Cancer Genetics and Epigenetics 2024, Vol.12, No.3, 125-136
http://medscipublisher.com/index.php/cge

Review Article Open Access

Prospects of Precision Treatment for Liver Cancer Based on Genome-Wide Association Studies

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Cancer Genetics and Epigenetics, 2024, Vol.12, No.3 doi: 10.5376/cge.2024.12.0015
Received: 26 Mar., 2024
Accepted: 05 May, 2024
Published: 18 May, 2024

Preferred citation for this article:
Li M.M., 2024, Prospects of precision treatment for liver cancer based on genome-wide association studies, Cancer Genetics and Epigenetics, 12(3): 126-136 (doi: 10.5376/cge.2024.12.0015)

Abstract Liver cancer remains a significant global health challenge, necessitating advanced treatment strategies such as precision medicine. This study explores the potential of genome-wide association studies (GWAS) to enhance precision treatment for liver cancer. It provides a comprehensive study of the progress in liver cancer research, highlighting advancements in molecular profiling, identification of molecular subtypes, and genomic alterations. It delves into the genetic insights gained from GWAS, including significant genetic variants and epigenetic factors. The study also discusses how to integrate GWAS findings into clinical practice, emphasizing translational research, personalized treatment plans, and clinical implementation. Case studies and clinical trials are presented to showcase successful implementations, ongoing trials, and lessons learned. Current challenges in precision treatment, such as tumor heterogeneity, drug resistance, and data interpretation, are examined. Additionally, the study studys advances in technology and methodology, including next-generation sequencing (NGS), CRISPR and genome editing, and bioinformatics. Future perspectives, including emerging therapies, the role of artificial intelligence, and the importance of collaborative research, are discussed. This study underscores the transformative potential of GWAS in liver cancer treatment and highlights the need for continued research and technological innovation.
Keywords Liver cancer; Precision medicine; Genome-wide association studies (GWAS); Personalized treatment; Genetic variants

1 Introduction

Liver cancer is a significant global health concern, ranking as the third leading cause of cancer-related deaths worldwide (Nakagawa et al., 2019). The disease is characterized by its high heterogeneity and poor prognosis, with various etiological factors such as hepatitis B and C infections, aflatoxin exposure, alcohol consumption, and metabolic diseases contributing to its development (Yi and Sahni, 2017). Despite advances in understanding the molecular mechanisms underlying liver cancer, early diagnosis remains challenging, and the survival rate is notably low due to rapid disease progression and limited effective treatment options.

Precision medicine represents a paradigm shift in cancer treatment, moving away from one-size-fits-all approaches to more personalized strategies that consider individual genetic, environmental, and lifestyle factors (Zugazagoitia et al., 2016). This approach has shown promise in improving treatment outcomes by targeting specific molecular alterations within tumors. Precision oncology, a subset of precision medicine, involves the use of genomic and molecular profiling to guide the selection of targeted therapies and immunotherapies, thereby optimizing treatment efficacy and minimizing adverse effects (Sicklick et al., 2019). However, challenges such as tumor heterogeneity, acquired resistance, and the complexity of interpreting large genomic datasets remain significant hurdles.

Genome-Wide Association Studies (GWAS) have emerged as a powerful tool in identifying genetic variants associated with various diseases, including liver cancer. By analyzing the genomes of large populations, GWAS can uncover common genetic markers that contribute to disease susceptibility and progression (Tsimberidou et al., 2020). In liver cancer, GWAS have identified several driver genes and mutations, such as those involved in the Wnt/β-catenin pathway, TP53/cell-cycle pathways, and telomere maintenance, which are crucial for hepatocarcinogenesis. These findings provide valuable insights into the molecular underpinnings of liver cancer and offer potential targets for precision treatment (Qiu et al., 2019).

The study is to explore the prospects of precision treatment for liver cancer based on findings from Genome-Wide Association Studies. By synthesizing current research, highlight the potential of GWAS in identifying actionable genetic alterations and guiding personalized therapeutic strategies. The ultimate goal is to improve clinical outcomes for liver cancer patients through the integration of genomic data into precision medicine frameworks.

2 Progress in Liver Cancer Research

2.1 Advancements in molecular profiling

Recent advancements in molecular profiling have significantly enhanced our understanding of liver cancer and its treatment. The integration of genomic and transcriptomic profiling has been pivotal in expanding precision cancer medicine. For instance, the WINTHER trial demonstrated that both DNA and RNA profiling could improve therapy recommendations and patient outcomes by identifying actionable mutations and guiding personalized treatment strategies (Rodón et al., 2019). Similarly, the MSK-IMPACT initiative has provided comprehensive genomic data from over 10,000 patients, revealing clinically relevant somatic mutations and novel noncoding alterations that can be targeted therapeutically. These large-scale profiling efforts underscore the importance of extensive molecular characterization in developing effective precision treatments for liver cancer.

2.2 Identification of molecular subtypes

The identification of molecular subtypes in liver cancer has been a crucial step towards personalized medicine. Genome sequencing studies have classified liver cancer into distinct molecular subtypes based on somatic mutation profiles, RNA expression profiles, and DNA methylation profiles, which are associated with patient prognosis (Nakagawa et al., 2019). This classification enables the stratification of patients into subgroups that may respond differently to specific therapies. For example, the I-PREDICT study highlighted the feasibility of using tumor DNA sequencing to recommend individualized combination therapies, which improved disease control rates and survival outcomes (Sicklick et al., 2019). These findings illustrate the potential of molecular subtyping to tailor treatments to the unique genetic makeup of each patient's tumor.

2.3 Genomic alterations in liver cancer

Genomic alterations play a critical role in the pathogenesis and progression of liver cancer. Comprehensive genomic studies have identified key driver mutations and pathways involved in hepatocarcinogenesis, such as the Wnt/β-catenin pathway, TP53/cell-cycle pathways, and telomere maintenance mechanisms. Additionally, structural variants, copy-number alterations, and virus integrations, particularly HBV integration into cancer-related genes, have been recognized as significant contributors to liver cancer development. The PERMED-01 clinical trial further demonstrated that extensive molecular profiling could identify actionable genetic alterations in a majority of patients, leading to matched therapies that improve clinical outcomes (Bertucci et al., 2019). These insights into the genomic landscape of liver cancer are essential for developing targeted therapies and improving patient prognosis. In summary, the progress in liver cancer research, driven by advancements in molecular profiling, the identification of molecular subtypes, and the understanding of genomic alterations, holds great promise for the future of precision treatment in liver cancer. By leveraging these insights, researchers and clinicians can develop more effective, personalized treatment strategies that improve patient outcomes (Malone et al., 2020).

3 Genetic Insights from GWAS in Liver Cancer

3.1 Methodology of GWAS

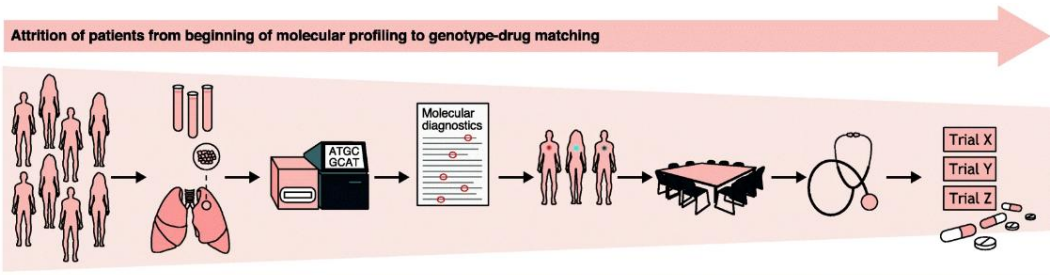
Genome-wide association studies (GWAS) have become a cornerstone in understanding the genetic underpinnings of various diseases, including liver cancer. The methodology involves scanning the entire genome of numerous individuals to identify genetic variants associated with specific traits or diseases. This approach has been instrumental in identifying biomarkers and genetic risk factors that contribute to liver cancer susceptibility and progression (Masotti et al., 2019). Typically, GWAS involves the collection of DNA samples from both affected individuals (cases) and unaffected individuals (controls). These samples are then genotyped to detect single nucleotide polymorphisms (SNPs) and other genetic variations. Advanced statistical methods are employed to analyze the data, aiming to find significant associations between genetic variants and liver cancer (Yadav et al., 2021).

3.2 Significant genetic variants identified

Several significant genetic variants have been identified through GWAS in liver cancer. Key driver genes and mutations frequently observed include those in the Wnt/β-catenin pathway, TP53/cell-cycle pathways, telomere maintenance, and chromatin regulators. Additionally, HBV integration into cancer-related genes is a notable driver event in hepatocarcinogenesis (Nakagawa et al., 2019). These genetic alterations are not limited to point mutations but also include structural variants, copy-number alterations, and virus integrations. The identification of these variants has provided valuable insights into the molecular mechanisms of liver cancer and has highlighted potential targets for precision medicine. For instance, actionable mutations have been identified that could guide the use of multi-kinase inhibitors and other targeted therapies, although the availability of molecular target therapies remains limited.

3.3 Epigenetic factors and their role

Epigenetic factors play a crucial role in the development and progression of liver cancer. DNA methylation profiles, for example, have been used to classify liver cancer subtypes and are associated with patient prognosis. Epigenetic modifications can influence gene expression without altering the DNA sequence, thereby contributing to cancer development. These modifications include DNA methylation, histone modification, and non-coding RNA regulation. The integration of epigenetic data with GWAS findings can provide a more comprehensive understanding of liver cancer biology and identify novel therapeutic targets(Figure 1). Moreover, the study of epigenetic changes in liver cancer can help in the development of biomarkers for early detection and personalized treatment strategies (Malone et al., 2019). In summary, GWAS has significantly advanced our understanding of the genetic and epigenetic landscape of liver cancer. The identification of key genetic variants and the role of epigenetic factors offer promising avenues for the development of precision treatments tailored to individual genetic profiles. Continued research in this area is essential for translating these findings into clinical practice and improving outcomes for liver cancer patients.



	Patient accrual	Sample collection	Laboratory operations	Variant interpretation	Clinical utility	Decision	Clinical interpretation	Trial matching
Examples of challenges	Patient factors: medical, logistics	Inadequacy of samples for profiling	Technical issues of NGS and other assays	Challenges with variant interpretation	Low rate of actionable results	Lack of access to MTB	Physician factors: busy clinics, lack of genomic understanding	Lack of access to drugs or clinical trials
Possible solutions	Appropriate patient selection, navigators, efficient consent and IRB aprocesses	Improvement in sample collection and processing, liquid biopsies	Advances in technology including limits of detection and coverage depth	Integrated knowledge bases, artificial intelligence tools for automation	Expansion of target identification beyond genomics	Increase availability to MTB e.g. virtual MTB	Navigators and tools to help physicians manage profiling results	Increase number and access to precision medicine trials; easier access to approved drugs

Figure 1 Molecular profiling for precision cancer therapies (Adopted from Malone et al., 2019)

Image caption: The process from genetic sequencing of patients to enrollment on genotype-matched clinical trials. MTB, molecular tumor board; IRB, institutional review board; NGS, next-generation sequencing (Adopted from Malone et al., 2019)

Malone et al. (2019) found that the process from molecular profiling to genotype-drug matching in clinical trials faces numerous challenges, leading to significant patient attrition. These challenges span various stages, including patient accrual, sample collection, laboratory operations, variant interpretation, clinical utility, decision-making, clinical interpretation, and trial matching. Specific issues include patient-related factors, inadequate sample collection, technical issues with next-generation sequencing (NGS), difficulties in variant interpretation, low rates of actionable results, lack of access to molecular tumor boards (MTBs), and insufficient access to drugs or clinical trials. Possible solutions proposed by the authors include better patient selection, improved sample processing,

technological advancements, integrated knowledge bases, expanded target identification, increased availability of MTBs, and enhanced navigation tools for physicians. These measures aim to streamline the pathway from molecular diagnostics to effective clinical trial matching, ultimately improving patient outcomes in precision medicine.

4 Integration of GWAS Findings into Clinical Practice

4.1 Translational research

Translational research bridges the gap between genome-wide association studies (GWAS) and clinical applications, enabling the identification of genetic variants that can be targeted for precision treatment in liver cancer. Recent advancements in next-generation sequencing (NGS) and GWAS have facilitated the discovery of numerous genetic mutations associated with liver cancer, such as those in the Wnt/β-catenin pathway, TP53/cell-cycle pathways, and telomere maintenance (Nakagawa et al., 2019). These findings have been instrumental in developing targeted therapies and improving patient outcomes. For instance, the I-PREDICT study demonstrated the feasibility of using tumor DNA sequencing to recommend individualized combination therapies, resulting in improved disease control and survival rates. Similarly, the integration of molecular profiling into clinical practice has shown promise in identifying actionable mutations and guiding personalized treatment plans (Malone et al., 2020).

4.2 Personalized treatment plans

Personalized treatment plans based on GWAS findings involve tailoring therapies to the genetic profile of individual patients. This approach has shown significant potential in improving treatment efficacy and patient outcomes. For example, a study on refractory metastatic solid tumor patients in China utilized comprehensive NGS testing to guide matched therapies, resulting in a notable proportion of patients achieving complete or partial remission (Wang, 2019). Additionally, the use of molecular tumor boards to discuss treatment recommendations based on genetic data has proven effective in optimizing therapy for patients with complex genetic profiles (Kato et al., 2020). The identification of biomarkers predictive of drug efficacy and tolerability through GWAS and NGS has further enhanced the ability to develop personalized treatment plans for liver cancer patients (Di Paolo et al., 2019).

4.3 Clinical implementation

The clinical implementation of GWAS findings involves several challenges, including the interpretation of complex genetic data and the integration of these findings into routine clinical practice. Despite these challenges, significant progress has been made in recent years. For instance, the establishment of multidisciplinary molecular tumor boards has facilitated the translation of genetic data into actionable treatment recommendations, leading to improved patient outcomes. Moreover, the development of bioinformatics tools and guidelines by regulatory authorities has supported the incorporation of genetic testing into clinical trials and routine practice (Di Paolo et al., 2019). The use of single-cell analysis and other advanced molecular characterization techniques has also provided deeper insights into tumor heterogeneity and resistance mechanisms, further enhancing the clinical implementation of precision medicine in liver cancer (Figure 2) (Heinrich et al., 2020). In conclusion, the integration of GWAS findings into clinical practice has the potential to revolutionize the treatment of liver cancer by enabling personalized and targeted therapies. Continued advancements in translational research, personalized treatment plans, and clinical implementation will be crucial in realizing the full potential of precision medicine for liver cancer patients (Sicklick et al., 2019).

Heinrich et al. (2020) found that single-cell analysis of the tumor immune environment in hepatocellular carcinoma (HCC) patients provides valuable insights into immune cell heterogeneity and dynamics. Through transcriptomic profiling, researchers can identify distinct immune subgroups and processes such as T cell clonality and trajectory. This approach also helps distinguish between various activation and exhaustion states of immune cells. By comparing tumor-infiltrating immune cells with those from non-tumorous sites, researchers can uncover organ-specific immune cell characteristics and understand the tumor's influence on its microenvironment. Additionally, this analysis facilitates the identification of functional suggestions, survival analyses, and subgroup

distributions. Overall, the findings highlight the complex interplay between the immune system and tumor cells, offering potential pathways for targeted therapies and improved patient outcomes in HCC.

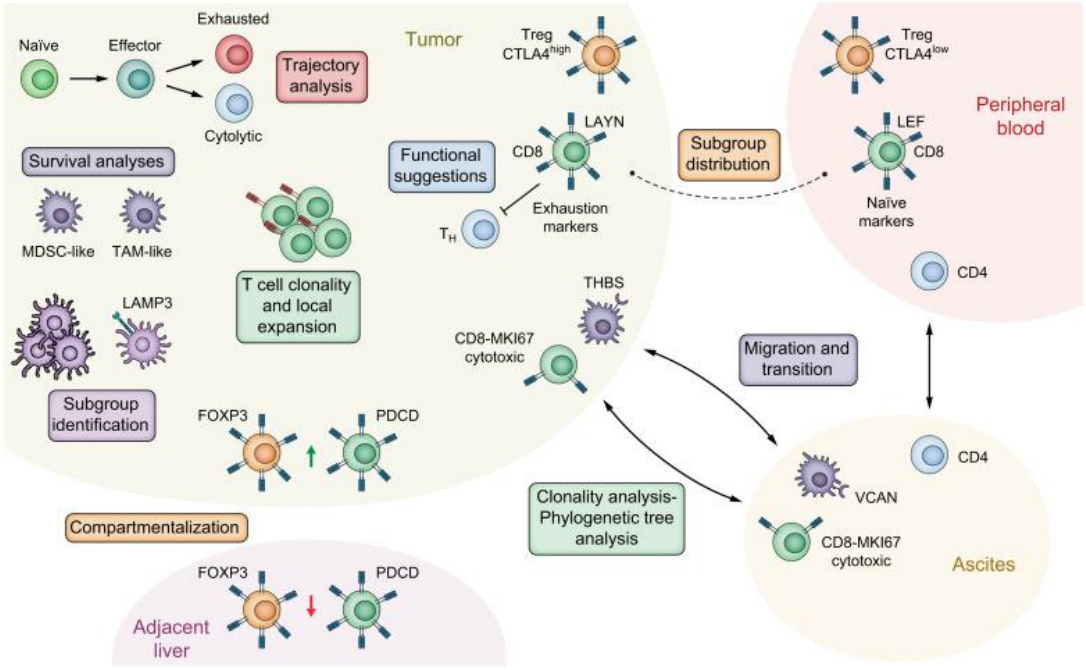


Figure 2 Tumor immune environment in HCC patients (Adopted from Heinrich et al., 2020)

Image caption: Transcriptomic profiling allows identification of immune subgroups, identification of processes like clonality and trajectory within T cells as well as identification of different states of activation and exhaustion. Comparison of tumour infiltrating immune cells with cells from non-tumourous sites can identify organ specific immune cell characteristics and gains information about tumour specific influences on its environment (Adopted from Heinrich et al., 2020)

5 Case Studies and Clinical Trials

5.1 Successful implementation

Precision treatment for liver cancer has shown promising results in several case studies and clinical trials. For instance, the WINTHER trial demonstrated that genomic and transcriptomic profiling could improve therapy recommendations and patient outcomes. In this trial, patients were navigated to therapy based on DNA sequencing or RNA expression, with a significant proportion showing stable disease or partial/complete response (Malone et al., 2020). Similarly, the I-PREDICT study highlighted the feasibility of personalized treatment with combination therapies, showing that targeting a larger fraction of identified molecular alterations correlated with improved disease control rates and longer progression-free and overall survival rates (Sicklick et al., 2019). Another successful implementation is seen in the study conducted at the Second Hospital of Tianjin Medical University, where genomic-guided individualized precision therapy was effective for a small proportion of patients with refractory metastatic solid tumors, including liver cancer. This study reported that 36.4% of patients showed complete or partial response to the treatment recommendations provided by a molecular tumor board (Wang, 2019).

5.2 Ongoing clinical trials

Several ongoing clinical trials are exploring the potential of precision treatment for liver cancer. The IMPACT 2 study is a randomized trial comparing progression-free survival in patients treated based on tumor genomic profiling versus those whose treatment was not selected based on genomic analysis. Preliminary results indicate that precision medicine is associated with favorable outcomes in selected patients (Tsimberidou et al., 2021). Additionally, the LIMORE project has developed a repository of liver cancer cell models to characterize the pharmacogenomic landscape of liver cancers. This project aims to discover gene-drug associations and predictive biomarker candidates for the selection of sorafenib-responding patients, thereby facilitating drug discovery in liver cancers (Figure 3) (Qiu et al., 2019).

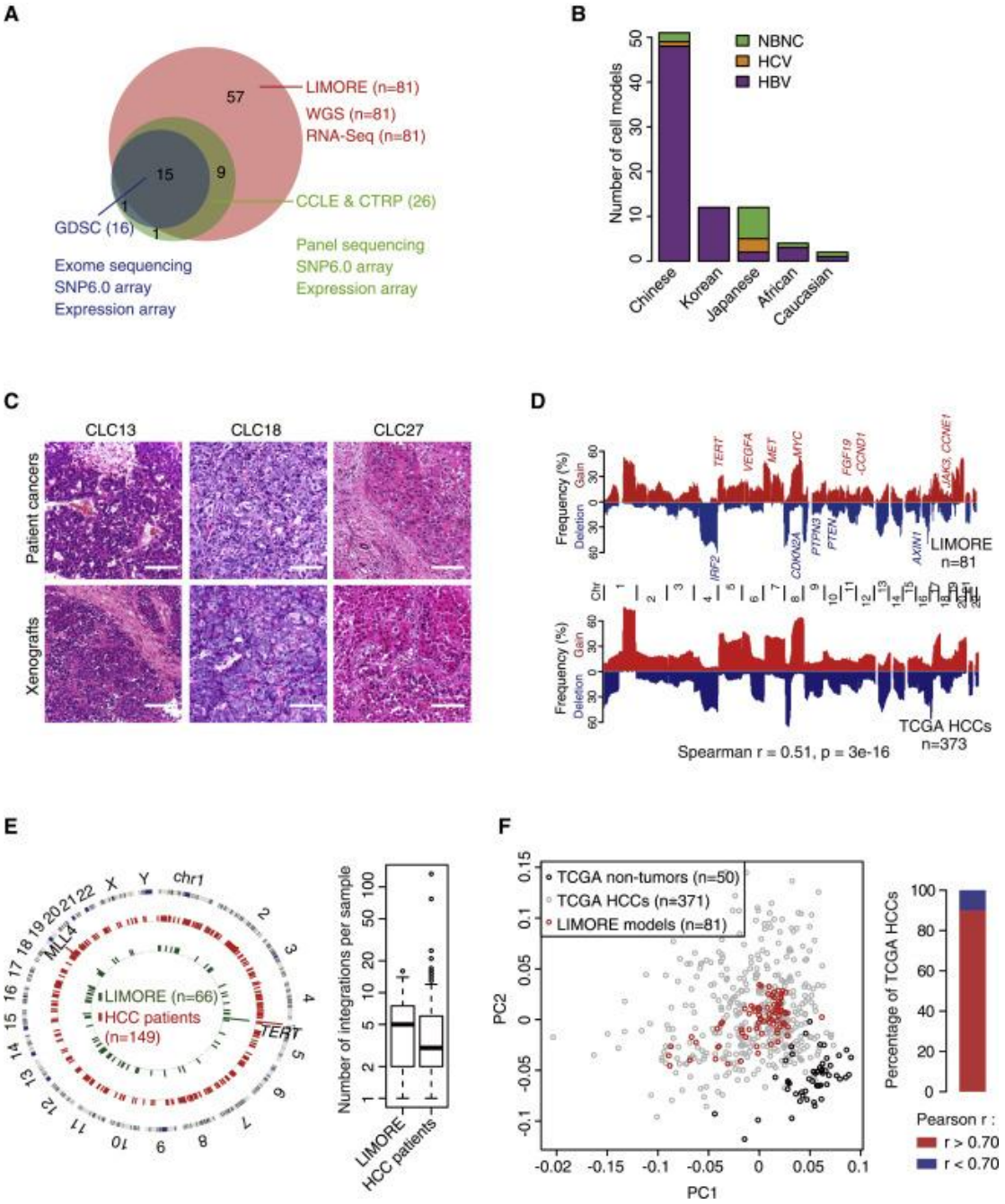


Figure 3 Comparison between LIMORE and primary liver cancers (Adopted from Qiu et al., 2019)

Image caption: (A) Numbers of cell models in LIMORE and other panels, (B) Population and virus status of patients whose tumors were used to generate LIMORE models. NBNC, non-HBV and non-HCV, (C) Representative hematoxylin and eosin stainings of subcutaneous tumors from LIMORE models and matched original cancers. Scale bars, 100 μm, (D) CNA frequencies in LIMORE and TCGA HCCs. Spearman correlation of CNA frequencies is shown. Chr, chromosome, (E) Circos plot shows HBV integration breakpoints in LIMORE and primary liver cancers (left) and box plot shows the number of HBV integrations in each LIMORE model and patient sample (right). For box-and-whisker plot, the box indicates interquartile range (IQR), the line in the box indicates the median, the whiskers indicate points within Q3 + 1.5 × IQR and Q1 – 1.5 × IQR, and the points beyond whiskers indicate outliers. Q1 and Q3 denote the first and third quartiles, respectively, (F) Comparison of gene expressions between LIMORE and TCGA HCCs. Principal component analysis using top 3,000 variable genes (left) and bar plot showing the percentage of TCGA HCCs highly correlated with at least one LIMORE model (right) (Adapted from Qiu et al., 2019)

Qiu et al. (2019) found that the LIMORE panel provides a comprehensive representation of liver cancer heterogeneity and its comparison with primary liver cancers. The study highlights the significant overlap between the LIMORE models and other established panels, indicating robust model coverage. Analysis of patient

populations revealed diverse viral statuses, including non-HBV and non-HCV cases, across different ethnic groups. The histological comparisons between LIMORE models and original cancers demonstrated consistency, reinforcing the panel's reliability. Copy number alteration (CNA) frequencies showed strong correlations between LIMORE and TCGA HCC datasets, confirming the genetic relevance of the models. The integration of HBV in LIMORE models closely mirrored that in primary liver cancers, with significant variability in integration sites and numbers. Principal component analysis (PCA) of gene expression data further validated the LIMORE panel's representativeness, as a substantial proportion of TCGA HCCs correlated highly with LIMORE models, emphasizing their utility in liver cancer research.

5.3 Lessons learned

The implementation of precision treatment for liver cancer has provided several valuable lessons. One key lesson is the importance of comprehensive molecular profiling. Studies have shown that a higher matching score, which indicates a greater alignment between identified molecular alterations and targeted therapies, correlates with better clinical outcomes (Rodón et al., 2019). This underscores the need for extensive genomic and transcriptomic analyses to guide treatment decisions. Another lesson is the necessity of a multidisciplinary approach. The involvement of molecular tumor boards, as seen in the study at the Second Hospital of Tianjin Medical University, has proven effective in improving the success rate of genomic-guided therapies. This approach ensures that treatment recommendations are based on a thorough evaluation of molecular data and clinical expertise. Furthermore, the heterogeneity of liver cancer poses a significant challenge. Precision treatment must account for the varied genetic susceptibilities, morphological diversity, and microenvironmental discrepancies of liver cancer. This requires ongoing research and the development of personalized treatment strategies that can adapt to the dynamic nature of tumor biology (Fu and Wang, 2018). In conclusion, while precision treatment for liver cancer holds great promise, its success depends on comprehensive molecular profiling, a multidisciplinary approach, and the ability to address the heterogeneity of the disease. Ongoing clinical trials and research efforts continue to refine these strategies, aiming to improve patient outcomes and expand the applicability of precision oncology.

6 Current Challenges in Precision Treatment

6.1 Tumor heterogeneity

Tumor heterogeneity remains a significant challenge in the precision treatment of liver cancer. The complexity and diversity of genetic alterations within and between tumors complicate the development of effective targeted therapies. For instance, liver cancers exhibit marked heterogeneity, which is difficult to model accurately in preclinical studies. This heterogeneity includes variations in immune microenvironment, metabolic reprogramming, and expression of drug targets, which can influence treatment outcomes (Zugazagoitia et al., 2016). Additionally, the existence of multiple subclones within a single tumor can lead to differential responses to therapy, further complicating treatment strategies (Sullivan et al., 2018).

6.2 Drug resistance

Drug resistance is another critical obstacle in the precision treatment of liver cancer (Kato et al., 2020). Many patients initially respond to targeted therapies but eventually develop resistance, leading to treatment failure. This resistance can arise from various mechanisms, including secondary mutations, activation of alternative signaling pathways, and phenotypic changes in cancer cells. For example, the underwhelming success of mutation-driven therapies in liver cancer is often due to a lack of functional insight into the genomic alterations that drive resistance. Moreover, the dynamic nature of tumor biology necessitates continuous monitoring and adaptation of treatment strategies to overcome resistance (Tsimberidou et al., 2021).

6.3 Data interpretation

The interpretation of large-scale genomic data poses a significant challenge in precision oncology. Next-generation sequencing (NGS) technologies have revolutionized the field by enabling comprehensive molecular profiling of tumors. However, the clinical utility of these data is often limited by the complexity of interpreting the results and translating them into actionable treatment plans. The integration of various molecular characterization strategies, such as transcriptomics, immunophenotyping, and single-cell analyses, can provide a

more comprehensive understanding of tumor biology but also adds to the complexity of data interpretation. Additionally, the lack of robust platforms to guide the interpretation of complex genomic data further hinders the effective implementation of precision treatment. In summary, addressing the challenges of tumor heterogeneity, drug resistance, and data interpretation is crucial for advancing the precision treatment of liver cancer. Continued research and the development of innovative strategies are essential to overcome these obstacles and improve patient outcomes (Tsimberidou et al., 2021).

7 Advances in Technology and Methodology

7.1 Next-Generation sequencing

Next-Generation Sequencing (NGS) has revolutionized the field of cancer genomics, providing a comprehensive and high-resolution view of the cancer genome. NGS technologies enable the sequencing of large numbers of nucleotides in a short time frame at an affordable cost, making it a valuable tool in both research and clinical settings (Marquardt and Andersen, 2012). The application of NGS in liver cancer has facilitated the identification of somatic and germline mutations, allowing for the classification of tumor subtypes based on genetic alterations (Wakai et al., 2018). This has led to the development of targeted therapies and personalized treatment strategies, which are crucial in the era of precision medicine (Horák et al., 2016). Despite its potential, the implementation of NGS in clinical practice faces several challenges, including the complexity of data interpretation and the need for standardization of sequencing procedures. The European Society for Medical Oncology (ESMO) has proposed recommendations for the use of NGS in oncology practice, emphasizing the importance of multigene panels and the need for quality control in routine NGS-based genomic testing. Additionally, the integration of NGS data with other molecular analyses, such as transcriptomics and epigenomics, holds promise for a more comprehensive understanding of liver cancer pathobiology.

7.2 CRISPR and genome editing

CRISPR and other genome editing technologies have emerged as powerful tools for studying and potentially treating liver cancer. These technologies allow for precise modifications of the genome, enabling researchers to investigate the functional roles of specific genes and genetic mutations in cancer development and progression. The combination of CRISPR with NGS can provide critical insights into the genetic and transcriptional heterogeneity of tumors, which is essential for understanding therapeutic resistance and relapse. Genome editing technologies also offer the potential for developing novel therapeutic strategies. For instance, CRISPR can be used to correct genetic mutations or to disrupt oncogenes, thereby inhibiting cancer growth. The integration of CRISPR with other advanced technologies, such as interaction mapping and machine learning, could further enhance our ability to identify and target key regulatory networks involved in liver cancer (Kyrochristos and Roukos, 2019).

7.3 Bioinformatics and data integration

The vast amount of data generated by NGS and other high-throughput technologies necessitates the use of advanced bioinformatics tools for data analysis and integration. Bioinformatics plays a crucial role in the interpretation of genomic data, enabling the identification of clinically actionable mutations and the prediction of patient response to targeted therapies (Shyr and Liu, 2013). The development of comprehensive knowledge bases and computational algorithms has facilitated the clinical implementation of NGS, allowing for more informed decision-making in precision oncology (Gagan and Van Allen, 2015). Data integration is also essential for overcoming the challenges posed by tumor heterogeneity and the "noise" in NGS data. By combining genomic, transcriptomic, and epigenomic data, researchers can gain a more holistic view of the molecular mechanisms underlying liver cancer. This integrative approach can help identify novel biomarkers and therapeutic targets, ultimately improving patient outcomes. In conclusion, advances in NGS, CRISPR, and bioinformatics are driving significant progress in the precision treatment of liver cancer. These technologies offer new opportunities for understanding the genetic basis of liver cancer and for developing personalized treatment strategies that are tailored to the unique molecular profiles of individual patients (Morganti et al., 2019). However, the successful implementation of these technologies in clinical practice requires ongoing efforts to address technical challenges and to ensure the standardization and validation of sequencing procedures (Colomer et al., 2020).

8 Future Perspectives

8.1 Emerging therapies

The landscape of liver cancer treatment is rapidly evolving with the advent of new therapeutic strategies. Recent advancements in genomics and molecular biomarkers have paved the way for more personalized treatment approaches. For instance, the development of immune checkpoint inhibitors such as Atezolizumab-Bevacizumab and Durvalumab-Tremelimumab has shown promising results in improving survival outcomes and enabling disease downstaging to curative resection (Moroney et al., 2023). Additionally, the integration of big 'omics' data, including genomics, transcriptomics, proteomics, and metabolomics, has facilitated the identification of new therapeutic targets and biomarkers, thereby enhancing the precision of treatment strategies. The use of targeted therapies like regorafenib, lenvatinib, and cabozantinib, along with immune checkpoint inhibitors, represents a significant leap forward in the management of hepatocellular carcinoma (HCC) (Chen et al., 2020).

8.2 Role of artificial intelligence

Artificial Intelligence (AI) is playing an increasingly pivotal role in the diagnosis, treatment, and management of liver cancer. AI technologies, including machine learning and deep learning, have demonstrated superior predictive performance compared to traditional statistical methods in various aspects of liver cancer care. For example, AI has been effectively used in predicting survival outcomes, treatment responses, and identifying prognostic factors in hepatocellular carcinoma (Lai et al., 2020). AI-driven radiogenomics, which combines radiological imaging with genomic data, has also shown great potential in stratifying patient risk, monitoring therapeutic approaches, and assessing clinical outcomes (Saxena et al., 2022). Moreover, AI applications in medical imaging diagnosis and adjuvant therapy have significantly improved the accuracy and efficiency of liver cancer management. The integration of AI in healthcare is expected to continue growing, offering new opportunities for personalized and evidence-based patient care (Rompianesi et al., 2022).

8.3 Collaborative research

The future of precision treatment for liver cancer heavily relies on collaborative research efforts. The complexity and heterogeneity of liver cancer necessitate a multidisciplinary approach involving oncologists, geneticists, bioinformaticians, and other healthcare professionals. Collaborative research initiatives are crucial for the development and validation of new biomarkers, therapeutic targets, and treatment algorithms. For instance, the establishment of public data sets related to HCC and the application of AI methods to these data sets have provided valuable insights into the mechanisms of HCC and facilitated the discovery of new drugs and biomarkers. Additionally, international collaborations and large-scale clinical trials are essential for overcoming the challenges associated with tumor heterogeneity and acquired resistance, ultimately leading to more effective and personalized treatment strategies. The integration of precision medicine and immunoprevention approaches in cancer prevention research further underscores the importance of collaborative efforts in advancing the field (Kensler et al., 2016). In conclusion, the prospects of precision treatment for liver cancer are promising, with emerging therapies, AI applications, and collaborative research playing key roles in shaping the future of liver cancer care. Continued advancements in these areas are expected to significantly improve patient outcomes and revolutionize the management of liver cancer.

9 Concluding Remarks

The exploration of precision treatment for liver cancer through genome-wide association studies (GWAS) has yielded several significant insights. Firstly, the identification of high-frequency driver genes and mutations, such as those in the Wnt/β-catenin pathway, TP53/cell-cycle pathways, telomere maintenance, and chromatin regulators, has been pivotal in understanding hepatocarcinogenesis. Additionally, the integration of HBV into cancer-related genes has been recognized as a critical driver event. Molecular classifications based on somatic mutations, RNA expression, and DNA methylation profiles have shown a strong correlation with patient prognosis, underscoring the potential of precision medicine in improving treatment outcomes. Despite these advancements, the clinical application of precision medicine in liver cancer remains challenging. The heterogeneity of liver cancer, both at the genetic and molecular levels, complicates the development of effective targeted therapies. Moreover, while next-generation sequencing (NGS) technologies have facilitated the identification of actionable mutations, the

translation of these findings into clinical practice is still limited by issues such as tumor heterogeneity and acquired resistance.

Future research should focus on several key areas to enhance the prospects of precision treatment for liver cancer. Firstly, expanding the scope of genomic and transcriptomic profiling to include a broader range of genetic alterations and their functional impacts will be crucial. This includes the exploration of noncoding regions and their role in liver cancer progression. Additionally, the development of comprehensive pharmacogenomic databases, such as the Liver Cancer Model Repository (LIMORE), can facilitate the discovery of novel gene-drug associations and predictive biomarkers. Another promising direction is the integration of multi-omics data to provide a more holistic view of tumor biology. Combining genomic, transcriptomic, proteomic, and metabolomic data can help identify new therapeutic targets and improve the accuracy of molecular classifications. Furthermore, the implementation of personalized combination therapies, as demonstrated in the I-PREDICT study, shows potential in overcoming the limitations of single-agent treatments and addressing tumor heterogeneity. Finally, the establishment of robust molecular tumor boards and the use of advanced computational tools for data analysis and interpretation will be essential in translating genomic findings into clinical practice. These efforts should be complemented by the development of adaptive clinical trial designs that can accommodate the dynamic nature of tumor biology and the evolving landscape of precision medicine.

The journey towards precision treatment for liver cancer is fraught with challenges, but the advancements in genome-wide association studies and molecular profiling offer a beacon of hope. By leveraging the power of genomics and integrating multi-omics data, we can move closer to realizing the full potential of precision medicine. The future of liver cancer treatment lies in our ability to personalize therapy based on the unique genetic and molecular landscape of each patient, ultimately improving survival rates and quality of life for those affected by this devastating disease. Continued collaboration between researchers, clinicians, and patients will be key to driving these innovations forward and achieving meaningful clinical outcomes.

Acknowledgments

The author sincere thanks to two anonymous peer reviewers for their valuable feedback on the first draft of this study.

Conflict of Interest Disclosure

The author affirms that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

References

Bertucci F., Gonçalves A., Guille A., Adélaïde J., Garnier S., Carbuccia N., Billon E., Finetti P., Sfumato P., Monneur A., Pêcheux C., Khran M., Brunelle S., Mescam L., Thomassin-Piana J., Poizat F., Charafe-Jauffret E., Turrini O., Lambaudie E., Provansal M., Extra J., Madroszyk A., Gilabert M., Sabatier R., Vicier C., Mamessier E., Chabannon C., Pakradouni J., Viens P., André F., Gravis G., Popovici C., Birnbaum D., and Chaffanet M., 2021, Prospective high-throughput genome profiling of advanced cancers: results of the PERMED-01 clinical trial, Genome Medicine, 13(1): 87.
https://doi.org/10.1186/s13073-021-00897-9

Chen B., Garmire L., Calvisi D., Chua M., Kelley R., and Chen X., 2020, Harnessing big 'omics' data and AI for drug discovery in hepatocellular carcinoma, Nature Reviews Gastroenterology and Hepatology, 17(4): 238-251.
https://doi.org/10.1038/s41575-019-0240-9

Colomer R., Mondéjar R., Romero-Laorden N., Alfranca A., Sánchez‐Madrid F., and Quintela-Fandino M., 2020, When should we order a next generation sequencing test in a patient with cancer?, EClinicalMedicine, 25: 87.
https://doi.org/10.1016/j.eclinm.2020.100487

Di Paolo A., Arrigoni E., Luci G., Cucchiara F., Danesi R., and Galimberti S., 2019, Precision medicine in lymphoma by innovative instrumental platforms, Frontiers in Oncology, 9: 1417.
https://doi.org/10.3389/fonc.2019.01417

Fu J., and Wang H., 2018, Precision diagnosis and treatment of liver cancer in China, Cancer Letters, 412: 283-288.
https://doi.org/10.1016/j.canlet.2017.10.008

Gagan J., and Van Allen E.M., 2015, Next-generation sequencing to guide cancer therapy, Genome Medicine, 7: 1-10.
https://doi.org/10.1186/s13073-015-0203-x

Heinrich S., Craig A., Ma L., Heinrich B., Greten T., and Wang X., 2020, Understanding tumor cell heterogeneity and its implication for immunotherapy in liver cancer by single cell analysis, J. Hepatol, 16: 36.

Horak, P., Fröhling, S., and Glimm, H., 2016, Integrating next-generation sequencing into clinical oncology: strategies, promises and pitfalls, ESMO Open, 1(5): e000094.
https://doi.org/10.1136/esmoopen-2016-000094

Kato S., Kim K., Lim H., Boichard A., Nikanjam M., Weihe E., Kuo D., Eskander R., Goodman A., Galanina N., Fanta P., Schwab R., Shatsky R., Plaxe S., Sharabi A., Stites E., Adashek J., Okamura R., Lee S., Lippman S., Sicklick J., and Kurzrock R., 2020, Real-world data from a molecular tumor board demonstrates improved outcomes with a precision N-of-One strategy, Nature Communications, 11(1): 4965.
https://doi.org/10.1038/s41467-020-18613-3

Kensler T., Spira A., Garber J., Szabo E., Lee J., Dong Z., Dannenberg A., Hait W., Blackburn E., Davidson N., Foti M., and Lippman S., 2016, Transforming cancer prevention through precision medicine and immune-oncology, Cancer Prevention Research, 9(1): 2-10.
https://doi.org/10.1158/1940-6207.CAPR-15-0406

Kyrochristos I.D., and Roukos D.H., 2019, Comprehensive intra-individual genomic and transcriptional heterogeneity: evidence-based colorectal cancer precision medicine, Cancer Treatment Reviews, 80: 101894.
https://doi.org/10.1016/j.ctrv.2019.101894

Lai Q., Spoletini G., Mennini G., Laureiro Z., Tsilimigras D., Pawlik T., and Rossi M., 2020, Prognostic role of artificial intelligence among patients with hepatocellular cancer: a systematic review, World Journal of Gastroenterology, 26(42): 6679.
https://doi.org/10.3748/wjg.v26.i42.6679

Malone E., Oliva M., Sabatini P., Stockley T., and Siu L., 2020, Molecular profiling for precision cancer therapies, Genome Medicine, 12: 1-19.
https://doi.org/10.1186/s13073-019-0703-1

Marquardt J.U., and Andersen J.B., 2012, Next-generation sequencing: application in liver cancer-past, present and future?, Biology, 1(2): 383-394.
https://doi.org/10.3390/biology1020383

Masotti M., Guo B., and Wu B., 2019, Pleiotropy informed adaptive association test of multiple traits using genome-wide association study summary data, Biometrics, 75(4): 1076-1085.
https://doi.org/10.1111/biom.13076

Morganti S., Tarantino P., Ferraro E., D Amico P., Viale G., Trapani D., Duso B., and Curigliano G., 2019, Complexity of genome sequencing and reporting: next generation sequencing (NGS) technologies and implementation of precision medicine in real life, Critical Reviews in Oncology/Hematology, 133: 171-182.
https://doi.org/10.1016/j.critrevonc.2018.11.008

Moroney J., Trivella J., George B., and White S., 2023, A paradigm shift in primary liver cancer therapy utilizing genomics, molecular biomarkers, and artificial intelligence, Cancers, 15(10): 2791.
https://doi.org/10.3390/cancers15102791

Nakagawa H., Fujita M., and Fujimoto A., 2019, Genome sequencing analysis of liver cancer for precision medicine, In Seminars in Cancer Biology, 55: 120-127.
https://doi.org/10.1016/j.semcancer.2018.03.004

Qiu Z., Li H., Zhang Z., Zhu Z., He S., Wang X., Wang P., Qin J., Zhuang L., Wang W., Xie F., Gu Y., Zou K., Li C., Wang C., Cen J., Chen X., Shu Y., Zhang Z., Sun L., Min L., Fu Y., Huang X., Lv H., Zhou H., Ji Y., Zhang Z., Meng Z., Shi X., Zhang H., Li Y., and Hui L., 2019, A pharmacogenomic landscape in human liver cancers, Cancer Cell, 36(2): 179-193.
https://doi.org/10.1016/j.ccell.2019.07.001

Rodón J., Soria J., Berger R., Miller W., Rubin E., Kugel A., Tsimberidou A., Saintigny P., Ackerstein A., Braña I., Loriot Y., Afshar M., Miller V., Wunder F., Bresson C., Martini J., Raynaud J., Mendelsohn J., Batist G., Onn A., Tabernero J., Schilsky R., Lazar V., Lee J., and Kurzrock R., 2019, Genomic and transcriptomic profiling expands precision cancer medicine: the WINTHER trial, Nature Medicine, 25(5): 751-758.
https://doi.org/10.1038/s41591-019-0424-4

Rompianesi G., Pegoraro F., Ceresa C., Montalti R., and Troisi R., 2022, Artificial intelligence in the diagnosis and management of colorectal cancer liver metastases, World Journal of Gastroenterology, 28(1): 108.
https://doi.org/10.3748/wjg.v28.i1.108

Saxena S., Jena B., Gupta N., Das S., Sarmah D., Bhattacharya P., Nath T., Paul S., Fouda M., Kalra M., Saba L., Pareek G., and Suri J., 2022, Role of artificial intelligence in radiogenomics for cancers in the era of precision medicine, Cancers, 14(12): 2860.
https://doi.org/10.3390/cancers14122860

Shyr D., and Liu Q., 2013, Next generation sequencing in cancer research and clinical application, Biological Procedures Online, 15: 1-11.
https://doi.org/10.1186/1480-9222-15-4

Sicklick J., Kato S., Okamura R., Schwaederlé M., Hahn M., Williams C., De P., Krie A., Piccioni D., Miller V., Ross J., Ross J., Benson A., Webster J., Stephens P., Lee J., Fanta P., Lippman S., Leyland-Jones B., and Kurzrock R., 2019, Molecular profiling of cancer patients enables personalized combination therapy: the I-PREDICT study, Nature Medicine, 25(5): 744-750.
https://doi.org/10.1038/s41591-019-0407-5

Sullivan K.M., Kenerson H.L., Pillarisetty V.G., Riehle K.J., and Yeung R.S., 2018, Precision oncology in liver cancer, Annals of Translational Medicine, 6(14): 285.
https://doi.org/10.21037/atm.2018.06.14

Tsimberidou A., Hong D., Fu S., Karp D., Piha-Paul S., Kies M., Ravi V., Subbiah V., Patel S., Tu S., Janku F., Heymach J., Johnson A., Zhang J., Berry D., Vining D., Futreal A., Miller V., Meric-Bernstam F., and Zhao L., 2021, Precision medicine: preliminary results from the initiative for molecular profiling and advanced cancer therapy 2 (IMPACT2) study, NPJ Precision Oncology, 5(1): 21.
https://doi.org/10.1038/s41698-021-00159-2

Tsimberidou A.M., Fountzilas E., Nikanjam M., and Kurzrock R., 2020, Review of precision cancer medicine: evolution of the treatment paradigm, Cancer Treatment Reviews, 86: 102019.
https://doi.org/10.1016/j.ctrv.2020.102019

Wakai T., Prasoon P., Hirose Y., Shimada Y., Ichikawa H., and Nagahashi M., 2019, Next-generation sequencing-based clinical sequencing: toward precision medicine in solid tumors, International Journal of Clinical Oncology, 24: 115-122.
https://doi.org/10.1007/s10147-018-1375-3

Wang H., 2019, Genomic-guided individualized precision therapy in refractory metastatic solid tumor patients with extensively poor performance status: a chinese single institutional prospective observational real-world study, Annals of Oncology, 30: v765.
https://doi.org/10.1093/annonc/mdz268.012

Yadav S.S., Chauhan V., Singh V., and Kohler S., 2024, The role of genetic data analysis for precision therapy in cancer, Diagnostic Applications of Health Intelligence, 4: 127-143.
https://doi.org/10.4018/978-1-7998-6527-8.ch006

Yi S., and Sahni N., 2017, Regulome networks and mutational landscape in liver cancer: an informative path to precision medicine, Hepatology, 66(1): 280-282.
https://doi.org/10.1002/hep.29220

Zugazagoitia J., Guedes C., Ponce S., Ferrer I., Molina-Pinelo S., and Paz-Ares L., 2016, Current challenges in cancer treatment, Clinical Therapeutics, 38(7): 1551-1566.
https://doi.org/10.1016/j.clinthera.2016.03.026