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Review article

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Hepatocellular carcinoma surveillance — utilization, barriers and the impact of changing aetiology

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Abstract

Hepatocellular carcinoma (HCC) is the third leading cause of cancer death worldwide. Surveillance for HCC is critical for early detection and treatment, but fewer than one-quarter of individuals at risk of HCC undergo surveillance. Multiple failures across the screening process contribute to the underutilization of surveillance, including limited disease awareness among patients and health-care providers, knowledge gaps, and difficulty recognizing patients who are at risk. Non-alcoholic fatty liver disease and alcohol-associated liver disease are the fastest-rising causes of HCC-related death worldwide and are associated with unique barriers to surveillance. In particular, more than one-third of patients with HCC related to non-alcoholic fatty liver disease do not have cirrhosis and therefore lack a routine indication for HCC surveillance on the basis of current practice guidelines. Semi-annual abdominal ultrasound with measurement of α-fetoprotein levels is recommended for HCC surveillance, but the sensitivity of this approach for early HCC is limited, especially for patients with cirrhosis or obesity. In this Review, we discuss the current status of HCC surveillance and the remaining challenges, including the changing aetiology of liver disease. We also discuss strategies to improve the utilization and quality of surveillance for HCC.

Sections

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Key points

- Fewer than one-quarter of patients with cirrhosis receive surveillance for hepatocellular carcinoma (HCC).
- Multiple patient-related and provider-related barriers limit the utilization of HCC surveillance; these barriers include limited disease awareness, knowledge gaps, lack of resources and failure to recognize patients at risk.
- Non-alcoholic fatty liver disease-related HCC develops in many people without cirrhosis, but routine HCC surveillance is not recommended in the absence of cirrhosis; surveillance should be individualized on the basis of additional risk factors.
- Unique barriers to HCC surveillance (for example, non-adherence, limited social report, stigma and psychological issues) are associated with alcohol-associated cirrhosis; a multidisciplinary approach is required to address these barriers.
- Ultrasonography has a suboptimal sensitivity for the detection of early-stage HCC and its performance can be poorer in the presence of obesity and non-alcoholic fatty liver disease-related or alcohol-related cirrhosis.
- Novel blood-based and imaging-based biomarkers for HCC surveillance are emerging but require validation.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related deaths worldwide[1,2]. In 2020, an estimated 905,700 people were diagnosed with liver cancer globally[3]. The prognosis of HCC is poor — 5-year overall survival rates are <20%[4,5]. Tumour stage at the time of diagnosis is the leading determinant of prognosis; 5-year survival rates exceed 55% among patients with early-stage HCC but median survival among those with advanced tumours is 1–2 years[4,6–13]. Over 90% of HCC occurs in the setting of advanced chronic liver disease or cirrhosis, and HCC is one of the leading causes of death among patients with liver disease[14,15].

Cirrhosis is the leading risk factor for HCC[16], and major society guidelines recommend that individuals with compensated cirrhosis should undergo surveillance using ultrasonography every 6 months[10,11,17]. This recommendation is supported, in part, by a randomized trial that involved individuals with chronic hepatitis B and demonstrated that surveillance reduced HCC mortality, though the percentage of participants with cirrhosis was not reported[18]. No randomized controlled trial of HCC surveillance specifically in patients with cirrhosis has been conducted[19]. Nevertheless, a meta-analysis of 59 cohort studies showed that HCC surveillance was associated with improved early-stage detection, receipt of curative treatment, and prolonged survival and that surveillance-related adverse effects were generally mild, strongly supporting the benefit of surveillance among patients with compensated cirrhosis[20]. Despite these benefits, HCC surveillance is underutilized and multiple patient-related, provider-related and disease-related barriers hinder surveillance[21–24].

The global epidemiology of HCC is changing owing to increases in non-alcoholic fatty liver disease (NAFLD) and alcohol-associated liver disease and decreases in HCC related to hepatitis B virus (HBV) and hepatitis C virus (HCV)[15]. These changes in underlying liver disease aetiology have important implications for HCC surveillance, including lower utilization of surveillance, gaps in disease awareness, and reduced sensitivity of ultrasound for early-stage detection of HCC and other focal liver lesions[25–27].

In this Review, we examine the current utilization of HCC surveillance and consider the implications of the changing aetiology of liver disease for surveillance. We highlight the barriers that limit HCC surveillance and propose strategies to improve the utilization and quality of surveillance for HCC.

Utilization of HCC surveillance

Guidelines from major societies, including the American Association for the Study of Liver Diseases (AASLD)[28], the European Association for the Study of the Liver (EASL)[11] and the Asia-Pacific Association for the Study of the Liver (APASL)[17], all recommend semi-annual ultrasound scans for patients with compensated cirrhosis (Table 1). APASL recommends HCC surveillance in specific subgroups of patients with chronic hepatitis B without cirrhosis such as African people, Asian men older than 40 years and Asian women older than 50 years[17] (Table 1). The AASLD recommends surveillance in people with chronic hepatitis B (men older than 40 years and women older than 50 years) who are from countries where chronic hepatitis B is endemic, and suggests that people from Africa living with chronic hepatitis B start surveillance from the age of 30 years[28,29]. The EASL recommends HCC surveillance in patients with chronic hepatitis B who are at intermediate or high risk of HCC on the basis of the PAGE-B score (calculated from age, sex and platelet count after receipt of tenofovir or entecavir)[30].

Despite the fact that a substantial number of patients meet the criteria for HCC surveillance, utilization is suboptimal[31] (Table 2). In the following sections, we review utilization of HCC surveillance in different groups. Important to keep in mind is that the majority of studies of HCC utilization in patients with cirrhosis and chronic hepatitis B were based on data from administrative databases, which are susceptible to bias related to errors in coding and incomplete records. Consequently, interpretation of these data requires caution.

Patients with cirrhosis

A systematic review and meta-analysis of 29 studies that included a total of 118,799 individuals estimated that HCC surveillance was utilized for just 22% of patients with cirrhosis[21]. The same study demonstrated that study setting is important: among study participants who were enrolled from hepatology or gastroenterology clinics, an estimated 74% of patients with cirrhosis received surveillance compared with just 9% in population-based studies[21]. Receipt of specialty care was not the only factor associated with different rates of HCC surveillance: two studies reported that older age was associated with a higher likelihood of receiving surveillance, and two others identified that people of African descent were less likely to receive surveillance than people of European descent[21,32–34].

Studies of HCC surveillance conducted in a real-world setting (excluding trials of HCC surveillance and studies of dedicated HCC surveillance programmes; Table 3) as well as studies published more recently are consistent with these observations[21]. For example, in a study of 15,543 insured adults with cirrhosis in the USA, patients were up-to-date with recommended surveillance for only an estimated 31% of the time[35]. Another study of 82,427 patients with cirrhosis in the USA determined that only 9% underwent HCC surveillance at least once

Table 1 | Recommendations for HCC surveillance

Condition	AASLD[29]	AGA[81]	EASL[11]	APASL[122]
Cirrhosis	Surveillance recommended in Child–Pugh stages A or B; individuals in Child–Pugh stage C should only undergo surveillance if they are eligible for liver transplantation	None	Surveillance is recommended in Child–Pugh stages A and B; individuals in Child–Pugh stage C should only undergo surveillance if they are awaiting liver transplantation	Surveillance is recommended for individuals with cirrhosis
Chronic hepatitis B without cirrhosis	Surveillance is recommended for men from endemic countries aged >40 years; women from endemic countries aged >50 years; people from Africa; people with a family history of HCC; people with a PAGE-B score ≥10	None	Individuals at intermediate or high risk of HCC (PAGE-B score ≥10)	Surveillance is recommended for Asian men aged >40 years, Asian women aged >50 years, Black people aged >20 years and people with a family history of HCC
Chronic hepatitis C without cirrhosis	Routine surveillance is not recommended	None	Individuals with stage 3 fibrosis may be considered for surveillance	Surveillance is recommended for patients with HCV cure treated with DAAs, regardless of fibrosis stage
NAFLD without cirrhosis	Routine surveillance is not recommended	Consider surveillance in advanced (stage 3–4) fibrosis	Individuals with stage 3 fibrosis may be considered for surveillance	None

AASLD, American Association for the Study of Liver Diseases; AGA, American Gastroenterology Association; APASL, Asia-Pacific Association for the Study of the Liver; DAA, directly acting antiviral; EASL, European Association for the Study of the Liver; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease.

every 6–12 months[36]. Given these data, the fact that most HCC cases are diagnosed outside of regular surveillance programmes is not surprising. Reinforcing this point, in a study of patients who had developed HCC, only 26% had received any HCC surveillance, a proportion that is similar to that of patients with cirrhosis who received HCC surveillance (22%)[21].

Patients with chronic hepatitis B without cirrhosis

A meta-analysis has indicated that the rate of HCC surveillance among patients with chronic hepatitis B without cirrhosis is 32%[37]. A study of four clinics in the USA determined that rates of HCC surveillance are lower among patients with chronic hepatitis B without cirrhosis than among those with cirrhosis (23.4% versus 38.4%)[38] (Table 4). Similarly, a USA-wide study of 6,831 patients with chronic hepatitis B without cirrhosis determined that only 39% of patients received any abdominal imaging after 6 months of follow-up[22].

Barriers to effective HCC surveillance

Multiple factors contribute to underutilization[39] of HCC surveillance (Box 1). Some of these factors are related to patients, others to health-care providers and still others to technical limitations of surveillance techniques. In the following sections, we discuss these factors and their effects on HCC surveillance.

Patient-related barriers

Many patients who know they have liver disease are unaware of or unclear about its clinical consequences and therefore do not seek care for their condition[40]. For example, a survey of 2,153 patients and guardians visiting hospitals in South Korea determined that 40% knew they had fatty liver or abnormal liver enzymes but only 48% of those who knew they had liver disease had visited a medical institution and only 69% of those with abnormal liver enzymes had consulted doctors[41]. A survey of patients with cirrhosis in the USA determined that the overall level of HCC-related knowledge, including knowledge that the risk of HCC is increased by cirrhosis and knowledge of the recommendations for surveillance, was high (summary score 77.7%)[42]. However, several knowledge gaps were identified such as the belief that a healthy diet precludes the need for HCC surveillance[42]. These data suggest that disease awareness varies by geographical location and culture, and interventions need to be tailored accordingly.

Beyond disease awareness and knowledge, multiple logistical factors for patients create barriers that contribute to low screening rates[43,44] (Box 1). Common barriers include costs, difficulty with scheduling ultrasound scans, difficulty with transportation and uncertainty about where to undergo surveillance[43,45]. Longer intervals between ultrasound ordering and scheduling as well as greater travel distance have also been associated with lower odds of ultrasound completion[33].

Provider-related barriers

The available data suggest that provider-related barriers (Box 1), such as a failure to detect early liver disease, recognize cirrhosis or order surveillance, contribute more to the underutilization of HCC surveillance than patient-related barriers[39,46]. A study of 1,201 patients with cirrhosis and HCC in the USA determined that 25% had unrecognized cirrhosis before diagnosis of HCC[47]. Furthermore, a study of primary care records from four countries (the UK, Italy, the Netherlands and Spain) determined that the prevalence of recorded NAFLD in adults was 1.9% in 2014

Table 2 | Estimated utilization of HCC surveillance

Condition	Burden in population	Estimated surveillance utilization
With cirrhosis	112 million individuals globally[188]	<25%[21]
Chronic hepatitis B without cirrhosis	>250 million individuals globally[189]	~33%[37]
NAFLD	1 in 3 adults[49] affected globally – low incidence of HCC but large at-risk population	Unknown
HCC	>900,000 per year[3]	~25% received surveillance before HCC diagnosis[21]

HCC, hepatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease.

Table 3 | Selected studies that provide data on the utilization of HCC surveillance in cirrhosis

Study	Study period	Location	Study setting	Study population	Utilization of surveillance
Clinical cohorts with data verified by chart review					
Mohammed et al.[190]	2007–2009	USA	Tertiary centre	369 patients with cirrhosis (alcohol 32%, NAFLD 23%, HCV 21%)	14% underwent surveillance scans every 6 months
Signorelli et al.[191]	2012–2014	Brazil	A tertiary centre and a private centre	253 patients with cirrhosis (alcohol 37.9%, HBV 13.8%)	6.3% received an ultrasound every 6 months
Tran et al.[34]	2001–2015	USA	Tertiary centre	2,366 patients with HCV cirrhosis	24.4% adhered to imaging every 6 months and 44% to imaging at least every 12 months
Administrative data base studies					
Palmer et al.[192]	2006–2007	USA	Data from an insurance claims data base	5,061 patients with cirrhosis (alcohol 59%, HCV 30%, HBV 4%)	26% underwent at least one imaging test over 15 months
Goldberg et al.[33]	2008–2010	USA	Data from the Veterans Health Administration	26,577 patients with cirrhosis (HCV, alcohol or a combination in >80% of included patients)	Up-to-date with ultrasound for HCC surveillance 17.8% of the time (mean for all patients)
Davila et al.[32]	1998–2005	USA	Data from the Veterans Health Administration	13,002 patients with HCV cirrhosis	12% received routine surveillance (ultrasound and AFP levels during at least 2 consecutive years in the 4 years after cirrhosis diagnosis)
Yeo et al.[36]	2007–2016	USA	Nationwide administrative claims data base	82,427 patients with cirrhosis (viral hepatitis 2.1%; NAFLD 6.9%; alcohol 2.8%; others 88.2%)	8.8% received surveillance every 6–12 months
Singal et al.[193]	2010–2012	USA	Integrated health-care delivery system in Washington State	1,137 patients with cirrhosis (HCV 28.9%, NASH 28.7%)	2% received surveillance every 6 months, 33% received ≥1 ultrasound during the 2-year follow-up period
Nguyen et al.[35]	2013–2019	USA	Nationwide administrative claims data	15,543 patients with cirrhosis (NASH 38.2%, HCV 29.1%, alcohol 27.3%)	Patients were up-to-date with recommended surveillance for only 31% (days covered/days of follow-up) of a median 1.3-year follow-up (any abdominal imaging was considered to provide 6 months of days covered)
Chang et al.[194]	2000–2015	Taiwan	National health insurance data base	4,641 patients with HCV cirrhosis	14% adhered to annual HCC surveillance (abdominal ultrasound and AFP test) during the follow-up period

We included studies that reported the utilization of hepatocellular carcinoma (HCC) surveillance in a real-world setting and excluded trials of HCC surveillance and studies of dedicated HCC surveillance programmes. AFP, α-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

(ref. 48), substantially lower than estimates from meta-analyses[48–50], suggesting substantial underdiagnosis and under-recording.

A meta-analysis has shown that receipt of surveillance was higher among patients at gastroenterology and hepatology clinics than in population-based cohorts (74% versus 9%), highlighting that barriers to surveillance utilization are more problematic among primary care providers than among specialist providers[21]. Indeed, a web-based survey of 133 primary care providers in the USA determined that more than one-quarter of primary care providers felt that HCC surveillance was outside the scope of primary care and deferred it to hepatologists[51]. In addition, 42% of primary care providers reported that they did not know up-to-date HCC surveillance recommendations, and some providers had misconceptions, such as believing that clinical examination and monitoring transaminases could be effective for HCC surveillance[51]. Providers reported multiple barriers to performing surveillance, including time constraints and competing clinical concerns[51]. A nationwide survey of 531 physicians in Thailand reported that 56% of practitioners who worked in a community setting had no access to an ultrasound machine compared with 3% of practitioners who worked at secondary or tertiary hospitals[45].

Together, these data indicate that multiple provider-level barriers and misconceptions contribute to suboptimal HCC surveillance, especially among primary care providers. Better education and logistical support for relevant health-care providers could, therefore, help improve rates of surveillance.

Limitations of ultrasonography

The overall sensitivity of ultrasonography for HCC at any stage is high at 84%, but its sensitivity for detecting early-stage HCC (defined by the Milan criteria) is much lower, at only 47% (63% when combined with measurement of α-fetoprotein (AFP))[52]. This lack of sensitivity for early disease is a major problem given that curative options are limited for advanced-stage HCC[11,17,28,53,54]. This poor detection of early HCC is related to operator dependence and difficulty with visualizing the liver, especially for patients with obesity or advanced cirrhosis[52,55].

Difficulty with visualization of the liver can be assessed with the Liver Imaging Reporting and Data System (LI-RADS) ultrasound visualization score, which was developed under the auspices of the American College of Radiology to standardize reporting of imaging-based surveillance tests for patients at risk of HCC[56]. This qualitative evaluation is categorized by the interpreting radiologist as follows: score A indicates no or minimal limitations; score B indicates moderate limitations that might obscure small masses; and score C indicates severe limitations that might substantially lower sensitivity for focal liver observations[57]. In a study in which 2,053 patients with cirrhosis

underwent ultrasound surveillance for HCC, the LI-RADS visualization score was B for 13% and C for 5% of patients[58]. Obesity, cirrhosis related to alcohol or non-alcoholic steatohepatitis (NASH), and Child–Pugh stage B or C were independent predictors of limited visualization (a LI-RADS score of B or C)[58]. This finding is critical, as it indicates that visualization limitations will become gradually more problematic given the increasing prevalence of obesity and NASH (see Implications of changing aetiology for surveillance).

Suboptimal visualization of the liver has diagnostic implications. In a study of 186 patients with HCC, the sensitivity of ultrasound for HCC was only 27.3% among patients for whom the LI-RADS visualization score was C, whereas sensitivity was >75% among patients for whom the LI-RADS visualization score was either A or B[59]. The association of visualization scores in HCC surveillance with clinical outcomes, such as overall survival, has not been studied directly, but these studies suggest that limited visualization is an important contributor to the suboptimal sensitivity of ultrasonography for the detection of early HCC.

Potential harm of ultrasound-based surveillance

Several studies have described physical harm to patients who have undergone ultrasonography as screening for HCC, although these harms seem infrequent and mostly mild. In a study of 680 patients with cirrhosis who underwent surveillance by ultrasonography and/or measurement of AFP, 28% of patients received either false-positive or indeterminate findings that resulted in physical harm[60]. In this study, mild harm was defined as one diagnostic computed tomography (CT) or magnetic resonance imaging (MRI) procedure, moderate harm as repeated CT or MRI procedures over time, and severe harm as any invasive procedure, including a biopsy, or a deleterious complication such as acute kidney injury from the contrast agent. Three of the 680 patients experienced severe harm (2 underwent biopsy and 1 underwent an angiogram), and 184 experienced mild or moderate harm[60]. In another prospective study of 614 patients with cirrhosis, 9% of participants were subjected to unnecessary cross-sectional imaging but none received an unnecessary biopsy[61].

In addition to the physical harm that can result from false-positive HCC surveillance tests, psychological harm is also a possibility. Though the psychological consequences have not been studied in the context of HCC surveillance specifically, data from prostate cancer screening suggest that false-positive results are associated with depression and anxiety[62].

Taken together, these data indicate that harms from HCC surveillance arise mainly from indeterminate or false-positive results, though most were mild. The harm caused could be further mitigated with a judicious approach to indeterminate results that involves close monitoring rather than early invasive diagnostic tests.

Implications of changing aetiology for surveillance

The aetiology of HCC has changed substantially in the past decade. On the basis of data from the Global Burden of Disease study, NAFLD and alcohol were the fastest-growing causes of liver cancer deaths globally between 2010 and 2019, whereas liver cancer deaths related to HBV and HCV declined in this period[15]. Additionally, the clear male predominance of liver cancer seen for most liver aetiologies was not observed with NAFLD-related HCC in another study based on the Global Burden of Disease data[63]. This lack of male predominance could be accounted for by the fact that a greater proportion of males drink alcohol at least moderately and therefore do not meet the criteria for NAFLD[64]. If proposed changes in nomenclature for NAFLD are adopted, more data will be required to determine the utilization of surveillance and survival on the basis of updated definitions that have a greater emphasis on the contributions of metabolic syndrome[65,66].

Although the incidence of HCC is lower among people with non-viral liver diseases, such as NAFLD and alcohol-related liver disease, than among those with HBV or HCV infection, the at-risk population is substantially larger[67–69]. Nearly one-third of the global adult population has NAFLD[49]. In addition, alcohol consumption is rising worldwide[25,33,49,50,67,68,70–72]. Collectively, these data indicate that the burden of HCC due to NAFLD and alcohol could increase in parallel with the obesity epidemic and increasing alcohol consumption[25,73,74]. Furthermore, despite the relative decline in age-adjusted death rates for liver cancer associated with HBV and HCV, these aetiologies accounted for an estimated 40% and 29%, respectively, of global liver cancer deaths in 2019, highlighting the continued importance of efforts to eliminate viral hepatitis[15].

Recent changes in the epidemiology of HCC have important implications for HCC surveillance. In the following sections, we consider these implications in relation to various aetiologies.

Table 4 | Selected studies that provide data for the utilization of HCC surveillance in cohorts with chronic hepatitis B

Study	Study period	Location	Study setting	Study population	Utilization of surveillance
Clinical cohorts with data verified by chart review					
Wang et al.[38]	1996–2013	USA	4 clinics	1,329 with chronic HBV (164 with cirrhosis)	38.4% of patients with cirrhosis had optimal HCC surveillance versus 23.4% of patients who did not have cirrhosis but met AASLD criteria for surveillance
Administrative data base studies					
Goldberg et al.[195]	2006–2010	USA	National insurance claims data base	4,576 patients with chronic HBV without known cirrhosis	6.7% had complete surveillance (one ultrasound every 6 months)
Tran et al.[196]	2007–2014	USA	National insurance claims data base	55,317 patients with chronic HBV infection (14.8% without known cirrhosis)	36.5% of patients without cirrhosis received at least annual surveillance
Nguyen et al.[22]	2013–2018	USA	National administrative claims data base	6,831 patients with chronic HBV without known cirrhosis	39.3% and 51.3% received any abdominal imaging after 6 months or 12 months, respectively

We included studies that reported the utilization of hepatocellular carcinoma (HCC) surveillance in patients with chronic hepatitis B virus (HBV) in a real-world setting and excluded trials of HCC surveillance and studies that included patients with chronic liver disease other than chronic hepatitis B. AASLD, American Association for the Study of Liver Diseases.

Box 1

Limitations for hepatocellular carcinoma surveillance and possible solutions

Patient-related barriers

Barriers

- Misconceptions regarding screening
- Difficulties with cost and/or insurance
- Lack of access to medical care
- Difficulty with scheduling
- Long intervals between medical appointments and ultrasound
- Difficulties with transportation

Interventions

- Education
- Case-finding approach to identify patients at risk of hepatocellular carcinoma
- Mailed outreach strategies
- Reminders

Provider-related barriers

Barriers

- Lack of knowledge regarding screening
- Failure to recognize patients at risk
- Time constraints
- Competing medical issues
- Lack of resources

Interventions

- Education
- Reminders based on electronic medical records
- Nurse-led protocols to coordinate surveillance
- Alert system if surveillance appointment is missed

Ultrasound-related barriers

Limitations of ultrasound

- Operator dependent
- Substantial proportion with limited visualization, especially in obesity and cirrhosis associated with non-alcoholic fatty liver disease or alcohol-related liver disease
- Potential harm from false positives or indeterminate results

Alternative biomarkers

- Combinations of existing biomarkers
- DNA methylation markers
- Cell-free DNA
- Circulating tumour DNA
- Extracellular vesicles
- Abbreviated magnetic resonance imaging

NAFLD-related HCC

NAFLD poses unique challenges to HCC surveillance that diminish its utilization and its efficacy (Box 2). A systematic review and meta-analysis of 61 studies (including a total of 94,636 individuals) demonstrated that 15% of HCC was secondary to NAFLD[26]. This meta-analysis also showed that 39% of patients with NAFLD-related HCC do not have cirrhosis, a higher proportion than that of patients with HCC due to other aetiologies (22% for HBV, 6% for HCV and 9% for alcohol-associated liver disease)[26]. Findings of a population-based study conducted in the USA were similar — 58% of patients with NAFLD-related HCC had known cirrhosis compared with 90% of patients with alcohol-related liver disease, 89% with HCV infection and 81% with HBV infection[75]. Collectively, these data highlight that more than one-third of patients with NAFLD-related HCC do not have cirrhosis and therefore lack a routine indication for HCC surveillance.

The challenge of low incidence in the absence of cirrhosis. Routine surveillance for HCC in patients with pre-cirrhotic NAFLD would be inappropriate because the incidence of HCC in such patients is low[76,77]. In one meta-analysis, the incidence of HCC in NAFLD without cirrhosis was just 0.03 per 100 person-years (95% CI 0.01–0.07) compared with 3.8 per 100 person-years (95% CI 2.47–5.78) in NAFLD with cirrhosis[68]. Similarly, in a prospective study of 1,773 adults with biopsy-proven NAFLD, the incidence of HCC over 4 years was lower in stage 0–2 fibrosis (0.04 per 100 person-years) than in stage 3 (0.34 per 100 person-years) and stage 4 (0.14 per 100 person-years)[78]. A population-based cohort study of adults with biopsy-proven NAFLD in Sweden also determined that the incidences of HCC per 1,000 person-years in NAFLD, NASH without fibrosis and non-cirrhotic fibrosis were 0.8, 1.2 and 2.3, respectively[79]. In the subset of patients with non-cirrhotic fibrosis and diabetes, the incidence was 7.2 per 1,000 person-years, and the 95% confidence intervals (0.8–23.0 per 1,000 person-years) overlapped with the threshold incidence above which HCC surveillance is conventionally considered cost-effective[28,79,80].

The low incidence of HCC in NAFLD without cirrhosis has challenged consensus over surveillance recommendations for this population (Table 1). The American Gastroenterology Association has advised that patients with NAFLD and non-invasive markers that are consistent with advanced fibrosis or cirrhosis should be considered for HCC screening[81]. The EASL guidelines recommend that patients with stage 3 fibrosis may be considered for surveillance (weak recommendation) on the basis of individual risk assessment[11]. Furthermore, the performance of widely available non-invasive tests, such as the Fibrosis-4 (FIB-4) and NAFLD fibrosis scores, in the diagnosis of advanced fibrosis in NAFLD is generally modest (area under the receiving operator curve of 0.76 and 0.73, respectively); therefore, use of these tests can result in misclassification and missed opportunities for surveillance[82]. By contrast, complex blood-based biomarkers, such as the Enhanced Liver Fibrosis Score (ELF), and imaging-based non-invasive tests for advanced fibrosis, such as vibration-controlled transient elastography and magnetic resonance elastography, are more accurate (area under the receiving operator curve of >0.8) for the diagnosis of advanced fibrosis but their availability can be limited[83–85]. The lack of consensus about HCC surveillance in NAFLD without cirrhosis and the challenges in diagnosing advanced fibrosis contribute to heterogeneity in clinical practice and confusion among care providers[11,29,81,86].

Value of additional risk factors. For patients with NAFLD without cirrhosis, the decision of whether or not to recommend surveillance should be individualized on the basis of various additional risk factors that have been associated with HCC such as type 2 diabetes mellitus (T2DM) and obesity[69,73]. In a meta-analysis of studies including 2,016 patients with NAFLD assessed by magnetic resonance elastography, analysis of data at the individual participant level determined that the presence of T2DM is a strong risk factor for HCC, even after adjustment for baseline liver stiffness[87], an effect that could be related to faster progression of fibrosis in patients with T2DM[88]. Evidence suggests that patients with NAFLD and suboptimal glycaemic control and those who use a combination of insulin and oral medications for T2DM are at increased risk of HCC[87,89]. In a study in the USA of patients with NAFLD without baseline cirrhosis, T2DM conferred the highest risk of progression to HCC (adjusted HR 2.77, 95% CI 2.03–3.77); the impact of obesity was more modest (adjusted HR 1.31, 95% CI 0.98–1.74)[90]. However, when multiple metabolic traits were present, the risk of HCC increased

substantially (adjusted HR 8.63, 95% CI 1.11–66.99 in the presence of T2DM, obesity and hypertension)[90].

In addition to metabolic risk factors, non-invasive markers of fibrosis could be useful for assessing the risk of HCC and identifying patients suitable for HCC surveillance. For example, longitudinal assessment of FIB-4 scores in patients with NAFLD demonstrated that patients with a FIB-4 score that was persistently >2.67 were at the highest risk of HCC[91]. Furthermore, patients whose FIB-4 score increased over time were at higher risk of HCC than those with a persistently low FIB-4 score[91].

Taken together, this evidence indicates that patients with NAFLD and advanced fibrosis who have suboptimal control of T2DM, persistently high FIB-4 scores and/or a combination of multiple metabolic risk factors are at increased risk of HCC, and HCC surveillance may be considered on an individual basis for these patients. Improved risk stratification strategies are required to identify which patients with NAFLD and advanced fibrosis are most likely to benefit from HCC surveillance[92]. Despite the fact that NAFLD is associated with increased risks of all-cause mortality, cardiovascular events and extra-hepatic cancers, one study has suggested that HCC surveillance is cost-effective for patients with advanced fibrosis and/or cirrhosis even after the risk of mortality from other causes is accounted for[93].

Practical challenges. Several studies have indicated that NAFLD and obesity are associated with limited ultrasound visualization in HCC surveillance for patients with cirrhosis[27,58,94]. In a prospective study of ultrasonography for HCC surveillance specifically in patients with NAFLD cirrhosis, the LI-RADS visualization score was C for 35% of participants, B for 63% and A (indicating minimal or no limitations) for only 2%[95]. In combination with the data on visualization scores discussed above (see Limitations of ultrasonography), these data indicate that visualization with ultrasonography for HCC screening is substantially poorer in patients with NAFLD than in patients with cirrhosis of other aetiologies, highlighting the need for alternative surveillance strategies in NAFLD cirrhosis (see Strategies to improve HCC surveillance).

Alcohol-related HCC

Despite the growing burden of alcohol-related HCC, alcohol-associated cirrhosis is often underdiagnosed, contributing to low surveillance rates and poor disease awareness[25,96,97]. In a study from the Italian Liver Cancer group in which 573 patients with alcohol-related HCC were compared with 1,642 patients with HCV-related HCC, the proportion of HCC diagnosed via a surveillance programme was lower for alcohol-related HCC than for HCV-related HCC (38% versus 69%)[98]. Similarly, a study in the USA of 178 patients with cirrhosis who were diagnosed with HCC determined that alcohol use disorder (defined in this study as drinking more than 40 g of alcohol per day) was associated with lower surveillance (OR 0.14, 95% CI 0.03–0.65)[39]. As a result of this low surveillance, patients with alcohol-associated HCC tend to present at a more advanced stage than those with HCC of other aetiologies[98–101].

Reasons for the lack of HCC surveillance among patients with alcohol-related cirrhosis include poor disease awareness, inadequate motivation, concomitant depression and anxiety, poor social support, stigma, competing medical issues, and inadequate screening for alcohol use disorder among care providers[39,102–105]. In addition, alcohol-related cirrhosis is associated with limited visualization with ultrasonography for HCC surveillance, which might reduce the efficacy of surveillance[58,59]. A multidisciplinary approach that involves primary care, hepatologists, psychiatrists, public health specialists and addiction specialists might be required to address these barriers and meaningfully improve surveillance utilization among patients with alcohol-associated cirrhosis[97].

An additional complication in the discussion of HCC surveillance for patients with alcohol-associated cirrhosis is that the value of such surveillance in this population is unclear. A nationwide study conducted in Denmark demonstrated 1-year, 5-year and 10-year risks of HCC as 0.9%, 3.6% and 6.0%, respectively, amounting to an annual HCC risk of ~0.7% per year; this risk is below the threshold at which HCC surveillance is thought to be cost-effective[106,107]. In this study, the likelihood of death from variceal bleeding or trauma was comparable to that from HCC[106]. Other competing causes of mortality in this population, such as alcoholic hepatitis due to continued alcohol consumption[105,108], and non-adherence to surveillance owing to alcohol-seeking behaviour further complicate the risk–benefit ratio for HCC surveillance. Furthermore, several experts have questioned the clinical utility of HCC surveillance in patients with cirrhosis of any aetiology given the lack of randomized data and the potential for harm[19]. These complex issues highlight the need for further evaluation of the risks and benefits of HCC surveillance in alcohol-associated cirrhosis. One meta-analysis has determined that T2DM, smoking, variceal bleeding and hepatic decompensation are associated with a higher risk of HCC among patients with alcohol-associated cirrhosis[67]; therefore, if patients with these risk factors undergo HCC surveillance, they need to be counselled on their increased risk and the importance of adherence to surveillance.

HCV-related HCC

Despite a decline in mortality from HCV-related HCC during the previous decade, HCV still accounted for nearly one-third of global liver cancer deaths in 2019 (ref. 15). Furthermore, the risk of HCC decreases after hepatitis C cure (achievement of a sustained virological response) but remains substantial for individuals with cirrhosis before treatment and remains elevated to a lesser degree in those with stage 3 fibrosis before treatment[109–120].

Evidence from one study suggested that HCC surveillance is cost-effective when used for patients with cirrhosis before hepatitis C treatment but not when used for patients with stage 3 fibrosis before

Box 2

Unique challenges and barriers to HCC surveillance in patients with non-alcoholic fatty liver disease

- Poor disease awareness
- More than one-third of patients have no cirrhosis
- Lack of consensus on surveillance in the absence of cirrhosis
- Limited visualization with ultrasound compromises the detection of early hepatocellular carcinoma (HCC)
- Patients have competing comorbidities and appointments
- At-risk population is huge but the incidence of HCC within this population is low

treatment[121]. However, several parameters used in this modelling study relied on data on the effectiveness and cost of treatment for advanced HCC that were obtained before the approval of more effective therapies such as atezolizumab plus bevacizumab; therefore, interpretation of this finding requires caution[121]. The AASLD recommends continuing HCC surveillance only for individuals with cirrhosis before hepatitis C treatment, whereas the EASL recommends that patients with pre-treatment stage 3 fibrosis may be considered for screening and the APASL[122] recommends screening for all patients with cured hepatitis C regardless of fibrosis stage[11,28,122] (Table 1).

Attempts have been made to stratify patients with cured hepatitis C according to their risk of HCC. For example, in a study based on the US Veterans Affairs national health-care system, predictors of HCC risk after hepatitis C cure were identified and models were developed to discriminate between individuals at high, medium and low risk of HCC[123]. However, 97% of participants were male and the models were only internally validated; therefore, whether these findings are generalizable is unclear. In a study conducted in Europe, the risk of HCC after hepatitis C cure among individuals with advanced chronic liver disease (defined by liver stiffness, hepatic venous pressure gradient or histology) was determined and used to generate risk models based on AFP levels, alcohol consumption, age, liver stiffness and albumin levels[118]. These models were externally validated in independent European cohorts and could identify more than two-thirds of patients who had an annual HCC risk of <1%. Further data — ideally validated externally in geographically and ethnically distinct cohorts — are required to determine optimal strategies for HCC screening among individuals with advanced fibrosis after hepatitis C cure[124].

HBV-related HCC

Chronic hepatitis B remains the leading cause of liver cancer deaths worldwide and accounted for 40% of global liver cancer deaths in 2019 (ref. 15). Despite the availability of effective antiviral therapy that substantially reduces the risk of HCC, only a minority of treatment-eligible patients receive antiviral treatment because hepatitis B is severely underdiagnosed[23,125–129]. Only four countries have achieved the WHO Global Health Sector Strategy on Viral Hepatitis 2020 interim target of a 10% reduction in deaths between 2015 and 2019 (ref. 130), and HBV-related HCC is likely to remain a major threat to public health over the next decade.

Multiple predictive models have been developed to stratify the risk of HCC among patients with antiviral-treated and antiviral-untreated chronic hepatitis B[30,131–142]. HBV DNA is an important component of risk scores in untreated individuals as it is a major predictor of HCC risk, but separate risk scores are needed for treated patients because the treatment suppresses HBV DNA[143,144]. Owing to the fluctuating nature of disease activity in untreated chronic hepatitis B, frequent reassessment of risk scores might be required, limiting the clinical applicability of risk scores that were derived from the untreated cohorts[139,145,146].

HCC risk scores developed in antiviral-treated cohorts could be used to identify patients who are at low risk of HCC and could therefore avoid HCC surveillance provided that the negative predictive value of the risk score is sufficiently high[139]. A study of 3,101 patients with antiviral-treated chronic hepatitis B in the USA independently evaluated 10 published HCC risk-prediction models and determined that none of the patients in the low-risk groups, defined by the PAGE-B, m-PAGE-B, AASL-HCC or REAL-B risk scores, developed HCC over a median follow-up of 4.5 years[30,137,140,147,148]. Currently, the EASL and AASLD guidelines recommend use of the PAGE-B score to identify patients with chronic hepatitis B who require HCC surveillance[11,29,137,149]. Prospective validation of these risk scores in ethnically and geographically diverse cohorts of patients with chronic hepatitis B will be useful to determine their clinical utility for guiding HCC surveillance.

Strategies to improve HCC surveillance

Utilization

Several interventions directed at patient-related and provider-related barriers have been proposed to increase the utilization of HCC surveillance (Box 1). In one study in Australia, patients were provided information sheets on HCC and the importance of surveillance to improve their knowledge; these sheets were mailed to patients with reminders to undergo HCC surveillance[150]. In addition, clinicians were provided with surveillance guidelines and protocols on the hospital intranet and a dedicated nurse was assigned to coordinate HCC screening[150]. These interventions improved the utilization of HCC screening (defined as appropriate surveillance within the preceding 6 months) from 46% to 92%[150]. In another multicentre randomized trial of a mailed outreach strategy conducted in the USA, patients with cirrhosis (based on International Classification of Disease codes or a FIB-4 score of >3.25) received a letter that contained information about HCC and a recommendation for screening[151]. Participants who did not respond received follow-up calls and reminders for their ultrasound appointments. Semi-annual HCC surveillance over 1 year was higher among patients who received the intervention than among those who received usual care (35% versus 22%).

Several studies have focused on interventions directed at care providers. In a study conducted in Italy, 120 primary care physicians participated in a training programme for the screening of individuals who are at risk of cirrhosis (for example, people with heavy alcohol use or who are positive for hepatitis B surface antigen or HCV antibodies) with ultrasonography and platelet counts[152]. This intervention was associated with an increase in the proportion of patients diagnosed with HCC during surveillance compared with before the training period (55% versus 35%)[152]. In a study conducted in the US Veterans Affairs health system, clinical reminders appeared on the electronic medical records of patients with cirrhosis, and the proportion that received adequate surveillance (two or more imaging scans in 18 months) at the intervention site increased by 51%[153]. In another study conducted in the USA, patients with cirrhosis were enrolled into a surveillance programme that enabled nurses to order surveillance tests and provided alerts to nurses if enrolled participants were 1 month or more behind on their surveillance[154]. After this intervention, 93% of participants underwent surveillance imaging at least once during a 1-year period compared with 74% during a 1-year period before the intervention[154].

Interventions have also been implemented to improve the detection of liver disease and HCC in the wider population. In a study conducted in Germany, a structured screening programme was implemented to detect early cirrhosis in people undergoing health checkups. In this screening programme, measurement of aspartate aminotransferase, alanine aminotransferase and platelet levels in routine serum tests was associated with a 59% increase in the odds of detecting early cirrhosis (after excluding individuals with decompensated cirrhosis)[155]. By identifying people with early cirrhosis who are at risk of HCC, and hence candidates for HCC surveillance, this approach could improve surveillance utilization and early detection of HCC but requires validation. Population-wide interventions implemented in Japan and Taiwan have dramatically improved HCC detection and survival[156,157]. In Japan, educational public lectures are conducted several times per

year in each prefecture, free testing for HBV and HCV is available, and the costs of HCC surveillance are covered by the national health insurance system[156,158]. These interventions have contributed to >56% of HCC cases in Japan being diagnosed via surveillance[156,159,160]. Similarly, HCC surveillance by ultrasonography is reimbursed in Taiwan under its universal health-care system[157], and this intervention has resulted in 39% of men and 52% of women receiving an ultrasound scan in the 12 months before a diagnosis of HCC[157,161].

Taken together, these data suggest that strategies to improve the education of patients and providers, case-finding approaches to detect cirrhosis, mailed outreach programmes and reminders generated through electronic medical records could be effective ways to improve the utilization of HCC surveillance. Nationwide, case-finding approaches that link patients at risk with a surveillance programme could also help to improve surveillance utilization and reduce mortality associated with HCC[162].

Quality

Ultrasound-based HCC surveillance is associated with multiple limitations, including limited sensitivity for early-stage disease, limited visualization, inter-operator variability and poor adherence[94]. Ultrasound image acquisition is complicated and operator dependent but is a key element in the diagnostic process[163]. Operators with more experience are more likely to be capable of identifying features that support or rule out differential diagnoses, resulting in greater accuracy[163]. In a study conducted in the USA in which 6,598 patients at risk of HCC underwent ultrasonography, the LI-RADS visualization score was worse for examinations performed by less experienced sonographers[164], and the EASL recommends that HCC surveillance by ultrasonography should be performed by 'experienced' personnel[11]. The rising prevalence of obesity, NAFLD and alcohol-associated liver disease could further compromise the sensitivity of ultrasound-based surveillance for HCC, necessitating improvements in biomarker tests for HCC[27].

Blood-based diagnostic markers of early HCC. Blood-based biomarkers could help to address some of the limitations of ultrasonography by producing objective results rather than operator-dependent findings. Early-phase studies of several biomarkers have produced encouraging results[165] (Box 1). A meta-analysis has shown that adding measurement of AFP to ultrasonography resulted in a pooled sensitivity of 63% for the detection of early HCC compared with 47% with ultrasonography alone[52]. However, AFP has limited sensitivity for HCC when used in isolation and is therefore insufficient alone as a screening test (though its performance is better in patients with cured hepatitis C and in patients with hepatitis B who are receiving nucleos(t)ide analogues)[166,167]. Serum levels of des-carboxy-prothrombin and AFP-L3 have been used for HCC surveillance in the clinical setting but their sensitivity for early HCC was <50%[168–170]. Combinations of existing biomarkers have also been used; such combinations include the GALAD (gender, age, AFP-L3, AFP, des-carboxy-prothrombin) score, the Doylestown algorithm (age, gender, log AFP, alkaline phosphatase and alanine aminotransferase) and the HES algorithm (AFP, rate of AFP change, alanine aminotransferase and platelet count)[171–174]. Several of these combinations have performed well in case–control studies, but early data from phase III trials suggest that the sensitivity of these algorithms for early-stage HCC is only ~55–60%[169,175].

Other emerging blood-based biomarkers of HCC include DNA methylation markers, cell-free DNA, circulating tumour DNA and extracellular vesicles, and results of studies in which these markers have been used are promising. In a case–control study in which DNA methylation markers (HOXA1, TSPYL5 and B3GALT6) were combined with sex and AFP, sensitivity was 82% in an independent validation cohort[176]. Similarly, a multi-analyte blood test that combined cell-free DNA methylation patterns, clinical variables and protein tumour markers had a sensitivity of 76% for early HCC compared with 57% for AFP[177]. An algorithm based on three extracellular vesicle subpopulations had a sensitivity that exceeded 90% in distinguishing early-stage HCC from cirrhosis in an external validation cohort[178]. Despite these encouraging preliminary results, these biomarkers require validation in large prospective studies[179]. Current and emerging blood-based biomarkers of HCC have been reviewed in detail elsewhere[165,180,181].

Magnetic resonance imaging. MRI with and without liver-specific contrast has been studied as an alternative method for HCC surveillance that could address the limitations of ultrasound-based screening[182]. In a prospective study conducted in South Korea that involved 407 patients with cirrhosis, comparison of complete MRI sequences with ultrasonography determined that detection of early-stage HCC was considerably higher with MRI (86.0% versus 27.9%)[182]. However, complete MRI might not be feasible as a screening tool owing to long image acquisition times, availability and cost[183].

Abbreviated MRI protocols could improve the feasibility of MRI as a screening tool as they involve a fraction of the sequences and reduce image acquisition time to less <15 min (ref. 184). A systematic review and meta-analysis of 15 studies determined that the sensitivity of abbreviated MRI for HCC was 86%, though this estimate was lower

Box 3

Future directions

- The focus of care for patients with hepatocellular carcinoma (HCC) should be shifted upstream towards early detection[46].
- A case-finding approach to link patients at risk with a surveillance programme could help to improve surveillance utilization and reduce mortality associated with HCC[155].
- Estimates of surveillance utilization should be standardized to report the percentage of patients that received semi-annual surveillance imaging.
- Multidisciplinary collaboration between public health, hepatology and primary care specialists as well as patient advocacy groups could help to improve the utilization of HCC surveillance, especially in the setting of cirrhosis associated with non-alcoholic fatty liver disease or alcohol-related liver disease, conditions associated with unique barriers to surveillance[97,197].
- Consensus regarding the utility of HCC surveillance in the setting of non-alcoholic fatty liver disease with advanced fibrosis and hepatitis C virus after sustained virological response could help to streamline care practices.
- Strategies should be developed for surveillance when visualization is severely limited with ultrasonography.
- Alternative strategies are needed to improve the quality of HCC surveillance, including novel blood-based biomarkers and advanced imaging modalities.

(69%) for the detection of HCC of <2 cm in diameter[185]. Comparison of abbreviated MRI, complete MRI and ultrasonography in patients with cirrhosis determined that the sensitivities for HCC were 86.0%, 90.7% and 27.9%, respectively[186]. A multicentre study of 161 patients with HCC published in 2023 determined that the sensitivity and specificity of abbreviated MRI for early-stage HCC (with surgical pathological findings as the reference) were 88% and 89%, respectively[187].

Emerging data suggest that abbreviated MRI could be particularly useful for HCC surveillance in the context of NAFLD cirrhosis given the high prevalence of obesity in this patient group, which tends to limit visualization with ultrasonography[27,94]. In a prospective, head-to-head study of abbreviated MRI versus ultrasonography for HCC surveillance in 54 patients with NAFLD cirrhosis, abbreviated MRI was associated with a lower proportion of severe limitations of visualization (19% versus 35%)[95]. Further validation of these data and analysis of the cost-effectiveness of abbreviated MRI are required. Regardless, access to MRI is likely to remain a barrier to its use for HCC surveillance.

Conclusions

HCC surveillance is associated with improved survival of patients with chronic hepatitis B or cirrhosis but is underutilized in clinical practice owing to multiple patient-related and provider-related barriers and considerable work is needed to improve surveillance rates (Box 3). Changes to HCC surveillance and interventions such as a case-finding approach and outreach strategies could improve surveillance rates. Several unique barriers to HCC surveillance are associated with NAFLD-associated and alcohol-associated cirrhosis, including poor performance of ultrasound-based surveillance, highlighting a need for surveillance modalities that are more effective in these growing patient populations. Novel blood-based and imaging-based biomarkers are promising for HCC surveillance but require prospective validation in large cohorts. Surveillance is essential for early detection of HCC and more resources need to be directed towards making early detection easier, thereby reducing the global burden of HCC.

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

D.Q.H. has served as an advisory board member for Eisai and Gilead and has received funding from the Singapore Ministry of Health's National Medical Research Council (MOH-000595-01). A.G.S. has served as a consultant or on advisory boards for AstraZeneca, Bayer, Eisai, Exact Sciences, Exelixis, Freenome, FujiFilm Medical Sciences, Genentech, Glycotest and GRAIL. P.L. has served on advisory boards and/or speaker bureaus for Abbvie, Arrowhead, Aligos, Alnylam, Antios, Bristol Myers Squibb, Eiger, Gilead Sciences, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Myr, Roche, Spring Bank and Vir Biotechnology. M.B. has received research support from Gilead and has served as an advisory board member for Abbvie, Gilead, GlaxoSmithKline, Janssen and Spring Bank. C.B.S. has received research grants from the American College of Radiology, Bayer, Foundation of NIH, GE Healthcare, Gilead, Pfizer, Philips and Siemens; has lab service agreements with Enanta, Gilead, ICON, Intercept, Nusirt, Shire, Synageva and Takeda; conducts institutional consulting for Bristol Myers Squibb, Exact Sciences, IBM–Watson and Pfizer; provides personal consulting for Blade, Boehringer, Epigenomics and Guerbet; receives royalties and/or honoraria from Medscape and Wolters Kluwer; owns stock options in Livivos; has an unpaid advisory board position at Quantix Bio; and serves as Chief Medical Officer for Livivos (unsalaried position with stock options) with appointment approved from his university. M.H.N. has received research support from AstraZeneca, B.K. Kee Foundation, CurveBio, Delfi, Enanta, Exact Science, Gilead, Glycotest, Helio Health, Innogen, the National Cancer Institute, Pfizer and Vir. She has served as an advisory board member or consultant to Eli Lilly, Exact Sciences, Exelixis, Gilead, GlaxoSmithKline and Intercept. R.L. received funding from the National Institute of Diabetes and Digestive and Kidney Diseases (P30DK120515) and serves as a consultant to 89bio, Aardvark Therapeutics, Altimmune, Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol-Myer Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse bio, Hightide, Inipharma, Intercept, Inventiva, Ionis, Janssen, Madrigal, Metacrine, NGM Biopharmaceuticals, Novartis, Novo Nordisk, Merck, Pfizer, Sagimet, Theratechnologies, Terns Pharmaceuticals and Viking Therapeutics. In addition, his institutes have received research grants from Arrowhead Pharmaceuticals, AstraZeneca, Boehringer-Ingelheim, Bristol Myers Squibb, Eli Lilly, Galectin Therapeutics, Galmed Pharmaceuticals, Gilead, Intercept, Hanmi, Intercept, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Novo Nordisk, Merck, Pfizer, Sonic Incytes and Terns Pharmaceuticals. F.K. declares no competing interests.

Additional information

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Review criteria PubMed was searched from inception to February 2023 using the terms "hepatocellular carcinoma", "surveillance" and "screening" without language restrictions. Original articles were evaluated. Studies were selected to provide data from diverse geographical locations on the utilization of hepatocellular carcinoma (HCC) surveillance in the presence of cirrhosis and chronic hepatitis B. We included studies that reported the utilization of HCC surveillance in a real-world setting. We excluded trials of HCC surveillance and studies of dedicated HCC surveillance programmes.

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