Review Article

The potential of multi- and single-cancer blood-based early detection tests in liver cancer screening

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Contributions: (I) Conception and design: Both authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

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Abstract: Liver cancer is one of the most common causes of cancer deaths worldwide. Although fatal when diagnosed at an advanced stage, liver cancer has a favorable prognosis when identified at an earlier stage. Guidelines for liver cancer screening do exist, currently recommending the use of ultrasound with or without hematologic markers for early detection of liver cancer. However, studies have revealed shortcomings in the current state of liver cancer screenings such as underutilization stemming from lack of primary care education and logistical barriers for patients, suboptimal sensitivity of current screening methods, and lack of screening for lower risk individuals. A multitude of liquid biopsy tests that use circulating genomic analytes for early detection of cancers are currently under development and have the potential clinical implications in the early detection of liver cancer. In this overview, we highlight limitations of current liver cancer screenings and the ongoing development of multicancer early detection tests as well as cancer specific blood tests for liver cancer. As these multi-analyte blood tests hold promise in filling the gaps of current shortcomings of liver cancer screenings, it is imperative for primary care physicians, oncologists, and hepatologists involved in the screening process to be aware of ongoing studies and the further research necessary to ascertain several parameters such as the cost-benefit ratio, mortality reduction, and sensitivities of the blood tests.

Keywords: Hepatocellular carcinoma (HCC); multi-cancer early detection tests; multi-analyte blood tests; liver cancer screening

Submitted Sep 10, 2024. Accepted for publication Jan 23, 2025. Published online Mar 06, 2025.
doi: 10.21037/jgo-24-686
View this article at: https://dx.doi.org/10.21037/jgo-24-686

Introduction

Liver cancer is the sixth most prevalent cancer overall and the third most common cause of oncologic deaths worldwide as of 2020 (1). Hepatocellular carcinoma (HCC) accounts for majority of primary liver cancers (2). Given this prevalence and high mortality of HCC, screening is crucial to diagnose the disease at an early stage as the prognosis for HCC is closely related to the staging of cancer and HCC is often difficult to find at an earlier stage given its indolent nature (3). Currently, various international professional societies for liver disease are in agreement that, at-risk patients, mainly patients with cirrhosis, should be screened for HCC (1,4-6). However, despite the existence of these guidelines for HCC screening, there has been an under-utilization (7-12). Furthermore, the professional societies have differences in their categorizations for at-risk patients based on regional prevalence of liver disease and, overall, guidelines for lower-risk patients are less established across the board, meaning HCC diagnosis for these lower-risk patients may be missed.

The ability to screen for and identify cancers through

testing blood for circulating genomic analytes is a relatively novel cancer screening test that has been gaining increasing attention. Multicancer early detection (MCED) tests analyze the circulating biomarkers in blood, mainly the methylation of circulating free DNA as DNA methylation is a well-known hallmark of cancer, to check for possibility of various cancers (13). Furthermore, cancers originating from different types of tissues can have different methylation patterns of circulating DNA which can be used to specifically identify the tissue origin of the cancer (14). The purpose of the MCED tests is to have a multi-cancer screening test that can detect tumors at an earlier stage when treatments are potentially more favorable. A multitude of MCED tests are in the process of being developed and undergoing clinical trials to disrupt the traditional single-organ screening paradigms. Multi-analyte tests for early detection of specific cancers are also under development to enhance the current screening protocols for various cancers. To have the strongest effects, these liquid biopsy tests must have a high sensitivity to early-stage cancers and, at the same time, have a high specificity to prevent any unnecessary burden for patients.

Current state of liver cancer screening

The American Association for the Study of Liver Diseases (AASLD) currently recommends semi-annual liver cancer screening for high-risk patients utilizing ultrasound, preferentially with alpha-fetoprotein (AFP) (4). Abdominal ultrasound has been the crux of screening for liver cancer as it is relatively inexpensive, noninvasive, and well-tolerated. The sensitivity and specificity of ultrasonography alone in detecting early-stage HCC in patients with cirrhosis have been reported to be at around 53% and 91%, respectively (15). However, the sensitivity may vary depending on the expertise of the ultrasound technician as well as the body habitus of the patient (16). With AFP, ultrasound has an improved reported sensitivity of 63% for early-stage HCC (15).

Although most are still in early development, other liver cancer screening techniques are currently being developed using biomarkers for liver cancer. Using AFP alone for early detection of HCC has faced criticism given its suboptimal sensitivity and specificity (17). Another biomarker is the *Lens culinaris* lectin binding subfraction of the AFP (18). The percentage of *Lens culinaris* lectin binding subfraction of AFP (AFP-L3%) was proposed as a diagnostic marker for HCC. However, the sensitivity and specificity were insufficient when detecting HCC alone. Des gamma carboxy prothrombin (DCP) is another biomarker that was proposed for early detection of HCC (19). Similarly with AFP-L3%, the sensitivity of DCP in detecting early-stage HCC was insufficient. While these biomarkers may not be used for HCC screening; these biomarkers are currently approved by the Food and Drug Administration (FDA) for risk stratification of HCC (4). GALAD, which stands for age, gender, AFP-L3%, AFP, and DCP, is a statistical model used for early detection of HCC (20). In the Hepatocellular carcinoma Early Detection Strategy (HEDS) study, the sensitivity and specificity showed greater promise compared to the individual biomarkers used alone and were found to be at 62% and 82%, respectively, for HCC (21). Nonetheless, GALAD is also currently only approved for risk stratification.

The current value of liver cancer screening

There is an uncertainty on whether liver cancer screening following the current guidelines improves mortality rates as there is research that supports both sides. A demonstration screening project in China demonstrated that screening for liver cancer in high-risk patients with hepatitis B virus (HBV) infection, specifically hepatitis B surface antigen (HBsAg)-positive, did not show a reduction in liver cancer mortality (22). In contrast, various studies show support for mortality decrease with liver cancer screening. One large randomized controlled trial (RCT) in patients with HBV infection showed a reduced mortality from HCC (83.2 versus 131.5 out of 100,000) with a hazard ratio of 0.63 (23). Furthermore, a meta-analysis of 52 different HCC screening studies with around 150,000 patients with HCC showed that HCC screening prolonged overall survival rates but also suggested more research was necessary to weight the harms and benefits (24).

The harms that arise from screening can be physical, financial, or psychological. In a relatively recent, retrospective cohort study of 680 patients identified with cirrhosis, 27.5% of patients experienced physical harm, which included any follow up tests, such as a computed tomography (CT), magnetic resonance imaging (MRI), liver biopsy, or angiogram, performed for false-positive or indeterminate results (25). The harm was more often related to ultrasound than AFP. There is less data on quantifying the potential psychological or financial harms of liver cancer. However, overall, most harms are mild in severity with liver cancer screening and current guideline by the AASLD suggests that potential discovery of HCC from

liver cancer surveillance appears to outweigh the potential harms (4).

Shortcomings of current liver cancer screening and potential of multi-analyte blood tests

Screening for HCC, despite the recommendation from AASLD, has been underutilized in clinical practice. A meta-analysis found that most studies demonstrated low surveillance rates below 30%, although single-center studies from tertiary care did report greater rates at 60–80% (12). The low surveillance rate was more pronounced for patients of low socioeconomic status and non-Caucasian patients. Screening rates for liver cancer is significantly lower than those of other cancers such as colon, breast, and cervical cancers, which have screening rates of greater than 70% (26). One study suggested that the difference in screening is likely due to a combination of issues, two of which are an under-recognition of high-risk patients with cirrhosis and insufficient education of primary care physicians who are in charge of screening for patients not in tertiary care (12). Gastroenterologists and hepatologists have significantly higher surveillance rates than patients followed by primary care physicians (52% versus 17%) which further highlights the need for education.

Although ultrasound is a non-invasive and well-tolerated test, its underutilization for liver cancer screening suggests potential logistical barriers of completing an ultrasound. In fact, the low screening rates of HCC has been attributed to different barriers that patients face. One study in a large urban hospital invited patients to complete surveys about HCC surveillance where almost half of patients reported barriers to obtain ultrasounds for HCC screening, including scheduling processes, costs of surveillance testing, and transportation difficulties (27). These seemingly small barriers must be considered as they are real for patients in that they compromise the adherence to HCC screening. Blood tests, such as the MCED tests or HCC-specific circulating genomic tests, do have the potential to fill in the gaps here as they would be more accessible for patients compared to an ultrasound.

Current guidelines for liver cancer screening recommend surveillance of only high-risk groups. This is mainly because screening of lower-risk groups has been found to be not cost-effective (4). Nonetheless, there is a heightened risk for these patients of developing HCC and, depending on the region, different liver diseases do warrant screening for liver cancer. One issue here may be the suboptimal sensitivity of ultrasonography, even when used in tandem with AFP with a sensitivity of 63%. Ultrasonography may also be unreliable depending on the expertise of the technician or the body habitus of the patient. Majority of current blood tests have had sensitivities for HCC greater than that of ultrasound without and with AFP. Furthermore, blood tests do not have the variable sensitivity that comes with the experience of the technician as well as the body habitus of the patient. While more development and data collection are necessary, blood tests show promise in these areas to improve early detection of HCC.

Potential of multi-cancer early detection

Most MCED tests are in their earlier stages of development, and are currently undergoing clinical trials for FDA approval. Several studies have already started to show promising results that favor their application in early cancer detection, while showing especially high sensitivities for liver cancer. Among the multitude of MCED tests, CancerSEEK and GALLERI tests by Exact Sciences and GRAIL, respectively, are furthest along with reported retrospective studies of cancer patients as well as ongoing prospective clinical studies in healthy populations. The outcome of these ongoing studies will be crucial in incorporating MCED into screening for various cancers, including HCC in the near future.

CancerSEEK

Exact Sciences acquired CancerSEEK in 2021; prior to the acquisition, Johns Hopkins University first reported on this MCED test in detecting eight common cancer types, ovary, liver, stomach, pancreas, esophagus, colorectum, lung, and breast cancers, through assaying for circulating proteins and circulating free DNA of established cancer patients and healthy individuals (28). Specifically, CancerSEEK was designed to assess multiple regions of driver genes commonly mutated in a variety of cancer types in addition to incorporating protein biomarkers that had been previously shown to detect one of the eight cancer types. The study found that CancerSEEK had a median sensitivity of 70% for the eight cancer types overall and a sensitivity of around 97% for liver cancer specifically, second highest among the eight. Furthermore, the sensitivities for stage I cancers were lower at 43% compared to later stages, 73% for stage II, and 78% for stage III. In contrast, the sensitivity for stage I liver cancer was the highest among

other stage I cancers at 100%. The overall specificity for the test was over 99%.

After the acquisition, DETECT-A study prospectively checked for feasibility of their MCED test with PET-CT imaging to detect cancer in a cohort of 10,006 women in Pennsylvania without a diagnosis of cancer (29). Of 9,991 participants, 4.9% showed a positive baseline test and 134 were confirmed to be positive in the confirmation component. Of those who had follow up testing, 64 patients were subsequently found to have cancer. The sensitivity and specificity of this MCED test was 27% and 99%, respectively. Of the cohort, 1.0% had unnecessary PET-CT imaging and 0.22% had futile invasive diagnostic procedures. Although the study showed that MCED tests combined with PET-CT could be safely incorporated into routine clinical care, the study failed to increase ovarian cancer detection in a meaningful way as four of six cases were stage IV cancers.

Currently underway is the ASCEND study (ClinicalTrials.gov identifier: NCT04213326). This will be the latest, prospective validation of a further refinement of the Exact Sciences MCED test. This test assays for four biomarkers simultaneously, including aneuploidy, DNA mutation, DNA methylation, and proteins, and was used to retrospectively evaluate a cohort of 4,196 samples (30). The test population consisted of subjects of age 50 years old or greater with or without a diagnosis of cancer in the United States and Europe. The overall sensitivity with the four biomarkers was improved to 61% and specificity of 98.2%.

Galleri

The Galleri test is another leading MCED test that is currently undergoing prospective clinical trials. The Galleri test was developed and validated from the Circulating Cell-free Genome Atlas (CCGA) study to be able to detect cancer signals across multiple cancer types while determining the cancer signal origin (CSO) utilizing circulating free DNA methylation as well as machine-based learning (31). In a multicenter study of 6,689 participants with or without cancer in North America, the assay showed a specificity of 99.3%, a sensitivity of 70%, and CSO accuracy of 93% (32). Sensitivity of the Galleri for liver/bile duct cancer was found to be particularly high across different stages with an overall sensitivity of 93.5% as well as specific sensitivities of 100% for stages I, II, and III and 70% for stage II (33).

For the Galleri test, the PATHFINDER study looked at a prospective cohort of 6,621 healthy patients without a history of cancer in the United States. The MCED test detected cancer signals in 1.4% (92 patients) of participants. Cancer was confirmed in 38% of cases with a specificity of 99.1%. SIMPLIFY was a large-scale observational cohort study in England and Wales that evaluated the MCED test in symptomatic patients referred from primary care (34). Of 5,461 participants, 323 had a positive MCED test result, of which 244 were diagnosed with cancer. Sensitivity of the MCED test in this study was 66.3% and specificity was 98.4%. Sensitivity increased with cancer stage, from 24.4% in stage I to 95.3% in stage IV. PATHFINDER-2 is an ongoing prospective study that is enrolling 50,000 asymptomatic participants in the United States (ClinicalTrials.gov identifier: NCT05155605). The NHS-Galleri study is another clinical trial that completed enrolling 140,000 asymptomatic participants in the United Kingdom as of 2023. Results have yet to come out.

Other MCED tests on liver cancer screening

Other multicancer blood tests are also currently under development. One such MCED test is the OverC multi-cancer detection blood test (MCDBT) by Burning Rock Dx. The THUNDER study in China was conducted to evaluate the early detection and localization of six cancers including colorectal, esophageal, liver, lung, ovary, and pancreatic cancers (35). MCDBT overall yielded a sensitivity of 69.1% and a specificity of 98.9% as well as a CSO accuracy of 83.2%. MCDBT had the highest sensitivity for liver cancer among the six cancers with sensitivities of 77.3% for stage I, 81.8% for stage II, and 95.0% for stage III, continuing the trend of particularly high sensitivities of these MCED tests for liver cancer specifically.

Liver cancer-specific genomic blood tests

While MCED tests assay for multiple possible cancers from a blood sample, cancer-specific early detection tests target one specific cancer using genomic analytes specific for that tumor. Studies for cancer-specific early detection liquid biopsy tests have already determined sensitivities and specificities for lung and colorectal cancers and Cologuard, a multi-analyte stool test specifically for colon cancer, has already been FDA approved for early detection of colorectal cancer (36-39). Such early detection tests for liver cancer also exist and are in early phases of development. HelioLiver test is a multi-analyte blood test that combines circulating

free DNA methylation markers and protein tumor markers (AFP, AFP-L3%, and DCP) specific for HCC to detect liver cancer. The ENCORE study enrolled 247 participants, including 122 subjects with HCC and 125 higher-risk subjects without HCC and compared the performance of the HelioLiver test to AFP and the GALAD score. Results suggested a superior performance of the HelioLiver test with an overall sensitivity of 85% and sensitivity for early-stage liver cancer (stages I and II) of 76%. The sensitivities of AFP alone and the GALAD score were lower at 62% and 75% for HCC overall and 57% and 65% for early-stage HCC, respectively. However, the HelioLiver test showed a lower specificity of 91% compared to that of AFP (97%) and GALAD score (94%).

Another liver cancer-specific blood test under development is the multitarget HCC blood test (mt-HBT). The mt-HBT combines information from three methylation markers, AFP, and patient sex to detect HCC (40). Similar to the HelioLiver test, mt-HBT demonstrated higher sensitivities at 88% overall and 82% for early-stage cancers but lower specificity at 87%. ALTUS is an ongoing, prospective study that is underway to check how well Oncoguard, another multianalyte blood test under development by Exact Sciences, is able to detect HCC, specifically for higher risk populations, which includes patients with cirrhosis and noncirrhotic patients with chronic hepatitis B infections (ClinicalTrials.gov identifier: NCT05064553).

Challenges of blood test implementation for liver cancer

One concern stems from findings that liquid biopsy tests in general are more sensitive when the cancer is more aggressive or at a later stage. This, in turn, means that sensitivities have been generally found to be lower at earlier stages. The goal of these multi-analyte blood tests is to detect HCC at an early stage when the disease is more indolent and curable. A failure of early detection with these blood tests would defeat their purpose. However, specifically for HCC, this concern is mitigated on two fronts. While the MCED tests from Exact Sciences and Burning Rock Dx have shown sensitivities that are lower at earlier stages, this drop is minimal and the sensitivities are still higher than those of current HCC screening methods. Furthermore, the same is seen for the HelioLiver test and the mt-HBT that demonstrate higher sensitivities for HCC compared to ultrasound, AFP, and GALAD score.

While the sensitivities and specificities of MCED for liver cancer and sensitivities of HCC-specific blood tests have been high, the specificity for the HCC-specific circulating genomic blood tests have been less than optimal at an average of around 90%. The false positives in liver cancer screening can create unnecessary burdens not only for the practice of medicine as a whole but also for the patients. False positives can lead to unnecessary imaging (ultrasound, CT scan, or MRI), which in turn would contribute to resource strain, as well as financial and psychosocial burdens for patients. Current blood tests are still under development and have room for improvement in minimizing the false positive rates. Additionally, depending on the clinical implementation of this novel screening method, the costs may be reduced, especially in cases where confirmatory ultrasound screening follows a positive blood test.

Other considerations are the mortality reduction potential of these blood tests with sustainable benefit and cost trade-offs. This will likely depend on a myriad of factors including the performance of the tests as well as their incorporation into the current diagnostic confirmation pathway in place for HCC. Current literature is split on whether HCC screening provides a mortality reduction. The AASLD suggests that there is a mortality reduction benefit for screening and that, for higher risk patients, the benefits outweigh the harm and risks involved with screening. Unfortunately, there are no studies that look at how liquid biopsy tests for HCC affect the mortality reduction and benefit-harm trade-offs and further studies are necessary to ascertain these parameters.

Clinical implications of blood tests for early detection of liver cancer

A myriad of MCED products as well as cancer-specific blood tests are currently under development with ongoing prospective studies. Some, such as Cologuard, have already been FDA approved. Given the continuing development of these blood tests, their clinical implications should be addressed sooner than later. As another screening tool for HCC, their incorporation into the current workflow should be deliberated. Furthermore, given the nature of these tests, the clinical specialties that take ownership of the results and subsequent diagnostic workup also need to be determined.

Cologuard is a multi-analyte blood test developed by Exact Sciences that has been FDA-approved specifically for the early detection of colorectal cancer (39). This test has expanded how colorectal cancer is screened. Currently,

this screening test is used for average-risk patients and, when results return positive, the next step is a screening colonoscopy. The liquid biopsies for HCC could play a similar role. Current guidelines indicate an ultrasound for initial screening followed by an MRI or a CT scan for a definitive diagnosis of liver cancer using the Liver Imaging Reporting and Data System (LI-RADS) diagnostic algorithm, which is based on imaging features including tumor size, arterial phase hyperenhancement (APHE) and delayed phase washout, and capsule appearance (4). MCED or HCC-specific blood tests could be used for initial screening of HCC given its low cost and logistically simple nature. This would enable screening of populations that previously had difficulty accessing liver cancer screening with an ultrasound. Following a positive blood test, an ultrasound could be ordered to check for the presence of a tumor. If ultrasound findings are concerning, then an MRI or a CT scan could be ordered for a more definitive HCC diagnosis.

Primary care providers' (PCPs) support for patient education of blood tests for HCC will be crucial as patients are usually adherent and interested in HCC screening when healthcare professionals do order screening (41). Current single-organ screening pathways are also currently largely managed by PCPs as a standard preventive care task. However, PCPs do face barriers in delivering these screenings such as inadequate support and uncertainty about their responsibility (42). This is compounded by the fact that PCPs report a lack of knowledge about the benefits of HCC screening and clinic time constraints with competing clinical concerns (41). Overall, the process of ordering blood tests is easier to access compared to ordering an ultrasound as is recommended by current screening guidelines for liver cancer. However, assistance with the following steps by an oncologist or a hepatologist including the diagnostic workup of a positive test may alleviate the stress put on PCPs and allow for a more optimal integration of the novel screening method.

Conclusions

MCED and cancer-specific multi-analyte liquid biopsy tests have the potential to improve the current liver cancer screening through enhanced early detection. This was the case with the noninvasive multitarget stool DNA test that is currently FDA approved for use in colorectal cancer screening. Liver cancer-specific blood tests are currently under clinical trials, as are the MCED tests that have been shown to have particularly high sensitivities for liver cancer. These tests are easily accessible and have the potential to cover the current gaps in liver cancer screening with ultrasound, including the low utilization rates, suboptimal sensitivities, and lack of coverage for lower risk patients. Ultimately, multiple prospective studies are necessary to ascertain important feasibility parameters for these blood tests such as the mortality reduction, cost effectiveness, and sensitivities. However, given the rapid development of these tests along with their intuitive appeal, the healthcare system must be prepared. Pathways for clinical implementation of these blood tests into current liver cancer screening guidelines needs to be mapped out. Medical and radiation oncologists as well as hepatologists, who have expertise in the use of advanced imaging for liver cancer screening and established connections to procedural subspecialists, will hold a crucial role in augmenting the impact of the blood tests by supporting PCPs in their implementation.

Acknowledgments

None.

Footnote

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-686/prf

Funding: This study was funded by the generosity of Robin and Roald Pettersen.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-686/coif). N.N. provided clinical consulting to Freenome and GRAIL two years ago (not ongoing) and received consulting fees. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Choi WJ, Nabavizadeh N. The potential of multi- and single-cancer blood-based early detection tests in liver cancer screening. J Gastrointest Oncol 2025;16(2):711-718. doi: 10.21037/jgo-24-686