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AIMS AND SCOPE

The primary aim of *World Journal of Hepatology* (*WJH*, *World J Hepatol*) is to provide scholars and readers from various fields of hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

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REVIEW

Genetic screening of liver cancer: State of the art

Milena Peruhova, Sonya Banova-Chakarova, Dimitrina Georgieva Miteva, Tsvetelina Velikova

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Abstract

Liver cancer, primarily hepatocellular carcinoma, remains a global health challenge with rising incidence and limited therapeutic options. Genetic factors play a pivotal role in the development and progression of liver cancer. This state-of-the-art paper provides a comprehensive review of the current landscape of genetic screening strategies for liver cancer. We discuss the genetic underpinnings of liver cancer, emphasizing the critical role of risk-associated genetic variants, somatic mutations, and epigenetic alterations. We also explore the intricate interplay between environmental factors and genetics, highlighting how genetic screening can aid in risk stratification and early detection *via* using liquid biopsy, and advancements in high-throughput sequencing technologies. By synthesizing the latest research findings, we aim to provide a comprehensive overview of the state-of-the-art genetic screening methods for liver cancer, shedding light on their potential to revolutionize early detection, risk assessment, and targeted therapies in the fight against this devastating disease.

Key Words: Hepatocellular carcinoma; Liver cancer; Genetic screening; Risk-associated genetic variants; Epigenetic alterations; Genetic biomarkers; Circulating tumor DNA; Next-generation sequencing

Core Tip: Unraveling the intricate genetic underpinnings of hepatocellular carcinoma (HCC) is paramount for understanding its development and progression. In line with this, genetic screening could be a powerful tool for patient risk stratification, spotlighting risk-associated genetic variants, somatic mutations, and epigenetic alterations contributing to HCC. Moreover, embracing next-generation sequencing and exploring genetic biomarkers, including circulating tumor DNA, opens new frontiers for effective risk assessment and early detection of liver cancer.

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INTRODUCTION

Primary liver cancer, with hepatocellular carcinoma (HCC) as its predominant form (75% of all cases), remains a formidable global health challenge, ranking among the leading causes of cancer-related mortality worldwide. Its prevalence has been on a disquieting rise, signaling an urgent need for more effective early detection and prevention strategies[1].

Globally, primary liver cancer has the highest incidence in Asia and Africa (> 8.4 cases *per* 100000 person-years). However, HCC incidence declined in many Asian countries but increased in India, America, Oceania and Europe[2].

Due to the intricate interplay of environmental factors contributing to liver carcinogenesis, it becomes increasingly apparent that genetic predisposition plays a pivotal role in shaping individual susceptibility[3]. The significance of genetic screening in the landscape of liver cancer cannot be overstated. Early detection has long been recognized as a linchpin in improving outcomes, and genetic screening offers a promising avenue to achieve this. By unraveling the intricate web of risk-associated genetic variants, somatic mutations, and epigenetic alterations, we gain the tools to stratify risk and intervene proactively, potentially preventing the progression of precancerous lesions to full-blown malignancy[3].

However, in the field of genetic screening for liver cancer, questions and challenges emerge. Are the currently available screening methodologies robust enough? What are the limitations and pitfalls of the existing approaches, and how can we overcome them? How do we integrate genetic screening into broader liver cancer prevention and management strategies?

This review critically examines the current state-of-the-art in genetic screening for liver cancer. Beyond providing an overview of prevalence and emphasizing the urgency of early detection, we scrutinize the rationale behind existing genetic screening practices.

It is of great importance for the overall survival of patients with HCC, to be detected at early stages of disease. For example, it has been determined that HCC detection before stage IV, reduces cancer-related deaths by ≥ 15% within 5 years[4]. Unfortunately, the screening tests that are used in clinical practice [ultrasound and serum level of alpha fetoprotein (AFP)] have low sensitivity and specificity[5].

The effectiveness of HCC surveillance depends on whether the screening tests in clinical practice can detect HCC at an early, which is a treatable stage. The recommended screening tests (ultrasound and AFP) are widely available and low cost, but the sensitivity and specificity of these tests are suboptimal. In a noncirrhotic liver, the sensitivity of ultrasound for detecting small HCC lesions is estimated to be only 60%[6].

A new perspective diagnostic tool, called multi-cancer early detection (MCED) has the potential to achieve early cancer detection by using signals for cancers from cell-free DNA (cfDNA) or other circulating analytes in the blood shed by tumors. It has to be underlined that the results from clinical studies of these tests have shown promising results concerning detecting cancers at earlier stages[7,8].

Recently published studies, demonstrated significant sensitivity for early detection of HCC using MCED assays. These methods use cfDNA mutation-based and circulating tumor DNA (ctDNA) methylation-based indicators, both in isolation and in conjunction with cancer-associated serum protein levels[9]. For example, this method is crucial for patients with non-alcoholic fatty liver disease (NAFLD) who may not meet the criteria for routine surveillance due to cost-effectiveness. Another interesting fact that has to be pointed out is that circulating tumor cells (CTCs) are not sufficiently sensitive for early detection of HCC, but can be used as a feasible tool in the surveillance of patients after liver resection, to detect tumor recurrence or tumor progression[10].

We also question their efficacy and explore the gaps in our current understanding, hypothesizing about untapped potentials and areas that demand further exploration. The objectives of this paper are twofold: To comprehensively survey the existing genetic screening landscape for liver cancer and to spur a critical dialogue that propels future research in directions that enhance our ability to combat this formidable adversary. By addressing these essential aspects, we aim to not only present the current state of affairs but also to stimulate further inquiry and innovation in the field of liver cancer genetics.

SEARCH STRATEGY

We conducted an extensive literature review to compile relevant studies on genetic screening for liver cancer. The search was performed in the major databases, including PubMed, Scopus, and Medline. The following combination of MESH

and free-text terms was utilized to ensure a comprehensive search: ("hepatocellular carcinoma" OR "liver cancer") AND ("genetic screening" OR "genetic testing" OR "genomic profiling"); ("risk-associated genetic variants" OR "genetic risk factors" OR "genetic predisposition") AND ("liver neoplasms" OR "hepatocellular carcinoma"); ("somatic mutations" OR "tumor mutations" OR "genetic alterations") AND ("liver cancer" OR "hepatocellular carcinoma"); ("epigenetic alterations" OR "DNA methylation" OR "histone modification") AND ("genetic screening" OR "liver cancer"); ("genetic biomarkers" OR "biomolecular markers" OR "genetic signatures") AND ("hepatocellular carcinoma" OR "liver neoplasms"); ("circulating tumor DNA" OR "liquid biopsy" OR "ctDNA") AND ("genetic screening" OR "liver cancer"); ("next-generation sequencing" OR "NGS" OR "genomic sequencing") AND ("hepatocellular carcinoma" OR "liver cancer").

The retrieved papers were selected based on their relevance to the genetic landscape of liver cancer, emphasizing risk factors, somatic mutations, epigenetic modifications, genetic biomarkers, and advanced sequencing techniques. The search strategy aimed to encompass a broad spectrum of genetic aspects associated with liver cancer, ensuring a comprehensive and up-to-date review.

GENETIC FACTORS ASSOCIATED WITH LIVER CANCER

Family predisposition and hereditary syndromes linked to liver cancer

The most common reasons associated with the development of HCC are hepatitis B (HBV) and hepatitis C (HCV) infection. Other risk factors that are attributed to the evolution of HCC are male gender, heavy alcohol drinking, older age, and some monogenic liver diseases such as hemochromatosis, alpha1-antitrypsin deficiency, and porphyria cutanea tarda[11]. It is essential to underline that transmission of HBV and HCV among family members, in association with other environmental risk factors, could be part of the familial aggregation of liver cancer. For example, in Eastern Asia, the percentage of familial clustering of HCC is significantly higher due to a higher incidence of HBV infection[12,13]. It has to be underlined that family history is a substantial risk factor associated with the development of HCC, even in cases without infections with HBV and HCV[14,15].

A study by Turati *et al*[16] investigates the role of the family history of HCC in the non-Asian population[16]. The authors established that a family history of liver cancer is a risk factor, independently from the presence of HBV and HCV. It was estimated that families with a positive family history have 2-to 3-fold in their HCC risk. Moreover, in cases with a positive family history of liver cancer and hepatitis B/C, it was estimated that these subjects have 70-fold elevated HCC risk compared to those without a family history and hepatitis[16].

It has to be underlined that the mechanism of development of HCC is based on the accumulation of epigenetic and genetic alterations in hepatocytes. The environmental factors most indirectly, lead to chronic inflammation of liver cells, generating liver disease. For example, different toxins and viruses have the potential directly to induce genomic alteration in cancer-driver genes in hepatocytes. For example, aflatoxin B1, alcohol consumption, or smoking could induce DNA damage, and HBV can directly activate oncogenes in liver cells through viral insertion mutagenesis[17,18].

It has to be pointed out that the development of severe chronic liver disease or liver cancer is strongly associated with individual background and gene polymorphisms, which can modulate the risk of HCC[19].

For example, it has been established that genetic polymorphisms in several genes (*PNPLA3*, *TM6SF2*, and *HSD17B13*) that encode proteins involved in lipid metabolism, are strongly connected with modulating the severity of non-alcoholic steatohepatitis (NASH) and alcohol-related chronic liver diseases. Another interesting fact is that these gene polymorphisms also modulate the risk of HCC. associated with either one of these risk factors. Genetic polymorphisms in several genes (*PNPLA3*, *TM6SF2*, and *HSD17B13*) that encode proteins involved in lipid metabolism modulate the severity of NASH and alcohol-related chronic liver diseases. These gene polymorphisms also modulate the risk of HCC [19].

It was established that genetic polymorphisms in *WNT3A*/*WNT9A* or in *TERT* have the potential to modulate the risk of HCC without impacting the process of development of chronic liver disease[20].

Exploration of common genetic mutations and variants in liver cancer development

In recent years, technological advances have helped elucidate different genetic alterations in genes and signaling pathways that underlie HCC. Understanding these alterations, such as different types of mutations, polymorphisms, genomic instability, and even target genes involved in HCC progression, will contribute to early diagnosis and development of workable target therapies for HCC.

It has been established that multiple genetic changes accumulate slowly in some genetic loci during the early stages of the hepatocarcinogenesis process. With the progressive development of HCC, the accumulation of these changes accelerates[21]. Research has shown that the affected genes in HCC are significant numbers and may be associated with a predisposition, faster progression, worse prognosis, and different signaling pathways[22-25].

All genomic methodologies and technologies that have been used in the past decade, such as genome-wide association studies, microarray analysis, flow cytometry, array comparative genome hybridization, the random amplified polymorphic DNA, Omics profiling, next-generation sequencing (NGS), *etc.* have improved our understanding of the biology and genetic of HCC.

In 2016, a study revealed the genetic heterogeneity of HCC[26]. It summarizes the genetic changes involved in the progression of HCC. The authors discussed the role of genomic/chromosomal instability and possible associations with clinical and pathological characteristics of HCC. They also summarized single nucleotide polymorphisms (SNPs) associated with HCC susceptibility and risk, frequently recurring somatic mutations and various signaling pathways involved in HCC[26].

Over the years, there is different evidence that mutations in *TERT*, *CTNNB1*, *TP53*, *AXIN1*, *ARID1A*, *ARID2*, *NFE2L2*, *KEAP1*, *RPS6KA3* and many other genes are associated with HCC[27-32]. Evidence also suggests an association between SNPs and susceptibility to HCC[33-36]. Research has identified various signaling pathways, such as Wnt/β-catenin signaling and PI3K-AKT-mTOR pathway, involved in the HCC development[26,37-40].

All these data show that molecular mechanisms and genetic alterations must be understood well, *i.e.*, the entire mutational profile in HCC, to develop preventive strategies and quality treatment for HCC patients.

Impact of gene-environment interactions on liver cancer risk

Multiple factors are involved in the occurrence of HCC. In developing HCC, the etiological factors and the underlying genetic landscape are essential. Most frequently, HCC develops based on cirrhosis-approximately 90%. Chronic viral hepatitis B and C are found in more than 70% of the cases of primary liver carcinoma. The other risk factors for HCC are NASH, chronic alcohol consumption, and aflatoxin[41]. Each one activates a different oncogenic pathway and has a specific genetic sign.

A plethora of studies recently described genetic alterations that appear in transformed liver tissues[42].

miRNAs (miRs) are small, single-stranded, non-coding RNAs (18-24 nucleotides) that post-transcriptionally regulate the expression of various oncogenes and tumor suppressor genes[43]. For instance, it has been established that many miRs are dysregulated during the process of transformation from HBV-infected liver to HCC. Some are shown in the table below[41,44] (Table 1).

Numerous studies investigate different miR panels for early diagnosis of HCC in patients with cirrhosis. Ganesan and Kulik[45] found that a combination of some serologic markers and miR-16 in patients with cirrhosis can help in early diagnosis of liver cancer in 92.4% of cases[45].

The occurrence of HCC is associated with various genetic changes. One of the most common is TERT-alternation. The involvement of several other molecular pathways in hepatocarcinogenesis has also been proven. Schulze *et al*[46] divided genetic alterations in HCC into eleven categories, including telomere maintenance, Wnt/β-catenin signaling, p53/cell cycle, oxidative stress, epigenetic regulation, PI3K-Akt-mTOR, MAPK, and hepatic differentiation[46]. One of the most often aberrated in HCC are the genes involved in the signaling of Wnt/β-catenin and p53/cell cycle. Based on this fact, it was established that the heterogeneity of HCC is due to several oncogenic pathways being involved in the process of carcinogenesis and not a single mutation[47].

Some specific mutations are found in HBV-related HCC, like-TP53 mutation. The same mutation is found in patients with liver cancer who are exposed to aflatoxin B1[48]. In patients with alcohol liver disease, mutation of TERT promoter C is catenin beta-1, and AT-rich interaction domain 1 is associated with the appearance of HCC[48,49] (Figure 1).

On the other hand, a loss-of-function of some genes like 17-beta-hydroxysteroid dehydrogenase 13 (HSD17B13 rs72613567) was considered protective for HCC in patients with alcoholic liver disease (ALD)[48].

The role of epigenetic modifications in HCC

Epigenetic modifications have emerged as pivotal contributors to the intricate landscape of HCC development and progression. As one of the most common and aggressive forms of liver cancer, HCC poses a significant global health burden. The understanding of genetic mutations alone fails to explain the complexities of HCC development, prompting an intensified focus on epigenetic alterations[50-52].

These modifications, encompassing DNA methylation, histone modifications, and non-coding RNA-mediated regulation, profoundly influence gene expression patterns, cell signaling, and tumor microenvironment interactions. In this section, we focus on the multifaceted role of epigenetic modifications in driving HCC progression, unraveling the intricate regulatory networks that orchestrate carcinogenic processes. By exploring the molecular nuances of epigenetic dysregulation, we aim to deepen insights into HCC pathogenesis and open new avenues for targeted therapeutic interventions[53].

Hypomethylation in HCC stimulated protooncogenes, such as c-jun, c-myc, *etc.*, and increased genomic instability *via* influencing mitotic recombinations, eventually promoting carcinogenesis. Furthermore, Calvisi *et al*[53] also demonstrated that global hypomethylation in liver cancer does not depend on other etiological factors[53].

Hypermethylation, associated with WNT/β-catenin signaling activation, *APC* inactivation, *p16INK4A* activation, *RASSF1A* and *NORE1A* activation, Mismatch repair system genes (*hMLH1*, *hMSH2*, and *hMSH3*) inactivation, *CTF1*, *PDK4*, *FZD8*, *ZNF334*, *MAD2L1*, *CCNB1*, *CDC20*, *CCND1*, *AR*, *ESR1*, *p53* and *MAPK* signaling regulation, also is linked to HCC[50].

Future research may allow the estimation of the prognostic and diagnostic value of integrated bioinformatic data from HCC cells and tissues. Bai *et al*[54] described methylation sites typical for HCC but not cholangiocarcinoma[54]. As Guo *et al*[55] showed, mTOR signaling could also be involved in the progression of HCC *via* epigenetic regulations[55].

An integrated bioinformatic analysis may also help to identify diagnostic biomarkers to differentiate between different types of liver cancer.

The alteration of chromatin structure, which allows or prevents transcription factors from accessing gene regulatory sites, may also contribute to cancer pathogenesis. Histone deacetylase (HDAC) 1 (HDAC1) and HDAC2 are associated with the development of HCC, but they do so in different ways. HDAC1 expression was found to be correlated with tumors that were moderately and poorly differentiated[56], while HDAC2 expression was found to be an independent negative survival predictor[57]. HDAC2 is involved in the epigenetic regulation of cell cycle, apoptosis, and differentiation, and it was discovered that HCC patients frequently had elevated levels of HDAC2[58]. Other histone modifications associated with HCC are upregulated HDAC8, HDAC5, HDAC9, and downregulated HDAC3, HDAC5.

Table 1 Altered microRNAs during the transition from chronic hepatitis B virus hepatitis to hepatocellular carcinoma

Upregulated	Downregulated
miR-18a	miR-26a
miR-21	miR-101
miR-221	miR-122
miR-222	miR-125b
miR-224	miR-145
	miR-199a
	miR-199b
	miR-200a
	miR-223

miR: MicroRNAs.

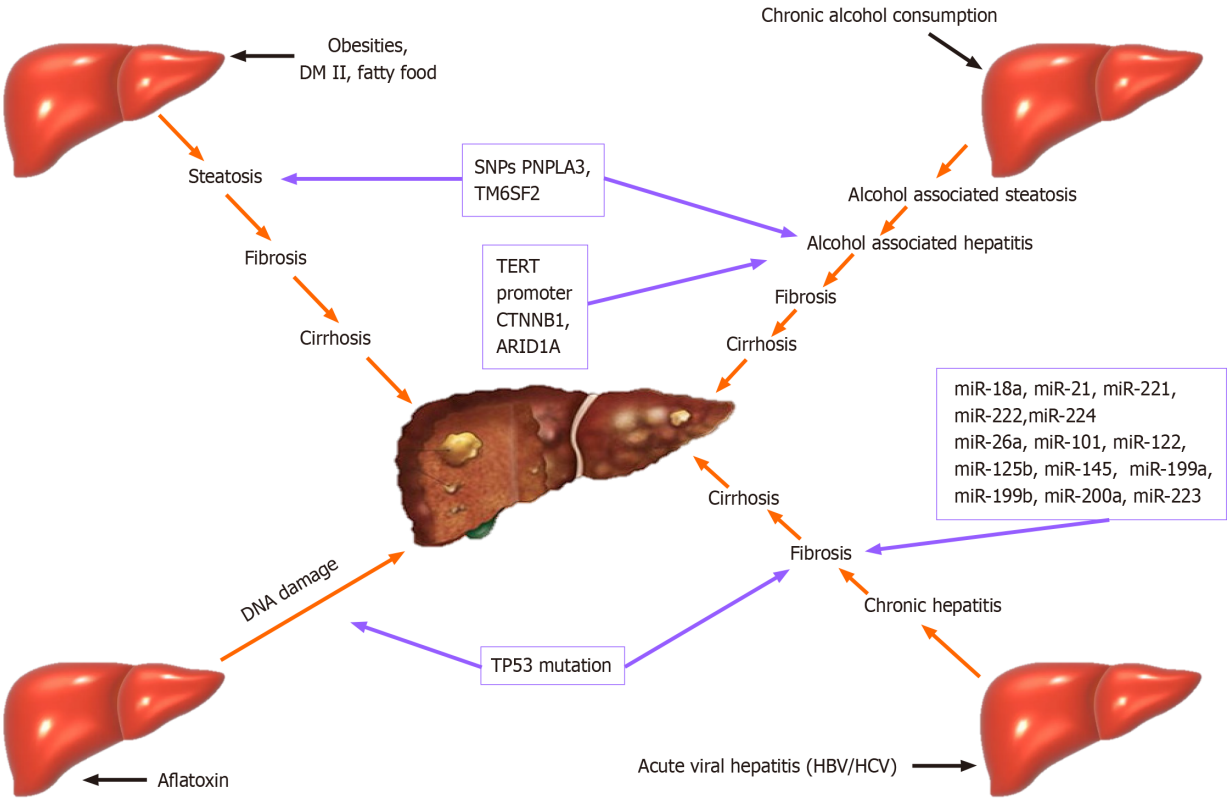

Figure 1 Etiological and genetic factors in the oncogenesis of primary liver cancer. DM: Diabetes mellitus; miR: MicroRNAs; TP53: Tumor protein P53; CTNNB1: Catenin beta-1; AARID1A: AT-rich interaction domain 1; HBV: Hepatitis B virus; HCV: Hepatitis C virus; SNPs: Single nucleotide polymorphisms.

It has been discovered that several miRs, including let-7, miR-34a, miR-221, miR-222, and miR-122, miR-369, miR-3174, miR-383, miR-361-5p, miR-186, are implicated in the pathogenesis of liver cancer[59,60]. However, synthetic inhibitors, including antisense oligonucleotides or AntimiRs, can target the dysfunction of particular miRs[61].

Furthermore, epigenetic regulation may affect the mechanisms of resistance to systemic therapy in HCC. Oura *et al*[62] showed some of the mechanisms of resistance to drugs, such as sorafenib, regorafenib, and lenvatinib, associated with epigenetic modifications and tumor microenvironment regulation[62].

According to a growing body of evidence, long non-coding RNAs (lncRNAs) are implicated in the pathophysiology of HCC[63]. HBV, one of the main etiologic factors for HCC, can alter the host's epigenome through various methods. Of the viral proteins, Hepatitis B viral protein has been identified as a key epigenetic regulator[64].

Both ALD and NAFLD are common etiologic factors for HCC. Published data suggest that specific epigenetic modifications may be linked to these etiologic factors for HCC. For example, miR-21, miR-34a, miR-182 upregulation and miR-122 downregulation have been linked to NAFLD[65].

Most preclinical studies showed that epigenetic remodeling is potentially reversible by drugs, and the list of available epigenetic modifiers and inhibitors is continuously expanding[59]. Consequently, in the era of precision medicine, unraveling the epigenetic modifications occurring in HCC may offer new insights for screening potential therapeutic targets and studying personalized intervention strategies for managing this tumor. The optimization of scheduling strategies is a very relevant issue when considering combination therapies with conventional chemotherapeutics, other targeted agents, or immune checkpoint inhibitors. This is because the simultaneous, sequential, or alternate administration of epigenetic drugs is necessary to maximize efficacy, potentiate synergists, and overcome resistances[66].

On the other hand, we have also discovered that epigenetic regulatory circuits are incredibly complicated, and we have only begun exploring the tip of the iceberg. Therefore, to fully comprehend the pathophysiological implications of the epigenetic machinery, all of its dimensions must be fully unlocked. Considering the sheer size of this task, artificial intelligence tools seem necessary for the molecular analyses of relevant experimental models and clinical samples[67].

CURRENT GENETIC SCREENING TECHNOLOGIES FOR HCC

One of the challenges in early detecting HCC is the lack of highly sensitive and specific screening techniques. Over the years, ultrasound, computed tomography, and magnetic resonance imaging techniques have significantly improved their detection sensitivity, but their safety and cost disadvantages remain.

The future of early HCC detection probably lies in high-throughput tests that allow specific detection of HCC. These tests are promising tools for diagnosis, prognostication, and patients' selection for personalized therapy in HCC. One of the most important discoveries in the field lies in the use of circulating liquid biomarkers ("liquid biopsy") [68]. Liquid biopsy involves molecular diagnostics of nucleic acids (DNA/RNA) derived from tumors or extracellular vesicles (EVs) in the blood. The method uses blood/plasma, ascitic fluid or urine. These biological samples contain except standard HCC biomarkers [AFP, AFP with a high lectin affinity (AFP-L3), Des-γ-Carboxy Prothrombin (DCP), Glypican-3 (GPC3), osteopontin (OPN), Dickkopf Wnt signaling pathway inhibitor 1] and CTCs, tumor cfDNA, EVs or tumor-educated platelets that can be used for biomarkers[69,70]. They can be taken consecutively at different periods and give robust information about the development in progression. In recent years, liquid biopsy technologies have significantly advanced and become more precise, especially with the introduction of the NGS technique. NGS technology is up and coming, but multiple factors still hinder efforts to develop personalized therapy.

Application of liquid biopsy in early diagnosis of HCC

cfDNA are small degraded nucleic acids (under 200 bp) from damaged cells. They are of malignant origin and circulate in the blood, called ctDNA. Their analysis allows for early diagnosis by conducting liquid biopsy in real-time. Many studies suggest they are suitable tools that accurately represent the HCC tumor development and genetic profile[71-75].

Over the years, the methylation pattern of cfDNA in liquid biopsy of HCC has been investigated because methylation patterns are known to be unique for each cell type and remain stable in some pathological conditions[76]. Methylation changes in such conditions are known to occur early in tumor development[77], and therefore, guidelines have been proposed for more accurate analysis of methylated circulating DNA in liquid biopsies[78].

Guo *et al*[72] recently demonstrated that epigenetic variants carried by ctDNA can be biomarkers for early HCC detection[72]. They used enzymatic methylation sequencing and identified over 200 CpGs with significant methylation differences between HCC and non-HCC samples. A study revealed that HCC could be distinguished from normal controls by quantitative analysis of multiple methylated genes in plasma[79,80]. By adding miR data to the methylation pattern of some of these genes, a predictive model for the diagnosis of HCC in patients with low AFP values was obtained. Simultaneous detection of tumor somatic mutations and quantification of cfDNA can also be used for early diagnosis of HCC. Research shows that using high-depth targeted massive sequencing of ctDNA could reveal tumor somatic genetic changes[81,82]. Droplet Digital PCR can detect ctDNA in HCC patients by targeting hot mutations[83].

Indeed, those early studies that focused on detecting tumor-specific mutations by deep sequencing, which resulted from inter- and/or intratumor heterogeneity, reduced the sensitivity of these methods. Therefore, an alternative approach is to investigate unique tumor DNA methylation profiles, as they are known to be a hallmark of cancer[84]. A pan-cancer study also strongly supported the fact that methylation profiles are more precise and sensitive cancer classifiers of cfDNA than detected tumor-specific mutations[85]. One of the most successful screening biomarkers to be used was SEPT9. To diagnose HCC, Oussalah *et al*[86] show the precision of PCR-based analysis of methylation of SEPT9 promoter in circulating cfDNA (mSEPT9)[86]. The mSEPT9 test showed high diagnostic accuracy and may be a promising epigenetic biomarker for HCC diagnosis.

In their study, Xu *et al*[87] identified an HCC-specific DNA methylation marker panel by comparing the methylation profiles of HCC tumor tissue and normal leukocytes[87]. They showed that plasma ctDNA and tumor DNA were highly correlated, although they did not consider cfDNA from other tissues found in the blood at different levels. This diagnostic prediction model showed high specificity and sensitivity, but if there is DNA contamination, it can potentially yield false positives. To address this challenge, Cheishvili *et al*[88] used over 12000 methylation profiles in The Cancer Genome Atlas (https://portal.gdc.cancer.gov/) and the Gene Expression Omnibus data repository collections (https://www.ncbi.nlm.nih.gov/geo/info/submission.html)[88]. They determined the DNA methylation sites, which are consistently unmethylated in all blood DNA and tissue samples. Thus, they identified four CpGs positions that were highly methylated in the HCC DNA methylation array set. They used a lot of HCC samples and a training dataset to find a single CpG site that was sufficient to distinguish HCC from different types of cancer and normal cells. Thus, they create the "epiLiver" test, which is very sensitive and accurate[88].

One way of intercellular communication is through small EVs. They are "cargo" vesicles that consist of proteins, DNA, RNA, miR and lipids. They are released from healthy, malignant, inflamed or apoptotic cells[89,90]. Liver cells are of different types and are capable of producing EVs. They can be found in serum, plasma, urine and other biological fluids. They are protected from degradation, making them suitable liquid biomarkers for diagnosing liver diseases[91-93]. In their study, Manea *et al*[69] have detailed the studies in the literature that reveal the role of EVs in the early diagnosis of HCC[69].

Overview of the impact of NGS technology on outcomes in HCC

NGS technology is used for DNA and RNA sequencing and variant/mutation detection. With it, hundreds and thousands of genes or whole genome can be sequenced for a short time. The mutations/variants detected by NGS are widely used for prediction, diagnosis, and even offering possible treatment for various diseases. The technology provides a relatively inexpensive platform for analyzing cancer genomes at single nucleotide resolution. Combining different NGS methodologies in early-stage HCC offers different opportunities for early diagnosis and identification of the cancer genes associated with HCC[94].

The accuracy of NGS generally depends on the length of coverage, and whole-genome sequencing (WGS) has a coverage of about 3 Gb[95]. Therefore, WGS can help detect various genetic variants, such as single nucleotide polymorphisms, copy number changes, and even genomic rearrangements[46]. The leading NGS platforms used for the genetic profiling of HCC include whole exome sequencing (WERS), RNA sequencing and methylated site profiling. With these methods, the significant oncogenes *MYC* and *TERT* of the early stage of HCC, and *ARID1A*, *MLL*, *JAK1*, *IGF2*, *etc.*, associated with the late stage, were identified genes[96,97]. A study recently provided a comprehensive list of genes and molecules that have been altered in the course of liver cancer[98].

Deep sequencing and WERS reveal the heterogeneity of HCC. Deep sequencing performed revealed frequent substitutions (C>T/G>A and T>C/A>G) that may explain the changes in the methylation profile observed in HCC[97]. A comparative study of whole exomes in advanced HCC cases compared with exomes from primary tumors revealed a lot of mutated genes[99]. Since mutations are found in primary tumors, they appear acquired during HCC progression.

The whole-genome array comparative genomic hybridization technique is widely used in screening for copy number changes[100]. This technique has been used in HCC research and has shown that there are chromosomal losses and gains in HCC. More than 30 recurrently altered regions have been associated with HCC[30,101,102]. Although many alterations have been identified, it is still challenging to associate these genes with altered regions and specific HCC phenotypes.

Applying NGS technologies in HCC does not bring immediate patient benefits but rapidly changes our understanding of HCC. Advances in NGS technologies and liquid biopsy techniques will undoubtedly lead to the possibility of earlier diagnosis, prognosis, and a more personalized approach to HCC treatment. Searching for specific substances/biomarkers secreted from the surface of circulating HCC cells would help HCC be diagnosed in the early stage and reduce mortality.

Genetic markers and biomarkers for early liver cancer detection

In the relentless battle against liver cancer, early detection stands as a paramount strategy for improving patient outcomes. This paper section focuses on the genetic markers and biomarkers, illuminating their pivotal role in the early detection of liver cancer. HCC, the predominant form of liver cancer, often eludes diagnosis until advanced stages, underscoring the urgency for reliable and sensitive tools for early identification. Genetic markers, ranging from somatic mutations to risk-associated genetic variants, harbor immense potential as discerning indicators of incipient liver malignancy[103].

Additionally, biomarkers, such as ctDNA, offer a non-invasive window into the molecular intricacies of liver cancer, which include the current landscape of genetic and biomarker-based approaches, aiming to unravel their diagnostic prowess and illuminate the promising avenues for enhancing the timely detection of liver cancer[104]. Since developing a treatment plan depends on knowing each patient's exact cause and stage, it is widely acknowledged that early diagnosis can significantly increase the chance of a patient's survival by implementing curative treatment. Accordingly, methods for diagnosing precision medication should be developed for early identification of HCC[104].

Early diagnosis is critical to the prognosis of HCC patients. Serum AFP is currently the most widely used biomarker for HCC diagnosis, but its sensitivity and specificity are about 50%[105].

Other biomarkers for early detection of liver cancer are AFP and its isoform AFP-L3, GPC3, DCP, OPN, golgi protein-73, *etc.*[41]. Genetic markers for HCC are miRs as miR-224, miR-766, miR-23, miR-10b, miR-106b, and miR-181 *etc*. Cancer antigen 19-9, carcinoembryonic antigen, matrix metalloproteinase 7, CYFRA 21-1-a fragment of cytokeratin 19, interleukin 6, S100 calcium-binding protein A6, cfDNA, cell-free RNA and lncRNAs, *etc.* are also liver cancer biomarkers[41,104].

It is important to note that liquid biopsy has been developed and implemented in clinical practice over the past few decades, and it primarily detects ctDNA, CTCs, exosomes, and circulating tumor RNA in bodily fluids such as plasma, urine, and cerebrospinal fluid. ctDNA is the most widely applied genetic biomarker derived from tumor tissue. It carries somatic mutations, single-nucleotide variants, DNA methylations, viral sequences, and physical characteristics linked to carcinogenesis[104].

We discuss the advantages and disadvantages, of genetic and other screening technologies for HCC in Table 2.

The choice of screening technology depends on the specific clinical context, resource availability, and the desired balance between sensitivity and specificity. A multimodal approach combining different technologies may offer a more comprehensive strategy for HCC screening.

Table 2 Genetic and other screening technologies for hepatocellular carcinoma

	Advantages	Disadvantages
AFP testing	Widely used; relatively cost-effective	Limited sensitivity, especially in early-stage HCC; prone to false positives/negatives
Genomic profiling (next-Generation sequencing, whole-genome sequencing)	High sensitivity for detecting genetic alterations; provides comprehensive genomic information	Costly; complex data analysis; may identify variants of uncertain significance
Liquid biopsy (circulating tumor DNA)	Non-invasive; potential for early detection; provides real-time monitoring	Limited sensitivity in early stages; technical challenges; standardization concerns
Imaging techniques (MRI, CT, ultrasound)	Commonly used; assesses tumor characteristics and location	Limited sensitivity for small lesions; exposure to radiation (CT); may not detect molecular changes
Molecular biomarkers (miRNA, methylation patterns)	High specificity; potential for early detection	Variable sensitivity; limited standardization; assay complexity
Circulating tumor cells analysis	May reflect metastatic potential; potential for real-time monitoring	Rare in early stages; technical challenges; standardization issues

CT: Computed tomography; MRI: Magnetic resonance imaging; HCC: Hepatocellular carcinoma; AFP: Alpha fetoprotein.

CHALLENGES AND OPPORTUNITIES IN GENETIC SCREENING OF HCC

Liver cancer, predominantly HCC, poses a formidable global health challenge, necessitating innovative approaches for early detection and risk stratification. Here, we present some intricacies of genetic screening, elucidating the challenges and opportunities that shape its current landscape[106].

Identification of at-risk populations and the need for targeted screening is critical. Unraveling the genetic underpinnings of liver cancer is pivotal for identifying individuals at elevated risk. The diverse interplay of genetic variants, environmental factors, and lifestyle choices necessitates targeted screening strategies. Understanding the nuances of at-risk populations enables the development of tailored screening programs, optimizing resources and focusing on those who benefit most[107].

Nevertheless, ethical considerations in genetic screening for liver cancer have become essential. As genetic screening becomes more sophisticated, ethical considerations loom larger. Balancing the potential benefits of early detection with protecting individuals' privacy and autonomy requires careful navigation. Ensuring informed consent, addressing potential stigmatization, and safeguarding against genetic discrimination are paramount in the ethical framework of liver cancer genetic screening[108].

We also must think about integrating genetic data into personalized medicine approaches. Genetic insights pave the way for personalized medicine in liver cancer. Tailoring interventions based on an individual's genetic profile holds immense promise for treatment efficacy. There is a need to explore the integration of genetic data into the broader landscape of personalized medicine, where targeted therapies and precision medicine converge to reshape the paradigm of liver cancer care[103].

However, there are also some limitations and areas for future research in liver cancer genetics. While genetic screening presents a transformative tool, acknowledging its limitations is crucial. Challenges like the complexity of gene-environment interactions, the need for large-scale datasets, and disparities in access to genetic screening demand attention. We also must bear in mind the potential limitations and chart the course for future research, outlining avenues to enhance the effectiveness and inclusivity of genetic screening for liver cancer[109].

CLINICAL IMPLICATIONS AND THERAPEUTIC ADVANCES

There are numerous staging systems for primary liver carcinoma, such as TNM, Okuda, (cancer of the liver Italian program), and CLIP system. Barcelona Clinic's liver cancer staging system is most commonly used for liver carcinoma because it reports not only the characteristics of cancer–its number, size and spread of cancer, but also the liver function and general health of the patient. It is recommended by American Association for the Study of Liver Diseases and the European Association for the Study of the Liver[110]. This staging system was updated for the last time in 2022 (Figure 2).

The earlier HCC is diagnosed, the better the survival rate–more than 70% of early-stage patients survive 5 years, while in advanced stages, only 20%[111].

Curative methods for HCC carcinoma are resection and liver transplantation (LT). Results from LT are very good with 1-year and 5-year survival, 90% and 70%, respectively. Patients on the transplant list have to wait. For this, local ablative methods such as transarterial chemoembolization (TACE) are applied. Guo *et al*[112] investigated which gene could predict prognosis after TACE (transarterial chemoembolization). Increased expressions of (PKM2) pyruvate kinase and peptide arginine deiminase IV indicate TACE resistance and poor prognosis[112]. Conversely, high expression of chromobox homolog 4 is associated with longer overall survival after TACE and higher sensitivity to doxorubicin[112].

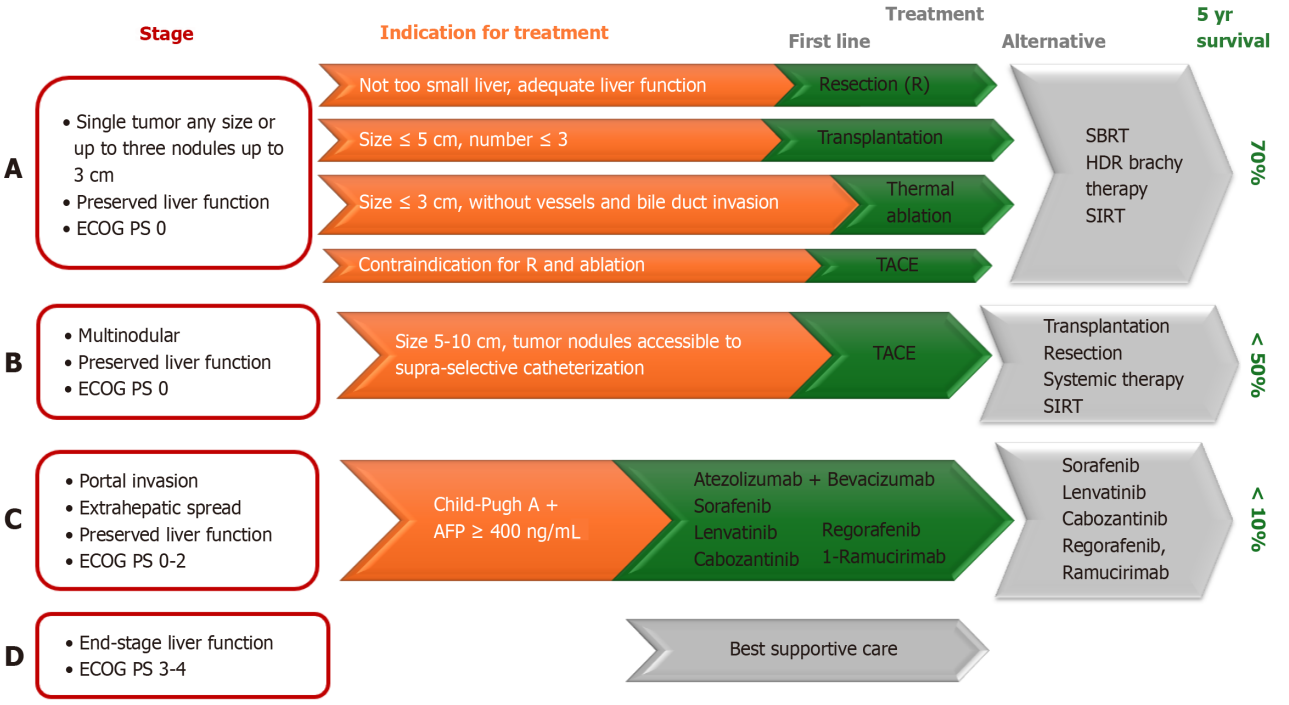

Figure 2 Barcelona clinic liver cancer staging system. The method of treatment is determined according to the stage. the method of treatment is determined according to the stage. RFA: Radiofrequency ablation; TACE: Transarterial chemoembolization; HIFU: High-intensity focused ultrasound; MWA: Microwave ablation; ECOG: Eastern cooperative oncology group; HDR: High dose rate; PS: Performance status; SBRT: Stereotactic body radiotherapy; SIRT: Selective internal radiotherapy; AFP: Alpha fetoprotein.

Patients with elevated expression of some genes, like *SERPINE1* have better drug sensitivity to lenvatinib[113].

In line with this, emerging therapies targeting specific genetic alterations in liver cancer are promising. The rapidly evolving landscape of liver cancer therapies is increasingly shaped by a nuanced understanding of genetic alterations driving HCC. This includes therapeutic advancements, exploring innovative strategies directly targeting specific genetic abnormalities, *etc.* From targeted molecular therapies to gene-based interventions, the arsenal against liver cancer is expanding, ushering in a new era where precision medicine meets the unique genetic signatures of individual tumors [114]. A critical aspect is also the patient education and awareness regarding genetic screening benefits. Empowering patients through education and fostering awareness about the benefits of genetic screening form a pivotal component of effective liver cancer management. The latter requires proactive patient engagement, unraveling the potential of genetic screening in facilitating early detection and personalized treatment plans. Patient education emerges as a linchpin as the medical landscape becomes more personalized, ensuring informed decisions and active participation in their healthcare journey[115,116].

FUTURE DIRECTIONS IN GENETIC SCREENING FOR LIVER CANCER

Advancements in technology and their potential impact on genetic screening: The horizon of genetic screening for liver cancer is poised for transformation through technological leaps: Cutting-edge advancements, from enhanced NGS techniques to integrating artificial intelligence and machine learning. These innovations promise heightened precision, sensitivity, and cost-effectiveness in detecting genetic alterations associated with HCC, fostering a more accessible and comprehensive approach to population-wide screening[117].

Integrating multi-omics data for a comprehensive understanding of liver cancer genetics is the future of genetic screening, which embraces a multi-omics approach beyond individual genes. Integrating genomics with transcriptomics, proteomics, and metabolomics enriches our understanding of the intricate molecular landscape of liver cancer: The potential of holistic, multi-dimensional data in unraveling complex interactions and identifying novel biomarkers, paving the way for a more nuanced and personalized understanding of liver cancer genetics[118].

Collaborative efforts and research initiatives to enhance genetic screening practices are a must. The journey towards effective genetic screening necessitates collaboration across disciplines and institutions. Highlighting collaborative research initiatives, it is mandatory to include collective efforts underway to standardize protocols, share data, and establish large-scale genetic databases. These endeavors foster a unified approach, ensuring the amalgamation of diverse datasets for more robust genetic screening practices[119].

Potential breakthroughs and innovations in liver cancer prevention through genetic insights hold the key to revolutionary breakthroughs in liver cancer prevention: the potential for targeted interventions, risk stratification, and personalized prevention strategies. As genetic screening evolves, identifying high-risk individuals and guiding preventive

measures becomes increasingly pivotal. It offers hope for a future where liver cancer can be intercepted at its earliest, most treatable stages[120].

It is well known that the HCC is characterized by significant clinical and molecular variability. Over the past 20 years, it has been published a lot of data, related to the most common molecular alterations in HCC, but unfortunately, this knowledge has not led to better prognostic evaluation or treatment of this cancer.

To open the door for new therapeutic approaches, every effort should be made to establish a connection between therapeutic response and the molecular subtypes of HCC. It is anticipated that the introduction of NGS technology will contribute significantly to clinical oncology paving the way for novel therapeutic strategies.

The molecular characterization of genetic alterations in HCC will facilitate the creation of prognostic biomarkers that can be employed in routine clinical practice. These biomarkers can be a useful tool in predicting prognosis and therapeutic response. The patient stratification for appropriate adjuvant and palliative treatments (including non-targeted therapies), early diagnosis, and surveillance of patients in the risk group, all depend on these markers (found in tumor tissue, blood, urine, *etc.*)[110].

CONCLUSION

In conclusion, this review has provided a comprehensive exploration of the current state-of-the-art in genetic screening for liver cancer, emphasizing its pivotal role in early detection and personalized prevention. The intricate interplay of risk-associated genetic variants, somatic mutations, and epigenetic alterations has been dissected to underscore the nuanced understanding of HCC development and progression. Key takeaways include emerging technologies' transformative potential, multi-omics data integration, and the imperative for collaborative efforts to refine screening practices. As we navigate these frontiers, it is evident that genetic insights will reshape the landscape of liver cancer prevention and management. This prompts a resounding call to action for continued advancements in liver cancer genetics, urging researchers, clinicians, and policymakers to forge ahead in a unified effort. Through sustained innovation, we can revolutionize patient outcomes and make substantial strides toward mitigating the global burden of liver cancer.

Personalized medicine promises that it will allow us to treat HCC on an individual basis by determining the patient's genetic and epigenetic background and then conceiving a specific course of treatment that takes into account both the patient's best outcome and lowest risk. Future developments hold out hope for early HCC detection, which is the most important obstacle in achieving good treatment results in these patients.

FOOTNOTES

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