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Review Article

Emerging Roles of Hepatocellular Carcinoma Gene Signatures in Prognosis and Immunotherapy: Challenges and Opportunities

Amany Wahb[1], Ghada A. Abdel-Aleem[2], Noha O. Shawky[3] and Mohamed El-Kassas[4,5*]

[1]*Medical Biochemistry and Molecular Biology Department, Faculty of Medicine, Capital University, Cairo, Egypt;* [2]*Medical Biochemistry and Molecular Biology Department, Faculty of Medicine, Tanta University, Tanta, Egypt;* [3]*Medical Physiology Department, Faculty of Medicine, Capital University, Cairo, Egypt;* [4]*Endemic Medicine Department, Faculty of Medicine, Capital University, Cairo, Egypt;* [5]*Applied Science Research Center, Applied Science Private University, Amman, Jordan*

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Abstract

Hepatocellular carcinoma (HCC) remains one of the most fatal cancers, primarily due to late diagnosis and the lack of effective early biomarkers. Recent advances in multi-omics and liquid biopsy technologies hold promise for improving early detection, prognostication, and monitoring of HCC. Understanding the immune landscape of HCC through genetic and epigenetic signatures is essential for identifying therapeutic targets and improving immunotherapy outcomes. This review aims to present current findings on immune-related biomarkers, multi-omics strategies, and biomarker validation in HCC. It also aims to evaluate the role of liquid biopsy and gene signatures in predicting treatment responses, with a specific focus on their applications in immunotherapy. The goal is to provide a comprehensive framework for integrating these emerging tools into clinical practice. The integration of multi-omics approaches has led to the identification of robust gene signatures that predict HCC prognosis and response to immune checkpoint inhibitors. Liquid biopsy technologies, including circulating tumor DNA, provide non-invasive alternatives for monitoring tumor evolution and therapeutic responses. Despite promising results, challenges remain in clinical validation, particularly in cross-platform reproducibility and the interpretation of complex multi-omics data. While genetic biomarkers are rapidly advancing, their clinical application in personalized medicine remains hindered by technical and ethical challenges, such as data privacy, informed consent, and method standardization. The integration of multi-omics data and liquid biopsies offers a promising path toward real-time, personalized treatment and the development of universal prognostic signatures for HCC. However, successful clinical adoption depends on cross-disciplinary collaboration to standardize data protocols and overcome challenges regarding accuracy, reproducibility, and patient privacy.

Introduction

Hepatocellular carcinoma (HCC) is the most prevalent form of primary liver cancer and ranks third in cancer-related mortality and sixth in incidence worldwide. HCC ranks first among males and second among females in Egypt in terms of both incidence and mortality.[1] The main risk factors for HCC are hepatitis C and hepatitis B viruses, tobacco use, excessive alcohol use, aflatoxin B1, obesity, diabetes mellitus, and steatotic liver disease linked to metabolic dysfunction.[2] Liver transplantation is a curative option for selected early-stage HCC (e.g., within Milan criteria), although recurrence still occurs in approximately 10–15% of cases. For unresectable tumors, oral multi-kinase inhibitors are used; however, their effectiveness is often limited by adverse toxic effects and the development of resistance. Recently, immunotherapy has emerged as a promising approach and shows potential to improve survival outcomes in advanced HCC.[3] Late-stage diagnosis, few curative choices, drug resistance, impaired liver function and comorbidities, and the absence of effective medicines for advanced patients represent major challenges in current HCC treatment. These limi-

Keywords: Hepatocellular carcinoma; Gene signatures; Gene expression profiling; Multi-omics; Liquid biopsy; Tumor immune microenvironment; Biomarker validation; Immunotherapy.

***Correspondence to:** Mohamed El-Kassas, Endemic Medicine Department, Faculty of Medicine, Capital University, Helwan, Cairo 11795, Egypt. ORCID: https://orcid.org/0000-0002-3396-6894. Tel: +201223417561, E-mail: m_elkassas@hq.helwan.edu.eg

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tations underscore the need for innovative strategies to improve outcomes and optimize HCC care.[4]

Precision treatment aims to tailor therapy modalities to each patient's molecular profile in order to maximize therapeutic efficacy and minimize adverse effects.[5] Multiple genetic and epigenetic alterations converge on key oncogenic signaling pathways in HCC, and hepatocarcinogenesis is a multi-step process rather than a single event.[4]

Multiple factors contribute to the clonal evolution of cancer, resulting in genomic, molecular, functional, and lineage heterogeneity of HCC. These factors include genomic mutations, the tumor microenvironment (TME), evolution and reprogramming of cancer cells, the transition from non-cancer to cancer cells, and epigenetic modifications.[6] All of these factors contribute to the complexity of the disease and are important for clinical observations, including tumor dormancy, therapy resistance, and recurrence following initial treatment.

Several previous reviews have summarized the molecular landscape of HCC and described gene signatures mainly from single-omics datasets or focused on either prognosis or immunotherapy in isolation.[3,7] These works have usually addressed tissue-based expression panels or immune biomarkers separately and often given limited attention to liquid biopsy–derived signatures or to the practical steps needed for biomarker validation and clinical implementation. In contrast, the present review aims to propose an integrated multi-omics framework for HCC that combines tissue and liquid biopsy signatures with the tumor immune microenvironment to predict immunotherapy response. By evaluating current findings on immune-related biomarkers and gene signatures, the review emphasizes assay standardization, external validation, and real-world feasibility to provide a clinician-facing synthesis that complements existing literature. Ultimately, this review aims to explicitly map these emerging diagnostic tools onto established staging systems and treatment pathways, providing a comprehensive framework for their successful integration into clinical practice.

A systematic review of the literature was conducted using the following databases: PubMed, Scopus, and Google Scholar. The search was conducted between 2015 and 2024 to identify relevant studies on gene signatures in HCC, with a specific focus on multi-omics approaches, biomarker validation, and immunotherapy responses. The search terms included "HCC gene signatures", "Liquid biopsy", "Biomarker validation", "Immune checkpoint inhibitors", and "Tumor microenvironment". The following inclusion criteria were applied to studies: published in English, focused on gene signatures in HCC, and provided clinical validation or preclinical research on gene signatures or biomarkers. The following exclusion criteria were applied: studies not focused on HCC or gene expression profiling, non-peer-reviewed articles or abstracts without full text available, and articles with insufficient data or methodological flaws.

Data were extracted from the selected studies based on the following parameters:

- *Gene signature composition:* list of genes included in each signature;
- *Validation cohort:* sample size and patient demographics;
- *Prognostic endpoint:* survival rates, disease-free survival;
- *Immunotherapy relevance:* whether the signature was used to predict response to immunotherapy.

These data were analyzed and summarized to provide an integrated comparison of gene signatures for HCC prognosis and immunotherapy response.

The molecular architecture and pathogenesis of HCC

Genetic heterogeneity in HCC

Both intrapatient and interpatient genetic heterogeneity—differences across tumors within the same patient or molecular variances between cancers in different patients—can arise. Furthermore, within a tumor, variation may occur across several areas.[8] For instance, Xue *et al*.[9] found that, at the intrapatient level, tumor thrombi and intrahepatic metastases tended to differ from the initial lesion in terms of copy number and mutation. Ding *et al*.[10] classified recurrent HCC as either multicentric or progressive, with the initial and recurrent tumors having different genetic characteristics in about half of patients. Recurrent tumors with multicentric HCC had a separate ancestry from the original tumor. Recurrent progressive HCC tumors were produced from the same clonal source and shared many mutations with the initial tumor.[10]

A list of genes with their interconnected pathways sharing an altered pattern of expression that can be implemented for diagnosis, prognosis, or therapy response prediction is referred to as a "gene signature". Gene expression profiling can indicate the potential for using a gene signature to directly inform clinical care and treatment.[11]

Extensive genetic research has remarkably enhanced our understanding of the genomic profile of HCC, which includes somatic mutations, copy number changes, and epigenetic modifications, key drivers of cancer development that influence disease prognosis.[3] High-throughput technologies, such as microarrays, DNA/RNA sequencing, and bioinformatics pipelines, can identify genomic subtypes that are clinically relevant and the distinctive genetic changes linked to these subtypes.[7] Moreover, progress in genome-wide screening techniques for HCC has enabled the discovery of genetic indicators and proteomic biomarkers that support both diagnosis and prediction of disease outcomes.[3]

Multi-omics landscape of HCC

Multi-omics, encompassing genomics, epigenomics, transcriptomics, glycoproteomics/glycomics, proteomics, and metabolomics, may yield multiple HCC biomarkers. In the fields of genomics and epigenomics, circulating tumor DNAs (ctDNAs) and their epigenetic modifications can serve as reliable biomarkers. Noncoding RNAs and messenger RNA (mRNAs) display significant changes in terms of transcriptomics. Proteomics has identified several potential protein biomarkers for HCC, including osteopontin, Dikkopf-1, alpha-1-fucosidase, Golgi protein-73, heat shock protein 90, and midkine.[12]

Key oncogenic pathway alterations in HCC (tumor protein p53 (TP53), telomerase reverse transcriptase (TERT), Wnt/β-catenin):

Several types of genomic changes in HCC, such as mutations, chromosomal rearrangements, alterations in gene copy numbers, and viral genome insertion, have been reported.[13] Cancer starts and spreads due to loss-of-function mutations in tumor suppressor genes and mutational activation of oncogenes. Studies using genome-wide sequencing have revealed recurring gene mutations in HCC and provided a landscape view of genetic changes. A number of genes were frequently altered in various studies, including TP53, the TERT promoter, and the cadherin-associated protein, indicating that these genes may be functionally important in HCC.[14]

TP53 plays a key role in regulating angiogenesis and apopto-

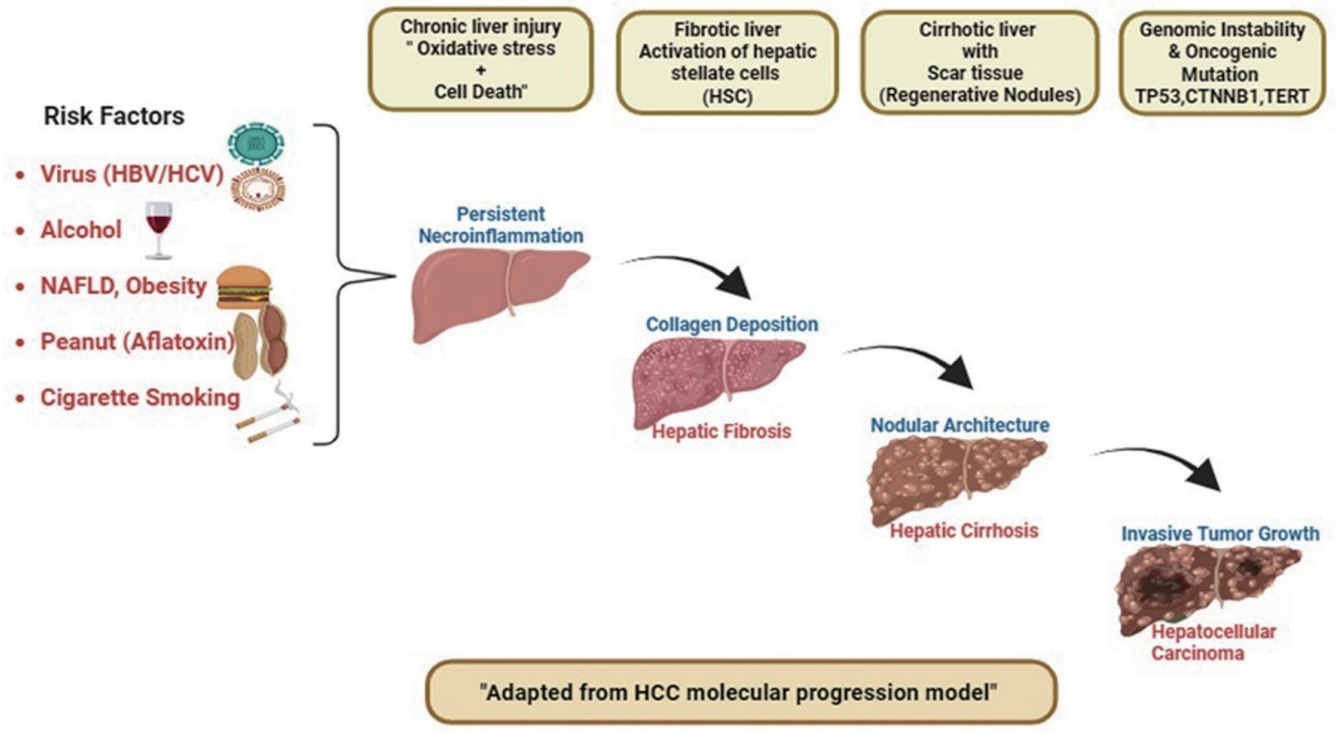

Fig. 1. Risk factors and pathogenesis of hepatocellular carcinoma (HCC). Multistep model of hepatocarcinogenesis showing the progression from normal hepatocytes to malignant transformation. Chronic liver injury, due to viral infections (HBV/HCV), metabolic diseases like nonalcoholic fatty liver disease (NAFLD), or toxins, leads to inflammation and oxidative stress, followed by fibrosis and cirrhosis. Genomic instability, epigenetic alterations, and oncogenic pathway activation (Wnt/β-catenin, telomerase reverse transcriptase (TERT), and tumor protein p53 (TP53)) contribute to the evolution from dysplastic nodules to early and advanced hepatocellular carcinoma.

sis. In nearly 50% of HCC cases, often triggered by aflatoxin B1 exposure or infections with hepatitis B and hepatitis C viruses, this gene is deactivated, making it the most frequently mutated gene in HCC. Alterations in genes related to the TP53 family, such as p63 and p73, have been associated with more aggressive tumor characteristics, including increased stem cell-like marker expression, higher Edmondson grades, reduced survival rates, and a greater likelihood of recurrence. Furthermore, TP53 dysfunction may contribute to immune suppression, positioning HCC as a promising candidate for immunotherapy (Fig. 1).[15,16]

A key enzyme for extending telomeres, TERT is a rate-limiting catalytic component of telomerase and plays a significant role in the process of tumorigenesis, including angiogenesis, invasion, metastasis, and cell growth.[17] With an overall frequency of about 60%, the TERT promoter mutation is common and arises in low-grade HCC and dysplastic nodules. Because it selects for oncogenic drivers for HCC that evade apoptosis with unrestricted telomerase activity, it is, therefore, essential in the early phases of carcinogenesis.[18] Furthermore, because it hinders hepatocytes' ability to respond to chronic inflammation during the healing phase, the loss of function of altered telomerase gene variants predisposes to the neoplastic process and speeds up the cirrhosis stage. Clinically, TERT promoter mutations have been linked to late intrahepatic recurrence after surgery, overall survival, and shorter disease-free survival.[19] β-catenin, as part of Wnt/β-catenin, a key signaling pathway involved in maintaining liver balance, promoting regeneration, and driving tumor formation, is found to be mutated in approximately 40% of HCC cases. This mutation has been linked to more aggressive forms of HCC, as it is commonly associated with advanced pathological traits such as vascular invasion, increased tumor size, lower differentiation grade, and a higher likelihood of recurrence.[3]

Epigenetic dysregulation

The term "epigenetic alterations" describes molecular modifications that impact gene function and result in potentially heritable phenotypic changes without altering a gene's DNA sequence, such as DNA methylation, chromatin remodeling, and noncoding RNAs. Important steps in early hepatocarcinogenesis are impacted by epigenetic alterations, which are very common in HCC.[20] According to Wu *et al*.,[21] E-cadherin (CDH1) hypermethylation was substantially greater in HCC tissues and was associated with a lower overall survival rate. In HCC studies, non-coding RNAs, such as microRNA (miRNAs), circular RNAs (circRNAs), and long non-coding RNAs (lncRNAs), have demonstrated encouraging outcomes as epigenetic regulators.[22] Although genetics provides the blueprint, proteomics examines the proteome to identify biomarkers and potential treatment targets and offer important insights into disease processes. The proteome changes in response to external stimuli and in different cells.[23] Detecting changes in protein function caused by post-translational modifications, such as phosphorylation, glycosylation, and acetylation, can be achieved through a range of analytical methods. These include mass spectrometry for identifying proteins, Edman sequencing for determining amino acid sequences, sodium dodecyl sulfate–polyacrylamide gel electrophoresis for measuring protein

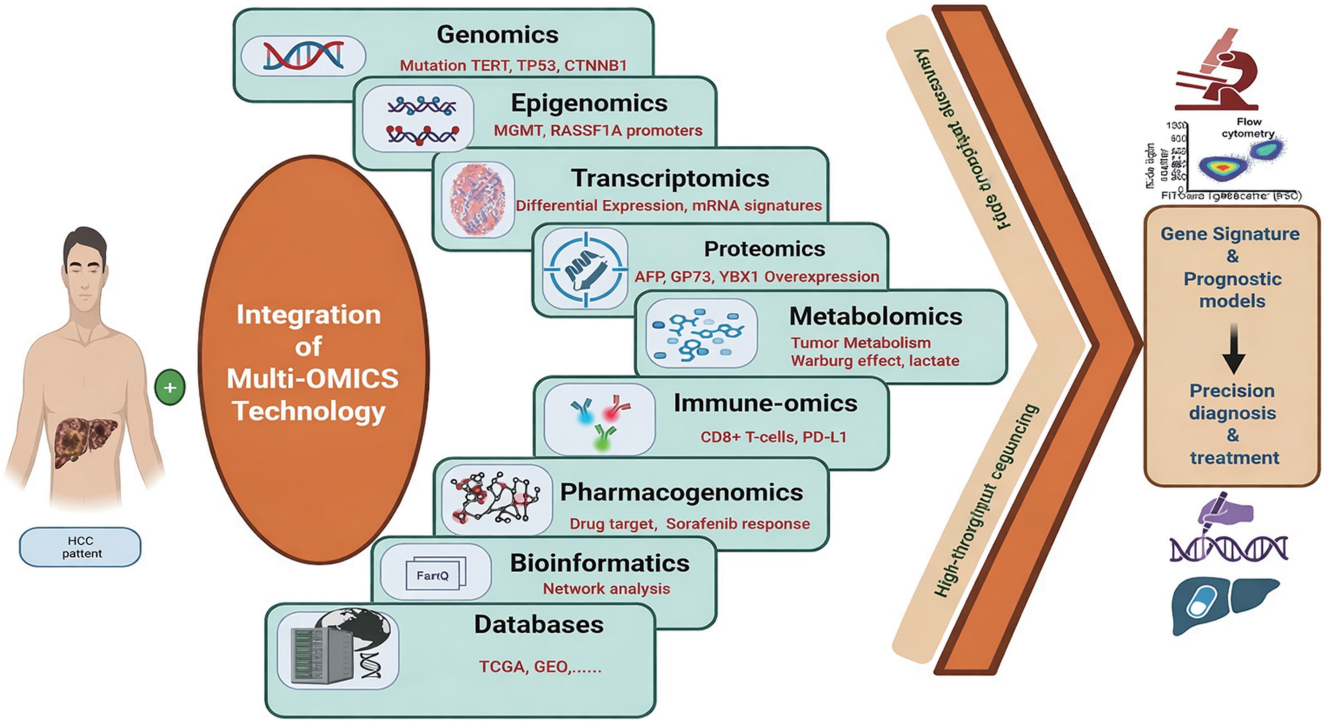

Fig. 2. Multi-omics integration in hepatocellular carcinoma (HCC) (genomics, transcriptomics, proteomics & metabolomics). Multi-omics integration framework in HCC. Comprehensive molecular profiling combines genomic alterations (e.g., TP53, CTNNB1, TERT mutations), epigenomic alterations (e.g., methylguanine-DNA methyltransferase (MGMT) and Ras association domain family member 1A (RASSF1A)), transcriptome signatures, proteomic biomarkers, and metabolic reprogramming to identify prognostic and predictive gene signatures. Integrated datasets like The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) enable biological insights, patient stratification, and the development of precision therapies.

levels, X-ray crystallography for revealing structural details, and interaction assays like enzyme-linked immunosorbent assay and the yeast two-hybrid system to study protein–protein relationships.[24]

Proteomics & metabolomics

Proteomics reveals mechanisms behind drug resistance, enabling more targeted therapeutic choices. It also identifies secreted biomarkers that support non-invasive disease monitoring and provides detailed insights into biological pathways. Once these biomarkers are clinically validated and ethically approved, they can inform clinical trial design and advance nanomedicine.[25] Moreover, proteomic profiling allows for functional classification of HCC based on protein activity, offering greater accuracy than transcriptomic methods in predicting how patients will respond to treatment.[26]

Metabolomics, the study of small-molecule metabolites, provides a real-time snapshot of the body's metabolic state and is a crucial tool for understanding and management of HCC. By analyzing metabolites from body fluids such as blood and urine, researchers can identify potential biomarkers for HCC diagnosis and prognosis, like kynurenine and taurocholic acid. This approach employs techniques such as nuclear magnetic resonance and mass spectrometry to discover biomarkers and assess drug effectiveness and safety. While metabolomics plays a pivotal role in advancing precision medicine for HCC, assisting in identifying the disease, forecasting treatment outcomes, and tracking therapeutic responses, it still faces challenges related to detecting trace metabolites, standardizing procedures, and creating comprehensive databases for widespread clinical use (Fig. 2).[27]

Gene signatures in HCC prognostication (discovery and validation)

HCC presents a unique challenge because it often develops in a cirrhotic liver, requiring simultaneous management of both malignancy and chronic liver disease. As a result, mortality in HCC may stem from different causes: recurrence or metastasis of the primary tumor, emergence of new primary tumors in the cirrhotic liver, or complications from liver failure. In advanced HCC, death is more often due to tumor progression, whereas in early-stage cases, mortality may result from new tumor development or cirrhosis-related complications. These distinctions make it critical to clearly define patient cohorts and clinical endpoints when developing prognostic signatures.[28,29] Gene expression–based signatures are increasingly recognized as reliable tools for risk stratification and outcome prediction in HCC, offering enhanced accuracy compared to conventional clinicopathological factors alone. These signatures are typically derived by profiling mRNA expression in tumor tissues and identifying prognostically relevant genes whose expression patterns are significantly associated with overall survival, disease-free survival, or recurrence risk (Fig. 3, Table 1).[30–38]

The role of genetic markers in HCC prognosis has become a pivotal aspect of personalized medicine. Gene signatures, derived from genomic, transcriptomic, and proteomic profiling, are increasingly used to predict patient outcomes, treatment responses, and recurrence risks. Traditional methodologies, such as microarray analysis and next-generation sequencing, enable the identification of gene expression patterns that correlate with clinical endpoints, including overall survival, disease-free survival, and response to immunotherapy.[39]

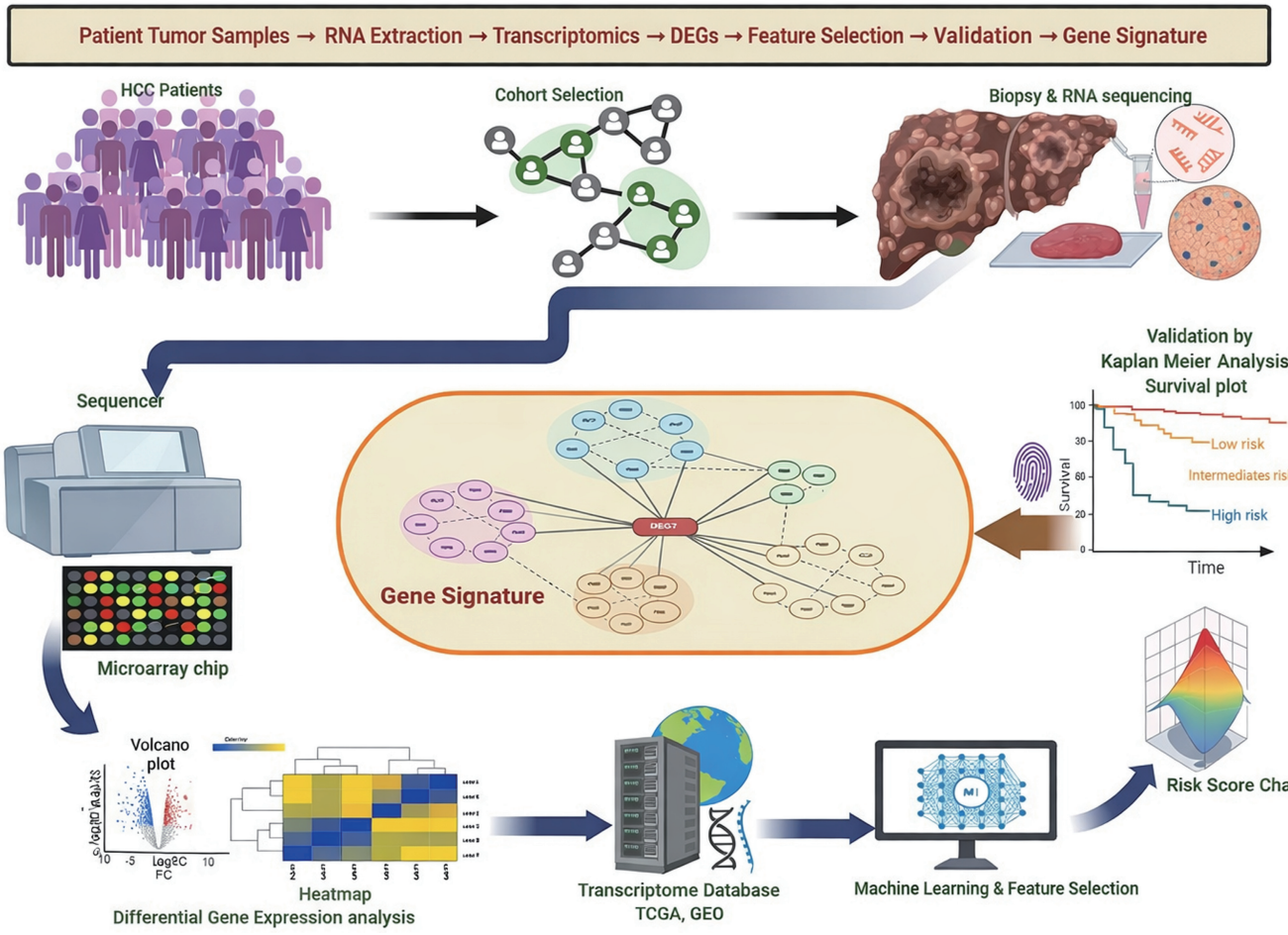

Fig. 3. Workflow of gene signature–guided precision medicine in hepatocellular carcinoma (HCC). Workflow for discovery and validation of prognostic gene signatures in hepatocellular carcinoma (HCC). Transcriptome datasets (e.g., The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO)) are analyzed to identify differentially expressed genes (DEGs). Feature selection using least absolute shrinkage and selection operator (LASSO) and Cox regression identifies robust prognostic markers. Gene signatures are validated in independent cohorts and used for stratifying patients into high- and low-risk groups based on survival analysis.

One challenge in the development of HCC-specific prognostic gene signatures is validating these signatures in diverse cohorts, including the use of publicly available HCC datasets. For instance, databases such as The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus provide extensive gene expression data from HCC patients, enabling researchers to identify and validate potential biomarkers across multiple cohorts.[40] For example, Xie *et al*.[41] used TCGA data to identify a seven-gene signature for predicting HCC prognosis, validated in external cohorts and correlated with immune infiltration patterns. This cross-platform validation method enhances the generalizability and clinical applicability of genetic markers in HCC.[41]

However, technical challenges, such as the use of fresh-frozen and formalin-fixed, paraffin-embedded (FFPE) samples in gene signature construction, remain a significant hurdle. FFPE samples are commonly used in clinical settings due to their long-term stability; however, they often exhibit RNA degradation and artifacts introduced during fixation. The use of FFPE samples in gene signature validation necessitates careful consideration of RNA extraction methods, quality control protocols, and data normalization techniques.[42]

Despite these challenges, multi-omics approaches are increasingly being used to combine genomic data with clinical and pathological characteristics to develop robust prognostic signatures. By integrating liquid biopsy technologies (e.g., cell-free DNA, ctDNA), researchers can further enhance prognostic accuracy in HCC, circumventing the limitations of FFPE tissue samples. This multimodal approach is crucial for improving the predictive performance of genetic signatures, enabling more personalized treatment strategies for HCC patients.

TME and immune classification:

Oncogenic pathways and the TME in HCC

High-throughput transcriptomic approaches, including RNA sequencing and microarray analysis, are used to compare HCC tissue with adjacent non-tumorous liver to identify genes that are significantly upregulated or downregulated in tumors. Candidate genes are then evaluated using univariate and multivariate Cox regression analysis to determine their independent prognostic value.[43] For each patient, a composite risk score is calculated by weighting

Table 1. Prognostic & immune gene signatures in HCC

Signature name/study	Gene list (representative)	Cohort(s) used	Validation status	Reference
Exercise-Related Immune Genes (2025, Front Immunol)	~6,908 exercise-related genes narrowed to key EIGs (e.g., STC2, BIRC5, EPO)	TCGA (424 pts), ICGC (233 pts)	External validation in ICGC; machine learning model	32
SIR-PS Immune Signature (2025, Front Immunol)	4 genes: STC2, BIRC5, EPO, GLP1R	TCGA-LIHC, 3 external cohorts, immunotherapy cohort	Validated in multiple cohorts and tissue chips	33
Four-Gene Signature (2022, BMC Cancer)	EZH2, FLVCR1, PTTG1, TRIP13	TCGA (training), ICGC (testing)	Validated by RT-qPCR and nomogram system	34
Macrophage-Related Signature (2022, Front Immunol)	18 genes including PON1, IL15RA, NEIL3, EPO, STC2	TCGA, GEO, ICGC Datasets	Validated across GEO and ICGC; independent OS predictor	35
M2-like Macrophage Prognostic Signature (2023, PLoS ONE)	Multi-gene MRPS via machine learning (specific genes not fully listed)	TCGA, GEO, ICGC Cohorts	Validated with AUCs ~0.7–0.76; immunotherapy response assessed	36
5-Gene Immune Signature (2021, Front Cell Dev Biol)	ATG10, IL18RAP, PRKCD, SLC11A1, SPP1	TCGA-LIHC, HCCDB18, GSE14520	Robust across multiple cohorts	37
10-Gene Immune Prognostic Signature (2022, Front Oncol)	HLA-G, S100A9, S100A10, DCK, CCL14, NRAS, EPO, IL1RN, GHR, RHOA	TCGA (374 HCC), GEO (160 non- HCC)	Validated by Kaplan-Meier, ROC, and immune infiltration analysis	38

The table consolidates key prognostic and immune gene signatures validated across multiple independent cohorts for hepatocellular carcinoma. AUC, area under the curve (receiver operating characteristic); EIGs, exercise-related immune genes; GEO, Gene Expression Omnibus; GSE, Gene Expression Omnibus Series accession number; HCCDB18, Hepatocellular Carcinoma Database 18; ICGC, International Cancer Genome Consortium; IO, immuno-oncology; KM, Kaplan–Meier; ML, machine learning; OS, overall survival; RT-qPCR, real-time quantitative polymerase chain reaction; SIR-PS, signature of immune-related prognostic signatures; TCGA, The Cancer Genome Atlas.

expression levels of the selected genes by their regression coefficients. Patients are classified into high- and low-risk groups based on median or optimal cutoff values of the score, which supports tailored surveillance and treatment decisions.[28]

Several multigene panels have been proposed and validated across independent cohorts. An eight-gene signature (DCAF13, FAM163A, GPR18, LRP10, PVRIG, S100A9, SGCB, and TNNI3K) has shown strong predictive accuracy for overall survival, with high-risk patients experiencing markedly shorter survival.[29] A nine-gene model (IQGAP3, BIRC5, PTTG1, STC2, CDKN3, PBK, EXO1, NEIL3, HOXD9) effectively discriminated prognostic groups and was validated in TCGA cohort.[43] A four-gene panel (ADH4, COL15A1, RET, and KCNJ16) was reported as a robust predictor of overall survival independent of clinicopathological variables.[31] A thirteen-gene score (LDHA, GPC1, GRM8, PPAT, SLC29A3, EMCN, GDI2, CBX2, LILRA2, ADAMTS5, GSR, WEE1, SLC1A5) stratified patients for both overall survival and recurrence risk.[39]

Clinically, these signatures can enhance prognostic accuracy and often outperform conventional staging systems, including Barcelona Clinic Liver Cancer (BCLC) and TNM, for predicting overall and disease-free survival.[29] They can guide individualized therapy by identifying patients at high risk who may merit prioritization for transplantation, consideration of adjuvant targeted strategies, or more intensive follow-up.[28] Moreover, selected molecular panels are under evaluation for earlier detection of HCC, when curative interventions are more feasible.[44]

While numerous gene signatures have been proposed, further validation in large, multiethnic cohorts remains critical to ensure clinical applicability. Future strategies may involve integrating gene signatures with other biomarkers—such as ctDNA, serum alpha-fetoprotein, and radiomic features—to build multimodal prognostic models with superior predictive power. Additionally, the application of machine learning algorithms is expected to refine the selection of prognostic genes and enhance the robustness of risk models.[43]

Gene signatures and the TME

The TME of HCC plays a central role in disease progression, therapeutic resistance, and clinical outcomes. Comprising immune cells, stromal components, endothelial cells, and extracellular matrix, the TME exerts a dynamic influence on tumor biology. Gene expression–based signatures have emerged as robust tools for profiling the TME, enabling classification of immune activity states, quantification of immune cell infiltration, and characterization of stromal–tumor interactions (Table 2).[36,38,45–55]

Immune cell infiltration: Role of gene expression in shaping or reflecting TME

Transcriptomic analyses can deconvolute bulk tumor gene expression data to infer the abundance of specific immune cell subsets, including tumor-infiltrating lymphocytes, tumor-associated macrophages, dendritic cells, and regulatory T cells.[56] High expression of CD8A, GZMB, and PRF1 genes is associated with cytotoxic T-cell infiltration and improved prognosis, while enrichment of M2 macrophage–associated genes (*CD163, MRC1*) correlates with immunosuppression and poor outcomes.[57] These immune infiltration signatures not only reflect the immune landscape but also predict responsiveness to immune checkpoint inhibitors (ICIs).

Immune "hot" vs. "cold" tumors

Gene expression profiling enables classification of HCC into immune "hot" (inflamed) and "cold" (non-inflamed) phenotypes. Inflamed tumors show high expression of interferon-γ–associated genes such as CXCL9, CXCL10, and IDO1, increased pro-

Table 2. Comprehensive and comparative analysis of the gene signatures in HCC

Gene signature	Gene list	Validation cohort	Prognostic/Predictive performance	Limitations	Reference
Immune-related signature	CD8A, CD274 (PD-L1), CTLA4, PDCD1 (PD-1), LAG3 B2M, SPP1, PPIA, and HRG	HCC patients (N ≈ 500)	Validated in multiple cohorts for predicting immunotherapy response	Requires broader validation across ethnic and geographic population	47,48
Prognostic signature for survival	CDC20, PTTG1, TOP2A, CXCL2, CXCL14, CYP2C9, MT1F, and GHR	Retrospective liver cancer cohorts	Predicts overall survival (OS) and disease-free survival (DFS)	Limited prospective and clinical trial validation	49
Tumor microenvironment (TME) signature	CAFs, EMT-related genes (ZEB1, TWIST1)	Early-stage HCC patients (N ≈ 250)	Predicts recurrence risk and metastatic potential	Needs longitudinal and cross-platform validation	34
Metabolic signature	SLC2A1 (GLUT1), PKM2, LDHA	Liver cancer cohorts, cell lines, xenograft models	Predicts metabolic reprogramming and chemotherapy response	Requires validation in large clinical cohorts	50
Oncolytic virus + immune signature	H101 plus nivolumab in refractory advanced hepatocellular carcinoma: an open-label, single-arm, pilot study	Clinical trial cohort (N ≈ 120)	Predicts response to combined oncolytic virus and immunotherapy	Trial heterogeneity, limited long-term follow-up	51
Gene signature for sorafenib response	BCL2, CASP3, MET, CTNNB1	Sorafenib-treated HCC patients (N ≈ 150)	Predicts sorafenib response and survival	Limited external cohort validation	52
Angiogenesis-related signature	VEGFA, KDR, ANGPT2, FGF2	Advanced HCC patients (N ≈ 300)	Associated with angiogenesis activity and poor prognosis	Not validated in early-stage HCC	53
mRNA-based stemness signature	ALDH1A1, SOX2, NANOG, OCT4	HCC patients and cell lines	Identifies stem-like traits; correlates with recurrence and metastasis	Requires validation in larger, diverse cohorts	54
Multi-omics immune signature	PD-1, CTLA4, CD8A, CXCL9, HLA-B, TLRs	Multi-omics HCC cohort (N ≈ 400)	Predicts immunotherapy success using integrative omics	Data integration and platform heterogeneity	32,55

This table highlights information on each signature's gene composition, key differences in their clinical applicability, validation cohort, prognostic/predictive performance, and limitations, with a clear comparative analysis. ALDH1A1, aldehyde dehydrogenase 1 family member A1; ANGPT2, angiopoietin 2; BCL2, B-cell lymphoma 2; CASP3, caspase 3; CD8A, CD8a molecule; CDC20, cell division cycle 20; CTLA4, cytotoxic T-lymphocyte associated protein 4; CTNNB1, catenin beta 1; CXCL, C-X-C motif chemokine ligand; DFS, disease-free survival; EMT, epithelial–mesenchymal transition; FGF2, fibroblast growth factor 2; HCC, hepatocellular carcinoma; IO, immuno-oncology; KDR, kinase insert domain receptor; LDHA, lactate dehydrogenase A; MET, MET proto-oncogene; N, approximate sample size; NANOG, Nanog Homeobox; OCT4, octamer-binding transcription factor 4; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PKM2, pyruvate kinase M2; PTTG1, pituitary tumor-transforming gene 1; Ref., reference; SLC2A1, solute carrier family 2 member 1; SOX2, SRY-box transcription factor 2; TLRs, Toll-like receptors; TME, tumor microenvironment; TOP2A, topoisomerase II alpha; VEGFA, vascular endothelial growth factor A.

grammed death-ligand 1 (PD-L1) levels, and signatures of active antigen presentation.[58] In contrast, non-inflamed tumors exhibit low immune-gene expression, sparse T-cell infiltration, and enrichment of Wnt/β-catenin pathway signaling that drives immune exclusion.[59] Therapeutically, inflamed tumors preferentially benefit from immune checkpoint blockade, whereas non-inflamed tumors often require immune priming, such as oncolytic viruses, radiotherapy, or vascular endothelial growth factor (VEGF)-targeted therapy, to achieve responsiveness.

Stromal and endothelial interactions: Inflammatory cytokine gene signatures

Beyond immune cells, the TME in HCC contains cancer-associated fibroblasts, endothelial cells, and pericytes that actively modulate tumor behavior. Gene signatures capturing stromal activation (e.g., *COL1A1, FAP, ACTA2*) and angiogenesis (*VEGFA, ANGPT2, PECAM1*) reveal the interplay between tumor cells and their supportive niches.[60] Similarly, inflammatory cytokine signatures—including elevated expression of *IL6, IL8, CCL2,* and *TGFB1*—are linked to chronic inflammation, immunosuppression, and epithelial-to-mesenchymal transition, thereby promoting tumor progression and metastasis.[61] Stromal–immune cross-talk signatures may also predict poor prognosis and resistance to targeted therapies, highlighting the value of integrated TME profiling in clinical decision-making.

Role of gene signatures in guiding immunotherapy for HCC

Immunotherapy has emerged as a transformative treatment modal-

ity in HCC, with ICIs such as nivolumab (anti–PD-1), pembrolizumab (anti–PD-1), atezolizumab (anti–PD-L1), and ipilimumab (anti–CTLA-4) achieving durable responses in subsets of patients. However, the heterogeneous nature of tumor biology results in variable treatment outcomes, necessitating reliable biomarkers to identify likely responders. Gene expression–based immune signatures have shown considerable promise in this context, enabling precise characterization of the tumor immune microenvironment and prediction of response to immunotherapy.[62–64]

Immunologically "hot" vs. "cold" tumors

Transcriptomic profiling of HCC tumors allows classification into immune-active ("hot") tumors—characterized by high immune infiltration, increased PD-L1 expression, and upregulation of interferon-γ–related genes—and immune-desert ("cold") tumors, which lack significant T-cell infiltration and show poor ICI responsiveness.[65] This immune classification has therapeutic implications: "hot" tumors are more likely to benefit from PD-1/PD-L1 blockade, whereas "cold" tumors may require combination strategies with agents such as VEGF inhibitors, oncolytic viruses, or cancer vaccines to induce immune activation.

Immune-related gene expression profiles (GEPs)

PD-1/PD-L1 response prediction

Several immune gene signatures, particularly those enriched for interferon-γ–induced transcripts (*CXCL9, CXCL10, IDO1, STAT1*), have been correlated with favorable responses to PD-1/PD-L1 blockade.[58] High expression of these signatures reflects an inflamed tumor immune microenvironment that is more susceptible to immune checkpoint inhibition.

Tumor immune microenvironment characterization

Gene expression panels can quantify immune cell subpopulations, including tumor-infiltrating lymphocytes, tumor-associated macrophages, and regulatory T cells, offering insights into the immunosuppressive or immunostimulatory nature of the tumor milieu.[66]

Integration with tumor mutational burden (TMB) and neoantigen load

Although HCC generally exhibits low-to-moderate TMB, integrating gene expression signatures with mutational data can enhance predictive power for immunotherapy response.[67] For instance, tumors with high TMB coupled with an immune-active GEP are more likely to elicit robust antitumor immunity.

Representative immune gene signature studies in HCC

The 17-gene immune signature developed by Sia *et al*.[68] stratifies HCC into immune subclasses, with the immune-active subtype showing high cytotoxic T-cell infiltration and improved survival after immune checkpoint inhibition. The T cell–inflamed GEP, first validated in melanoma and adapted for HCC, includes interferon-stimulated genes, chemokines, and cytotoxic markers that predict response to anti–PD-1 therapy.[58] Exhaustion-related gene signatures assessing PDCD1, LAG3, TIGIT, and HAVCR2 delineate T-cell dysfunction states within HCC and can guide combination immunotherapy strategies.[69]

Clinical integration and future perspectives

Combining immune-related gene signatures with clinical staging systems like BCLC and TNM, in addition to radiomic biomarkers, may allow for a multidimensional patient stratification model, improving the selection of candidates for immunotherapy. Furthermore, integration of GEPs with liquid biopsy approaches—such as ctDNA, nucleic acids from tumors, including circulating tumor RNA, and peripheral immune profiling—may facilitate non-invasive, real-time monitoring of immunotherapy response in HCC.[46]

Future developments will likely leverage artificial intelligence and machine learning to refine predictive immune signatures and integrate genomic, transcriptomic, and proteomic data into composite decision-support tools for personalized immuno-oncology in HCC.

Clinical-trial evidence for cold/hot tumor conversion strategies

Mechanistic rationale & clinical-trial evidence

Contemporary research increasingly recognizes that the immunological phenotype of HCC—whether "cold" (immune-deserted or immune-excluded) or "hot" (immune-inflamed)—can strongly influence response to immunotherapy. Accordingly, strategies aiming to transform cold tumors into hot, inflamed, T cell–rich tumors are gaining traction.[70]

Oncolytic virus therapy (OVT) has emerged as a robust approach. Oncolytic viruses infect and lyse tumor cells, causing immunogenic cell death, release of tumor-associated antigens, danger signals like damage-associated molecular patterns, and pathogen-associated molecular patterns, which collectively activate antigen-presenting cells, recruit T cells, and reshape the TME toward an inflamed phenotype.[71]

Preclinical models combining OVT with checkpoint blockade (e.g., anti–PD-1/PD-L1) demonstrated synergistic inhibition of tumor growth and increased infiltration of cytotoxic $CD8^+$ T cells.[72]

Clinical trial evidence supports that integrating immune-activating therapies with standard modalities like radiotherapy can sensitize cold tumors to immunotherapy. For instance, a recent phase II trial using stereotactic body radiotherapy followed by anti–PD-1 therapy led to enhanced neoantigen presentation, systemic T-cell expansion (tumor and peripheral), and durable responses even in initially "cold" tumors.[73,74]

Apart from OVT and radiotherapy, other promising strategies include a combination of immunogenic cell death–inducing chemotherapy or targeted therapy, modulation of the tumor stroma to enhance T-cell infiltration, and use of biomaterial-based delivery systems (e.g., nanoparticles, cytokine-secreting vectors) to reshape the TME.[75]

These converging lines of evidence suggest that the effectiveness of immunotherapy in "cold" tumors is not precluded but can be enhanced by appropriately timed combinatorial strategies—especially when they induce inflammation, antigen release, and immune-sensitizing alterations in the TME.

Clinical implications for HCC & recommendations

For HCC patients with immunologically "cold" tumors (e.g., low lymphocyte infiltration, "immune desert" phenotype, low PD-L1 expression), incorporating oncolytic viruses (engineered to express immune-stimulatory cytokines/chemokines) could prime the tumor for subsequent immune checkpoint blockade.[76,77] Radiotherapy (or radioembolization)—widely applied in HCC—may serve a dual role: direct cytotoxicity plus immune priming via antigen release and enhanced presentation, thereby converting the TME into a more immunologically active state before immune checkpoint therapy.[78]

Clinical trial design for HCC immunotherapy should consider

sequential or combinatory regimens: first an immune-priming intervention (OVT, RT, oncolytic + cytokine virus, immunogenic cell death-inducing chemotherapy), followed by checkpoint inhibitors—optimized for timing, dose, and patient selection (e.g., baseline TME phenotype).[78,79] Given the dynamic and reversible nature of TME phenotypes, repeated monitoring (e.g., via liquid biopsy, immunophenotyping, or imaging) could guide adaptive therapy—turning "cold → hot" when needed, and maintaining "hot" status for durable response.[80]

Recent clinical trials integrating gene signatures and immunotherapy in HCC

Exploratory analyses of prospective immunotherapy trials in HCC have begun to integrate tumor gene expression signatures with clinical outcomes, providing proof-of-concept for the clinical utility of immune-related gene signatures. In the phase I/II CheckMate 040 study of nivolumab in advanced HCC, transcriptomic profiling of baseline tumor samples identified an "inflammatory" or effector T-cell gene expression signature that was enriched in responders and associated with improved overall response rate and overall survival. These signatures typically included genes related to interferon-γ signaling, cytotoxic T-cell activity, and chemokines such as CXCL9/CXCL10, indicating that a pre-existing inflamed microenvironment can predict benefit from PD-1 blockade.[81]

More broadly, recent reviews and translational studies synthesizing data across trials of atezolizumab plus bevacizumab, tremelimumab plus durvalumab, and other ICI–based regimens in HCC have reinforced the concept that multi-gene immune signatures outperform single biomarkers such as PD-L1 immunohistochemistry. T-effector gene signatures, interferon-response modules, and other composite immune-expression panels have consistently correlated with higher response rates and longer survival in these cohorts, whereas WNT/β-catenin pathway activation and "non-inflamed" signatures are linked to primary resistance.[82]

In parallel, several prognostic and immunotherapy-related gene signatures have been derived from publicly available multi-omics datasets and tested in patients receiving ICIs. For example, tumor immunotherapy–related multigene signatures have been shown to stratify patients into high- and low-risk groups with distinct immune infiltration patterns and differential predicted sensitivity to PD-1/PD-L1 blockade.[83]

Similarly, radiomics-integrated models that combine imaging features with transcriptomic immune signatures have recently been developed to predict response and survival in advanced HCC patients treated with ICI-based combination therapy, illustrating how gene signatures can be embedded in multimodal predictive tools.[84]

Yao *et al*.[85] developed immune-related gene signatures that not only stratified HCC patients by prognosis but also predicted those more likely to benefit from immune checkpoint blockade, thereby bridging bulk transcriptomic profiling and practical treatment decision-making.

Together, these studies illustrate an emerging trend in which gene and multi-omics signatures are no longer purely prognostic research tools but are increasingly embedded in clinical-trial correlative analyses to refine patient selection and elucidate mechanisms of primary or acquired resistance to ICI-based combinations in HCC.

Advantages of multi-omics integration vs. single-omics

Early work on prognostic and predictive biomarkers in HCC relied largely on single-omics layers, such as gene-expression profiling alone. Although these studies provided important proof-of-principle, single-omics signatures are often platform-dependent, sensitive to batch effects, and only partially capture the complexity of the TME. In contrast, multi-omics integration—typically combining genomics, transcriptomics, epigenomics, proteomics, and sometimes metabolomics—offers a more comprehensive view of tumor biology and immune contexture.[86]

Recent HCC studies have demonstrated that multi-omics–derived signatures can define molecular subtypes with distinct immune landscapes, metabolic states, and clinical outcomes, and that these integrated models frequently outperform single-layer signatures in prognostic accuracy and robustness across cohorts. For example, multi-omics frameworks that incorporate methylome + transcriptome, or integrate radiomics with specific genetic drivers (such as TPX2 or PDHA1), have yielded clinically actionable risk models that better predict survival and potential benefit from immunotherapy than expression-only panels.[85,87]

As multi-omics datasets and computational frameworks mature, such integrative signatures are likely to become central to precision stratification and rational combination-therapy design in HCC. In this context, multi-omics integration not only enhances biological interpretability—by linking driver alterations to downstream immune phenotypes—but also improves cross-platform stability, which is essential for eventual clinical translation.

Role of non-coding RNAs in immune evasion & immunotherapy resistance in HCC

In recent years, non-coding RNAs, including miRNAs, circRNAs, and lncRNAs, have emerged as key regulators of immune evasion and resistance to immunotherapy in HCC.[22] Unlike conventional mRNAs, circRNAs are characterized by their covalently closed loop structure, which confers increased stability compared to linear RNAs. This structural stability allows circRNAs to regulate gene expression post-transcriptionally, particularly by acting as miRNA sponges.[88]

In HCC, Chen *et al*.[89] demonstrated that the circRNA circPRDM4 is significantly influenced by hypoxia. The study reveals that circPRDM4 upregulates PD-L1 expression via the hypoxia-inducible factor-1 alpha pathway. While this increased PD-L1 expression is typically associated with a favorable response to anti–PD-1 immunotherapy and positive prognostic indicators, it simultaneously triggers downstream mechanisms that suppress the immune system's ability to attack malignant cells, ultimately facilitating immune evasion.[89]

lncRNAs are another class of non-coding RNAs implicated in immunotherapy resistance. Studies on HCC have shown upregulated lncRNAs such as HULC and HOTAIR. HULC may promote angiogenesis and carcinogenesis by inducing cell proliferation and activating the CREB transcription factor, key processes, whereas HOTAIR contributes to maintaining the TME by promoting CCL2 expression. Notably, the absence of HOTAIR has been associated with increased sensitivity of HCC to chemotherapy.[90] Hence, the lncRNA HOTAIR is involved in the epigenetic regulation of immune-related genes by enhancing the immune-suppressive phenotype of HCC tumors. For instance, the lncRNA MALAT1 has been shown to regulate immune checkpoint expression, particularly by modulating PD-L1 expression in tumor cells, thus contributing to immune evasion.[91]

These non-coding RNAs, by regulating various immune checkpoints and modulating the TME, are crucial in resistance to immune therapies such as ICIs, thus complicating the treatment of HCC.

Ethical and implementation challenges in genetic research

There are significant privacy and security concerns regarding the collection, storage, and use of genetic data. Preventing genetic discrimination and controlling the possible psychological effects on patients who learn of their risks are among the ethical considerations. Ensuring that patient data is securely maintained and handled ethically, and establishing rules and regulations for the storage of individuals' genetic information, are essential to preserving public confidence in genomic medicine.[92]

The implementation of genetic research, particularly in fields such as multi-omics, liquid biopsy, and biomarker validation, presents a range of ethical, legal, and social challenges. As this research involves sensitive patient data, including genetic information, addressing these issues is critical for the widespread adoption of these technologies. Therefore, concrete solutions to the major ethical challenges should be studied and managed as follows:

Data privacy and protection

Ensuring that personal data, including genetic information, is protected from unauthorized access, misuse, and breaches is paramount. The sensitivity of genetic data heightens concerns about privacy and the potential for stigmatization or discrimination based on genetic predispositions. Therefore, robust data anonymization protocols and secure data-sharing mechanisms to ensure patient privacy should be established. Genetic data should be de-identified and stored in secure, encrypted databases with restricted access. Institutions should implement regular audits and adhere to international privacy standards, such as the General Data Protection Regulation in the European Union. National and international data-sharing agreements that allow for collaborative research while maintaining strict privacy and confidentiality should be established.[93]

Genetic counseling

Genetic research can reveal significant information about a patient's genetic predispositions, including risks for certain diseases or responses to therapies. However, the implications of such findings can be complex and may cause distress for patients. Therefore, genetic counseling should be integrated into the research process. Professional genetic counselors should provide pre- and post-test counseling to help patients understand the potential impact of their genetic results. These counselors can also assist in interpreting results, ensuring that patients are fully informed about the potential implications of genetic findings.[94]

Informed consent

Obtaining informed consent for genetic research can be difficult due to the complexity of the information involved, the potential for incidental findings, and the long-term implications of data usage. Therefore, the informed consent process should be clear, comprehensive, and understandable, and should include interactive tools (e.g., video or digital media) to explain genetic research concepts. Patients should be informed about the purpose of the study, the types of data that will be collected, and the potential risks and benefits. It is also essential to discuss the possibility of incidental findings and to ensure that patients have the right to opt out of the study at any time. Ethical guidelines should require dynamic consent models that allow participants to be informed over time about how their data are used, particularly in long-term studies. This approach may enhance transparency and ensure that participants are aware of the evolving nature of genetic research.[95,96]

Ethical issues in genetic data usage

The use of genetic data raises issues such as the potential for discrimination, biotechnology exploitation, and the commercialization of genetic information without patient consent. Additionally, there are concerns about genetic data ownership. This can be managed by specifying ethical guidelines that ensure patients retain ownership of their genetic data and have the right to revoke consent at any time. There should be transparency regarding how genetic data is used and who profits from it. Clear policies on data ownership and benefit sharing should be implemented to ensure that patients' genetic data is not used for profit without their consent. Genetic research should comply with ethical guidelines that prohibit the commercialization of genetic data without patient involvement.[97]

Precision oncology and clinical decision-making

The preceding sections established the biological and clinical relevance of gene expression–based signatures in HCC, progressing from molecular heterogeneity and prognostic stratification to immune and TME–related classification. While these signatures demonstrate robust associations with survival, recurrence risk, and immune phenotypes, their ultimate value lies in their ability to inform real-world clinical decisions. Precision oncology represents the translational bridge between molecular profiling and patient-centered care, integrating gene signatures with established clinical frameworks to guide therapeutic selection, sequencing, and surveillance strategies.[98]

At this stage, molecular risk stratification is no longer considered in isolation but is interpreted alongside tumor burden, liver function, and performance status to optimize individualized treatment pathways.[99]

In this context, Figure 4 is presented to visually synthesize how gene signature–derived risk groups and immune phenotypes can be operationalized within clinical decision-making algorithms, thereby aligning molecular insights with therapeutic choices such as locoregional therapy, targeted agents, and ICIs. Placing this figure now emphasizes the transition from prognostic knowledge to actionable precision medicine, underscoring the clinical applicability of gene signatures beyond prognostication toward treatment personalization and adaptive management in HCC.

Limitations in the clinical translation of HCC gene signatures

Despite the significant prognostic and predictive potential of HCC gene signatures, several major shortcomings currently impede their successful clinical translation. Foremost among these is profound tumor heterogeneity, which confounds accurate molecular profiling and drives drug resistance and treatment failure. Furthermore, the generalizability of these biomarkers is hindered by insufficient cross-cohort validation across diverse demographic populations, compounded by a critical lack of standardized detection platforms and reproducible assay protocols.

Therapeutic efficacy is additionally challenged by complex dynamics within the TME, notably the role of non-coding RNAs—such as circRNAs and lncRNAs—in mediating immune evasion and immunotherapy resistance. Finally, the integration of these molecular tools into routine care faces substantial ethical and implementation challenges; widespread adoption necessitates strict adherence to data privacy regulations, secure informed consent, and transparent data ownership frameworks to prevent commercial

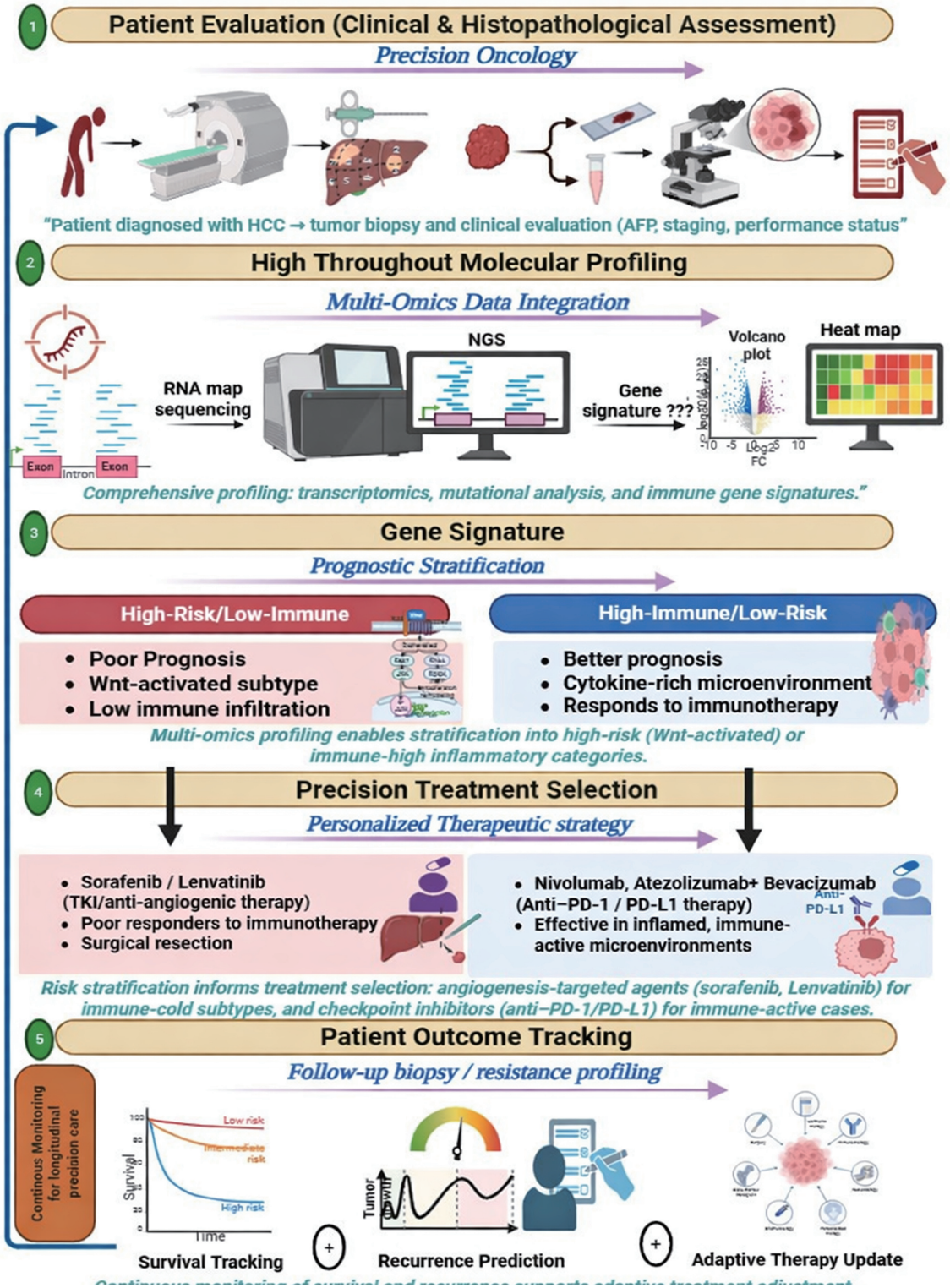

Fig. 4. Precision oncology – Gene signature–guided therapy in hepatocellular carcinoma (HCC). Precision oncology–based clinical decision-making for HCC. Patients with confirmed HCC undergo integrated clinical, histopathological, and molecular assessment. Multi-omics profiling—including RNA signatures, mutation panels, and molecular subtyping—enables stratification into high-risk immune-low (Wnt-activated) or immune-high inflammatory categories. Risk stratification informs treatment selection: angiogenesis-targeted agents (sorafenib, lenvatinib) for immune-cold subtypes, and checkpoint inhibitors (anti–PD-1/PD-L1) for immune-active cases. Early-stage disease may be managed with surgical or locoregional therapy (TACE). Continuous monitoring of survival and recurrence supports adaptive treatment adjustment and longitudinal precision care.

exploitation. Collectively, these biological, technical, and ethical limitations summarize the current gaps in clinical applicability, directly informing the targeted research priorities and multi-omics frameworks required to overcome these barriers in future investigations.

Opportunities and future directions

The rapid development of high-throughput technologies has enabled the simultaneous collection of diverse "omics" datasets—including genomics, transcriptomics (mRNA), and epigenomics (DNA methylation)—from the same biological samples. While individual omics layers offer limited insights, their integration provides a comprehensive understanding of biological systems. A multi-omics approach significantly improves the prediction of disease clinical outcomes compared with single-data analysis. Consequently, there is a critical demand for new integrated computational methods that can interact with data layers to advance disease research and personalized medicine.[100]

In order to create algorithms and models based on supervised, unsupervised, or reinforcement learning, machine learning relies on large and varied datasets, including pathology, radiological imaging, and omics data.[101] Preclinical and clinical research are used to further investigate and validate health-related patterns in HCC through AI integration in multi-omics. To find disease-related biomarkers and forecast patient outcomes, tools such as DeepOmix and MOGONET (a multi-omic graph neural network model) combine several omics data types.[100]

Methylation-expression multi-omics gene pair signatures are uniquely designed for HCC studies, providing customized approaches for predicting outcomes, diagnosing disease, and identifying potential therapeutic targets. Wang *et al*.[102] combined single-cell transcriptomics, proteomics, and epigenomics to ascertain the effects of multiple phenotypes on HCC metastasis in five HCC cell lines. These studies examine how various omics approaches can distinguish between HCC etiologies, which impact tumor growth and resistance to treatment.[102] By employing ten machine-learning algorithms to conduct a comprehensive analysis of large-scale, multi-center HCC datasets, Wen *et al*.[103] created a unified prognostic model powered by artificial intelligence known as CAIPS, which demonstrates significant clinical value in categorizing patient risk and forecasting treatment outcomes.

Conclusions

While significant strides have been made in identifying gene signatures for HCC prognosis, there remains a critical gap in translating these findings into routine clinical practice. One promising future research direction is the development of integrative multi-omics platforms that combine genomic, transcriptomic, and proteomic data with clinical parameters to create more robust and universally applicable predictive biomarkers. Additionally, the integration of liquid biopsy for continuous monitoring of tumor dynamics holds significant potential for real-time personalization of treatment regimens.

However, several clinical implementation challenges persist, particularly in ensuring data accuracy, patient confidentiality, and reproducibility across different platforms. Overcoming these barriers will require a collaborative approach between clinicians, bioinformaticians, and regulatory bodies to standardize bioinformatics pipelines, biomarker validation protocols, and clinical trial methodologies. Achieving these objectives will pave the way for the widespread adoption of precision medicine in HCC and improve outcomes for patients facing this aggressive cancer.

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Conflict of interest

Dr. Mohamed El-Kassas serves as an editorial board member of *Gene Expression*. The authors have no other conflict of interest to note.

Author contributions

Conceptualization and study design (AW, GAA, NOS and ME), resources and acquisition of data (AW and GAA), analysis and interpretation of data (AW and GAA), writing—original draft preparation (AW, GAA, NOS and ME), critical revision of the manuscript for important intellectual content (AW and GAA), and supervision (ME). All authors have read and agreed to the published version of the manuscript.

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