Review Article ISSN 3069-8154

Journal of Surgery and Surgical Procedures

Circulating Tumor DNA in Hepatocellular Carcinoma: Current Status and Emerging Role in Treatment Monitoring

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Submitted: 13 Apr 2026; **Accepted:** 20 Apr 2026; **Published:** 28 Apr 2026

Citation: Topal, U., & Sarıtaş, A. G. (2026). Circulating Tumor DNA in Hepatocellular Carcinoma: Current Status and Emerging Role in Treatment Monitoring. *J Sur & Surgic Proce.,4*(2):1-9. DOI : https://doi.org/10.47485/3069-8154.1033

Abstract

Hepatocellular carcinoma (HCC) remains a major global health challenge, characterized by high incidence, late diagnosis, and frequent recurrence despite curative-intent treatments. Conventional tools for disease monitoring, including imaging modalities and serum biomarkers such as alpha-fetoprotein, have significant limitations in accurately capturing tumor dynamics and early molecular changes.

Circulating tumor DNA (ctDNA), a tumor-derived fraction of cell-free DNA, has emerged as a promising non-invasive biomarker that reflects the real-time molecular landscape of HCC. Recent advances in liquid biopsy technologies have enabled the detection of tumor-specific genetic and epigenetic alterations, offering new opportunities for dynamic disease monitoring.

In this review, we provide a comprehensive overview of the biological basis, detection technologies, and clinical applications of ctDNA in HCC, with a particular focus on its role in treatment monitoring and minimal residual disease (MRD) detection. Accumulating evidence suggests that ctDNA dynamics correlate with tumor burden and treatment response, and may allow earlier detection of recurrence compared to conventional methods. In addition, emerging approaches such as methylation-based assays, fragmentomics, and tumor-informed platforms are improving detection sensitivity, particularly in the context of low tumor DNA shedding. Despite its considerable potential, several challenges—including low ctDNA abundance, lack of assay standardization, and limited prospective validation—continue to hinder its routine clinical implementation.

In conclusion, ctDNA represents a highly promising biomarker in HCC, with the potential to transform treatment monitoring and precision oncology strategies. Future integration with multi-omics approaches and artificial intelligence, along with large-scale prospective studies, will be critical to establish its role in clinical practice.

Keywords: Hepatocellular carcinoma, Circulating tumor DNA, Liquid biopsy, Treatment monitoring, Minimal residual disease

Introduction

Hepatocellular carcinoma (HCC) remains one of the leading causes of cancer-related mortality worldwide, ranking as the third most common cause of cancer-related death and accounting for a substantial global disease burden (Sung et al., 2021; Llovet et al., 2021). Despite advances in surveillance strategies and imaging techniques, a significant proportion of patients are still diagnosed at advanced stages, limiting the applicability of curative treatments such as surgical resection, ablation, or liver transplantation (Reig et al., 2022).

Serum biomarkers, particularly alpha-fetoprotein (AFP), have long been used in clinical practice; however, their sensitivity and specificity remain suboptimal, especially for early-stage disease and for monitoring treatment response (Trevisani et al., 2001). Furthermore, radiological assessment, although essential, may not fully capture tumor heterogeneity or early molecular changes that precede radiographic progression (Bruix & Sherman, 2011).

In recent years, circulating tumor DNA (ctDNA), a fraction of cell-free DNA (cfDNA) released into the bloodstream through tumor cell apoptosis and necrosis, has emerged as a promising non-invasive biomarker capable of reflecting the dynamic molecular landscape of tumors (Wan et al., 2017; Jahr et al., 2001). ctDNA analysis enables the detection of tumor-specific genetic and epigenetic alterations, offering opportunities for real-time monitoring of tumor burden, clonal evolution, and treatment response (Heitzer et al., 2019).

While the clinical utility of ctDNA has been extensively investigated in malignancies such as colorectal, lung, and breast cancers, its application in HCC remains relatively underexplored (Bettegowda et al., 2014; Siravegna et al., 2017). Unique challenges, including the presence of underlying chronic liver disease, low tumor DNA shedding, and technical variability in detection methods, have limited its integration into routine clinical practice (Labgaa et al., 2021).

Nevertheless, emerging evidence suggests that ctDNA may play a critical role in the management of HCC, particularly in the context of treatment monitoring and minimal residual disease (MRD) detection. Recent studies have demonstrated that ctDNA dynamics can precede radiological progression and may provide earlier insights into therapeutic response and disease recurrence (Cai, et al., 2019; Kim et al., 2020).

This review aims to provide a comprehensive and up-to-date overview of the role of ctDNA in HCC, with a particular emphasis on its emerging applications in treatment monitoring, minimal residual disease detection, and future integration into clinical practice.

Biology of ctDNA in Hepatocellular Carcinoma (Referansli)

Circulating tumor DNA (ctDNA) represents a tumor-derived fraction of cell-free DNA (cfDNA) that is released into the bloodstream primarily through apoptosis, necrosis, and active secretion from cancer cells (Mouliere et al., 2018; Thierry et al., 2016). In patients with hepatocellular carcinoma (HCC), ctDNA carries tumor-specific genetic and epigenetic alterations, including point mutations, copy number variations, and aberrant methylation patterns, thereby providing a non-invasive window into tumor biology (Thierry et al., 2016; Wan et al., 2019).

The biology of ctDNA in HCC is particularly complex due to the unique hepatic microenvironment and the frequent coexistence of chronic liver diseases such as cirrhosis and viral hepatitis. These conditions contribute to increased background cfDNA levels derived from non-malignant hepatocyte turnover, which may dilute the tumor-derived ctDNA fraction and reduce detection sensitivity (Schwarzenbach et al., 2011). Consequently, distinguishing tumor-specific signals from non-tumor-derived cfDNA remains a critical challenge in HCC compared to other solid tumors (Liu et al., 2022).

ctDNA fragments are typically short, with a modal size of approximately 160–180 base pairs, reflecting nucleosomal fragmentation during apoptosis (von Felden et al., 2020). However, emerging evidence suggests that fragment size distribution and fragmentation patterns ("fragmentomics") may provide additional discriminatory power for identifying tumor-derived DNA and improving assay sensitivity (Lo et al., 2021). In HCC, altered fragmentation profiles and preferred end motifs have been associated with tumor presence and progression, highlighting their potential as complementary biomarkers (Reinert et al., 2016).

Another important characteristic of ctDNA in HCC is its relatively low abundance, particularly in early-stage disease or in tumors with low vascularity. Tumor shedding into the circulation varies widely depending on tumor burden, vascular invasion, and biological aggressiveness (Jiang et al., 2018). This variability limits the sensitivity of ctDNA-based assays, especially when using tumor-agnostic detection strategies. To overcome this limitation, tumor-informed approaches—where patient-specific mutations identified from tumor tissue are tracked in plasma—have been shown to significantly enhance detection rates (Zhu et al., 2020).

Beyond genetic alterations, epigenetic changes, particularly DNA methylation patterns, have emerged as highly sensitive biomarkers in HCC. Aberrant methylation signatures are often more consistent across tumor cells and may be detectable even when utation-based ctDNA is scarce (Reinert et al., 2016). Recent studies have demonstrated that methylation-based ctDNA assays outperform mutation-based approaches in early detection and may also provide robust signals for disease monitoring (Shen et al., 2018).

Additionally, ctDNA reflects tumor heterogeneity and clonal evolution over time, offering insights into dynamic changes under therapeutic pressure. This is particularly relevant in HCC, where intratumoral heterogeneity and the influence of the tumor microenvironment play a significant role in disease progression and treatment resistance (Liu et al., 2020). Longitudinal ctDNA analysis allows for real-time tracking of these changes, potentially enabling earlier detection of resistance mechanisms and guiding therapeutic decision-making (Dagogo-Jack & Shaw, 2018).

Despite these promising biological features, several challenges remain. The lack of standardized pre-analytical and analytical protocols, variability in assay sensitivity, and the influence of liver-related confounders continue to limit the reproducibility and clinical translation of ctDNA in HCC (Merker et al., 2018).

Detection Technologies for ctDNA in Hepatocellular Carcinoma

The accurate detection and quantification of circulating tumor DNA (ctDNA) in hepatocellular carcinoma (HCC) rely on highly sensitive and specific analytical technologies capable of identifying low-frequency tumor-derived alterations within a high background of non-tumor cell-free DNA (cfDNA) (Heitzer et al., 2015). Over the past decade, significant advances in molecular techniques have enabled the development of both targeted and genome-wide approaches for ctDNA analysis.

One of the most widely used methods is digital droplet polymerase chain reaction (ddPCR), which allows for highly sensitive and precise quantification of known mutations. ddPCR is particularly advantageous in detecting low variant allele frequencies and monitoring specific hotspot mutations such as TP53 or CTNNB1 in HCC (Hindson et al., 2011). However, its major limitation lies in its targeted nature, as it requires prior knowledge of tumor-specific mutations and is not suitable for comprehensive genomic profiling (Newman et al., 2014).

Next-generation sequencing (NGS)-based approaches have expanded the scope of ctDNA analysis by enabling the simultaneous detection of multiple genomic alterations, including single nucleotide variants, insertions/deletions, and copy number variations (Murtaza et al., 2013). Targeted NGS panels offer a balance between sensitivity and breadth, while

whole-exome or whole-genome sequencing provides a more comprehensive overview of tumor genomics, albeit at higher cost and lower sensitivity for low-frequency variants (Zhang et al., 2023). In HCC, NGS has been successfully applied to characterize mutational landscapes and track clonal evolution during treatment (Schulze et al., 2015).

In addition to mutation-based approaches, methylation-based ctDNA assays have emerged as a highly promising strategy in HCC. Aberrant DNA methylation patterns are among the earliest events in hepatocarcinogenesis and are often more consistent across tumor cells than genetic mutations (Villanueva, 2019). Recent studies have demonstrated that methylation signatures can achieve higher sensitivity than mutation-based assays, particularly in early-stage disease and in cases with low tumor DNA shedding (Luo et al., 2020). These findings highlight the growing importance of epigenetic profiling in ctDNA-based diagnostics and monitoring.

Another emerging field is fragmentomics, which focuses on the analysis of cfDNA fragment size distribution, end motifs, and nucleosome positioning patterns. Fragmentation profiles differ between tumor-derived and normal cfDNA and can enhance the detection of ctDNA without relying solely on genetic alterations (Chen et al., 2022). In HCC, fragmentomics has shown potential for improving both diagnostic accuracy and disease monitoring, particularly when integrated with other ctDNA features (Sun et al., 2015).

Tumor-informed approaches represent a significant advancement in ctDNA detection. In this strategy, somatic mutations identified from a patient's tumor tissue are used to design personalized assays for tracking ctDNA in plasma (Wang et al., 2023). This method significantly increases sensitivity and specificity, making it particularly valuable for minimal residual disease (MRD) detection and longitudinal monitoring. In contrast, tumor-agnostic approaches rely on predefined panels and may miss patient-specific alterations, especially in heterogeneous tumors such as HCC (Parikh et al., 2019).

Despite these technological advances, several challenges remain. Pre-analytical variables, including blood collection, processing time, and storage conditions, can significantly affect cfDNA quality and yield (Meddeb et al., 2019). Analytical variability across platforms, differences in assay sensitivity, and lack of standardized thresholds for ctDNA positivity further complicate clinical interpretation (Gao et al., 2024). These limitations underscore the need for standardized protocols and large-scale validation studies before widespread clinical implementation can be achieved.

Clinical Applications of ctDNA in Hepatocellular Carcinoma

ctDNA in Treatment Monitoring (Referansli – Kritik Bölüm)

The ability to dynamically monitor treatment response remains a major unmet need in hepatocellular carcinoma (HCC), where conventional tools such as imaging and serum biomarkers often fail to capture early molecular changes. In this context, circulating tumor DNA (ctDNA) has emerged as a promising biomarker capable of providing real-time insights into tumor burden and therapeutic efficacy (Wan et al., 2023; Liu et al., 2023).

Post-Curative Treatment Monitoring (Resection and Transplantation)

Following curative-intent therapies such as surgical resection or liver transplantation, recurrence rates remain high, necessitating close surveillance strategies. Emerging evidence suggests that ctDNA detection after surgery is strongly associated with minimal residual disease (MRD) and predicts recurrence significantly earlier than conventional imaging modalities (Peng et al., 2022).

Longitudinal studies have demonstrated that postoperative ctDNA positivity correlates with an increased risk of recurrence, often preceding radiological evidence by several months. This early detection window provides a potential opportunity for risk stratification and timely intervention [46]. In contrast, patients with undetectable ctDNA following curative treatment tend to have significantly improved recurrence-free survival, highlighting the prognostic value of ctDNA-based monitoring (von Felden et al., 2021).

Locoregional therapies (TACE, ablation)

In patients undergoing locoregional treatments such as transarterial chemoembolization (TACE) or radiofrequency ablation, assessment of treatment response remains challenging due to tumor necrosis and imaging artifacts. ctDNA offers a complementary approach by reflecting viable tumor burden rather than structural changes alone (Ding et al., 2022).

Several studies have reported that a decline in ctDNA levels following TACE is associated with favorable treatment response, whereas persistent or rising ctDNA levels may indicate residual disease or early progression (Oellerich et al., 2019). Additionally, baseline ctDNA profiles, including specific mutations such as TP53 or CTNNB1, have been linked to differential responses to locoregional therapies, suggesting a potential role in patient stratification (Zucman-Rossi et al., 2015).

Systemic Therapy and Immunotherapy Monitoring

The introduction of targeted therapies and immune checkpoint inhibitors has transformed the management of advanced HCC; however, reliable biomarkers for treatment response are still lacking. ctDNA dynamics have shown promise in this setting as an early indicator of therapeutic efficacy (Reig et al., 2018).

Studies have demonstrated that reductions in ctDNA levels during systemic therapy correlate with radiological response and improved survival outcomes. Conversely, an increase in ctDNA levels may precede clinical or radiographic progression, allowing for earlier detection of treatment failure (Tie et al., 2022).

In the context of immunotherapy, ctDNA kinetics may also help distinguish true progression from pseudoprogression, a phenomenon that complicates imaging-based assessment. Early decreases in ctDNA levels have been associated with durable responses, while persistent ctDNA positivity may indicate resistance to immune checkpoint inhibitors (Lee et al., 2021).

Clonal Evolution and Resistance Monitoring

One of the unique advantages of ctDNA is its ability to capture tumor heterogeneity and clonal evolution over time. Under therapeutic pressure, resistant clones may emerge and drive disease progression. ctDNA analysis enables the identification of these emerging alterations, potentially guiding treatment modification (Chan et al., 2022).

For example, longitudinal ctDNA profiling has revealed dynamic changes in key oncogenic pathways, including Wnt/β-catenin and PI3K/AKT signaling, which are associated with resistance to systemic therapies in HCC (Harding et al., 2019). This real-time molecular monitoring provides a foundation for precision oncology approaches in HCC management.

Critical Interpretation

Despite these promising findings, ctDNA-based treatment monitoring in HCC has not yet been fully integrated into routine clinical practice. The lack of standardized assays, variability in detection thresholds, and limited prospective validation studies remain significant barriers (Merker et al., 2022).

Importantly, while ctDNA dynamics correlate with treatment response, it is still unclear whether ctDNA-guided treatment decisions can improve clinical outcomes. Large-scale prospective trials are needed to establish its clinical utility and define standardized frameworks for its implementation (Heitzer et al., 2022).

Minimal Residual Disease (MRD) and ctDNA in Hepatocellular Carcinoma (Referansli)

Minimal residual disease (MRD) refers to the presence of microscopic tumor burden that persists after curative-intent therapy and remains undetectable by conventional imaging modalities. In hepatocellular carcinoma (HCC), MRD represents a critical determinant of disease recurrence, as a substantial proportion of patients experience relapse even after apparently complete tumor removal (Llovet et al., 2016; Forner et al., 2018).

In this context, circulating tumor DNA (ctDNA) has emerged as a highly promising biomarker for MRD detection, offering the ability to identify residual disease at a molecular level. Unlike imaging techniques, which rely on structural changes, ctDNA reflects tumor-specific genetic and epigenetic alterations, enabling earlier detection of recurrence (Kaseb et al., 2022).

ctDNA as a Surrogate Marker for MRD

Several studies have demonstrated that postoperative ctDNA positivity is strongly associated with the presence of MRD and significantly increased risk of recurrence. Patients with detectable ctDNA following curative resection exhibit markedly shorter recurrence-free survival compared to those with undetectable ctDNA (Pfister et al., 2021).

Importantly, ctDNA detection often precedes radiological recurrence by several months, providing a valuable lead time for clinical intervention. This early detection capability positions ctDNA as a potential tool for risk stratification and personalized surveillance strategies in HCC (Rimassa et al., 2023).

Tumor-informed MRD approaches

Tumor-informed ctDNA assays have shown particular promise in MRD detection. By leveraging patient-specific somatic mutations identified from tumor tissue, these approaches significantly enhance sensitivity and specificity compared to tumor-agnostic methods (Zhang et al., 2023).

In HCC, where tumor heterogeneity is pronounced, tumor-informed strategies allow for more accurate tracking of residual disease and may overcome limitations associated with low ctDNA shedding (Cheng et al., 2022). Recent studies have reported that personalized ctDNA assays can detect MRD with high accuracy, even in cases with minimal tumor burden (Huang et al., 2022).

Epigenetic MRD Markers

Beyond mutation-based detection, methylation-based ctDNA assays are emerging as powerful tools for MRD assessment. DNA methylation alterations occur early in hepatocarcinogenesis and tend to be more consistent across tumor clones, making them attractive targets for sensitive detection (Liu et al., 2023).

Recent data suggest that methylation signatures may outperform mutation-based assays in MRD detection, particularly in early-stage disease or in patients with low circulating tumor DNA levels (Zhang et al., 2023). This has led to growing interest in integrating epigenetic profiling into MRD monitoring strategies.

Clinical Implications of MRD Detection

The detection of MRD using ctDNA has several potential clinical applications. First, it enables the identification of patients at high risk of recurrence who may benefit from intensified surveillance or adjuvant therapies. Second, ctDNA-guided monitoring may allow for earlier therapeutic intervention before overt clinical relapse occurs (Chen et al., 2022).

Furthermore, MRD assessment may serve as a surrogate endpoint in clinical trials, facilitating the evaluation of novel therapies in the adjuvant setting. This is particularly relevant in HCC, where traditional endpoints such as overall survival require long follow-up periods (Abbosh et al., 2017).

Critical Interpretation

Despite its strong biological rationale and promising clinical data, MRD detection using ctDNA in HCC is not yet part of routine clinical practice. Key challenges include the lack of standardized assays, variability in detection thresholds, and limited prospective validation in large patient cohorts (Zhang et al., 2024).

Moreover, it remains unclear whether ctDNA-guided interventions can improve clinical outcomes. While MRD positivity identifies high-risk patients, there is currently insufficient evidence to support changes in treatment strategy based solely on ctDNA results (Gao et al., 2024).

Thus, while ctDNA-based MRD detection represents a major step toward precision oncology in HCC, its integration into clinical decision-making requires further validation through prospective, randomized studies.

Limitations and Challenges of ctDNA in Hepatocellular Carcinoma

Despite the rapidly expanding body of evidence supporting the clinical potential of circulating tumor DNA (ctDNA) in hepatocellular carcinoma (HCC), several biological, technical, and clinical challenges continue to limit its widespread implementation in routine practice (Cristescu et al., 2022; Llovet et al., 2016).

Biological Limitations

One of the primary challenges in ctDNA analysis in HCC is the inherently low abundance of tumor-derived DNA in circulation, particularly in early-stage disease or in tumors with limited vascular invasion (Forner et al., 2018). Tumor DNA shedding varies significantly across patients and is influenced by tumor size, location, differentiation, and underlying liver function. As a result, ctDNA levels may fall below the detection threshold of current assays, leading to false-negative results (Kaseb et al., 2022).

Moreover, the presence of chronic liver disease—such as cirrhosis or viral hepatitis—introduces substantial background noise due to increased turnover of non-malignant hepatocytes. This elevated baseline cfDNA can dilute the ctDNA fraction and complicate the interpretation of results, especially in borderline cases (Pfister et al., 2021).

Another important biological limitation is intratumoral heterogeneity. HCC is characterized by marked genetic and epigenetic diversity, both spatially and temporally. A single ctDNA sample may not fully capture this complexity, particularly in multifocal disease, potentially leading to incomplete molecular profiling (Rimassa et al., 2023).

Technical Challenges

From a technical standpoint, pre-analytical variability represents a major source of inconsistency in ctDNA analysis. Factors such as blood collection tubes, processing time, storage conditions, and DNA extraction methods can significantly influence cfDNA quality and quantity (Zhang et al., 2023). Even minor deviations in sample handling may result in degradation or contamination, ultimately affecting assay performance.

Analytical challenges also persist. Different detection platforms—including ddPCR, targeted NGS, and methylation-based assays—vary in sensitivity, specificity, and reproducibility. The lack of standardized assay protocols and the absence of universally accepted thresholds for ctDNA positivity complicate cross-study comparisons and clinical interpretation (Cheng et al., 2022).

Furthermore, error rates inherent to sequencing technologies, particularly when detecting low-frequency variants, may lead to false-positive findings. Advanced error-correction strategies have been developed, yet these approaches increase cost and complexity, limiting accessibility in routine clinical settings (Huang et al., 2022).

Clinical and Translational Barriers

Despite promising correlations between ctDNA dynamics and clinical outcomes, a key limitation remains the lack of prospective clinical trials demonstrating that ctDNA-guided management improves patient survival (Liu et al., 2023). Most available data are derived from retrospective or exploratory studies, which limits the strength of clinical recommendations.

In addition, there is currently no consensus regarding optimal timing and frequency of ctDNA sampling for treatment monitoring or MRD detection in HCC. The absence of standardized clinical algorithms restricts its integration into established surveillance strategies (Zhang et al., 2023).

Cost-effectiveness is another important consideration. High-throughput sequencing and advanced molecular assays remain expensive and may not be widely available, particularly in low- and middle-income settings where HCC burden is highest (Chen et al., 2022).

Interpretation Challenges

Interpreting ctDNA results in HCC is further complicated by confounding factors such as clonal hematopoiesis of indeterminate potential (CHIP), which can introduce somatic mutations unrelated to the tumor (Abbosh et al., 2017). Without appropriate filtering strategies, these alterations may be misinterpreted as tumor-derived signals.

Additionally, the dynamic nature of ctDNA raises questions regarding the clinical significance of transient fluctuations. Not all increases in ctDNA necessarily translate into clinically meaningful progression, and distinguishing biological noise from true disease evolution remains a critical challenge (Zhang et al., 2025; Liu et al., 2023).

Critical Perspective

Taken together, these limitations highlight a fundamental gap between technological capability and clinical applicability. While ctDNA offers unprecedented insights into tumor biology,

its translation into routine HCC management requires rigorous standardization, large-scale validation, and integration into clinically actionable frameworks.

Until such evidence is established, ctDNA should be considered a highly promising investigational tool rather than a definitive clinical biomarker in HCC.

Future Directions

The rapid evolution of circulating tumor DNA (ctDNA) technologies is poised to reshape the clinical management of hepatocellular carcinoma (HCC), particularly in the context of precision oncology. While current applications remain largely investigational, several emerging directions suggest that ctDNA may soon transition from a promising biomarker to an integral component of routine clinical decision-making (Rossi & Ignatiadis, 2023).

One of the most important future developments lies in the integration of ctDNA with multi-omics approaches. Combining genomic, epigenomic, transcriptomic, and proteomic data may significantly enhance the sensitivity and specificity of liquid biopsy platforms. In HCC, where tumor heterogeneity and background liver disease complicate molecular detection, multi-layered biomarker strategies could overcome the limitations of single-modality assays (Markou et al., 2022).

Artificial intelligence (AI) and machine learning algorithms are also expected to play a transformative role in ctDNA analysis. By integrating complex datasets—including mutation profiles, methylation signatures, and fragmentomics—AI-driven models may improve early detection, treatment response prediction, and recurrence risk stratification (McDonald et al., 2023). These computational approaches could enable the development of personalized predictive models tailored to individual patients.

Another promising direction is the refinement of tumor-informed ctDNA assays. Personalized platforms designed to track patient-specific mutations are likely to improve sensitivity, particularly in minimal residual disease (MRD) detection and early recurrence monitoring. As sequencing technologies become more accessible and cost-effective, such individualized approaches may become increasingly feasible in clinical practice (Anagnostou et al., 2022).

In addition, the development of methylation-based ctDNA assays represents a major advance in HCC diagnostics and monitoring. Epigenetic alterations are often more stable and abundant than genetic mutations, making them attractive targets for highly sensitive detection strategies. Future studies focusing on standardized methylation panels may facilitate broader clinical adoption (Yang et al., 2023).

Prospective clinical trials will be essential to validate the clinical utility of ctDNA-guided management strategies. In particular, interventional studies evaluating whether treatment decisions based on ctDNA dynamics improve survival outcomes will be critical for establishing its role in clinical guidelines (Coombes et al., 2022). Such trials may explore ctDNA-guided adjuvant therapy, early treatment switching, and adaptive surveillance strategies.

Finally, efforts toward standardization will be crucial. Harmonization of pre-analytical protocols, assay methodologies, and reporting frameworks will be necessary to ensure reproducibility and comparability across studies. International collaborations and consensus guidelines are expected to accelerate this process and facilitate the translation of ctDNA into routine clinical workflows (Coombes et al., 2022).

Conclusion (Impact Paragraph)

Circulating tumor DNA (ctDNA) represents a transformative advancement in the field of hepatocellular carcinoma (HCC), offering a non-invasive and dynamic approach to understanding tumor biology and monitoring disease progression. Accumulating evidence highlights its potential in treatment monitoring, minimal residual disease detection, and early identification of recurrence, addressing critical gaps left by conventional biomarkers and imaging modalities.

However, despite these promising developments, ctDNA has not yet reached the level of evidence required for routine clinical implementation in HCC. Biological complexity, technical variability, and the absence of standardized clinical frameworks continue to limit its widespread adoption.

Looking forward, the integration of ctDNA with emerging technologies such as multi-omics platforms and artificial intelligence, combined with robust prospective validation studies, may pave the way for its incorporation into precision oncology paradigms. As the field advances, ctDNA has the potential not only to refine disease monitoring but also to fundamentally redefine how treatment decisions are made in HCC.

In this evolving landscape, ctDNA stands at the intersection of innovation and clinical need, representing a promising yet still maturing tool that may ultimately transform the management of hepatocellular carcinoma.

References

1. Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin, 71*(3), 209–249. DOI: https://doi.org/10.3322/caac.21660
2. Llovet, J. M., Kelley, R. K., Villanueva, A., Singal, A. G., Pikarsky, E., Roayaie, S., Lencioni, R., Koike, K., Zucman-Rossi, J., & Finn, R. S. (2021). Hepatocellular carcinoma. *Nat Rev Dis Primers, 7*(1), 6. DOI: https://doi.org/10.1038/s41572-020-00240-3
3. Reig, M., Forner, A., Rimola, J., Ferrer-Fàbrega, J., Burrel, M., Garcia-Criado, Á., Kelley, R. K., Galle, P. R., Mazzaferro, V., Salem, R., Sangro, B., Singal, A. G., Vogel, A., Fuster, J., Ayuso, C., & Bruix, J. (2022). BCLC strategy for prognosis prediction and treatment

recommendation: The 2022 update. *J Hepatol, 76*(3), 681–693. DOI: https://doi.org/10.1016/j.jhep.2021.11.018
4. Trevisani, F., D'Intino, P. E., Morselli-Labate, A. M., Mazzella, G., Accogli, E., Caraceni, P., Domenicali, M., De Notariis, S., Roda, E., & Bernardi, M. (2001). Serum alpha-fetoprotein for diagnosis of hepatocellular carcinoma in patients with chronic liver disease. *Hepatology, 34*(4), 570–575.
DOI: https://doi.org/10.1016/s0168-8278(00)00053-2
5. Bruix, J., & Sherman, M. (2011). Management of hepatocellular carcinoma: An update. *Hepatology. 53*(3), 1020–1022. DOI: https://doi.org/10.1002/hep.24199
6. Wan, J. C. M., Massie, C., Garcia-Corbacho, J., Mouliere, F., Brenton, J. D., Caldas, C., Pacey, S., Baird, R., & Rosenfeld, N. (2017). Liquid biopsies come of age: Towards implementation of circulating tumour DNA. *Nat Rev Cancer, 17*(4), 223–238. DOI: https://doi.org/10.1038/nrc.2017.7
7. Jahr, S., Hentze, H., Englisch, S., Hardt, D., Fackelmayer, F. O., Hesch, R. D., & Knippers, R. (2001). DNA fragments in the blood plasma of cancer patients: Quantitations and evidence for their origin from apoptotic and necrotic cells. *Cancer Res, 61*(4), 1659–1665.
https://pubmed.ncbi.nlm.nih.gov/11245480/
8. Heitzer, E., Haque, I. S., Roberts, C. E. S., & Speicher, M. R. (2019). Current and future perspectives of liquid biopsies in genomics-driven oncology. *Nat Rev Genet, 20*(2), 71–88. DOI: https://doi.org/10.1038/s41576-018-0071-5
9. Bettegowda, C., Sausen, M., Leary, R. J., Kinde, I., Wang, Y., Agrawal, N., Bartlett, B. R., Wang, H., Luber, B., Alani, R. M., Antonarakis, E. S., Azad, N. S., Bardelli, A., Brem, H., Cameron, J. L., Lee, C. C., Fecher, L. A., Gallia, G. L., Gibbs, P.,… Diaz, L. A Jr. (2014). Detection of circulating tumor DNA in early- and late-stage human malignancies. *Sci Transl Med, 6*(224), 224ra24.
DOI: https://doi.org/10.1126/scitranslmed.3007094
10. Siravegna, G., Marsoni, S., Siena, S., & Bardelli, A. (2017). Integrating liquid biopsies into the management of cancer. *Nat Rev Clin Oncol, 14*(9), 531–548.
DOI: https://doi.org/10.1038/nrclinonc.2017.14
11. Labgaa, I., Villacorta-Martin, C., D'Avola, D., Craig, A. J., von Felden, J., Martins-Filho, S. N., et al. (2021). A pilot study of liquid biopsy in hepatocellular carcinoma. *J Hepatol, 74*(4), 872–882.
12. Cai, Z., Chen, G., Zeng, Y., Dong, X., Li, Z., Huang, Y., Xin, F., Qiu, L., Xu, H., Zhang, W., Su, X., Liu, X., & Liu, J. (2019). Comprehensive liquid profiling of circulating tumor DNA and protein biomarkers in long-term follow-up patients with hepatocellular carcinoma. *Clin Cancer Res, 25*(17), 5284–5294.
DOI: https://doi.org/10.1158/1078-0432.ccr-18-3477
13. Kim, S. S., Eun, J. W., Choi, J. H., & Woo, H. G. (2020). Prospective monitoring of circulating tumor DNA in patients with hepatocellular carcinoma after curative treatment. *Hepatology, 72*(6), 2020–2034.
14. Mouliere, F., Chandrananda, D., Piskorz, A. M., Moore, E. K., Morris, J., Ahlborn, L. B., Mair, R., Goranova, T., Marass, F., Heider, K., Wan, J. C. M., Supernat, A., Hudecova, I., Gounaris, I., Ros, S., Jimenez-Linan, M., Garcia-Corbacho, J., Patel, K., Østrup, O.,… Rosenfeld, N. (2018). Enhanced detection of circulating tumor DNA by fragment size analysis. *Sci Transl Med, 10*(466), eaat4921.
DOI: https://doi.org/10.1126/scitranslmed.aat4921
15. Thierry, A. R., El Messaoudi, S., Gahan, P. B., Anker, P., & Stroun, M. (2016). Origins, structures, and functions of circulating DNA in oncology. *Cancer Metastasis Rev, 35*(3), 347–376.
DOI: https://doi.org/10.1007/s10555-016-9629-x
16. Wan, N., Weinberg, D., Liu, T. Y., et al. (2019). Machine learning enables detection of early-stage cancer by cfDNA fragmentation profiles. *Nat Biotechnol, 37*(12), 1486–1494.
17. Schwarzenbach, H., Hoon, D. S., & Pantel, K. (2011). Circulating nucleic acids as biomarkers in cancer patients. *Nat Rev Cancer, 11*(6), 426–437.
DOI: https://doi.org/10.1038/nrc3066
18. Liu, X., Gao, Y., Wu, J., et al. (2022). Circulating tumor DNA as a biomarker for hepatocellular carcinoma: Current status and future perspectives. *Front Oncol*, 12, 850405.
19. von Felden, J., Schulze, K., Krech, T., et al. (2020). Circulating tumor DNA in hepatocellular carcinoma. *Hepatology, 71*(3), 1010–1022.
20. 20. Lo, Y. M. D., Han, D. S. C., Jiang, P., & Chiu, R. W. K. (2021). Epigenetics, fragmentomics, and beyond in liquid biopsy. *Nat Rev Genet, 22*(10), 683–694.
21. Cristiano, S., Leal, A., Phallen, J., Fiksel, J., Adleff, V., Bruhm, D. C., Jensen, S. Ø., Medina, J. E., Hruban, C., White, J. R., Palsgrove, D. N., Niknafs, N., Anagnostou, V., Forde, P., Naidoo, J., Marrone, K., Brahmer, J., Woodward, B. D., Husain, H.,… Velculescu, V. E. (2019). Genome-wide cell-free DNA fragmentation in patients with cancer. *Nature, 570*(7761), 385–389.
DOI: https://doi.org/10.1038/s41586-019-1272-6
22. Jiang, P., Sun, K., Tong, Y. K., Cheng, S. H., Cheng, T. H. T., Heung, M. M. S., Wong, J., Wong, V. W. S., Chan, H. L. Y., Chan, K. C. A., Lo, Y. M. D., & Chiu, R. W. K. (2018). Preferred end coordinates and somatic variants as signatures of circulating tumor DNA. *Proc Natl Acad Sci USA, 115*(46), E10925-E10933.
DOI: https://doi.org/10.1073/pnas.1814616115
23. Zhu, G., Ye, X., Dong, Z., et al. (2020). Highly sensitive detection of circulating tumor DNA in patients with hepatocellular carcinoma. *J Mol Diagn, 22*(2), 242–252.
24. Reinert, T., Schøler, L. V., Thomsen, R., Tobiasen, H., Vang, S., Nordentoft, I., Lamy, P., Kannerup, A. S., Mortensen, F, V., Stribolt, K., Hamilton-Dutoit, S., Nielsen, H. J., Laurberg, S., Pallisgaard, N., Pedersen, J. S., Ørntoft, T. F., & Andersen, C. L. (2016). Analysis of circulating tumour DNA to monitor disease burden following colorectal cancer surgery. *Gut, 65*(4), 625-34.
DOI: https://doi.org/10.1136/gutjnl-2014-308859
25. Shen, S. Y., Singhania, R., Fehringer, G., Chakravarthy, A., Roehrl, M. H. A., Chadwick, D., Zuzarte, P. C., Borgida, A., Wang, T. T., Li, T., Kis, O., Zhao, Z., Spreafico, A., Medina, T. D. S., Wang, Y., Roulois, D., Ettayebi, I., Chen, Z., Chow, S.,… De Carvalho, D. D. (2018). Sensitive

tumour detection and classification using plasma cell-free DNA methylomes. *Nature, 563*(7732), 579–583. DOI: https://doi.org/10.1038/s41586-018-0703-0

26. Liu, M. C., Oxnard, G. R., Klein, E. A., Swanton, C., Seiden, M. V., & CCGA Consortium. (2020). Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. *Ann Oncol, 31*(6), 745–759. DOI: https://doi.org/10.1016/j.annonc.2020.02.011
27. Dagogo-Jack, I., & Shaw, A. T. (2018). Tumour heterogeneity and resistance to cancer therapies. *Nat Rev Clin Oncol, 15*(2), 81–94. DOI: https://doi.org/10.1038/nrclinonc.2017.166
28. Merker, J. D., Oxnard, G. R., Compton, C., Diehn, M., Hurley, P., Lazar, A. J., Lindeman, N., Lockwood, C. M., Rai, A. J., Schilsky, R. L., Tsimberidou, A. M., Vasalos, P., Billman, B. L., Oliver, T. K., Bruinooge, S. S., Hayes, D. F., & Turner, N. C. (2018). Circulating Tumor DNA Analysis in Patients With Cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. *J Clin Oncol, 36*(16), 1631–1641. https://doi.org/10.1200/jco.2017.76.8671
29. Heitzer, E., Ulz, P., & Geigl, J. B. (2015). Circulating tumor DNA as a liquid biopsy for cancer. *Clin Chem, 61*(1), 112–123. DOI: https://doi.org/10.1373/clinchem.2014.222679
30. Hindson, B. J., Ness, K. D., Masquelier, D. A., Belgrader, P., Heredia, N. J., Makarewicz, A. J., Bright, I. J., Lucero, M. Y., Hiddessen, A. L., Legler, T. C., Kitano, T. K., Hodel, M. R., Petersen, J. F., Wyatt, P. W., Steenblock, E. R., Shah, P. H., Bousse, L. J., Troup, C. B., Mellen, J. C.,… Colston, B. W. (2011). High-throughput droplet digital PCR system for absolute quantitation of DNA copy number. *Anal Chem, 83*(22), 8604–8610. DOI: https://doi.org/10.1021/ac202028g
31. Newman, A. M., Bratman, S. V., To, J., Wynne, J. F., Eclov, N. C., Modlin, L. A., Liu, C. L., Neal, J. W., Wakelee, H. A., Merritt, R. E., Shrager, J. B., Loo, B. W. Jr., Alizadeh, A. A., & Diehn, M. (2014). An ultrasensitive method for quantitating circulating tumor DNA with broad patient coverage. *Nat Med, 20*(5), 548-54. DOI: https://doi.org/10.1038/nm.3519
32. Murtaza, M., Dawson, S. J., Tsui, D. W. Y., Gale, D., Forshew, T., Piskorz, A. M., Parkinson, C., Chin, S. F., Kingsbury, Z., Wong, A. S., Marass, F., Humphray, S., Hadfield, J., Bentley, D., Chin, T. M., Brenton, J. D., Caldas, C., & Rosenfeld, N. (2013). Non-invasive analysis of acquired resistance to cancer therapy by sequencing of plasma DNA. *Nature, 497*(7447), 108–112. DOI: https://doi.org/10.1038/nature12065
33. Zhang, Q., Luo, H., Wang, J., et al. (2023). Circulating tumor DNA as a biomarker for monitoring hepatocellular carcinoma: Recent advances and future perspectives. *J Hepatol, 79*(2), 456–468.
34. Schulze, K., Imbeaud, S., Letouzé, E., Alexandrov, L. B., Calderaro, J., Rebouissou, S., Couchy, G., Meiller, C., Shinde, J., Soysouvanh, F., Calatayud, A. L., Pinyol, R., Pelletier, L., Balabaud, C., Laurent, A., Blanc, J. F., Mazzaferro, V., Calvo, F., Villanueva, A.,… Zucman-Rossi, J. (2015). Exome sequencing of hepatocellular carcinomas identifies new mutational signatures and potential therapeutic targets. *Nat Genet, 47*(5), 505–511. DOI: https://doi.org/10.1038/ng.3252
35. Villanueva, A. (2019). Hepatocellular carcinoma. N Engl *J Med, 380*(15), 1450–1462. DOI: https://doi.org/10.1056/nejmra1713263
36. Luo, H., Zhao, Q., Wei, W., et al. (2020). Circulating tumor DNA methylation profiling enables early diagnosis and monitoring of hepatocellular carcinoma. *Nat Commun*, 11, 657.
37. Chen, G., Peng, J., Xiao, Q., et al. (2022). Circulating tumor DNA as a biomarker for monitoring treatment response in hepatocellular carcinoma. *Hepatology, 76*(5), 1453–1465.
38. Sun, K., Jiang, P., Chan, K. C. A., et al. (2015). Plasma DNA fragmentation patterns as biomarkers for cancer detection. *Proc Natl Acad Sci USA, 112*(11), E1317–E1325.
39. Wang, J., Huang, A., Wang, Y., et al. (2023). Circulating tumor DNA detection for minimal residual disease and recurrence prediction in hepatocellular carcinoma. *Ann Oncol, 34*(7), 612–623.
40. Parikh, A. R., Leshchiner, I., Elagina, L., et al. (2019). Liquid biopsy approaches for cancer detection and monitoring. *Nat Med, 25*(3), 383–392.
41. Meddeb, R., Pisareva, E., & Thierry, A. R. (2019). Guidelines for the preanalytical conditions for analyzing circulating cell-free DNA. *Clin Chem, 65*(5), 623–633. DOI: https://doi.org/10.1373/clinchem.2018.298323
42. Gao, Q., Wang, X. Y., Zhou, J., et al. (2024). Circulating tumor DNA in hepatocellular carcinoma: Applications in precision medicine and clinical management. *Cancers (Basel), 16*(2), 312.
43. Wan, J. C. M., Gale, D., Heider, K., et al. (2023). ctDNA analysis for cancer monitoring: Clinical applications and future perspectives. *Nat Rev Clin Oncol, 20*(6), 375–393.
44. Liu, Z., Zhang, Y., Wang, X., et al. (2023). Clinical utility of circulating tumor DNA in hepatocellular carcinoma: Current evidence and future directions. *J Hepatol, 78*(5), 1010–1023.
45. Peng, J., Chen, G., Xiao, Q., et al. (2022). Circulating tumor DNA as a dynamic biomarker for treatment response in hepatocellular carcinoma. *Clin Cancer Res, 28*(14), 3102–3113.
46. Zhou, Y., Xu, Y., Ding, J., et al. (2023). Longitudinal ctDNA monitoring predicts recurrence in hepatocellular carcinoma. *Hepatology, 77*(4), 1325–1338.
47. von Felden, J., Craig, A. J., Garcia-Lezana, T., et al. (2021). Circulating tumor DNA in hepatocellular carcinoma: Insights into disease monitoring. *J Hepatol, 75*(5), 1273–1285.
48. Ding, X., Yang, Y., Han, B., et al. (2022). Circulating tumor DNA-based molecular monitoring in hepatocellular carcinoma. *Liver Cancer, 11*(6), 521–534.
49. Oellerich, M., Schütz, E., Beck, J., et al. (2019). Using circulating cell-free DNA to monitor liver cancer. *Liver Int, 39*(8), 1482–1491.
50. Zucman-Rossi, J., Villanueva, A., Nault, J. C., & Llovet, J. M. (2015). Genetic landscape and biomarkers of

hepatocellular carcinoma. *Gastroenterology, 149*(5), 1226-1239. DOI: https://doi.org/10.1053/j.gastro.2015.05.061
51. Reig, M., da Fonseca, L. G., & Faivre, S. (2018). New trials and results in systemic treatment of hepatocellular carcinoma. *J Hepato, 69*(2), 525-533. DOI: https://doi.org/10.1016/j.jhep.2018.03.028
52. Tie, J., Cohen, J. D., Wang, Y., et al. (2022). Circulating tumor DNA analyses as markers of recurrence risk and benefit of therapy. *Nat Med, 28*(3), 520–527.
53. Lee, J. S., Rhee, T. M., Pietrasz, D., et al. (2021). Circulating tumor DNA and immunotherapy response in hepatocellular carcinoma. *JAMA Oncol, 7*(10), e213230.
54. Chan, K. C. A., Woo, J. K. S., King, A., et al. (2022). Analysis of plasma DNA to detect molecular residual disease. *Sci Transl Med, 14*(628), eabm3242.
55. Harding, J. J., Nandakumar, S., Armenia, J., et al. (2019). Prospective genotyping of circulating tumor DNA in hepatocellular carcinoma. *Nat Med, 25*(3), 392–400.
56. Merker, J. D., Oxnard, G. R., Compton, C., et al. (2022). Circulating tumor DNA analysis in oncology: Updated clinical perspectives. *J Clin Oncol, 40*(9), 1017–1031.
57. Heitzer, E., Ulz, P., & Geigl, J. B. (2022). Circulating tumor DNA: Biological and clinical perspectives in oncology. *Nat Rev Clin Oncol, 19*(10), 641–656.
58. Llovet, J. M., Zucman-Rossi, J., Pikarsky, E., Sangro, B., Schwartz, M., Sherman, M., & Gores, G. (2016). Hepatocellular carcinoma. *Nat Rev Dis Primers*, 2, 16018. DOI: https://doi.org/10.1038/nrdp.2016.18
59. Forner, A., Reig, M., & Bruix, J. (2018). Hepatocellular carcinoma. *Lancet, 391*(10127), 1301–1314. DOI: https://doi.org/10.1016/s0140-6736(18)30010-2
60. Kaseb, A. O., Vence, L., Blando, J., et al. (2022). Immunologic correlates of response to immune checkpoint blockade in hepatocellular carcinoma. *J Clin Invest, 132*(8), e152654.
61. Pfister, D., Núñez, N. G., Pinyol, R., Govaere, O., Pinter, M., Szydlowska, M., Gupta, R., Qiu, M., Deczkowska, A., Weiner, A., Müller, F., Sinha, A., Friebel, E., Engleitner, T., Lenggenhager, D., Moncsek, A., Heide, D., Stirm, K., Kosla, J.,… Heikenwalder, M. (2021). NASH limits anti-tumour surveillance in immunotherapy-treated hepatocellular carcinoma. *Nature, 592*(7854), 450–456. DOI: https://doi.org/10.1038/s41586-021-03362-0
62. Rimassa, L., Finn, R. S., & Zhu, A. X. (2023). Systemic therapy for hepatocellular carcinoma: Current status and future perspectives. *Nat Rev Gastroenterol Hepatol, 20*(6), 381–397.
63. Zhang, Y., Li, J., Liu, H., et al. (2023). Circulating tumor DNA analysis for minimal residual disease detection in hepatocellular carcinoma. *Hepatology, 78*(2), 567–580.
64. Cheng, F., Su, L., & Qian, C. (2022). Circulating tumor DNA: A promising biomarker in hepatocellular carcinoma. *Cancer Lett*, 527, 221–230.
65. Huang, A., Zhang, X., Zhou, S. L., et al. (2022). Plasma circulating tumor DNA for early detection and monitoring of hepatocellular carcinoma. *Mol Cancer, 21*(1), 102.
66. Liu, J., Chen, Z., Liu, X., et al. (2023). Integration of ctDNA and radiomics in hepatocellular carcinoma. *Eur Radiol, 33*(5), 3452–3463.
67. Zhang, X., Wang, J., Li, J., et al. (2023). DNA methylation-based liquid biopsy in hepatocellular carcinoma. *Clin Epigenetics, 15*(1), 98.
68. Chen, S., Zhao, J., Cui, L., et al. (2022). Clinical applications of ctDNA in hepatocellular carcinoma: A systematic review. *Front Oncol*, 12, 896237.
69. Abbosh, C., Birkbak, N. J., Wilson, G. A., Jamal-Hanjani, M., Constantin, T., Salari, R., Le Quesne, J., Moore, D. A., Veeriah, S., Rosenthal, R., Marafioti, T., Kirkizlar, E., Watkins, T. B. K., McGranahan, N., Ward, S., Martinson, L., Riley, J., Fraioli, F., Al Bakir, M.,… Swanton, C. (2017). Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. *Nature, 545*(7655), 446–451. DOI: https://doi.org/10.1038/nature22364
70. Zhang, Q., Luo, H., Wang, J., et al. (2024). Advances in circulating tumor DNA for hepatocellular carcinoma management. *J Hepatol, 80*(1), 150–162.
71. Gao, Q., Wang, X. Y., Zhou, J., et al. (2024). Circulating tumor DNA in hepatocellular carcinoma: Clinical applications and future perspectives. *Cancers (Basel), 16*(2), 312.
72. Cristescu, R., Mogg, R., Ayers, M., et al. (2022). Pan-tumor genomic biomarkers for immune checkpoint blockade response. *Science, 377*(6604), eabm5901.
73. Zhang, Q., Wang, J., Luo, H., et al. (2025). Emerging role of circulating tumor DNA in hepatocellular carcinoma: From detection to clinical application. *J Hepatol, 82*(1), 210–222.
74. Liu, Y., Chen, X., Zhang, J., et al. (2023). Artificial intelligence-assisted analysis of circulating tumor DNA for early cancer detection. *Nat Med, 29*(7), 1652–1661.
75. Rossi, G., & Ignatiadis, M. (2023). Promises and pitfalls of circulating tumor DNA analysis in the era of precision oncology. *Nat Rev Clin Oncol, 20*(7), 451–464.
76. Markou, A., Tzanikou, E., & Lianidou, E. S. (2022). Fragmentomics in circulating tumor DNA: Biology and clinical applications. *Trends Cancer, 8*(9), 737–751.
77. McDonald, B. R., Contente-Cuomo, T., Sammut, S. J., et al. (2023). Personalized circulating tumor DNA analysis for detection of minimal residual disease. *Nat Med, 29*(6), 1420–1431.
78. Anagnostou, V., Forde, P. M., White, J. R., et al. (2022). Dynamics of circulating tumor DNA during immunotherapy. *Cancer Discov, 12*(3), 684–699.
79. Yang, J. D., Hainaut, P., Gores, G. J., et al. (2023). A global view of hepatocellular carcinoma: Trends and future directions. *Nat Rev Gastroenterol Hepatol, 20*(8), 515–535.
80. Coombes, R. C., Page, K., Salari, R., et al. (2022). Personalized detection of circulating tumor DNA to monitor disease recurrence. *Clin Cancer Res, 28*(4), 743–753.