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REVIEW

Novel biomarkers and strategies for HCC diagnosis and care

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INTRODUCTION

Liver cancer is the third most common cause of cancer death worldwide, the majority of which (70%–95%) is HCC that most commonly develops in the setting of chronic liver disease. While traditional risk factors for HCC (ie, viral hepatitis, alcohol use) remain important, rates of HCC in patients with metabolic dysfunction–

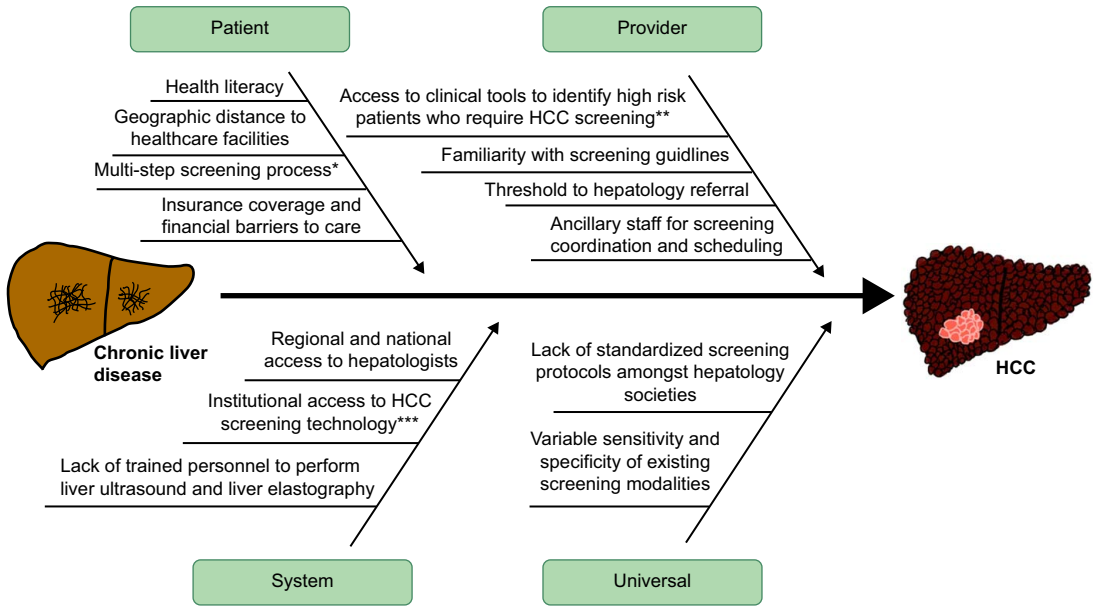

FIGURE 1 Challenges in effective surveillance. *For example: obtaining an order for the exam, scheduling an imaging exam, and going to an imaging appointment **such as liver elastography, MRI, or biopsy for diagnosis of advanced fibrosis. ***CT/MRI machines, liver elastography machines, and laboratory assays.

Abbreviations: AFP, alpha-fetoprotein; DCP, Des-γ-carboxy prothrombin; GALAD, gender, Age, AFP-L3, AFP, and DCP; US, ultrasound.

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associated liver disease are rising. Despite increasing HCC incidence, HCC surveillance rates remain low, with adherence in fewer than 25% of those at risk for HCC.[1] Since HCC mortality significantly increases between early-stage and late-stage diagnoses, it is imperative to improve rates of early HCC diagnosis to decrease HCC-related mortality.[1,2]

DIAGNOSTIC CHALLENGES AND TREATMENT RESPONSE ASSESSMENT IN HCC

There are significant challenges to HCC surveillance at patient, provider, and system levels (Figure 1). Patient-level barriers include multi-step processes to undergo testing, adherence to biannual HCC screening, medical literacy surrounding the importance of adhering to HCC surveillance, insurance status, and access to care.[1,2] On a provider level, time limitations during office visits, staying up to date with evolving hepatology society guidelines (Figure 2), and reliability of surveillance tests present barriers to both ensuring adherence to recommended surveillance in high-risk patients and early HCC diagnosis.[1–3] System-level barriers to HCC surveillance include referral gaps from internists to hepatology specialists, the limited number of hepatologists geographically, insurance coverage of HCC screening tests, and institutional access to abdominal imaging and liver elastography machines.[1]

International practice guidelines for HCC surveillance remain largely unchanged in the last 2 decades, relying on some combination of abdominal ultrasound (US) and alpha-fetoprotein (AFP) (Figure 2).[4–6] US is widely recommended as the initial screening test due to low cost and accessibility despite low sensitivity for early-stage HCC detection (47% for US alone, 63% for US with AFP).[1] HCC treatment response is currently evaluated using serial cross-sectional imaging and serum AFP after treatment.[4]

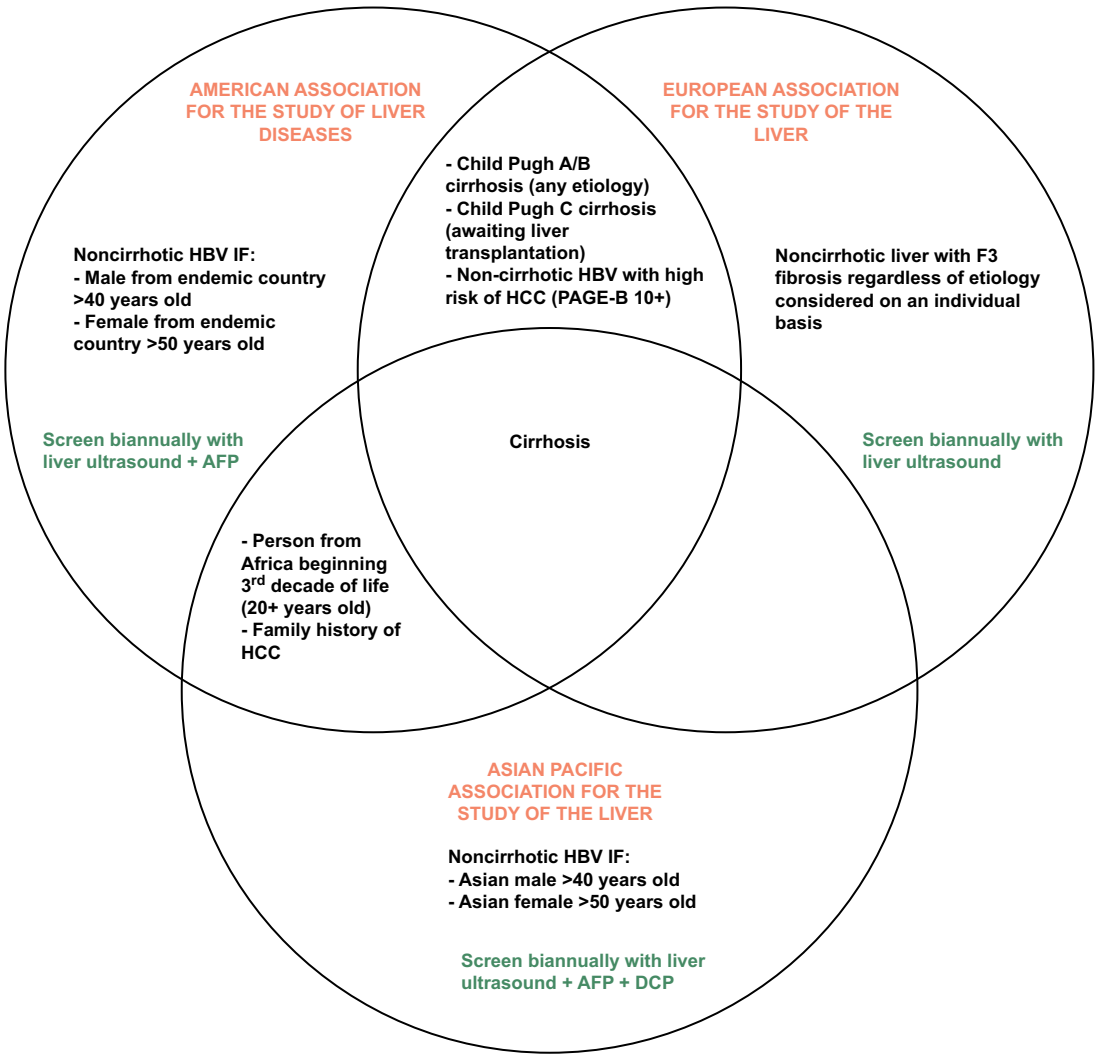

FIGURE 2 Summary of surveillance guidelines by society. Abbreviation: AFP, alpha-fetoprotein; DCP, Des-γ-carboxy prothrombin.

TABLE 1 Summary of biomarkers in use and in development

	Mechanism	Use	Sensitivity, %	Specificity, %	Phase of development	Reference
Serum Biomarkers						
AFP (cutoff 20 ng/mL)	Glycoprotein secreted by the adult liver in inflammatory states (ie, chronic HBV or HCV) Linked to the growth of HCC and evasion of intrinsic anti-tumor mechanisms Up to 20% of HCC are non-AFP producing	Early detection, response to treatment AFP > 400 ng/mL is a poor prognostic indicator-ramicurumab effective in this population	39–64	76–97	Phase V	[7,8]
AFP-L3%	Subfraction of AFP	Early detection	62	90	Phase III	[9,10]
DCP	Prothrombin variant produced by HCC; levels vary with vitamin K levels	Early detection	40	81	Phase III	[9,10]
Liquid biopsy techniques						
CTC	HCC tumor cells that enter the peripheral circulation	Early detection, Response to treatment	95	73	Phase III	[11]
cfDNA	Peripherally circulating nucleic acids released with cell turnover/apoptosis in malignant and inflammatory states	Early detection, Response to treatment	91–96.8	43–98.8	Phase II, III	[12–15]
cfRNA	Coding and noncoding RNA segments circulating in peripheral blood associated with tumor progression	Response to treatment	Variable depending on RNA segment	Variable depending on RNA segment	Phase III	[16]
DNA methylation markers	Changes in methylation patterns of HCC oncogenes and tumor suppressor genes	Response to treatment	Variable depending on gene	Variable depending on gene	Phase II	[15]
Extracellular vesicles	Membrane vesicles released by cells in both normal physiologic and pathologic states; contain bioactive molecules that can act at nearby or distant sites and are often involved in tumor growth	Early detection	70–89	47–82	Phase III	[17]
Clinical algorithms						
GALAD	Gender, age, AFP-L3%, AFP, DCP	Early detection	54–72	90	Phase III published; Phase IV/V in progress	[3]
Doylestown Plus	AFP, age, gender, alkaline phosphatase, alanine aminotransferase	Early detection	90	95	Phase III	[18]
HCC early detection screening algorithm	AFP, rate of AFP change, age, alanine aminotransferase, platelets	Early detection	53	48	Phase II-III	[10]

Abbreviations: AFP, alpha-fetoprotein; CfDNA, cell-free DNA;CfRNA, Cell-free RNA; CTC, circulating tumor cells; DCP, Des-γ-carboxy prothrombin; GALAD, Gender, Age, AFP-L3, AFP, and DCP.

CURRENT BIOMARKERS AND THEIR ROLES IN HCC CARE

The International Liver Cancer Association has published guidelines for the development and clinical application of biomarkers; many remain in the early stages of study (Table 1).[19]

AFP: The sensitivity of AFP alone to detect early-stage HCC is low (Table 1), in part because over 20% of HCC tumors do not produce AFP. In those that do, higher AFP levels are associated with more aggressive tumors, worse prognosis, and poorer treatment response. AFP trends are used for risk stratification in clinical trials and transplant eligibility. However, AFP alone is inadequate for early detection or treatment response in HCC.[7]

AFP-L3/DCP: AFP is fucosylated to become AFP-L3 during HCC growth.[9] AFP-L3/AFP ratio (AFP-L3%) may be particularly useful in diagnosis and prognosis in patients with low-AFP–producing tumors.[3] DCP has been incorporated into some HCC screening algorithms in conjunction with AFP and US because it is not elevated in chronic liver disease or cirrhosis.[6]

Because no biomarker has been validated as a standalone screening test, many studies have developed predictive models that utilize a combination of demographics, common laboratory values, and biomarkers, such as the Doylestown algorithm, the HCC Early Detection Screening algorithm, and the GALAD (Gender, Age, AFP-L3, AFP, and DCP) score (Table 1).[3,10,18]

Of these, the GALAD score is the most advanced in development. It has been validated in international populations from multiple liver disease states.[3] In Phase 3 biomarker studies, GALAD has shown high sensitivity for diagnosis of early- and any-stage HCC,[3] and an ongoing phase IV/V randomized control trial using GALAD for early HCC detection holds promise for incorporation into society guidelines.[20]

FUTURE STEPS ON BIOMARKERS IN HCC

Liquid biopsy techniques isolate and analyze tumor components in peripheral blood (eg, DNA/RNA fragments, tumor cells, and extracellular vesicles).[21] Liquid biopsy is used for early detection and treatment response monitoring in acute myeloid leukemia and solid tumors such as prostate, breast, lung, colorectal, and ovarian cancer.[21] Liquid biopsy in HCC is under active study (Table 1). Several whole genome sequencing and next-generation sequencing techniques of cell-free DNA have been validated with machine learning models in international patient cohorts to distinguish patients with HCC from those with cirrhosis and chronic liver disease with areas under the curve greater than 0.95.[12–14] Though these are in earlier investigative phases than GALAD, their high sensitivity and specificity and relatively low-cost show promise for future use. Cell-free DNA and other liquid biopsy targets have also been studied to evaluate response to treatment—future applications may include individualized adjustments to systemic therapy or better selection of patients for liver transplantation for HCC cure.

It is worth noting that although many biomarkers and noninvasive algorithms are in development, none have adequate prospective data for adoption into guidelines. Currently, the American Association of Liver Disease recommends US with AFP every 6 months in high-risk patients.[4] While we await accessible, affordable, and reliable biomarkers that might increase adherence to HCC surveillance and early detection, it is also important for practitioners to understand and identify high-risk patients for surveillance. For example, the American Association of Liver Disease recommends noninvasive fibrosis evaluations in patients with metabolic dysfunction–associated liver disease and certain comorbid conditions[4] (Fig. 1).

For patients who require HCC surveillance, practitioners and health systems should work toward feasible solutions to support adherence to current guidelines—emphasizing the rationale and importance of surveillance to patients and arranging for its practical achievement (eg, scheduling imaging, lab collection, and clinic appointments on the same day; leveraging automated reminders to patients or in electronic medical records; or designing systems for local surveillance with reliable communication of findings to specialist providers).

Barriers to practical use and the rising global HCC burden necessitate better methods to risk stratify patients for HCC, detect it early, and individualize patient therapies. The last several years have brought rapid advances in the discovery and early validation of noninvasive biomarkers, whose future prospective study is likely to bring more accurate and accessible tools for HCC care.

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CONFLICTS OF INTEREST

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