 50 years • Anyone with coinfection with hepatitis delta virus • Anyone with a family history of HCC (first-degree relative) • People from other racial groups, according to risk scores (e.g., PAGE-B)

EASL (7)	Patients at high risk of developing HCC: 1. Surveillance should be performed by experienced personnel in all high-risk populations [defined as] using abdominal ultrasound every six months *(evidence moderate; recommendation strong)* 2. Tumour biomarkers for accurate early detection are still lacking. The data available show that the biomarkers tested (i.e. Alphafeto-protein (AFP), Lectin-reactive alphafeto-protein (AFP-L3) and des-gamma-carboxyprothrombin (DCP)) are suboptimal in terms of cost-effectiveness for routine surveillance of early HCC *(evidence low).* Categories of adult patients in whom surveillance is recommended: 1. Cirrhotic patients, Child-Pugh stage A and B *(evidence low; recommendation strong)* 2. Cirrhotic patients, Child-Pugh stage C awaiting liver transplantation *(evidence low; recommendation strong)* 3. Non-cirrhotic HBV patients at intermediate or high risk of HCC* (according to PAGE-B† classes for Caucasian subjects, respectively 10–17 and ≥18 score points) *(evidence low; recommendation weak)* 4. Non-cirrhotic F3 patients, regardless of aetiology may be considered for surveillance based on an individual risk assessment *(evidence low; recommendation weak)* * Patients at low HCC risk left untreated for HBV and without regular six months surveillance must be reassessed at least yearly to verify progression of HCC risk. † PAGE-B (Platelet, Age, Gender, hepatitis B) score is based on decade of age (16–29 = 0, 30–39 = 2, 40–49 = 4, 50–59 = 6, 60–69 = 8, ≥70 = 10), gender (M = 6, F = 0) and platelet count (≥200,000/µl = 0, 100,000–199,999/µl = 1, <100,000/µl = 2): a total sum of ≤9 is considered at low risk of HCC (almost 0% HCC at five years) a score of 10–17 at intermediate risk (3% incidence HCC at five years) and ≥18 is at high risk (17% HCC at five years).

GESA HCC Consensus Statement (6)	Patients with chronic hepatitis B 1. HCC surveillance should be undertaken in noncirrhotic individuals with chronic hepatitis B infection who are at increased risk of HCC. *(Evidence quality: Low; Grade of recommendation: Strong)* Patients with cirrhosis 1. HCC surveillance should be offered to all patients with cirrhosis if they are suitable and willing to receive treatment. *(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)* Populations in whom surveillance of HCC should be performed 1. People with cirrhosis (any aetiology)* 2. People with chronic hepatitis B infection without cirrhosis ▪ Asian men older than 40 years ▪ Asian women older than 50 years ▪ Sub-Saharan Africans older than 20 years ▪ Indigenous and Torres Strait Islander people older than 50 years ** If patients are suitable for, and willing to receive, treatment.*

AASLD: American Association for the Study of Liver Diseases; EASL: European Association for the Study of the Liver; NICE: UK National Institute for Health and Care Excellence; WHO: World Health Organization; GESA: Gastroenterological Society of Australia

References

1. World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2015. 134 p.

2. National Institute for Health and Care Excellence. Hepatitis B (chronic); diagnosis and management. Clinical guideline [CG165] Last updated October 2017 [Internet]. London: NICE; 2013 [cited 2022 Jun 16]. Available from: https://www.nice.org.uk/guidance/cg165

3. National Institute for Health and Care Excellence. Cirrhosis in Over 16s: Assessment and Management. NICE guideline [NG50] [Internet]. London: NICE; 2016 [cited 2021 Dec 8]. Available from: https://www.nice.org.uk/guidance/ng50

4. 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. 2019;13(1):1–1.

5. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018 Apr;67(4):1560–99.

6. Gastroenterological Society of Australia. Hepatocellular Carcinoma Consensus Statement Working Group. Australian recommendations for the management of hepatocellular carcinoma: a consensus statement. [Internet]. Melbourne: Gastroenterological Society of Australia; 2020 [cited 2022 Sep 12]. Available from: https://www.gesa.org.au/resources/hepatocellular- carcinoma-hcc-management-consensus/

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

8. Gastroenterological Society of Australia. Australian consensus recommendations for the management of hepatitis B infection. Melbourne: Gastroenterological Society of Australia; 2022.

9. Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM). Decision making in Hepatitis B [Internet]. [cited 2023 Jan 30]. Available from: https://ashm.org.au/wp-content/uploads/2022/08/ASHM-Decision-Making-in-Hepatitis-B-2021- update-2.pdf

10. Omata M, Cheng AL, 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 Jul;11(4):317–70

Appendix D1. Technical report for question 1

Systematic Review Question 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

This systematic review addresses the PICO shown in Table 1.

Table 1. PICO for systematic review question 1.

Population	Intervention	Comparator	Outcomes	Study design
People with: non-cirrhotic liver disease or Cirrhotic patients who have been treated for HCV with direct acting antivirals	HCC surveillance	No surveillance Usual or standard care	Overall mortality Liver disease-related mortality Liver cancer mortality Proportion of liver cancers that are early-stage Cost-effectiveness	Randomised controlled trials Cohort studies Modelling studies

HCC = hepatocellular carcinoma; HCV = chronic hepatitis C

1. METHODS

1.1 Selection Criteria

Table 2. Selection criteria for interventional studies examining the effects of surveillance for individuals at higher risk of HCC.

PICO 1	***Inclusion***	***Exclusion***
Study type	Intervention	Diagnostic accuracy Observational
Study design	RCTs and cohort studies (if no RCT evidence) or systematic review thereof Modelling studies	Case series Case-control Review (not systematic)
Population	≥18 years Adults with non-cirrhotic: Liver disease (any aetiology) Chronic hepatitis B (HBV) Chronic hepatitis C (HCV) Alcohol - related liver disease (ARLD) Metabolic associated fatty liver disease (MAFLD) – covers NASH and NAFLD All Patients with HCV, HBV, MAFLD or ARLD and cirrhotic status not reported Cirrhotic patients who have been treated for HCV with direct acting antivirals	People who have previously undergone treatment for liver cancer Children <80% non-cirrhotic ie ≥ 20% cirrhotic

Intervention	HCC surveillance programs (ultrasound, AFP, other)	Provides no details about the surveillance program Ad hoc surveillance Single screen offered GALAD surveillance
Comparator	No surveillance Standard or usual care	No comparator Historical control
Outcome	*Actual or state transition-modelled:* Overall mortality - adjusted analyses if cohort study Liver disease-related mortality - adjusted analyses if cohort study HCC/liver cancer specific mortality - adjusted analyses if cohort study % early/treatable stage HCC or liver cancer at diagnosis Cost-effectiveness (cost per QALY, DALY or life-years saved) based on state transition modelling, RCT or adjusted cohort study results	Mortality outcome and unadjusted analyses if cohort study Cancer incidence Costs only, costs per life saved Incremental cost of additional early-stage diagnosis
Publication date	2000 onwards	
Publication type	Original journal article Letter or comment that reports original data	Conference abstracts Editorials Letters and comments that do not report original data
Language	English	

AFP = alpha-fetoprotein; *DALY = disability-adjusted life years; GALAD score = score based on gender, age, Lens culinaris agglutinin-reactive AFP, total AFP, and des-γ-carboxyprothrombin; HCC = hepatocellular carcinoma; NAFLD = Non-alcoholic fatty liver disease; NASH = Non-alcoholic steatohepatitis; QALY = quality-adjusted life years; RCTs = randomised controlled trials*

[a]Hepatocellular carcinoma is the liver cancer of primary interest.

[b]Where the outcome reported is liver cancer it is assumed that most of the cancers are HCC.

[c]Chronic HBV infection, chronic HCV infection, alcohol-related liver disease and metabolic-associated fatty liver disease are the aetiologies of interest.

[d]Modelling studies were restricted to state-transition models.

[e]Where the population was people with chronic HBV infection it was assumed that over 80% were non-cirrhotic.

1.2 Definitions and terminology

For the purpose of this review:

Compensated cirrhosis included Child-Pugh Class A cirrhosis.

Early-stage HCC includes Barcelona Clinic Liver Cancer (BCLC) stage 0/A, meeting Milan criteria, or China Liver Cancer Study group stage I:

1. *The Barcelona Clinic Liver Cancer (BCLC*) staging classification system assesses the number and size of liver tumours, overall performance status (ECOG PS) and liver function (using Child-Pugh classification):
    a. BCLC stage 0 (very early-stage); ECOG performance score = 0, Child-Pugh A, single tumour < 20mm;

b. BCLC stage A (early-stage); ECOG performance score = 0, Child-Pugh A-B, single tumour of any size or up to 3 tumours all < 30mm).

2. *The Milan criteria* focus on liver transplantation eligibility. Those eligible for transplantation are described as within Milan criteria and are defined as having one tumour measuring ≤ 50 mm in diameter, or 2-3 tumours ≤ 30 mm in diameter without vascular extension or metastasis.
3. The *China Liver Cancer study group staging* system classifies HCC as stage I (subclinical stage/early-stage) if there are no obvious cancer symptoms and signs (tumour usually < 5 cm in diameter).

Where results were given by BCLC stage and another staging system, the BCLC results were presented.

Fibrotic status *was as* reported by authors.

Liver cancer refers to primary liver cancer

Metabolic-associated fatty liver disease includes non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

1.3 Guidelines

Relevant recent (2015 onwards) guidelines were identified by scanning the citations identified by the literature search (described below) and a summary of these guidelines was reviewed by Expert Advisory Group members as part of Phase 1 of the *Roadmap to Liver Cancer Control* project.

To be considered for adoption by the Working Group guidelines had to be evidence-based and meet the pre-specified criteria of scores of greater or equal to 70% for the following domains: rigour of development, clarity of presentation and editorial independence of the AGREE II instrument (8). Guidelines were not considered for adoption by the Working Group if they were not based on systematic reviews of the evidence, i.e. did not report using systematic methods to search for evidence, did not clearly describe the criteria for selecting the evidence or did not assess the risk of bias or where this is not possible, appraise the quality of the evidence.

1.4 Literature searches

Medline (including MEDLINE Epub Ahead of Print, I-Process & Other Non-Indexed Citations) and Embase databases were searched on 1 February 2022 combining text terms and/or, database-specific subject headings for liver cancer, surveillance and ultrasound or liver disease. Searches were limited to articles published in English from 1 January 2000

onwards. A complete list of the terms used is included as Appendix 1. The Cochrane Database of Systematic Reviews was searched on 31 March 2022 combining the search terms “liver cancer” and “screen”. Reference lists of included articles, recent relevant guidelines and systematic reviews were checked for potential additional articles.

1.5 Data extraction and analyses

If an effect estimate was not presented but the necessary data were available and adjusted estimates were not required, the risk ratio and 95% confidence interval was calculated using a tool available at *https://sample-size.net/risk-ratio/*. For cost-effectiveness studies, if the cost-effectiveness ratio was not reported for the comparison of interest, it was calculated using the reported costs and outcomes for the intervention and the comparator if the necessary data were available. For the modelled outcomes of mortality and percentage liver cancer 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. In this report, a narrative synthesis for all but one of the outcomes are presented as the results of the two randomised controlled trials were highly heterogeneous and pooling of results was not considered appropriate for cost-effectiveness analyses. A pooled analysis was undertaken for one outcome to assist with the GRADE assessment of imprecision.

1.6 Risk of bias assessments and quality appraisals

The risk of bias of randomised controlled trials was assessed using the Cochrane Collaboration Risk of Bias-II tool (9). For cluster randomised trials we used this tool with additional questions addressing sources of bias specific to cluster randomised controlled trials (10).

The risk of bias of cohort observational studies was assessed using a modified version of the Newcastle-Ottawa Scale designed specifically to assess the risk of bias in aetiological cohort studies (11).

The quality of cost-effectiveness studies was assessed using a modified version of the CHEC-extended checklist (12). This tool appraises the specification of the population, interventions and comparators modelled, the modelling and cost-effectiveness methods, and the robustness and fitness for purpose of the model. Unlike a risk of bias assessment tool, its focus is not the critical assessment of the sources of bias. However, some of the questions do inform an assessment of the risk of bias and thus whether the results are likely to reflect the true effect of the intervention. Assessments for some of the CHEC-extended checklist

questions were used to inform GRADE assessments of modelled studies, including the risk of bias.

1.7 GRADE assessment of the certainty of the evidence

A GRADE approach was used to assess the certainty of the body of evidence for the effect of HCC surveillance when compared with no HCC surveillance for each outcome (13).

For non-modelling studies, the certainty of the body of evidence was rated high, moderate, low or very low based on assessment of risk of bias, indirectness of the results, imprecision (width of 95% confidence intervals) of the results, inconsistency or heterogeneity of the results, and publication bias based on guidance for assessing narrative syntheses provided by Murad 2017 and additional guidance for the assessment of imprecision provided by Guyatt 2011, Zeng 2021 and Brignardello-Petersen 2021 (14–17). For the assessment of imprecision, any decrease in mortality was considered clinically important, and an increase of at least 5 percentage points in the percentage of liver cancer diagnosed at an early stage was considered clinically important. As per GRADE guidance, studies started with a high level of certainty in the evidence and were downgraded in a stepwise manner from *high* to *moderate* to *low* to *very low* if there were serious concerns regarding risk of bias, indirectness, imprecision, inconsistency and/or publication bias. The exception was observational cohort studies which started with a low level of certainty and were downgraded if there were serious concerns or upgraded if the effect estimate was large (greater than 2.0 or less than 0.5), presence of a dose response gradient, or when plausible residual confounders increased certainty. Where there was only one study, inconsistency could not be rated.

GRADE was originally designed to assess the certainty of the results of a meta-analysis of the evidence for interventions from randomised controlled trials however, for results from modelling studies, GRADE assessments were not recommended (18,19). However, the NHMRC GRADE working group has recently changed their position as outlined in Brozek 2021 (20) and has provided a general approach to the GRADE assessment of modelling studies with more specific guidance planned but not published as at May 2022. In the absence of specific criteria, we assessed the risk of bias, indirectness and inconsistency of the evidence from each study based on the general principles explained by Brozek 2021 (20); downgrading from an initial high level of certainty if there were serious concerns. Downgrading was based on an assessment of the level of concern for each of following issues: risk of bias, indirectness and inconsistency. Assessments ranged from no serious concerns (no downgrade), serious concerns (downgrade by one level) or very serious concerns (downgrade by two levels). The certainty of the body of evidence for each outcome

was then rated as either high, moderate, low or very low based on the degree of downgrading. We did not assess imprecision based on reported results of probabilistic sensitivity analyses or other sensitivity analyses as currently these types of analyses are designed to assess sensitivity to changes in variable values, rather than imprecision. Assessment of publication bias for individual studies was not applicable as all studies reported results of models developed de novo.

We then assessed the certainty of the body of the evidence by assessing the risk of bias, indirectness, inconsistency and publication bias across all studies based on the principles explained by Brozek 2021 (20). As we could not assess imprecision we presented two final assessments of the certainty of the evidence, where one is conservative (downgraded for imprecision) and one is not adjusted for imprecision). This was done so that GRADE assessments could be compared with those of other study designs. Similarly, as for non-modelled studies, where there was only one study inconsistency could not be rated.

Definitions of the GRADE ratings of certainty are presented in Appendix 2.

2. RESULTS

2.1 Guidelines searches

No recent relevant guidelines based on systematic reviews were identified.

2.2 Literature searches

Figure 1 outlines the process of identifying relevant articles for this systematic review. The combined Medline and Embase search identified 5356 citations and the search of the Cochrane Database of Systematic Reviews 18 citations, resulting in a total of 5374 citations. Titles and abstracts were examined, and 59 articles were retrieved for a more detailed evaluation. An additional eight potential citations were identified from the reference lists of included articles, recent relevant guidelines, and systematic reviews.

Seven studies reported in seven articles met the inclusion criteria and were included in the review: two randomised controlled trials and five modelling studies. No interventional cohort studies were identified.

The retrieved articles that were not included and the reasons for their exclusion are documented in Appendix 3. In summary, most articles were excluded because the population was not relevant, the publication type was not relevant, or the study type or design was not relevant.

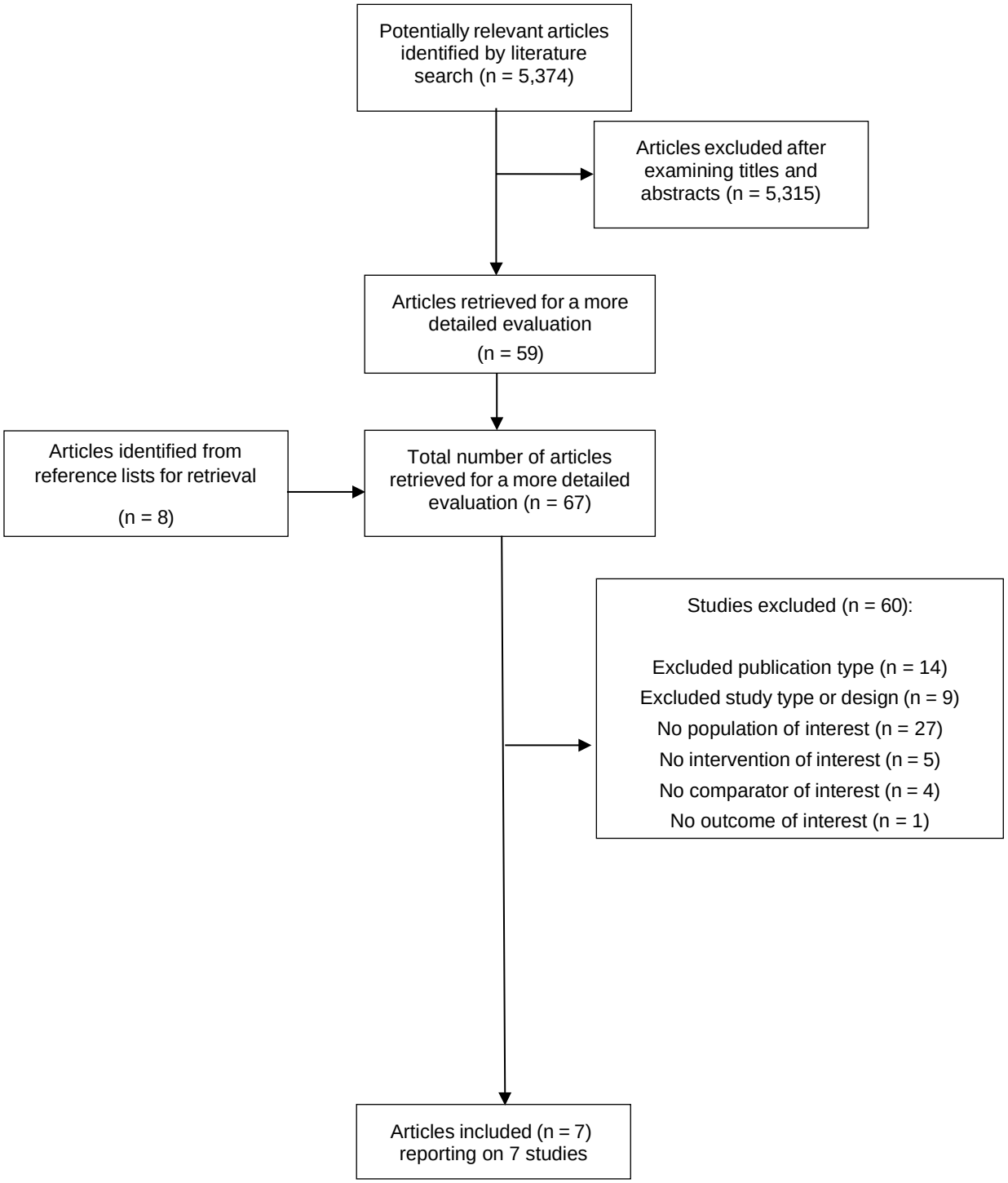


Figure 1. Process of inclusion and exclusion of studies.

2.3 Characteristics of included studies

The characteristics of included studies are described in Table 3.

Table 3. Study characteristics for the studies comparing surveillance with no surveillance for people with non-cirrhotic liver disease or cirrhotic patients who have been treated for HCV with direct acting antivirals.

Study (Country)	***Study design***	***Population***	***Participants***	***Intervention***	***Comparison***	***Cycle length***	***Follow-up***	***Outcomes***	***Conflicts of interest considered***
Zhang 2004 (China)(21)	Cluster RCT (over 300 sites)	Patients with HBV or chronic hepatitis recruited between January 1993 and December 1995 aged 35-59 years Excluded patients with HCC at baseline: No	N = 18816 (analysed) Mean age: 41-42 years at start Male: 63% Non-cirrhotic: NR (assume > 80%) HBV: 91.7% (8.3% history of hepatitis) Treated for HBV: NR HCC incidence: 0.27% (time period NR)	**Surveillance** **6-monthly US + AFP** AFP cut-off: ≥ 20 ng/ml Compliance (attended screening rounds offered): 58.2% N = 9373	**No surveillance** Usual access to health care N = 9443	NA	Range: 3-5 years	HCC-related mortality % early-stage disease	No
Chen 2003 (China)(22)	RCT	Men with HBV (HBsAg positive) resident in 23 townships in Qidong recruited in 1989 aged 30-59 years or in 1992 aged 30-69 years Excluded patients with HCC at baseline: Yes for outcomes of liver cancer mortality and proportion liver cancer diagnosed at an early stage	N = 5581 (analysed) Mean age: 41 years at start Male: 100% Non-cirrhotic: NR (assume > 80%) HBV: 100% Treated for HBV: NR Liver cancer incidence: 12.9 per 1000 person years	**Surveillance** **6-monthly AFP + ALT** (with screening cancelled in 1991) until April 1993 AFP cut-off: ≥ 20 ng/ml ALT cut-off: ≥ 40 units Compliance (attended all scheduled screening rounds): 28.8% N = 3712 (68.8% recruited in 1989)	**No surveillance** Underwent baseline AFP test AFP cut-off: ≥ 20 ng/ml N = 1869 (72.0% recruited in 1989)	NA	Mean: 5 years	Overall mortality Liver cancer-related mortality % early-stage disease	No – Authors acknowledge funders
Robotin 2009 (Australia)(23)	Model (Markov) Not validated	Australian Asian-born patients with chronic HBV infection (HBsBAg positive) aged 35 years at start Time period: NR Excluded patients with HCC detected at baseline: NR	N = 10,000 Age: 35 years at start Male: 60% Non-cirrhotic: 100% at start Aetiology: HBV Treated for HBV: 2% HCC incidence per year *Cirrhotic:* 4.5% *Non-cirrhotic:* 0.2%	**Risk-stratified surveillance** **6-monthly US + AFP** AFP cut-off NR Risk assessment based on HBV DNA levels Compliance: NR	**Usual care** ~ 1% undergo surveillance	12 months	Time horizon: 50 years	Liver disease - related mortality Cost/QALY gained	Yes - Authors report no conflicts of interest to declare
Sangmala 2014 (Thailand)(24)	Model (Markov)	Patients with chronic HBV infection (HBsAg positive –	N = NR Age: 40 years at start Male: NR	**Surveillance** *8 different strategies*	**No surveillance**	6 months or 12 months	Time horizon: Lifetime	Cost/QALY gained	No – Authors acknowledge funders

	Not validated	active carriers) aged 40 years at start Time period: NR Excluded patients with HCC detected at baseline: NR	Non-cirrhotic: NR (assume > 80%) Aetiology: HBV Treated for viral hepatitis: 0% HCC incidence: NR	6-monthly or 12-monthly **US + AFP** AFP cut-off: > 20ng/ml **US** **CT** **MRI** Compliance: unclear					
Chang 2011 (Taiwan)(25)	Model (Markov) Not validated	Patients with chronic HBV infection (carriers) without cirrhosis aged 50 years at start Time period: NR Excluded patients with HCC detected at baseline: Yes	N = NR Age: 50 years at start Male: NR Cirrhotic: 0% Aetiology: HBV Treated for viral hepatitis: NR HCC incidence: 0.001% per year	**Surveillance** **12-monthy US** **3-monthly US** if patient develops cirrhosis Compliance (not defined): 100%	**No surveillance**	3 months	Time horizon: 25 years	Cost/life years gained	No
Uyei 2019 (USA)(26)	Model (Markov) Validated	HCV patients with cirrhosis who undergo DAA treatment aged 60 years at start Time period: NR Excluded patients with HCC detected at baseline: Yes	N = NR Age: 60 years at start Male: NR Cirrhotic (compensated): 100% Aetiology: HCV DAA-treated: Yes HCC incidence for compensated cirrhosis: *Early stage* 0.01% per year	**Surveillance** *3 different strategies* **3-monthly US** **6-monthly US** **12-monthly US** Compliance (not defined): 100%	**No surveillance** No routine HCC surveillance	NR	Time horizon: Lifetime	Cost/QALY gained	Yes – Authors report no conflicts of interest to declare
Farhang Zangneh 2019 (Canada)(27)	Model (Markov) Not validated	HCV populations aged 50 years at start 1. HCV patients with **cirrhosis (F4)** after DAA-induced sustained virologic response 2. HCV patients with **advanced fibrosis (F3)** after DAA-induced sustained virologic response Time period: NR Excluded patients with HCC detected at baseline: No	N = 10,000 Age: 50 years at start Male: NR Cirrhotic (compensated): 100% or Advanced fibrosis (F3): 100% Aetiology: HCV DAA-treated: Yes HCC incidence: *Cirrhotic:* 1.82% per year *Advanced fibrosis*: 0.34%.per year	**Surveillance** **6-monthly US** **12-monthly US** Adherence (not defined): 95%	**No surveillance** Screen none	1 month	Time horizon: Lifetime	Cost/QALY gained	Yes – Authors report no conflicts of interest to declare

AFP = alpha-fetoprotein; ALT = alanine transaminase; CT = computed tomography; DAA = direct acting antiviral, HCC = hepatocellular carcinoma; HBV = chronic hepatitis B; HCV = chronic hepatitis C; HBsAg = serum hepatitis B surface antigen; NA = not applicable; MRI = magnetic resonance imaging; NR = not reported; QALY = quality-adjusted life years; RCT = randomised controlled trial; US = ultrasound

2.4 Results by outcomes of interest

1. Overall mortality – results are shown in Table 4
2. Liver disease-related mortality – results are shown in Table 5
3. Liver cancer mortality – results are shown in Table 6
4. Proportion of liver cancers diagnosed at an early stage -– results are shown in Table 7
5. Life-years, quality-adjusted life-years or disability-adjusted life-years gained – results are shown in Table 8
6. Cost-effectiveness – results are shown in Table 8

*Table 4. Results of study comparing surveillance with no surveillance for the outcome of **overall mortality**.*

Study (Liver disease)	***Study design***	***Outcome***	***Outcome metric***	***Follow-up***	***Surveillance***	***No surveillance***	***Effect estimate (95%CI)***
*6-monthly **AFP**+**ALT** vs no surveillance*							
Chen 2003(22) (HBV – non-cirrhotic and cirrhotic)	RCT	Overall mortality	Deaths per 100,000 person years	Mean: 5 years	1842.8	1788.4	RR = 0.97 (0.77-1.22)*

** Calculated by review team using data presented in Table 1 of Chen 2003 using STATA*
AFP = alpha-fetoprotein, ALT = alanine transaminase; HBV = chronic hepatitis B; RCT = randomised controlled trial; RR = rate ratio

*Table 5. Results of study comparing risk-stratified surveillance with usual care for the outcome of **liver disease-related mortality**.*

Study (Liver disease)	***Study design***	***Outcome***	***Outcome metric***	***Follow-up***	***Risk-stratified surveillance***	***Usual care***	***Effect estimate***
***Risk stratified** surveillance vs usual care*							
Robotin 2009(23) (HBV – non-cirrhotic at start)	Model (Markov)	Liver disease (HCC or HBV)-related mortality	%	50 years	33.6	33.8	NA

HBV = chronic hepatitis B; HCC = hepatocellular carcinoma; NA = not applicable

*Table 6. Results of studies comparing surveillance with no surveillance for the outcome of **HCC or liver cancer-related mortality**.*

Study ***(Liver disease)***	***Study design***	***Outcome***	***Outcome metric***	***Follow-up***	***Surveillance***	***No surveillance***	***Effect estimate*** ***(95%CI)***
*6-monthly **US+AFP** vs no surveillance*							
Zhang 2004(21) (HBV – non-cirrhotic and cirrhotic)	Cluster RCT	HCC-related mortality	HCC deaths per 100,000 person years	Range: 3-5 years	83.2	131.5	RR = 0.63 (0.41-0.98) The rate of HCC-related mortality is 0.63 times lower for those who undergo surveillance than that for those who did not
*6-monthly **AFP+ALT** vs no surveillance*							
Chen 2003(22) (HBV – non-cirrhotic and cirrhotic)	RCT	Liver cancer-related mortality	Liver cancer deaths per 100,000 person years	Mean: 5 years	1138.1	1113.9	RR = 0.86 (0.69-1.07)* The rate of HCC-related mortality is 0.86 times lower for those who undergo surveillance than that for those who did not however the confidence interval crosses 1.0 and thus includes increases as well as decreases

** Adjusted for age, AFP at initial test and year of entering the cohort and excludes liver cancers diagnosed within 2 months of the baseline screen*
AFP = alpha-fetoprotein, ALT = alanine transaminase; HBV = chronic hepatitis B; HCC = hepatocellular carcinoma; RCT = randomised controlled trial; RR = rate ratio

*Table 7. Results of studies comparing surveillance with no surveillance for the outcome of **proportion of HCC or liver cancers that are early stage at diagnosis**.*

Study ***(Liver disease)***	***Study design***	***Outcome***	***Outcome metric***	***Follow-up***	***Surveillance***	***No surveillance***	***Effect estimate*** ***(95%CI)***
*6-monthly **US+AFP** vs no surveillance*							
Zhang 2004(21) (HBV – non-cirrhotic and cirrhotic)	Cluster RCT	Early-stage HCC (% liver cancer China Liver Cancer Study Group stage I)	% HCC (n/N)	Range: 3-5 years	60.5 (52/86)	0 (0/67)	Cannot calculate effect estimate - the proportion of liver cancer diagnosed at an early stage is much higher for those who undergo regular surveillance than that for those who did not
*6-monthly **AFP+ALT** vs no surveillance*							
Chen 2003(22) (HBV – non-cirrhotic and cirrhotic)	RCT	Early-stage liver cancer (% liver cancer China Liver Cancer Study Group stage I)	% total liver cancer (n/N)	Mean: 5 years	27.9 (67/240)^	3.7 (4/108)^	RR = 7.54 (2.82 -20.14)* the proportion of liver cancer diagnosed at an early stage is 7.54 times higher for those who undergo regular surveillance than that for those who did not

^Excluded cancers diagnosed within 2 months of initial screen (prevalent cancers)

*Calculated by technical team using tool at https://sample-size.net/risk-ratio/
AFP = alpha-fetoprotein, ALT = alanine transaminase; HBV = chronic hepatitis B; HCC = hepatocellular carcinoma; RCT = randomised controlled trial; RR = rate ratio

Table 8. Results of studies comparing surveillance with no surveillance for the outcomes of ***cost-effectiveness and life years, or quality-adjusted life years gained****.*

Study (Liver disease)	***Economic perspective***	***Discount rate***	***Costs currency and year***	***Medical costs included***	***Evidence bases for differences in health outcomes***	***Clinical Effect***	***Willingness to pay threshold/ indicative benchmark used***	***CER***	***Probabilistic sensitivity analysis***	***Largest sources of uncertainty***
Populations with non-cirrhotic liver disease										
Risk-stratified surveillance vs usual care										
Robotin 2009(23) (HBV-non cirrhotic at start)	Payer's (health care funder)	5% p/a for costs and health outcomes	Australian dollars (AU$) 2006	Risk assessments Surveillance Diagnostic investigations Early-stage treatments including ablation but not transplantation TACE	Relative risk of 0.6 for HBV death with surveillance program for HCC patients	0.014 QALY gained per person (discounted NR	NR	AU$401,516 per QALY gained Unable to state if surveillance is cost effective when compared with no surveillance as no willingness to pay threshold or indicative benchmark reported	No	NR for surveillance only
Surveillance vs no surveillance										
Sangmala 2014(24) (HBV – cirrhotic and non-cirrhotic)	Societal	3% p/a for costs and health outcomes	Thai Baht (THB) 2013	Surveillance Diagnostic investigations Early-stage treatments including transplantation and ablation TACE Chemotherapy Palliative care HCC follow-up	Sensitivity and specificity of US (64% and 97%) AFP (49% and 92%) CT (58% and 91%) MRI (85% and 79%) Proportions of surveillance detected HCC and non-surveillance-detected HCC undergoing different treatments	QALYs gained per person for: *6-monthly* US 0.32 US+AFP 0.72 CT 1.3 MRI 1.83 *12-monthly* US 0.1 US+AFP 0.24 CT 0.44 MRI 0.62	160,000 THB per QALY gained	THB per QALY gained for: *6-monthly* US 118,796 US+AFP 123,451 CT 175,853 MRI 187,064 *12-monthly* US 252,921 US+AFP 273,568 CT 384,236 MRI 407,143 **Surveillance with 6-monthly US or US+ AFP cost effective** when compared	Yes Probability of 6-monthly surveillance being the **most** cost-effective of those studied at 160,000THB/ QALY threshold US+AFP 28% CT 27% MRI 26.5% US 17%	Reported for 6-monthly US surveillance: costs of liver transplantation and palliative care, and HCV utility

								with no surveillance		
Chang 2011(25) (HBV – non-cirrhotic)	Payer's (health care funder)	3% p/a for both costs and health outcomes	United States dollars (US$) 2005-2009	Surveillance Diagnostic investigations Early-stage treatments including transplantation and ablation HCC follow-up	Sensitivity of ultrasound (70%) Tumour growth rate Probability of accidental HCC diagnosis before presenting with clinical symptoms	0.26 life years gained per person	NR	US$20,856 per life year gained Unable to state if surveillance is cost effective when compared with no surveillance as no willingness to pay threshold for the setting (Taiwan) or indicative benchmark reported	No	Probability of incidental diagnosis of HCC and HCC incidence for patients without cirrhosis
Farhang Zangneh 2019(27) (DAA-treated HCV with advanced fibrosis after sustained virologic response)	Payer's (health care funder)	5% p/a for costs and health outcomes	Canadian dollars (C$) 2015	Surveillance Diagnostic investigations Early-stage treatments including transplantation and ablation Chemotherapy Palliative care HCC follow-up	Sensitivities of 6- monthly and 12-monthly ultrasound surveillance (70% and 50%), probability of asymptomatic to symptomatic HCC conversion and proportions of patients with different sizes and numbers of HCC	6-monthly US 0.072 12 monthly US 0.067	C$50,000 per QALY gained	C$ per QALY gained for: 6-monthly US 188,157 12 monthly US 111,667 **Surveillance** with 6-monthly or 12-monthly US **not cost effective** when compared with no surveillance	Yes 65% probability of 6-monthly US being cost-effective for HCV patients with cirrhosis after DAA-induced sustained virologic response	HCC incidence, probability of HCC becoming symptomatic and age when undergo surveillance
Populations with cirrhotic DAA-treated chronic hepatitis C										
Uyei 2019(26) (HCV – cirrhotic DAA treated)	Payer's (health care funder)	3% p/a for both costs and health outcomes	United States dollars (US$) 2016	Surveillance Diagnostic investigations Early-stage treatments including transplantation and ablation TACE Chemotherapy Palliative care HCC follow-up (NR) includes cancer recurrence	Sensitivity of ultrasound for small tumours (50%) and large tumours (75%) Probability of progressing from early to more advanced disease	QALYs gained per person for: 3-monthly US 0.019 6-monthly US 0.010 12-monthly US 0.002	US$100,000 -150,000 per QALY gained	US$ per QALY* gained for: 3-monthly US 140,000 6-monthly US 51,000 12-monthly US dominated no surveillance ie it was cheaper and more effective than no surveillance **Surveillance with 6-monthly and 12-monthly**	No	Not reported for comparison of interest For the comparisons of different US frequencies: ultrasound sensitivity for small tumours, ultrasound specificity, rates of ablation and HCC incidence for compensated cirrhosis,

								US cost effective when compared with no surveillance		likelihood of HCV treatment and compliance to surveillance protocol
Farhang Zangneh 2019 (27)(DAA-treated HCV with cirrhosis after sustained virologic response)	Payer's (health care funder)	5% p/a for costs and health outcomes	Canadian dollars (C$) 2015	Surveillance Diagnostic investigations Early-stage treatments including transplantation and ablation Chemotherapy Palliative care HCC follow-up	Sensitivities of 6- monthly and 12-monthly ultrasound surveillance (70% and 50%), probability of asymptomatic to symptomatic HCC conversion and proportions of patients with different sizes and numbers of HCC	QALYs gained per person for: 6-monthly US 0.591 12 monthly US 0.452	C$50,000 per QALY gained	C$ per QALY gained for: 6-monthly US 43,229 12 monthly US 34,307 **Surveillance with 6-monthly and 12-monthly US cost effective** when compared with no surveillance	Yes 65% probability of 6-monthly US being cost-effective for HCV patients with cirrhosis after DAA-induced sustained virologic response	HCC incidence, probability of HCC becoming symptomatic and age when undergo surveillance

**Calculated by review team from data in Uyei 2019 Table 3 rounded to first 2 digits*

AFP = alpha-fetoprotein; DAA = direct acting antiviral; CER = cost-effectiveness ratio; CT = computed tomography; DAA = direct acting antiviral; HCC = hepatocellular carcinoma; HBV = chronic hepatitis B; HCV = chronic hepatitis C; MRI = magnetic resonance imaging; NR = not reported; p/a = per annum; QALY = quality-adjusted life years; TACE = transarterial chemoembolization; US = ultrasound

2.5 Risk of bias and quality appraisal assessments

The results of the risk of bias assessments for the included randomised controlled trials are shown in Table 9.

The results of the quality appraisal of the included modelling studies are shown in Table 10.

Table 9. Risk of bias assessments for included randomised controlled trials using the Cochrane risk of bias assessment tool (version 2).*

Source of bias	***Chen 2003***(22)	***Zhang 2004***(21)
Randomisation process	Some concerns	Some concerns
Cluster design	Not applicable	High risk
Deviations from intended interventions	Some concerns	Low risk
Missing outcome data	Some concerns	High risk
Outcome measurement	High risk - Overall mortality	Some concerns – HCC-related mortality
	High risk - Liver cancer-related mortality	
	High risk – % HCC diagnosed at an early stage	High risk – % HCC diagnosed at an early stage
Selection of reported results	Some concerns	Some concerns
Overall Rating	**High risk of bias**	**High risk of bias**

HCC = hepatocellular carcinoma
**Key to overall risk of bias rating:*

1. *High risk of bias – high risk of bias in any domain (source of bias)*
2. *Moderate risk of bias – moderate or low risk of bias in all domains, no domains high risk*
3. *Low risk of bias – all domains low risk of bias, no domains moderate or high risk*

Table 10. Quality appraisal for modelled outcomes using the CHEC-extended (modified) checklist.

Checklist question	***Robotin 2009***(23) *Costs/QALYs gained*	***Robotin 2009***(23) *Liver disease-related death*	***Sangmala 2014***(24) *Costs/QALYs gained*	***Chang 2011***(25) *Costs/life years gained*	***Uyei 2019***(26) *Costs/QALYs gained*	***Farhang Zangneh 2019***(27) *Costs/QALYs gained*
1. Is the study population *clearly* described?	Yes	Yes	No	No	No	No
2. Are competing alternatives *clearly* described?	No	No	Yes	Yes	Yes	Yes
3. Is a *well-defined* research question posed in answerable form?	Yes	Yes	Yes	Yes	Yes	Yes
4. Is the economic study design *appropriate* to the stated objective?	Yes	Yes	Yes	Yes	Yes	Yes
5. Are the structural assumptions and the validation methods of the model properly reported?	Yes	Yes	Yes	Yes	Yes	Yes
6. Is the chosen time horizon *appropriate* in order to include relevant costs and consequences?	Yes	Yes	Yes	Yes	Yes	Yes
7. Are *all important and relevant* costs for each alternative identified?	No	No	Yes	No	Yes	No
8. Are all costs measured *appropriately* in physical units?	Yes	NA	Yes	Yes	Yes	Yes
9. Are costs valued *appropriately*?	Yes	NA	Yes	Yes	Yes	Yes
10. Are *all important and relevant* outcomes for each alternative identified? Does the study report costs per life-years, QALYs or DALYs?	Yes	NA	Yes	Yes	Yes	Yes
11. Are all outcomes measured *appropriately*? Do the authors critically appraise sources of data underpinning effect of surveillance?	No	No	No	No	No	No
12. Are outcomes valued *appropriately*?	Yes	NA	Yes	NA	Yes	Yes

13. Is *an appropriate* incremental analysis of costs and outcomes of alternatives performed?	Yes	NA	Yes	Yes	Yes	Yes
14. Are all future costs and outcomes discounted *appropriately*?	Yes	NA	Yes	No	No	Yes
15. Are all important variables, whose values are uncertain, *appropriately* subjected to sensitivity analysis? Was a probabilistic sensitivity analysis undertaken?	No	No	Yes	No	No	Yes
16. Does the article/report indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Yes	Yes	No	No	Yes	Yes

DALY = disability-adjusted life years; NA = not applicable; QALY = quality-adjusted life years

3. GRADE assessment of the certainty of the evidence

Overall mortality – assessments are shown in Table 11.

Liver disease-related mortality - assessments are shown in Table 12.

HCC or liver cancer-related mortality - assessments are shown in Table 13.

Proportion of liver cancers diagnosed at an early stage – assessments are shown in Table 14.

Cost-effectiveness – assessments are shown in Tables 15-17.

*Table 11. GRADE assessment of the certainty of the evidence for the outcome of **overall mortality** from RCT evidence.*

GRADE domain	***Rating***	***Reason for downgrading or upgrading***	***Certainty of evidence***
Overall mortality			
Risk of bias	Very serious concerns (-2)	One study with high risk of bias due to measurement of the outcome.	Very low
Indirectness	Serious concerns (-1)	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 concerns (-1)	Single study with rate ratio (95% CI) = 0.97 (0.77-1.22). 95% confidence crosses 1.0.	
Inconsistency	Not assessable	Only one study - Not possible to assess.	
Publication bias	Undetected	Undetected – one large study (N = 5581).	
Other – cohort studies only – upgrading factors	Not applicable		

DAA = direct acting antivirals; HBV = chronic hepatitis B; HCV = chronic hepatitis C; RCT = randomised controlled trial

*Table 12. GRADE assessment of the certainty of the evidence for the outcome of modelled **liver disease-related mortality**.*

GRADE domain	***Rating***	***Reason for rating***	***Certainty of evidence***
Liver disease-related mortality			
Risk of bias	Very serious concerns (-2)	Data underpinning effect of surveillance not critically appraised plus some important medical treatments were not included in the model.	Low to very low
Indirectness	No serious concerns	This study was in a HBV population and reports % cirrhotic at baseline and rate of surveillance for comparator, usual care.	
Imprecision	Not assessable	Not possible to assess.	
Inconsistency	Not assessable	Only one study so overall inconsistency cannot be assessed.	
Publication bias	Undetected	Single study.	
Other – cohort studies only – upgrading factors	Not applicable		

HBV = chronic hepatitis B

*Table 13. GRADE assessment of the certainty of the evidence for the outcome of **liver cancer-related mortality** from RCT evidence.*

GRADE domain	***Rating***	***Reason for downgrading or upgrading***	***Certainty of evidence***
HCC or liver cancer-related mortality			
Risk of bias	Very serious concerns (-2)	Both studies high risk of bias. In Chen 2003 (22) this was due to the measurement of the outcome. In Zhang 2004 (21) this was due to the application of cluster design and missing outcome data.	Very low
Indirectness	Serious concerns (-1)	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 concerns (-1)	In Chen 2003 (22) the 95% confidence interval crossed 1.0 (rate ratio (95%CI) = 0.86 (0.69-1.07)). In Zhang 2004 (21) 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 (21)) that did not adjust for cluster design.	

Inconsistency	No serious concerns	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 (21)) and the other using AFP and ALT (Chen 2003 (22)).	
Publication bias	Undetected	Undetected – two studies with differing results. Zhang 2004 (21) showed a decrease in liver-related deaths with surveillance. Chen 2003 (22) showed no effect with surveillance (Chen 2003 (22)). Highly unlikely any recent RCTs addressing this question have been undertaken due to the acceptability and ethics of such trials.	
Other – cohort studies only – upgrading factors	Not applicable		

AFP = alpha-fetoprotein; ALT = alanine transaminase; DAA = direct acting antivirals; HBV = chronic hepatitis B; HCV = chronic hepatitis C; RCT = randomised controlled trial

*Table 14. GRADE assessment of the certainty of the evidence for the outcome of **proportion of liver cancer early-stage at diagnosis** from RCT evidence.*

GRADE domain	***Rating***	***Reason for downgrading or upgrading***	***Certainty of evidence***
Early-stage HCC at diagnosis			
Risk of bias	Very serious concerns (-2)	Both studies high risk of bias. In Chen 2003 (22) this was due to a high risk of bias due to the measurement of the outcome. In Zhang 2004 (21) this was due to a high risk of bias arising from the application of cluster design, missing outcome data, and measurement of the outcome.	Very low
Indirectness	Serious concerns (-1)	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 concerns (-1)	In both studies the proportion of cancer diagnosed at early stage increased. In Zhang 2004 (21) 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 (22) 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.	
Inconsistency	No serious concerns	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 (21) used ultrasound and AFP while Chen 2003 (22) used AFP and ALT.	
Publication bias	Undetected	Both studies reported similar results for this outcome however, they reported differing results for liver cancer-related mortality. Highly unlikely any recent RCTs addressing this question have been undertaken due to the acceptability and ethics of such trials.	

Other – cohort studies only – upgrading factors	Not applicable		

AFP = alpha-fetoprotein; ALT = alanine transaminase; DAA = direct acting antivirals; HBV = chronic hepatitis B; HCC = hepatocellular carcinoma; HCV = chronic hepatitis C; RCTs = randomised controlled trials; RR = risk ratio

Table 15. GRADE assessment of the certainty of the evidence for modelled outcomes for individual studies.

Study and outcome		***GRADE domain***			
		Risk of bias	***Indirectness***	***Imprecision***	***Inconsistency***
R**obotin 2009**(23) Cost effectiveness and liver disease-related mortality	*Rating*	Very serious concerns	No serious concerns	Not assessable	No serious concerns
	Reason for rating	Authors do not critically appraise sources of data underpinning effect of surveillance and some important medical treatments not included in model	HBV population, reports % cirrhotic at baseline and rate of surveillance for comparator, usual care		No PSA undertaken however, parameters based on individual studies rather than pooled estimates
Sangmala 2014(24) Cost effectiveness	*Rating*	Serious concerns	Serious concerns	Not assessable	No serious concerns
	Reason for rating	Authors do not critically appraise sources of data underpinning effect of surveillance	HBV population, does not report % cirrhotic at baseline		PSA undertaken
Chang 2011(25) Cost effectiveness	*Rating*	Very serious concerns	No serious concerns	Not assessable	Serious concerns
	Reason for rating	Authors do not critically appraise sources of data underpinning effect of surveillance and some important medical treatments not included in model	HBV population and reports % cirrhotic at baseline		No PSA undertaken and used pooled estimates for at least 18 parameters however, only undertook sensitivity analyses for 5 parameters
Uyei 2019(26) Cost effectiveness	*Rating*	Serious concerns	No serious concerns	Not assessable	No serious concerns
	Reason for rating	Authors do not critically appraise sources of data underpinning effect of surveillance	Reports % cirrhosis compensated at baseline		No PSA undertaken and used pooled estimates for several parameters however, undertook sensitivity analysis for each of the parameters
Farhang Zangneh 2019(27) Cost effectiveness	*Rating*	Very serious concerns	No serious concerns	Not assessable	No serious concerns
	Reason for rating	Authors do not critically appraise sources of data underpinning effect of surveillance and medical treatment for intermediate stage disease not included in model	Reports % cirrhosis compensated at baseline		PSA undertaken

HBV = chronic hepatitis B; HCC = hepatocellular carcinoma; PSA = probabilistic sensitivity analysis

Table 16. GRADE assessment of the certainty of the body of evidence for the outcome of cost-effectiveness – non-cirrhotic populations.

GRADE domain	***Rating***	***Reason for rating***	***Certainty of evidence***
Cost effectiveness			
Risk of bias	Very serious concerns (-2)	Data underpinning effect of surveillance not critically appraised plus some important medical treatments were not included in the model in three of the four studies (Robotin 2009 (23); Chang 2011 (25); Farhang Zangneh 2019 (27)).	Low to very low

Indirectness	No serious concerns	HBV or HCV population. Three out of four studies reported proportion cirrhotic at baseline. Only Sangmala 2014 (24) did not report the proportion with cirrhotic disease at baseline, it was assumed to be <20%.	
Imprecision	Not assessable	Not possible to assess	
Inconsistency	No serious concerns	Some inconsistency. Unable to state if surveillance is cost effective when compared with no surveillance in two studies (Robotin 2009 (23); Chang 2011 (25)) as no willingness to pay threshold or indicative benchmark reported. The cost-effectiveness ratio for the study assessing risk-stratified surveillance was very high and thus unlikely to be cost-effective (Robotin 2009 (23)). Of the remaining two studies, surveillance with either 6-monthly US or US+AFP when compared with no surveillance was cost effective for HCV patients (Sangmala 2014 (24)). US surveillance was not cost effective for HCV patients with advanced fibrosis after DAA-induced sustained virologic response (Farhang Zangneh 2019 (27)). Inconsistencies can be explained by differences in the clinical effects of the interventions due to differences in the intervention eg risk-stratified screening versus screening for all HBV patients and the modelled populations (age, antiviral treatments and aetiology), and also differences in perspective and the costs of the type and mix of treatments offered for early-stage and more advanced-stage HCC ie different times and settings of the studies.	
Publication bias	Undetected	The results varied with surveillance cost effective in Sangmala 2014 (24) but not cost-effective in Farhang Zangneh 2019 (27).	
Other – cohort studies only – upgrading factors	Not applicable		

AFP = alpha-fetoprotein; DAA = direct acting antiviral; HBV = chronic hepatitis B; HCC = hepatocellular carcinoma; HCV = chronic hepatitis C; US = ultrasound

Table 17. GRADE assessment of the certainty of the body of evidence for the outcome of cost-effectiveness - cirrhotic DAA-treated chronic hepatitis C populations.

GRADE domain	***Rating***	***Reasons for rating***	***Certainty of evidence***
Cost effectiveness			
Risk of bias	Very serious concerns (-2)	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 (27).	Low to very low
Indirectness	No serious concerns	Both studies report proportion of cirrhosis that is compensated at baseline.	
Imprecision	Not assessable	Not possible to assess	
Inconsistency	No serious concerns	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 (26)) versus cirrhotic following sustained DAA-induced virologic response (Farhang Zangneh 2019 (27)).	
Publication bias	Undetected	Only two studies assessing surveillance in an emerging patient population, one of which reported surveillance was not cost-effective in another patient group (Farhang Zangneh 2019).	

Other – cohort studies only – upgrading factors	Not applicable		

DAA = direct acting antiviral; HCV = chronic hepatitis C

4. SUMMARY OF FINDINGS

*Table 18. Summary of findings for surveillance vs no surveillance for people with **non-cirrhotic liver disease**.*

Outcome	***Number of participants (studies)***	***Certainty of the evidence (GRADE)***	***Relative effect (95% CI)***	***Anticipated absolute effect (95% CI)***		
				Metric	***Risk with no surveillance***	***Risk with surveillance***
Overall mortality	5,581 (1 RCT)	Very low[1]	Rate ratio = 0.97 (0.77-1.22)	Deaths per 100,000 person years	1,788.4	1,734.7 (1,377.1-2,181.8)**
Liver disease-related mortality	10,000 (1 modelling study)	Low to very low[2]	Not calculable*	%	33.8	33.6 (risk-stratified surveillance)
HCC or liver-cancer related mortality	24,397 (5,581+18,816) (2 RCTs)	Very low[3]	*6 monthly US+AFP* Rate ratio = 0.63 (0.41-0.98) *6 monthly AFP+ALT* Rate ratio = 0.86 (0.69-1.07)	Deaths per 100,000 person years	131.5 1,113.9	82.8 (53.9-128.9)** 958.0 (768.6-1,191.9)**
% Liver cancer diagnosed at an early stage	24,397 (2 RCTs)	Very low[4]	*6 monthly US+AFP* Not calculable *6 monthly AFP+ALT* Risk ratio = 7.54 (2.82 -20.14)	%	0 3.7	60.5 27.9 (10.4-74.5)**
Cost effectiveness	NR (4 modelling studies)	Low to very low[5]	Surveillance (6-monthly US or US+AFP) is cost effective for HBV patients when compared with no surveillance (1 study) Cost effectiveness for HBV patients not reported (2 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)	NA	NA	NA

[1] *One study with very serious concerns regarding risk of bias and serious concerns regarding indirectness*
[2] *Modelling study with very serious concerns regarding risk of bias*
[3] *Very serious concerns regarding risk of bias and serious concerns regarding indirectness*
[4] *Very serious concerns regarding risk of bias and serious concerns regarding indirectness*
[5] *Modelling studies with very serious concerns regarding risk of bias*
** 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.*
*** 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; DAA = direct acting antiviral; HBV = chronic hepatitis B; HCV =chronic hepatitis C; NA = not applicable; NR= not reported; RCT = randomised controlled trial; US = ultrasound

*Table 19. Summary of findings for surveillance vs no surveillance for people with **DAA-treated cirrhotic chronic hepatitis C**.*

Outcome	*Number of participants (studies)*	*Certainty of the evidence (GRADE)*	*Relative effect (95% CI)*	*Anticipated absolute effect (95% CI)*	
				Risk with no surveillance	*Risk with surveillance*
Cost effectiveness	NR (2 modelling studies)	Low to very low[1]	Surveillance with 6-monthly and 12-monthly US is cost effective when compared with no surveillance (2 studies)	NA	NA

[1]*Modelling studies with very serious concerns regarding risk of bias*

DAA = direct acting antiviral; HCV = chronic hepatitis C; NA = not applicable; NR = not reported; US = ultrasound

Table 20. Evidence summary for surveillance vs no surveillance for people with ***non-cirrhotic liver disease &*** *people with* ***DAA-treated cirrhotic chronic hepatitis C****.*

Evidence summary	**GRADE certainty of evidence**	**References**
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.	Very low	Chen 2003 (22) Zhang 2004 (21)
For people with chronic HBV infection a single cost-effectiveness analysis estimated that HCC surveillance using 6-monthly liver ultrasound and AFP or ultrasound alone, is cost-effective compared with no surveillance in Thailand.	Low to very low	Sangmala 2014 (24)
For patients with cirrhosis after a sustained virologic response to DAA treatment for HCV, HCC surveillance with 6-monthly liver ultrasound is cost-effective	Low to very low	Uyei 2019 (26) Farhang Zangneh 2019 (27)
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.	Low to very low	Farhang Zangneh 2019 (27)
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.	Not applicable	

REFERENCES

1. World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2015. 134 p.

2. National Institute for Health and Care Excellence. Hepatitis B (chronic); diagnosis and management. Clinical guideline [CG165] Last updated October 2017 [Internet]. London: NICE; 2013 [cited 2022 Jun 16]. Available from: https://www.nice.org.uk/guidance/cg165

3. National Institute for Health and Care Excellence. Cirrhosis in Over 16s: Assessment and Management. NICE guideline [NG50] [Internet]. London: NICE; 2016 [cited 2021 Dec 8]. Available from: https://www.nice.org.uk/guidance/ng50

4. 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. 2019;13(1):1–1.

5. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018 Apr;67(4):1560–99.

6. Gastroenterological Society of Australia. Hepatocellular Carcinoma Consensus Statement Working Group. Australian recommendations for the management of hepatocellular carcinoma: a consensus statement. [Internet]. Melbourne: Gastroenterological Society of Australia; 2020 [cited 2022 Sep 12]. Available from: https://www.gesa.org.au/resources/hepatocellular-carcinoma-hcc-management-consensus/

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

8. AGREE Next Steps Consortium. The AGREE II Instrument [Internet]. 2017. Available from: http://www.agreetrust.org/resource-centre/agree-ii/

9. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022) [Internet]. Cochrane; 2022. Available from: www.training.cochrane.org/handbook

10. Eldridge S, Campbell MK, Campbell MJ, Drahota AK, Giraudeau B, Reeves BC, et al. Revised Cochrane risk of bias tool for randomized trials (RoB 2) Additional considerations for cluster-randomized trials (RoB 2 CRT) [Internet]. 2021 [cited 2022 Feb 1]. Available from: https://drive.google.com/file/d/1yDQtDkrp68_8kJiIUdbongK99sx7RFI-/view

11. Kirk M, Smurthwaite K, Braunig J, Trevener S, D'Este C, Lucas R, et al. The PFAS Health Study: Systematic Literature Review [Internet]. Canberra: The Australian National University; 2018. p. 161–3. Available from: https://openresearch-repository.anu.edu.au/handle/1885/241032

12. Odnoletkova I, Goderis G, Pil L, Nobels F, Aertgeerts B, Annemans L, et al. Cost-Effectiveness of Therapeutic Education to Prevent the Development and Progression of Type 2 Diabetes: Systematic Review. J Diabetes Metab. 2014;05(09):in appendix.

13. NHMRC. Guidelines for Guidelines: Assessing certainty of evidence [Internet]. 2019. Available from: https://nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence

14. Murad MH, Mustafa RA, Schünemann HJ, Sultan S, Santesso N. Rating the certainty in evidence in the absence of a single estimate of effect. Evid Based Med. 2017 Jun;22(3):85–7.

15. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol. 2011 Dec;64(12):1283–93.

16. Zeng L, Brignardello-Petersen R, Hultcrantz M, Siemieniuk RAC, Santesso N, Traversy G, et al. GRADE guidelines 32: GRADE offers guidance on choosing targets of GRADE certainty of evidence ratings. J Clin Epidemiol. 2021 Sep;137:163–75.

17. Brignardello-Petersen R, Guyatt GH, Mustafa RA, Chu DK, Hultcrantz M, Schünemann HJ, et al. GRADE guidelines 33: Addressing imprecision in a network meta-analysis. J Clin Epidemiol. 2021 Nov;139:49–56.

18. Brunetti M, Shemilt I, Pregno S, Vale L, Oxman AD, Lord J, et al. GRADE guidelines: 10. Considering resource use and rating the quality of economic evidence. J Clin Epidemiol. 2013 Feb;66(2):140–50.

19. Holger Schünemann, Jan Brożek, Gordon Guyatt, Andrew Oxman. GRADE Handbook - Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach [Internet]. 2013 [cited 2022 Apr 26]. Available from: https://gdt.gradepro.org/app/handbook/handbook.html

20. Brozek JL, Canelo-Aybar C, Akl EA, Bowen JM, Bucher J, Chiu WA, et al. GRADE Guidelines 30: the GRADE approach to assessing the certainty of modeled evidence—An overview in the context of health decision-making. J Clin Epidemiol. 2021 Jan;129:138–50.

21. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol. 2004 Jul;130(7):417–22.

22. 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):204–9.

23. 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 May;50(5):990–8.

24. 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. Asian Pac J Cancer Prev. 2014 Nov 6;15(20):8993–9004.

25. Chang Y, Lairson DR, Chan W, Lu SN, Aoki N. Cost-effectiveness of screening for hepatocellular carcinoma among subjects at different levels of risk: Cost-effectiveness of screening for HCC. J Eval Clin Pract. 2011 Apr;17(2):261–7.

26. 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.

27. Farhang Zangneh H, Wong WWL, 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 Aug;17(9):1840-1849.e16.

28. 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 Open. 2021 Jun 24;4(6):e2114680.

29. 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.

30. 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 Health. 2021 Oct;24(10):1454–62.

31. 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 Apr 19;OF1–8.

32. 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 Dec;65(6):1086–93.

33. Parikh ND, Singal AG, Hutton DW, Tapper EB. Cost-Effectiveness of Hepatocellular Carcinoma Surveillance: An Assessment of Benefits and Harms. Am J Gastroenterol. 2020 Oct;115(10):1642–9.

34. 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):1418–24.

35. 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 Apr;98(7):1166–75.

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

37. 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. 2010/06/16 ed. 2010 May;25(5):951–6.

38. 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. Intern Med J. 2013 Jul;43(7):772–7.

39. 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 Feb;1(1):53–60.

40. 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):551–6.

41. Byford S, Raftery J. Economics notes: Perspectives in economic evaluation. BMJ. 1998 May 16;316(7143):1529–30.

42. Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun Wong V, Castellanos M, Aller-de la Fuente R, Metwally M, et al. Fibrosis Severity as a Determinant of Cause-Specific Mortality in Patients With Advanced Nonalcoholic Fatty Liver Disease: A Multi-National Cohort Study. Gastroenterology. 2018 Aug 1;155(2):443-457.e17.

43. 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 Aug;21(8):938–43.

44. Hong TP. An Australian population-based study of the incidence and outcomes of hepatocellular carcinoma: the Hepatomas of Melbourne Epidemiological Research (HoMER) study [Internet]. 2019 [cited 2019 Jul 11]. Available from: http://hdl.handle.net/11343/225659

45. Wallace MC, Preen DB, Short MW, Adams LA, Jeffrey GP. Hepatocellular carcinoma in Australia 1982-2014: Increasing incidence and improving survival. Liver Int. 2019 Mar;39(3):522–30.

46. Nguyen ALT, Si L, Lubel JS, Shackel N, Yee KC, Wilson M, et al. Construction and validation of a microsimulation model for hepatocellular carcinoma surveillance in Australia. In Submission;

47. Alavi M, Law MG, Grebely J, Amin J, Hajarizadeh B, George J, et al. Time to decompensated cirrhosis and hepatocellular carcinoma after an HBV or HCV notification: A population-based study. J Hepatol. 2016 Nov;65(5):879–87.

48. Jepsen P, Vilstrup H, Andersen PK. The clinical course of cirrhosis: The importance of multistate models and competing risks analysis. Hepatology. 2015 Jul 1;62(1):292–302.

49. Canfell K, Kim JJ, Brisson M, Keane A, Simms KT, Caruana M, et al. Mortality impact of achieving WHO cervical cancer elimination targets: a comparative modelling analysis in 78 low-income and lower-middle-income countries. The Lancet. 2020 Feb;395(10224):591–603.

50. Haq MI, Drake TM, Goh TL, Ahmed A, Forrest E, Barclay S, et al. Effect of Hepatocellular Carcinoma Surveillance Programmes on Overall Survival in a Mixed Cirrhotic UK Population: A Prospective, Longitudinal Cohort Study. J Clin Med. 2021 Jun 24;10(13):2770.

51. Consumer Price Index, Australia, March 2022 | Australian Bureau of Statistics [Internet]. 2022 [cited 2022 Jun 12]. Available from: https://www.abs.gov.au/statistics/economy/price-indexes-and-inflation/consumer-price-index-australia/latest-release

52. Department of Health, Australian Government. MBS Online: Medicare Benefits Schedule. [homepage on the internet] [Internet]. Canberra, ACT: Commonwealth of Australia; Available from: http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/Home

53. Xiao Y, Howell J, Gemert C, Thompson AJ, Seaman CP, McCulloch K, et al. Enhancing the hepatitis B care cascade in Australia: A cost-effectiveness model. J Viral Hepat. 2020 May;27(5):526–36.

54. Reeve R, Srasuebkul P, Langton JM, Haas M, Viney R, Pearson SA, et al. Health care use and costs at the end of life: a comparison of elderly Australian decedents with and without a cancer history. BMC Palliat Care. 2017 Jun 21;17(1):1.

55. McPhail SM, Amarasena S, Stuart KA, Hayward K, Gupta R, Brain D, et al. Assessment of health-related quality of life and health utilities in Australian patients with cirrhosis. JGH Open. 2021 Jan;5(1):133–42.

56. Global Burden of Disease Collaborative Network. Global Burden of Disease (GBD 2019) [Internet]. Seattle, United States of America: Institute for Health Metrics and Evaluation (IHME); 2021 [cited 2022 Jun 12]. Available from: https://www.healthdata.org/gbd/2019

57. 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 Jan;44(1):217–31.

58. NSW Cancer Registry. Data request: Hepatocellular carcinoma (coded as C22.0 or C22.9) incidence and mortality). Private communication; unpublished.; 2021 Aug.

59. Tzartzeva K, Obi J, Rich NE, Parikh ND, Marrero JA, Yopp A, et al. Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Patients With Cirrhosis: A Meta-analysis. Gastroenterology. 2018 May 1;154(6):1706-1718.e1.

60. Cheng RM. Novel Biomarkers of Hepatocellular Carcinoma [Internet]. The University of Sydney; 2018. Available from: http://hdl.handle.net/2123/20294

61. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. Circulation. 2016 Feb 9;133(6):601–9.

62. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. Stat Med. 2017 Nov 30;36(27):4391–400.

APPENDICES

Appendix 1: Medline and Embase database (via Ovid platform) search strategy

#	Searches
1	carcinoma, hepatocellular/
2	liver neoplasms/
3	liver cell carcinoma/
4	liver tumor/
5	liver cancer/
6	1 or 2 or 3 or 4 or 5
7	((hepato* or liver or hepatic) adj3 (cancer or carcinoma* or neoplasm* or tumor* or tumour*)).tw.
8	(hepatoma* or hepatocarcinoma* or hcc).tw.
9	7 or 8
10	Early diagnosis/
11	Early detection of cancer/
12	population surveillance/
13	cancer screening/
14	mass screening/
15	disease surveillance/
16	10 or 11 or 12 or 13 or 14 or 15
17	screen*.tw.
18	surveil*.tw.
19	17 or 18
20	6 or 9
21	16 or 19
22	20 and 21
23	fatty liver/ or non-alcoholic fatty liver disease/ or hepatitis/ or hepatitis, viral, human/
24	(hepatitis or HBV or fatty liver or NAFLD or MAFLD or steatohepatitis or NASH or steatosis or non-cirrhotic or noncirrhotic or no cirrhosis or no cirrhotic or without cirrhosis or without cirrhotic).tw.
25	Ultrasonography/
26	(ultrasound or ultrasonograph*).tw.
27	22 or 23 or 24 or 25 or 26
28	22 and 27
29	limit 28 to english language
30	limit 29 to humans

31	limit 30 to yr="2000 -Current"
32	limit 31 to conference abstracts [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) PubMed not MEDLINE,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]
33	limit 32 to medline
34	32 not 33
35	31 not 34
36	limit 35 to yr="2000 - 2010"
37	35 not 36
38	remove duplicates from 36
39	remove duplicates from 37
40	38 or 39

Appendix 2: GRADE assessment of the certainty of the evidence

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Appendix 3: Excluded Studies

Article	PMID/DOI	Reason for exclusion
Abe 2020	https://dx.doi.org/10.1371/journal.pone.0243473	No intervention of interest
Amarapurkar 2009	http://dx.doi.org/10.1111/j.1440-1746.2009.05805.x	Excluded study type or design
Basyigit 2015	http://dx.doi.org/10.1097/MEG.0000000000000426	Excluded publication type
Bolondi 2001	PMID: 11156649	No population of interest
Cadier 2017	doi: 10.1002/hep.28961	No population of interest
Carter 2021	https://dx.doi.org/10.1016/j.jval.2021.04.1286	No population of interest
Chayanupatkul 2017	http://dx.doi.org/10.1016/j.jhep.2017.06.005	Excluded publication type
Chen 2002	http://dx.doi.org/10.1002/ijc.10122	No population of interest
Chen 2020	https://doi.org/10.1177/0022242920913025	No intervention of interest
Cucchetti 2014	https://doi.org/10.1016/j.jhep.2014.03.037	No population of interest
Davila 2007	DOI: 10.1097/MCG.0b013e3180381560	No population of interest
El-Serag 2011	DOI: 10.1136/gut.2010.230508	No population of interest
Foerster 2018	http://dx.doi.org/10.1002/lt.25309	Excluded publication type

Gaba 2013	PMID: 24018494	No population of interest
Giannini 2000	PMID: 11100360	No population of interest
Gounder 2016	http://dx.doi.org/10.3402/ijch.v75.31115	Excluded study type or design
Heffernan 2019	https://dx.doi.org/10.1016/S0140-6736%2818%2932277-3	No intervention of interest
Ioannou 2019	http://dx.doi.org/10.1016/j.jhep.2018.09.026	Excluded publication type
Ji 2019	http://dx.doi.org/10.1016/j.jhep.2018.09.016	Excluded publication type
Ji 2018	http://dx.doi.org/10.1038/s41598-018-31119-9	No population of interest
Kemp 2005	DOI: 10.1111/j.1440-1746.2005.03844.x	No population of interest
Khan 2018	http://dx.doi.org/10.1002/cld.707	Excluded publication type
Kim 2019	http://dx.doi.org/10.1002/hep.30330	No population of interest
Kolly 2016	http://dx.doi.org/10.3390/diagnostics6020022	Excluded publication type
Kuehn 2010	http://dx.doi.org/10.1001/jama.2010.161	Excluded publication type
Kuo 2010	DOI: 10.1016/j.ejca.2009.12.018	No population of interest
Leykum 2007	DOI: 10.1016/j.cgh.2007.01.014	No population of interest
McMahon 2000	http://dx.doi.org/10.1053/jhep.2000.17914	No comparator of interest
Merle 2021	https://dx.doi.org/10.1016/j.clinre.2021.101722	Excluded publication type
Mourad 2014	http://dx.doi.org/10.1002/hep.26944	No population of interest
Pascual 2008	DOI: 10.1111/j.1478-3231.2008.01710.x	No population of interest
Patel 2018	http://dx.doi.org/10.1016/j.amjmed.2017.09.036	Excluded publication type
Poustchi 2011	https://dx.doi.org/10.1002/hep.24581	No population of interest
Qian 2010	http://dx.doi.org/10.1111/j.1440-1746.2009.06203.x	No population of interest
Ren 2006	https://dx.doi.org/10.3748/wjg.v12.i29.4656	No comparator of interest
Robotin 2012	https://dx.doi.org/10.3748/wjg.v18.i42.6106	No comparator of interest
Ruelas-Villavicencio 2004	PMID: 15657557	No comparator of interest
Rugge 2006	PMID: 16451784	Excluded publication type
Ruggeri 2012	http://dx.doi.org/10.2147/rmhp.s18677	Excluded study type or design
Saab 2004	http://dx.doi.org/10.1016/j.ehbc.2004.05.003	Excluded publication type
Saquib 2015	https://dx.doi.org/10.1093/ije/dyu140	Excluded study type or design
Shih 2010	PMID: 20123585	No population of interest
Shim 2020	http://dx.doi.org/10.1002/cam4.3421	No intervention of interest
Singal 2017	http://dx.doi.org/10.1097/MCG.0000000000000708	No population of interest
Spadaccini 2018	http://dx.doi.org/10.1016/j.hbpd.2018.10.006	Excluded study type or design
Tanaka 2006	doi: 10.1111/j.1478-3231.2006.01270.x	No population of interest
Taura 2005	PMID: 16142364	No population of interest
Tavakoli 2017	http://dx.doi.org/10.1007/s10620-017-4595-x	No population of interest
Tong 2010	doi: 10.1007/s10620-009-1059-y	No population of interest
Trevisani 2002	DOI: 10.1111/j.1572-0241.2002.05557.x	No population of interest
Trevisani 2004	doi: 10.1111/j.1572-0241.2004.30137.x	No population of interest
Wang 2021	http://dx.doi.org/10.1016/j.cgh.2021.09.040	No intervention of interest
Wang 2011	doi: 10.1038/ajg.2012.445	Excluded publication type
Wong 2008	doi: 10.1111/j.1478-3231.2007.01576.x	No population of interest
Wun 2003	DOI: 10.1002/14651858.CD002799	Excluded study type or design
Xie 2015	http://dx.doi.org/10.1007/s12032-015-0534-x	Excluded publication type
Yamashita 2014	http://dx.doi.org/10.1007/s00535-013-0921-z	No outcome of interest
Yu 2004	doi: 10.1097/00130404-200409000-00009	Excluded study type or design

Appendix D2. Technical report for question 2

Systematic Review Question 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

This systematic review addresses the PICO shown in Table 2.

Table 2. PICO for systematic review question 2.

Population	Intervention	Comparator	Outcomes	Study design
HCC patients with non-cirrhotic liver disease or Cirrhotic patients with HCC who have been treated for HCV with direct acting antivirals	Previous HCC surveillance	No previous surveillance	Survival Proportion of liver cancers that are early stage at diagnosis Cost-effectiveness	Observational cohort studies

HCC = hepatocellular carcinoma; HCV = chronic viral hepatitis C

1. METHODS

1.1 Selection Criteria

Table 2. Selection criteria for observational studies examining the effects of prior participation in surveillance programs for individuals with HCC.

PICO 2	***Inclusion***	***Exclusion***
Study type	Observational	Diagnostic accuracy
Study design	Observational prospective or retrospective cohort studies Systematic reviews thereof	Case series Case-control studies Review (not systematic)
Population	≥18 years Patients with HCC or liver cancer with non-cirrhotic: Liver disease (any aetiology) Chronic hepatitis B (HBV) Chronic hepatitis C (HCV) Alcohol -related liver disease (ARLD) Metabolic associated fatty liver disease (MAFLD) Cirrhotic patients who have been treated for HCV with direct acting antivirals	Children <80% non-cirrhotic ie ≥ 20% cirrhotic Restricted to liver cancer patients undergoing liver resection or transplant

Exposure	Prior participation in HCC surveillance program	Provides no details about the surveillance program Ad hoc surveillance Single screen offered Surveillance-detected GALAD surveillance
Comparator	No prior participation in HCC surveillance program	No comparator Historical control Non surveillance detected
Outcome	Survival/mortality – adjusted analyses or matched study % early/treatable stage HCC or liver cancer at diagnosis Cost-effectiveness based on adjusted analyses or matched study (QALY gained, DALY gained or life years gained)	Survival unadjusted analyses (unless matched study) Costs only Costs per lives saved Incremental cost of additional early-stage diagnosis
Publication date/timeframe	2000 onwards	
Publication type	Original journal article Letter or comment that reports original data	Conference abstracts Editorials Letters and comments that do not report original data
Language	English	

HCC = hepatocellular carcinoma; DALY = disability-adjusted life years; GALAD score = score based on gender, age, Lens culinaris agglutinin-reactive AFP, total AFP, and des-γ-carboxyprothrombin; QALY = quality-adjusted life years
[a] *Hepatocellular carcinoma is the liver cancer of primary interest.*
[b] *Chronic HBV infection, chronic HCV infection, alcohol-related liver disease and metabolic-associated fatty liver disease are the aetiologies of interest.*

1.2 Definitions and terminology

For the purpose of this review:

Early-stage HCC includes Barcelona Clinic Liver Cancer (BCLC) stage 0/A, meeting Milan criteria, or China Liver Cancer Study group stage I.

1. *The Barcelona Clinic Liver Cancer (BCLC*) staging classification system assesses the number and size of liver tumours, overall performance status (ECOG PS) and liver function (using Child-Pugh classification):
    a. BCLC stage 0 (very early-stage); ECOG performance score = 0, Child-Pugh A, single tumour < 20mm;

b. BCLC stage A (early-stage); ECOG performance score = 0, Child-Pugh A-B, single tumour of any size or up to 3 tumours all < 30mm).

2. *The Milan criteria* focus on liver transplantation eligibility. Those eligible for transplantation are described as within Milan criteria and are defined as having one tumour measuring ≤ 50 mm in diameter, or 2-3 tumours ≤ 30 mm in diameter without vascular extension or metastasis.
3. The *China Liver Cancer study group staging* system classifies HCC as stage I (subclinical stage/early-stage) if there are no obvious cancer symptoms and signs (tumour usually < 5 cm in diameter).

Where results were given by BCLC stage and another staging system, the BCLC results were presented.

Fibrotic status *was as* reported by authors.

Generalisability refers to whether the evidence can be directly applied to the target population.

Metabolic-associated fatty liver disease includes non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

Sojourn time refers to the time from when cancer becomes screen detectable until it becomes symptomatic.

1.3 Guidelines

Relevant recent (2015 onwards) guidelines were identified by scanning the citations identified by the literature search (described below) and a summary of these guidelines was reviewed by Expert Advisory Group members as part of Phase 1 of the *Roadmap to Liver Cancer Control* project.

To be considered for adoption by the Working Group guidelines had to be evidence-based and meet the pre-specified criteria of scores of greater or equal to 70% for the following domains: rigour of development, clarity of presentation and editorial independence of the AGREE II instrument (8). Guidelines were not considered for adoption by the Working Group if they were not based on systematic reviews of the evidence, i.e. did not report using systematic methods to search for evidence, did not clearly describe the criteria for selecting the evidence or did not assess the risk of bias or where this is not possible, appraise the quality of the evidence.

1.4 Literature searches

Medline (including MEDLINE Epub Ahead of Print, I-Process & Other Non-Indexed Citations) and Embase databases were searched on 1 February 2022 combining text terms and/or database-specific subject headings for liver cancer, surveillance and ultrasound or liver disease. Searches were limited to articles published in English from 1 January 2000 onwards. A complete list of the terms used is included as Appendix 1. The Cochrane Database of Systematic Reviews was searched on 31 March 2022 combining the search terms “liver cancer” and “screen”. Reference lists of included articles, recent relevant guidelines and systematic reviews were checked for potential additional articles.

1.5 Data extraction and analyses

If an effect estimate was not presented but the necessary data were available and adjusted estimates were not required, the risk ratio and 95% confidence interval was calculated using a tool available at *https://sample-size.net/risk-ratio/*. Where there were several possible comparators the comparator least likely to result in biased results was selected. A narrative synthesis for each of the outcomes is presented as only one study was included for each of the reported outcomes.

1.6 Risk of bias assessments and quality appraisals

The risk of bias of cohort observational studies was assessed using a modified version of the Newcastle-Ottawa Scale designed specifically to assess the risk of bias in aetiological cohort studies (11).

1.7 GRADE assessment of the certainty of the evidence

A GRADE approach was used to assess the certainty of the body of evidence for the effect of previous HCC surveillance when compared with no previous HCC surveillance for each outcome (13).

For non-modelling studies the certainty of the body of evidence was rated high, moderate, low or very low based on assessment of risk of bias, indirectness of the results, imprecision (extent of 95% confidence intervals) of the results, inconsistency or heterogeneity of the results, and publication bias based on guidance for assessing narrative syntheses provided by Murad 2017 and additional guidance for the assessment of imprecision provided by Guyatt 2011, Zeng 2021 and Brignardello-Petersen 2021 (14–17). For the assessment of imprecision any decrease in mortality was considered clinically important, and an increase of at least 5 percentage points in the percentage of liver cancer diagnosed at an early stage was considered clinically important. The clinical threshold for clinical importance was used to assess imprecision (16). Where the use of a clinical importance threshold was not possible, as for mortality outcomes, we calculated the ratio of the upper to the lower limit of the

confidence interval and considered ratios less than 3.0 for rate ratios as indicative of no serious concerns regarding imprecision (personal communication with GRADE group, October 2021). As per GRADE guidance (19), observational cohort studies started with a low level of certainty and were downgraded if there were serious concerns or upgraded if the effect estimate was large (greater than 2.0 or less than 0.5), presence of a dose response gradient, or when plausible residual confounders increase certainty. Where there was only one study inconsistency could not be rated.

Definitions of the GRADE ratings of certainty are presented in Appendix 2.

2. RESULTS

2.1 Guidelines searches

No recent relevant guidelines based on systematic reviews were identified.

2.2 Literature searches

Figure 1 outlines the process of identifying relevant articles for this systematic review. The combined Medline and Embase search identified 5356 citations and the search of the Cochrane Database of Systematic Reviews 18 citations, resulting in a total of 5374 citations. Titles and abstracts were examined, and 85 articles were retrieved for a more detailed evaluation. An additional nine potential citations were identified from the reference lists of included articles, recent relevant guidelines, and systematic reviews.

Two observational cohort studies reported in two articles met the inclusion criteria and were included in the review.

The retrieved articles that were not included and the reasons for their exclusion are documented in Appendix 3. In summary, most articles were excluded because they did not include the population of interest (n = 66) or an intervention of interest (n = 13), or they did not report relevant comparative data for the outcome of interest (n = 4).

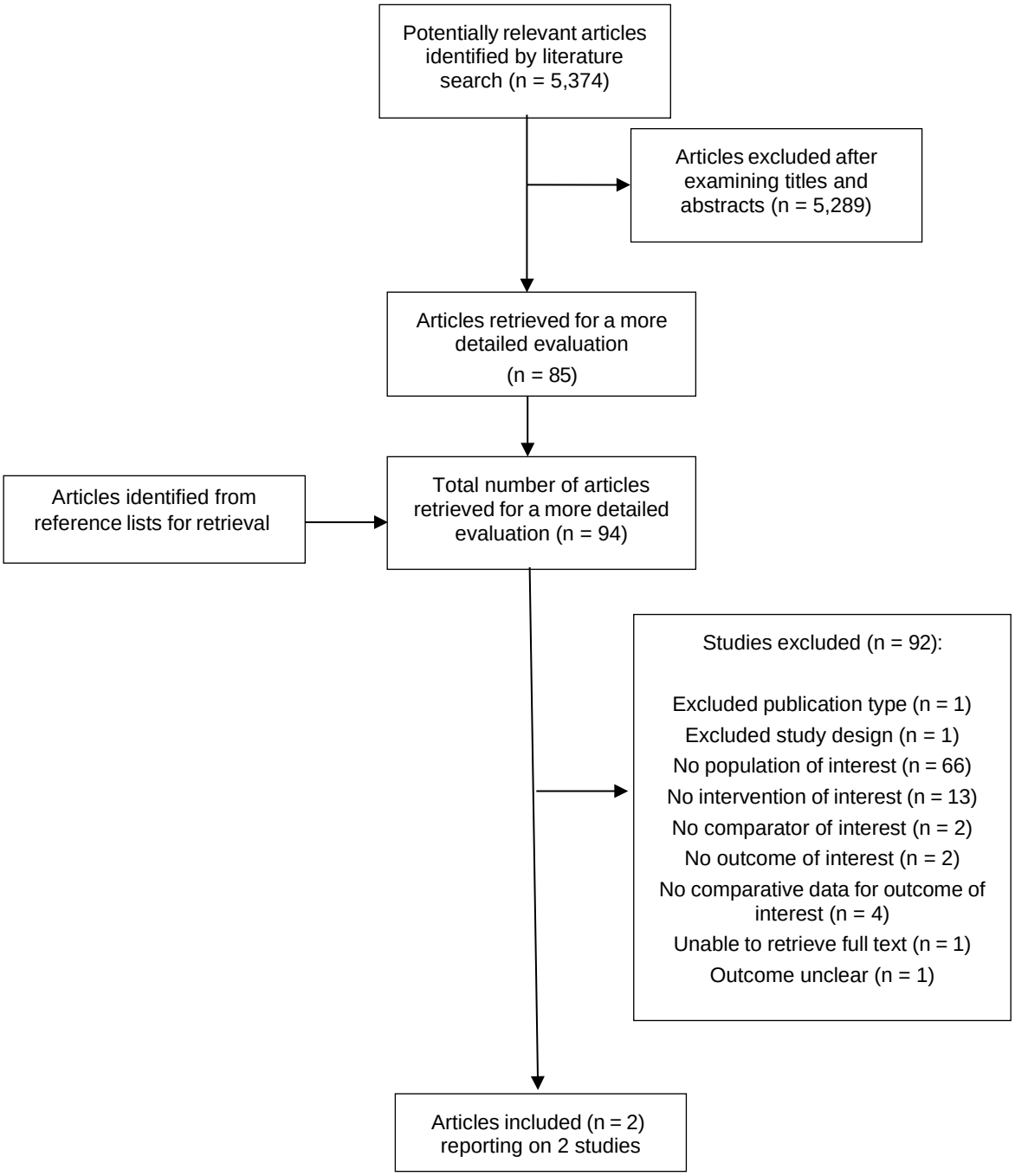


Figure 1. Process of inclusion and exclusion of studies.

2.3 Characteristics of included studies

The characteristics of included studies are described in Table 3.

Table 3. Study characteristics of studies comparing US surveillance with no regular surveillance for people with HCC.

Study (Country)	***Study design***	***Population***	***Participants***	***Intervention***	***Comparison***	***Follow-up***	***Outcomes***	***Conflicts of interest considered***
Kuo 2021 (28) (Taiwan)	Retrospective cohort	Patients with non-cirrhotic HCV diagnosed with HCC in Taiwan between 2003 and 2015 with recorded BCLC stage Age range: NR Excluded patients with HCC cancer detected at baseline: Yes	N = 2223 (analysed) Age: NR Male: 59.3% Non-cirrhotic: 100% Aetiology: HCV DAA-treated: NR	**Surveillance** US in 3-9 months prior to diagnosis Does not include most patients diagnosed on first screen N = 1917	**No regular surveillance** Last US in 28-39 months prior to diagnosis N = 306	Maximum range: 2.00 - 14.75 years	% early-stage disease	Yes - Authors report no conflicts of interest to declare
Wu 2016 (29) (Taiwan)	Retrospective cohort	Non-cirrhotic patients diagnosed with HCC in Taiwan between 2002 and 2007 Age range: NR Excluded patients with HCC cancer detected at baseline: Yes	N = 7425 (analysed) Age: NR Male: NR Non-cirrhotic: 100% Aetiology: mixed	**Surveillance** US in 3-9 months prior to diagnosis Does not include most patients diagnosed on first screen N = 5853	**No regular surveillance** Last US in 28-39 months prior to diagnosis N = 1572	Maximum range: 5 - 11 years	HCC mortality	Yes - Authors report no conflicts of interest to declare

BCLC = Barcelona Clinic Liver Cancer; DAA = direct acting antiviral; HCC = hepatocellular cancer; HCV = chronic hepatitis C; NR = not reported; US = ultrasound

2.4 Results by outcomes of interest

1. Overall mortality – results are shown in Table 4.
2. Liver disease-related mortality – no results found.
3. Liver cancer mortality – no results found.
4. Proportion of liver cancers diagnosed at an early stage – results are shown in Table 5.
5. Life-years, quality-adjusted life-years or disability-adjusted life-years gained – no results found.

6. Cost-effectiveness – no results found.

Table 4. Results for study comparing US surveillance with no regular surveillance – overall mortality.

Study	***Study design***	***Outcome***	***Outcome metric***	***US surveillance***	***No regular US surveillance***	***Effect estimate (95%CI)***	***Factors adjusted for in HR analyses***
Wu 2016 (29) (Non-cirrhotic – mixed aetiology)	Retrospective cohort	Overall mortality	5-year cumulative mortality after adjustment for lead-time bias assuming a sojourn time of 140 days (95%CI)	59.2 (58.0-60.5)	72.5 (70.3-74.7)	HR = 0.80 (0.75-0.85) ie the risk of HCC mortality for those who underwent regular surveillance is 0.80 times lower than that for those who did not	Age, sex, aetiology, comorbidities, concomitant drugs including antivirals, hospital level and lead time bias

HCC = hepatocellular cancer; HR = hazard ratio; US = ultrasound

Table 5. Results for study comparing US surveillance with no regular surveillance – proportion of HCC that are early-stage at diagnosis.

Study	***Study design***	***Outcome***	***Outcome metric***	***US Surveillance***	***No regular US surveillance***	***Effect estimate (95%CI)****	***Factors adjusted for in analyses***
Kuo 2021 (28) (Non-cirrhotic - HCV)	Retrospective cohort	Early-stage HCC (% HCC BCLC stage 0/A)	% total HCC (n/N)	75.4% (1446/1917) *Male subgroup* 73.4% (827/1127) *Female subgroup* 78.4% (619/790)	46.4% (142/306) *Male subgroup* 38.5% (74/192) *Female subgroup* 59.6% (68/114)	RR = 1.63 (1.44-1.84) ie the proportion of HCC diagnosed at an early stage is 1.63 times higher for those who undergo regular surveillance than that for those who did not *Male subgroup* RR = 1.90 (1.59-2.80) *Female subgroup* RR = 1.31 (1.12-1.53)	Subgroup analyses by sex

**Calculated by technical team using tool at https://sample-size.net/risk-ratio/*

BCLC = Barcelona Clinic Liver Cancer; HCC = hepatocellular cancer; HCV = chronic hepatitis C; RR = risk ratio; US = ultrasound

2.5 Risk of bias assessments

The results of the risk of bias assessments for the included observational cohort studies are shown in Table 6.

Table 6. Risk of bias assessments for the outcomes of proportion of HCC diagnosed at an early stage and overall mortality using the modified Newcastle-Ottawa Scale tool.

Source of bias	***Proportion of HCC early-stage at diagnosis*** *(Kuo 2021)* (28)	***Overall mortality*** *(Wu 2016)* (29)
Cohort selection	Low	Low
Participation	Low	Low
Ascertainment and measurement of exposure	Low	Moderate
Timing of outcome relative to exposure measurement	Low	Low
Nature and measurement of outcome	Low	Low
Completeness of follow-up	Low	Low
Adequacy of follow-up	Low	Low
Differences in follow-up	Low	Low
Missing exposure data	Low	Low
Control of confounding	Moderate	Low
Over-adjustment	Low	Low
Conflicts of interest	Low	Low
Overall risk of bias	**Moderate**	**Moderate**

HCC = hepatocellular carcinoma

Key to overall risk of bias rating

1. High risk of bias – high risk of bias in any domain (source of bias)
2. Moderate risk of bias – moderate or low risk of bias in all domains, no domains high risk
3. Low risk of bias – all domains low risk of bias, no domains moderate or high risk

3. GRADE ASSESSMENT OF THE CERTAINTY OF THE EVIDENCE

Overall mortality – assessments are shown in Table 7.

Liver disease-related mortality - no evidence found.

HCC or liver cancer mortality - no evidence found.

Proportion of liver cancers diagnosed at an early stage – assessments are shown in Table 8.

Life-years, quality-adjusted life-years or disability-adjusted life-years gained - no evidence found.

Cost-effectiveness – no evidence found.

Table 7. GRADE assessment of the certainty of the evidence for the outcome overall mortality.

GRADE domain	***Rating***	***Reason for downgrading or upgrading***	***Certainty of evidence***
Overall mortality			
Risk of bias	Serious (-1)	Moderate risk of bias due to ascertainment of surveillance status. Confounding well adjusted for.	Very low
Indirectness	Serious concerns (-1)	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 concerns	HR (95%CI) = 0.80 (0.75-0.85) and the effect is moderate.	
Inconsistency	Not applicable	Only one study - Not possible to assess.	
Publication bias	Undetected	Undetected – one large study based on national data (N = 7425).	
Other – cohort studies only – upgrading factors	No change	HR (95%CI) = 0.80 (0.75-0.85) > 0.5.	

HR = hazard ratio; US = ultrasound

Table 8. GRADE assessment of the certainty of the evidence for the outcome proportion of HCC early-stage at diagnosis.

GRADE domain	***Rating***	***Reason for downgrading or upgrading***	***Certainty of evidence***
Proportion of HCC early-stage at diagnosis			
Risk of bias	Serious concerns (-1)	Moderate risk of bias. Potential important confounders age, comorbidities and DAA status not adjusted for.	Very low
Indirectness	Serious concerns (-1)	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 concerns	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.	
Inconsistency	Not applicable	Only one study - Not possible to assess.	
Publication bias	Undetected	Undetected – one study based on national data (N = 2223).	
Other – cohort studies only – upgrading factors	No change	RR (95%CI) = 1.63 (1.44-1.84) < 2.0.	

DAA = direct acting antivirals; HCC = hepatocellular carcinoma; RR = risk ratio; US = ultrasound

4. SUMMARY OF FINDINGS

Table 9. Summary of findings for previous surveillance vs no previous surveillance for people diagnosed with HCC.

Outcome	***Number of participants (studies)***	***Certainty of the evidence (GRADE)***	***Relative effect (95% CI)***	***Anticipated absolute effects (95% CI)***		
				Metric	***Risk with no regular surveillance***	***Risk with regular surveillance***
Overall mortality	7,425 (1 cohort study(29))	Very low[1]	HR = 0.80 (0.75-0.85)	5-year cumulative	72.5 (70.3-74.7)	58.0 (56.2-59.8)*
Proportion of HCC early-stage at diagnosis	2223 (1 cohort study(28))	Very low[2]	RR = 1.63 (1.44-1.84)	%	46.4	75.6 (66.8-85.4)*

[1]One large cohort study using Taiwanese national data with a moderate risk of bias associated with ascertainment of surveillance status and serious concerns regarding indirectness of evidence as may include some cirrhotic patients

[2] One cohort study using Taiwanese national data with a moderate risk of bias associated with control of confounding and serious concerns regarding indirectness of evidence as may include some cirrhotic patients

** Calculated by review team by applying risk ratio or hazard ratio and its 95% confidence interval to the risk with no regular surveillance*
HCC = hepatocellular carcinoma; HR = hazard ratio; RR = risk ratio

REFERENCES

1. World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2015. 134 p.

2. National Institute for Health and Care Excellence. Hepatitis B (chronic); diagnosis and management. Clinical guideline [CG165] Last updated October 2017 [Internet]. London: NICE; 2013 [cited 2022 Jun 16]. Available from: https://www.nice.org.uk/guidance/cg165

3. National Institute for Health and Care Excellence. Cirrhosis in Over 16s: Assessment and Management. NICE guideline [NG50] [Internet]. London: NICE; 2016 [cited 2021 Dec 8]. Available from: https://www.nice.org.uk/guidance/ng50

4. 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. 2019;13(1):1–1.

5. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018 Apr;67(4):1560–99.

6. Gastroenterological Society of Australia. Hepatocellular Carcinoma Consensus Statement Working Group. Australian recommendations for the management of hepatocellular carcinoma: a consensus statement. [Internet]. Melbourne: Gastroenterological Society of Australia; 2020 [cited 2022 Sep 12]. Available from: https://www.gesa.org.au/resources/hepatocellular-carcinoma-hcc-management-consensus/

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

8. AGREE Next Steps Consortium. The AGREE II Instrument [Internet]. 2017. Available from: http://www.agreetrust.org/resource-centre/agree-ii/

9. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022) [Internet]. Cochrane; 2022. Available from: www.training.cochrane.org/handbook

10. Eldridge S, Campbell MK, Campbell MJ, Drahota AK, Giraudeau B, Reeves BC, et al. Revised Cochrane risk of bias tool for randomized trials (RoB 2) Additional considerations for cluster-randomized trials (RoB 2 CRT) [Internet]. 2021 [cited 2022 Feb 1]. Available from: https://drive.google.com/file/d/1yDQtDkrp68_8kJilUdbongK99sx7RFI-/view

11. Kirk M, Smurthwaite K, Braunig J, Trevener S, D'Este C, Lucas R, et al. The PFAS Health Study: Systematic Literature Review [Internet]. Canberra: The Australian National University; 2018. p. 161–3. Available from: https://openresearch-repository.anu.edu.au/handle/1885/241032

12. Odnoletkova I, Goderis G, Pil L, Nobels F, Aertgeerts B, Annemans L, et al. Cost-Effectiveness of Therapeutic Education to Prevent the Development and Progression of Type 2 Diabetes: Systematic Review. J Diabetes Metab. 2014;05(09):in appendix.

13. NHMRC. Guidelines for Guidelines: Assessing certainty of evidence [Internet]. 2019. Available from: https://nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence

14. Murad MH, Mustafa RA, Schünemann HJ, Sultan S, Santesso N. Rating the certainty in evidence in the absence of a single estimate of effect. Evid Based Med. 2017 Jun;22(3):85–7.

15. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol. 2011 Dec;64(12):1283–93.

16. Zeng L, Brignardello-Petersen R, Hultcrantz M, Siemieniuk RAC, Santesso N, Traversy G, et al. GRADE guidelines 32: GRADE offers guidance on choosing targets of GRADE certainty of evidence ratings. J Clin Epidemiol. 2021 Sep;137:163–75.

17. Brignardello-Petersen R, Guyatt GH, Mustafa RA, Chu DK, Hultcrantz M, Schünemann HJ, et al. GRADE guidelines 33: Addressing imprecision in a network meta-analysis. J Clin Epidemiol. 2021 Nov;139:49–56.

18. Brunetti M, Shemilt I, Pregno S, Vale L, Oxman AD, Lord J, et al. GRADE guidelines: 10. Considering resource use and rating the quality of economic evidence. J Clin Epidemiol. 2013 Feb;66(2):140–50.

19. Holger Schünemann, Jan Brożek, Gordon Guyatt, Andrew Oxman. GRADE Handbook - Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach [Internet]. 2013 [cited 2022 Apr 26]. Available from: https://gdt.gradepro.org/app/handbook/handbook.html

20. Brozek JL, Canelo-Aybar C, Akl EA, Bowen JM, Bucher J, Chiu WA, et al. GRADE Guidelines 30: the GRADE approach to assessing the certainty of modeled evidence—An overview in the context of health decision-making. J Clin Epidemiol. 2021 Jan;129:138–50.

21. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol. 2004 Jul;130(7):417–22.

22. 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):204–9.

23. 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 May;50(5):990–8.

24. 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. Asian Pac J Cancer Prev. 2014 Nov 6;15(20):8993–9004.

25. Chang Y, Lairson DR, Chan W, Lu SN, Aoki N. Cost-effectiveness of screening for hepatocellular carcinoma among subjects at different levels of risk: Cost-effectiveness of screening for HCC. J Eval Clin Pract. 2011 Apr;17(2):261–7.

26. 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.

27. Farhang Zangneh H, Wong WWL, 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 Aug;17(9):1840-1849.e16.

28. 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 Open. 2021 Jun 24;4(6):e2114680.

29. 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.

30. 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 Health. 2021 Oct;24(10):1454–62.

31. 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 Apr 19;OF1–8.

32. 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 Dec;65(6):1086–93.

33. Parikh ND, Singal AG, Hutton DW, Tapper EB. Cost-Effectiveness of Hepatocellular Carcinoma Surveillance: An Assessment of Benefits and Harms. Am J Gastroenterol. 2020 Oct;115(10):1642–9.

34. 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):1418–24.

35. 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 Apr;98(7):1166–75.

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

37. 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. 2010/06/16 ed. 2010 May;25(5):951–6.

38. 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. Intern Med J. 2013 Jul;43(7):772–7.

39. 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 Feb;1(1):53–60.

40. 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):551–6.

41. Byford S, Raftery J. Economics notes: Perspectives in economic evaluation. BMJ. 1998 May 16;316(7143):1529–30.

42. Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun Wong V, Castellanos M, Aller-de la Fuente R, Metwally M, et al. Fibrosis Severity as a Determinant of Cause-Specific Mortality in Patients With Advanced Nonalcoholic Fatty Liver Disease: A Multi-National Cohort Study. Gastroenterology. 2018 Aug 1;155(2):443-457.e17.

43. 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 Aug;21(8):938–43.

44. Hong TP. An Australian population-based study of the incidence and outcomes of hepatocellular carcinoma: the Hepatomas of Melbourne Epidemiological Research (HoMER) study [Internet]. 2019 [cited 2019 Jul 11]. Available from: http://hdl.handle.net/11343/225659

45. Wallace MC, Preen DB, Short MW, Adams LA, Jeffrey GP. Hepatocellular carcinoma in Australia 1982-2014: Increasing incidence and improving survival. Liver Int. 2019 Mar;39(3):522–30.

46. Nguyen ALT, Si L, Lubel JS, Shackel N, Yee KC, Wilson M, et al. Construction and validation of a microsimulation model for hepatocellular carcinoma surveillance in Australia. In Submission;

47. Alavi M, Law MG, Grebely J, Amin J, Hajarizadeh B, George J, et al. Time to decompensated cirrhosis and hepatocellular carcinoma after an HBV or HCV notification: A population-based study. J Hepatol. 2016 Nov;65(5):879–87.

48. Jepsen P, Vilstrup H, Andersen PK. The clinical course of cirrhosis: The importance of multistate models and competing risks analysis. Hepatology. 2015 Jul 1;62(1):292–302.

49. Canfell K, Kim JJ, Brisson M, Keane A, Simms KT, Caruana M, et al. Mortality impact of achieving WHO cervical cancer elimination targets: a comparative modelling analysis in 78 low-income and lower-middle-income countries. The Lancet. 2020 Feb;395(10224):591–603.

50. Haq MI, Drake TM, Goh TL, Ahmed A, Forrest E, Barclay S, et al. Effect of Hepatocellular Carcinoma Surveillance Programmes on Overall Survival in a Mixed Cirrhotic UK Population: A Prospective, Longitudinal Cohort Study. J Clin Med. 2021 Jun 24;10(13):2770.

51. Consumer Price Index, Australia, March 2022 | Australian Bureau of Statistics [Internet]. 2022 [cited 2022 Jun 12]. Available from: https://www.abs.gov.au/statistics/economy/price-indexes-and-inflation/consumer-price-index-australia/latest-release

52. Department of Health, Australian Government. MBS Online: Medicare Benefits Schedule. [homepage on the internet] [Internet]. Canberra, ACT: Commonwealth of Australia; Available from: http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/Home

53. Xiao Y, Howell J, Gemert C, Thompson AJ, Seaman CP, McCulloch K, et al. Enhancing the hepatitis B care cascade in Australia: A cost-effectiveness model. J Viral Hepat. 2020 May;27(5):526–36.

54. Reeve R, Srasuebkul P, Langton JM, Haas M, Viney R, Pearson SA, et al. Health care use and costs at the end of life: a comparison of elderly Australian decedents with and without a cancer history. BMC Palliat Care. 2017 Jun 21;17(1):1.

55. McPhail SM, Amarasena S, Stuart KA, Hayward K, Gupta R, Brain D, et al. Assessment of health-related quality of life and health utilities in Australian patients with cirrhosis. JGH Open. 2021 Jan;5(1):133–42.

56. Global Burden of Disease Collaborative Network. Global Burden of Disease (GBD 2019) [Internet]. Seattle, United States of America: Institute for Health Metrics and Evaluation (IHME); 2021 [cited 2022 Jun 12]. Available from: https://www.healthdata.org/gbd/2019

57. 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 Jan;44(1):217–31.

58. NSW Cancer Registry. Data request: Hepatocellular carcinoma (coded as C22.0 or C22.9) incidence and mortality). Private communication; unpublished.; 2021 Aug.

59. Tzartzeva K, Obi J, Rich NE, Parikh ND, Marrero JA, Yopp A, et al. Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Patients With Cirrhosis: A Meta-analysis. Gastroenterology. 2018 May 1;154(6):1706-1718.e1.

60. Cheng RM. Novel Biomarkers of Hepatocellular Carcinoma [Internet]. The University of Sydney; 2018. Available from: http://hdl.handle.net/2123/20294

61. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. Circulation. 2016 Feb 9;133(6):601–9.

62. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. Stat Med. 2017 Nov 30;36(27):4391–400.

APPENDICES

Appendix 1: Medline and Embase database (via Ovid platform) search strategy

#	Searches
1	carcinoma, hepatocellular/
2	liver neoplasms/
3	liver cell carcinoma/
4	liver tumor/
5	liver cancer/
6	1 or 2 or 3 or 4 or 5
7	((hepato* or liver or hepatic) adj3 (cancer or carcinoma* or neoplasm* or tumor* or tumour*)).tw.
8	(hepatoma* or hepatocarcinoma* or hcc).tw.
9	7 or 8
10	Early diagnosis/
11	Early detection of cancer/
12	population surveillance/
13	cancer screening/
14	mass screening/
15	disease surveillance/
16	10 or 11 or 12 or 13 or 14 or 15
17	screen*.tw.
18	surveil*.tw.
19	17 or 18
20	6 or 9
21	16 or 19
22	20 and 21
23	fatty liver/ or non-alcoholic fatty liver disease/ or hepatitis/ or hepatitis, viral, human/
24	(hepatitis or HBV or fatty liver or NAFLD or MAFLD or steatohepatitis or NASH or steatosis or non-cirrhotic or noncirrhotic or no cirrhosis or no cirrhotic or without cirrhosis or without cirrhotic).tw.
25	Ultrasonography/
26	(ultrasound or ultrasonograph*).tw.
27	22 or 23 or 24 or 25 or 26
28	22 and 27

29	limit 28 to english language
30	limit 29 to humans
31	limit 30 to yr="2000 -Current"
32	limit 31 to conference abstracts [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) PubMed not MEDLINE,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]
33	limit 32 to medline
34	32 not 33
35	31 not 34
36	limit 35 to yr="2000 - 2010"
37	35 not 36
38	remove duplicates from 36
39	remove duplicates from 37
40	38 or 39

Appendix 2: GRADE assessment of the certainty of the evidence

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Appendix 3: Excluded Studies

Article	PMID/DOI or link	Reason for exclusion
Aby 2019	https://journals.lww.com/jcge/Abstract/2019/02000/Inadequate_Hepatocellular_Carcinoma_Screening_in.16.aspx	No population of interest
Allaire 2021	https://www.sciencedirect.com/science/article/pii/S221074012030111X	No comparative data for outcome of interest
Bae 2021	https://www.eymj.org/pdf/10.3349/ymj.2021.62.8.758	No population of interest

Bolondi 2001	http://dx.doi.org/10.1136/gut.48.2.251	No population of interest
Bucci 2016	https://onlinelibrary.wiley.com/doi/abs/10.1111/apt.13485	No population of interest
Butt 2013	http://dx.doi.org/10.1186/1756-0500-6-137	No population of interest
Chaiteerakij 2017	http://dx.doi.org/10.5604/16652681.1235485	No population of interest
Chan 2008	http://dx.doi.org/10.1097/SLA.0b013e31816a747a	No population of interest
Chen 2003	https://doi.org/10.1258/096914103771773320	Outcome unclear
Chen 2016	https://www.cghjournal.org/article/S1542-3565(16)00046-X/fulltext	No comparative data for outcome of interest
Chen 2021	https://aasldpubs.onlinelibrary.wiley.com/doi/10.1002/hep4.1606	No outcome of interest
Chiang 2017	https://bmjopen.bmj.com/content/7/6/e015936	No population of interest
Chinnaratha 2019	http://dx.doi.org/10.1007/s12029-018-0171-7	No population of interest
Cucchetti 2012	https://doi.org/10.1016/j.jhep.2011.11.022	No population of interest
Debes 2018	https://onlinelibrary.wiley.com/doi/10.1111/liv.13502	No population of interest
deLemos 2020	https://journals.lww.com/ctg/Fulltext/2020/03000/Distinctive_Features_and_Outcomes_of.20.aspx	No population of interest
Demir 2015	https://link.springer.com/article/10.1007/s15010-015-0751-4	No population of interest
Dohmen 2000	http://dx.doi.org/10.1016/S1386-6346%2899%2900094-7	Unable to access full text
Duininck 2019	https://onlinelibrary.wiley.com/doi/10.1002/jso.25738	No population of interest
Edenvik 2015	http://dx.doi.org/10.1111/liv.12764	No population of interest
El-Serag 2011	http://dx.doi.org/10.1136/gut.2010.230508	No population of interest
Eltabbakh 2015	http://dx.doi.org/10.1007/s12032-014-0432-7	No population of interest
Eskesen 2014	http://dx.doi.org/10.1016/j.canep.2014.10.005	No population of interest
Farinati 2001	https://archives-acen.revuesonline.com/article.jsp?articleId=24253	No population of interest
Frey 2015	http://dx.doi.org/10.4414/smw.2015.14200	No population of interest
Gabo 2013	https://doi.org/10.1016/S1665-2681(19)31318-3	No population of interest

Giannini 2013	http://dx.doi.org/10.1016/j.dld.2012.08.018	No intervention of interest
Han 2013	http://dx.doi.org/10.1097/MCG.0b013e3182755c13	No population of interest
Hassan 2019	https://onlinelibrary.wiley.com/doi/10.1111/imj.14304	No population of interest
Hester 2019	https://jnccn.org/view/journals/jnccn/17/4/article-p322.xml	No population of interest
Hong 2018	https://onlinelibrary.wiley.com/doi/abs/10.5694/mja18.00373	No population of interest
Huang 2018	https://journals.lww.com/jcge/Abstract/2018/07000/Rate_of_Nonsurveillance_and_Advanced.17.aspx	No population of interest
Im 2019	http://dx.doi.org/10.4143/crt.2018.430	No population of interest
Inthasotti 2019	http://www.jmatonline.com/index.php/jmat/article/view/10465	No population of interest
Ioannou 2019	https://www.journal-of-hepatology.eu/article/S0168-8278(19)30291-0/fulltext#relatedArticles	No population of interest
Ji 2018	https://doi.org/10.1038/s41598-018-31119-9	No population of interest
Kadri 2013	http://dx.doi.org/10.1016/j.ejso.2013.09.029	No intervention of interest
Kim 2018	https://onlinelibrary.wiley.com/doi/10.1111/apt.14623	No population of interest
K-Kutala 2015	https://dx.doi.org/10.1016/j.dld.2014.12.010	No intervention of interest
Kwon 2020	http://dx.doi.org/10.5009/gnl18522	No population of interest
Lang 2020	http://dx.doi.org/10.1080/00365521.2020.1718747	No population of interest
Leykum 2007	http://dx.doi.org/10.1016/j.cgh.2007.01.014	No comparative data for outcome of interest
Li 2020	https://www.proquest.com/docview/2268837246?accountid=14757	No population of interest
Majerovic 2019	http://dx.doi.org/10.1007/s12029-017-0011-1	No population of interest
Mansoor 2019	http://www.bmrat.org/index.php/BMRAT/article/view/577	No population of interest
Miquel 2012	http://dx.doi.org/10.4321/S1130-01082012000500004	No population of interest
Mohamad 2016	https://link.springer.com/article/10.1007/s12072-015-9679-0	No intervention of interest
Mohsen 2017	https://www.wjgnet.com/1007-9327/full/v23/i15/2763.htm	No population of interest

Mules 2018	https://journal.nzma.org.nz/journal-articles/hepatitis-b-virus-related-hepatocellular-carcinoma-presenting-at-an-advanced-stage-is-it-preventable	No population of interest
Munaf 2014	http://koreascience.or.kr/article/JAKO201433150757726.page	No intervention of interest
Nguyen 2009	http://dx.doi.org/10.1111/j.1440-1746.2008.05577.x	No intervention of interest
Nilsson 2019	https://www.tandfonline.com/doi/full/10.1080/00365521.2019.1649454	No population of interest
Noda 2010	http://dx.doi.org/10.1007/s00535-009-0131-x	No population of interest
Oeda 2016	https://www.jstage.jst.go.jp/article/internalmedicine/55/19/55_55.6730/_pdf	No population of interest
Parker 2014	http://dx.doi.org/10.5694/mja13.11117	No population of interest
Perumpail 2015	http://dx.doi.org/10.1007/s10620-015-3821-7	No intervention of interest
Piscaglia 2016	https://aasldpubs.onlinelibrary.wiley.com/doi/10.1002/hep.28368	No population of interest
Rattanasupar 2021	http://journal.waocp.org/article_89806.html	No population of interest
Romero-Gutierrez 2019	https://www.reed.es/ArticuloFicha.aspx?id=3898&hst=0&idR=77&tp=1&AspxAutoDetectCookieSupport=1	Excluded study design
Sarkar 2012	http://dx.doi.org/10.1111/j.1365-2893.2011.01577.x	No intervention of interest
Sato 2009	http://dx.doi.org/10.1007/s12072-009-9145-y	No comparator of interest
Schauer 2019	https://onlinelibrary.wiley.com/doi/10.1111/jvh.13179	No population of interest
Schauer 2020	https://pubmed.ncbi.nlm.nih.gov/32438374/	No population of interest
Schutte 2014	http://dx.doi.org/10.1186/1471-230X-14-117	No intervention of interest
Shindo 2015	http://dx.doi.org/10.1155/2015/687484	No population of interest
Sinclair 2013	http://dx.doi.org/10.1111/imj.12068	No intervention of interest
Singal 2013	http://dx.doi.org/10.1038/ajg.2012.449	No population of interest
Stroffolini 2011	http://dx.doi.org/10.1016/j.dld.2011.05.002	No population of interest
Tanaka 2006	http://dx.doi.org/10.1111/j.1478-3231.2006.01270.x	No population of interest
Tateishi 2019	https://link.springer.com/article/10.1007/s00535-018-1532-5	No population of interest

Thein 2015	http://dx.doi.org/10.1371/journal.pone.0138907	No population of interest
Tong 2010	http://dx.doi.org/10.1097/MCG.0b013e3181b4b68b	No population of interest
Tong 2010	http://dx.doi.org/10.1007/s10620-009-1059-y	No population of interest
Tong 2017	https://aasldpubs.onlinelibrary.wiley.com/doi/10.1002/hep4.1047	No population of interest
Toyoda 2006	http://dx.doi.org/10.1016/j.cgh.2006.06.007	No population of interest
Toyoda 2008	http://dx.doi.org/10.1111/j.1440-1746.2007.05138.x	No comparative data for outcome of interest
Toyoda 2016	https://onlinelibrary.wiley.com/doi/10.1111/hepr.12613	No population of interest
Tran 2018	https://bmjopengastro.bmj.com/content/5/1/e000192	No population of interest
Van Meer 2015	http://dx.doi.org/10.1016/j.jhep.2015.06.012	No population of interest
Walker 2016	https://onlinelibrary.wiley.com/doi/10.1111/apt.13505	No population of interest
Weinmann 2014	http://dx.doi.org/10.1097/MCG.0b013e3182a8a793	No intervention of interest
Wong 2008	http://dx.doi.org/10.1111/j.1478-3231.2007.01576.x	No population of interest
Yamashita 2014	https://doi.org/10.1007/s00535-013-0921-z	No outcome of interest
Yang 2011	http://dx.doi.org/10.1016/j.cgh.2011.03.027	No population of interest
Yang 2011	http://dx.doi.org/10.1016/j.cgh.2010.08.019	No intervention of interest
Yotsuyanagi 2020	https://onlinelibrary.wiley.com/doi/10.1111/hepr.13439	No comparator of interest
Younossi 2015	http://dx.doi.org/10.1002/hep.28123	No intervention of interest
Yu 2004	http://dx.doi.org/10.1097/00130404-200409000-00009	No population of interest
Yuen 2004	https://doi.org/10.1002/hep.510310211	No population of interest
Zapata 2010	http://dx.doi.org/10.4321/s1130-01082010000800005	No population of interest
Zhu 2019	https://onlinelibrary.wiley.com/doi/10.1111/apt.15461	Excluded publication type

Appendix D3. Technical report for question 3

Systematic Review Question 3: Does HCC surveillance improve liver cancer outcomes for Aboriginal and Torres Strait Islander people?

PICO

This systematic review addresses the PICO shown in Table 3.

Table 3. PICO for systematic review question 3.

Population	Intervention	Comparator	Outcomes	Study design
Aboriginal and Torres Strait Islander peoples	HCC surveillance programs	No surveillance Usual or standard care	Overall mortality Liver disease-related mortality Liver cancer mortality Proportion of liver cancers that are early-stage Cost-effectiveness	Randomised controlled trials Cohort or case-control studies Modelling studies

HCC = hepatocellular carcinoma

1. METHODS

1.1 Selection Criteria

Table 2. Selection criteria for studies examining the effect of HCC surveillance programs amongst Aboriginal and Torres Strait Islander people.

PICO 3	Inclusion	Exclusion
Study type	Intervention Observational	Diagnostic accuracy
Study design	RCTs Cohort or case-control studies Modelling studies or systematic review thereof Case series (Single arm) – if none of the above	Case report Review (not systematic)
Population	≥18 years Aboriginal and Torres Strait Islander peoples • With or without liver disease • With liver disease – cirrhotic or non-cirrhotic (any aetiology) • With HCC or liver cancer (observational studies)	People who have previously undergone treatment for liver cancer Children Restricted to liver cancer patients undergoing liver resection and/or transplant
Intervention	HCC surveillance programs (ultrasound, AFP, other)	Provides no details about the surveillance program Ad hoc surveillance Single screen offered Surveillance-detected (observational studies) GALAD score surveillance
Comparator	No surveillance Standard or usual care	No comparator Historical control Non-surveillance detected* (observational studies)
Outcome	*Actual or state transition-modelled:* Overall mortality Liver related mortality HCC/liver cancer specific mortality	Cancer incidence Unadjusted survival analyses (observational studies) Non-surveillance detected (observational studies)

	Survival (observational studies) % early/treatable stage HCC or liver cancer at diagnosis Cost-effectiveness (QALY, DALY or life-years gained)	Costs only, costs per life saved Incremental cost of additional early-stage diagnosis
Publication date	2000 onwards	
Publication type	Original journal article Letter or comment that reports original data	Conference abstracts Editorials Letters and comments that do not report original data
Language	English	

AFP = alpha-fetoprotein; DALY = disability-adjusted life years; GALAD score = score based on gender, age, Lens culinaris agglutinin-reactive AFP, total AFP, and des-γ-carboxyprothrombin; HCC = hepatocellular carcinoma; QALY = quality-adjusted life years; RCTs = randomised controlled trials

**Cancers not detected by surveillance i.e., interval cancer for those undergoing surveillance and cancers detected amongst those not undergoing surveillance.*

[a]HCC is the liver cancer of primary interest.

[b]Chronic HBV infection, chronic HCV infection, alcohol-related liver disease, and metabolic-associated fatty liver disease are the aetiologies of interest.

[c]Modelling studies were restricted to state-transition models.

1.2 Definitions and terminology

For the purpose of this review:

Applicability (sometimes referred to as transferability) refers to whether the evidence can be applied to the Australian healthcare context.

Early-stage HCC includes Barcelona Clinic Liver Cancer (BCLC) stage 0/A, meeting Milan criteria, or China Liver Cancer Study group stage I:

1. *The Barcelona Clinic Liver Cancer (BCLC*) staging classification system assesses the number and size of liver tumours, overall performance status (ECOG PS) and liver function (using Child-Pugh classification):
    a. BCLC stage 0 (very early stage); ECOG performance score = 0, Child-Pugh A, single tumour < 20mm;
    b. BCLC stage A (early stage); ECOG performance score = 0, Child-Pugh A-B, single tumour of any size or up to 3 tumours all < 30mm).
2. *The Milan criteria* focus on liver transplantation eligibility. Those eligible for transplantation are described as within Milan criteria and are defined as having one tumour measuring ≤ 50 mm in diameter, or 2-3 tumours ≤ 30 mm in diameter without vascular extension or metastasis.
3. The *China Liver Cancer study group staging* system classifies HCC as stage I (subclinical stage/early stage) if there are no obvious cancer symptoms and signs (tumour usually < 5 cm in diameter).

Where results were given by BCLC stage and another staging system, the BCLC results were presented.

Fibrotic status was as reported by authors.

Generalisability refers to whether the evidence can be directly applied to the target population.

Metabolic-associated fatty liver disease includes non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

1.3 Guidelines

Relevant recent (2015 onwards) guidelines were identified by scanning the citations identified by the literature search (described below) and a summary of these guidelines was reviewed by Expert Advisory Group members as part of Phase 1 of the *Roadmap to Liver Cancer Control* project.

To be considered for adoption by the Working Group guidelines had to be evidence-based and meet the pre-specified criteria of scores of greater or equal to 70% for the following domains: rigour of development, clarity of presentation, and editorial independence of the AGREE II instrument (8). Guidelines were not considered for adoption if they were not based on systematic reviews of the evidence, i.e. did not report using systematic methods to search for evidence, did not clearly describe the criteria for selecting the evidence or did not assess the risk of bias or where this is not possible, appraise the quality of the evidence.

1.4 Literature searches

Medline (including MEDLINE Epub Ahead of Print, I-Process & Other Non-Indexed Citations) and Embase databases were searched on 1 February 2022 combining text terms and/or database-specific subject headings for liver cancer, surveillance, and Australia. Searches were limited to articles published in English from 1 January 2000 onwards. A complete list of the terms used is included as Appendix 1. The Cochrane Database of Systematic Reviews was searched on 31 March 2022 combining the search terms “liver cancer” and “screen”. Reference lists of included articles, recent relevant guidelines and systematic reviews were checked for potential additional articles.

1.5 Data extraction and analyses

If an effect estimate was not presented but the necessary data were available and adjusted estimates were not required, the risk ratio and 95% confidence interval was calculated using a tool available at *https://sample-size.net/risk-ratio/.* For cost-effectiveness studies, if the cost-effectiveness ratio was not reported for the comparison of interest, it was calculated

using the reported costs and outcomes for the intervention and the comparator if the necessary data were available. In this report, a narrative synthesis is presented as only one study met the inclusion criteria for this review.

1.6 Quality appraisals

The quality of cost-effectiveness studies was assessed using a modified version of the CHEC-extended checklist (12). This tool appraises the specification of the population, interventions and comparators modelled, the modelling and cost-effectiveness methods, and the robustness and fitness for purpose of the model. Unlike a risk of bias assessment tool, its focus is not the critical assessment of the sources of bias. However, some of the questions do inform an assessment of the risk of bias and thus whether the results are likely to reflect the true effect of the intervention. Assessments for some of the CHEC-extended checklist questions were used to inform GRADE assessments of modelled studies, including the risk of bias.

1.7 GRADE assessment of the certainty of the evidence

A GRADE approach was used to assess the certainty of the body of evidence for the effect of HCC surveillance when compared with no surveillance or standard/usual care for each outcome (13).

GRADE was originally designed to assess the certainty of the results of a meta-analysis of the evidence for interventions from randomised controlled trials however, for results from modelling studies, GRADE assessments were not recommended (18,19). However, the NHMRC GRADE Working Group has recently changed their position as outlined in Brozek 2021 (20) and has provided a general approach to the GRADE assessment of modelling studies with more specific guidance planned but not published as at May 2022. In the absence of specific criteria, we assessed the risk of bias, indirectness and inconsistency of the evidence from each study based on the general principles explained by Brozek 2021 (20); downgrading from an initial high level of certainty if there were serious concerns. Downgrading was based on an assessment of the level of concern for each of following issues: risk of bias, indirectness and inconsistency. Assessments ranged from no serious concerns (no downgrade), serious concerns (downgrade by one level) or very serious concerns (downgrade by two levels). The certainty of the body of evidence for each outcome was then rated as either high, moderate, low or very low based on the degree of downgrading. We did not assess imprecision based on reported results of probabilistic sensitivity analyses or other sensitivity analyses as currently these types of analyses are designed to assess sensitivity to changes in variable values, rather than imprecision.

Assessment of publication bias for individual studies was not applicable as all studies reported results of models developed de novo.

We then assessed the certainty of the body of the evidence by assessing the risk of bias, indirectness, inconsistency and publication bias across all studies based on the principles explained by Brozek 2021 (20). As we could not assess imprecision we presented two final assessments of the certainty of the evidence, where one is conservative (downgraded for imprecision) and one is not adjusted for imprecision)., This was done so that GRADE assessments could be compared with those of other study designs. Similarly, as for non-modelled studies, where there was only one study inconsistency could not be rated.

Definitions of the GRADE ratings of certainty are presented in Appendix 2.

2. RESULTS

2.1 Guidelines searches

No recent relevant guidelines based on systematic reviews were identified.

2.2 Literature searches

Figure 1 outlines the process of identifying relevant articles for this systematic review. The combined Medline and Embase search identified 370 citations and the search of the Cochrane Database of Systematic Reviews 18 citations, resulting in a total of 388 citations. Titles and abstracts were examined, and 54 articles were retrieved for a more detailed evaluation. No further potential citations were identified from the reference lists of included articles, recent relevant guidelines, and systematic reviews. One modelling study reported in one article met the inclusion criteria and was included in the review. No RCTs or interventional cohort studies were identified.

The retrieved articles that were not included and the reasons for their exclusion are documented in Appendix 3. In summary, most articles were excluded because they did not include the population of interest (n = 32), publication type of interest (n = 7) or study type or design of interest (n = 6).

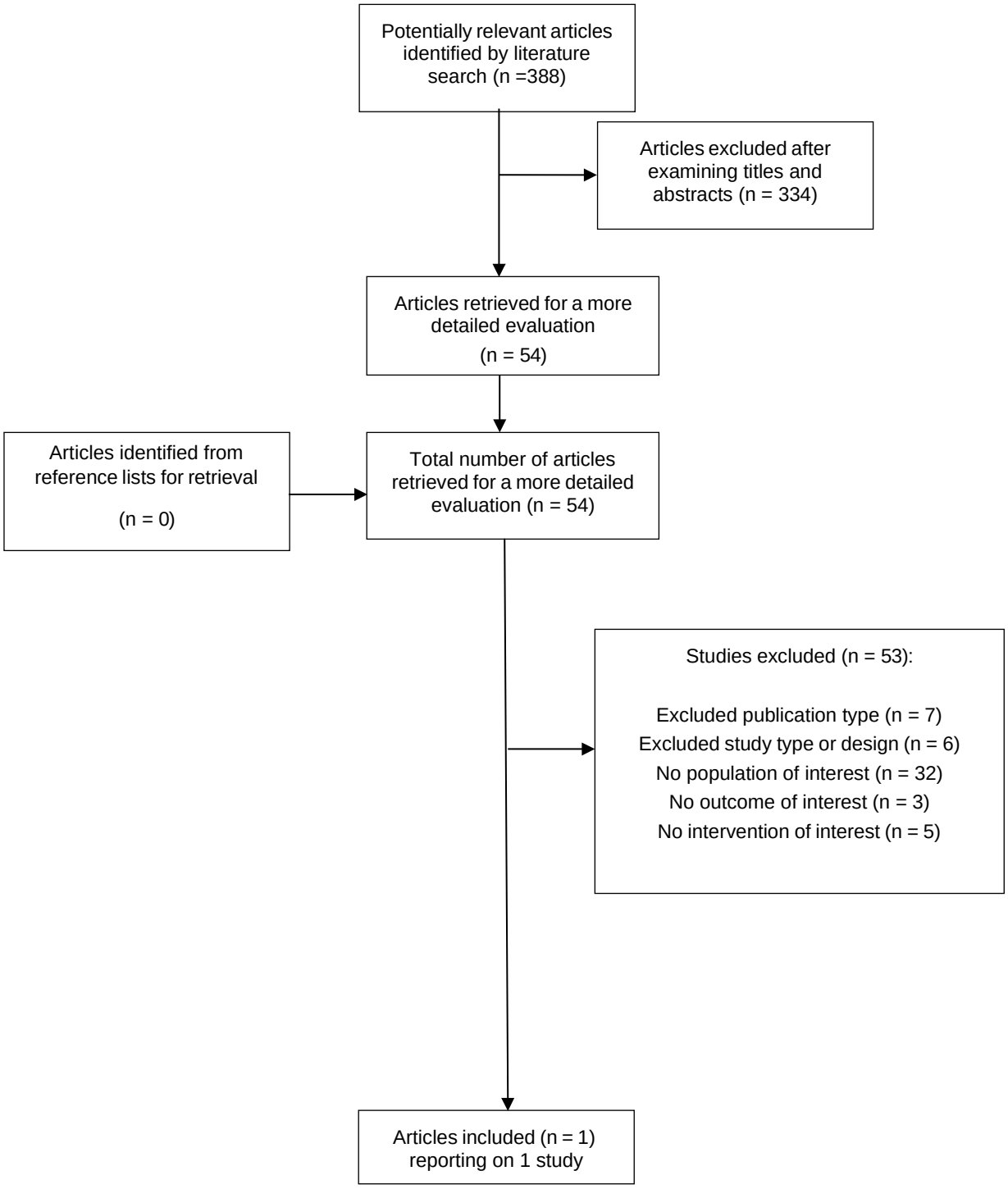


Figure 1. Process of inclusion and exclusion of studies.

2.3 Characteristics of included study

The characteristics of the included study are described in Table 3.

Table 3. Study characteristics for the study comparing surveillance with usual care for Aboriginal and Torres Strait Islander peoples.

Study (Country)	Study design	Population	Participants	Intervention	Comparison	Cycle length	Follow-up	Outcomes	Conflicts of interest considered
Carter 2021 (30) (Australia)	Model (Markov) Not validated	Aboriginal and Torres Strait Islander patients with compensated cirrhosis with mean starting age of 50 years Time period NR Excluded patients with HCC detected at baseline: NR	N = NR Mean age: 50 years at start Male: % NR Cirrhotic: 100% (100% compensated) Aetiology: Mixed Treated for viral hepatitis: NR Remote dwelling: NR HCC incidence per year for usual care: 3.02%	**Surveillance** 6-monthly US or **Risk-stratified surveillance** 6-monthly US Risk assessment based on Liver Outcome Score_HCC* Participation: NR 100%?	**Usual care** ~ 18% undergo surveillance	6-months	Time horizon: 20 years	Cost/QALY gained	Yes – Potential or perceived conflicts of interest declared

**Liver Outcome Score _HCC stratifies 5-year HCC occurrence in patients with chronic liver disease based on alkaline phosphatase, alpha-2-macroglobulin, age, and sex*
HCC = hepatocellular carcinoma; NR = not reported; QALY = quality-adjusted life years; US = ultrasound

2.4 Results by outcomes of interest

1. Overall mortality – no results found
2. Liver disease-related mortality – no results found
3. Liver cancer mortality – no results found
4. Proportion of liver cancers diagnosed at an early stage – no results found
5. Life-years, quality-adjusted life-years or disability-adjusted life-years gained – results are shown in Table 4
6. Cost-effectiveness - results are shown in Table 4

Table 4. Results of studies comparing surveillance with usual care for the outcome of modelled cost-effectiveness analyses.

Study (Liver disease)	Economic perspective	Discount rate	Costs currency and year	Medical costs included	Evidence bases for differences in health outcomes	Clinical Effect	Willingness to pay threshold	CER	Probabilistic sensitivity analysis	Three largest sources of uncertainty
Carter 2021 (30) (Cirrhotic)	Payer's (health system)	3% p/a for costs and health outcomes	Australian dollar (AU$) 2019	Surveillance Diagnostic investigations Early-stage treatments including transplantation and ablation TACE SBR TARE Chemotherapy Palliative care HCC follow-up	Rates of HCC with and without surveillance US false negative rate of 6% Proportion (%) of HCC that are early, intermediate and advanced-stage with surveillance (81, 8, 11) and without surveillance (47, 24, 29)#	NR	AU$50,000 per QALY gained	***Surveillance*** AU$21,874 per QALY gained*^ **Surveillance cost effective** when compared with no surveillance ***Risk-stratified surveillance*** AU$34,665 per QALY gained*^ **Risk-stratified surveillance cost effective** when compared with no surveillance	Undertaken for general population but not for Aboriginal and Torres Strait Islander population	NR for Aboriginal and Torres Strait Islander population For risk-stratified screening for all cirrhotic patients the most sensitive parameters were proportion of population at low risk, and probabilities that HCC is early stage with screening and with no screening

**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 CER decreases with increasing risk of presenting with advanced-stage HCC;*

#Surveillance did not include routine AFP testing;

^Costs for surveillance include AFP testing

CER = cost effectiveness ratio; HCC = hepatocellular cancer; NR = not reported; p/a = per annum; QALY = quality-adjusted life years; SBR = stereotactic body radiation; TACE = transarterial chemoemobolisation; TARE = transarterial radioemobilisation; US = ultrasound

2.5 Quality appraisal assessment

The results of the quality appraisal assessment of the included modelling study are shown in Table 5.

Table 5. Quality appraisal for cost-effectiveness outcome using the CHEC-extended (modified) checklist.

Checklist question	**Carter 2021**(30) **CER**
1. Is the study population clearly described?	No
2. Are competing alternatives clearly described?	Yes
3. Is a well-defined research question posed in answerable form?	Yes
4. Is the economic study design appropriate to the stated objective?	Yes
5. Are the structural assumptions and the validation methods of the model properly reported?	No
6. Is the chosen time horizon appropriate in order to include relevant costs and consequences?	Yes
7. Are all important and relevant costs for each alternative identified?	Yes
8. Are all costs measured appropriately in physical units?	Yes
9. Are costs valued appropriately?	Yes
10. Are all important and relevant outcomes for each alternative identified? Does the study report costs per life-years, QALYs or DALYs?	Yes
11. Are all outcomes measured appropriately? Do the authors critically appraise sources of data underpinning effect of surveillance?	No
12. Are outcomes valued appropriately?	Unclear
13. Is an appropriate incremental analysis of costs and outcomes of alternatives performed?	Yes
14. Are all future costs and outcomes discounted appropriately?	No
15. Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis? Was a probabilistic sensitivity analysis undertaken?	Yes
16. Does the article/report indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Yes

CER = cost effectiveness ratio; DALY = disability-adjusted life years; QALY = quality-adjusted life years

3. GRADE ASSESSMENT OF THE CERTAINTY OF THE EVIDENCE

Overall mortality – no evidence found

Liver disease-related mortality - no evidence found

Liver cancer mortality - no evidence found

Proportion of liver cancers diagnosed at an early stage - no evidence found

Life-years, quality-adjusted life-years or disability-adjusted life-years gained – no evidence found

Cost-effectiveness - results are shown in Table 6-7

Table 6. GRADE assessment of the certainty of the evidence for the outcome of cost-effectiveness for individual studies.

GRADE domains	***Rating***	***Reasons for rating***	***Certainty of evidence***
Outcome: Cost-effectiveness			
Risk of bias	Very serious (-2)	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	Low to very low
Indirectness	No serious concerns	Does not report sex, % aetiologies or treated for viral hepatitis for population of interest although not a serious concern for indirectness	
Imprecision	Not assessable		
Inconsistency	No serious concerns	Probabilistic sensitivity analysis undertaken, no serious concerns for the model	
Publication bias	Not applicable	Model developed de novo	

Table 7. GRADE assessment of the certainty of the body of evidence for the outcome of cost-effectiveness.

GRADE domains	***Rating***	***Reasons for rating***	***Certainty of evidence***
Outcome: Cost-effectiveness			
Risk of bias	Very serious (-2)	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	Low to very low
Indirectness	No serious concerns	Does not report sex, % aetiologies or treated for viral hepatitis for population of interest although not a serious concern for indirectness	
Imprecision	Not assessable		

Inconsistency	Not assessable	Single study so overall inconsistency cannot be assessed	
Publication bias	Not detected	One study	

4. SUMMARY OF FINDINGS

Table 8. Summary of findings for surveillance compared to usual care for Aboriginal and Torres Strait Islander people.

Outcomes	***Number of participants (studies)***	***Certainty of the evidence (GRADE)***	***Relative effect***
Cost effectiveness per life year gained	NR (1 modelling study)	Low to very low[1]	***Surveillance*** AU$21,874 per QALY gained*^ surveillance cost effective using a willingness to pay threshold of 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

[1]Very serious concerns regarding risk of bias
**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
NR = not reported; CI = confidence interval; QALY = quality-adjusted life years

Table 9. Evidence summary for surveillance compared to usual care for Aboriginal and Torres Strait Islander people.

Evidence summary	**GRADE certainty of evidence**	**References**
One cost-effectiveness study estimated that for Aboriginal and Torres Strait Islander people with cirrhosis, surveillance and risk-based surveillance with 6-monthly liver ultrasound were cost-effective when compared to no surveillance.	Low to very low	Carter 2021 (30)

REFERENCES

1. World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2015. 134 p.

2. National Institute for Health and Care Excellence. Hepatitis B (chronic); diagnosis and management. Clinical guideline [CG165] Last updated October 2017 [Internet]. London: NICE; 2013 [cited 2022 Jun 16]. Available from: https://www.nice.org.uk/guidance/cg165

3. National Institute for Health and Care Excellence. Cirrhosis in Over 16s: Assessment and Management. NICE guideline [NG50] [Internet]. London: NICE; 2016 [cited 2021 Dec 8]. Available from: https://www.nice.org.uk/guidance/ng50

4. 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. 2019;13(1):1–1.

5. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018 Apr;67(4):1560–99.

6. Gastroenterological Society of Australia. Hepatocellular Carcinoma Consensus Statement Working Group. Australian recommendations for the management of hepatocellular carcinoma: a consensus statement. [Internet]. Melbourne: Gastroenterological Society of Australia; 2020 [cited 2022 Sep 12]. Available from: https://www.gesa.org.au/resources/hepatocellular-carcinoma-hcc-management-consensus/

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

8. AGREE Next Steps Consortium. The AGREE II Instrument [Internet]. 2017. Available from: http://www.agreetrust.org/resource-centre/agree-ii/

9. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022) [Internet]. Cochrane; 2022. Available from: www.training.cochrane.org/handbook

10. Eldridge S, Campbell MK, Campbell MJ, Drahota AK, Giraudeau B, Reeves BC, et al. Revised Cochrane risk of bias tool for randomized trials (RoB 2) Additional considerations for cluster-randomized trials (RoB 2 CRT) [Internet]. 2021 [cited 2022 Feb 1]. Available from: https://drive.google.com/file/d/1yDQtDkrp68_8kJiIUdbongK99sx7RFI-/view

11. Kirk M, Smurthwaite K, Braunig J, Trevener S, D'Este C, Lucas R, et al. The PFAS Health Study: Systematic Literature Review [Internet]. Canberra: The Australian National University; 2018. p. 161–3. Available from: https://openresearch-repository.anu.edu.au/handle/1885/241032

12. Odnoletkova I, Goderis G, Pil L, Nobels F, Aertgeerts B, Annemans L, et al. Cost-Effectiveness of Therapeutic Education to Prevent the Development and Progression of Type 2 Diabetes: Systematic Review. J Diabetes Metab. 2014;05(09):in appendix.

13. NHMRC. Guidelines for Guidelines: Assessing certainty of evidence [Internet]. 2019. Available from: https://nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence

14. Murad MH, Mustafa RA, Schünemann HJ, Sultan S, Santesso N. Rating the certainty in evidence in the absence of a single estimate of effect. Evid Based Med. 2017 Jun;22(3):85–7.

15. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol. 2011 Dec;64(12):1283–93.

16. Zeng L, Brignardello-Petersen R, Hultcrantz M, Siemieniuk RAC, Santesso N, Traversy G, et al. GRADE guidelines 32: GRADE offers guidance on choosing targets of GRADE certainty of evidence ratings. J Clin Epidemiol. 2021 Sep;137:163–75.

17. Brignardello-Petersen R, Guyatt GH, Mustafa RA, Chu DK, Hultcrantz M, Schünemann HJ, et al. GRADE guidelines 33: Addressing imprecision in a network meta-analysis. J Clin Epidemiol. 2021 Nov;139:49–56.

18. Brunetti M, Shemilt I, Pregno S, Vale L, Oxman AD, Lord J, et al. GRADE guidelines: 10. Considering resource use and rating the quality of economic evidence. J Clin Epidemiol. 2013 Feb;66(2):140–50.

19. Holger Schünemann, Jan Brożek, Gordon Guyatt, Andrew Oxman. GRADE Handbook - Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach [Internet]. 2013 [cited 2022 Apr 26]. Available from: https://gdt.gradepro.org/app/handbook/handbook.html

20. Brozek JL, Canelo-Aybar C, Akl EA, Bowen JM, Bucher J, Chiu WA, et al. GRADE Guidelines 30: the GRADE approach to assessing the certainty of modeled evidence—An overview in the context of health decision-making. J Clin Epidemiol. 2021 Jan;129:138–50.

21. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol. 2004 Jul;130(7):417–22.

22. 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):204–9.

23. 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 May;50(5):990–8.

24. 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. Asian Pac J Cancer Prev. 2014 Nov 6;15(20):8993–9004.

25. Chang Y, Lairson DR, Chan W, Lu SN, Aoki N. Cost-effectiveness of screening for hepatocellular carcinoma among subjects at different levels of risk: Cost-effectiveness of screening for HCC. J Eval Clin Pract. 2011 Apr;17(2):261–7.

26. 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.

27. Farhang Zangneh H, Wong WWL, 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 Aug;17(9):1840-1849.e16.

28. 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 Open. 2021 Jun 24;4(6):e2114680.

29. 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.

30. 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 Health. 2021 Oct;24(10):1454–62.

31. 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 Apr 19;OF1–8.

32. 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 Dec;65(6):1086–93.

33. Parikh ND, Singal AG, Hutton DW, Tapper EB. Cost-Effectiveness of Hepatocellular Carcinoma Surveillance: An Assessment of Benefits and Harms. Am J Gastroenterol. 2020 Oct;115(10):1642–9.

34. 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):1418–24.

35. 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 Apr;98(7):1166–75.

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

37. 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. 2010/06/16 ed. 2010 May;25(5):951–6.

38. 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. Intern Med J. 2013 Jul;43(7):772–7.

39. 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 Feb;1(1):53–60.

40. 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):551–6.

41. Byford S, Raftery J. Economics notes: Perspectives in economic evaluation. BMJ. 1998 May 16;316(7143):1529–30.

42. Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun Wong V, Castellanos M, Aller-de la Fuente R, Metwally M, et al. Fibrosis Severity as a Determinant of Cause-Specific Mortality in Patients With Advanced Nonalcoholic Fatty Liver Disease: A Multi-National Cohort Study. Gastroenterology. 2018 Aug 1;155(2):443-457.e17.

43. 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 Aug;21(8):938–43.

44. Hong TP. An Australian population-based study of the incidence and outcomes of hepatocellular carcinoma: the Hepatomas of Melbourne Epidemiological Research (HoMER) study [Internet]. 2019 [cited 2019 Jul 11]. Available from: http://hdl.handle.net/11343/225659

45. Wallace MC, Preen DB, Short MW, Adams LA, Jeffrey GP. Hepatocellular carcinoma in Australia 1982-2014: Increasing incidence and improving survival. Liver Int. 2019 Mar;39(3):522–30.

46. Nguyen ALT, Si L, Lubel JS, Shackel N, Yee KC, Wilson M, et al. Construction and validation of a microsimulation model for hepatocellular carcinoma surveillance in Australia. In Submission;

47. Alavi M, Law MG, Grebely J, Amin J, Hajarizadeh B, George J, et al. Time to decompensated cirrhosis and hepatocellular carcinoma after an HBV or HCV notification: A population-based study. J Hepatol. 2016 Nov;65(5):879–87.

48. Jepsen P, Vilstrup H, Andersen PK. The clinical course of cirrhosis: The importance of multistate models and competing risks analysis. Hepatology. 2015 Jul 1;62(1):292–302.

49. Canfell K, Kim JJ, Brisson M, Keane A, Simms KT, Caruana M, et al. Mortality impact of achieving WHO cervical cancer elimination targets: a comparative modelling analysis in 78 low-income and lower-middle-income countries. The Lancet. 2020 Feb;395(10224):591–603.

50. Haq MI, Drake TM, Goh TL, Ahmed A, Forrest E, Barclay S, et al. Effect of Hepatocellular Carcinoma Surveillance Programmes on Overall Survival in a Mixed Cirrhotic UK Population: A Prospective, Longitudinal Cohort Study. J Clin Med. 2021 Jun 24;10(13):2770.

51. Consumer Price Index, Australia, March 2022 | Australian Bureau of Statistics [Internet]. 2022 [cited 2022 Jun 12]. Available from: https://www.abs.gov.au/statistics/economy/price-indexes-and-inflation/consumer-price-index-australia/latest-release

52. Department of Health, Australian Government. MBS Online: Medicare Benefits Schedule. [homepage on the internet] [Internet]. Canberra, ACT: Commonwealth of Australia; Available from: http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/Home

53. Xiao Y, Howell J, Gemert C, Thompson AJ, Seaman CP, McCulloch K, et al. Enhancing the hepatitis B care cascade in Australia: A cost-effectiveness model. J Viral Hepat. 2020 May;27(5):526–36.

54. Reeve R, Srasuebkul P, Langton JM, Haas M, Viney R, Pearson SA, et al. Health care use and costs at the end of life: a comparison of elderly Australian decedents with and without a cancer history. BMC Palliat Care. 2017 Jun 21;17(1):1.

55. McPhail SM, Amarasena S, Stuart KA, Hayward K, Gupta R, Brain D, et al. Assessment of health-related quality of life and health utilities in Australian patients with cirrhosis. JGH Open. 2021 Jan;5(1):133–42.

56. Global Burden of Disease Collaborative Network. Global Burden of Disease (GBD 2019) [Internet]. Seattle, United States of America: Institute for Health Metrics and Evaluation (IHME); 2021 [cited 2022 Jun 12]. Available from: https://www.healthdata.org/gbd/2019

57. 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 Jan;44(1):217–31.

58. NSW Cancer Registry. Data request: Hepatocellular carcinoma (coded as C22.0 or C22.9) incidence and mortality). Private communication; unpublished.; 2021 Aug.

59. Tzartzeva K, Obi J, Rich NE, Parikh ND, Marrero JA, Yopp A, et al. Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Patients With Cirrhosis: A Meta-analysis. Gastroenterology. 2018 May 1;154(6):1706-1718.e1.

60. Cheng RM. Novel Biomarkers of Hepatocellular Carcinoma [Internet]. The University of Sydney; 2018. Available from: http://hdl.handle.net/2123/20294

61. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. Circulation. 2016 Feb 9;133(6):601–9.

62. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. Stat Med. 2017 Nov 30;36(27):4391–400.

APPENDICES

Appendix 1: Medline and Embase database (via Ovid platform) search strategy

#	Searches
1	carcinoma, hepatocellular/
2	liver neoplasms/
3	liver cell carcinoma/
4	liver tumor/
5	liver cancer/
6	or/1-5
7	((hepato* or liver or hepatic) adj3 (cancer or carcinoma* or neoplasm* or tumor* or tumour*)).tw.
8	(hepatoma* or hepatocarcinoma* or hcc).tw.
9	or/7-8
10	Early diagnosis/
11	Early detection of cancer/
12	population surveillance/
13	mass screening/
14	cancer screening/
15	disease surveillance/
16	or/10-15
17	screen*.tw.
18	surveil*.tw.
19	17 or 18
20	6 or 9
21	16 or 19
22	20 and 21
23	australia.in.
24	22 and 23
25	limit 24 to english language
26	limit 25 to human
27	limit 26 to yr="2000 -Current"
28	remove duplicates from 27

29	limit 28 to conference abstracts [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) PubMed not MEDLINE,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]
30	limit 29 to medline
31	29 not 30
32	28 not 31

Appendix 2: GRADE assessment of the certainty of the evidence

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Appendix 3: Overview of Studies

Included Study

Author	Title	PMID/DOI
Carter 2021	Cost-Effectiveness of a Serum Biomarker Test for Risk-Stratified Liver Ultrasound Screening for Hepatocellular Carcinoma	https://dx.doi.org/10.1016/j.jval.2021.04.1286

Excluded Studies by PMID/DOI

Article	PMID/DOI	Reason for exclusion
Adams 2020	http://dx.doi.org/10.1111/jgh.15009	No population of interest
Bertot 2017	http://dx.doi.org/10.1002/hep4.1018	No population of interest
Carville 2012	https://search.informit.org/doi/10.3316/informit.130848966380090	Excluded publication type
Chen 2004	http://dx.doi.org/10.1016/j.jhep.2003.12.002	No population of interest
Chinnaratha 2019	http://dx.doi.org/10.1007/s12029-018-0171-7	No population of interest
El-Atem 2016	http://dx.doi.org/10.1111/imj.13008	No population of interest
Fisher 2003	http://dx.doi.org/10.5694/j.1326-5377.2003.tb05070.x	Excluded study type or design
Frazer 2000	http://dx.doi.org/10.1053/crad.1999.0265	Excluded publication type
Gellert 2007	http://dx.doi.org/10.1111/j.1445-5994.2007.01392.x	No population of interest
George 2018	http://dx.doi.org/10.1111/imj.13973	No population of interest

Hanson 2020	http://dx.doi.org/10.1371/journal.pone.0238719	No intervention of interest
Harris 2017	http://dx.doi.org/10.1111/1754-9485.12595	No population of interest
Hla 2020	http://dx.doi.org/10.1186/s12939-020-01180-w	No outcome of interest
Hong 2018	http://dx.doi.org/10.5694/mja18.00373	No population of interest
Huang 2018	http://dx.doi.org/10.1097/MCG.0000000000000916	No population of interest
Jeffrey 2020	http://dx.doi.org/10.5694/mja2.50808	Excluded study type or design
Jeffrey 2020	http://dx.doi.org/10.5694/mja2.50521	Excluded study type or design
Kemp 2005	http://dx.doi.org/10.1111/j.1440-1746.2005.03844.x	No population of interest
Kennedy 2013	http://dx.doi.org/10.1111/imj.12166	No population of interest
Kutaiba 2021	http://dx.doi.org/10.1016/j.jhep.2021.06.041	Excluded publication type
Larcos 2020	https://dx.doi.org/10.5694/mja2.50806	Excluded publication type
Lockart 2021	http://dx.doi.org/10.1111/jvh.13475	No intervention of interest
Low 2021	https://dx.doi.org/10.4251/wjgo.v13.i12.2149	No population of interest
Maher 2012	http://dx.doi.org/10.1016/S1473-3099%2811%2970355-3	Excluded publication type
Majeed 2019	http://dx.doi.org/10.1053/j.gastro.2018.09.060	No population of interest
Mohsen 2017	https://dx.doi.org/10.3748/wjg.v23.i15.2763	No outcome of interest
Nazareth 2016	http://dx.doi.org/10.1111/ijn.12472	No population of interest
Nguyen 2021	http://dx.doi.org/10.1016/j.jval.2020.11.014	Excluded study type or design
Nicoll 2002	https://dx.doi.org/10.5694/j.1326-5377.2002.tb04247.x	Excluded study type or design
Parker 2014	http://dx.doi.org/10.5694/mja13.11117	No intervention of interest
Poustchi 2011	http://dx.doi.org/10.1002/hep.24581	No population of interest
Qian 2010	http://dx.doi.org/10.1111/j.1440-1746.2009.06203.x	No population of interest
Roberts 2006	http://dx.doi.org/10.1111/j.1440-1746.2006.04211.x	Excluded publication type
Roberts 2007	http://dx.doi.org/10.1111/j.1440-1746.2006.04459.x	No population of interest
Robotin 2009	http://dx.doi.org/10.1016/j.jhep.2008.12.022	No population of interest
Robotin 2010	http://dx.doi.org/10.1186/1472-6963-10-215	No population of interest
Robotin 2012	https://dx.doi.org/10.3748/wjg.v18.i42.6106	No population of interest
Robotin 2014	http://dx.doi.org/10.2471/BLT.13.130344	Excluded study type or design
Robotin 2018	http://dx.doi.org/10.2147/CLEP.S146275	No population of interest
Roder 2007	https://search.informit.org/doi/10.3316/informit.442837862726536	No intervention of interest
Rodrigues 2021	http://dx.doi.org/10.1177/1357633X211024108	No outcome of interest
Sheppard-Law 2018	http://dx.doi.org/10.1111/jocn.14367	No population of interest
Sinclair 2013	http://dx.doi.org/10.1111/imj.12068	No population of interest
Subramaniam 2012	http://dx.doi.org/10.1111/j.1445-5994.2011.02711.x	No population of interest
Sutherland 2017	http://dx.doi.org/10.1111/1754-9485.12513	No population of interest
Tai 2002	http://dx.doi.org/10.1046/j.1440-1746.2002.02747.x	No population of interest
Taye 2021	http://dx.doi.org/10.1002/jgh3.12580	No population of interest
Thein 2012	http://dx.doi.org/10.1111/j.1872-034X.2012.01037.x	No population of interest
Vongsuvanh 2016	http://dx.doi.org/10.1371/journal.pone.0155800	No population of interest
Wigg 2021	http://dx.doi.org/10.1016/j.eclinm.2021.100919	No intervention of interest
Wong 2013	http://dx.doi.org/10.1111/j.1445-5994.2012.02755.x	No population of interest

Worland 2017	http://dx.doi.org/10.1007/s12029-017-0006-y	No population of interest
Zeng 2020	http://dx.doi.org/10.1136/gutjnl-2020-321627	Excluded publication type

Excluded Studies by Title

Author	Title	Reason for exclusion
Adams 2020	Nonalcoholic fatty liver disease burden: Australia, 2019–2030	No population of interest
Bertot 2017	Nonalcoholic fatty liver disease-related cirrhosis is commonly unrecognized and associated with hepatocellular carcinoma	No population of interest
Carville 2012	Recognising the role of infection: Preventing liver cancer in special populations	Excluded publication type
Chen 2004	Hepatitis B virus transmission and hepatocarcinogenesis: A 9 year retrospective cohort of 13 676 relatives with hepatocellular carcinoma	No population of interest
Chinnaratha 2019	Improved Survival of Hepatocellular Carcinoma Patients Diagnosed with a Dedicated Screening Programme-a Propensity Score Adjusted Analysis	No population of interest: Indigenous status collected at baseline but not reported
El-Atem 2016	Patterns of service utilisation within Australian hepatology clinics: High prevalence of advanced liver disease	No population of interest
Fisher 2003	Management of chronic hepatitis B virus infection in remote-dwelling Aboriginals and Torres Strait Islanders: an update for primary healthcare providers	Excluded study type or design: Clinical correspondence review
Frazer 2000	Ultrasound screening for hepatocellular carcinoma (HCC) in cirrhosis (multiple letters)	Excluded publication type: Letter no original data
Gellert 2007	Hepatocellular carcinoma in Sydney South West: Late symptomatic presentation and poor outcome for most	No population of interest
George 2018	Non-alcoholic fatty liver disease patients attending two metropolitan hospitals in Melbourne, Australia: high risk status and low prevalence	No population of interest
Hanson 2020	Chronic hepatitis B in remote, tropical Australia; successes and challenges	No intervention of interest: No surveillance program detailed
Harris 2017	Targeted ultrasound of the liver: Impact on scanning time of a new approach in chronic liver disease	No population of interest
Hla 2020	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	No outcome of interest
Hong 2018	Surveillance improves survival of patients with hepatocellular carcinoma: a prospective population-based study	No population of interest: Indigenous status not recorded
Huang 2018	Rate of Nonsurveillance and Advanced Hepatocellular Carcinoma at Diagnosis in Chronic Liver Disease	No population of interest
Jeffrey 2020 (Oct)	Hepatocellular carcinoma surveillance in Australia: time to improve the diagnosis of cirrhosis and use liver ultrasound	Excluded study type or design: letter
Jeffrey 2020 (Feb)	Hepatocellular carcinoma surveillance in Australia: time to improve the diagnosis of cirrhosis and use liver ultrasound	Excluded study type or design: Review
Kemp 2005	Survival in hepatocellular carcinoma: Impact of screening and etiology of liver disease	No population of interest:
Kennedy 2013	Optimisation of hepatocellular carcinoma surveillance in patients with viral hepatitis: A quality improvement study	No population of interest
Kutaiba 2021	Risk factors and screening intervals are crucial for evaluating the cost effectiveness of abbreviated MRI in HCC screening	Excluded publication type
Larcos 2020	Hepatocellular carcinoma surveillance in Australia: time to improve the diagnosis of cirrhosis and use liver ultrasound	Excluded publication type: Letter no original data
Lockart 2021	Hepatitis C virus cure before hepatocellular carcinoma diagnosis is associated with improved survival	No intervention of interest: Outcome of mortality unadjusted HR by indigenous status reported but not linked to surveillance

Low 2021	Hepatocellular carcinoma surveillance and quantile regression for determinants of underutilisation in at-risk Australian patients	No population of interest: Indigenous status not recorded
Maher 2012	Hepatocellular carcinoma surveillance and quantile regression for determinants of underutilisation in at-risk Australian patients	Excluded publication type: Comment no original data
Majeed 2019	RE: No Association Between Screening for Hepatocellular Carcinoma and Reduced Cancer-Related Mortality in Patients With Cirrhosis	No population of interest
Mohsen 2017	Patients with non-viral liver disease have a greater tumor burden and less curative treatment options when diagnosed with hepatocellular carcinoma	No outcome of interest
Nazareth 2016	Nurse-led hepatocellular carcinoma surveillance clinic provides an effective method of monitoring patients with cirrhosis	No population of interest
Nguyen 2021	A Systematic Review and Narrative Synthesis of Health Economic Evaluations of Hepatocellular Carcinoma Screening Strategies	Excluded study type or design
Nicoll 2002	Gastroenterology and hepatology	Excluded study type or design: Clinical update, no original data
Parker 2014	Hepatocellular carcinoma in Australia's Northern Territory: High incidence and poor outcome	No intervention of interest: Ad hoc or no surveillance
Poustchi 2011	Feasibility of conducting a randomized control trial for liver cancer screening: Is a randomized controlled trial for liver cancer screening feasible or still needed?	No population of interest
Qian 2010	Efficacy and cost of a hepatocellular carcinoma screening program at an Australian teaching hospital	No population of interest
Roberts 2006	Re: Impact of screening on survival for hepatocellular carcinoma [3]	Excluded publication type
Roberts 2007	Hepatocellular carcinoma in an Australian tertiary referral hospital 1975-2002: Change in epidemiology and clinical presentation	No population of interest
Robotin 2009	Antiviral therapy for hepatitis B-related liver cancer prevention is more cost-effective than cancer screening	No population of interest
Robotin 2010	Using a population-based approach to prevent hepatocellular cancer in New South Wales, Australia: effects on health services utilisation	No population of interest
Robotin 2012	Cost of treating chronic hepatitis B: Comparison of current treatment guidelines	No population of interest
Robotin 2014	Hepatocellular carcinoma in Australia's Northern Territory: High incidence and poor outcome	Excluded study type or design: Summary of activities
Robotin 2018	Using a chronic hepatitis b registry to support population-level liver cancer prevention in sydney, Australia	No population of interest
Roder 2007	Epidemiology of cancer in Indigenous Australians: Implications for service delivery	No intervention of interest: No surveillance
Rodrigues 2021	A nurse-led, telehealth-driven hepatitis C management initiative in regional Victoria: Cascade of care from referral to cure	No outcome of interest: Indigenous status reported but no surveillance related outcomes reported
Sheppard-Law 2018	Utilisation of hepatocellular carcinoma screening in Australians at risk of hepatitis B virus-related carcinoma and prescribed anti-viral therapy	No population of interest
Sinclair 2013	Epidemiology of hepatitis B-associated hepatocellular carcinoma in Victoria	No population of interest
Subramaniam 2012	Hepatitis B status in migrants and refugees: Increasing health burden in Western Australia	No population of interest
Sutherland 2017	Diffusion-weighted MRI for hepatocellular carcinoma screening in chronic liver disease: Direct comparison with ultrasound screening	No population of interest
Tai 2002	Eight-year nationwide survival analysis in relatives of patients with hepatocellular carcinoma: Role of viral infection	No population of interest
Taye 2021	Remoteness of residence predicts tumor stage, receipt of treatment, and mortality in patients with hepatocellular carcinoma	No population of interest

Thein 2012	Survival after diagnosis of hepatocellular carcinoma and potential impact of treatment in a hepatitis B or C infected cohort	No population of interest
Vongsuvanh 2016	Midkine increases diagnostic yield in AFP negative and NASH-related hepatocellular carcinoma	No population of interest
Wigg 2021	Hepatocellular carcinoma amongst Aboriginal and Torres Strait Islander peoples of Australia	No intervention of interest: No surveillance
Wong 2013	Improved survival trend of patients with hepatocellular carcinoma at an Australian tertiary hospital between 1995-2009	No population of interest
Worland 2017	Hepatocellular Carcinoma Screening Utilising Serum Alpha-Fetoprotein Measurement and Abdominal Ultrasound Is More Effective than Ultrasound Alone in Patients with Non-viral Cirrhosis	No population of interest
Zeng 2020	Prioritisation and the initiation of HCC surveillance in CHB patients: Lessons to learn from the COVID-19 crisis	Excluded publication type

Appendix D4. Technical report for question 4

Systematic Review Question 4: Does HCC surveillance improve liver cancer outcomes for Asian or Pacific-born people in Australia?

PICO

This systematic review addresses the PICO shown in Table 4.

Table 4. PICO for systematic review question 4.

Population	Intervention	Comparator	Outcomes	Study design
Asian or Pacific-born people in Australia	HCC surveillance programs	No surveillance Usual or standard care	Overall mortality Liver disease-related mortality Liver cancer mortality Proportion of liver cancers that are early stage Cost-effectiveness	Randomised controlled trials Cohort or case-control studies Modelling studies

HCC = hepatocellular carcinoma

1. METHODS

1.1 Selection Criteria

Table 2. Selection criteria for studies examining the effect of HCC surveillance programs amongst Asian or Pacific-born people in Australia.

PICO 4	Inclusion	Exclusion
Study type	Intervention Observational	Diagnostic accuracy
Study design	RCTs Cohort or case-control studies Modelling studies or systematic review thereof Case series (Single arm) – if none of the above	Case report Review (not systematic)
Population	≥ 18 years Asian or Pacific-born populations in Australia • With or without liver disease • With liver disease – cirrhotic or non-cirrhotic (any aetiology) • With HCC or liver cancer (observational studies)	People who have previously undergone treatment for liver cancer Children Restricted to liver cancer patients undergoing liver resection and/or transplant "Asian" or Pacific ethnicity rather than country of birth Restricted to people born in India, Sri Lanka, Bangladesh or Pakistan
Intervention	HCC surveillance programs (ultrasound, AFP, other)	Provides no details about the surveillance program Ad hoc surveillance Single screen offered Surveillance detected (observational studies) GALAD score surveillance
Comparator	No surveillance Standard or usual care	No comparator Historical control Non surveillance detected (observational studies)*
Outcome	*Actual or state transition-modelled:* Overall mortality	Cancer incidence

	Liver related mortality HCC/liver cancer specific mortality Survival (observational studies) % early/treatable stage HCC or liver cancer at diagnosis Cost-effectiveness (QALY, DALY or life-years gained)	Unadjusted survival analyses (observational studies) Costs only, costs per life saved Incremental cost of additional early-stage diagnosis
Publication date	2000 onwards	
Publication type	Original journal article Letter or comment that reports original data	Conference abstracts Editorials Letters and comments that do not report original data
Language	English	

AFP = alpha-fetoprotein; DALY = disability-adjusted life years; GALAD score = score based on gender, age, Lens culinaris agglutinin-reactive AFP, total AFP, and des-γ-carboxyprothrombin; HCC = hepatocellular carcinoma; QALY = quality-adjusted life years; RCTs = randomised controlled trials;

** Cancers not detected by surveillance i.e., interval cancer for those undergoing surveillance and cancers detected amongst those not undergoing surveillance.*

[a] HCC is the liver cancer of primary interest.

[b] Chronic HBV infection, chronic HCV infection, alcohol-related liver disease and metabolic-associated fatty liver disease are the aetiologies of interest.

[c] Modelling studies were restricted to state-transition models.

1.2 Definitions and terminology

For the purpose of this review:

Early-stage HCC includes Barcelona Clinic Liver Cancer (BCLC) stage 0/A, meeting Milan criteria, or China Liver Cancer Study group stage I:

1. *The Barcelona Clinic Liver Cancer (BCLC*) staging classification system assesses the number and size of liver tumours, overall performance status (ECOG PS) and liver function (using Child-Pugh classification):
    a. BCLC stage 0 (very early stage); ECOG performance score = 0, Child-Pugh A, single tumour < 20mm;
    b. BCLC stage A (early stage); ECOG performance score = 0, Child-Pugh A-B, single tumour of any size or up to 3 tumours all < 30mm).
2. *The Milan criteria* focus on liver transplantation eligibility. Those eligible for transplantation are described as within Milan criteria and are defined as having one tumour measuring ≤ 50 mm in diameter, or 2-3 tumours ≤ 30 mm in diameter without vascular extension or metastasis.
3. The *China Liver Cancer study group staging* system classifies HCC as stage I (subclinical stage/early stage) if there are no obvious cancer symptoms and signs (tumour usually < 5 cm in diameter).

    Where results were given by BCLC stage and another staging system, the BCLC results were presented.

Fibrotic status *was as* reported by authors.

Generalisability refers to whether the evidence can be directly applied to the target population.

Metabolic-associated fatty liver disease includes non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

1.3 Guidelines

Relevant recent (2015 onwards) guidelines were identified by scanning the citations identified by the literature search (described below) and a summary of these guidelines was reviewed by Expert Advisory Group members as part of Phase 1 of the *Roadmap to Liver Cancer Control* project. To be considered for adoption by the Working Group, guidelines had to be evidence-based and meet the pre-specified criteria of scores of greater or equal to 70% for the following domains: rigour of development, clarity of presentation, and editorial independence of the AGREE II instrument (8). Guidelines were not considered for adoption by the Working Group if they were not based on systematic reviews of the evidence, i.e. did not report using systematic methods to search for evidence, did not clearly describe the criteria for selecting the evidence or did not assess the risk of bias or where this is not possible, appraise the quality of the evidence.

1.4 Literature searches

Medline (including MEDLINE Epub Ahead of Print, I-Process & Other Non-Indexed Citations) and Embase, databases were searched on 1 February 2022 combining text terms and/or database-specific subject headings for liver cancer, surveillance, and Australia. Searches were limited to articles published in English from 1 January 2000 onwards. A complete list of the terms used is included as Appendix 1. The Cochrane Database of Systematic Reviews was searched on 31 March 2022 combining the search terms “liver cancer” and “screen”. Reference lists of included articles, recent relevant guidelines and systematic reviews were checked for potential additional articles.

1.5 Data extraction and analyses

If an effect estimate was not presented but the necessary data were available and adjusted estimates were not required, the risk ratio and 95% confidence interval was calculated using a tool available at *https://sample-size.net/risk-ratio/*. For cost-effectiveness studies, if the cost-effectiveness ratio was not reported for the comparison of interest, it was calculated using the reported costs and outcomes for the intervention and the comparator if the necessary data were available. In this report, a narrative synthesis is presented as only one study met the inclusion criteria for this review.

1.6 Quality appraisals

The quality of cost-effectiveness studies was assessed using a modified version of the CHEC-extended checklist (12). This tool appraises the specification of the population, interventions and comparators modelled, the modelling and cost-effectiveness methods, and the robustness and fitness for purpose of the model. Unlike a risk of bias assessment tool, its focus is not the critical assessment of the sources of bias. However, some of the questions do inform an assessment of the risk of bias and thus whether the results are likely to reflect the true effect of the intervention. Assessments for some of the CHEC-extended checklist questions were used to inform GRADE assessments of modelled studies, including the risk of bias.

1.7 GRADE assessment of the certainty of the evidence

A GRADE approach was used to assess the certainty of the body of evidence for the effect of HCC surveillance when compared with no HCC surveillance or standard/usual care for each outcome (13).

GRADE was originally designed to assess the certainty of the results of a meta-analysis of the evidence for interventions from randomised controlled trials however, for results from modelling studies, GRADE assessments were not recommended (18,19). However, the NHMRC GRADE Working Group has recently changed their position as outlined in Brozek 2021 (20) and has provided a general approach to the GRADE assessment of modelling studies with more specific guidance planned but not published as at May 2022. In the absence of specific criteria, we assessed the risk of bias, indirectness and inconsistency of the evidence from each study based on the general principles explained by Brozek 2021 (20); downgrading from an initial high level of certainty if there were serious concerns. Downgrading was based on an assessment of the level of concern for each of following issues: risk of bias, indirectness and inconsistency. Assessments ranged from no serious concerns (no downgrade), serious concerns (downgrade by one level) or very serious concerns (downgrade by two levels). The certainty of the body of evidence for each outcome was then rated as either high, moderate, low or very low based on the degree of downgrading. Assessment of imprecision based on probabilistic sensitivity analyses or other sensitivity analyses was not considered possible as currently these analyses are designed to assess sensitivity to changes in variable values rather than imprecision. Assessment of publication bias for individual studies was not applicable as all studies reported results of models developed de novo.

We then assessed the certainty of the body of the evidence by assessing the risk of bias, indirectness, inconsistency and publication bias across all studies based on the principles explained by Brozek 2021 (20). As we could not assess imprecision we presented two final

assessments of the certainty of the evidence, where one is conservative (downgraded for imprecision) and one is not adjusted for imprecision). This was done so that GRADE assessments could be compared with those of other study designs. Similarly, as for non-modelled studies, where there was only one study inconsistency could not be rated.

Definitions of the GRADE ratings of certainty are presented in Appendix 2.

2. RESULTS

2.1 Guidelines searches

No recent relevant guidelines based on systematic reviews were identified.

2.2 Literature searches

Figure 1 outlines the process of identifying relevant articles for this systematic review. The combined Medline and Embase search identified 370 citations and the search of the Cochrane Database of Systematic Reviews 18 citations, resulting in a total of 388 citations. Titles and abstracts were examined, and 54 articles were retrieved for a more detailed evaluation. No further potential citations were identified from the reference lists of included articles, recent relevant guidelines, and systematic reviews.

One modelling study reported in one article met the inclusion criteria and was included in the review. No RCTs or interventional cohort studies were identified.

The retrieved articles that were not included and the reasons for their exclusion are documented in Appendix 3. In summary, most articles were excluded because they did not include the population of interest (n = 28), outcome of interest (n = 8), publication type of interest (n = 7) or study type or design of interest (n = 6).

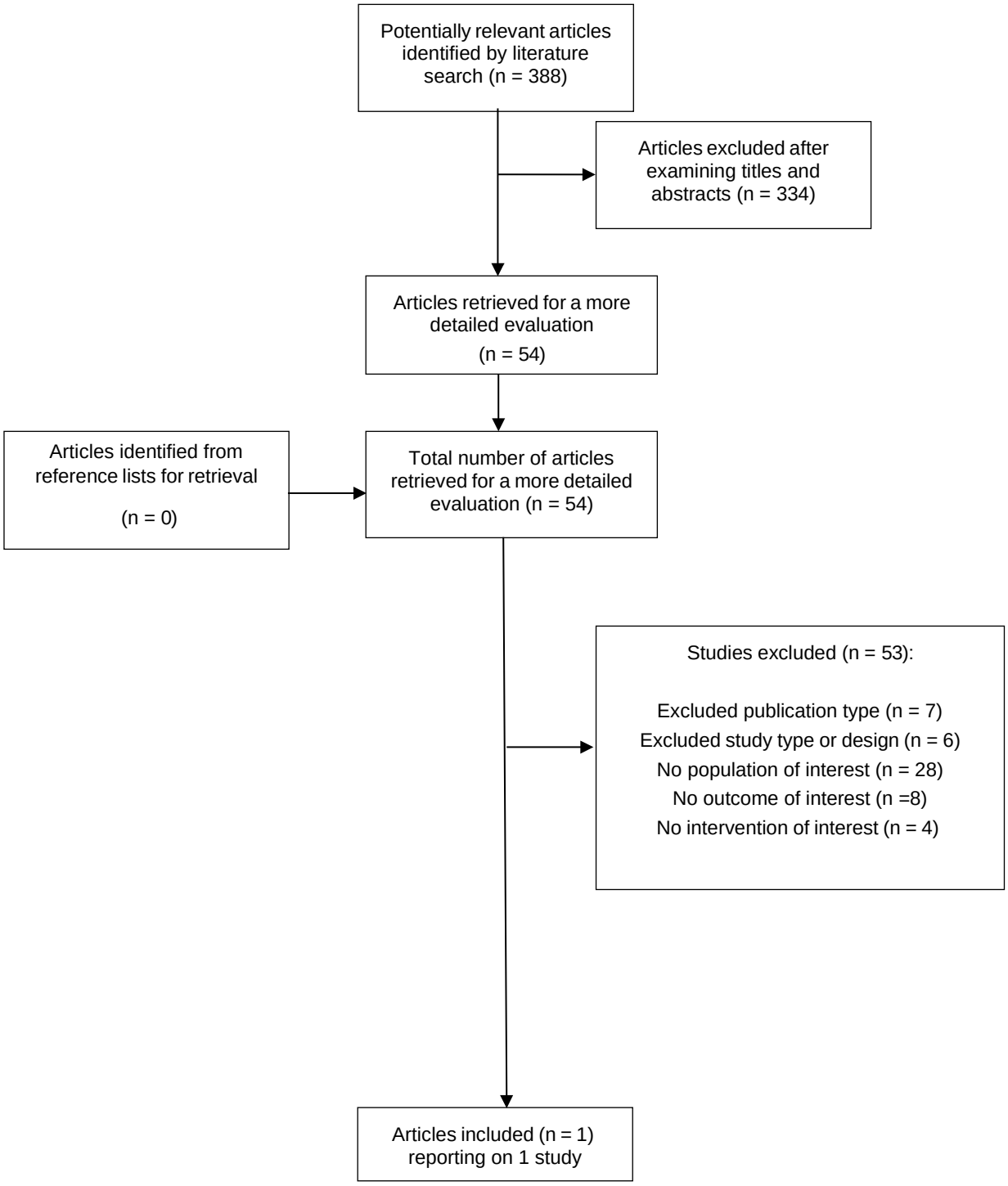


Figure 1. Process of inclusion and exclusion of studies.

2.3 Characteristics of included study

The characteristics of the included study are described in Table 3.

Table 3. Study characteristics for the study comparing risk-stratified surveillance with usual care for Asian or Pacific-born people in Australia.

Study (Country)	Study design	Population	Participants	Intervention	Comparison	Cycle length	Follow-up	Outcomes	Conflicts of interest considered
Robotin 2009 (23) (Australia)	Model (Markov) Not validated	Australian Asian-born patients with chronic HBV infection (HBsBAg positive) aged 35 years at start Time period NR Excluded patients with HCC detected at baseline: NR	N = 10,000 Age: 35 years at start Male: 60% Non-cirrhotic: 100% at start Aetiology: HBV Treated for HBV: 2% HCC incidence (per year) Cirrhotic: 4.5% Non-cirrhotic: 0.2%	**Risk-stratified surveillance** 6-monthly US + AFP AFP cut-off NR Risk assessment based on HBV DNA levels Participation: NR	**Usual care** ~ 1% undergo surveillance	12 months	Time horizon: 50 years	Liver disease mortality Cost/QALY gained	Yes - authors report no conflicts of interest to declare

AFP = alpha-fetoprotein; HBV = chronic hepatitis B; HBsAg = serum hepatitis B surface antigen; HCC = hepatocellular carcinoma; NR = not reported; QALY = quality-adjusted life years; US = ultrasound

2.4 Results by outcomes of interest

1. Overall mortality – no results found
2. Liver disease-related mortality – results are shown in Table 4
3. Liver cancer mortality – no results found
4. Proportion of liver cancers diagnosed at an early stage – no results found

5. Life-years, quality-adjusted life-years or disability-adjusted life-years gained – results are shown in Table 5
6. Cost-effectiveness - results are shown in Table 5

Table 4. Results of study comparing risk-stratified surveillance with usual care for the outcome of modelled liver disease-related mortality.

Study	Study design	Outcome	Outcome metric	Follow-up	Risk-stratified surveillance	Usual care	Effect estimate
Robotin 2009 (23) (HBV-non cirrhotic at start)	Model (Markov)	Liver disease (HCC or HBV)-related mortality	%	50 years	33.6	33.8	NA

HBV = chronic hepatitis B; HCC = hepatocellular cancer; NA = not applicable

Table 5. Results of study comparing risk-stratified surveillance with usual care for the outcome of modelled cost-effectiveness and quality-adjusted years gained.

Study (Liver disease)	Economic perspective	Discount rate	Costs currency and year	Medical costs included	Evidence bases for the effectiveness of surveillance technology	Clinical Effect	Willingness to pay threshold/ indicative benchmark used	CER	Probabilistic sensitivity analysis	Three largest sources of uncertainty
Robotin 2009 (23) (HBV-non cirrhotic at start)	Payer's (health care funder)	5% p/a for costs and health outcomes	Australian dollar (AU$) 2006	Risk assessments Surveillance Diagnostic investigations Early-stage treatments including ablation but not transplantation TACE	Relative risk of 0.6 for HBV death with surveillance program for HCC patients	0.014 QALY gained per person (discounted NR)	NR	AU$401,516 per QALY gained	No	NR for surveillance only

CER = cost effectiveness ratio; HBV = chronic hepatitis B; HCC = hepatocellular cancer; NR = not reported; p/a = per annum; QALY = quality-adjusted life years; TACE = transarterial chemoemobolisation; US = ultrasound

2.5 Quality appraisal assessments

The results of the quality appraisal assessment of the included modelling study are shown in Table 6. The results are presented separately for outcomes relating to cost effectiveness ratio and death related to liver disease.

Table 6. Quality appraisal for cost-effectiveness and other modelled outcomes using the CHEC-extended (modified) checklist.

Checklist question	**Robotin 2009**(23) **CER**	**Robotin 2009**(23) **Liver disease-related death**
1. Is the study population *clearly* described?	Yes	Yes
2. Are competing alternatives *clearly* described?	No	No
3. Is a *well-defined* research question posed in answerable form?	Yes	Yes
4. Is the economic study design *appropriate* to the stated objective?	Yes	Yes
5. Are the structural assumptions and the validation methods of the model properly reported?	Yes	Yes
6. Is the chosen time horizon *appropriate* in order to include relevant costs and consequences?	Yes	Yes
7. Are *all important and relevant* costs for each alternative identified?	No	No
8. Are all costs measured *appropriately* in physical units?	Yes	NA
9. Are costs valued *appropriately*?	Yes	NA
10. Are *all important and relevant* outcomes for each alternative identified? Does the study report costs per Life-years, QALYs or DALYs?	Yes	NA
11. Are all outcomes measured *appropriately*? Do the authors critically appraise sources of data underpinning effect of surveillance?	No	No
12. Are outcomes valued *appropriately*?	Yes	NA
13. Is *an appropriate* incremental analysis of costs and outcomes of alternatives performed?	Yes	NA
14. Are all future costs and outcomes discounted *appropriately*?	Yes	NA
15. Are all important variables, whose values are uncertain, *appropriately* subjected to sensitivity analysis? Was a probabilistic sensitivity analysis undertaken?	No	No
16. Does the article/report indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Yes	Yes

CER = cost effectiveness ratio; DALY = disability-adjusted life years; NA = not applicable; QALY = quality-adjusted life years

3. GRADE ASSESSMENT OF THE CERTAINTY OF THE EVIDENCE

Overall mortality – no evidence found

Liver disease-related mortality - results are shown in Tables 7-8

Liver cancer mortality - no evidence found

Proportion of liver cancers diagnosed at an early stage – no evidence found

Life-years, quality-adjusted life-years or disability-adjusted life-years gained – results are shown in Tables 7-8

Cost-effectiveness - results are shown in Tables 7-8

Table 7. GRADE assessment of the certainty of the evidence for modelled evidence from individual studies.

GRADE domain	***Rating***	***Reason for rating***	***Certainty of evidence***
Outcomes: Cost-effectiveness, liver disease-related mortality and QALYs gained			
Risk of bias	Very serious concerns (-2)	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	Very low
Indirectness	No serious concerns	Although does not report AFP threshold, this is not a serious concern.	
Imprecision	Not assessable		
Inconsistency	Serious concerns (-1)	Serious concerns regarding model inconsistency No pooled estimates identified however data sources cited for some parameters missing or incorrect so cannot be certain no pooled estimates used	
Publication bias	Not applicable	Model developed de novo	

AFP = alpha-fetoprotein; NA = not applicable; HCC = hepatocellular carcinoma; QALY = quality-adjusted life years

Table 8. GRADE assessment of the certainty of the body of evidence for cost-effectiveness and other modelled outcomes.

GRADE domain	***Rating***	***Reason for rating***	***Certainty of evidence***
Outcomes: Cost-effectiveness, liver disease-related mortality and QALYs gained			

Risk of bias	Very serious concerns (-2)	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	Low to very low
Indirectness	No serious concerns	Although does not report AFP threshold, this is not a serious concern.	
Imprecision	Not assessable		
Inconsistency	Not assessable	Single study so overall inconsistency cannot be assessed	
Publication bias	Undetected	Single study	

AFP = alpha-fetoprotein; NA = not applicable; HCC = hepatocellular carcinoma; QALY = quality-adjusted life years

4. SUMMARY OF FINDINGS

Table 9. Summary of findings for risk-stratified surveillance compared to usual care for Asian or Pacific-born people in Australia.

Outcome	***Number of participants (studies)***	***Certainty of the evidence (GRADE)***	***Relative effect (95% CI)***	***Modelled rates***		
				Metric	***Usual Care***	***Risk-stratified surveillance***
Liver disease-related mortality	N = 10 000 (1 modelling study)	Low to very low[1]	NA	Cumulative per 100 patients	33.8	33.6
QALYs gained	N = 10 000 (1 modelling study)	Low to very low[1]	0.014 QALY gained per person	NA	NA	NA
Cost-effectiveness	N = 10 000 (1 modelling study)	Low to very low[1]	AU$401,516 per QALY gained	NA	NA	NA

[1]*Very serious concerns regarding the risk of bias*
NR = not applicable; CI = confidence interval; QALY = quality-adjusted life years

Table 10. Evidence summary for risk-stratified surveillance compared to usual care for Asian or Pacific-born people in Australia.

Evidence summary	**GRADE certainty of evidence**	**References**
No studies were identified that evaluated the effects of HCC surveillance on liver cancer outcomes specifically in Pacific-born people living in Australia.	Not applicable	
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.	Low to very Low	Robotin 2009 (23)
There is a high prevalence of HCC among Asian-born and Pacific-born people in Australia.	Not applicable	Yu 2022 (31), Waziry 2016 (32)

REFERENCES

1. World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2015. 134 p.

2. National Institute for Health and Care Excellence. Hepatitis B (chronic); diagnosis and management. Clinical guideline [CG165] Last updated October 2017 [Internet]. London: NICE; 2013 [cited 2022 Jun 16]. Available from: https://www.nice.org.uk/guidance/cg165

3. National Institute for Health and Care Excellence. Cirrhosis in Over 16s: Assessment and Management. NICE guideline [NG50] [Internet]. London: NICE; 2016 [cited 2021 Dec 8]. Available from: https://www.nice.org.uk/guidance/ng50

4. 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. 2019;13(1):1–1.

5. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018 Apr;67(4):1560–99.

6. Gastroenterological Society of Australia. Hepatocellular Carcinoma Consensus Statement Working Group. Australian recommendations for the management of hepatocellular carcinoma: a consensus statement. [Internet]. Melbourne: Gastroenterological Society of Australia; 2020 [cited 2022 Sep 12]. Available from: https://www.gesa.org.au/resources/hepatocellular-carcinoma-hcc-management-consensus/

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

8. AGREE Next Steps Consortium. The AGREE II Instrument [Internet]. 2017. Available from: http://www.agreetrust.org/resource-centre/agree-ii/

9. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022) [Internet]. Cochrane; 2022. Available from: www.training.cochrane.org/handbook

10. Eldridge S, Campbell MK, Campbell MJ, Drahota AK, Giraudeau B, Reeves BC, et al. Revised Cochrane risk of bias tool for randomized trials (RoB 2) Additional considerations for cluster-randomized trials (RoB 2 CRT) [Internet]. 2021 [cited 2022 Feb 1]. Available from: https://drive.google.com/file/d/1yDQtDkrp68_8kJilUdbongK99sx7RFI-/view

11. Kirk M, Smurthwaite K, Braunig J, Trevener S, D'Este C, Lucas R, et al. The PFAS Health Study: Systematic Literature Review [Internet]. Canberra: The Australian National University; 2018. p. 161–3. Available from: https://openresearch-repository.anu.edu.au/handle/1885/241032

12. Odnoletkova I, Goderis G, Pil L, Nobels F, Aertgeerts B, Annemans L, et al. Cost-Effectiveness of Therapeutic Education to Prevent the Development and Progression of Type 2 Diabetes: Systematic Review. J Diabetes Metab. 2014;05(09):in appendix.

13. NHMRC. Guidelines for Guidelines: Assessing certainty of evidence [Internet]. 2019. Available from: https://nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence

14. Murad MH, Mustafa RA, Schünemann HJ, Sultan S, Santesso N. Rating the certainty in evidence in the absence of a single estimate of effect. Evid Based Med. 2017 Jun;22(3):85–7.

15. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol. 2011 Dec;64(12):1283–93.

16. Zeng L, Brignardello-Petersen R, Hultcrantz M, Siemieniuk RAC, Santesso N, Traversy G, et al. GRADE guidelines 32: GRADE offers guidance on choosing targets of GRADE certainty of evidence ratings. J Clin Epidemiol. 2021 Sep;137:163–75.

17. Brignardello-Petersen R, Guyatt GH, Mustafa RA, Chu DK, Hultcrantz M, Schünemann HJ, et al. GRADE guidelines 33: Addressing imprecision in a network meta-analysis. J Clin Epidemiol. 2021 Nov;139:49–56.

18. Brunetti M, Shemilt I, Pregno S, Vale L, Oxman AD, Lord J, et al. GRADE guidelines: 10. Considering resource use and rating the quality of economic evidence. J Clin Epidemiol. 2013 Feb;66(2):140–50.

19. Holger Schünemann, Jan Brożek, Gordon Guyatt, Andrew Oxman. GRADE Handbook - Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach [Internet]. 2013 [cited 2022 Apr 26]. Available from: https://gdt.gradepro.org/app/handbook/handbook.html

20. Brozek JL, Canelo-Aybar C, Akl EA, Bowen JM, Bucher J, Chiu WA, et al. GRADE Guidelines 30: the GRADE approach to assessing the certainty of modeled evidence—An overview in the context of health decision-making. J Clin Epidemiol. 2021 Jan;129:138–50.

21. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol. 2004 Jul;130(7):417–22.

22. 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):204–9.

23. 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 May;50(5):990–8.

24. 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. Asian Pac J Cancer Prev. 2014 Nov 6;15(20):8993–9004.

25. Chang Y, Lairson DR, Chan W, Lu SN, Aoki N. Cost-effectiveness of screening for hepatocellular carcinoma among subjects at different levels of risk: Cost-effectiveness of screening for HCC. J Eval Clin Pract. 2011 Apr;17(2):261–7.

26. 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.

27. Farhang Zangneh H, Wong WWL, 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 Aug;17(9):1840-1849.e16.

28. 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 Open. 2021 Jun 24;4(6):e2114680.

29. 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.

30. 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 Health. 2021 Oct;24(10):1454–62.

31. 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 Apr 19;OF1–8.

32. 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 Dec;65(6):1086–93.

33. Parikh ND, Singal AG, Hutton DW, Tapper EB. Cost-Effectiveness of Hepatocellular Carcinoma Surveillance: An Assessment of Benefits and Harms. Am J Gastroenterol. 2020 Oct;115(10):1642–9.

34. 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):1418–24.

35. 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 Apr;98(7):1166–75.

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

37. 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. 2010/06/16 ed. 2010 May;25(5):951–6.

38. 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. Intern Med J. 2013 Jul;43(7):772–7.

39. 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 Feb;1(1):53–60.

40. 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):551–6.

41. Byford S, Raftery J. Economics notes: Perspectives in economic evaluation. BMJ. 1998 May 16;316(7143):1529–30.

42. Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun Wong V, Castellanos M, Aller-de la Fuente R, Metwally M, et al. Fibrosis Severity as a Determinant of Cause-Specific Mortality in Patients With Advanced Nonalcoholic Fatty Liver Disease: A Multi-National Cohort Study. Gastroenterology. 2018 Aug 1;155(2):443-457.e17.

43. 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 Aug;21(8):938–43.

44. Hong TP. An Australian population-based study of the incidence and outcomes of hepatocellular carcinoma: the Hepatomas of Melbourne Epidemiological Research (HoMER) study [Internet]. 2019 [cited 2019 Jul 11]. Available from: http://hdl.handle.net/11343/225659

45. Wallace MC, Preen DB, Short MW, Adams LA, Jeffrey GP. Hepatocellular carcinoma in Australia 1982-2014: Increasing incidence and improving survival. Liver Int. 2019 Mar;39(3):522–30.

46. Nguyen ALT, Si L, Lubel JS, Shackel N, Yee KC, Wilson M, et al. Construction and validation of a microsimulation model for hepatocellular carcinoma surveillance in Australia. In Submission;

47. Alavi M, Law MG, Grebely J, Amin J, Hajarizadeh B, George J, et al. Time to decompensated cirrhosis and hepatocellular carcinoma after an HBV or HCV notification: A population-based study. J Hepatol. 2016 Nov;65(5):879–87.

48. Jepsen P, Vilstrup H, Andersen PK. The clinical course of cirrhosis: The importance of multistate models and competing risks analysis. Hepatology. 2015 Jul 1;62(1):292–302.

49. Canfell K, Kim JJ, Brisson M, Keane A, Simms KT, Caruana M, et al. Mortality impact of achieving WHO cervical cancer elimination targets: a comparative modelling analysis in 78 low-income and lower-middle-income countries. The Lancet. 2020 Feb;395(10224):591–603.

50. Haq MI, Drake TM, Goh TL, Ahmed A, Forrest E, Barclay S, et al. Effect of Hepatocellular Carcinoma Surveillance Programmes on Overall Survival in a Mixed Cirrhotic UK Population: A Prospective, Longitudinal Cohort Study. J Clin Med. 2021 Jun 24;10(13):2770.

51. Consumer Price Index, Australia, March 2022 | Australian Bureau of Statistics [Internet]. 2022 [cited 2022 Jun 12]. Available from: https://www.abs.gov.au/statistics/economy/price-indexes-and-inflation/consumer-price-index-australia/latest-release

52. Department of Health, Australian Government. MBS Online: Medicare Benefits Schedule. [homepage on the internet] [Internet]. Canberra, ACT: Commonwealth of Australia; Available from: http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/Home

53. Xiao Y, Howell J, Gemert C, Thompson AJ, Seaman CP, McCulloch K, et al. Enhancing the hepatitis B care cascade in Australia: A cost-effectiveness model. J Viral Hepat. 2020 May;27(5):526–36.

54. Reeve R, Srasuebkul P, Langton JM, Haas M, Viney R, Pearson SA, et al. Health care use and costs at the end of life: a comparison of elderly Australian decedents with and without a cancer history. BMC Palliat Care. 2017 Jun 21;17(1):1.

55. McPhail SM, Amarasena S, Stuart KA, Hayward K, Gupta R, Brain D, et al. Assessment of health-related quality of life and health utilities in Australian patients with cirrhosis. JGH Open. 2021 Jan;5(1):133–42.

56. Global Burden of Disease Collaborative Network. Global Burden of Disease (GBD 2019) [Internet]. Seattle, United States of America: Institute for Health Metrics and Evaluation (IHME); 2021 [cited 2022 Jun 12]. Available from: https://www.healthdata.org/gbd/2019

57. 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 Jan;44(1):217–31.

58. NSW Cancer Registry. Data request: Hepatocellular carcinoma (coded as C22.0 or C22.9) incidence and mortality). Private communication; unpublished.; 2021 Aug.

59. Tzartzeva K, Obi J, Rich NE, Parikh ND, Marrero JA, Yopp A, et al. Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Patients With Cirrhosis: A Meta-analysis. Gastroenterology. 2018 May 1;154(6):1706-1718.e1.

60. Cheng RM. Novel Biomarkers of Hepatocellular Carcinoma [Internet]. The University of Sydney; 2018. Available from: http://hdl.handle.net/2123/20294

61. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. Circulation. 2016 Feb 9;133(6):601–9.

62. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. Stat Med. 2017 Nov 30;36(27):4391–400.

APPENDICES

Appendix 1: Medline and Embase database (via Ovid platform) search strategy

#	Searches
1	carcinoma, hepatocellular/
2	liver neoplasms/
3	liver cell carcinoma/
4	liver tumor/
5	liver cancer/
6	or/1-5
7	((hepato* or liver or hepatic) adj3 (cancer or carcinoma* or neoplasm* or tumor* or tumour*)).tw.
8	(hepatoma* or hepatocarcinoma* or hcc).tw.
9	or/7-8
10	Early diagnosis/
11	Early detection of cancer/
12	population surveillance/
13	mass screening/
14	cancer screening/
15	disease surveillance/
16	or/10-15
17	screen*.tw.
18	surveil*.tw.
19	17 or 18
20	6 or 9
21	16 or 19
22	20 and 21
23	australia.in.
24	22 and 23
25	limit 24 to english language
26	limit 25 to human
27	limit 26 to yr="2000 -Current"
28	remove duplicates from 27

29	limit 28 to conference abstracts [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) PubMed not MEDLINE,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]
30	limit 29 to medline
31	29 not 30
32	28 not 31

Appendix 2: GRADE assessment of the certainty of the evidence

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Appendix 3: Overview of studies

Included Study

Author	Title	PMID/DOI
Robotin 2009	Antiviral therapy for hepatitis B-related liver cancer prevention is more cost-effective than cancer screening	http://dx.doi.org/10.1016/j.jhep.2008.12.022

Excluded studies by DOI

Article	PMID/DOI	Reason for exclusion
Adams 2020	http://dx.doi.org/10.1111/jgh.15009	No population of interest
Bertot 2017	http://dx.doi.org/10.1002/hep4.1018	No population of interest
Carter 2021	https://dx.doi.org/10.1016/j.jval.2021.04.1286	No population of interest
Carville 2012	https://search.informit.org/doi/10.3316/informit.130848966380090	Excluded publication type
Chen 2004	http://dx.doi.org/10.1016/j.jhep.2003.12.002	No population of interest
Chinnaratha 2019	http://dx.doi.org/10.1007/s12029-018-0171-7	No population of interest
El-Atem 2016	http://dx.doi.org/10.1111/imj.13008	No population of interest
Fisher 2003	http://dx.doi.org/10.5694/j.1326-5377.2003.tb05070.x	Excluded study type or design
Frazer 2000	http://dx.doi.org/10.1053/crad.1999.0265	Excluded publication type
Gellert 2007	http://dx.doi.org/10.1111/j.1445-5994.2007.01392.x	No intervention of interest
George 2018	http://dx.doi.org/10.1111/imj.13973	No population of interest

Hanson 2020	http://dx.doi.org/10.1371/journal.pone.0238719	No intervention of interest
Harris 2017	http://dx.doi.org/10.1111/1754-9485.12595	No population of interest
Hla 2020	http://dx.doi.org/10.1186/s12939-020-01180-w	No population of interest
Hong 2018	http://dx.doi.org/10.5694/mja18.00373	No population of interest
Huang 2018	http://dx.doi.org/10.1097/MCG.0000000000000916	No population of interest
Jeffrey 2020	http://dx.doi.org/10.5694/mja2.50808	Excluded study type or design
Jeffrey 2020	http://dx.doi.org/10.5694/mja2.50521	Excluded study type or design
Kemp 2005	http://dx.doi.org/10.1111/j.1440-1746.2005.03844.x	No outcome of interest
Kennedy 2013	http://dx.doi.org/10.1111/imj.12166	No outcome of interest
Kutaiba 2021	http://dx.doi.org/10.1016/j.jhep.2021.06.041	Excluded publication type
Larcos 2020	https://dx.doi.org/10.5694/mja2.50806	Excluded publication type
Lockart 2021	http://dx.doi.org/10.1111/jvh.13475	No population of interest
Low 2021	https://dx.doi.org/10.4251/wjgo.v13.i12.2149	No population of interest
Maher 2012	http://dx.doi.org/10.1016/S1473-3099%2811%2970355-3	Excluded publication type
Majeed 2019	http://dx.doi.org/10.1053/j.gastro.2018.09.060	No outcome of interest
Mohsen 2017	https://dx.doi.org/10.3748/wjg.v23.i15.2763	No population of interest
Nazareth 2016	http://dx.doi.org/10.1111/ijn.12472	No population of interest
Nguyen 2021	http://dx.doi.org/10.1016/j.jval.2020.11.014	Excluded study type or design
Nicoll 2002	https://dx.doi.org/10.5694/j.1326-5377.2002.tb04247.x	Excluded study type or design
Parker 2014	http://dx.doi.org/10.5694/mja13.11117	No population of interest
Poustchi 2011	http://dx.doi.org/10.1002/hep.24581	No population of interest
Qian 2010	http://dx.doi.org/10.1111/j.1440-1746.2009.06203.x	No population of interest
Roberts 2006	http://dx.doi.org/10.1111/j.1440-1746.2006.04211.x	Excluded publication type
Roberts 2007	http://dx.doi.org/10.1111/j.1440-1746.2006.04459.x	No outcome of interest
Robotin 2012	https://dx.doi.org/10.3748/wjg.v18.i42.6106	No intervention of interest
Robotin 2010	http://dx.doi.org/10.1186/1472-6963-10-215	No outcome of interest
Robotin 2014	http://dx.doi.org/10.2471/BLT.13.130344	Excluded study type or design
Robotin 2018	http://dx.doi.org/10.2147/CLEP.S146275	No outcome of interest
Roder 2007	https://search.informit.org/doi/10.3316/informit.442837862726536	No population of interest
Rodrigues 2021	http://dx.doi.org/10.1177/1357633X211024108	No population of interest
Sheppard-Law 2018	http://dx.doi.org/10.1111/jocn.14367	No outcome of interest
Sinclair 2013	http://dx.doi.org/10.1111/imj.12068	No population of interest
Subramaniam 2012	http://dx.doi.org/10.1111/j.1445-5994.2011.02711.x	No outcome of interest
Sutherland 2017	http://dx.doi.org/10.1111/1754-9485.12513	No population of interest
Tai 2002	http://dx.doi.org/10.1046/j.1440-1746.2002.02747.x	No population of interest
Taye 2021	http://dx.doi.org/10.1002/jgh3.12580	No population of interest
Thein 2012	http://dx.doi.org/10.1111/j.1872-034X.2012.01037.x	No intervention of interest
Vongsuvanh 2016	http://dx.doi.org/10.1371/journal.pone.0155800	No population of interest
Wigg 2021	http://dx.doi.org/10.1016/j.eclinm.2021.100919	No population of interest
Wong 2013	http://dx.doi.org/10.1111/j.1445-5994.2012.02755.x	No population of interest
Worland 2017	http://dx.doi.org/10.1007/s12029-017-0006-y	No population of interest
Zeng 2020	http://dx.doi.org/10.1136/gutjnl-2020-321627	Excluded publication type

Appendix D5. Technical report for question 5

Systematic Review Question 5: Does HCC surveillance improve liver cancer outcomes for sub-Saharan Africa-born people in Australia?

PICO

This systematic review addresses the PICO shown in Table 5.

Table 5. PICO for systematic review question 5.

Population	Intervention	Comparator	Outcomes	Study design
Sub-Saharan Africa-born people in Australia	HCC surveillance programs	No surveillance Usual or standard care	Overall mortality Liver disease-related mortality Liver cancer mortality Proportion of liver cancers that are early stage Cost-effectiveness	Randomised controlled trials Cohort or case-control studies Modelling studies

HCC – hepatocellular carcinoma

1. METHODS

1.1 Selection Criteria

Table 2. Selection criteria for PICO 5 for studies assessing effects of HCC surveillance programs amongst people born in sub-Saharan Africa in Australia.

PICO 5	Inclusion	Exclusion
Study type	Intervention Observational	Diagnostic accuracy
Study design	RCTs Cohort or case-control studies Modelling studies or systematic review thereof Case series (Single arm) – if none of the above	Case report Review (not systematic)
Population	≥ 18 years Sub-Saharan Africa-born people in Australia • With or without liver disease • With liver disease – cirrhotic or non-cirrhotic (any aetiology) • With HCC or liver cancer (observational studies)	People who have previously undergone treatment for liver cancer Children Restricted to liver cancer patients undergoing liver resection and/or transplant Restricted to people born in Egypt, Morocco, Libya, Algeria or Tunisia
Intervention	HCC surveillance programs (ultrasound, AFP, other)	Provides no details about the surveillance program Ad hoc surveillance Single screen offered Surveillance detected (observational studies) GALAD score surveillance
Comparator	No surveillance Standard or usual care	No comparator Historical control Non surveillance detected (observational studies)*
Outcome	*Actual or state transition-modelled:* Overall mortality	Cancer incidence

	Liver-related mortality HCC/liver cancer specific mortality Survival (observational studies) % early/treatable stage HCC or liver cancer at diagnosis Cost-effectiveness (QALY, DALY or life-year gained)	Unadjusted survival analyses (observational studies) Incremental cost of additional early-stage diagnosis Costs only, costs per life saved
Publication date	2000 onwards	
Publication type	Original journal article Letter or comment that reports original data	Conference abstracts Editorials Letters and comments that do not report original data

AFP = alpha-fetoprotein; DALY = disability adjusted life years; GALAD score = score based on gender, age, Lens culinaris agglutinin-reactive AFP, total AFP, and des-γ-carboxyprothrombin; HCC = hepatocellular carcinoma; QALY = quality-adjusted life years; RCTs = randomised controlled trials

**Cancers not detected by surveillance i.e., interval cancer for those undergoing surveillance and cancers detected amongst those not undergoing surveillance.*

[a]HCC is the liver cancer of primary interest.

[b]Chronic HBV infection, chronic HCV infection, alcohol-related liver disease, and metabolic-associated fatty liver disease are the aetiologies of interest.

[c]Modelling studies were restricted to state-transition models.

1.2 Definitions and terminology

For the purpose of this review:

Early-stage HCC includes Barcelona Clinic Liver Cancer (BCLC) stage 0/A, meeting Milan criteria, or China Liver Cancer Study group stage I:

1. *The Barcelona Clinic Liver Cancer (BCLC*) staging classification system assesses the number and size of liver tumours, overall performance status (ECOG PS) and liver function (using Child-Pugh classification):
    a. BCLC stage 0 (very early stage); ECOG performance score = 0, Child-Pugh A, single tumour < 20mm;
    b. BCLC stage A (early stage); ECOG performance score = 0, Child-Pugh A-B, single tumour of any size or up to 3 tumours all < 30mm).
2. *The Milan criteria* focus on liver transplantation eligibility. Those eligible for transplantation are described as within Milan criteria and are defined as having one tumour measuring ≤ 50 mm in diameter, or 2-3 tumours ≤ 30 mm in diameter without vascular extension or metastasis.
3. The *China Liver Cancer study group staging* system classifies HCC as stage I (subclinical stage/early stage) if there are no obvious cancer symptoms and signs (tumour usually < 5 cm in diameter).

    Where results were given by BCLC stage and another staging system, the BCLC results were presented.

Fibrotic status *was as* reported by authors.

Generalisability refers to whether the evidence can be directly applied to the target population.

Metabolic-associated fatty liver disease includes non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

1.3 Guidelines

Relevant recent (2015 onwards) guidelines, were identified by scanning the citations identified by the literature search (described below) and a summary of these guidelines was reviewed by Expert Advisory Group members as part of Phase 1 of the *Roadmap to Liver Cancer Control* project. To be considered for adoption by the Working Group, guidelines had to be evidence-based and meet the pre-specified criteria of scores of greater or equal to 70% for the following domains: rigour of development, clarity of presentation, and editorial independence of the AGREE II instrument (8). Guidelines were not considered for adoption if they were not based on systematic reviews of the evidence, i.e. did not report using systematic methods to search for evidence, did not clearly describe the criteria for selecting the evidence or did not assess the risk of bias or where this is not possible, appraise the quality of the evidence.

1.4 Literature searches

Medline (including MEDLINE Epub Ahead of Print, I-Process & Other Non-Indexed Citations) and Embase, databases were searched on 1 February 2022 combining text terms and/or database-specific subject headings for liver cancer, surveillance and Australia. Searches were limited to articles published in English from 1 January 2000 onwards. A complete list of the terms used is included as Appendix 1. The Cochrane Database of Systematic Reviews was searched on 31 March 2022 combining the search terms “liver cancer” and “screen”. Reference lists of included articles, recent relevant guidelines and systematic reviews were checked for potential additional articles.

1.5 Data extraction and analyses

If an effect estimate was not presented but the necessary data were available and adjusted estimates were not required, the risk ratio and 95% confidence interval was calculated using a tool available at *https://sample-size.net/risk-ratio/*. For cost-effectiveness studies, if the cost-effectiveness ratio was not reported for the comparison of interest it was calculated using the reported costs and outcomes for the intervention and the comparator if the necessary data were available. In this report, a narrative synthesis is presented as only one study met the inclusion criteria for this review.

2. RESULTS

2.1 Guidelines searches

No recent relevant guidelines based on systematic reviews were identified.

2.2 Literature searches

Figure 1 outlines the process of identifying relevant articles for this systematic review. The combined Medline and Embase search identified 370 citations and the search of the Cochrane Database of Systematic Reviews 18 citations, resulting in a total of 388 citations. Titles and abstracts were examined and 54 articles were retrieved for a more detailed evaluation. No further potential citations were identified from the reference lists of included articles, recent relevant guidelines and systematic reviews.

None of the potentially relevant studies met the inclusion criteria.

The retrieved articles that were not included and the reasons for their exclusion are documented in Appendix 3. In summary, most articles were excluded because they did not include the population of interest (n = 37), publication type of interest (n = 7) or study type or design of interest (n = 7).

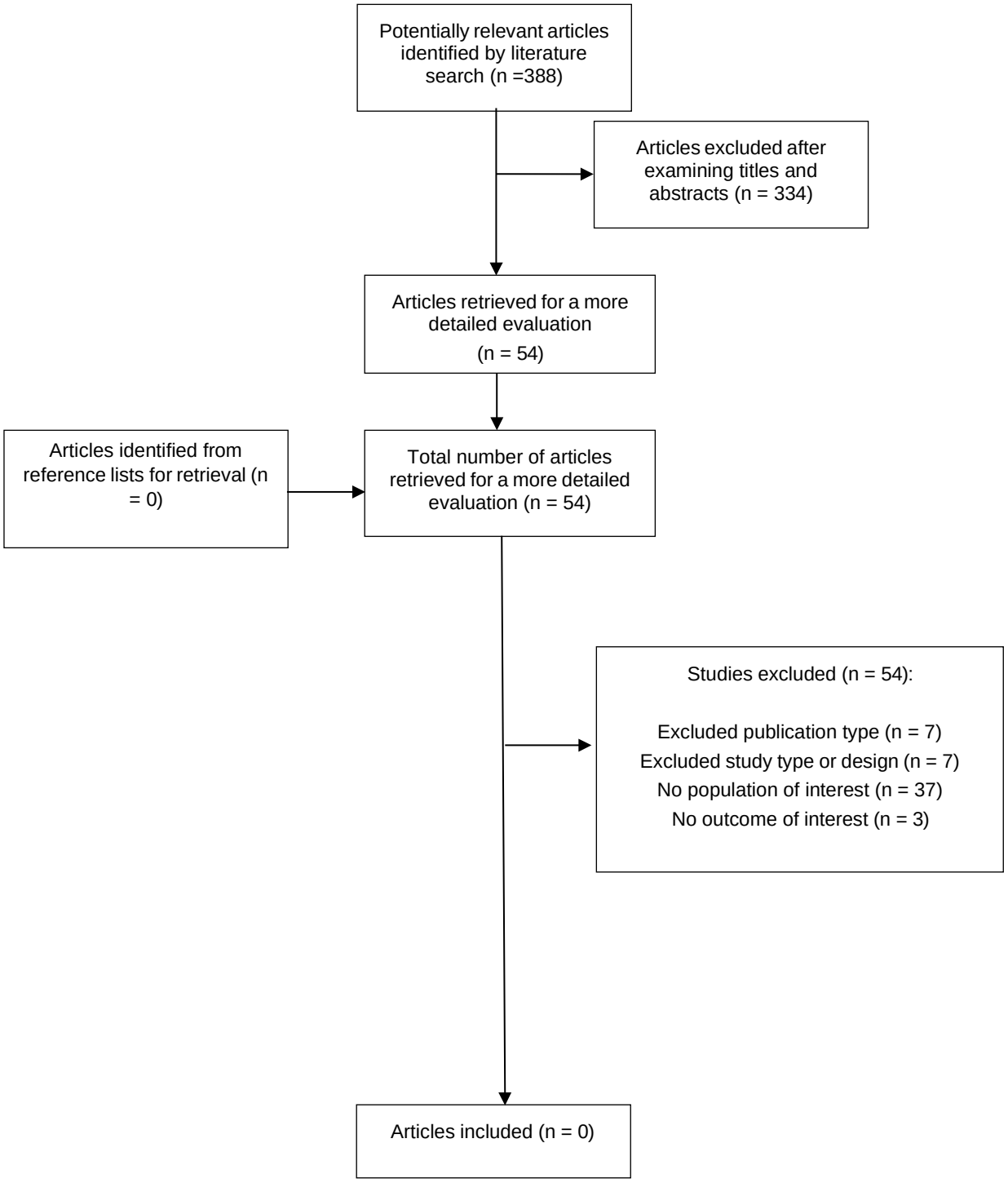


Figure 1. Process of inclusion and exclusion of studies.

Table 3. Evidence summary for HCC surveillance programs amongst Australian residents born in sub-Saharan Africa in Australia.

Evidence summary	GRADE certainty of evidence	References
No studies were identified that evaluated the effects of HCC surveillance on liver cancer outcomes specifically for sub-Saharan born people living in Australia.	Not applicable	

REFERENCES

1. World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2015. 134 p.

2. National Institute for Health and Care Excellence. Hepatitis B (chronic); diagnosis and management. Clinical guideline [CG165] Last updated October 2017 [Internet]. London: NICE; 2013 [cited 2022 Jun 16]. Available from: https://www.nice.org.uk/guidance/cg165

3. National Institute for Health and Care Excellence. Cirrhosis in Over 16s: Assessment and Management. NICE guideline [NG50] [Internet]. London: NICE; 2016 [cited 2021 Dec 8]. Available from: https://www.nice.org.uk/guidance/ng50

4. 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. 2019;13(1):1–1.

5. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018 Apr;67(4):1560–99.

6. Gastroenterological Society of Australia. Hepatocellular Carcinoma Consensus Statement Working Group. Australian recommendations for the management of hepatocellular carcinoma: a consensus statement. [Internet]. Melbourne: Gastroenterological Society of Australia; 2020 [cited 2022 Sep 12]. Available from: https://www.gesa.org.au/resources/hepatocellular-carcinoma-hcc-management-consensus/

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

8. AGREE Next Steps Consortium. The AGREE II Instrument [Internet]. 2017. Available from: http://www.agreetrust.org/resource-centre/agree-ii/

9. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022) [Internet]. Cochrane; 2022. Available from: www.training.cochrane.org/handbook

10. Eldridge S, Campbell MK, Campbell MJ, Drahota AK, Giraudeau B, Reeves BC, et al. Revised Cochrane risk of bias tool for randomized trials (RoB 2) Additional considerations for cluster-randomized trials (RoB 2 CRT) [Internet]. 2021 [cited 2022 Feb 1]. Available from: https://drive.google.com/file/d/1yDQtDkrp68_8kJiIUdbongK99sx7RFI-/view

11. Kirk M, Smurthwaite K, Braunig J, Trevener S, D'Este C, Lucas R, et al. The PFAS Health Study: Systematic Literature Review [Internet]. Canberra: The Australian National University; 2018. p. 161–3. Available from: https://openresearch-repository.anu.edu.au/handle/1885/241032

12. Odnoletkova I, Goderis G, Pil L, Nobels F, Aertgeerts B, Annemans L, et al. Cost-Effectiveness of Therapeutic Education to Prevent the Development and Progression of Type 2 Diabetes: Systematic Review. J Diabetes Metab. 2014;05(09):in appendix.

13. NHMRC. Guidelines for Guidelines: Assessing certainty of evidence [Internet]. 2019. Available from: https://nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence

14. Murad MH, Mustafa RA, Schünemann HJ, Sultan S, Santesso N. Rating the certainty in evidence in the absence of a single estimate of effect. Evid Based Med. 2017 Jun;22(3):85–7.

15. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol. 2011 Dec;64(12):1283–93.

16. Zeng L, Brignardello-Petersen R, Hultcrantz M, Siemieniuk RAC, Santesso N, Traversy G, et al. GRADE guidelines 32: GRADE offers guidance on choosing targets of GRADE certainty of evidence ratings. J Clin Epidemiol. 2021 Sep;137:163–75.

17. Brignardello-Petersen R, Guyatt GH, Mustafa RA, Chu DK, Hultcrantz M, Schünemann HJ, et al. GRADE guidelines 33: Addressing imprecision in a network meta-analysis. J Clin Epidemiol. 2021 Nov;139:49–56.

18. Brunetti M, Shemilt I, Pregno S, Vale L, Oxman AD, Lord J, et al. GRADE guidelines: 10. Considering resource use and rating the quality of economic evidence. J Clin Epidemiol. 2013 Feb;66(2):140–50.

19. Holger Schünemann, Jan Brożek, Gordon Guyatt, Andrew Oxman. GRADE Handbook - Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach [Internet]. 2013 [cited 2022 Apr 26]. Available from: https://gdt.gradepro.org/app/handbook/handbook.html

20. Brozek JL, Canelo-Aybar C, Akl EA, Bowen JM, Bucher J, Chiu WA, et al. GRADE Guidelines 30: the GRADE approach to assessing the certainty of modeled evidence—An overview in the context of health decision-making. J Clin Epidemiol. 2021 Jan;129:138–50.

21. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol. 2004 Jul;130(7):417–22.

22. 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):204–9.

23. 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 May;50(5):990–8.

24. 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. Asian Pac J Cancer Prev. 2014 Nov 6;15(20):8993–9004.

25. Chang Y, Lairson DR, Chan W, Lu SN, Aoki N. Cost-effectiveness of screening for hepatocellular carcinoma among subjects at different levels of risk: Cost-effectiveness of screening for HCC. J Eval Clin Pract. 2011 Apr;17(2):261–7.

26. 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.

27. Farhang Zangneh H, Wong WWL, 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 Aug;17(9):1840-1849.e16.

28. 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 Open. 2021 Jun 24;4(6):e2114680.

29. 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.

30. 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 Health. 2021 Oct;24(10):1454–62.

31. 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 Apr 19;OF1–8.

32. 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 Dec;65(6):1086–93.

33. Parikh ND, Singal AG, Hutton DW, Tapper EB. Cost-Effectiveness of Hepatocellular Carcinoma Surveillance: An Assessment of Benefits and Harms. Am J Gastroenterol. 2020 Oct;115(10):1642–9.

34. 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):1418–24.

35. 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 Apr;98(7):1166–75.

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

37. 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. 2010/06/16 ed. 2010 May;25(5):951–6.

38. 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. Intern Med J. 2013 Jul;43(7):772–7.

39. 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 Feb;1(1):53–60.

40. 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):551–6.

41. Byford S, Raftery J. Economics notes: Perspectives in economic evaluation. BMJ. 1998 May 16;316(7143):1529–30.

42. Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun Wong V, Castellanos M, Aller-de la Fuente R, Metwally M, et al. Fibrosis Severity as a Determinant of Cause-Specific Mortality in Patients With Advanced Nonalcoholic Fatty Liver Disease: A Multi-National Cohort Study. Gastroenterology. 2018 Aug 1;155(2):443-457.e17.

43. 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 Aug;21(8):938–43.

44. Hong TP. An Australian population-based study of the incidence and outcomes of hepatocellular carcinoma: the Hepatomas of Melbourne Epidemiological Research (HoMER) study [Internet]. 2019 [cited 2019 Jul 11]. Available from: http://hdl.handle.net/11343/225659

45. Wallace MC, Preen DB, Short MW, Adams LA, Jeffrey GP. Hepatocellular carcinoma in Australia 1982-2014: Increasing incidence and improving survival. Liver Int. 2019 Mar;39(3):522–30.

46. Nguyen ALT, Si L, Lubel JS, Shackel N, Yee KC, Wilson M, et al. Construction and validation of a microsimulation model for hepatocellular carcinoma surveillance in Australia. In Submission;

47. Alavi M, Law MG, Grebely J, Amin J, Hajarizadeh B, George J, et al. Time to decompensated cirrhosis and hepatocellular carcinoma after an HBV or HCV notification: A population-based study. J Hepatol. 2016 Nov;65(5):879–87.

48. Jepsen P, Vilstrup H, Andersen PK. The clinical course of cirrhosis: The importance of multistate models and competing risks analysis. Hepatology. 2015 Jul 1;62(1):292–302.

49. Canfell K, Kim JJ, Brisson M, Keane A, Simms KT, Caruana M, et al. Mortality impact of achieving WHO cervical cancer elimination targets: a comparative modelling analysis in 78 low-income and lower-middle-income countries. The Lancet. 2020 Feb;395(10224):591–603.

50. Haq MI, Drake TM, Goh TL, Ahmed A, Forrest E, Barclay S, et al. Effect of Hepatocellular Carcinoma Surveillance Programmes on Overall Survival in a Mixed Cirrhotic UK Population: A Prospective, Longitudinal Cohort Study. J Clin Med. 2021 Jun 24;10(13):2770.

51. Consumer Price Index, Australia, March 2022 | Australian Bureau of Statistics [Internet]. 2022 [cited 2022 Jun 12]. Available from: https://www.abs.gov.au/statistics/economy/price-indexes-and-inflation/consumer-price-index-australia/latest-release

52. Department of Health, Australian Government. MBS Online: Medicare Benefits Schedule. [homepage on the internet] [Internet]. Canberra, ACT: Commonwealth of Australia; Available from: http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/Home

53. Xiao Y, Howell J, Gemert C, Thompson AJ, Seaman CP, McCulloch K, et al. Enhancing the hepatitis B care cascade in Australia: A cost-effectiveness model. J Viral Hepat. 2020 May;27(5):526–36.

54. Reeve R, Srasuebkul P, Langton JM, Haas M, Viney R, Pearson SA, et al. Health care use and costs at the end of life: a comparison of elderly Australian decedents with and without a cancer history. BMC Palliat Care. 2017 Jun 21;17(1):1.

55. McPhail SM, Amarasena S, Stuart KA, Hayward K, Gupta R, Brain D, et al. Assessment of health-related quality of life and health utilities in Australian patients with cirrhosis. JGH Open. 2021 Jan;5(1):133–42.

56. Global Burden of Disease Collaborative Network. Global Burden of Disease (GBD 2019) [Internet]. Seattle, United States of America: Institute for Health Metrics and Evaluation (IHME); 2021 [cited 2022 Jun 12]. Available from: https://www.healthdata.org/gbd/2019

57. 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 Jan;44(1):217–31.

58. NSW Cancer Registry. Data request: Hepatocellular carcinoma (coded as C22.0 or C22.9) incidence and mortality). Private communication; unpublished.; 2021 Aug.

59. Tzartzeva K, Obi J, Rich NE, Parikh ND, Marrero JA, Yopp A, et al. Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Patients With Cirrhosis: A Meta-analysis. Gastroenterology. 2018 May 1;154(6):1706-1718.e1.

60. Cheng RM. Novel Biomarkers of Hepatocellular Carcinoma [Internet]. The University of Sydney; 2018. Available from: http://hdl.handle.net/2123/20294

61. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. Circulation. 2016 Feb 9;133(6):601–9.

62. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. Stat Med. 2017 Nov 30;36(27):4391–400.

APPENDICES

Appendix 1: Medline and Embase database (via Ovid platform) search strategy

#	Searches
1	carcinoma, hepatocellular/
2	liver neoplasms/
3	liver cell carcinoma/
4	liver tumor/
5	liver cancer/
6	or/1-5
7	((hepato* or liver or hepatic) adj3 (cancer or carcinoma* or neoplasm* or tumor* or tumour*)).tw.
8	(hepatoma* or hepatocarcinoma* or hcc).tw.
9	or/7-8
10	Early diagnosis/
11	Early detection of cancer/
12	population surveillance/
13	mass screening/
14	cancer screening/
15	disease surveillance/
16	or/10-15
17	screen*.tw.
18	surveil*.tw.
19	17 or 18
20	6 or 9
21	16 or 19
22	20 and 21
23	australia.in.
24	22 and 23
25	limit 24 to english language
26	limit 25 to human
27	limit 26 to yr="2000 -Current"
28	remove duplicates from 27

29	limit 28 to conference abstracts [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) PubMed not MEDLINE,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]
30	limit 29 to medline
31	29 not 30
32	28 not 31

Appendix 2: GRADE assessment of the certainty of the evidence

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Appendix 3: Overview of studies

Excluded studies by DOI

Article	PMID/DOI	Reason for exclusion
Adams 2020	http://dx.doi.org/10.1111/jgh.15009	No population of interest
Bertot 2017	http://dx.doi.org/10.1002/hep4.1018	No population of interest
Carter 2021	https://dx.doi.org/10.1016/j.jval.2021.04.1286	No population of interest
Carville 2012	https://search.informit.org/doi/10.3316/informit.130848966380090	Excluded publication type
Chen 2004	http://dx.doi.org/10.1016/j.jhep.2003.12.002	No population of interest
Chinnaratha 2019	http://dx.doi.org/10.1007/s12029-018-0171-7	No population of interest
El-Atem 2016	http://dx.doi.org/10.1111/imj.13008	No population of interest
Fisher 2003	http://dx.doi.org/10.5694/j.1326-5377.2003.tb05070.x	Excluded study type or design
Frazer 2000	http://dx.doi.org/10.1053/crad.1999.0265	Excluded publication type
Gellert 2007	http://dx.doi.org/10.1111/j.1445-5994.2007.01392.x	No population of interest
George 2018	http://dx.doi.org/10.1111/imj.13973	No population of interest
Hanson 2020	http://dx.doi.org/10.1371/journal.pone.0238719	No population of interest
Harris 2017	http://dx.doi.org/10.1111/1754-9485.12595	No population of interest

Hla 2020	http://dx.doi.org/10.1186/s12939-020-01180-w	No population of interest
Hong 2018	http://dx.doi.org/10.5694/mja18.00373	No population of interest
Huang 2018	http://dx.doi.org/10.1097/MCG.0000000000000916	No population of interest
Jeffrey 2020	http://dx.doi.org/10.5694/mja2.50808	Excluded study type or design
Jeffrey 2020	http://dx.doi.org/10.5694/mja2.50521	Excluded study type or design
Kemp 2005	http://dx.doi.org/10.1111/j.1440-1746.2005.03844.x	No population of interest
Kennedy 2013	http://dx.doi.org/10.1111/imj.12166	No population of interest
Kutaiba 2021	http://dx.doi.org/10.1016/j.jhep.2021.06.041	Excluded publication type
Larcos 2020	https://dx.doi.org/10.5694/mja2.50806	Excluded publication type
Lockart 2021	http://dx.doi.org/10.1111/jvh.13475	No population of interest
Low 2021	https://dx.doi.org/10.4251/wjgo.v13.i12.2149	No population of interest
Maher 2012	http://dx.doi.org/10.1016/S1473-3099%2811%2970355-3	Excluded publication type
Majeed 2019	http://dx.doi.org/10.1053/j.gastro.2018.09.060	No population of interest
Mohsen 2017	https://dx.doi.org/10.3748/wjg.v23.i15.2763	No population of interest
Nazareth 2016	http://dx.doi.org/10.1111/ijn.12472	Excluded study type or design
Nguyen 2021	http://dx.doi.org/10.1016/j.jval.2020.11.014	Excluded study type or design
Nicoll 2002	https://dx.doi.org/10.5694/j.1326-5377.2002.tb04247.x	Excluded study type or design
Parker 2014	http://dx.doi.org/10.5694/mja13.11117	No population of interest
Poustchi 2011	http://dx.doi.org/10.1002/hep.24581	No population of interest
Qian 2010	http://dx.doi.org/10.1111/j.1440-1746.2009.06203.x	No population of interest
Roberts 2006	http://dx.doi.org/10.1111/j.1440-1746.2006.04211.x	Excluded publication type
Roberts 2007	http://dx.doi.org/10.1111/j.1440-1746.2006.04459.x	No outcome of interest
Robotin 2012	https://dx.doi.org/10.3748/wjg.v18.i42.6106	No population of interest
Robotin 2009	http://dx.doi.org/10.1016/j.jhep.2008.12.022	No population of interest
Robotin 2010	http://dx.doi.org/10.1186/1472-6963-10-215	No population of interest
Robotin 2014	http://dx.doi.org/10.2471/BLT.13.130344	Excluded study type or design
Robotin 2018	http://dx.doi.org/10.2147/CLEP.S146275	No population of interest
Roder 2007	https://search.informit.org/doi/10.3316/informit.442837862726536	No population of interest
Rodrigues 2021	http://dx.doi.org/10.1177/1357633X211024108	No population of interest
Sheppard-Law 2018	http://dx.doi.org/10.1111/jocn.14367	No outcome of interest
Sinclair 2013	http://dx.doi.org/10.1111/imj.12068	No population of interest
Subramaniam 2012	http://dx.doi.org/10.1111/j.1445-5994.2011.02711.x	No outcome of interest
Sutherland 2017	http://dx.doi.org/10.1111/1754-9485.12513	No population of interest
Tai 2002	http://dx.doi.org/10.1046/j.1440-1746.2002.02747.x	No population of interest
Taye 2021	http://dx.doi.org/10.1002/jgh3.12580	No population of interest
Thein 2012	http://dx.doi.org/10.1111/j.1872-034X.2012.01037.x	No population of interest

Vongsuvanh 2016	http://dx.doi.org/10.1371/journal.pone.0155800	No population of interest
Wigg 2021	http://dx.doi.org/10.1016/j.eclinm.2021.100919	No population of interest
Wong 2013	http://dx.doi.org/10.1111/j.1445-5994.2012.02755.x	No population of interest
Worland 2017	http://dx.doi.org/10.1007/s12029-017-0006-y	No population of interest
Zeng 2020	http://dx.doi.org/10.1136/gutjnl-2020-321627	Excluded publication type

Appendix D6. Technical report for question 6

Systematic Review Question 6: Does the addition of alpha-fetoprotein testing to 6- monthly ultrasound imaging for HCC surveillance improve liver cancer outcomes?

PICO

This systematic review addresses the PICO shown in Table 6.

Table 6. PICO for systematic review question 6.

Population	Intervention	Comparator	Outcomes	Study design
Adults with cirrhotic or non-cirrhotic liver disease undergoing HCC surveillance	HCC surveillance with 6-monthly ultrasound + AFP	HCC surveillance with 6-monthly ultrasound only	Overall mortality Liver disease-related mortality Liver cancer mortality Proportion of liver cancers that are early stage Cost-effectiveness	Randomised controlled trials Interventional cohort studies Modelling studies Australian non-comparative studies - case series or above study designs with single arm analysis of intervention **or** comparator

AFP = alpha-fetoprotein; HCC = hepatocellular carcinoma

1. METHODS

1.1 Selection Criteria

Table 7. Selection criteria for interventional studies comparing ultrasound surveillance with or without AFP for individuals at higher risk of HCC.

PICO 6	***Inclusion***	***Exclusion***
Study type	Intervention	Diagnostic accuracy Observational
Study design	RCTs and cohort studies (if no RCT evidence) or systematic review thereof Modelling studies Australian non-comparative studies - case series or above study designs with single arm analysis of intervention or comparator	Case-control or no comparator for non-Australian studies Review (not systematic)
Population	≥18 years Adults with cirrhotic or non-cirrhotic liver disease undergoing HCC surveillance	People who have previously undergone treatment for liver cancer Children
Intervention	HCC surveillance with 6-monthly ultrasound + AFP	
Comparator	HCC surveillance with 6-monthly ultrasound only	No comparator for non-Australian studies Historical control

Outcome	*Actual or state transition-modelled:* Overall mortality – adjusted analyses if cohort study Liver-related mortality - adjusted analyses if cohort study HCC/liver cancer specific mortality – adjusted analyses if cohort study % early/treatable stage HCC or liver cancer at diagnosis Cost-effectiveness (cost per QALY, DALY or life-years gained) based on state transition modelling, RCT or adjusted cohort study results	Mortality outcome and unadjusted analyses if cohort study Cancer incidence Costs only, costs per life saved Incremental cost of additional early-stage diagnosis Based on case-control study or paired cohort study results
Publication date/timeframe	2000 onwards	
Publication type	Original journal article Letter or comment that reports original data	Conference abstracts Editorials Letters and comments that do not report original data
Language	English	

AFP = alpha-fetoprotein; DALY = disability adjusted life years; HCC = hepatocellular carcinoma; QALY = quality-adjusted life years; RCTs = randomised controlled trials
[a] Hepatocellular carcinoma is the liver cancer of primary interest.
[b] Where the outcome reported is liver cancer it is assumed that most of the cancers are HCC.
[c] Chronic HBV infection, chronic HCV infection, alcohol-related liver disease and metabolic-associated fatty liver disease are the aetiologies of interest.
[d] Modelling studies were restricted to state-transition models.

1.2 Definitions and terminology

For the purpose of this review:

Compensated cirrhosis included Child-Pugh Class A cirrhosis

Early-stage HCC includes Barcelona Clinic Liver Cancer (BCLC) stage 0/A, meeting Milan criteria, or China Liver Cancer Study group stage I:

1. *The Barcelona Clinic Liver Cancer (BCLC*) staging classification system assesses the number and size of liver tumours, overall performance status (ECOG PS) and liver function (using Child-Pugh classification):
    a. BCLC stage 0 (very early stage); ECOG performance score = 0, Child-Pugh A, single tumour < 20mm;
    b. BCLC stage A (early stage); ECOG performance score = 0, Child-Pugh A-B, single tumour of any size or up to 3 tumours all < 30mm).
2. *The Milan criteria* focus on liver transplantation eligibility. Those eligible for transplantation are described as within Milan criteria and are defined as having one tumour measuring ≤ 50 mm in diameter, or 2-3 tumours ≤ 30 mm in diameter without vascular extension or metastasis.

3. The *China Liver Cancer study group staging* system classifies HCC as stage I (subclinical stage/early stage) if there are no obvious cancer symptoms and signs (tumour usually < 5 cm in diameter).

Where results were given by BCLC stage and another staging system, the BCLC results were presented.

Metabolic-associated fatty liver disease includes non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).

1.3 Guidelines

Relevant recent (2015 onwards) guidelines, were identified by scanning the citations identified by the literature search (described below) and a summary of these guidelines was reviewed by Expert Advisory Group members as part of Phase 1 of the *Roadmap to Liver Cancer Control* project.

To be considered for adoption by the Working Group, guidelines had to be evidence-based and meet the pre-specified criteria of scores of greater or equal to 70% for the following domains: rigour of development, clarity of presentation, and editorial independence of the AGREE II instrument (8). Guidelines were not considered for adoption by the Working Group if they were not based on systematic reviews of the evidence, i.e. did not report using systematic methods to search for evidence, did not clearly describe the criteria for selecting the evidence or did not assess the risk of bias or where this is not possible, appraise the quality of the evidence.

1.4 Literature searches

Medline (including MEDLINE Epub Ahead of Print, I-Process & Other Non-Indexed Citations) and Embase, databases were searched on 1 February 2022 combining text terms and/or database-specific subject headings for liver cancer, surveillance, HCC, ultrasound, and Australia. Searches were limited to articles published in English from 1 January 2000 onwards. A complete list of the terms used is included as Appendix 1. The Cochrane Database of Systematic Reviews was searched on 31 March 2022 combining the search terms “liver cancer” and “screen” or “surveillance” or “ultrasound”. Reference lists of included articles, recent relevant guidelines and systematic reviews were checked for potential additional articles.

1.5 Data extraction and analyses

For cost-effectiveness studies, if the cost-effectiveness ratio (CER) was not reported for the comparison of interest it was calculated using the reported costs and outcomes for the intervention and the comparator if this data were available. For the modelled outcomes of

mortality and percentage liver cancer 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. In this report, a narrative synthesis for each of the outcomes was undertaken as it was anticipated based on a previous scoping review that results for each outcome would likely be heterogenous and pooling of results was not considered appropriate for cost-effectiveness analyses.

1.6 Quality appraisals

The quality of cost-effectiveness studies was assessed using a modified version of the CHEC-extended checklist (12). This tool appraises the specification of the population, interventions and comparators modelled, the modelling and cost-effectiveness methods, and the robustness and fitness for purpose of the model. Unlike a risk of bias assessment tool, its focus is not the critical assessment of the sources of bias. However, some of the questions do inform an assessment of the risk of bias and thus whether the results are likely to reflect the true effect of the intervention. Assessments for some of the CHEC-extended checklist questions were used to inform GRADE assessments of modelled studies, including the risk of bias.

Single arm studies do not provide evidence of effect and thus are not part of the evidence base for any recommendations. Consequently, we did not assess the risk of bias of single arm studies.

1.7 GRADE assessment of the certainty of the evidence

A GRADE approach was used to assess the certainty of the body of evidence for the effect of surveillance when compared with no surveillance for each outcome (13).

For non-modelling studies, the certainty of the body of evidence was rated high, moderate, low or very low based on assessment of risk of bias, indirectness of the results, imprecision (width of 95% confidence intervals) of the results, inconsistency or heterogeneity of the results, and publication bias based on guidance for assessing narrative syntheses provided by Murad 2017 and additional guidance for the assessment of imprecision provided by Guyatt 2011, Zeng 2021 and Brignardello-Petersen 2021 (14–17). For the assessment of imprecision, any decrease in mortality was considered clinically important, and an increase of at least 5 percentage points in the percentage of liver cancer diagnosed at an early stage was considered clinically important. As per GRADE guidance, studies started with a high level of certainty in the evidence and were downgraded in a stepwise manner from *high* to *moderate* to *low* to *very low* if there were serious concerns regarding risk of bias,

indirectness, imprecision, inconsistency and/or publication bias. The exception was observational cohort studies which started with a low level of certainty and were downgraded if there were serious concerns or upgraded if the effect estimate was large (greater than 2.0 or less than 0.5), presence of a dose response gradient, or when plausible residual confounders increased certainty. Where there was only one study, inconsistency could not be rated.

GRADE was originally designed to assess the certainty of the results of a meta-analysis of the evidence for interventions from randomised controlled trials however, for results from modelling studies, GRADE assessments were not recommended (18,19). However, the NHMRC GRADE Working Group has recently changed their position as outlined in Brozek 2021 (20) and has provided a general approach to the GRADE assessment of modelling studies with more specific guidance planned but not published as at May 2022. In the absence of specific criteria, we assessed the risk of bias, indirectness and inconsistency of the evidence from each study based on the general principles explained by Brozek 2021 (20); downgrading from an initial high level of certainty if there were serious concerns. Downgrading was based on an assessment of the level of concern for each of following issues: risk of bias, indirectness and inconsistency. Assessments ranged from no serious concerns (no downgrade), serious concerns (downgrade by one level) or very serious concerns (downgrade by two levels). The certainty of the body of evidence for each outcome was then rated as either high, moderate, low or very low based on the degree of downgrading. We did not assess imprecision based on reported results of probabilistic sensitivity analyses or other sensitivity analyses as currently these types of analyses are designed to assess sensitivity to changes in variable values, rather than imprecision. Assessment of publication bias for individual studies was not applicable as all studies reported results of models developed de novo.

We then assessed the certainty of the body of the evidence by assessing the risk of bias, indirectness, inconsistency and publication bias across all studies based on the principles explained by Brozek 2021 (20). As we could not assess imprecision we presented two final assessments of the certainty of the evidence, where one is conservative (downgraded for imprecision) and one is not adjusted for imprecision). This was done so that GRADE assessments could be compared with those of other study designs. Similarly, as for non-modelled studies, where there was only one study inconsistency could not be rated.

Definitions of the GRADE ratings of certainty are presented in Appendix 2.

2. RESULTS

2.1 Guidelines searches

Two sets of guidelines based on systematic reviews were identified that contained potentially relevant recommendations; the *American Association for the Study of Liver Diseases (AASLD) Guidelines for the treatment of hepatocellular carcinoma* (4)) and the *UK National Institute for Health and Care excellence (NICE) 2016 Guidelines on cirrhosis in over 16s: Assessment and Management* (3). Both recommended 6-monthly ultrasound with or without AFP. The AADSL guidelines found that there were no studies comparing 6-monthly ultrasound and AFP surveillance and with 6-monthly ultrasound surveillance only. The NICE guidelines did not attempt to address this question.

2.2 Literature searches

Figure 1 outlines the process of identifying relevant articles for this systematic review. The combined Medline and Embase search identified 1961 citations and the search of the Cochrane Database of Systematic Reviews 39 citations, resulting in a total of 2000 citations. Titles and abstracts were examined, and 102 articles were retrieved for a more detailed evaluation. An additional 21 potential citations were identified from the reference lists of included articles, recent relevant guidelines, and systematic reviews.

Ten studies reported in ten articles met the inclusion criteria and were included in the review; four comparative studies reporting cost-effectiveness outcomes (four modelling studies) and six non-comparative Australian studies reporting the proportion of liver cancers that are early stage, or mortality-related outcomes (two case-series, one modelling study, two retrospective and one prospective cohort studies with single arm analysis of intervention or comparator). No RCTs or comparative interventional cohort studies meeting inclusion criteria were identified.

The retrieved articles that were not included and the reasons for their exclusion are documented in Appendix 3. In summary, most articles were excluded because they did not report an intervention of interest (n = 45), or they were an excluded publication type (n = 25).

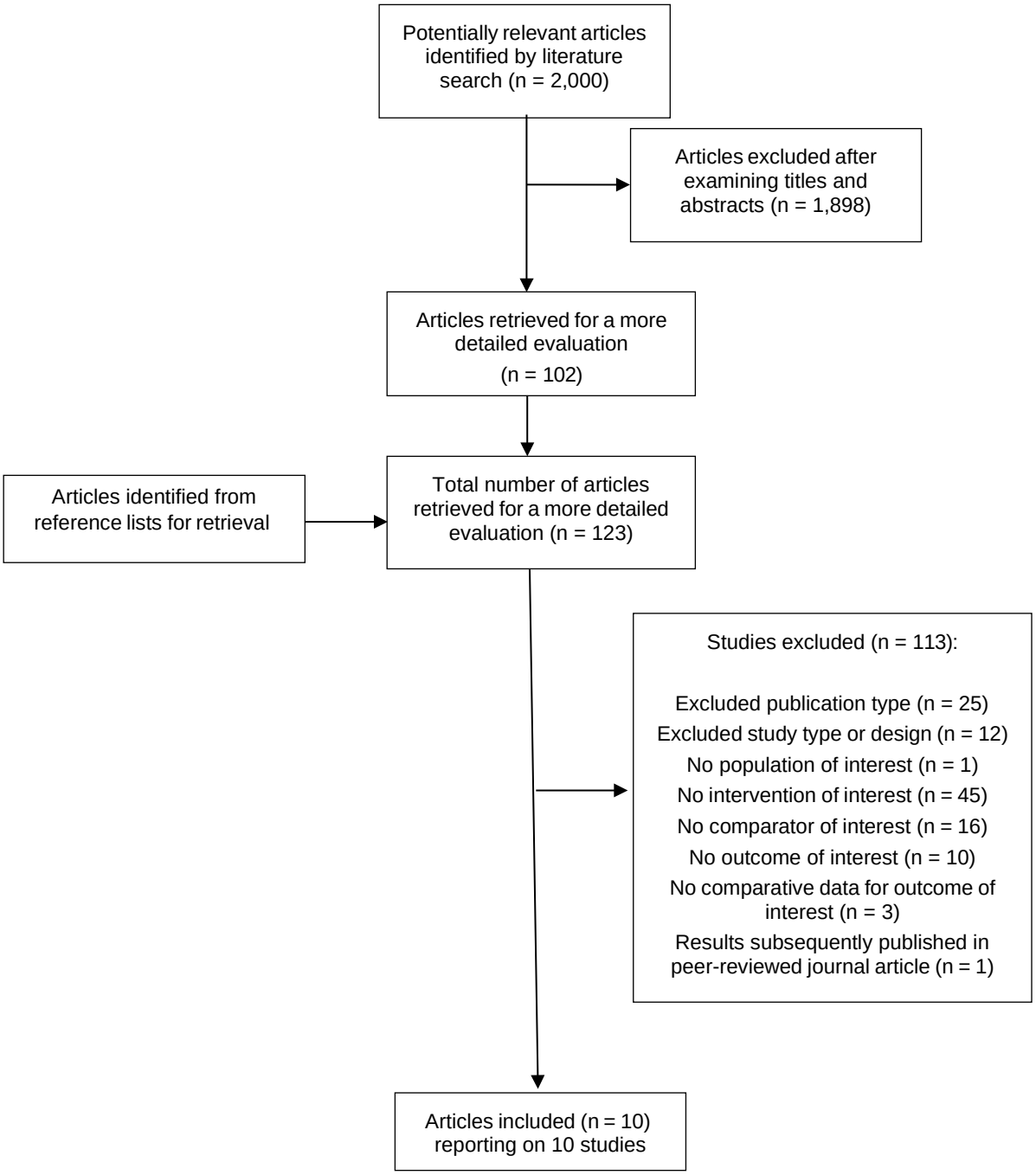


Figure 1. Process of inclusion and exclusion of studies.

2.3 Characteristics and results of included studies

2.3.1 Comparative studies: Study characteristics

The characteristics of the four comparative studies comparing 6-monthly ultrasound + AFP with 6-monthly ultrasound only surveillance are described in Table 3.

Table 8. Study characteristics of studies comparing 6-monthly ultrasound + AFP with 6-monthly ultrasound only surveillance.

Study (Country)	Study design	Population	Participants	Intervention	Comparison	Cycle length	Follow-up	Outcomes	Conflicts of interest considered
Sangmala 2014 (24) (Thailand)	Model (Markov) Not validated	Patients with chronic HBV infection (HBsAg positive – active carriers) aged 40 years at start Time period: NR Excluded patients with HCC detected at baseline: NR	N = NR Age: 40 years at start Male: NR Cirrhotic: NR (% compensated: NR) Aetiology: HBV Treated for viral hepatitis: 0% HCC incidence: NR	**6-monthly US + AFP surveillance** AFP cut-off: > 20ng/ml Compliance (not defined): Unclear	**6-monthly US surveillance** Compliance (not defined): Unclear	6 months	Time horizon: Lifetime	Cost/QALY gained	No – Authors acknowledge funders
Parikh 2020 (33) (USA)	Model (Markov - microsimulation) Not validated	Patients with compensated cirrhosis Age: NR Time period: NR Excluded patients with HCC detected at baseline: NR	N = 1,000,000 Age: NR Male: NR Cirrhotic: 100% (100% compensated) Aetiology: NR Treated for viral hepatitis: NR HCC incidence: 2% per year	**6-monthly US + AFP surveillance** AFP cut-off: NR Adherence (not defined): 100%	**6-monthly US surveillance** Adherence (not defined): 100%	NA	Time horizon: Lifetime	Cost/QALY gained Overall mortality % Early-stage HCC	Yes - Authors report potential competing interests – 3 of 4 authors been on advisory boards and consultants to test manufacturing companies
Andersson 2008 (34) (USA)	Model (Markov) Not validated	Patients with compensated cirrhosis aged 50 years at start Time period: NR Excluded patients with HCC detected at baseline: NR	N = NR Age: 50 years at start Male: NR Cirrhotic: 100% (100% compensated) Aetiology: NR Treated for viral hepatitis: NR	**6-monthly US + AFP surveillance** AFP cut-off: > 20ng/ml Compliance (not defined): 100%	**6-monthly US surveillance** Compliance (not defined): 100%	NR	Time horizon: Lifetime	Cost/QALY gained	Yes - Authors report no conflicts of interest to declare

			HCC incidence: 5% per year						
Thompson Coon 2008 (35) (UK)	Model (Markov) Not validated	Patients with compensated cirrhosis aged ≤ 70 years Time period: NR Excluded patients with HCC detected at baseline: NR	N = NR Age: ≤ 70 years Male: NR Cirrhotic: 100% (100% compensated) Aetiology: Mixed 58% ARLD, 7% HBV, 35% HCV **3 subpopulations** ARLD patients: N = NR Mean age: 53 years at start Male: 70% HCC incidence: 1.7% per year HBV patients: N = NR Mean age: 44 years at start Male: 87% Treated for HBV: NR HCC incidence: 2.2% per year HCV patients: N = NR Mean age: 54 years at start Male: 58% Treated for HCV: NR HCC incidence: 3.7% per year	**6-monthly US + AFP surveillance** AFP cut-off: ≥ 400ng/ml Compliance (not defined): 100%	**6-monthly US surveillance** Compliance (not defined): 100%	1 month	Time horizon: Lifetime	Cost/QALY gained	No – Authors acknowledge funders

AFP = alpha-fetoprotein; ARLD = alcohol-related liver disease; HCC = hepatocellular carcinoma; HBV = chronic hepatitis B; HCV = chronic hepatitis C; HBsAg = serum hepatitis B surface antigen; MAFLD = metabolic-associated fatty liver disease; NR = not reported; QALY = quality-adjusted life years; US = ultrasound

2.3.2 Comparative studies: Results

The results of the four comparative studies comparing 6-monthly ultrasound + AFP with 6-monthly ultrasound only surveillance are described by outcome of interest as follows:

1. Proportion of liver cancers diagnosed at an early stage – results are shown in Table 4.
2. Overall mortality – results are shown in Table 5.
3. Liver cancer mortality – no results found.
4. Liver disease-related mortality – no results found.
5. Life-years, quality-adjusted life-years or disability-adjusted life-years gained – no results found.
6. Cost-effectiveness – results are shown in Table 6.

Table 9. Results for studies comparing HCC 6-monthly US + AFP with 6-monthly US only surveillance – proportion of HCC that are early stage.

Study (Liver disease)	Study design	Outcome	Outcome metric	Follow-up	6-monthly US + AFP	6-monthly US
Parikh 2020 (33) (Cirrhotic)	Model (Markov)	Early-stage HCC (% HCC that met Milan criteria)	% total HCC	Lifetime	91%	83%

AFP = alpha-fetoprotein; HCC = hepatocellular carcinoma; US = ultrasound

Table 10. Results for studies comparing HCC 6-monthly US + AFP with 6-monthly US only surveillance – overall mortality.

Study (Liver disease)	Study design	Outcome	Outcome metric	Follow-up	6-monthly US + AFP	6-monthly US
Parikh 2020 (33) (Cirrhotic)	Model (Markov)	Overall mortality	Survival	Lifetime	10.9 years	10.8 years

AFP = alpha-fetoprotein; HCC = hepatocellular carcinoma; US = ultrasound

Table 11. Results for studies comparing HCC 6-monthly US + AFP with 6-monthly US only surveillance – cost-effectiveness analyses.

Study (Liver disease)	Economic perspective	Discount rate	Costs currency and year	Medical costs included	Evidence bases for effectiveness of surveillance technology	Clinical effect	Willingness to pay threshold/ indicative benchmark used	CER	Probabilistic sensitivity analysis	Two or three largest sources of uncertainty
Sangmala 2014 (24)	Societal	3% pa for costs and	Thai Baht (THB) 2013	Surveillance Diagnostic investigations	Sensitivity and specificity of US (64% and 97%)	0.41 QALY gained per person with	160,000 THB per	~125,000 THB per	Yes but not for	NR for comparison of interest

(HBV – cirrhotic and non-cirrhotic)		health outcomes		Early-stage treatments including transplantation and ablation TACE Chemotherapy Palliative care HCC follow-up	and AFP (49% and 92%) Proportions of surveillance detected HCC and non-surveillance-detected HCC undergoing different treatments	the addition of AFP	QALY gained	QALY gained* **AFP + US cost effective when compared with US only**	comparison of interest	Reported for 6-monthly US surveillance: costs of liver transplantation and palliative care, and HCV utility
Parikh 2020 (33) (Cirrhotic)	Payer's	3% pa	US dollar (US$) 2018	Surveillance Diagnostic investigations Early-stage treatments including transplantation and ablation TACE SBR Chemotherapy Palliative care HCC follow-up	Sensitivity *US+AFP:* HCC met Milan criteria 63% HCC did not meet Milan criteria 97% *US* HCC met Milan criteria 45% HCC did not meet Milan criteria 84% Specificity *US+AFP:* 84% *US:* 91% Probabilities of disease progression	0.02 QALY gained per person with the addition of AFP	US$100,000 per QALY gained	AFP + US dominates US alone i.e. is more effective with lower costs	Yes Probability US+AFP most preferred: 80.3%	Reports model sensitive to changes in sensitivity of ultrasound and the incidence of HCC in decompensated cirrhosis
Andersson 2008 (34) (Cirrhotic)	Payer's (health system)	Discounted costs and health outcomes rate NR	US dollar (US$) 2004	Surveillance Diagnostic investigations Early-stage treatments including transplantation and ablation Palliative care HCC follow-up	Sensitivity and specificity of US (75% and 95%) and AFP (60% and 87%) Tumour doubling time of 117-195 days	0.03 QALY gained per person (discounted) with the addition of AFP	US$50,000 per QALY gained	US$73,500 per QALY gained **AFP + US not cost effective when compared with US only**	No	NR specifically states if US sensitivity < 65% or AFP specificity >95% US + AFP is preferred
Thompson Coon 2008 (35) (Cirrhotic Mixed, ARLD, HBV or HCV)	Payer's (health system)	3.5% pa for costs and QALYs	British pound (£) 2004-2005	Surveillance Diagnostic investigations Early-stage treatment including transplantation but not ablation	Probability of detection by US, AFP and incidentally or on symptomatic presentation of small, medium and large HCCs	QALY gained per person with the addition of AFP Mixed 0.017 HBV 0.052 HCV 0.019	£30,000 per QALY gained	£/QALY ** gained per person with the addition of AFP Mixed 29,000 HBV 12,000	Yes but not for comparison of interest	NR for comparison of interest Reports model sensitive to changes in tumour growth rate, mortality

				Ablation and TACE for advanced disease HCC follow-up	and proportions of treatments for each HCC size	ARLD 0.011		HCV 32,000 ARLD 36,000 **AFP + US cost effective when compared with US only for patients with HBV or patients without specified aetiology**		following transplant and excess mortality associated with undiagnosed large tumours and discount rates

~ approximately; AFP = alpha-fetoprotein; ARLD = alcohol-related liver disease; CER = cost-effectiveness ratio; HCC = hepatocellular carcinoma; HBV = chronic hepatitis B; HCV = chronic hepatitis C; MAFLD = metabolic-associated fatty liver disease; NA = not applicable; NR = not reported; pa = per annum; QALY = quality-adjusted life years; TACE = transarterial chemoembolisation; US = ultrasound

**Calculated by review team from data in Sangmala 2014 Table 2 rounded to first 3 digits*

***Calculated by review team from data in Thompson-Coon 2008 Table 5 rounded to first 2 digits*

2.3.3 Non-comparative studies: Study characteristics and results

The characteristics and results of the six Australian non-comparative studies with 6-monthly ultrasound + AFP surveillance or 6-monthly ultrasound only surveillance are described in Table 7. Outcomes of interest are described for these studies as follows:

1. Proportion of liver cancers diagnosed at an early stage – results are shown in Table 7.
2. Overall mortality – results are shown in Table 7.
3. Liver cancer mortality – results are shown in Table 7.
4. Liver disease-related mortality – no results found.
5. Life-years, quality-adjusted life-years or disability-adjusted life-years gained – not applicable.
6. Cost-effectiveness – not applicable.

Table 12. Study characteristics and descriptive results of non-comparative Australian studies for 6-monthly ultrasound + AFP surveillance or for 6-monthly ultrasound only surveillance.

Study (Country/State)	Study design	Population	Participants	Intervention	Follow-up	% Early stage HCC	HCC mortality rate per 100 participants	Liver disease mortality rate per 100 participants	Overall mortality rate per 100 participants	Survival
6-monthly US + AFP surveillance										
Nazareth 2016 (36) (Western Australia)	Retrospective case-series	**Patients with cirrhosis or advanced fibrosis** referred to Nurse-Led HCC Surveillance Clinic at Royal Perth Hospital between 2009-2015 Excluded patients with HCC detected at baseline: NR	N = 76 Mean age: 57 years Male: 74% Cirrhotic: 58% (Child Pugh A: 97.3%) Aetiology: Mixed 92.1% HCV, 2.6% HBV, 2.6% NASH, 2.6% ARLD Treated for viral hepatitis: Yes HCC incidence: NR	**6-monthly US + AFP surveillance** AFP cut-off: 11KIU/L Participation rate: 92.7%* Adherence: 65% averaging an US every 7 months**	Ongoing at time of publication	NR	1.3	NR	NR	NA
Qian 2010 (37)(Victoria)	Retrospective case-series	**Patients** of any age **with cirrhosis and male non-cirrhotic patients with HBV aged >40 years** who underwent HCC surveillance at Austin hospital Melbourne between 1998-2004 Excluded patients with HCC detected at baseline: Yes	N = 268^ Mean age: 57.1 years Male: 69% Cirrhotic: 89% (% compensated/ Child Pugh A: NR) Aetiology: Mixed 34% HCV, 22% ARLD, 19% HBV, 2% NASH Treated for viral hepatitis: NR HCC incidence: 2.7%	**6-monthly US + AFP surveillance** AFP cut-off: NR Adherence: Median interval between surveillance rounds: US: 6.5 months AFP: 4.0 months	Mean: 3 years	77% met Milan criteria 80% HCV met Milan criteria 63% HBV met Milan criteria 100% ARLD met Milan criteria	4.1	NR	14.2^^	NA
Kennedy 2013 (38) (South Australia)	Prospective cohort – single arm analysis	**Patients with HBV or HCV** who underwent HCC surveillance at Flinders Medical Centre Adelaide in 2007-2009 Excluded patients with HCC detected at baseline: NR	N = 114 Mean age: 52 years Male: 75% Cirrhotic: 97% (Child Pugh A: NR) Aetiology: 84% HCV, 16% HBV Treated for viral hepatitis: NR HCC incidence: NR	**6-monthly US + AFP surveillance** AFP cut-off: NR Adherence (Four complete cycles of US + AFP over 2 years): 64% of mean 20 patients audited	3.5 years	75% non-advanced disease who received curative treatment (n=3/4) *Assumed no HCC diagnosed outside of program*	NR	NR	NR	NA
6-monthly US only surveillance										

Carter 2021 (30) (Australia)	Model (Markov) - single arm analysis	**Patients with compensated cirrhosis** with mean starting age of 50 years Time period: NR Excluded patients with HCC detected at baseline: NA	N = NR Mean age: 50 years at start Male: NR Cirrhotic: 100% (100% compensated) Aetiology: Mixed Treated for viral hepatitis: NR HCC incidence: 1.51%	**6-monthly US surveillance** Adherence/participation: NR	Time horizon: 20 years	75.3% BCLC stage 0/A	9.45	NR	NR	NA
Bertot 2017(39) (Western Australia)	Retrospective cohort – single arm analysis	**Patients with cirrhosis** related to **NAFLD** who underwent HCC surveillance at Sir Charles Gairdner Hospital in Nedlands between 2009-2015. Excluded patients with HCC detected at baseline: Yes	N = 49 Mean age: NR Male: NR Cirrhotic: 100% (% compensated/Child Pugh A: NR) Aetiology: MAFLD HCC incidence: NR	**6-monthly US surveillance** Participation: NR Adherence: NR	Median: 5.9 years	50% BCLC stage A	NR	NR	NR	NA
Huang 2018 (40) (Western Australia)	Retrospective cohort – single arm analysis	**Patients diagnosed with HCC** at Sir Charles Gairdner Hospital Nedlands between 2006-2014 who underwent surveillance for ≥ 1 year prior to diagnosis Excluded patients with HCC detected at baseline: Yes	N = 128 Mean age: 60 years Male: 77% Cirrhotic: 94%% (Child Pugh A: 71%) Aetiology: Mixed 41% HCV, 15% HBV, 19% ARLD, 14% ARLD + viral hepatitis, 6% MAFLD Treated for viral hepatitis: NR HCC incidence: NA	**6-monthly US surveillance** Adherence/participation: NR	Mean: 2.3 years	81% BCLC stage 0/A 59% BCLC stage A	NA	NR	NR	Median: 52 months

AFP = alpha-fetoprotein; ARLD = alcohol-related liver disease; BCLC = Barcelona Clinic Liver Cancer; HCC = hepatocellular carcinoma; HBV = hepatitis B viral infection; HCV = hepatitis C viral infection; MAFLD = metabolic-associated fatty liver disease; NA = not applicable; NASH = non-alcoholic steatohepatitis; NR = not reported; QALY = quality-adjusted life years; US = ultrasound
**Nazareth 2016: Excludes four patients without medical records available*
***Nazareth 2016: Of the 62 patients that attended at least one follow-up after initial US*
^Qian 2010: One HCC with cryptogenic aetiology was not included in analyses
^^Qian 2010: Denominator includes 29 patients that were lost to follow-up (including one patient with HCC) or discharged

2.4 Critical appraisal assessments

The results of the quality appraisal of the included modelling studies are shown in Table 8.

Table 13. Quality appraisal for cost-effectiveness outcome using the CHEC-Extended (modified) tool.

Checklist question	**Andersson 2008**(34) **Cost/QALY gained**	**Thompson-Coon 2008**(35) **Cost/QALY gained**	**Sangmala 2014**(24) **Cost/QALY gained**	**Parikh 2020**(33) **Cost/QALY gained**	**Parikh 2020**(33) **% Early-stage HCC**	**Parikh 2020**(33) **Overall mortality**
1. Is the study population *clearly* described?	No	No	No	No	No	No
2. Are competing alternatives *clearly* described?	Yes	Yes	Yes	No	No	No
3. Is a *well-defined* research question posed in answerable form?	Yes	Yes	Yes	Yes	Yes	Yes
4. Is the economic study design *appropriate* to the stated objective?	Yes	Yes	Yes	Yes	Yes	Yes
5. Are the structural assumptions and the validation methods of the model properly reported?	Yes	Yes	Yes	Yes	Yes	Yes
6. Is the chosen time horizon *appropriate* in order to include relevant costs and consequences?	Yes	Yes	Yes	Yes	Yes	Yes
7. Are *all important and relevant* costs for each alternative identified?	No	No	Yes	Yes	NA	Yes
8. Are all costs measured *appropriately* in physical units?	Yes	Yes	Yes	Yes	NA	NA
9. Are costs valued *appropriately*?	No	Yes	Yes	Yes	NA	NA
10. Are *all important and relevant* outcomes for each alternative identified? Does the study report costs per life-years, QALYs or DALYs?	Yes	Yes	Yes	Yes	NA	NA
11. Are all outcomes measured *appropriately*? Do the authors critically appraise sources of data underpinning effect of surveillance?	No	No	No	No	No	No
12. Are outcomes valued *appropriately*?	No	Yes	Yes	Yes	NA	NA
13. Is *an appropriate* incremental analysis of costs and outcomes of alternatives performed?	Yes	Yes	Yes	Yes	NA	NA
14. Are all future costs and outcomes discounted *appropriately*?	No	Yes	Yes	No	NA	NA
15. Are all important variables, whose values are uncertain, *appropriately* subjected to sensitivity analysis? Was a probabilistic sensitivity analysis undertaken?	No	Yes	Yes	Yes	Yes	Yes
16. Does the article/report indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Yes	No	No	Yes	Yes	Yes

DALY = disability-adjusted life years; NA = not applicable; QALY = quality-adjusted life years

3. GRADE ASSESSMENT OF THE CERTAINTY OF THE EVIDENCE

Proportion of liver cancers diagnosed at an early stage – assessments are shown for individual study in Table 9 (Parikh 2020) and overall in Table 11.

Overall mortality – assessments are shown for individual study in Table 9 (Parikh 2020) and overall in Table 11.

Liver cancer mortality – no results found.

Liver disease-related mortality – no results found.

Life-years, quality-adjusted life-years or disability-adjusted life-years gained – no results found.

Cost-effectiveness – assessments are shown for individual studies in Table 9. The overall assessment for a chronic hepatitis B population is shown in Table 10 and for cirrhotic populations in Table 12.

Table 14. GRADE assessment of the certainty of the evidence for modelled outcomes for individual studies.

Study and outcome		***GRADE domains***				***Certainty of evidence***
		Risk of bias	***Indirectness***	***Imprecision***	***Inconsistency***	
Sangmala 2014(24) Cost effectiveness	*Rating*	Serious concerns (-1)	No serious concerns	Not assessable	No serious concerns	Moderate
	Reason for rating	Authors do not critically appraise sources of data underpinning effect of surveillance	Does not report sex or proportion of HBV patients undergoing antiviral treatment for population of interest although not a serious concern for indirectness		PSA undertaken	
Parikh 2020(33) Cost effectiveness, overall mortality and % HCC early-stage disease at diagnosis	*Rating*	Serious concerns (-1)	Serious concerns (-1)	Not assessable	No serious concerns	Low
	Reason for rating	Authors do not critically appraise sources of data underpinning effect of surveillance	AFP threshold not reported		PSA undertaken	
Andersson 2008(34) Cost effectiveness	*Rating*	Very serious concerns (-2)	No serious concerns	Not assessable	No serious concerns	Low
	Reason for rating	Authors do not critically appraise sources of data underpinning effect of surveillance and some important medical treatments not included in model	Does not report age, sex or aetiology for population of interest although not a serious concern for indirectness		PSA not undertaken. Appear to use pooled estimates (multiple citations for same parameter) heterogeneity estimates not considered however sensitivity analyses performed for all model parameters	

Thompson Coon 2008(35) Cost effectiveness	*Rating*	Very serious concerns (-2)	No serious concerns	Not assessable	No serious concerns	Low
	Reason for rating	Authors do not critically appraise sources of data underpinning effect of surveillance and some important medical treatments not included in model	Does not report sex for population of interest although not a serious concern for indirectness		PSA undertaken	

AFP = alpha-fetoprotein; HCC = hepatocellular carcinoma; PSA = probabilistic sensitivity analysis

Table 15. GRADE assessment of the certainty of the body of evidence for the outcome of cost-effectiveness – Chronic hepatitis B population.

GRADE domains	***Rating***	***Reasons for downgrading***	***Certainty of evidence***
Outcome: **Cost effectiveness**			
Risk of bias	Serious concerns (-1)	Data underpinning effect of surveillance not critically appraised	Moderate to low
Indirectness	No serious concerns	Single study which reports AFP threshold	
Imprecision	Not assessable	Not possible to assess	
Inconsistency	Not assessable	No serious concerns re model inconsistency however only one study so overall inconsistency cannot be assessed	
Publication bias	Undetected	Single study	

AFP = alpha-fetoprotein

Table 16. GRADE assessment of the certainty of the body of evidence for the modelled outcomes of overall mortality and proportion of HCC diagnosed at an early stage - Cirrhotic population.

GRADE domains	***Rating***	***Reasons for downgrading***	***Certainty of evidence***
Outcome: **Overall mortality and proportion HCC diagnosed at an early stage**			
Risk of bias	Serious concerns (-1)	Data underpinning effect of surveillance not critically appraised	Low to very low
Indirectness	Serious concerns (-1)	Single study which did not report an AFP threshold	
Imprecision	Not assessable	Not possible to assess	
Inconsistency	Not assessable	No serious concerns re model inconsistency however only one study so overall inconsistency cannot be assessed	
Publication bias	Undetected	Single study	

AFP = alpha-fetoprotein

Table 17. GRADE assessment of the certainty of the body of evidence for the outcome of cost-effectiveness - Cirrhotic population.

GRADE domains	***Rating***	***Reasons for downgrading***	***Certainty of evidence***
Outcome: **Cost- effectiveness**			
Risk of bias	Very serious concerns (-2)	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(34); Thompson Coon 2008(35))	Low to very low
Indirectness	No serious concerns	Only one of the three studies (Parikh 2020(33)) did not report an AFP threshold	
Imprecision	Not assessable	Not possible to assess	

Inconsistency	No serious concerns	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(34)). 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.	
Publication bias	Undetected	The result varied with the addition of AFP to ultrasound; more effective and less expensive in one study (Parikh 2020(33)), cost effective for some but not all aetiologies in a second study (Thompson Coon 2008(35)) and not cost-effective in the third study (Andersson 2008(34))	

AFP = alpha-fetoprotein; HCC = hepatocellular carcinoma; QALY = quality-adjusted life years; TACE = transarterial chemoembolisation

4. SUMMARY OF FINDINGS

Table 18. Summary of findings for 6-monthly ultrasound + AFP compared to 6-monthly ultrasound only surveillance for people with chronic hepatitis B.

Outcome	***Number of participants (studies)***	***Certainty of the evidence (GRADE)***	***Relative effect (95% CI)***	***Anticipated absolute effects (95% CI)***		
				Metric	***Risk 6-monthly US only surveillance***	***Risk with 6-monthly US + AFP surveillance***
Cost-effectiveness	N = NR (1 modelling study)	Moderate to low[1]	AFP + US cost effective when compared with US only	NA	NA	NA

AFP = alpha-fetoprotein; NA = not applicable; NR = not reported; US = ultrasound

[1]Serious concerns regarding the risk of bias and either no or serious concerns regarding imprecision as imprecision not assessable

Table 19. Summary of findings 6-monthly ultrasound + AFP compared to 6-monthly ultrasound only surveillance for people with cirrhosis.

Outcome	***Number of participants (studies)***	***Certainty of the evidence (GRADE)***	***Relative effect (95% CI)***	***Anticipated absolute effects (95% CI)***		
				Metric	***Risk 6-monthly US only surveillance***	***Risk with 6-monthly US + AFP surveillance***
% HCC that are early stage	N = 1,000,000 (1 modelling study)	Low to very low[1]	Not calculable*	% total HCC	83%	91%
Overall mortality	N = 1,000,000 (1 modelling study)	Low to very low[1]	Not calculable*	Mean survival	10.8 years	10.9 years
Cost-effectiveness	N = NR (3 modelling studies)	Low to very low[2]	AFP + US is more effective and has lower costs than US alone (1 study). AFP + US is cost effective when compared with US only for HBV patients and patients without specified aetiology (1 study). AFP is not cost effective when compared with US only (1 study).	NA	NA	NA

AFP = alpha-fetoprotein; HCC = hepatocellular carcinoma; NA = not applicable; NR = not reported; US = ultrasound

[1]Serious concerns regarding the risk of bias and indirectness and either no or serious concerns regarding imprecision as imprecision not assessable

[2]Very serious concerns regarding the risk of bias and either no or serious concerns regarding imprecision as imprecision not assessable
** For the modelled outcomes of mortality and percentage liver cancer 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.*

Table 20. Evidence summary of findings 6-monthly ultrasound + AFP compared to 6-monthly ultrasound only surveillance for people with cirrhosis and people with chronic hepatitis B.

Evidence summary	**GRADE certainty of evidence**	**References**
A recent modelling study based on data from the USA 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 liver ultrasound than with liver ultrasound alone.	Low to very low	Parikh 2020 (33)
For individuals with cirrhosis, three cost-effectiveness modelling studies reported conflicting findings on the cost-effectiveness of surveillance using AFP and liver ultrasound when compared with surveillance using liver ultrasound only	Low to very low	Parikh 2020 (33) Andersson 2008 (34) Thompson-Coon 2008 (35)
For individuals with chronic HBV in Thailand, a single cost-effectiveness modelling study estimated that surveillance with AFP and liver ultrasound was more cost effective when compared with liver ultrasound only.	Moderate to low	Sangmala 2014 (24)

REFERENCES

1. World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2015. 134 p.

2. National Institute for Health and Care Excellence. Hepatitis B (chronic); diagnosis and management. Clinical guideline [CG165] Last updated October 2017 [Internet]. London: NICE; 2013 [cited 2022 Jun 16]. Available from: https://www.nice.org.uk/guidance/cg165

3. National Institute for Health and Care Excellence. Cirrhosis in Over 16s: Assessment and Management. NICE guideline [NG50] [Internet]. London: NICE; 2016 [cited 2021 Dec 8]. Available from: https://www.nice.org.uk/guidance/ng50

4. 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. 2019;13(1):1–1.

5. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018 Apr;67(4):1560–99.

6. Gastroenterological Society of Australia. Hepatocellular Carcinoma Consensus Statement Working Group. Australian recommendations for the management of hepatocellular carcinoma: a consensus statement. [Internet]. Melbourne: Gastroenterological Society of Australia; 2020 [cited 2022 Sep 12]. Available from: https://www.gesa.org.au/resources/hepatocellular-carcinoma-hcc-management-consensus/

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

8. AGREE Next Steps Consortium. The AGREE II Instrument [Internet]. 2017. Available from: http://www.agreetrust.org/resource-centre/agree-ii/

9. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022) [Internet]. Cochrane; 2022. Available from: www.training.cochrane.org/handbook

10. Eldridge S, Campbell MK, Campbell MJ, Drahota AK, Giraudeau B, Reeves BC, et al. Revised Cochrane risk of bias tool for randomized trials (RoB 2) Additional considerations for cluster-randomized trials (RoB 2 CRT) [Internet]. 2021 [cited 2022 Feb 1]. Available from: https://drive.google.com/file/d/1yDQtDkrp68_8kJiIUdbongK99sx7RFI-/view

11. Kirk M, Smurthwaite K, Braunig J, Trevener S, D'Este C, Lucas R, et al. The PFAS Health Study: Systematic Literature Review [Internet]. Canberra: The Australian National University; 2018. p. 161–3. Available from: https://openresearch-repository.anu.edu.au/handle/1885/241032

12. Odnoletkova I, Goderis G, Pil L, Nobels F, Aertgeerts B, Annemans L, et al. Cost-Effectiveness of Therapeutic Education to Prevent the Development and Progression of Type 2 Diabetes: Systematic Review. J Diabetes Metab. 2014;05(09):in appendix.

13. NHMRC. Guidelines for Guidelines: Assessing certainty of evidence [Internet]. 2019. Available from: https://nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence

14. Murad MH, Mustafa RA, Schünemann HJ, Sultan S, Santesso N. Rating the certainty in evidence in the absence of a single estimate of effect. Evid Based Med. 2017 Jun;22(3):85–7.

15. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol. 2011 Dec;64(12):1283–93.

16. Zeng L, Brignardello-Petersen R, Hultcrantz M, Siemieniuk RAC, Santesso N, Traversy G, et al. GRADE guidelines 32: GRADE offers guidance on choosing targets of GRADE certainty of evidence ratings. J Clin Epidemiol. 2021 Sep;137:163–75.

17. Brignardello-Petersen R, Guyatt GH, Mustafa RA, Chu DK, Hultcrantz M, Schünemann HJ, et al. GRADE guidelines 33: Addressing imprecision in a network meta-analysis. J Clin Epidemiol. 2021 Nov;139:49–56.

18. Brunetti M, Shemilt I, Pregno S, Vale L, Oxman AD, Lord J, et al. GRADE guidelines: 10. Considering resource use and rating the quality of economic evidence. J Clin Epidemiol. 2013 Feb;66(2):140–50.

19. Holger Schünemann, Jan Brożek, Gordon Guyatt, Andrew Oxman. GRADE Handbook - Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach [Internet]. 2013 [cited 2022 Apr 26]. Available from: https://gdt.gradepro.org/app/handbook/handbook.html

20. Brozek JL, Canelo-Aybar C, Akl EA, Bowen JM, Bucher J, Chiu WA, et al. GRADE Guidelines 30: the GRADE approach to assessing the certainty of modeled evidence—An overview in the context of health decision-making. J Clin Epidemiol. 2021 Jan;129:138–50.

21. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol. 2004 Jul;130(7):417–22.

22. 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):204–9.

23. 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 May;50(5):990–8.

24. 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. Asian Pac J Cancer Prev. 2014 Nov 6;15(20):8993–9004.

25. Chang Y, Lairson DR, Chan W, Lu SN, Aoki N. Cost-effectiveness of screening for hepatocellular carcinoma among subjects at different levels of risk: Cost-effectiveness of screening for HCC. J Eval Clin Pract. 2011 Apr;17(2):261–7.

26. 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.

27. Farhang Zangneh H, Wong WWL, 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 Aug;17(9):1840-1849.e16.

28. 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 Open. 2021 Jun 24;4(6):e2114680.

29. 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.

30. 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 Health. 2021 Oct;24(10):1454–62.

31. 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 Apr 19;OF1–8.

32. 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 Dec;65(6):1086–93.

33. Parikh ND, Singal AG, Hutton DW, Tapper EB. Cost-Effectiveness of Hepatocellular Carcinoma Surveillance: An Assessment of Benefits and Harms. Am J Gastroenterol. 2020 Oct;115(10):1642–9.

34. 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):1418–24.

35. 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 Apr;98(7):1166–75.

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

37. 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. 2010/06/16 ed. 2010 May;25(5):951–6.

38. 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. Intern Med J. 2013 Jul;43(7):772–7.

39. 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 Feb;1(1):53–60.

40. 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):551–6.

41. Byford S, Raftery J. Economics notes: Perspectives in economic evaluation. BMJ. 1998 May 16;316(7143):1529–30.

42. Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun Wong V, Castellanos M, Aller-de la Fuente R, Metwally M, et al. Fibrosis Severity as a Determinant of Cause-Specific Mortality in Patients With Advanced Nonalcoholic Fatty Liver Disease: A Multi-National Cohort Study. Gastroenterology. 2018 Aug 1;155(2):443-457.e17.

43. 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 Aug;21(8):938–43.

44. Hong TP. An Australian population-based study of the incidence and outcomes of hepatocellular carcinoma: the Hepatomas of Melbourne Epidemiological Research (HoMER) study [Internet]. 2019 [cited 2019 Jul 11]. Available from: http://hdl.handle.net/11343/225659

45. Wallace MC, Preen DB, Short MW, Adams LA, Jeffrey GP. Hepatocellular carcinoma in Australia 1982-2014: Increasing incidence and improving survival. Liver Int. 2019 Mar;39(3):522–30.

46. Nguyen ALT, Si L, Lubel JS, Shackel N, Yee KC, Wilson M, et al. Construction and validation of a microsimulation model for hepatocellular carcinoma surveillance in Australia. In Submission;

47. Alavi M, Law MG, Grebely J, Amin J, Hajarizadeh B, George J, et al. Time to decompensated cirrhosis and hepatocellular carcinoma after an HBV or HCV notification: A population-based study. J Hepatol. 2016 Nov;65(5):879–87.

48. Jepsen P, Vilstrup H, Andersen PK. The clinical course of cirrhosis: The importance of multistate models and competing risks analysis. Hepatology. 2015 Jul 1;62(1):292–302.

49. Canfell K, Kim JJ, Brisson M, Keane A, Simms KT, Caruana M, et al. Mortality impact of achieving WHO cervical cancer elimination targets: a comparative modelling analysis in 78 low-income and lower-middle-income countries. The Lancet. 2020 Feb;395(10224):591–603.

50. Haq MI, Drake TM, Goh TL, Ahmed A, Forrest E, Barclay S, et al. Effect of Hepatocellular Carcinoma Surveillance Programmes on Overall Survival in a Mixed Cirrhotic UK Population: A Prospective, Longitudinal Cohort Study. J Clin Med. 2021 Jun 24;10(13):2770.

51. Consumer Price Index, Australia, March 2022 | Australian Bureau of Statistics [Internet]. 2022 [cited 2022 Jun 12]. Available from: https://www.abs.gov.au/statistics/economy/price-indexes-and-inflation/consumer-price-index-australia/latest-release

52. Department of Health, Australian Government. MBS Online: Medicare Benefits Schedule. [homepage on the internet] [Internet]. Canberra, ACT: Commonwealth of Australia; Available from: http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/Home

53. Xiao Y, Howell J, Gemert C, Thompson AJ, Seaman CP, McCulloch K, et al. Enhancing the hepatitis B care cascade in Australia: A cost-effectiveness model. J Viral Hepat. 2020 May;27(5):526–36.

54. Reeve R, Srasuebkul P, Langton JM, Haas M, Viney R, Pearson SA, et al. Health care use and costs at the end of life: a comparison of elderly Australian decedents with and without a cancer history. BMC Palliat Care. 2017 Jun 21;17(1):1.

55. McPhail SM, Amarasena S, Stuart KA, Hayward K, Gupta R, Brain D, et al. Assessment of health-related quality of life and health utilities in Australian patients with cirrhosis. JGH Open. 2021 Jan;5(1):133–42.

56. Global Burden of Disease Collaborative Network. Global Burden of Disease (GBD 2019) [Internet]. Seattle, United States of America: Institute for Health Metrics and Evaluation (IHME); 2021 [cited 2022 Jun 12]. Available from: https://www.healthdata.org/gbd/2019

57. 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 Jan;44(1):217–31.

58. NSW Cancer Registry. Data request: Hepatocellular carcinoma (coded as C22.0 or C22.9) incidence and mortality). Private communication; unpublished.; 2021 Aug.

59. Tzartzeva K, Obi J, Rich NE, Parikh ND, Marrero JA, Yopp A, et al. Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Patients With Cirrhosis: A Meta-analysis. Gastroenterology. 2018 May 1;154(6):1706-1718.e1.

60. Cheng RM. Novel Biomarkers of Hepatocellular Carcinoma [Internet]. The University of Sydney; 2018. Available from: http://hdl.handle.net/2123/20294

61. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. Circulation. 2016 Feb 9;133(6):601–9.

62. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. Stat Med. 2017 Nov 30;36(27):4391–400.

APPENDICES

Appendix 1: Medline and Embase database (via Ovid platform) search strategies

#	Searches
1	carcinoma, hepatocellular/
2	liver neoplasms/
3	liver cell carcinoma/
4	liver tumor/
5	liver cancer/
6	1 or 2 or 3 or 4 or 5
7	((hepato* or liver or hepatic) adj3 (cancer or carcinoma* or neoplasm* or tumor* or tumour*)).tw.
8	(hepatoma* or hepatocarcinoma* or hcc).tw.
9	7 or 8
10	Early diagnosis/
11	Early detection of cancer/
12	population surveillance/
13	cancer screening/
14	mass screening/
15	disease surveillance/
16	10 or 11 or 12 or 13 or 14 or 15
17	screen*.tw.
18	surveil*.tw.
19	17 or 18
20	6 or 9
21	16 or 19
22	20 and 21
23	fatty liver/ or non-alcoholic fatty liver disease/ or hepatitis/ or hepatitis, viral, human/
24	(hepatitis or HBV or fatty liver or NAFLD or MAFLD or steatohepatitis or NASH or steatosis or non-cirrhotic or noncirrhotic or no cirrhosis or no cirrhotic or without cirrhosis or without cirrhotic).tw.
25	Ultrasonography/
26	(ultrasound or ultrasonograph*).tw.
27	22 or 23 or 24 or 25 or 26
28	22 and 27
29	limit 28 to english language
30	limit 29 to humans

31	limit 30 to yr="2000 -Current"
32	limit 31 to conference abstracts [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) PubMed not MEDLINE,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]
33	limit 32 to medline
34	32 not 33
35	31 not 34
36	limit 35 to yr="2000 - 2010"
37	35 not 36
38	remove duplicates from 36
39	remove duplicates from 37
40	38 or 39

#	**Searches**
1	carcinoma, hepatocellular/
2	liver neoplasms/
3	liver cell carcinoma/
4	liver tumor/
5	liver cancer/
6	or/1-5
7	((hepato* or liver or hepatic) adj3 (cancer or carcinoma* or neoplasm* or tumor* or tumour*)).tw.
8	(hepatoma* or hepatocarcinoma* or hcc).tw.
9	or/7-8
10	Early diagnosis/
11	Early detection of cancer/
12	population surveillance/
13	mass screening/
14	cancer screening/
15	disease surveillance/
16	or/10-15
17	screen*.tw.
18	surveil*.tw.
19	17 or 18
20	6 or 9
21	16 or 19

22	20 and 21
23	australia.in.
24	22 and 23
25	limit 24 to english language
26	limit 25 to human
27	limit 26 to yr="2000 -Current"
28	remove duplicates from 27
29	limit 28 to conference abstracts [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) PubMed not MEDLINE,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]
30	limit 29 to medline
31	29 not 30
32	28 not 31

Appendix 2: GRADE assessment of the certainty of the evidence

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Appendix 3: Excluded Studies

Article	Available from (DOI or link)	Reason for exclusion
Adams, L. A. 2020	http://dx.doi.org/10.1111/jgh.15009	No intervention of interest
Aljabiri, M. R. 2007	http://dx.doi.org/10.1002/lt.21324	Excluded study type or design
Allard, N. 2017	https://pubmed.ncbi.nlm.nih.gov/29101924/	No intervention of interest
Anonymous 2007	http://dx.doi.org/10.1002/lt.21242	Excluded publication type
Arguedas, M. R. 2003	https://doi.org/10.1016/S0002-9270(02)06049-5	No comparator of interest
Bischof, D. A. 2014	http://dx.doi.org/10.1136/ebmed-2014-110036	Excluded publication type
Bolondi, L. 2001	http://dx.doi.org/10.1136/gut.48.2.251	No comparator of interest
Cadier, B. 2017	https://doi.org/10.1002/hep.28961	No intervention of interest
Carville, K. S. 2012	https://search.informit.org/doi/10.3316/informit.130848966380090	Excluded publication type

Chang, T. S. 2015	http://dx.doi.org/10.1038/ajg.2015.100	Excluded study type or design
Chang, Y. 2011	https://doi.org/10.1111/j.1365-2753.2010.01432.x	No intervention of interest
Chen, C. H. 2004	http://dx.doi.org/10.1016/j.jhep.2003.12.002	No comparator of interest
Chen, Y. 2020	https://doi.org/10.1177/0022242920913025	No intervention of interest
Chinnaratha, M. A. 2019	http://dx.doi.org/10.1007/s12029-018-0171-7	No intervention of interest
Chung, J. W. 2017	https://doi.org/10.18632/oncotarget.22498	No intervention of interest
Cucchetti, A. 2012	https://doi.org/10.1016/j.jhep.2011.11.022	No comparator of interest
El-Atem, N. A. 2016	http://dx.doi.org/10.1111/imj.13008	No outcome of interest
Eltabbakh, M. 2015	http://dx.doi.org/10.1007/s12032-014-0432-7	No outcome of interest
Farhang Zangneh, H. 2019	https://doi.org/10.1016/j.cgh.2018.12.018	No intervention of interest
Fisher, D. A. 2003	https://doi.org/10.5694/j.1326-5377.2003.tb05070.x	Excluded publication type
Frazer, C. 2000	http://dx.doi.org/10.1053/crad.1999.0265	Excluded publication type
Frenette, C. 2016	https://www.hematologyandoncology.net/files/2016/06/HCCFrenette-1.pdf	Excluded publication type
Frey, R. S. 2015	http://dx.doi.org/10.4414/smw.2015.14200	No intervention of interest
Gellert, L. 2007	http://dx.doi.org/10.1111/j.1445-5994.2007.01392.x	No intervention of interest
George, E. S. 2018	http://dx.doi.org/10.1111/imj.13973	Excluded publication type
Giannini, E. G. 2012	http://dx.doi.org/10.1586/egh.12.30	Excluded publication type
Goossens, N. 2017	https://dx.doi.org/10.1038/ctg.2017.26	No intervention of interest
Gounder, P. P. 2016	http://dx.doi.org/10.3402/ijch.v75.31115	No intervention of interest
Hanson, J. 2020	http://dx.doi.org/10.1371/journal.pone.0238719	No intervention of interest
Harris, N. 2017	http://dx.doi.org/10.1111/1754-9485.12595	No intervention of interest
Hla, T. K. 2020	http://dx.doi.org/10.1186/s12939-020-01180-w	No outcome of interest
Hong, T. P. 2018	http://dx.doi.org/10.5694/mja18.00373	No intervention of interest
Jeffrey, G. P. 2020	http://dx.doi.org/10.5694/mja2.50808	Excluded publication type
Jeffrey, G. P. 2020	http://dx.doi.org/10.5694/mja2.50808	Excluded publication type
Jeffrey, G. P. 2020	http://dx.doi.org/10.5694/mja2.50521	Excluded publication type
Kemp, W. 2005	http://dx.doi.org/10.1111/j.1440-1746.2005.03844.x	No intervention of interest
Kim, D. H. 2022	https://dx.doi.org/10.1136/gutjnl-2020-323615	Excluded study type or design
Kim, H.-L. 2019	https://dx.doi.org/10.1002/hep.30330	No intervention of interest
Kuo, M. J. 2016	https://doi.org/10.3748/wjg.v22.i12.3460	No intervention of interest
Kutaiba, N. 2021	http://dx.doi.org/10.1016/j.jhep.2021.06.041	Excluded publication type
Kwon, J. W. 2020	https://doi.org/10.5009/gnl18522	No comparator of interest
Larcos, G. 2020	https://dx.doi.org/10.5694/mja2.50806	Excluded publication type
Larcos, G. 2020	https://dx.doi.org/10.5694/mja2.50806	Excluded publication type
Lee, Y. W. 2014	http://dx.doi.org/10.4143/crt.2014.46.3.223	No comparator of interest
Lim, J. 2019	http://dx.doi.org/10.1002/cld.761	Excluded study type or design
Lima, P. H. 2019	http://dx.doi.org/10.2214/AJR.18.20341	No intervention of interest
Lin, O. S. 2004	http://dx.doi.org/10.1111/j.1365-2036.2004.01963.x	No comparator of interest
Lockart, I. 2021	http://dx.doi.org/10.1111/jvh.13475	No intervention of interest
Low, E. S. 2021	https://dx.doi.org/10.4251/wjgo.v13.i12.2149	No intervention of interest
Maher, L. 2012	http://dx.doi.org/10.1016/S1473-3099%2811%2970355-3	Excluded publication type

Majeed, A. 2019	http://dx.doi.org/10.1053/j.gastro.2018.09.060	No intervention of interest
Mallat, D. B. 2002	http://dx.doi.org/10.1016/S0002-9270%2802%2905454-0	Excluded publication type
Mancebo, A. 2018	http://dx.doi.org/10.1111/jgh.14108	No comparator of interest
Mancebo, A. 2017	http://dx.doi.org/10.1097/MCG.0000000000000734	No comparator of interest
Mohsen, W. 2017	https://dx.doi.org/10.3748/wjg.v23.i15.2763	No intervention of interest
Nguyen, A. L. T. 2021	http://dx.doi.org/10.1016/j.jval.2020.11.014	Excluded study type or design
Nicoll, A. J. 2002	https://dx.doi.org/10.5694/j.1326-5377.2002.tb04247.x	Excluded publication type
Niravath, P. 2011	http://dx.doi.org/10.1136/fg.2010.003244	No intervention of interest
Nouso, K. 2008	https://doi.org/10.1111/j.1440-1746.2007.05054.x	No intervention of interest
Oh, C. M. 2020	http://dx.doi.org/10.5009/GNL19388	Excluded publication type
Panjawong, W. 2018	http://www.jmatonline.com/index.php/jmat/article/view/9132	No comparator of interest
Parker, C. 2014	http://dx.doi.org/10.5694/mja13.11117	No comparative data for outcome of interest
Paul, S. B. 2008	https://doi.org/10.1007/s12072-008-9054-5	No intervention of interest
Pocha, C. 2013	https://doi.org/10.1111/apt.12370	No comparator of interest
Poustchi, H. 2011	http://dx.doi.org/10.1002/hep.24581	No intervention of interest
Roberts, S. 2006	http://dx.doi.org/10.1111/j.1440-1746.2006.04211.x	Excluded publication type
Roberts, S. K. 2007	http://dx.doi.org/10.1111/j.1440-1746.2006.04459.x	No intervention of interest
Robotin, M. 2012	https://dx.doi.org/10.3748/wjg.v18.i42.6106	No intervention of interest
Robotin, M. C. 2018	http://dx.doi.org/10.2147/CLEP.S146275	No outcome of interest
Robotin, M. C. 2014	http://dx.doi.org/10.2471/BLT.13.130344	Excluded publication type
Robotin, M. C. 2010	http://dx.doi.org/10.1186/1472-6963-10-215	No outcome of interest
Robotin, M. C. 2009	http://dx.doi.org/10.1016/j.jhep.2008.12.022	No outcome of interest
Roder, D. 2007	https://portal.sahmriresearch.org/en/publications/epidemiology-of-cancer-in-indigenous-australians-implications-for	Excluded publication type
Rodrigues, B. 2021	http://dx.doi.org/10.1177/1357633X211024108	No intervention of interest
Ruelas-Villavicencio, A. L. 2004	https://www.elsevier.es/en-revista-annals-hepatology-16-articulo-in-whom-how-how-often-S1665268119320939	No outcome of interest
Saab, S. 2003	https://doi.org/10.1053/jlts.2003.50120	No population of interest
Sangiovanni, A. 2004	http://dx.doi.org/10.1053/j.gastro.2003.12.049	No intervention of interest
Santagostino, E. 2003	http://dx.doi.org/10.1182/blood-2002-10-3310	No comparator of interest
Sheppard-Law, S. 2018	http://dx.doi.org/10.1111/jocn.14367	Excluded study type or design
Shih, S. T. 2010	https://doi.org/10.1016/s0929-6646(10)60020-4	No comparator of interest
Sinclair, M. 2013	http://dx.doi.org/10.1111/imj.12068	No intervention of interest
Singal, A. G. 2014	https://doi.org/10.1371/journal.pmed.1001624	Excluded study type or design
Singal, A. G. 2012	http://dx.doi.org/10.1158/1055-9965.EPI-11-1005	No intervention of interest
Sinn, D. H. 2015	https://pubmed.ncbi.nlm.nih.gov/25916058/	No intervention of interest
Subramaniam, K. 2012	http://dx.doi.org/10.1111/j.1445-5994.2011.02711.x	No outcome of interest
Sutherland, T. 2017	http://dx.doi.org/10.1111/1754-9485.12513	Excluded study type or design
Tai, D. I. 2002	http://dx.doi.org/10.1046/j.1440-1746.2002.02747.x	No comparator of interest
Tanaka, H. 2012	https://doi.org/10.1111/j.1872-034X.2011.00936.x	No intervention of interest
Taye, B. W. 2021	http://dx.doi.org/10.1002/jgh3.12580	No intervention of interest
Taylor, E. J. 2017	http://dx.doi.org/10.1002/hep.29315	No intervention of interest

Tayob, N. 2021	http://dx.doi.org/10.1016/j.cgh.2020.07.065	No outcome of interest
Tayob, N. 2016	http://dx.doi.org/10.1016/j.cgh.2015.07.049	No intervention of interest
Thein, H. H. 2012	http://dx.doi.org/10.1111/j.1872-034X.2012.01037.x	No intervention of interest
Thompson Coon, J. 2007	https://doi.org/10.3310/hta11340	Results subsequently published in peer-reviewed journal article
Trevisani, F. 2007	http://dx.doi.org/10.1111/j.1572-0241.2007.01395.x	No intervention of interest
Trevisani, F. 2002	http://dx.doi.org/10.1016/S0002-9270%2801%2904119-3	No comparator of interest
Trinchet, J. C. 2011	http://dx.doi.org/10.1002/hep.24545	No comparative data for outcome of interest
Tzartzeva, K. 2018	http://dx.doi.org/10.1053/j.gastro.2018.01.064	Excluded study type or design
Tzartzeva, K. 2018	http://dx.doi.org/10.1080/17474124.2018.1512855	Excluded publication type
Uyei, J. 2019	https://dx.doi.org/10.1371/journal.pone.0221614	No intervention of interest
Violi, V. N. 2020	https://doi.org/10.1007/s00330-020-07014-1	No intervention of interest
Vongsuvanh, R. 2016	http://dx.doi.org/10.1371/journal.pone.0155800	No intervention of interest
Webb, G. J. 2015	http://dx.doi.org/10.7861/clinmedicine.15-2-139	No comparative data for outcome of interest
Wigg, A. J. 2021	http://dx.doi.org/10.1016/j.eclinm.2021.100919	No intervention of interest
Wolf, D. C. 2003	http://dx.doi.org/10.1053/jlts.2003.50139	Excluded publication type
Wong, N. 2013	http://dx.doi.org/10.1111/j.1445-5994.2012.02755.x	No intervention of interest
Worland, T. 2017	http://dx.doi.org/10.1007/s12029-017-0006-y	No outcome of interest
Xie, Z. R. 2015	http://dx.doi.org/10.1007/s12032-015-0534-x	Excluded publication type
Xiong, Z. 2017	Biomedical Research 28 (2017): 9616-9626.	Excluded study type or design
Zeng, G. 2020	http://dx.doi.org/10.1136/gutjnl-2020-321627	Excluded study type or design
Zhang, B.H. 2004	https://doi.org/10.1007/s00432-004-0552-0	No comparator of interest
Zhang, J. Z. 2019	http://dx.doi.org/10.3727/105221619X15553433838609	Excluded study type or design
Zhang, X. P. 2018	http://dx.doi.org/10.1053/j.gastro.2018.03.071	Excluded publication type

Appendix D7. Modelling results

15 July 2022

Summary

A model designed to simulate Australian patients with cirrhosis at risk of developing hepatocellular carcinoma (HCC), *Policy1-Liver*, was developed by the Daffodil Centre. *Policy1-Liver* included Australian data, where available, and capturing costs and health outcomes on short and long timescales.

Using *Policy1-Liver,* it was found that six-monthly HCC surveillance could reduce a patient with cirrhosis' chance of HCC death by 14-15% over their lifetime. Both six-monthly ultrasound and six-monthly ultrasound with AFP were found to be cost-effective, with cost-effectiveness ratios of $26,122 and $28,140 per QALY saved, respectively, compared to no surveillance.

Cost-effectiveness of hepatocellular carcinoma surveillance

Introduction

In Australia, the burden of liver cancer has escalated sharply, nearly doubling in incidence over 2001-2021, and is expected to continue increasing over the coming decades. The most common form of liver cancer, hepatocellular carcinoma (HCC), is typically caused by the presence of chronic viral hepatitis infection, alcohol-related liver disease, and/or metabolic-associated fatty liver disease.

If detected early, HCC can be more successfully treated, improving survival. The best intervention for early detection is regular HCC surveillance for high-risk patients through six-monthly ultrasound, with or without alpha-fetoprotein (AFP) testing. However, there is conflicting and incomplete evidence regarding the balance of costs and potential health impact of HCC surveillance.

The aim of this project was to model the health impact and cost-effectiveness of surveillance for cirrhotic patients. This modelling was completed using *Policy1-Liver*, a model of cirrhosis and HCC development designed to simulate disease progression in the Australian setting.

Methods

The model structure of *Policy1-Liver* is included in **Appendix 1: Model Structure and Parameters**, and the mathematical framework used is included in **Appendix 2: Time-to-event distribution modelling**.

We simulated the development of compensated cirrhosis into decompensated cirrhosis and/or HCC and compared health outcomes in people undergoing routine surveillance (Scenario) and not undergoing routine surveillance (Comparator).

The relevant healthcare costs were estimated, and health outcomes expressed as quality-adjusted life years (QALYs). All costs and QALYs are discounted from age 50. Included costs are shown in *Table 21*. All costs use Australian sources and are presented in 2022 Australian dollars. The study took a *health system perspective*;(41) indirect costs such as productivity losses and travel costs were not included.

Patient classification as “compensated cirrhosis” was based on the definitions used in the original studies; see *Table 22* for the relevant sources. For example, in Vilar-Gomez et al,(42) cirrhosis (F4 fibrosis) was confirmed by an independent histologic assessment upon trial recruitment, and a sample of the cohort were selected to assess the agreement of pathology diagnosis.

Patients can progress from compensated cirrhosis to decompensated cirrhosis, undiagnosed HCC, or death; from decompensated cirrhosis to undiagnosed HCC or death; from undiagnosed HCC to diagnosis, later stages or death, and from diagnosed HCC to death or recovery. The parameters governing these transitions are listed in Appendix 1 *Table 22*, *Table 23*, and *Table 24*.

Patients with diagnosed HCC have their treatments, costs, and survival rates determined based on their stage at diagnosis. These are shown in Appendix 1 *Table 23* and *Table 25*. For all costs and health state utilities, 5% annual discounting was applied from age 50.

Surveillance was modelled using either ultrasound alone, or ultrasound and AFP, for patients with compensated cirrhosis. For this initial analysis, surveillance was assumed to occur at six-monthly intervals. The inclusion of surveillance means patients are more likely to have their HCC detected at an earlier stage.

The modelled cohort was 50-year-olds with compensated cirrhosis, based on data availability. Age-specific risks are not explicitly incorporated in the modelling; outcomes are instead dependent on time since entering a health state/diagnosis. The overall cost-effectiveness is likely to be similar for patients entering the modelling at other ages, as the results are dominated by the impact of treatment costs.

To address the uncertainty associated with the model parameters, one-way sensitivity analyses of key variables were completed.

Results

The results of the initial analysis are shown in Table 20. Providing surveillance using six-monthly ultrasound alone would reduce a cirrhotic patient's probability of dying of HCC by one in seven and gain an average of 0.72 undiscounted quality-adjusted life-years, while six-monthly ultrasound with AFP would gain an average of 0.76 quality-adjusted life-years.

Among those that contract HCC, the probability of being diagnosed at early-stage disease would nearly double for those that undergo HCC surveillance. On average, patients with cirrhosis would experience 12.8 surveillance events over their lifetime and have an average total HCC surveillance and treatment cost of $137,654-138,950 (2022 AUD), compared to $131,086 for those who do not undergo surveillance.

The discounted cost-effectiveness of six-monthly ultrasound surveillance would be $26,122/QALY compared to no surveillance, below the indicative willingness-to-pay threshold of $50,000/QALY often used in Australia (43). This indicates that six-monthly ultrasound surveillance would be cost-effective. Similarly, six-monthly surveillance with ultrasound and AFP would have a discounted cost-effectiveness of $28,140/QALY compared to no surveillance and be cost-effective. Compared to surveillance with ultrasound alone, six-monthly ultrasound with AFP would have an incremental cost-effectiveness of $62,856/QALY, slightly above the willingness-to-pay threshold.

This modeling and the resulting estimates will be refined and extended as development on *Policy1-Liver* continues, as model assumptions are refined and emerging data is incorporated.

Sensitivity analysis

One-way sensitivity analyses were completed on the parameters governing the modelled

- probability of decompensation events,
- probability of HCC development,
- probability of death for cirrhotic patients,
- probability of death for diagnosed HCC,
- HCC stage at diagnosis for patients diagnosed with HCC,
- specificity and sensitivity of surveillance,
- HCC diagnosis procedure allocations,
- disutility associated with cancer care, and
- treatment type allocations.

These sensitivity analyses are shown in Figure 2 and found that the cost-effectiveness was most sensitive to parameters regarding survival and diagnosis of early stage HCCs. Lower Stage A survival rates made surveillance less cost-effective ($36,887/QALY vs $26,122/QALY baseline). Other parameters showing sensitivity include proportion of HCCs diagnosed at Stage A or B in the absence of surveillance, transition rates from cirrhosis to HCC or death, Stage B or C HCC survival, and ultrasound specificity and sensitivity. In all

cases, 6-monthly ultrasound with or without AFP remained under $50,000/QALY saved, indicating cost-effectiveness. Further development on *Policy1-Liver* will include additional sensitivity analyses including a robust probabilistic sensitivity analysis.

Future Model Development

The current iteration of *Policy1-Liver* is designed to generate cost-effectiveness outcomes for cirrhotic patients without decompensated liver, with a health systems perspective. *Policy1-Liver* is designed to be extensible and development will continue to address further aspects of HCC surveillance in more detail.

RISK FACTOR SPECIFIC MODELLING

Currently, *Policy1-Liver* models patients who have been diagnosed with compensated cirrhosis, without reference to the primary cause of that cirrhosis, i.e. their disease aetiology, In cirrhotic patients, this is typically one or more of chronic hepatitis B (HBV) infection, chronic hepatitis C (HCV) infection, alcohol-related liver disease (ARLD), and metabolic-associated fatty liver disease (MAFLD), which was previously diagnosed as non-alcoholic fatty liver disease (NAFLD).

Development is planned to model each of these risk groups separately. By modelling specific patient groups, *Policy1-Liver* will be able to generate more precise cost-effectiveness estimates, as the risk of developing HCC differs for each of these groups.

Modelling of pre-cirrhotic ARLD and MAFLD is currently planned and due to be completed in 2023. This will estimate the burden of ARLD and MAFLD related HCC which could be prevented by HCC surveillance in Australia, as well as the cost-effectiveness of surveillance in these groups.

Modelling is also planned for pre-cirrhotic patients with chronic HBV and HCV infection. Particular care is required for these risk groups, as hepatitis is highly prevalent in CALD communities and amongst Aboriginal and Torres Strait Islander Australians. As these groups are also affected by complex health inequities, different life expectancies, and a higher prevalence of comorbidities, it will be a significant challenge to capture these risk groups in detail. The impact of interventions such as antivirals and vaccination must also be incorporated into the modelling to capture the true risk of HCC; for instance, the efforts by the Hep B PAST program towards the elimination of Chronic Hepatitis B from Indigenous Australians in the Northern Territory.

AGE-SPECIFIC DISEASE PROGRESSION

Currently, an individual's risk of disease progression (cirrhosis to decompensation, HCC, etc) is primarily dependent on their time since diagnosis. The impact of a patient's age on their risk of disease is captured only indirectly, through their time spent in a particular disease state.

In future development, age-dependent health risks will be incorporated into the modelling, including the evolving risk of HCC, stage at diagnosis, and survival, dependent on age. As *Policy1-Liver* is designed to incorporate flexible and detailed data on evolving disease risk, we will be able to incorporate these rates in the existing framework, unlike simpler Markov-type modelling. This will be informed by existing Australian studies and data from Australian Institute of Health and Welfare and the NSW Cancer Registry.

We will also capture life expectancy in additional detail, capturing not only the patient's age but also sex and liver disease status. By capturing patient's age-dependent health risks in detail, we will also be able to capture different starting ages with a greater degree of accuracy, and confidently determine the cost-effectiveness of screening for people under age 50, such as 40. We would also be able to assess different cut-offs where surveillance would not be recommended past a certain age.

DETAILED COSTS AND ADDITIONAL ECONOMIC PERSPECTIVES

In any economic analysis, the goal is to capture all relevant costs as accurately and in as much detail as possible. In a real-world setting, this is complex and evolving. In future development of *Policy1-Liver*, we will consult with experts to establish more accurate real-world costs, including those associated with surveillance and diagnosis.

Currently, the costs associated with treatment are derived from a study by Hong et al,(44) which captures holistic costs for patients undergoing treatment, stratified by their primary curative treatment modality (where applicable). Although this methodology can capture incidental costs in more detail than a simpler approach such as tallying individual item costs, it does rely on having a sufficiently large cohort. In future modelling, we will assess alternative data sources for treatment costs, including the analysis completed by Wallace et al(45) and the economic modelling of Nguyen et al (46).

Currently, the modelling takes a health systems perspective and thus captures costs to the health care provider. Health economics analysis can also capture a societal perspective, whereby direct and indirect costs to the patient are considered. These would include costs such as travel to surveillance, and productivity costs. These are particularly relevant when considering patients in remote and regional communities, where ultrasound screening is not readily available. This may also be addressed by the use of portable ultrasound – with sufficient data, the use of portable ultrasound as a surveillance methodology could be considered for future modelling.

DETAILED DIAGNOSTIC AND SURVEILLANCE TECHNOLOGIES

Currently, the modelling is for patients diagnosed with cirrhosis, from studies confirmed via independent verification. In practice, patients are unlikely to have such verification, and many patients identified as having cirrhotic liver may instead have earlier-stage fibrosis. Emerging less invasive technologies may lead to less accurate diagnoses. We plan to capture the use of such technologies, and the potential cost and health implications for patients who receive a false positive diagnosis of cirrhosis.

Table 20. Health and cost-effectiveness outcomes of HCC surveillance. Discounting is 5% annually from age 50. Costs are from a health-system perspective.

Outcomes	No Surveillance[1]	Six-monthly ultrasound	Six-monthly ultrasound & AFP
Lifetime probability of HCC incidence/mortality			
Incidence, all stages	25.3%	25.3%	25.3%
Incidence, early (BCLC Stage 0/A)	11.9%	20.1%	20.4%
Incidence, intermediate (BCLC Stage B)	6.1%	2.2%	1.9%
Incidence, late (BCLC Stage C/D)	7.3%	3.0%	3.0%
HCC mortality – among all cirrhosis patients	15.2%	13.0%	12.9%
HCC mortality – among patients with HCC	60.1%	51.4%	51.0%
Relative mortality prob. vs no surveillance	-	14.4%	15.1%
Costs and resource use per person			
Lifetime surveillance events (median)	-	12.80	12.82
Surveillance costs (lifetime, mean)	$0	$1,907	$1,901
Treatment and diagnostic costs (mean)	$131,086	$137,654	$138,950
Total (undiscounted, mean)	$131,086	$139,561	$140,851
Total (discounted, mean)	$83,754	$90,992	$92,005
Health outcomes			
QALYs (undiscounted)	17.2261	17.9485	17.9894
QALYs (discounted)	5.9004	6.1775	6.1936
Cost-effectiveness ratio			
vs no surveillance	-	$26,122/QALY	$28,140/QALY
incremental[2]	-	$26,122/QALY	$62,856/QALY

[1] *Patients who did not receive regular surveillance.*

[2] *vs the previous most cost-effective option; six-monthly ultrasound vs no surveillance, and six-monthly ultrasound with AFP vs six-monthly ultrasound.*

Figure 1. Stage at diagnosis for patients undergoing (from top to bottom) no surveillance, six-monthly ultrasound, six-monthly ultrasound with AFP.

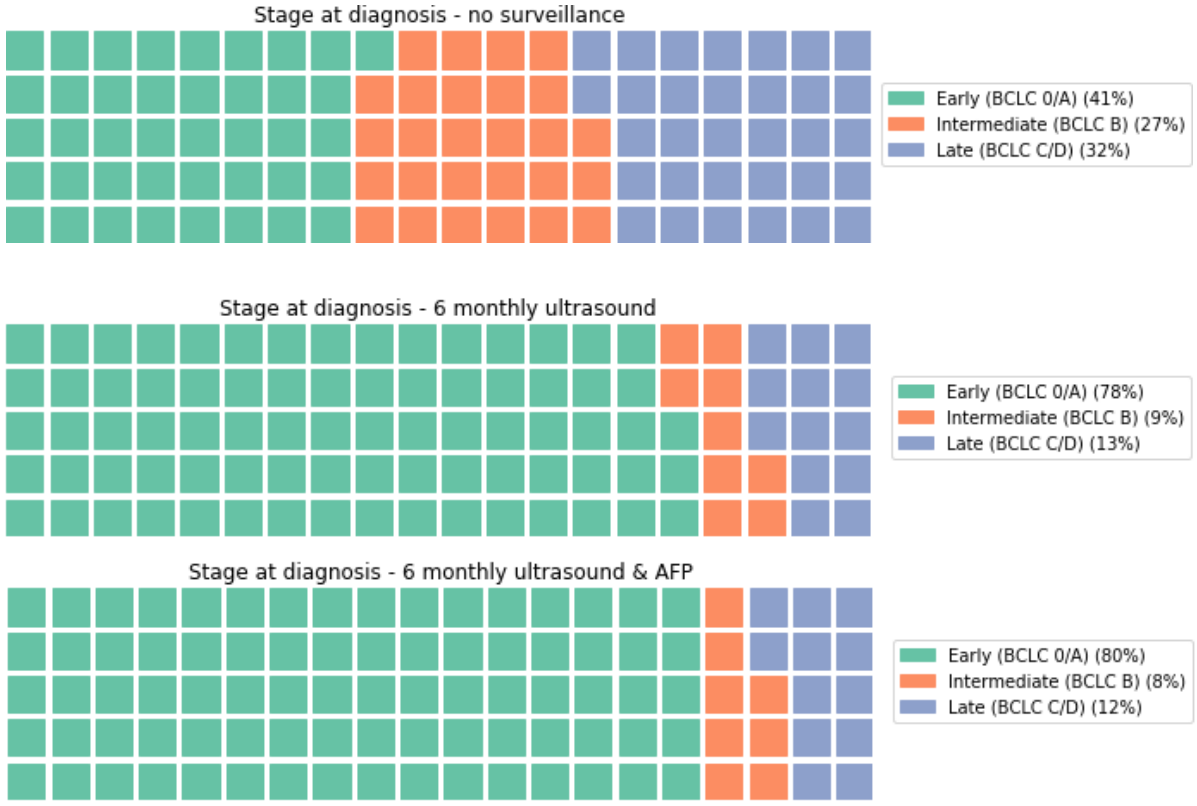
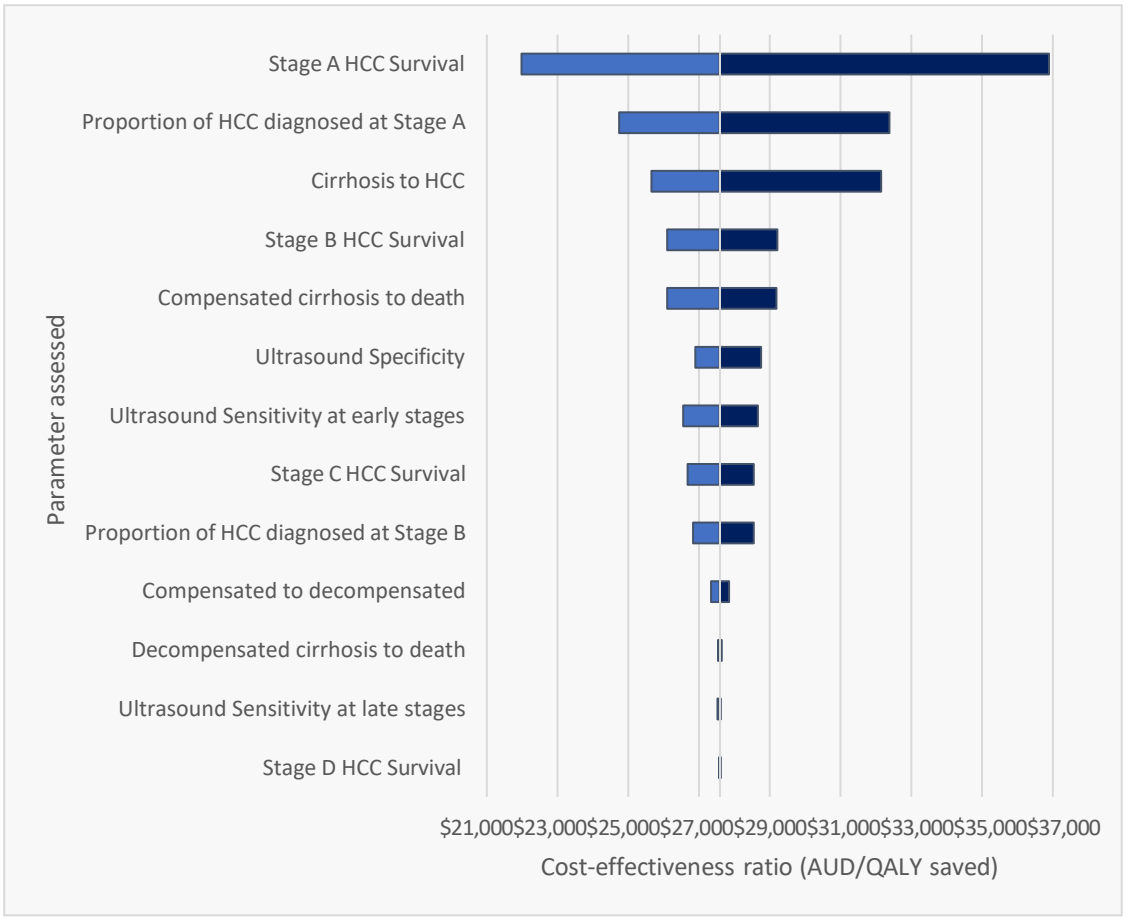


Figure *2*. Sensitivity analysis of modelled natural history parameters, showing the effect on cost-effectiveness of six-monthly ultrasound. The ranges used for the parameters are shown in Table 3-6.



Appendix 1: Model Structure and Parameters

Policy1-Liver is a mathematical model developed by the Daffodil Centre to estimate health and economic outcomes relating to hepatocellular cancer, surveillance, and treatment in Australia.

A model which captures HCC and surveillance accurately must allow for the complex and potentially short timeframes on which cirrhosis can develop into HCC, and HCC can progress to more advanced stages (47). Additionally, multi-state models and competing risk analysis must be used to accurately describe the progression of liver cirrhosis to decompensation, HCC, and death from either HCC or other causes (48).

To ensure this was properly captured in the modelling, a *time-to-event distribution* framework was developed for *Policy1-Liver*. This model structure is based on the time-to-event modelling used by the Daffodil Centre in *Policy1-Cervix,* a model of HPV transmission, HPV vaccination, cervical precancer, cancer survival, screening, diagnosis and treatment (49). As *Policy1-Liver* has fewer interrelated health states than *Policy1-Cervix*, instead of a microsimulation approach where individuals have event times sampled from a distribution, a likelihood distribution of the remaining time spent transitioning between any two states is generated instead. This methodology is detailed in Appendix 2: Time-to-event distribution modelling.

Health states

Policy1-Liver models individuals from compensated cirrhosis diagnosis. The model structure is illustrated in *Figure 3*.

Individuals with compensated cirrhosis transition to either liver decompensation, HCC (undiagnosed), or non-HCC death. Individuals with decompensated cirrhosis transition to either HCC (undiagnosed)or HCC death. The time-to-event distribution for each of these is based on time series data from trials shown in *Table 22*.

Individuals with undiagnosed HCC are classified as either early (BCLC Stage 0/A), intermediate (BCLC Stage B), or late stage (BCLC Stage C/D). Individuals with undiagnosed HCC can experience either upstaging (early to intermediate or intermediate to late), non-surveillance diagnosis (either symptomatic or incidental), or death. The time-to-event distribution for each of these is either based on calibration targets or time series data from trials and is shown in *Table 23*. The stage at diagnosis for HCC, with and without surveillance, is shown in *Table 24*.

Individuals with diagnosed HCC can experience either HCC deaths, or if they survive with HCC for five years, are classified as HCC survivors. Survival rates are dependent on the stage at diagnosis - upstaging after diagnosis is not explicitly modelled but is captured in the survival data. The time-to-event distribution for survival is based on time series data from trials and is shown in *Table 23*.

Surveillance

Surveillance is modelled as discrete events occurring at regular intervals after the diagnosis of compensated cirrhosis. Individuals without HCC can experience either a true negative surveillance event, or a false positive surveillance event, initiating a subsequent diagnostic event. Individuals with undiagnosed HCC can experience either a true positive surveillance event, causing a diagnostic event and instantaneous transition to diagnosed HCC, or a false positive, remaining undiagnosed.

Policy1-Liver currently models surveillance through regular ultrasound, and regular ultrasound with AFP. The stage at diagnosis for cohorts with and without surveillance is used to inform the HCC progression and detection rates (*Table 23*). The sensitivity and specificity of surveillance are shown in *Table 24*.

Diagnosis to confirm a suspected HCC, either after symptomatic development, a true positive surveillance event, or a false positive surveillance event, was modelled as CT or MRI, with additional biopsy in the small number of cases where imaging was insufficient. The proportion of patients undergoing each diagnostic procedure is shown in *Table 24*.

HCC treatments

Treatment procedure allocations for patients by stage are shown in *Table 25*. This includes both primary treatment and any secondary follow-up procedures. The "primary" treatment is used to classify costs for each patient (see **Costs and utilities** below). These data were chosen as they are both locally relevant and based on real-world observations, rather than ideal treatment recommendations which may not reflect the complexities in practice.

The primary treatments identified were liver transplant, liver resection, ablation (including RFA, MWA and PEI), TACE (including TACE with cisplantin, TACE with doxorubicin, and SIRT), and palliation/best supportive care.

HCC survival

Survival after diagnosis is stratified by stage. Five-year survival is based on data from the NSW Cancer Registry (NSWCR), as this data is provided for a large local dataset and is relatively complete. For detailed survival, including survival by stage, year since diagnosis, and surveillance, reference data from Haq et al (50) was used for hazard ratios between groups.

Patients who survive for five years after cancer diagnosis are then classified as HCC survivors, and assigned a life expectancy based on their age and liver function.

Costs and utilities

Costs associated with treatments are listed in *Table 21*. All costs are reported in 2022 Australian dollars, with the health CPI index used to inflate costs where necessary (51). Costs for individual surveillance and diagnostic procedures were collated from MBS Online (52).

Costs relating to HCC treatment were classified according to the primary form of treatment, following the methodology from Hong et al (44). This approach was chosen as these costs are the most inclusive of all additional costs during a patient's HCC treatment.

Other costs include annual costs of cirrhosis care for patients with and without decompensation, and end-of-life costs for cancer patients and non-cancer patients. To ensure relevance, all costs were identified from Australian sources.

Utilities were calculated for all patients. Disutilities were identified for patients with compensated and decompensated cirrhosis, and HCC patients. Disutilities for HCC patients were classified according to their phase of care: diagnostic/initial phase (first year post diagnosis), terminal phase (final year before death), and ongoing phase (any time between diagnostic phase and terminal phase/recovery). Years lived at perfect health were valued as having 1 utility, and any disutilities were subtracted from this to calculated the QALYs lived.

For all costs and utilities, a 5% annual discounting was applied from age 50.

Table 21. Costs and utilities relating to cirrhosis, HCC surveillance and treatment. All costs in 2022 AUD, with the consumer price index (CPI)(51) *for health used for adjustment where necessary. Costs are from a health-system perspective.*

Item	Value	Range	Source
Annual cirrhosis care costs			
Compensated	$4,713	$1,108-8,772	Xiao et al, 2019 (53)
Decompensated	$22,701	$10,464-34,939	
Surveillance-related costs			
Ultrasound	$115.75	-	MBS Online (52) As of July 2022.
AFP	$24.35	-	
GP Visit	$39.75	-	
CT (diagnostic)	$499.50	-	
MRI (diagnostic)	$558.80	-	
Liver biopsy (diagnostic)[3]	$377.2	-	
Treatment-related costs[4]			
Liver transplant	$320,107	-	Hong, 2019 (44)
Liver resection	$73,310	-	
Ablation (RFA/MWA/PEI)[5]	$94,611	-	
TACE[6]	$76,482	-	
Sorafenib	$42,338	-	
End-of-life costs			
Death from cancer	$44,945	$44,015-45,873	Reeve et al, 2017 (54)
Death from other causes	$31,513	$30,767-32,259	
Disutilities (annual)			
Compensated cirrhosis	0.32	0.31-0.33	McPhail et al, 2021 (55)
Decompensated cirrhosis	0.38	0.36-0.40	
HCC – Diagnostic Phase	0.288	0.193-0.399	Global Burden of Disease, 2019 (56)
HCC – Controlled Phase	0.049	0.031-0.072	
HCC – Terminal Phase	0.540	0.377-0.687	

Table 22. Model transition rates and calibration targets – cirrhosis progression rates. Unless noted, these values are for a cohort without regular surveillance.

Description	Model	Target	Range	Source
Cirrhosis Decompensation				
1 year probability	1.59%	1.59%	0.17-3.01%	Vilar-Gomez et al, 2018 (42)
10 year probability	33.7%	33.7%	28.4-39.1%	
HCC development				
1 year probability	1.54%	1.53%	0.14-2.93%	Vilar-Gomez et al, 2018 (42)
10 year probability	16.2%	15.6%	11.5-19.7%	
Death (compensated cirrhosis)				
1 year probability	3.97%	3.97%	2.62-5.31%	

[3] *Including anesthesia costs.*

[4] *Patient treatment costs are overall costs classified according to their primary treatment, following the methodology in Hong et al.*(44) *Patients may have further treatments -these costs are included in the figures presented.*

[5] *Proportion of patients allocated to RFA/MWA/PEI based on the proportions reported in Hong et al.*(44)

[6] *Including TACE with cisplantin, TACE with doxorubicin, and SIRT.*

10 year probability	39.7%	39.4%	36.1-42.8%	D'Amico et al, 2006 (57)
Death (decompensated cirrhosis)				
1 year probability	38.3%	38.3%	35.0-41.6%	D'Amico et al, 2006 (57)
10 year probability	91.1%	91.1%	89.2-93.0%	

Table 23. Model transition rates and calibration targets – HCC progression rates. Unless noted, these values are for a cohort without regular surveillance.

Description	Model	Target	Source
HCC: Early (Stage 0/A), undiagnosed			Calibration target for stage at diagnosis, with and without regular ultrasound surveillance (see Table *24*)
Annual progression to intermediate stage	16.6%	N/A	
Annual detection at early stage	16.9%	N/A	
HCC: Intermediate (Stage B), undiagnosed			
Annual progression to late Stage	41.3%	N/A	
Annual detection at intermediate stage	47.1%	N/A	
HCC: Late (Stage C/D), undiagnosed			
Annual detection at late stage	73.1%	N/A	
HCC: Five-year survival probability			
Local spread (Stage 0/A/B)	47.7%	47.7%	NSW Cancer Registry(58)
Regional/Distant Spread (Stage C/D)	20.6%	20.6%	
HCC: Hazard ratio for five-year survival by stage			
Stage B vs Stage 0/A	0.508	0.508	Haq et al, 2021(50)
Stage D vs Stage C	0.841	0.841	

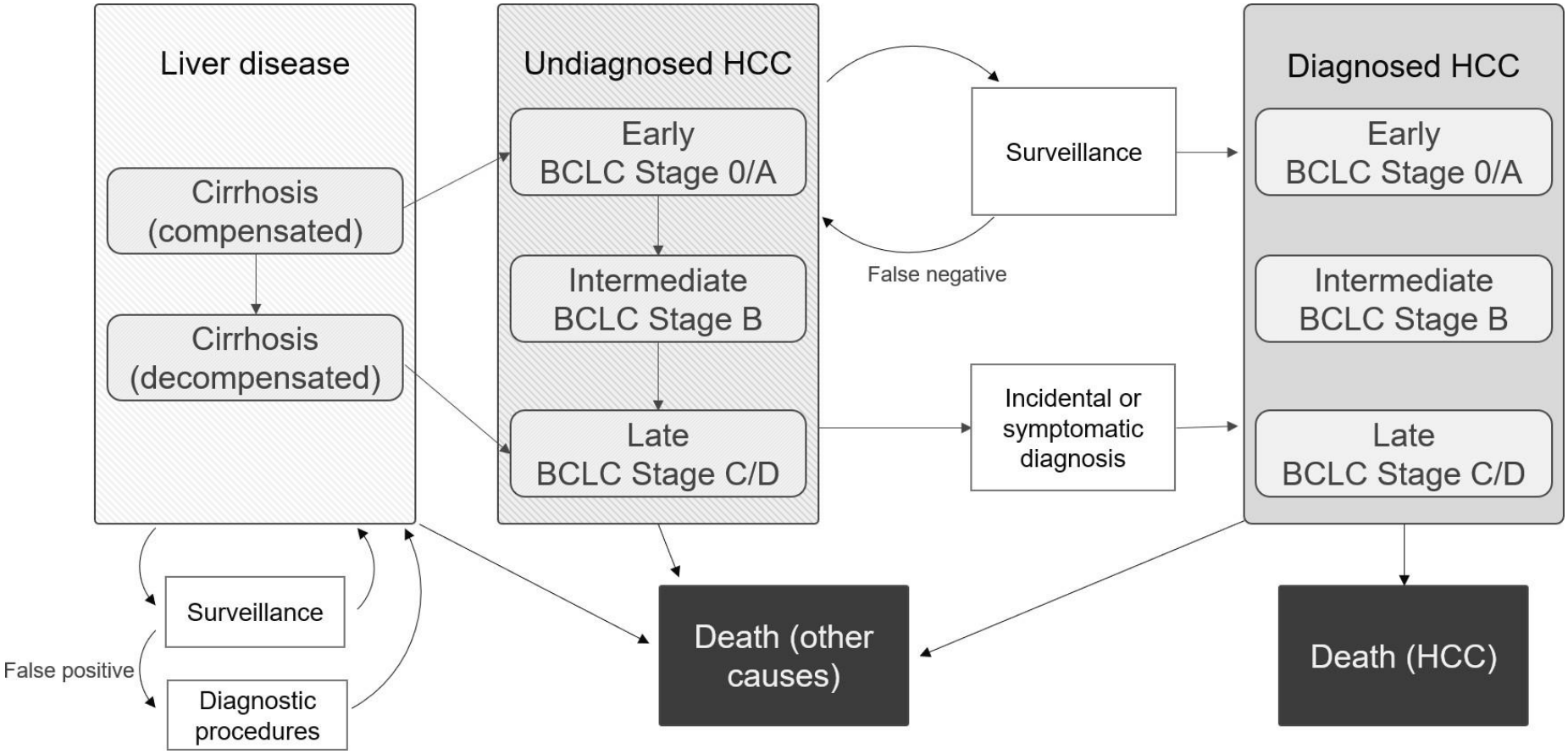
Table 24. HCC diagnosis parameters.

Description	Model	Target	Range	Source
Ultrasound for HCC detection				
Sensitivity (early stage HCC)	53%	53%	35-70%	Tzartzeva et al, 2018 (59)
Sensitivity (intermediate/late stage HCC)	84%	84%	67-92%	
Specificity	91%	91%	86-94%	
Ultrasound and AFP for HCC detection				
Sensitivity (early stage HCC)	63%	63%	48-75%	Tzartzeva et al, 2018 (59)
Sensitivity (intermediate/late stage HCC)	97%	97%	91-99%	
Specificity	84%	84%	77-89%	
Procedures for HCC diagnosis				
CT	80%			Nguyen et al, 2022 (46)
MRI	20%			
Biopsy	10%			
HCC: Stage at diagnosis (no surveillance)				
Early (Stage 0/A)	47%	47%	39-55%	Huang et al, 2017 (40)
Intermediate (Stage B)	24%	24%	17-31%	
Late (Stage C/D)	29%	29%	18-40%	
HCC: Stage at diagnosis (six-monthly ultrasound surveillance)				
Early (Stage 0/A)	81%	81%	-	Huang et al, 2017 (40)
Intermediate (Stage B)	8%	8%	-	
Late (Stage C/D)	11%	11%	-	
HCC: Stage at diagnosis (six-monthly ultrasound and AFP surveillance)				
Early (Stage 0/A)	83%	-	-	Model outcome based on test characteristics
Intermediate (Stage B)	7%	-	-	
Late (Stage C/D)	10%	-	-	

Table 25. HCC treatment allocations.

Primary treatment	Secondary treatment(s)	Proportion	Range	Source
Early (Stage A/0)				
Transplant	-	19.0%		
Resection	-	13.8%		
Ablation	-	25.6%		
TACE	-	34.8%		
Resection	Ablation/TACE, then sorafenib	3.4%		
Ablation	Sorafenib	1.5%		
TACE	Sorafenib	2.0%		
Intermediate (Stage B)				
Transplant	-	8.3%		
Resection	-	8.3%		
Ablation	-	17.7%		
TACE	-	24.0%		
Ablation	Sorafenib	14.1%		
TACE	Sorafenib	19.2%		
Resection	Sorafenib	8.3%		
Late (Stage C/D)				
Ablation	-	3.4%		
TACE	-	4.6%		
Ablation	Sorafenib	6.8%		
TACE	Sorafenib	9.2%		
Ablation	Palliation	11.9%		
TACE	Palliation	16.1%		
Sorafenib	Palliation	16.0%		
Palliation	-	32.0%		

Figure 3. Simplified schematic of *Policy1-Liver*.



Appendix 2: Time-to-event distribution modelling

The time-to-event distribution framework is based around a set of health states, S_i, and the transitions between these health states, represented by the distribution $T_{i,j}(t,\tau)$ defined by

$$P\big(\text{an individual is in state } S_i \text{ at time } t \text{ and will enter state } S_j \text{ before time } t+\tau\big) = \int_0^\tau T_{i,j}(t,s)\mathrm{d}\,s.$$

These distributions are in turn generated by the time-to-event functions $d_{i,j}(\tau)$, the distribution of times for an individual to transition from state S_i to state S_j. These are then related by

$$\frac{\partial}{\partial t} T_{i,j}(t,\tau) = \frac{\partial}{\partial \tau} T_{i,j}(t,\tau) + \sum_k T_{k,i}(t,0) d_{i,j}(\tau).$$

The first two terms of this equation are a transport equation, indicating that as time t progresses, the distribution $T_{i,j}(t,\tau)$ concurrently shifts towards the "terminus" $\tau = 0$. The third term shows progression between one state and another – when the distribution reaches $\tau = 0$, the distribution is moved to the next states according to the function $d_{i,j}(\tau)$.

The distributions $d_{i,j}(\tau)$ are determined by the relevant data for the problem being analysed. In the simplest example, for a state S_i with a single transition to a state S_j at a constant hazard rate of $\lambda_{i,j}$, the time-to-event distribution is given by the probability distribution function corresponding to the survival function for remaining in that state, $d_{i,j}(\tau) = \lambda_{i,j} e^{-\lambda_{i,j}\tau}$.

More generally, for states with more than one possible transition and/or non-constant hazard rates, these distributions are given by

$$d_{i,j}(\tau) = \lambda_{i,j}(\tau) \hat{S}_i(\tau)$$

where $\hat{S}_i(\tau)$ is the *all-cause survival function* for people entering state S_i defined by

$$\hat{S}_i(\tau) = e^{-\Lambda_i(\tau)}$$

and $\Lambda_i(\tau)$ is the *cumulative hazard function* for individuals in state S_i

$$\Lambda_i(\tau) = \sum_j \left(\int_0^\tau \lambda_{i,j}(s)\mathrm{d}s\right).$$

See e.g. Austin et al (61) for a full derivation of the above. The hazard rates $\lambda_{i,j}(\tau)$ can also be made to depend on covariates X like $\lambda_{i,j}(\tau|X)$ as per Cox proportional hazards models, or in the case of more than one competing risk, a Fine-Gray subdistribution hazard model.(62)

The distributions $d_{i,j}(\tau)$ satisfy

$$\sum_k \int_0^\infty d_{i,k}(\tau)\mathrm{d}\,\tau \leq 1.$$

If a state S_i is a terminal state (i.e., death), this sum will be zero as $d_{i,j}(\tau) = 0$ for all j – there are no subsequent states. Otherwise this sum would usually be 1, as all individuals would eventually reach a terminal state.

The initial conditions for the distribution $T_{i,j}(0,\tau)$ must be specified, based on the setting. Typically for some i one selects $T_{i,j}(0,\tau) = d_{i,j}(\tau)$ for all j as an initial condition, and $T_{k,l}(0,\tau) = 0$ for all $k \neq i$.

The number of individuals in a state S_i at a given time t can be calculated by

$$\sum_{j} \int_{0}^{\infty} T_{i,j}(0,\tau) + \sum_{k} \int_{0}^{t} T_{k,i}(s,0)\,ds - \sum_{j} \int_{0}^{t} T_{i,j}(s,0)\,ds.$$

In practice, this model is implemented by discretizing each transition distribution and representing it as a list in Python 3.9. For each discrete timestep, elements at $\tau = 0$ are "popped" from the top of the list and distributed to the other transition distribution lists.

Further technical details will be published in an upcoming manuscript.

References

1. World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2015. 134 p.

2. National Institute for Health and Care Excellence. Hepatitis B (chronic); diagnosis and management. Clinical guideline [CG165] Last updated October 2017 [Internet]. London: NICE; 2013 [cited 2022 Jun 16]. Available from: https://www.nice.org.uk/guidance/cg165

3. National Institute for Health and Care Excellence. Cirrhosis in Over 16s: Assessment and Management. NICE guideline [NG50] [Internet]. London: NICE; 2016 [cited 2021 Dec 8]. Available from: https://www.nice.org.uk/guidance/ng50

4. 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. 2019;13(1):1–1.

5. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018 Apr;67(4):1560–99.

6. Gastroenterological Society of Australia. Hepatocellular Carcinoma Consensus Statement Working Group. Australian recommendations for the management of hepatocellular carcinoma: a consensus statement. [Internet]. Melbourne: Gastroenterological Society of Australia; 2020 [cited 2022 Sep 12]. Available from: https://www.gesa.org.au/resources/hepatocellular-carcinoma-hcc-management-consensus/

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

8. AGREE Next Steps Consortium. The AGREE II Instrument [Internet]. 2017. Available from: http://www.agreetrust.org/resource-centre/agree-ii/

9. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022) [Internet]. Cochrane; 2022. Available from: www.training.cochrane.org/handbook

10. Eldridge S, Campbell MK, Campbell MJ, Drahota AK, Giraudeau B, Reeves BC, et al. Revised Cochrane risk of bias tool for randomized trials (RoB 2) Additional considerations for cluster-randomized trials (RoB 2 CRT) [Internet]. 2021 [cited 2022 Feb 1]. Available from: https://drive.google.com/file/d/1yDQtDkrp68_8kJiIUdbongK99sx7RFI-/view

11. Kirk M, Smurthwaite K, Braunig J, Trevener S, D'Este C, Lucas R, et al. The PFAS Health Study: Systematic Literature Review [Internet]. Canberra: The Australian National University; 2018. p. 161–3. Available from: https://openresearch-repository.anu.edu.au/handle/1885/241032

12. Odnoletkova I, Goderis G, Pil L, Nobels F, Aertgeerts B, Annemans L, et al. Cost-Effectiveness of Therapeutic Education to Prevent the Development and Progression of Type 2 Diabetes: Systematic Review. J Diabetes Metab. 2014;05(09):in appendix.

13. NHMRC. Guidelines for Guidelines: Assessing certainty of evidence [Internet]. 2019. Available from: https://nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence

14. Murad MH, Mustafa RA, Schünemann HJ, Sultan S, Santesso N. Rating the certainty in evidence in the absence of a single estimate of effect. Evid Based Med. 2017 Jun;22(3):85–7.

15. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol. 2011 Dec;64(12):1283–93.

16. Zeng L, Brignardello-Petersen R, Hultcrantz M, Siemieniuk RAC, Santesso N, Traversy G, et al. GRADE guidelines 32: GRADE offers guidance on choosing targets of GRADE certainty of evidence ratings. J Clin Epidemiol. 2021 Sep;137:163–75.

17. Brignardello-Petersen R, Guyatt GH, Mustafa RA, Chu DK, Hultcrantz M, Schünemann HJ, et al. GRADE guidelines 33: Addressing imprecision in a network meta-analysis. J Clin Epidemiol. 2021 Nov;139:49–56.

18. Brunetti M, Shemilt I, Pregno S, Vale L, Oxman AD, Lord J, et al. GRADE guidelines: 10. Considering resource use and rating the quality of economic evidence. J Clin Epidemiol. 2013 Feb;66(2):140–50.

19. Holger Schünemann, Jan Brożek, Gordon Guyatt, Andrew Oxman. GRADE Handbook - Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach [Internet]. 2013 [cited 2022 Apr 26]. Available from: https://gdt.gradepro.org/app/handbook/handbook.html

20. Brozek JL, Canelo-Aybar C, Akl EA, Bowen JM, Bucher J, Chiu WA, et al. GRADE Guidelines 30: the GRADE approach to assessing the certainty of modeled evidence—An overview in the context of health decision-making. J Clin Epidemiol. 2021 Jan;129:138–50.

21. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol. 2004 Jul;130(7):417–22.

22. 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):204–9.

23. 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 May;50(5):990–8.

24. 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. Asian Pac J Cancer Prev. 2014 Nov 6;15(20):8993–9004.

25. Chang Y, Lairson DR, Chan W, Lu SN, Aoki N. Cost-effectiveness of screening for hepatocellular carcinoma among subjects at different levels of risk: Cost-effectiveness of screening for HCC. J Eval Clin Pract. 2011 Apr;17(2):261–7.

26. 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.

27. Farhang Zangneh H, Wong WWL, 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 Aug;17(9):1840-1849.e16.

28. 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 Open. 2021 Jun 24;4(6):e2114680.

29. 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.

30. 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 Health. 2021 Oct;24(10):1454–62.

31. 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 Apr 19;OF1–8.

32. 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 Dec;65(6):1086–93.

33. Parikh ND, Singal AG, Hutton DW, Tapper EB. Cost-Effectiveness of Hepatocellular Carcinoma Surveillance: An Assessment of Benefits and Harms. Am J Gastroenterol. 2020 Oct;115(10):1642–9.

34. 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):1418–24.

35. 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 Apr;98(7):1166–75.

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

37. 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. 2010/06/16 ed. 2010 May;25(5):951–6.

38. 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. Intern Med J. 2013 Jul;43(7):772–7.

39. 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 Feb;1(1):53–60.

40. 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):551–6.

41. Byford S, Raftery J. Economics notes: Perspectives in economic evaluation. BMJ. 1998 May 16;316(7143):1529–30.

42. Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun Wong V, Castellanos M, Aller-de la Fuente R, Metwally M, et al. Fibrosis Severity as a Determinant of Cause-Specific Mortality in Patients With Advanced Nonalcoholic Fatty Liver Disease: A Multi-National Cohort Study. Gastroenterology. 2018 Aug 1;155(2):443-457.e17.

43. 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 Aug;21(8):938–43.

44. Hong TP. An Australian population-based study of the incidence and outcomes of hepatocellular carcinoma: the Hepatomas of Melbourne Epidemiological Research (HoMER) study [Internet]. 2019 [cited 2019 Jul 11]. Available from: http://hdl.handle.net/11343/225659

45. Wallace MC, Preen DB, Short MW, Adams LA, Jeffrey GP. Hepatocellular carcinoma in Australia 1982-2014: Increasing incidence and improving survival. Liver Int. 2019 Mar;39(3):522–30.

46. Nguyen ALT, Si L, Lubel JS, Shackel N, Yee KC, Wilson M, et al. Construction and validation of a microsimulation model for hepatocellular carcinoma surveillance in Australia. In Submission;

47. Alavi M, Law MG, Grebely J, Amin J, Hajarizadeh B, George J, et al. Time to decompensated cirrhosis and hepatocellular carcinoma after an HBV or HCV notification: A population-based study. J Hepatol. 2016 Nov;65(5):879–87.

48. Jepsen P, Vilstrup H, Andersen PK. The clinical course of cirrhosis: The importance of multistate models and competing risks analysis. Hepatology. 2015 Jul 1;62(1):292–302.

49. Canfell K, Kim JJ, Brisson M, Keane A, Simms KT, Caruana M, et al. Mortality impact of achieving WHO cervical cancer elimination targets: a comparative modelling analysis in 78 low-income and lower-middle-income countries. The Lancet. 2020 Feb;395(10224):591–603.

50. Haq MI, Drake TM, Goh TL, Ahmed A, Forrest E, Barclay S, et al. Effect of Hepatocellular Carcinoma Surveillance Programmes on Overall Survival in a Mixed Cirrhotic UK Population: A Prospective, Longitudinal Cohort Study. J Clin Med. 2021 Jun 24;10(13):2770.

51. Consumer Price Index, Australia, March 2022 | Australian Bureau of Statistics [Internet]. 2022 [cited 2022 Jun 12]. Available from: https://www.abs.gov.au/statistics/economy/price-indexes-and-inflation/consumer-price-index-australia/latest-release

52. Department of Health, Australian Government. MBS Online: Medicare Benefits Schedule. [homepage on the internet] [Internet]. Canberra, ACT: Commonwealth of Australia; Available from: http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/Home

53. Xiao Y, Howell J, Gemert C, Thompson AJ, Seaman CP, McCulloch K, et al. Enhancing the hepatitis B care cascade in Australia: A cost-effectiveness model. J Viral Hepat. 2020 May;27(5):526–36.

54. Reeve R, Srasuebkul P, Langton JM, Haas M, Viney R, Pearson SA, et al. Health care use and costs at the end of life: a comparison of elderly Australian decedents with and without a cancer history. BMC Palliat Care. 2017 Jun 21;17(1):1.

55. McPhail SM, Amarasena S, Stuart KA, Hayward K, Gupta R, Brain D, et al. Assessment of health-related quality of life and health utilities in Australian patients with cirrhosis. JGH Open. 2021 Jan;5(1):133–42.

56. Global Burden of Disease Collaborative Network. Global Burden of Disease (GBD 2019) [Internet]. Seattle, United States of America: Institute for Health Metrics and Evaluation (IHME); 2021 [cited 2022 Jun 12]. Available from: https://www.healthdata.org/gbd/2019

57. 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 Jan;44(1):217–31.

58. NSW Cancer Registry. Data request: Hepatocellular carcinoma (coded as C22.0 or C22.9) incidence and mortality). Private communication; unpublished.; 2021 Aug.

59. Tzartzeva K, Obi J, Rich NE, Parikh ND, Marrero JA, Yopp A, et al. Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Patients With Cirrhosis: A Meta-analysis. Gastroenterology. 2018 May 1;154(6):1706-1718.e1.

60. Cheng RM. Novel Biomarkers of Hepatocellular Carcinoma [Internet]. The University of Sydney; 2018. Available from: http://hdl.handle.net/2123/20294

61. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. Circulation. 2016 Feb 9;133(6):601–9.

62. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. Stat Med. 2017 Nov 30;36(27):4391–400.

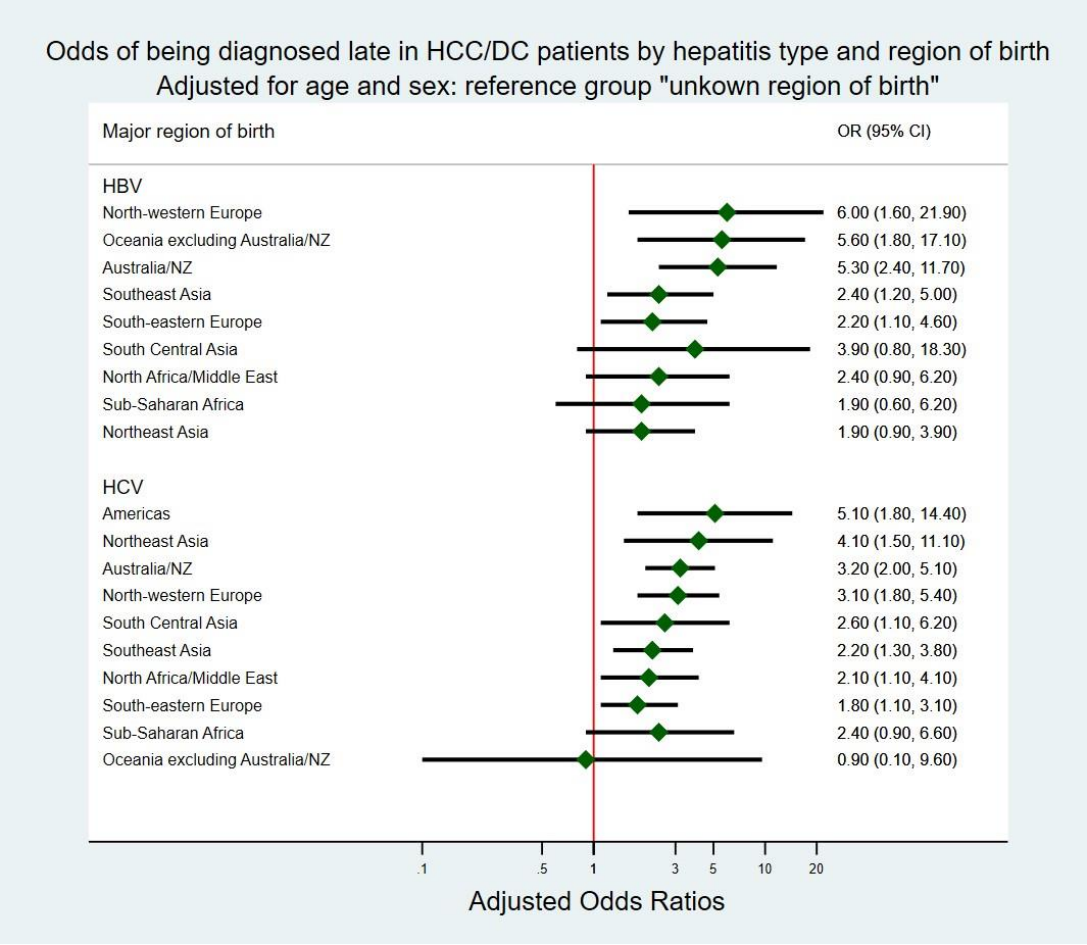
Appendix E. Data on Sub-Saharan African-born population in Australia

Supplement to *Clinical practice guidelines for hepatocellular carcinoma surveillance for people at high risk in Australia* – Chapter 7, containing data produced by The Doherty Institute and data extracted from the 2016 Australian Census Data.

Incidence of late diagnosis

In Victoria, there is no statistically robust evidence that those born in sub-Saharan Africa are more or less likely to experience late diagnosis of chronic hepatitis B (HBV) relative to incidence of hepatocellular carcinoma (HCC) and/or decompensated cirrhosis (DC). However, this analysis is limited by low sample size. In general, late diagnosis was more common in those born outside of HBV endemic regions.

Figure 1: Age and sex adjusted odds of having a late diagnosis of HBV (chronic hepatitis B) or HCV (chronic hepatitis C) in patients with HCC or DC, 1997-2016, Victoria.



Cascade of HBV care, including history of receiving ultrasound

Table 1: Cascade of care indicators for Victorians with chronic HBV born in sub-Saharan Africa, 2018 (countries with sufficient sample size included).

Country of birth	Proportion who have ever had a hepatitis B viral load	Proportion who have ever had an abdominal ultrasound
Ethiopia	68.6%	73.3%
Ghana	78.8%	76.5%
Kenya	57.9%	79.0%
Liberia	86.4%	76.1%
Mauritius	69.2%	65.5%
Nigeria	67.6%	71.4%
Sierra Leone	65.7%	74.3%
Somalia	54.4%	69.2%
South Africa	58.8%	56.4%
South Sudan	87.5%	62.5%
Sudan	74.8%	77.3%
Zimbabwe	69.4%	69.4%
Sub-Saharan Africa total	64.8%	72.1%
Overseas-born total	63.5%	73.7%
Total population	57.9%	71.2%

Comparison of estimated prevalence with diagnosed cases by country of birth

Note this analysis is limited by low population numbers limiting the robustness of modelled outputs, however estimates were generated for the following countries:

- Sudan: 85.3% of cases estimated to be diagnosed*
- Somalia: 32.7%
- Ethiopia: 44.6%
- Liberia: 55.0%
- Kenya: 18.8%

It should also be considered that particularly for populations with a higher average age, a diagnosis may have occurred prior to the availability of hepatitis B notifications in Victoria (1991).

**Diagnosis represented by a positive test notified to the Victorian Government Department of Health; not necessarily representative of true clinical diagnosis.*

2021 Australian Census data for sub-Saharan African-born population in Australia

Table 2. Sub-Saharan African-born population in Australia comparison with data for the Australian population.

	Census 2021 Sub-Saharan born population in Australia (N=372,151)*		Census 2021 Australia (N=25,422,788)*	
	n	%	n	%
Sex				
Male	182,562	49.1	12,545,154	49.3
Female	189,586	50.1	12,877,635	50.7
Age group (years)				
20-29	52,849	16.0	3,351,215	17.3
30-39	69,442	21.0	3,691,909	19.1
40-49	73,245	22.2	3,284,809	17.0
50-59	61,654	18.7	3,152,858	16.3
60-69	41,972	12.7	2,766,562	14.3
70-79	22,159	6.7	1,982,689	10.2
80+	8,930	2.7	1,096,939	5.7
Educational attainment (Level of Highest Educational Attainment)				
Secondary Education (Years 9 and below)	10,653	2.9	1,490,444	5.9
Secondary Education (Years 10 and above)	76,867	20.7	6,149,224	24.2
Certificate/diploma	98,605	26.5	5,303,607	20.9
University degree or higher	138,451	37.2	5,464,626	21.5
Income (Annual)				
Negative/Nil income	32,920	8.8	1,806,408	7.7
1-15,599	25,090	6.7	2,145,502	9.2
15,600-25,999	36,251	9.7	3,173,621	13.6
26,000-41,599	41,868	11.3	2,851,856	12.2
41,600-64,999	59,971	16.1	3,143,341	13.4
65,000-90,999	54,001	14.5	2,012,548	8.6
91,000-103,999	20,235	5.4	638,966	2.7
104,000 or more	71,218	19.1	1,558,299	6.7

*Not included in table: Supplementary census data, Not stated census data, Not applicable census data

Table 3. Sub-Saharan African-born population diversity in Australia by sub-region.

Region	Census 2021 sub-Saharan born population in Australia (N=372, 151)
Central and West Africa[1]	37, 998
Southern and East Africa[2]	334, 151
Total	372, 151

[1] Benin, Burkina Faso, Cameroon, Cabo Verde, Central African Republic, Chad, Congo, Republic of Congo, Democratic Republic of Cote d'Ivoire, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria, Sao Tome and Principe, Senegal, Sierra Leone, Togo

[2]Angola, Botswana, Burundi, Comoros, Djibouti, Eritrea, Ethiopia, Kenya, Lesotho, Madagascar, Malawi, Mauritius, Mayotte, Mozambique, Namibia, Reunion, Rwanda, St Helena, Seychelles, Somalia, South Africa, Eswatini, Tanzania, Uganda, Zambia, Zimbabwe, Southern and East Africa (not elsewhere classified)

Table 4. Sub-Saharan African-born population diversity by country.

Country	n
Total	*372, 151*
Central and West Africa, nfd	126
Benin	84
Burkina Faso	54
Cameroon	520
Cabo Verde	38
Central African Republic	128
Chad	86
Congo, Republic of	2193
Congo, Democratic Republic of	6148
Cote d'Ivoire	588
Equatorial Guinea	14
Gabon	47
Gambia	114
Ghana	6322
Guinea	941
Guinea-Bissau	15
Liberia	3187
Mali	46
Mauritania	39
Niger	31
Nigeria	12883
Sao Tome and Principe	21
Senegal	423
Sierra Leone	3651
Togo	300
Southern and East Africa, nfd	319
Angola	511
Botswana	1433
Burundi	2711

Comoros	23
Djibouti	180
Eritrea	5629
Ethiopia	14092
Kenya	22348
Lesotho	134
Madagascar	311
Malawi	1503
Mauritius	25981
Mayotte	0
Mozambique	914
Namibia	1535
Reunion	182
Rwanda	1064
St Helena	34
Seychelles	2502
Somalia	8101
South Africa	189207
Eswatini	324
Tanzania	4371
Uganda	4163
Zambia	6847
Zimbabwe	39714
Southern and East Africa, nec	11

nfd: Not further defined; nec: Not elsewhere classified

Table 5. Sub-Saharan African-born population - Year of arrival in Australia.

	From region (n (%))		
Year of arrival in Australia	**Sub-Saharan Africa (Total)**	**Central and West Africa**	**Southern and East Africa**
1905-1950	355	6 (1.7)	346 (97.5)
1951-1960	1707	81 (4.7)	1630 (95.5)
1961-1970	12369	461 (3.7)	11905 (96.2)
1971-1980	19878	604 (3.0)	19276 (97.0)
1981-1990	36605	1181 (3.2)	35422 (96.8)
1991-2000	46408	2198 (4.7)	44211 (95.3)
2001-2010	131626	13447 (10.2)	118185 (89.8)
2011-2020	114663	18745 (16.3)	95916 (83.7)
Arrived 1 Jan 2021-10 Aug 2021	2507	334 (13.3)	2174 (86.7)
Not stated	6042	948 (15.7)	5093 (84.3)

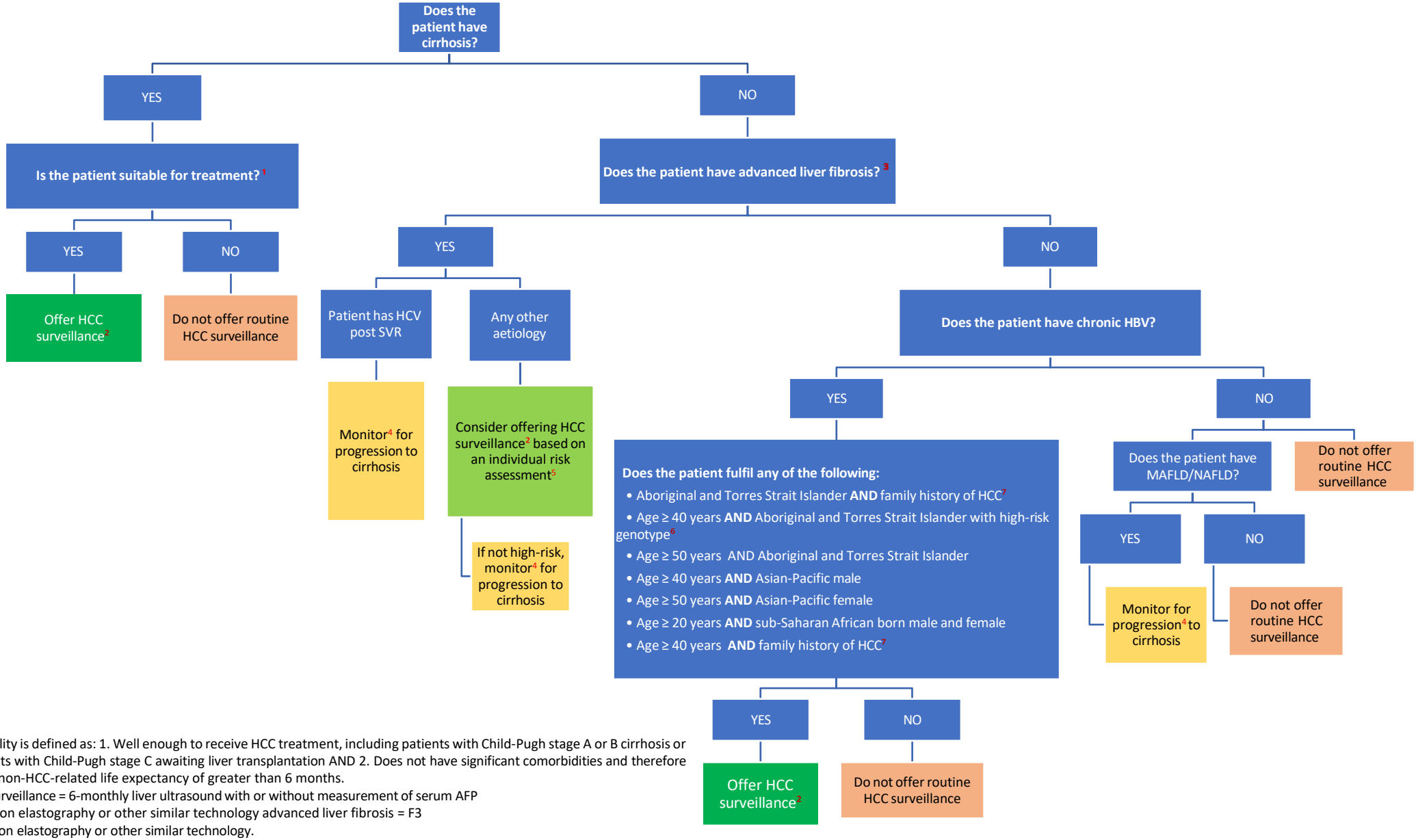
Table 6. Sub-Saharan African-born population – language spoken.

Language spoken	**n (%)**
English only	207296 (55.7)
Other language	162684 (43.72)
Not stated	2177 (0.77)

Source

Australian Bureau of Statistics. Census of population and housing (2021). TableBuilder. https://www.abs.gov.au/statistics/microdata-tablebuilder/tablebuilder. Accessed 12 Dec 2022

Appendix F. Decision aid



[1] 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.

[2] HCC surveillance = 6-monthly liver ultrasound with or without measurement of serum AFP

[3] Based on elastography or other similar technology advanced liver fibrosis = F3

[4] Based on elastography or other similar technology.

[5] Individual risk assessment would be based on individual patient risk factors and characteristics

[6] Either individually confirmed (e.g.C4) or epidemiologically likely. NB: genotype testing is not routinely offered and not subsidised through the Medicare Benefits Schedule)

[7] 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.

Appendix G. Guideline Recommendations Comparison

2023 AUSTRALIAN GUIDELINES	EXISTING GUIDELINES	COMPARISON
Adapted evidence-based recommendation: Do not routinely offer surveillance for HCC for people who have limited projected life expectancy^. *^Does have significant comorbidities and therefore has a non-HCC-related life expectancy of less than 6 months.*	• **NICE (Cirrhosis: 2016** (1)**)** Do not offer surveillance for HCC for people who are receiving end of life care.	The 2023 Australian guidelines include the terminology *"routinely offer"* and *"people who have limited projected life expectancy"*
HCC surveillance in people with liver cirrhosis		
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). *(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.*	• **NICE (Cirrhosis: 2016** (1)**)** Patients with cirrhosis (recommendations 1.2.4–1.2.6): 1. Offer ultrasound (with or without measurement of serum alpha-fetoprotein) every 6 months as surveillance for hepatocellular carcinoma (HCC) for people with cirrhosis who do not have hepatitis B virus infection. 2. For people with cirrhosis and hepatitis B virus infection, see the surveillance testing for hepatocellular carcinoma in adults with chronic hepatitis B section in NICE's hepatitis B (chronic) guideline.	No difference
	• **AASLD (HCC: 2018** (2)**)** Patients with cirrhosis (recommendations 1A-1C) 1A. The AASLD recommends surveillance of adults with cirrhosis because it improves overall survival. Quality/Certainty of Evidence: Moderate Strength of Recommendation: Strong 1C. The AASLD recommends not performing surveillance of patients with cirrhosis with Child's class C unless they are on the transplant waiting list, given the low anticipated survival for patients with Child's C cirrhosis. Quality/Certainty of the Evidence: Low Strength of Recommendation: Conditional	No difference

	• **EASL (HCC: 2018** (3)**)** Categories of adult patients in whom surveillance is recommended: 1. Cirrhotic patients, Child-Pugh stage A and B (evidence low; recommendation strong) 2. Cirrhotic patients, Child-Pugh stage C awaiting liver transplantation (evidence low; recommendation strong)	No difference
	• **GESA (HCC: 2020** (4)**)** Patients with cirrhosis (any aetiology*) 1. HCC surveillance should be offered to all patients with cirrhosis if they are suitable and willing to receive treatment. (Evidence quality: Low; Grade of recommendation: Strong) * *If patients are suitable for, and willing to receive, treatment.*	No difference
	• **GESA (HBV: 2022** (5)**)** HCC surveillance should be offered to all people with cirrhosis, as well as non-cirrhotic individuals at increased risk of HCC	No difference
	• **ASHM (HBV: 2022** (6)**)** Hepatocellular Carcinoma Surveillance is recommended for patients with CHB in these groups: o People with cirrhosis	No difference
Adapted 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 HCC treatment. *(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.*	• **GESA (HCC: 2020** (4)**)** Patients with cirrhosis **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)*	No difference
	• **APASL (HCC: 2017 update** (7)) Surveillance for HCC should be undertaken in high-risk groups of patients and is recommended (B2). The high-risk groups: o Cirrhotic hepatitis patients ▪ HBV ▪ HCV ▪ NASH	No difference

HCC surveillance in people without liver cirrhosis		
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]** *[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..*	• **WHO (HBV: 2015**(9)**)** Patients with chronic hepatitis B 1. Routine surveillance for HCC with abdominal ultrasound and alpha-fetoprotein testing every six months is recommended for: • persons with cirrhosis, regardless of age or other risk factors (Strong recommendation, low quality of evidence) • persons with a family history of HCC (Strong recommendation, low quality of evidence) • persons aged over 40 years (lower age may apply according to regional incidence of HCC), without clinical evidence of cirrhosis (or based on aspartate aminotransferase to platelet ratio index (APRI) score ≤2), and with HBV DNA level >2000 IU/mL (where HBV DNA testing is available). (Conditional recommendation, low quality of evidence)	No difference
	• **NICE (HBV: 2013 updated 2017**(10)**)** Patients with chronic hepatitis B (recommendations 17.1–17.3): • Perform 6-monthly surveillance for HCC by hepatic ultrasound and alpha-fetoprotein testing in people with significant fibrosis (METAVIR stage greater than or equal to F2 or Ishak stage greater than or equal to 3) or cirrhosis. • In people without significant fibrosis or cirrhosis (METAVIR stage less than F2 or Ishak stage less than 3), consider 6-monthly surveillance for HCC if the person is older than 40 years and has a family history of HCC and	The 2023 Australian guidelines include: - the requirement for both family history AND age > 40, - allowance for HCC surveillance at a lower age according to regional incidence of HCC in country of birth where HBV is endemic, and no specification of HBV DNA levels

	HBV DNA greater than or equal to 20,000 IU/ml. • Do not offer surveillance for HCC in people without significant fibrosis or cirrhosis (METAVIR stage less than F2 or Ishak stage less than 3) who have HBV DNA less than 20,000 IU/ml and are younger than 40 years.	
	• **EASL (HCC:2018**(3)**)** Categories of adult patients in whom surveillance is recommended: • Non-cirrhotic HBV patients at intermediate or high risk of HCC* (according to PAGE-B† classes for Caucasian subjects, respectively 10–17 and ≥18 score points) *(evidence low; recommendation weak)* ** Patients at low HCC risk left untreated for HBV and without regular six months surveillance must be reassessed at least yearly to verify progression of HCC risk.* *† PAGE-B (Platelet, Age, Gender, hepatitis B) score is based on decade of age (16–29 = 0, 30–39 = 2, 40–49 = 4, 50–59 = 6, 60–69 = 8, ≥70 = 10), gender (M = 6, F = 0) and platelet count (≥200,000/µl = 0, 100,000–199,999/µl = 1, <100,000/µl = 2): a total sum of ≤9 is considered at low risk of HCC (almost 0% HCC at five years) a score of 10–17 at intermediate risk (3% incidence HCC at five years) and ≥18 is at high risk (17% HCC at five years).*	The 2023 Australian guidelines do not include specification of HBV DNA levels
	• **AASLD (HBV: 2018**(8)**)** Guidance Statements for HCC Screening in Hepatitis B surface antigen (HBsAg)-Positive Persons: • For HBsAg-positive persons at high risk for HCC who are living in areas where ultrasound is not readily available, screening with AFP every 6 months should be performed. • All HBsAg-positive patients with cirrhosis should be screened with ultrasound examination with or without AFP every 6 months.	The 2023 Australian guidelines do not include a recommendation to provide HCC surveillance using AFP alone.
	• **GESA (HCC: 2020**(4)**)** Patients with chronic hepatitis B • HCC surveillance should be undertaken in noncirrhotic individuals with chronic hepatitis B infection who are at increased risk of HCC. (Evidence quality: Low; Grade of recommendation: Strong)	No difference
	• **GESA (HBV: 2022**(5)**)** Liver ultrasound should be performed every 6 months in people with CHB infection who require HCC surveillance. • Populations with chronic hepatitis B in whom surveillance for HCC should be performed:	The 2023 Australian guidelines include: - the requirement for both family history AND age > 40, no specification of coinfection with

	• People without cirrhosis: • With coinfection with hepatitis delta virus • With family history of HCC (first-degree relative) • Observed HBsAg loss with prior indications for HCC surveillance	hepatitis delta virus or observed HBsAg loss
	• **APASL (HCC: 2017 update** (7)) Surveillance for HCC should be undertaken in high-risk groups of patients and is recommended (B2). The high-risk groups: • Cirrhotic hepatitis patients • HBV • Chronic HBV carriers • Noncirrhotic (HBsAg positive) • History of HCC in the family	The 2023 Australian guidelines include: - the requirement for both family history AND age > 40, consideration for the age of the earliest case in the family in determining the age to start HCC surveillance
	• **ASHM (HBV: 2022** (6)**)** Hepatocellular Carcinoma Surveillance is recommended for patients with CHB in these groups: • Anyone with a family history of HCC (first-degree relative)	The 2023 Australian guidelines include: - the requirement for both family history AND age > 40, - consideration for the age of the earliest case in the family in determining the age to start HCC surveillance
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.*		

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. *[#] Fibrosis stage should be based on the pre-treatment assessment.*	• **EASL (HCC: 2018** (3)**)** Categories of adult patients in whom surveillance is recommended: . - Non-cirrhotic F3 patients, regardless of aetiology may be considered for surveillance based on an individual risk assessment *(evidence low; recommendation weak)*	The 2023 Australian guidelines include the terminology *"People with HCV and F3 fibrosis", "Sustained virologic response to DAA treatment"* and *"Do not routinely offer HCC surveillance"*
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.*	Not applicable	Not applicable
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 (with 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.*	Not applicable	Not applicable

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.*	Not applicable	Not applicable
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.*	Not applicable	Not applicable
HCC surveillance in Aboriginal and Torres Strait Islander people		
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.	• **GESA (HCC: 2020** (4)**)** Populations in whom surveillance of HCC should be performed: • People with chronic hepatitis B infection without cirrhosis: ▪ Indigenous and Torres Strait Islander people older than 50 years ** If patients are suitable for, and willing to receive, treatment.*	No difference
	• **GESA (HBV: 2022** (5)**)** Populations with chronic hepatitis B in whom surveillance for HCC should be performed: 1. People without cirrhosis: ` ○ Aboriginal and Torres Strait Islander people older than 50 years† † Based on Northern Territory linkage data	No difference

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 if the genotype is epidemiologically likely. **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.*	• **GESA (HCC: 2020** (4)**)** Populations in whom surveillance of HCC should be performed: • People with chronic hepatitis B infection without cirrhosis: ▪ Indigenous and Torres Strait Islander people older than 50 years ** If patients are suitable for, and willing to receive, treatment.*	Differences: The 2023 Australian guidelines specify HCC surveillance if there is a family history of HCC OR a younger age (≥ 40) with a high-risk HBV genotype
	• **GESA (HBV: 2022** (5)**)** Populations with chronic hepatitis B in whom surveillance for HCC should be performed: • People without cirrhosis: ` ▪ Aboriginal and Torres Strait Islander people older than 50 years† † Based on Northern Territory linkage data	Differences: The 2023 Australian guidelines specify a younger age (≥ 40) with high-risk features
	• **ASHM (HBV: 2022** (6)**)** Hepatocellular Carcinoma Surveillance is recommended for patients with CHB in these groups: • Aboriginal and Torres Strait Islander people > 50 years • Anyone with a family history of HCC (first-degree relative)	The 2023 Australian guidelines specify a younger age (≥ 40) with high-risk features

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.	Not applicable	Not applicable
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.	Not applicable	Not applicable
HCC surveillance in people of Asian or Pacific background		
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**	• **AASLD (HBV: 2018** (8)**)** HBsAg-positive adults at high risk for HCC (including Asian or black men over 40 years and Asian women over 50 years of age), persons with a first-degree family member with a history of HCC, or persons with HDV should be screened with ultrasound examination with or without AFP every 6 months.	No difference
	• **GESA (HCC: 2020** (4)**)** Populations in whom surveillance of HCC should be performed: - Asian men older than 40 years - Asian women older than 50 years *If patients are suitable for, and willing to receive, treatment.*	No difference

background without chronic HBV infection, follow recommendations in these guidelines based on their aetiology.	• **GESA (HBV: 2022** (5)**)** Populations with chronic hepatitis B in whom surveillance for HCC should be performed: ○ Māori and Pacific Islander men older than 40 years and women older than 50 years* ○ People without cirrhosis: ○ Asian men older than 40 years ○ Asian women older than 50 years ** Reliable data not available, but HCC incidence is likely to be increased.*	No difference
	• **APASL (HCC: 2017 update** (7)) Surveillance for HCC should be undertaken in high-risk groups of patients and is recommended (B2). The high-risk groups: • Chronic HBV carriers • Asian females >50years • Asian males >40 years	No difference
	• **ASHM (HBV: 2022** (6)**)** Hepatocellular Carcinoma Surveillance is recommended for patients with CHB in these groups: • Asian males > 40 years • Asian females > 50 years • Maori and Pacific Islander females > 50 years • Maori and Pacific Islander males > 40 years	No difference
HCC surveillance in people of sub-Saharan African background		
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**	• **AASLD (HBV: 2018**(8)**)** HBsAg-positive adults at high risk for HCC (including Asian or black men over 40 years and Asian women over 50 years of age), persons with a first-degree family member with a history of HCC, or persons with HDV should be screened with ultrasound examination with or without AFP every 6 months.	The 2023 Australian guidelines state HCC surveillance could be considered for anyone born in sub-Saharan Africa 20 years and over.
	• **GESA (HCC: 2020**(4)**)** Populations in whom surveillance of HCC should be performed • People with chronic hepatitis B infection without cirrhosis: ▪ Sub-Saharan Africans older than 20 years	The 2023 Australian guidelines include the terminology *"Consider family history when determining age to commence HCC surveillance"*
	• **GESA (HBV: 2022** (5)**)** Populations with chronic hepatitis B in whom surveillance for HCC should be performed: • People without cirrhosis: ▪ Sub-Saharan Africans older than 20 years* ** Reliable data not available, but HCC incidence is likely to be increased.*	

background 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.*	• **APASL (HCC: 2017 update** (7)) Surveillance for HCC should be undertaken in high-risk groups of patients and is recommended (B2). The high-risk groups: • Chronic HBV carriers • Africans aged >20 years	
	• **ASHM (HBV: 2022** (6)**)** Hepatocellular Carcinoma Surveillance is recommended for patients with CHB in these groups: • Sub-Saharan African people > 20 years • Anyone with a family history of HCC (first-degree relative)	
HCC surveillance in Australia: Effectiveness and cost-effectiveness		
Evidence-based recommendation: In people for whom HCC surveillance is recommended, consider offering 6-monthly alpha-fetoprotein testing in addition to ultrasound.	• **GESA (HCC: 2020** (4)**)** 3. Surveillance for HCC should be undertaken using liver ultrasound every 6 months. 4. Combining alpha-fetoprotein testing with liver ultrasound may be considered for surveillance of HCC.	No difference
	• **AASLD (HCC: 2018** (2)**)** Patients with cirrhosis (recommendations 1A-1C) 1B. The AASLD recommends surveillance using ultrasound, with or without AFP, every 6 months. Quality/Certainty of Evidence: Low Strength of Recommendation: Conditional	No difference
	• **EASL (HCC: 2018** (3)**)** Patients at high risk of developing HCC: Tumour biomarkers for accurate early detection are still lacking. The data available show that the biomarkers tested (i.e. Alphafeto-protein (AFP), Lectin-reactive alphafeto-protein (AFP-L3) and des-gamma-carboxyprothrombin (DCP)) are suboptimal in terms of cost-effectiveness for routine surveillance of early HCC *(evidence low).*	No specifications for tumour biomarker testing alone.
	• **APASL (HCC: 2017 update** (7)) The combination of US and serum AFP measurement performed biannually should be used as a surveillance strategy for HCC (B2.)	The 2023 Australian guidelines include the terminology consider offering to AFP with ultrasound

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.		
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.		

References

1. National Institute for Health and Care Excellence. Cirrhosis in Over 16s: Assessment and Management. NICE guideline [NG50] [Internet]. London: NICE; 2016 [cited 2021 Dec 8]. Available from: https://www.nice.org.uk/guidance/ng50

2. 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. 2019;13(1):1–1.

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

4. Gastroenterological Society of Australia. Hepatocellular Carcinoma Consensus Statement Working Group. Australian recommendations for the management of hepatocellular carcinoma: a consensus statement. [Internet]. Melbourne: Gastroenterological Society of Australia; 2020 [cited 2022 Sep 12]. Available from: https://www.gesa.org.au/resources/hepatocellular-carcinoma-hcc-management-consensus/

5. Gastroenterological Society of Australia. Australian consensus recommendations for the management of hepatitis B infection. Melbourne: Gastroenterological Society of Australia; 2022.

6. Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM). Decision making in Hepatitis B [Internet]. [cited 2023 Jan 30]. Available from: https://ashm.org.au/wp-content/uploads/2022/08/ASHM-Decision-Making-in-Hepatitis-B-2021- update-2.pdf

7. Omata M, Cheng AL, 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 Jul;11(4):317–70.

8. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018 Apr;67(4):1560–99.

9. World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2015. 134 p.

10. National Institute for Health and Care Excellence. Hepatitis B (chronic); diagnosis and management. Clinical guideline [CG165] Last updated October 2017 [Internet]. London: NICE; 2013 [cited 2022 Jun 16]. Available from: https://www.nice.org.uk/guidance/cg165

Appendix H1. NHMRC requirements

Governance and stakeholder involvement

Mandatory requirement	Fulfilled	Location in document
A.1 The organisation/s responsible for developing and publishing the guideline is/are named.	Yes	Guidelines, Administrative report
A.2 Sources of funding for guideline development, publication and dissemination are stated.	Yes	Guidelines, Administrative report
A.3 A multidisciplinary group that includes end-users, relevant disciplines and clinical experts is convened to develop the purposes, scope and content of the guideline, and the process and criteria for selecting member are described.	Yes	Guidelines, Administrative report
A.4 Consumers participate in the guideline development, and the processes employed to recruit, involve and support consumer participants are described.	Yes	Guidelines, Administrative report
A.5 A complete list of all the people involved in the guideline development process is provided, including the following information for each person: name, profession or discipline, organisational affiliation and role in the guideline development process.	Yes	Guidelines
A.6 Potential competing interests are identified, managed and documented, and a competing interest declaration is completed by each member of the guideline development group.	Yes	Guidelines, Administrative report
A.7 A list of organisations that will be approached to endorse the guideline is provided.	Yes	Guidelines, Administrative report
A.8 The guideline development process includes participation by representatives of Aboriginal and Torres Strait Islander peoples and culturally and linguistically diverse communities (as appropriate to the clinical need and context), and the processes employed to recruit, involve and support these participants are described.	Yes	Guidelines, Administrative report
Desirable Requirement		
A.2.1 The amount and percentage of total funding received from each funding source is stated.	No	N/A

Scope and purpose

Mandatory requirement	Fulfilled	Location in document
B.1 The purpose of the guideline is stated, including the clinical questions (see Requirement C.1), issue or problems the guideline addresses.	Yes	Guidelines, Administrative report
B.2 The health care settings to which the recommendations apply is described, including the health system level (e.g. primary care, acute care) and clinical stage (e.g. whether the guideline covers prevention, screening, assessment, treatment, rehabilitation or monitoring).	Yes	Guidelines, Administrative report
B.3. The intended end users of the guideline are clearly defined, and any relevant exceptions are identified.	Yes	Guidelines, Administrative report
B.4 The population to which the guideline recommendations will apply is defined (e.g. children, adolescents, adults or older adults) and population subgroups for which specific information is required are identified and described.	Yes	Guidelines, Administrative report
B.5 Issues relevant to Aboriginal and Torres Strait Islander peoples (such as particular risks, treatment considerations or sociocultural considerations) are identified and described	Yes	Guidelines
Desirable requirement		
B.5.1 Issues relevant to special-needs groups such as culturally and linguistically diverse communities or groups with low socioeconomic status (e.g. particular risks, treatment considerations or sociocultural considerations) are identified and described.	Yes	Guidelines

Evidence review

Mandatory requirement	Fulfilled	Location in document
C.1 Clinical questions addressed by the guideline are stated in a structured and consistent format to define the boundaries of the topic, i.e. by specifying the relevant population, intervention/s (e.g. treatment/s or diagnostic test/s), comparator/s and outcomes measured.	Yes	Technical report, Guidelines
C.2. Systematic searches for evidence are undertaken and the search strategy is documented, including the search terms and databases searched.	Yes	Technical report
C.3. The population groups specified in the search strategy include Aboriginal and Torres Strait Islander peoples and any population subgroups that have been identified (see Requirement B.4 and B5).	Yes	Technical report

C.4. The publication period covered by the searches is stated, and the latest date is within 12 months of the first day of public consultation and within 20 months of submission of the final draft guideline to NHMRC for approval.	Yes	Technical report
C.5. The inclusion and exclusion criteria used to select studies for appraisal are described.	Yes	Technical report
C.6. For each clinical question, the developer has provided an evidence table, which summarises the systematic assessment and critical appraisal of all studies that meet the inclusion criteria (i.e. the body of evidence on which a recommendation will be based). Each evidence table should include information on study design, outcomes, level of evidence, the findings of meta-analysis (if performed) and other relevant information.	Yes	Technical report
C.7 For each clinical question, the developer has provided an evidence statement form, which documents the synthesis and evaluation of the body of evidence to determine the grade of each recommendation, in accordance with NHMRC-approved method (GRADE8).	Yes	Technical report
C.8 For each recommendation, the developer has provided an evidence summary, which briefly states the outcomes of each clinical studies on which the recommendation was based.	Yes	Guidelines
C.9 A recommended date for future update of the guideline is identified.	Yes	Guidelines
Desirable requirement		
C.3.1 The population groups specified in the search strategy include groups such as culturally and linguistically diverse communities or other groups for whom specific sociocultural factors (including ethnicity, gender, age, disability, socioeconomic status and location) in prevention or treatment outcomes should be considered.	Yes	Technical report
C.3.2 Search strategies include search terms to identify evidence related to consumers' perceptions and experiences.	No	N/A
C.3.3 Dependent on the guideline scope, the search strategy is designed to identify evidence for all relevant alternatives for screening, prevention, diagnosis or treatment of the condition addressed by the guideline, including relevant complementary and alternative medicine approaches.	No	N/A
C.3.4 Search strategies include search terms to identify evidence related to cost effectiveness and resource implications of practice.	Yes	Technical report, Guidelines

C.8.1 If gaps in the evidence are identified during the evidence review, these are described in the guideline and areas for further research are noted.	Yes	Guidelines

Guideline recommendations

Mandatory requirement	Fulfilled	Location in document
D.1 The wording of recommendations is specific, unambiguous, clearly describes the action/s to be taken by users and matches the strength of the body of evidence.	Yes	Guidelines
D.2 The wording of recommendations is written in plain English and is consistent throughout the guideline.	Yes	Guidelines
D.3 For each evidence-based recommendation, the supporting references are listed and the grade of recommendation is indicated in accordance with NHMRC-approved method (GRADE8).	Yes	Guidelines
D.4 Recommendations formulated in the absence of quality evidence (where a systematic review of the evidence was conducted as part of the search strategy) are clearly labelled. The preferred term for this type of recommendation is a consensus-based recommendation.	Yes	Guidelines
D.5 Any further recommendations included in the guideline, where the subject matter is outside of the scope of search strategy, are clearly labelled as such. The preferred term for this type of recommendation is a practice point.	Yes	Guidelines
D.6 The method used to arrive at consensus-based recommendations or practice points (Requirements D.4 and D.5) (e.g. voting or formal methods, such as Delphi) is documented.	Yes	Administrative report
D.7 Areas of major debate about the evidence and the recommendations are identified and the various significant viewpoints are outlined in the guideline text (even if the guideline development working group members eventually reached a decision).	Yes	Guidelines
D.8 The strengths and limitations of the body of evidence reviewed are described in the guideline text and areas of uncertainty are acknowledged.	Yes	Guidelines
D.9 The guideline acknowledges current national guideline recommendations approved by NHMRC or endorsed by major authorities, and any deviations from these are explicitly noted in the guideline text and the rationale provided.	Yes	Guidelines
D.10 Where a guideline makes any recommendation/s specifying intervention/s that are	No	N/A

not available or restricted in Australia, the text clearly indicates this, and the developer has consulted the relevant authority/ies (see Requirement F.3).		
D.11 Where evidence is identified showing that Aboriginal and Torres Strait Islander peoples or other population groups have specific prevention or treatment outcomes, this evidence is clearly identified and considered in the formulation of the recommendations.	Yes	Guidelines
D.12 The harms (risks or side effects) and benefits of each recommended intervention and its alternatives are described in the guideline text and the rationale for the recommendation is explained.	No	N/A
D.13 Any safety, legal or potential misuse issues related to the clinical recommendations are identified and described in the guideline text.	No	N/A
D.14 The potential impact of each recommendation on clinical practice or outcomes is described in the text.	Yes	Guidelines
D.15 The guideline and recommendations have been assessed by at least 2 reviewers, independent of the guideline development process, using the AGREE II instrument.3, 5	Yes	Administrative report
Desirable requirement		
D.2.1 Recommendations are formulated using consistent grammar, syntax and wordings, so they can readily be adapted for electronic implementation strategies (e.g. electronic decision support systems and automatic data collection).	Yes	Guidelines
D.8.1 Recommendations that are likely to be affected by new evidence after the guideline has been approved (e.g. major clinical trials underway at the time of guideline publication) are identified and the implications for the guideline recommendations are explained in the guideline text.	Yes	Guidelines
D.9.1 Clinical recommendations that deviate from current practice are identified.	Yes	Guidelines
D.9.2 The resource implications and cost effectiveness of any recommended practice, compared with current or established practice, are explicitly stated in the guideline text.	Yes	Guidelines
D.11.1 Where evidence is identified showing that sociocultural factors (including ethnicity, gender, age, disability, socioeconomic status and location) affect treatment or prevention outcomes (see Requirement C.3.1), this evidence is clearly	Yes	Guidelines

identified and considered in the formulation of the recommendations.		
D.12.1 Absolute measures of both efficacy and harm are stated for each management option where evidence is available, e.g. expressed as number needed to treat (NNT), number needed to screen (NNS), or number needed to harm (NNH) as relevant to the recommendation	Not relevant	N/A
D.13.1 Ethical issues are considered when formulating the recommendations and any such issues identified and described	Yes	Guidelines
D.16 If evidence for complementary and alternative medicine options is identified, the risks and benefits of these are stated in the guideline text and appropriate recommendations included.	No	N/A
D.17 If there is a lack of rigorous evidence for a complementary and alternative medicine/therapy commonly used in practice, this is explicitly stated in the guideline text.	No	N/A
D.18 Recommendations that consider consumer self-management options are included, where relevant.	No	N/A
D.19 Recommendations emphasise consumer and carer involvement in treatment and care decisions, where relevant.	No	N/A

Guideline structure and style

Mandatory requirement	Fulfilled	Location in document
E.1 The guideline includes a title page listing: (i) the date of publication (ii) the authorship (organisation or individuals) (iii) the publisher (iv) copyright information including the copyright holder (v) address for requesting permission to reproduce material in the text (vi) the ISBN number (vii) a preferred citation for the guideline publication.	Yes	Guidelines
E.2 The guideline is easy to navigate and includes a table of contents or index with hyperlinks or bookmarks to facilitate navigation.	Yes	Guidelines

E.3 The guideline includes a brief (e.g. 1-page) plain English summary.	Yes	Guidelines
E.4 The guideline includes an executive summary that lists all recommendations and their grade using NHMRC-approved method (GRADE). The summary of recommendations is available as a separate document, and the guideline text states where to obtain this document.	Yes	Guidelines, Summary of recommendations
E.5 A glossary of technical terms, acronyms and abbreviations is provided, and terms are used consistently throughout the guideline.	Yes	Guidelines
E.6 Where medicines are mentioned in the guideline, generic names are used and brand names are avoided.	Yes	Guidelines
E.7 The document design and layout enables recommendations to be identified easily within the text and is suitable for people with visual impairment.	Yes	Guidelines
E.8 References in the text are clearly identified and the citations clearly listed. For electronic references, the source location (e.g. website address) and date accessed is stated.	Yes	Guidelines
E.9 Chapter and heading levels are consistent, clearly distinguishable by the document design and layout, and assist with the navigation throughout each topic of the guideline.	Yes	Guidelines
E.10 The guideline information is sequenced in a logical manner which is applicable to the intended end user.	Yes	Guidelines
E.11 The technical report is either (i) included in the guideline document, or (ii) provided in a readily accessible location, such as a website, which is indicated in the guideline.	Yes	Guidelines
E.12 The administrative report is either (i) included in the guideline document, or (ii) provided in a readily accessible location, such as a website, which is indicated in the guideline.	Yes	Guidelines

Public consultation

Mandatory requirement	Fulfilled	Location in document
F.1 The process for public consultation on the draft guideline complies with Section 14A of the NHMRC Act 1992 (Cwlth) and accompanying regulations.	Yes	Administrative report
F.2 Details of submissions received during public consultation and the response of the guideline development working group to the submissions (including whether, why and how the guideline was	Yes	Public consultation submissions summary

altered) are provided as a separate document to the NHMRC.		
F.3 During the public consultation period, the developer has undertaken and documented consultation with: • the Director-General, Chief Executive or Secretary of each state, territory and Commonwealth health department • other relevant government departments as appropriate to your guideline topic • relevant authority/iesv , when a guideline makes any recommendation/s specifying interventions that are not available or restricted in Australia (see Requirement D.10).	Yes	Administrative report, Public consultation submissions summary
F.4 The developer has identified and consulted with key professional organisations (such as specialty colleges) and consumer organisations that will be involved in, or affected by, the implementation of the clinical recommendations of the guideline.	Yes	Administrative report, Public consultation submissions summary
Desirable requirement		
F.2.1 A version of the public consultation submissions summary is publicly available, with submissions de-identified.	Yes	Administrative report, Public consultation submissions summary

Dissemination and implementation of guidelines

Mandatory requirement	**Fulfilled**	**Location in document**
G.1 A plan for the dissemination of the guideline is submitted as a separate document from the clinical practice guideline	Yes	Dissemination plan
G.2 Key recommendations that are most likely to lead to improvements in health outcomes are highlighted for consideration in implementation.	Yes	Dissemination plan
Desirable requirement		
G.3 A practical implementation plan is provided as a separate document, based on: - considerations of the Australian health care context and identification of appropriate - organisation/s where the key recommendations may be directed.	Yes	Dissemination plan
G.4 Resources to support implementation of the guidelines are developed, such as summaries and other tools for different health care professionals, and the guideline indicates where these can be obtained	Yes	Dissemination plan

G.5 Accompanying consumer information is provided.	No	N/A
G.6 Versions of the plain English summary and consumer information are available in different languages, if appropriate.	No	N/A
G.7 Suggestions for local adaptation and adoption of the guideline are provided.	No	N/A
G.8 Measures are developed for determining the extent to which key guideline recommendations are implemented.	No	N/A
G.9 An evaluation strategy is developed and described to assess the extent to which guideline recommendations are adopted into routine practice.	No	N/A

Appendix H2. Administrative report

Date: February 2023

1. Background

Liver cancer in Australia was estimated to result in 2,905 new cancer cases and 2,492 cancer deaths in 2022, and these rates are 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 due to liver cancer increased from 2.3 to an estimated 7.3 per 100,000 population (11).

Survival rates for liver cancer are poor, with many patients diagnosed at a late stage when curative treatment is not available. Given the growing burden of liver cancer and poor survival outcomes, opportunities to improve outcomes are actively being sought. Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, and its active surveillance is a promising intervention to facilitate early detection. HCC surveillance, as implemented internationally, targets people with cirrhosis as well as high-risk people such as those with chronic hepatitis infections, using ultrasound and/or measurement alpha-fetoprotein, which can detect early lesions and/or early-stage tumours when curative treatment or improved survival is possible.

Previous work has highlighted the lack of official guidelines based on systematic reviews of the evidence specific to the Australian context. HCC surveillance provision in Australia is guided by international guidelines, some of which are based on systematic review, and a recently developed Australian expert consensus statement. Current practice indicates a clear need for the development of evidence-based HCC surveillance guidelines for the Australian context that consider risk categorisation and priority populations at a national level.

A. Purpose and scope

These clinical practice guidelines were developed as part of a project entitled “Roadmap to Liver Cancer Control” constituting one component of Phase 2 of the “Roadmap” and based on the result of a scoping review conducted in Phase 1. Based on the evidence and current practice identified in Phase 1, the Expert Advisory Group formulated the following clinical questions for the guidelines:

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

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. These guidelines do not cover chronic hepatitis B (HBV)/chronic hepatitis C (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 recurrence.

B. 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.

C. Target populations

These guidelines cover a range of Australian populations:

- people at high-risk of HCC:
  - people with cirrhosis
  - people with chronic infection with HBV or HCV
  - people with ARLD
  - people with MAFLD
- people from sub-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.

D. Healthcare settings in which the guideline 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:

- general practice
- 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
- alcohol and other drug treatment services
- prison health services

E. Funding

Cancer Council Australia (CCA) was funded by the Department of Health and Aged Care to develop these guidelines. CCA sub-contracted The Daffodil Centre, a joint venture between the University of Sydney and Cancer Council NSW, to perform the systematic reviews and additional modelling, and provide project co-ordination to support guideline development.

F. 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 10 years.

2. Governance

The project was commissioned and funded by the Department of Health and Aged Care (the Department) and the guideline development was led by the Daffodil Centre (DC) on behalf of Cancer Council Australia (CCA). The DC was responsible for the project management, systematic reviews and predictive modelling of the guidelines. They worked closely with a multi-disciplinary working group. The working group was led by eminent clinicians in the area of liver disease and liver cancer, Professor Jacob George and Dr Nicole Allard. The co-Chairs were nominated by the CCA CEO, who is the convenor of the guidelines, senior executive sponsor, and is independent from the guideline experts and responsible for delivery of the guidelines. The co-Chairs were then approved by the Department.

A complete list of all members involved in the guideline development process can be found in the Clinical guidelines Appendix I.

2.1 Expert Advisory group

The Expert Advisory Group (EAG) included specialists from various disciplines as well as consumers (listed in Guidelines Appendix I) and was formed to provide guidance and expert advice on the research questions and interpretation of the evidence. The EAG was led by two co-chairs, Professor Jacob George and Dr Nicole Allard, who also jointly chaired the Working Party responsible for developing the forthcoming guidelines.

2.2 Working group

Each working group included key healthcare professional representatives and representatives. Members were selected in conjunction with the co-Chairs based on areas of expertise and clinical experience that would be most usefully applied to assessing the evidence and application of HCC surveillance. The co-Chairs aimed to ensure demographic, geographic and years in clinical practice diversity across the working group members.

Prospective members of the working group were invited by the CCA to a meeting with members of the Project Team who explained the purpose of the guidelines, the expectations of their potential involvement and answered any questions. Once they agreed to participate, each individual was asked to declare any conflicts of interest and formalise their participation. An information session was held (and recorded) for all members and then each smaller group held an introductory meeting so all members could meet each other and discuss their personal or clinical experience as related to liver disease and liver cancer. Support for all members was available through the Project Team as required.

The working group was broken down into sub-groups, which were co-ordinated by a working group lead. The lead helped the working party to work collaboratively, ensuring a balanced contribution from all members as they reviewed the evidence provided by the DC technical team. Under the lead's guidance, the working party sub-groups reviewed and discussed the results of the systematic review, edited and commented on a draft evidence summary provide by the DC technical team and developed recommendations and/or practice points to reflect the best available evidence. The sub-group deliberated on recommendations and practice points until a consensus was reached within the group. Where there was a query or discrepancy, the co-Chairs contributed to the discussion and facilitated a final decision. The DC technical team also engaged an independent Medical Editor to ensure consistency

between guideline chapters and provide editorial assistance. The co-Chairs oversaw the entire process and, where necessary, resolved any disputes.

2.3 Project team

Execution of the overall project (i.e. management and strategic leadership) was done by the project team under the guidance of the Expert Advisory Group. The project team also included members from the systematic review team and modelling team who contributed to development of the technical reports and modelling reports (a complete list of the project team can be found in the Clinical guidelines Appendix I). An experienced medical editor was also engaged to review the guidelines throughout the development process.

3. Managing conflicts of interest

Conflict of interest was assessed and managed according to Cancer Council Australia's *A Code of Practice for Declaring and Dealing with Conflicts of Interest.*

All members were asked to declare in writing any interests relevant to the project, and development of any subsequent material. The Chairs were responsible for evaluating all declarations. The evaluation of possible conflicts of interest was guided by *A Code of Practice for Declaring and Dealing with Conflicts of Interest.*

Members had the option to submit a curriculum vitae (CV) to provide details of declarations, summarise their experience, skills and publications in the liver cancer field. However, it was not compulsory to submit a CV. The Chairs could request a CV if necessary.

All members were responsible for updating their conflict of interest statements if a new interest arose. The members received a formal reminder to review their statements and ensure it was up-to-date at the start of each subsequent phase.

Throughout the development process no significant conflicts of interest were identified.

A summary of the COI declarations is published with the Clinical guidelines in Appendix J.

4. Consumer involvement

Three representatives with lived experience have been part of the larger "Roadmap to Liver Cancer Control" project since its inception and contributed to the review of Phase 1 results and, together with other experts, developing the clinical questions that have underpin the guideline development.

As part of the guideline development a Community Reference Group (CRG) was formed (members are detailed in Appendix I). This included people with lived experience of liver cancer or precursor conditions, carers, research advocates and representatives of consumer organisations and specifically representatives from groups such as Aboriginal and Torres Strait Islander Peoples, culturally and linguistically diverse communities, and people who live in rural/remote regions. Members of the CRG were recruited through contacts across the Cancer Council and EAG networks. We also used a snowballing method to identify and invite additional members for the CRG.

Prospective members of the CRG were invited to a meeting with members of the Project Team who explained the purpose of the guidelines, the expectations of their potential involvement and answered any questions. Once they agreed to participate, each individual was asked to declare any conflicts of interest and formalise their participation. An information session was held (and recorded) as well as an introductory meeting so all members could meet each other and discuss their personal or clinical experience as related to liver disease and liver cancer. Support for all CRG members was available through the Project Team as required.

The CRG reviewed the guidelines from a lived experience perspective and was engaged from the early draft through to the final draft stage. The group advised on aspects of the guideline affecting the target clinical population, including applicability, inclusivity and health literacy. The CRG also assisted in identifying any implementation issues, gaps and areas for future research.

5. Potential endorsing organisations

In addition to the National Health and Medical Research Council (NHMRC) approval, endorsement of the guidelines was sought from several organisations (listed fully in the guidelines Appendix A).

6. Independent review using the AGREE II framework

In line with NHMRC requirements, the guidelines and recommendations were assessed by two independent reviewers using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument. AGREE II is the new (2010) internationally used tool developed to assess the methodological quality and reporting of practice guidelines. The draft guidelines and recommendations were scored very highly (overall 6) by both reviewers, with no significant issues identified.

7. Public consultation

The draft guidelines were released for targeted expert consultation and public consultation over a period of 30 days in October 2022. The public consultation process complied with Section 14A of the NHMRC Act 1992 (Commonwealth) and accompanying regulations.

The draft guidelines were made publicly available on the CCA website during the public consultation period. The following organisations and individuals were specifically invited to provide feedback.

Organisations/Bodies:

- Burnet Institute
- Cancer Australia
- Cancer Council NSW
- Cancer Council QLD
- Cancer Council SA
- Cancer Council TAS
- Cancer Council VIC

- Cancer Council WA
- Cancer Institute NSW
- Gastroenterological Society of Australia (GESA)
- Liver Foundation
- National Aboriginal Community Controlled Health Organisation (NACCHO)
- The Kirby Institute
- Wellbeing South Australia
- Hepatitis Australia
- Hepatitis QLD
- Consumers Health Forum of Australia

Individuals:

- Minister for Health
- Chief Health Officer NSW
- Chief Health Officer VIC
- Chief Health Officer QLD
- Chief Health Officer WA
- Chief Health Officer SA
- Chief Health Officer NT
- Chief Health Officer ACT
- Chief Health Officer TAS

In total, eight submissions were received during the public consultation period, two of which were from individual commenters and the remaining six on behalf of organisations. Overall feedback was positive, with comments noting the need for more emphasis on cultural sensitivity and safety. One comment noted that the guidelines appeared to be a duplication of efforts with recent consensus statements. This was acknowledged and a guidelines comparison document was created (see Appendix G) to clearly outline similarities and differences with existing guidelines. The working groups, alongside the community reference group, considered all feedback submissions and agreed on appropriate amendments in response to comments and proposed changes. The final guidelines are expected to be released by May 2023.

References

1. National Institute for Health and Care Excellence. Cirrhosis in Over 16s: Assessment and Management. NICE guideline [NG50] [Internet]. London: NICE; 2016 [cited 2021 Dec 8]. Available from: https://www.nice.org.uk/guidance/ng50

2. 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. 2019;13(1):1–1.

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

4. Gastroenterological Society of Australia. Hepatocellular Carcinoma Consensus Statement Working Group. Australian recommendations for the management of hepatocellular carcinoma: a consensus statement. [Internet]. Melbourne: Gastroenterological Society of Australia; 2020 [cited 2022 Sep 12]. Available from:

https://www.gesa.org.au/resources/hepatocellular-carcinoma-hcc-management-consensus/

5. Gastroenterological Society of Australia. Australian consensus recommendations for the management of hepatitis B infection. Melbourne: Gastroenterological Society of Australia; 2022.

6. Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM). Decision making in Hepatitis B [Internet]. Available from: https://ashm.org.au/wp-content/uploads/2022/08/ASHM-Decision-Making-in-Hepatitis-B-2021-update-2.pdf

7. Omata M, Cheng AL, 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 Jul;11(4):317–70.

8. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018 Apr;67(4):1560–99.

9. World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; 2015. 134 p.

10. National Institute for Health and Care Excellence. Hepatitis B (chronic); diagnosis and management. Clinical guideline [CG165] Last updated October 2017 [Internet]. London: NICE; 2013 [cited 2022 Jun 16]. Available from: https://www.nice.org.uk/guidance/cg165

11. Australian Institute of Health and Welfare. Cancer data in Australia [Internet]. Canberra: Australian Institute of Health and Welfare; 2022 [cited 2022 Jul 5]. Available from: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia

12. 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. 2020/02/25 ed. 2020 Apr;212(7):297-299.e1.

13. 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 Jul 1;77(1):128–39.

Appendix H3. Dissemination plan

Reviewing current evidence and developing evidence-based recommendations for clinical care are only the first steps to ensuring that evidence-based hepatocellular carcinoma (HCC) surveillance is available for people at high risk of HCC. Following publication, the Clinical Guidelines must be disseminated to all those involved in HCC surveillance to inform and assist people at high risk of HCC.

These 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. The Clinical Guidelines are intended for use by healthcare professionals, administrators, funders and policy makers who plan, organise and deliver care for people at high risk of HCC.

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 (12,13).

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. Cancer Council Australia (CCA) will be responsible for and lead the implementation of the final guidelines, with guidance from the technical team and the Working Group. CCA is following a multi-strategy approach for the dissemination and implementation of the guidelines, as this has been shown to positively influence guideline uptake.

The guidelines will be published online via the CCA website, alongside the suite of Clinical Guidelines, making them a web-based global resource. A short-form PDF version may be available on request for reference, including all recommendations. The online guideline version increases availability as well as accessibility, and usage will be tracked and analysed with a web analytics solution.

CCA will undertake media and PR activity including, press releases to appropriate medical media contacts and PR activity in trade and clinical publications. In addition, the final guideline will be launched via email alert to professional organisations, interested groups and clinical experts in the field, directing them via URL link to the wiki guidelines and all associated resources. Australian health websites, such as EviQ will be approached to link to the online guidelines.

Promotion and dissemination will also be conducted through publication of papers in peer-reviewed journals, promotion at scientific meetings, national and international conferences and other continuing medical education events. Working Group members, and other identified local opinion leaders may be identified and approached to facilitate dissemination and act as champions for the guidelines.

The guidelines will be included in an education module being developed by the Liver Foundation with GPs. Further implementation options are explored as part of the Roadmap project.

Appendix I. Working group members and contributors

Project team

Name	Discipline/Expertise	Organisational Affiliation	Role
Dr Eleonora Feletto	Epidemiology/Cancer Control	Daffodil Centre	Project Lead
Ms Cathelijne van Kemenade	Cancer Control	Daffodil Centre	Program Manager (to Oct 2022)
Dr Joachim Worthington	Mathematical Modelling	Daffodil Centre	Research Fellow
Ms Claire Latumahina	Public Health	Daffodil Centre	Research Assistant (from July 2022)
Ms Amanda McAtamney	Public Policy	Cancer Council Australia	Public Health Policy Manager
Ms Megan Varlow	Public Policy/Cancer Control	Cancer Council Australia	Director Cancer Control Policy
Ms Suzanne Hughes	Systematic review methodology	Daffodil Centre	Systematic Reviewer
Ms Chelsea Carle	Systematic review methodology	Daffodil Centre	Systematic Reviewer
Dr Denise Campbell	Systematic review methodology	Daffodil Centre	Systematic Reviewer
Ms Victoria Freeman	Systematic review methodology	Daffodil Centre	Systematic Reviewer
Dr Susan Yuill	Systematic review methodology	Daffodil Centre	Systematic Reviewer

Expert Advisory Group

Name	Discipline/Expertise	Organisational Affiliation	Role
Professor Jacob George	Hepatology/Research	Storr Liver Centre	Co-Chair
Dr Nicole Allard	Primary Care/Epidemiology	The Doherty Institute	Co-Chair
Professor Stuart Roberts	Gastroenterology	The Alfred Hospital, Gastroenterology Dept Monash University Central Clinical School	Member
Professor Leon Adams	Gastroenterology	University of Western Australia, Department of Hepatology, Sir	Member

		Charles Gairdner Hospital	
Dr Belinda Greenwood-Smith	Primary Care (NT)/Public Health/Aboriginal and Torres Strait Islander Health	Northern Territory Government	Member
Associate Professor Patricia Valery	Epidemiology	QIMR Berghofer Medical Research Institute	Member
Associate Professor Jane Davies	Infectious Diseases/Aboriginal and Torres Strait Islander Health	Menzies – School of Health Research, Health Research, Charles Darwin University Royal Darwin and Palmerston Hospitals	Member
Ms Rosalie Altus	Nursing	South Australian Government	Member
Ms Natali Smud	Population Health (CALD)	NSW Health	Member (up until 24/10/2022)
Professor Andrew Wilson	Public Health, Health Policy and Epidemiology	Menzies Centre for Health Policy and Economics, Australian Prevention Partnership Centre, Pharmaceutical Benefits Advisory Committee	Member
Mr David Fry	Consumer representation	Consumer	Member
Ms Nafisa Yussf	Consumer representation (CALD)	The Doherty Institute	Member
Ms Catherine Brown	Consumer representation	Consumer	Member

Implementation team

Name	**Discipline/Expertise**	**Organisational Affiliation**	**Role**
Professor Karen Canfell	Epidemiology/Cancer control research	Daffodil Centre	Advisory
Mr Paul Grogan	Cancer policy	Daffodil Centre	Advisory
Ms Kate Broun	Cancer prevention and screening	Cancer Council Victoria	Advisory

Working groups

Name	Discipline/Expertise	Organisational Affiliation	Role
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?			
Professor Stuart Roberts	Gastroenterology	The Alfred Hospital, Gastroenterology Dept Monash University Central Clinical School	Lead
Dr Emily He	Gastroenterology	Concord Hospital, Daffodil Centre Gastrointestinal Cancers, Policy and Evaluation	Member
Associate Professor Simone Strasser	Hepatology	Royal Prince Alfred Hospital and University of Sydney	Member
Professor Gail Matthews	Infectious Diseases	The Kirby Institute	Member
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?			
Professor Leon Adams	Gastroenterology	University of Western Australia, Department of Hepatology, Sir Charles Gairdner Hospital	Lead
Dr Belinda Greenwood-Smith	Primary Care (NT)/Public Health/Aboriginal and Torres Strait Islander Health	Northern Territory Government	Member
Dr Oyekoya Ayonrinde	Gastroenterology/Hepatology	University of Western Australia, Fiona Stanley Hospital	Member
Ms Rosalie Altus	Nursing	South Australian Government	Member
Clinical Associate Professor Michael Wallace	Gastroenterology/Hepatology	University of Western Australia, Sir Charles Gairdner Hospital	Member
PICO 3. Does HCC surveillance improve liver cancer outcomes for Aboriginal and Torres Strait Islander people?			
Associate Professor Jane Davies	Infectious Diseases/Aboriginal and Torres Strait Islander Health	Menzies – School of Health Research, Health Research, Charles Darwin University	Lead

		Royal Darwin and Palmerston Hospitals	
Dr Kirsty Campbell	Gastroenterology	Royal Darwin Hospital	Member
Ms Paula Binks	Aboriginal and Torres Strait Islander Health/Hepatitis B and HCC research	Menzies – School of Health Research	Member
Professor Alan Wigg	Gastroenterology/Hepatology	South Australian Government	Member
Ms Teresa De Santis	Aboriginal Health Practitioner Coordinator	NT Health	Member
PICO 4. Does HCC surveillance improve liver cancer outcomes for Asian or Pacific-born people in Australia?			
Associate Professor Behzad Hajarizadeh	Epidemiology/Hepatitis	The Kirby Institute	Lead
Associate Professor Anouk Dev	Gastroenterology	Monash Health Monash University	Member
Associate Professor Patricia Valery	Cancer Epidemiology/Chronic disease/Indigenous Health Research	QIMR Berghofer Medical Research Institute	Member
Dr Ken Liu	Gastroenterology/Hepatology	NSW Health	Member
PICO 5. Does HCC surveillance improve liver cancer outcomes for sub-Saharan Africa-born people in Australia?			
Dr Jennifer MacLachlan	Epidemiology/Hepatitis	The Doherty Institute	Lead
Associate Professor Ammar Majeed	Gastroenterology	Alfred Health	Member
Dr William Mude	Public Health/Disease Surveillance	Central Queensland University	Member
Ms Natali Smud	Population Health (CALD)	NSW Health	Member (up until 24/10/2022)
PICO 6. Does the addition of alpha-fetoprotein testing to 6-monthly ultrasound imaging for HCC surveillance improve liver cancer outcomes?			
Associate Professor Suzanne Mahady	Clinical Epidemiology/Gastroenterology	Monash University	Lead
Associate Professor Jessica Howell	Gastroenterology/Hepatology and Public Health	St Vincent's Hospital Melbourne, University of Melbourne, Burnett Institute	Member
Dr Cameron Gofton	Hepatology	NSW Health	Member

Dr Siddharth Sood	Gastroenterology/Hepatology	The Royal Melbourne Hospital	Member
Community Reference Group			
Dr Kate Holliday	Nursing/Research	Centre For Community-Driven Research	Lead
Dr Katelin Haynes	CEO	Hepatitis Queensland	Member (up until 11/07/2022)
Associate Professor Thomas Tu	Consumer representation and Hepatitis B Research	The University of Sydney	Member
Ms Catherine Brown	Consumer representation	Consumer	Member
Mr John Didlick	Hepatitis Policy	Hepatitis Australia	Member
Dr Lynne Pezzullo	Chair	Liver Foundation	Member (up until 13/10/2022)
Mr David Fry	Consumer representation	Consumer	Member
Ms Nafisa Yussf	Consumer representation	The Doherty Institute	Member
Mr Russell Shewan	CEO	LiverWELL	Member

Appendix J. Conflict of interest register

Conflict of interest was assessed and managed according to Cancer Council Australia's *A Code of Practice for Declaring and Dealing with Conflicts of Interest.*

All members were asked to declare in writing any interests relevant to the project, and development of any subsequent material. The Chairs were responsible for evaluating all declarations. The evaluation of possible conflicts of interest was guided by *A Code of Practice for Declaring and Dealing with Conflicts of Interest.*

Members had the option to submit a curriculum vitae (CV) to provide details of declarations, summarise their experience, skills and publications in the liver cancer field. However, it was not compulsory to submit a CV. The Chairs could request a CV if necessary.

All members were responsible for updating their conflict of interest statements if a new interest arose. The members received a formal reminder to review their statements and ensure it was up-to-date at the start of each subsequent phase.

Throughout the development process no significant conflicts of interest were identified

Expert Advisory Group (EAG), Working Group and Community Reference Group Members

Name	Position(s) as relevant to this project	Relevant financial interests	Relevant professional and organisational experience	Other relationships/activities
Dr Nicole Allard (EAG co-Chair)	MBBS, FRACGP, MPH, PhD General Practitioner, Cohealth, Footscray, VIC; Researcher, WHO Collaborating Centre for Viral Hepatitis, Peter Doherty Institute for Infection and Immunity; Honorary Lecturer, Department of Medicine, University of Melbourne; Board Member, Hepatitis VIC	No interests declared	**Publications**: peer-reviewed (CV provided) **Speeches/lectures**: conferences (no honoraria/sponsorship) **Development of related materials**: ASHM resources	No interests declared
Professor Jacob George AM (EAG co-Chair)	MBBS, FRACP, PhD, FAASLD Robert W. Storr Chair of Hepatic Medicine, Sydney Medical School; Director, Storr Liver Centre, The Westmead Institute for Medical Research; Head, Department of Gastroenterology & Hepatology, Westmead Hospital Chair, Liver Faculty, Gastroenterological Society of Australia	**Consultancy/honorarium:** Honoraria for presentations on Sirtex: Audit on HCC pathways at Westmead Hospital and Bayer Symposium Brisbane **Support for travel/accommodation**: Advisory board of Eisai and Bayer (pharmaceuticals), Roche, Astra Zeneca	**Publications**: Many (CV provided) **Development of related materials:** ALA HCC Guidelines	No interests declared
Professor Leon Adams	MBBS FRACP PHD Consultant Hepatologist in the Liver Transplant Unit at Sir Charles Gairdner Hospital Gastroenterologist/hepatologist, Hollywood Private Hospital Associated Professor, Faculty of Health and Medical Sciences, University of WA Executive Committee, Liver Faculty GESA	Advisory board for Pfizer, Novartis and Roche Diagnostics. Speaker fees: Gilead	**Publications**: publications regarding hepatocellular carcinoma (HCC) epidemiology in Australia, surveillance practices and HCC management – see appendices **Development of related materials**: 2019 GESA HCC Management Guidelines	No interests declared
Ms Rosalie Altus	Clinical Practice Consultant Viral Hepatitis Liaison Nurse Flinders Medical Centre, SA	**Meals & beverages**: Sponsored education meetings	No interests declared	No interests declared
Associate Professor Jane Davies	MBBS, MRCP(UK), DTM&H, FACP, PhD Co-Director of Infectious	**Meals & beverages:** ~3-4 evidence update lunch meetings per year where	**Publications:** peer-reviewed (CV provided)	**Relationships**: ASH, ASID, WHO (CV provided)

	Diseases, Infectious Diseases and General Medicine Physician, Royal Darwin and Palmerston Hospitals Principal Research Fellow, Menzies School of Health Research, Charles Darwin University	food is provided by pharmaceutical companies. (CV provided)	**Speeches/Lectures:** health professional education courses for ASHM on viral hepatitis, conference presentations (CV provided) **Development of related materials:** ASHM resources (CV provided)	**Activities**: Hep B consensus guidelines working group; Hep B testing working group
Dr Belinda Greenwood-Smith	MBBS, MPH Co-ordinator of the CDC Central Australia Northern Territory, Australia Rural Medical Practitioner	No interests declared	**Speeches/lectures**: Education sessions to remote medical practitioners **Other**: NT Viral Hepatitis Advisory Group	No interests declared
Professor Stuart Roberts	MBBS MD FRACP Director of Hepatology, Department of Gastroenterology, The Alfred Hospital, Melbourne, Victoria Adjunct Clinical Professor Gastroenterology Monash University Central Clinical School Melbourne	No interests declared	None declared	No interests declared
Ms Natali Smud	Strategy and Engagement manager, Multicultural HIV and Hepatitis Service (MHAHS) Diversity Programs & Strategy Hub, Population Health, Sydney Local Heath District	No interests declared	**Speeches/lectures**: not specified (CV provided) **Expert testimony**: not specified (CV provided) **Development of related materials:** not specified (CV provided) **Other**: not specified (CV provided)	No interests declared
Associate Professor Patricia Valery	Senior Research Fellow and Head of the Cancer and Chronic Disease Research Group at the QIMR Berghofer Medical Research Institute QLD	No interests declared	**Publications**: Petrick JL, Braunlin M, Laversanne M, Valery PC, Bray F, McGlynn KA. International trends in liver cancer incidence, overall and by histologic subtype,	**Relationships**: 2016-present European Association for the Study of the Liver (EASL); 2017-present Member of the Gastroenterological Society of Australia (GESA);

			1978-2007. Int J Cancer. Oct 1 2016;139(7):1534-1545; Valery PC, Baade PA, Stuart KA, Leggett BA, Macdonald GA, Whiteman DC, Crawford DH, Clark PJ. Five-year conditional survival for patients with hepatocellular carcinoma in Queensland, Australia. GastroHep. 2019;1:61-69; Valery PC, Laversanne M, Clark PJ, Petrick JL, McGlynn KA, Bray F. Projections of primary liver cancer to 2030 in 30 countries worldwide. Hepatology. Aug 31 2017. **Speeches/Lectures**: 2018- Invited speaker at the Brisbane Inter-Hospital Liver Group (BILG) meeting. "Conditional survival in hepatocellular carcinoma in Queensland"; 2015- Invited speaker at the Brisbane Cancer Conference. 'Supportive care needs of people with liver cancer and cirrhosis'	2015-present Member of the Network Centre for Liver Disease Research, School of Medicine, Univ. of Queensland
Professor Andrew Wilson	Co- Director of the Menzies Centre for Health Policy and Economics Co-Director, Australian Prevention Partnership Centre Chair, Pharmaceutical Benefits Advisory Committee	No interests declared	None declared	No interests declared
Dr Oyekoya Ayonrinde	Hepatologist at Fiona Stanley Hospital in Perth and a clinician researcher with UWA and Curtin University	No interests declared	None declared	**Relationships:** Standard academic meetings Resonance Health – adviser

				Sun Pharmaceuticals - adviser Norgine – speaker NOVO Nordisk – advisory panel
Ms Paula Binks	None declared	No interests declared	Development of related materials, including guidelines, standards, educational materials or fact sheets;	Other (e.g. unpaid advisory roles) Consultancy: Eisai Australia – HCC in Indigenous Australians
Ms Catherine Brown	None declared	No interests declared	Publications;	Yes, I am affiliated or associated with an organisation/s whose interests are either aligned with or opposed to the subject matter of the proposed committee(s).
Dr Kirsty Campbell	Employment with Royal Darwin Hospital since 2016 Employment in private practice (Ologist) since 2021	**Meals and beverages:** Occasional sponsored meal (usually lunch) by drug reps for Norgine, Ferring, AbbVie 2 x dinner meetings with AVANT	Publications;	Yes, I am affiliated or associated with an organisation/s whose interests are either aligned with or opposed to the subject matter of the proposed committee(s). Board membership: Board of Directors GESA since 2021
Associate Professor Anouk Dev	None declared	No interests declared	Publications; Speeches/lectures ; Development of related materials, including guidelines, standards, educational materials or fact sheets;	**Relationships:** Board membership: Advisory Board Gilead , Eisai, Roche Consultancy: Eisai Gilead Roche
Mr John Didlick	Policy Analyst at Hepatitis Australia - the peak national community hepatitis organisation. I have no personal interest and	**Support for travel/accommodation:** In the relevant period have received support for travel and accommodation to	Development of related materials, including guidelines, standards, educational materials or fact sheets;	No interests declared

	receive no benefit beyond my policy work.	attend hepatitis conferences and associated sideline meetings.		
Mr David Fry	None declared	No interests declared	Development of related materials, including guidelines, standards, educational materials or fact sheets for Cancer Council Victoria; minor roles as consumer developing leaflets/booklets etc. Reviewed publications for Cancer Council Victoria over several years Speeches/lectures for Cancer Council Victoria 'Lived Experience' video for LiverWell	Some voluntary interviews etc. for Hepatitis Victoria and Hepatitis Australia Various voluntary roles with Cancer Council Victoria On Community Reference Committee Cancer Council Victoria. Presenter and Judge on 2022 Young Australians' Cancer Initiatives University Cancer Case Competition. (Liver Cancer this year).
Dr Cameron Gofton	None declared	No interests declared	None declared	No interests declared
Associate Professor Behzad Hajarizadeh	None declared	No interests declared	Publications	No interests declared
Dr Katelin Haynes	CEO of Hepatitis Queensland, consumer NGO organisation which undertakes health promotion work for people living with or at risk of viral hepatitis.	**Grants**: Hepatitis Queensland received grants from Gilead International to undertake health promotion work for people living with or at risk of viral hepatitis.	Publications; Development of related materials, including guidelines, standards, educational materials or fact sheets;	Board Member of Hepatitis Australia, the national peak, non-profit hepatitis organisation and charity in Australia representing the interests of people affected by viral hepatitis. Yes, there other activities that could be perceived potentially to influence my contribution.;
Dr Emily He	Senior Research Fellow Daffodil Centre Gastrointestinal Cancers, Policy and Evaluation	No interests declared	None declared	No interests declared
Dr Kate Holliday	None declared	No interests declared	None declared	No interests declared
Associate Professor Jessica Howell	St Vincent's Hospital Melbourne, University of Melbourne, Burnet Institute (all paid positions) and	**Grants**: Eisai peer reviewed investigator initiated grant support (2020) ($10,000, 2020) for work assessing	Development of related materials, including guidelines, standards, educational materials or fact	Consultancy: Education lecture HCC in indigenous Australians 2022, Eisai

	adjunct non paid position Monash University	the impact of COVID on the HCC OCP cascade of care-funding ends	sheets; Publications; Speeches/lectures	Yes, I am affiliated or associated with an organisation/s whose interests are either aligned with or opposed to the subject matter of the proposed committee(s).
Dr Ken Liu	None declared	No interests declared	Publications;	Yes, I am affiliated or associated with an organisation/s whose interests are either aligned with or opposed to the subject matter of the proposed committee(s). Yes, there other activities that could be perceived potentially to influence my contribution.
Dr Jennifer MacLachlan	None declared	No interests declared	Publications; Speeches/lectures; Development of related materials, including guidelines, standards, educational materials or fact sheets;	No interests declared
Associate Professor Suzanne Mahady	None declared	No interests declared	None declared	No interests declared
Associate Professor Ammar Majeed	None declared	**Grants**: National Blood Authority, research grant, 120k, for research project of bleeding risk in patients with liver disease **Meals and beverages:** Meals support by pharmaceutical companies to the weekly Alfred Gastroenterology Audit meeting.	Publications;	No interests declared
Professor Gail Matthews	None declared	**Grants:** Research grants Abbvie and Gilead	Development of related materials, including guidelines, standards,	Consultancy: Speakers fees Janssen Ad board Gilead and AZ

			educational materials or fact sheets;	Yes, I am affiliated or associated with an organisation/s whose interests are either aligned with or opposed to the subject matter of the proposed committee(s).
Dr William Mude	None declared	No interests declared	Publications; Speeches/lectures; Development of related materials, including guidelines, standards, educational materials or fact sheets;	No interests declared
Dr Lynne Pezzullo	Chair of the Liver Foundation and believe this is a positive for involvement in the Roadmap, not a conflict.	**Support for travel/accommodation:** I may receive a small stipend and travel expense reimbursement in the future 12 months, in my role as Chair of the Liver Foundation. None of the travel/accommodation reimbursements I have or will receive are from entities that have an interest in the Committee (e.g. NDIA, ICMI Speakers & Entertainers, Deloitte). As a partner of Deloitte till 31 May 2020 I could claim entertainment expenses; however these were for internal events or for clients, none of whom had/has an interest in the Committee. I have not received such benefits since retiring from Deloitte. As a partner of Deloitte till 31 May 2020 I could claim	Publications;	Board member: I was a paid Board member of the Social Research Centre (an ANU Enterprise) for 6 years prior to completion of that role in August 2021. I do not receive remuneration for the following; I am a director - The Canberra Hospital Foundation, The Farm in Galong, Bubble Hotel/Dining Dome. None of these boards (apart from the Liver Foundation) has an interest in the Committee, and the interest of the Liver Foundation is not pecuniary but collaborative, as a relevant stakeholder. Consultancy: I receive consultancy fees through my company Well & Wise Ltd but this is mainly for work in the disability sector and for speaking engagements or facilitation roles. I was a Partner at Deloitte receiving consultancy fees retiring 31 May 2020. None of these

		other expenses (e.g. conference fees); however these were for internal or client-related matters, none of whom had/has an interest in the Committee. I have not received such benefits since retiring from Deloitte. **Meals and beverages:** As a partner of Deloitte till 31 May 2020 I could claim meal and beverage expenses; however these were for internal or client-related matters, none of whom had/has an interest in the Committee. I have not received such benefits since retiring from Deloitte.		consultancies in the past or looking forward has an interest in the Committee. Yes, I am affiliated or associated with an organisation/s whose interests are either aligned with or opposed to the subject matter of the proposed committee(s).;
Ms Teresa De Santis	None declared	No interests declared	None declared	Other (e.g. unpaid advisory roles);
Mr Russell Shewan	None declared	No interests declared	None declared	No interests declared
Dr Siddharth Sood	MBBS FRACP PhD, Head of Hepatology Department of Gastroenterology & Hepatology RMH, Clinical Associate Professor Department of Medicine University of Melbourne	**Grants:** CSL research grant (just approved may 2022) for clinical research study into cost-effectiveness of albumin use in decompensated cirrhosis	Publications; Speeches/lectures;	Consultancy: Advisory board for EISAI (makers of lenvatinib - treatment for HCC)
Associate Professor Simone Strasser	Chair, Clinical and Scientific Committee, The Liver Foundation Past President, The Gastroenterological Society of Australia	No interests declared	Speeches/lectures; Publications; Development of related materials, including guidelines, standards, educational materials or fact sheets; Other (e.g. unpaid advisory roles);	Consultancy: Personal: AstraZeneca, Roche, Eisai, Ipsen, Gilead, AbbVie, MSD, Chiesi, CSL Behring, Guebert Australia, Norgine, bit.bio, Dr Falk Family: Pfizer, Miltenyi Biotec,Pearce IP, Cynata Personal: Astra Zeneca - ASCO-GI virtual Jan 2022 registration

				Yes, I am affiliated or associated with an organisation/s whose interests are either aligned with or opposed to the subject matter of the proposed committee(s).
Associate Professor Thomas Tu	Group Leader – Molecular Viral Hepatitis group Storr Liver Centre Westmead Institute for Medical Research and University of Sydney, Sydney, Australia	**Grants**: All below are paid to institution. - CIA – Gilead Investigator Sponsored Research Grant "Investigating Treatment Engagement and Monitoring in Hep B-affected communities (ITEM-B study)" 2022-23, AUD $157,000 over 1.5 years - CIB – NHMRC Ideas Grant "Inhibiting host TM6SF2 to cure Hepatitis B" 2021-2023, AUD $684,841 over 3 years - CIB – Australian Centre for HIV and Hepatitis Virology Research (ACH2) Project Grant "Development of a diagnostic assay to measure hepatitis B virus ccc DNA" 2021, AUD $88,000 over 1 year - CIA – ACH2 Project Grant "Quantifying integrated and episomal HBV DNA in fine needle aspirate liver biopsies" 2019-2021, AUD $130,500 over 1.5 years **Support for travel/accommodation:** •Invited member of National HBV Consensus Statement Community Oversight Group (2019-2020) -	Other (e.g. unpaid advisory roles); Publications; Speeches/lectures ; Development of related materials, including guidelines, standards, educational materials or fact sheets; Invited talk HBV-TAG 2021 Conference: honorarium Invited talk Science of HBV Cure 2021 ONLINE: honorarium	None of the below are paid positions: • Founder and Director, HepBcommunity.org online support network for people living with Hepatitis B to connect with each another and with medical/scientific experts in the field (2020-) • Committee member of Hepatitis B Foundation Anti-Discrimination Working Group (2021-) • Committee Member, International Coalition to Eliminate HBV Stakeholder Consulting Group (2020-) • Board Member, Emerging Scientific and Medical Advisory Board, Hepatitis B Foundation, USA (2021-) • President of Australian Centre for Hepatitis Virology (2021-; Secretary 2020-2021) • Board Director for Hepatitis Australia (2020-) • Director of Hep B Voices Australia, community advocacy group for people affected by Hepatitis B (2021-) Consultancy: •Invited Advisor for Gilead Science's "Train the Trainer" Hepatitis B program (2021-)

		accommodation and travel for meeting in Melbourne - Invited talk The Science of HBV Cure Meeting 2022, Singapore: accommodation, flight, and honorarium - Invited talk HEP DART 2021, Mexico: accommodation, flight, and honorarium		•Invited Advisor for GlaxoSmithKline Digital Education Global Steering Advice Group (2021-) •Invited Speaker for GlaxoSmithKline "Ambitious for Patients" internal event (Oct 2021) •Invited Consultant for Excision BioTherapeutics (2021-) •Advisory Group Member for the Centre for Social Research in Health (University of Sydney) Stigma Indicators Program (2021-) •Invited Advisor for Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine B Referred Program (2021-) •Invited speaker for short course "Enhancing trust, reducing stigma for effective and equitable health care" developed by Centre for Social Research in Health, UNSW (2021) •Invited Advisory Committee member for Gilead Science's Virtual Medical Affairs Advisory Program (2020) Yes, I am affiliated or associated with an organisation/s whose interests are either aligned with or opposed to the subject matter of the proposed committee(s).
Clinical Associate Professor Michael Wallace	None declared	No interests declared	None declared	No interests declared

Professor Alan Wigg	None declared	Grants: - MRFF GRANT 2022 - Norgine Grant 2021	Publications: Multiple publications on HCC and liver disease in Indigenous Australians Speeches/lectures: - Adelaide liver group 2021 - AGW 2020 - VH 2022	Eisa honorarium 2022
Ms Nafisa Yussf	None declared	No interests declared	None declared	Unpaid board membership - Co-founder and Director of Hepatitis B Voices Australia - Australian Muslim Women's Centre for Human Rights. Consultancy: ASHM National Hepatitis B Advisory Group Co-chair ASHM National Hepatitis B (B Referred project) Community Advisory Group Work-related conferences, publications, contributing to guidelines, standards, educational materials or fact sheets; (Viral Hepatitis Conference, World Hepatitis Alliance etc)