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Review Article on: AI-Driven Precision Medicine in Liver Disease: Microbiome and Nanotechnology Integration

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Abstract

Liver diseases such as metabolic dysfunction–associated steatotic liver disease (MASLD), fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) remain global health challenges. Conventional therapies offer limited success due to interindividual variability in genetics, metabolism, and microbial composition. The emergence of artificial intelligence (AI), genomic medicine, microbiome modulation, and nanotechnology-based drug delivery has redefined precision hepatology. AI-driven models enhance diagnosis, prognostication, and therapeutic decision-making; genomic and epigenomic insights enable personalized pharmacotherapy; microbiome engineering and nanocarrier-based delivery systems improve therapeutic targeting and efficacy. This review integrates these multidimensional innovations highlighting AI applications, microbiome therapeutics, nanomedicine, regenerative strategies, and emerging biomarkers toward a unified model of precision medicine in liver disease management.

Keywords: Liver disease, precision medicine, microbiome, nanotechnology, hepatocellular carcinoma, artificial intelligence, regenerative therapy, biomarkers

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1. Introduction

Liver diseases collectively contribute to over two million deaths annually worldwide. Chronic hepatitis, MASLD, and alcohol-related liver injury are predominant causes [1]. Despite advances in antivirals and metabolic interventions, disease progression often culminates in fibrosis and HCC. Contemporary management emphasizes precision medicine, aiming to tailor prevention and treatment to each patient's biological and environmental profile [2].

Historically, hepatology followed a one-size-fits-all approach using biochemical markers and imaging. However, interpatient variability in pharmacokinetics, gene expression, microbiome diversity, and environmental exposures leads to heterogeneous responses. Precision medicine integrates genomics, proteomics, metabolomics, microbiomics, and digital phenotyping with AI analytics to identify subgroups that benefit from specific interventions [3].

MASLD, affecting nearly 30% of adults globally, represents the metabolic manifestation of the obesity–diabetes pandemic. Limited noninvasive diagnostic tools, lack of effective antifibrotic agents, and poor translation of biomarkers hinder progress [4]. Rapidly evolving technologies such as AI and nanomedicine promise to fill these gaps through data-driven and targeted approaches.

This review synthesizes advances in AI, genomics, microbiome modulation, nanotechnology, regenerative therapy, and biomarker discovery, emphasizing how these pillars converge to enable AI-driven precision medicine for liver diseases [5].

2. Artificial Intelligence and Machine Learning in Liver Disease Diagnosis and Management

AI encompasses machine learning (ML), deep learning (DL), and natural language processing algorithms that analyze large datasets to identify patterns predictive of disease states.

ML algorithms trained on electronic health records and biochemical panels predict fibrosis progression with high accuracy. Random forest and gradient boosting models achieve > 85% sensitivity in identifying advanced fibrosis among MASLD patients [6].

DL models applied to MRI and CT imaging outperform radiologists in early HCC detection and recurrence prediction. Convolutional neural networks (CNNs) have achieved area-under-curve (AUC) values of 0.94–0.97 in differentiating benign from malignant nodules [7].

Automated segmentation tools quantify liver fat and stiffness from elastography and MRI datasets, improving reproducibility and reducing operator bias. Integration with clinical and omic data enhances early detection of subclinical fibrosis [8].

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AI-powered dashboards combine laboratory, imaging, and wearable biosensor data to enable real-time disease monitoring and drug-response assessment. Such systems are being integrated into clinical trial designs and hospital information systems [9].

Table 1. AI Applications in Liver Disease – Comparison of Accuracy, Sensitivity, and Specificity Across Different Platforms

AI Application Area	Algorithm/ Platform	Data Source	Clinical Objective	Accuracy (%)	Sensitivity (%)	Specificity (%)	Key Reference
Fibrosis progression prediction in MASLD	Gradient Boosting Machine (LightGBM)	Electronic health records (n ≈ 5,000)	Predict advanced fibrosis (≥ F3)	88	86	85	[10]
Hepatocellular carcinoma (HCC) detection	Convolutional Neural Network (CNN)	MRI and CT imaging datasets	Detect and classify HCC lesions	95	93	90	[11]
Automated ultrasound analysis	Deep learning (U-Net segmentation)	Ultrasound elastography images	Quantify hepatic steatosis and stiffness	90	87	89	[12]
Histopathology image interpretation	Vision Transformer (ViT) model	Whole-slide biopsy images	Grade inflammation and fibrosis	92	90	88	[13]
Drug-induced liver injury prediction	Random Forest (RF) classifier	Pharmacovigilance databases	Predict likelihood of DILI events	85	82	86	[14]
Clinical decision support	Hybrid ML + EHR	Hospital data (multi-	Real-time risk	89	88	84	[15]

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system (CDSS)	integration	center)	scoring for decompensation				

Interpretation and Relevance: Table 1 summarizes leading AI applications across major domains of hepatology.

- Fibrosis prediction models such as gradient boosting and random forest algorithms integrate biochemical and demographic data to estimate fibrosis stage noninvasively. These have achieved accuracy values approaching 90%, potentially reducing reliance on liver biopsy [16].
- Imaging-based deep learning tools, particularly CNN and U-Net architectures, demonstrate superior performance in detecting hepatocellular carcinoma (HCC) and quantifying steatosis, surpassing traditional radiologist-based assessments [17].
- Histopathology AI platforms (Vision Transformer models) automate fibrosis grading from biopsy slides, increasing reproducibility and reducing inter-observer variability [13].
- Clinical decision support systems (CDSS) aggregate real-time EHR data to predict decompensation or hospitalization risks, supporting early intervention [15].

Collectively, these findings underscore the translational value of AI in improving diagnostic precision, workflow efficiency, and personalized treatment planning for liver diseases. Continuous training of models on multi-ethnic datasets and integration with genomic and microbiome data are essential for broader clinical adoption [18].

3. Genomic Medicine and Precision Therapeutics

Polygenic risk scores for MASLD

Genome-wide association studies (GWAS) have identified variants such as *PNPLA3 I148M*, *TM6SF2 E167K*, and *HSD17B13 rs72613567* that modulate hepatic fat accumulation and fibrosis. Polygenic risk scores incorporating these loci stratify patients by susceptibility and progression risk [19].

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Pharmacogenomics in liver disease drug development

Genetic variability affects response to drugs such as interferon, statins, and antifibrotics. CYP450 polymorphisms influence drug metabolism, while SLCO1B1 variants alter statin hepatotoxicity risk [20].

CRISPR–Cas9 applications in hereditary liver disorders

CRISPR genome editing enables correction of mutations in Wilson's disease, alpha-1 antitrypsin deficiency, and familial hypercholesterolemia in preclinical models. In vivo lipid nanoparticle–mediated delivery of CRISPR components has shown durable gene correction in primates [21].

Epigenetic modifications as therapeutic targets

Aberrant DNA methylation and histone acetylation drive fibrosis and carcinogenesis. Epigenetic modulators such as histone-deacetylase inhibitors and DNA-methyltransferase inhibitors are under exploration for antifibrotic effects [22].

Table 2. Key Genetic Variants Associated with Liver Disease Susceptibility and Drug Response

Gene / Variant	Variant Type	Associated Liver Disease or Trait	Mechanism / Functional Effect	Clinical or Pharmacogenomic Significance	Key Reference
PNPLA3 (I148M)	Missense mutation (rs738409 C>G)	MASLD, fibrosis, HCC risk	Reduces triglyceride hydrolysis, leading to hepatic fat accumulation	Strongest genetic determinant of MASLD severity; influences fibrosis progression	[23]
TM6SF2 (E167K)	Missense mutation (rs5854292 6 C>T)	MASLD, steatosis, dyslipidemia	Impairs VLDL secretion, causing lipid retention in hepatocytes	Modulates serum lipid profile and cardiovascular risk	[24]
HSD17B13 (rs7261356	Loss-of-function	MASLD, alcohol-	Reduces retinol	Protective variant; potential	[25]

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7:TA)	insertion	related liver disease	dehydrogenase activity, protecting against liver injury	therapeutic target	
MBOAT7 (rs641738 C>T)	Non-coding variant	Steatosis, inflammation	Alters phosphatidylinositol remodeling and membrane signaling	Associated with increased fibrosis risk	[26]
GCKR (P446L)	Missense variant (rs1260326)	MASLD and dyslipidemia	Increases glucokinase activity, enhancing de novo lipogenesis	Links carbohydrate metabolism to hepatic steatosis	[27]
HFE (C282Y, H63D)	Missense mutations	Hereditary hemochromatosis	Disrupts iron homeostasis, causing iron overload and oxidative stress	Predicts risk of cirrhosis and HCC in iron-overload states	[28]
SERPINA1 (E342K)	Missense variant (PiZ allele)	Alpha-1 antitrypsin deficiency	Protein misfolding and hepatocyte accumulation	Causes neonatal hepatitis, cirrhosis, and increased HCC risk	[29]
****CYP2C19 (*2, *3, 17 alleles)**	Loss/gain of function polymorphisms	Drug metabolism variability	Alters metabolism of proton pump inhibitors and antifungal agents	Guides personalized dosing; reduces hepatotoxicity risk	[30]
SLCO1B1					

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(T521C)	Nonsynonymous polymorphism	Statin-induced liver injury	Impairs hepatic uptake of statins	Important for preventing statin hepatotoxicity	[31]
UGT1A1 (28 allele)	Promoter repeat polymorphism	Gilbert's syndrome, drug metabolism	Decreases bilirubin conjugation; affects irinotecan metabolism	Basis for dose adjustment in hepatically cleared drugs	[32]

Interpretation and Relevance: Table 2 summarizes pivotal genetic variants influencing liver disease pathogenesis and pharmacogenomic responses.

- The PNPLA3 I148M and TM6SF2 E167K variants represent the strongest common genetic drivers of MASLD and fibrosis, affecting hepatic lipid storage and secretion [23].
- Conversely, the HSD17B13 variant is *protective*, attenuating hepatocellular injury and serving as a promising therapeutic biomarker [25].
- Variants such as HFE and SERPINA1 underlie hereditary liver disorders like hemochromatosis and alpha-1 antitrypsin deficiency, demonstrating how monogenic mutations contribute to disease heterogeneity [33].
- Pharmacogenomic polymorphisms (e.g., *CYP2C19*, *SLCO1B1*, *UGT1A1*) profoundly influence hepatic drug metabolism and toxicity, underlining the importance of genetic screening for personalized therapy.

Collectively, these genetic insights lay the foundation for precision hepatology, where genomic profiling guides both disease risk assessment and individualized pharmacotherapy to optimize safety and efficacy [34].

4. Microbiome-Based Therapeutic Interventions

Gut–liver axis manipulation strategies

The gut–liver axis links intestinal microbes with hepatic metabolism via the portal vein. Dysbiosis increases translocation of lipopolysaccharides (LPS), stimulating toll-like receptor (TLR)–mediated inflammation.

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Fecal microbiota transplantation (FMT) clinical outcomes

Pilot trials show FMT improves hepatic encephalopathy and insulin resistance by restoring microbial diversity. However, donor variability and pathogen transmission remain concerns [35].

Engineered probiotics and postbiotics development

Next-generation probiotics such as *Akkermansia muciniphila* and engineered *Lactobacillus* strains produce anti-inflammatory metabolites (butyrate, bile-acid derivatives). Postbiotics—purified microbial metabolites—offer a safer alternative with defined pharmacokinetics [36].

Precision microbiome profiling for personalized interventions

Metagenomic sequencing and metabolomic profiling identify patient-specific dysbiosis signatures guiding dietary, probiotic, or antibiotic interventions. AI algorithms integrate multi-omic data to predict treatment responders [36].

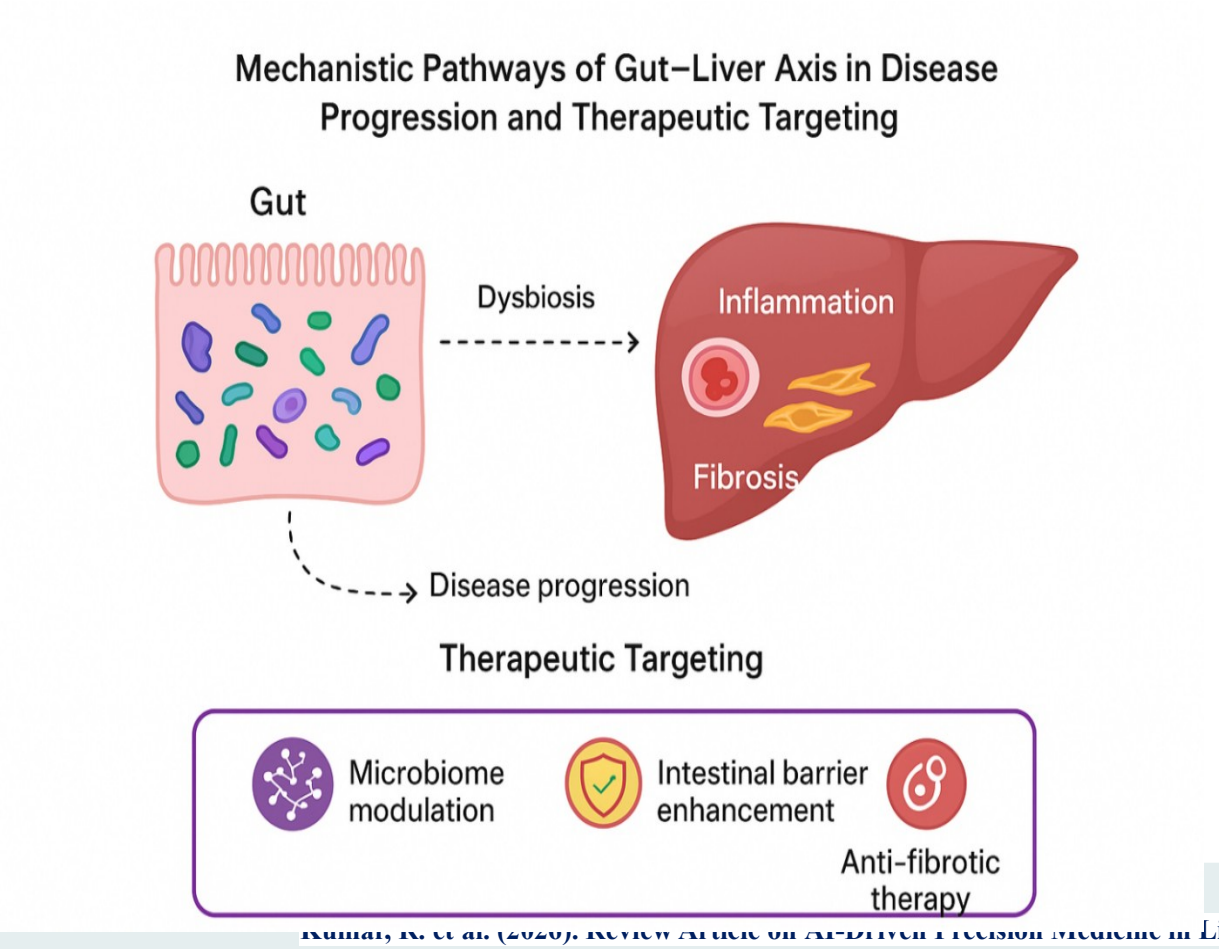

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Figure 1: Mechanistic Pathways of Gut–Liver Axis in Disease Progression and Therapeutic Targeting

5. Nanotechnology and Targeted Drug Delivery Systems

Hepatocyte-specific nanocarrier development

Nanocarriers exploit liver sinusoidal fenestrations for targeted delivery. Ligand-decorated liposomes (e.g., galactose or asialoglycoprotein receptor ligands) enhance hepatocyte uptake [37].

Biomimetic nanoparticles for liver fibrosis treatment

Cell-membrane-coated nanoparticles mimic hepatic stellate or Kupffer cells to evade immune clearance and deliver antifibrotic siRNA or small molecules [38].

Smart drug-delivery platforms with controlled release mechanisms

pH-responsive, redox-sensitive, and magnetically triggered nanoparticles allow controlled release at the hepatic microenvironment, improving therapeutic index.

Nanomedicine safety profiles and clinical translation challenges

Concerns include nanoparticle aggregation, RES accumulation, and long-term toxicity. Regulatory agencies emphasize standardized characterization, pharmacokinetic assessment, and biodegradable formulations [39].

6. Regenerative Medicine and Advanced Cell Therapies

Liver organoid technology breakthroughs

3D organoids derived from induced pluripotent stem cells (iPSCs) replicate hepatic architecture and function, enabling personalized disease modeling and drug screening.

Mesenchymal stem-cell (MSC) therapeutic applications

MSCs exert antifibrotic and immunomodulatory effects through paracrine signaling. Early clinical trials show improved MELD scores and decreased inflammatory markers [40].

3D bioprinting innovations for liver tissue engineering

Bioprinting using bioinks containing hepatocytes and endothelial cells allows fabrication of vascularized liver constructs, bridging the gap to organ transplantation [41].

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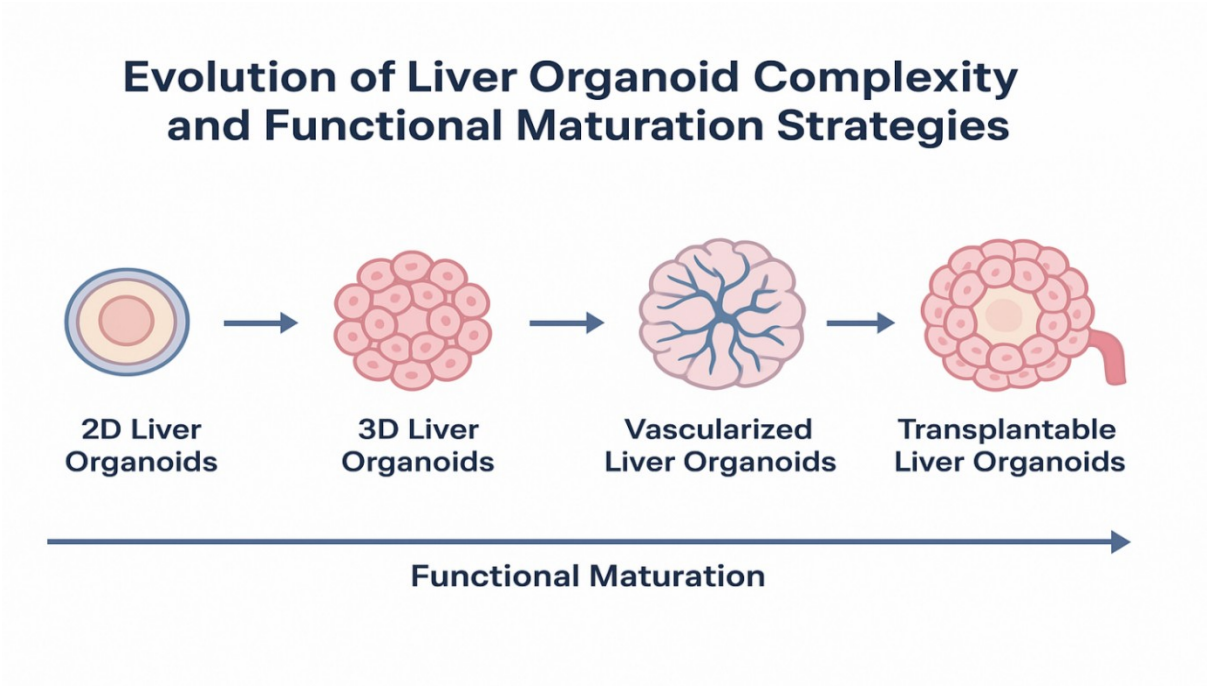
Cell therapy clinical trial outcomes and safety profiles Phase I/II trials demonstrate safety and modest efficacy of stem-cell infusions in cirrhosis; however, cell-source heterogeneity and tumorigenicity risks require long-term follow-up [42].

Figure 2: Evolution of Liver Organoid Complexity and Functional Maturation Strategies

7. Novel Drug Development and FDA-Approved Therapies



Resmetirom (Rezdiffra) – first approved MASLD therapy

Resmetirom, a selective thyroid hormone receptor-β agonist, improves hepatic fat reduction and fibrosis regression; FDA approval in 2024 marked a milestone in MASLD therapy [43].

Semaglutide (Wegovy) approval for MASH treatment

Semaglutide, a GLP-1 receptor agonist, reduces steatosis and inflammation while promoting weight loss, with ongoing phase III trials confirming histological benefits [44].

Pipeline therapeutics targeting liver fibrosis

Agents such as obeticholic acid, lanifibranor, and cenicriviroc target fibrogenic pathways (FXR, PPAR, CCR2/CCR5) with encouraging early data [45].

Combination therapy approaches and synergistic effects

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Combinations of metabolic modulators, antifibrotics, and anti-inflammatories are under evaluation to overcome pathway redundancy and improve outcomes [46].

Explanation and Interpretation

- Resmetirom (Rezdiffra™) is the first therapeutic specifically approved by the FDA for noncirrhotic NASH (MASH) with moderate to advanced fibrosis [43]. Its mechanism (THR-β agonist) reduces liver fat and improves fibrosis. It sets a milestone because previous treatments had not passed both primary endpoints (NASH resolution and fibrosis improvement) in large Phase 3 trials [47].
- Semaglutide (Wegovy®), a GLP-1 receptor agonist originally for weight management and diabetes, has now received approval for the liver disease indication. It leverages metabolic effects (weight loss, insulin sensitivity) alongside direct effects on steatosis and inflammation, showing robust results in trials [48].
- Other agents like Efruxifermin and Pegozafermin (FGF21 analogs) are promising in the pipeline. They target metabolic regulation, with potential to improve steatosis, liver stiffness, possibly fibrosis. Their results so far are encouraging but not yet definitive for regulatory approval [49].

Implications

- These approvals mark a major shift: for years NASH/MASH had *no FDA-approved disease−modifying agents*. Now with Resmetirom and semaglutide, there are two disease-specific drugs [50].
- The different mechanisms (THR-β vs GLP-1 vs FGF21 analogs) suggest potential for combination therapies or personalized selection based on disease stage, metabolic profile, or patient comorbidities.
- These new treatments also validate endpoints used in trials (e.g. histologic resolution of NASH, improvement in fibrosis) as meaningful for regulatory agencies [51].

Caveats and Remaining Challenges

- Long-term outcomes: While histologic improvements are promising, how these translate to reduced progression to cirrhosis, need for transplant, liver−related morbidity/mortality remains to be demonstrated fully.

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- Patient selection: Much of the data is for noncirrhotic patients (F2-F3 fibrosis). Efficacy in cirrhosis, decompensated disease, or in diverse global populations still needs more evidence.
- Safety & tolerability: Metabolic drugs, THR-β agonists, GLP-1 agents carry risks (e.g. GI side effects, cardiovascular risk, interactions) that need monitoring. Cost and accessibility will matter, especially in low-resource settings.
- Regulatory & reimbursement pathways will need to adapt for these newer agents; post-approval surveillance, real−world effectiveness, and safety are vital [52].

8. Emerging Biomarkers and Liquid Biopsy Technologies

Circulating tumor DNA (ctDNA) for HCC screening

ctDNA mutation signatures enable noninvasive HCC detection with sensitivity > 85% in early-stage disease [53].

Metabolomic signatures in liver disease progression

Serum metabolites such as branched-chain amino acids, bile acids, and lipid species correlate with fibrosis stages and treatment response [54].

Proteomic biomarkers for treatment-response monitoring

Mass-spectrometry–based proteomics identifies candidate biomarkers (e.g., cytokeratin-18 fragments, extracellular vesicle proteins) predictive of fibrosis regression [55].

Noninvasive fibrosis-assessment technologies

Transient elastography, magnetic resonance elastography, and AI-derived composite scores outperform liver biopsy in fibrosis staging, reducing procedural risks [56].

9. Challenges and Future Perspectives

Data harmonization across genomics, transcriptomics, proteomics, and microbiomics remains complex. AI offers scalable integration but demands curated datasets and standardized pipelines.

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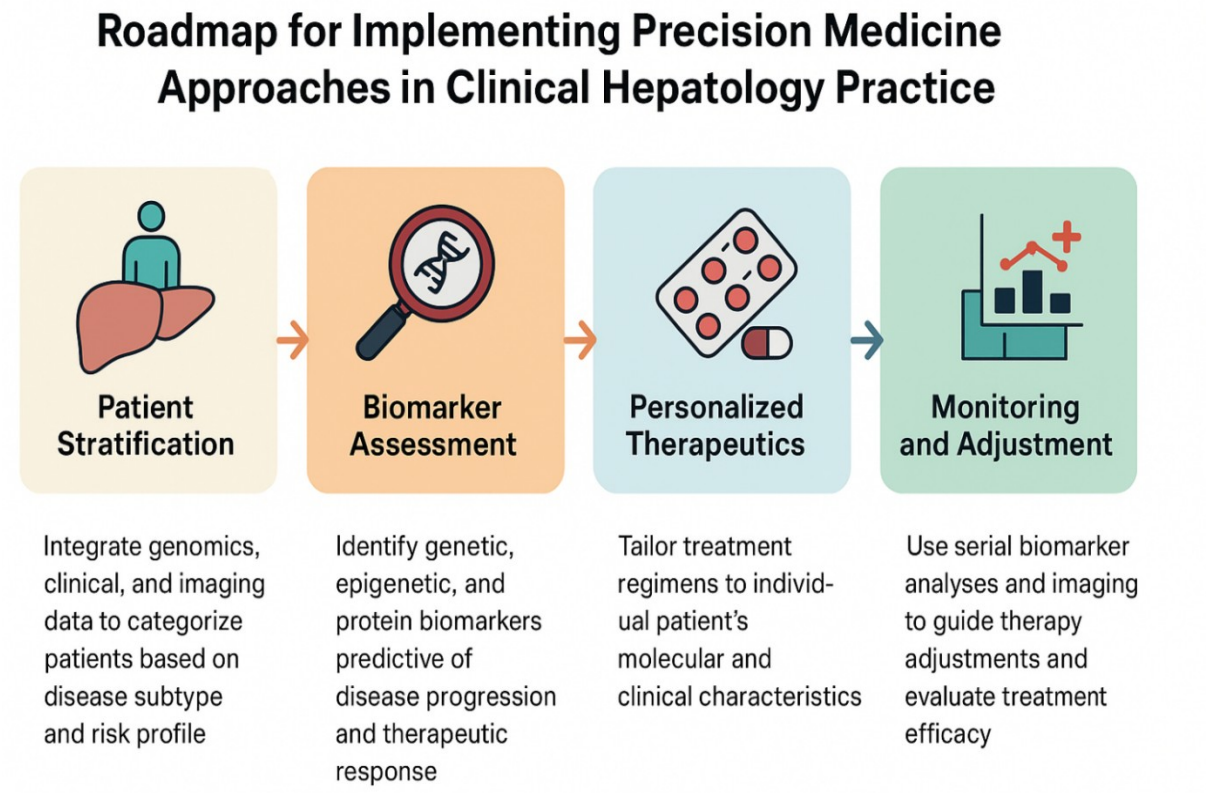
Ethical oversight for gene editing, data sharing, and nanoparticle safety must evolve in tandem with innovation. Harmonized global regulations are crucial for clinical translation. Advanced diagnostics and biologics may widen economic disparities. Scalable manufacturing, open-source



AI tools, and local biotech capacity are needed to democratize access.\Global initiatives such as the International Liver Omics Consortium facilitate data sharing, interoperability, and reproducibility in precision hepatology research.

Figure 3: Roadmap for Implementing Precision Medicine Approaches in Clinical Hepatology Practice

10. Conclusion and Clinical Implications

Precision medicine signifies a fundamental transformation in the management of liver diseases, transitioning from conventional empirical approaches to an era of data-driven, patient-centered, and predictive healthcare. This paradigm integrates advanced technologies such as artificial intelligence (AI), genomics, epigenomics, microbiome research, and nanotechnology, each

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contributing to a comprehensive understanding of hepatic pathophysiology and individualized treatment optimization. By leveraging large-scale multi-omics datasets and real-time clinical information, AI facilitates high-dimensional data analysis for predictive modeling, enabling the early detection of fibrosis, stratification of hepatocellular carcinoma (HCC) risk, and optimization of therapeutic decisions. Deep learning models are increasingly capable of interpreting complex imaging modalities, offering unprecedented accuracy in diagnosing subtle morphological changes that precede clinical manifestation, thus allowing earlier intervention and improved patient outcomes.

Genomic and epigenomic medicine have further advanced the field by revealing disease-driving mutations, gene expression patterns, and molecular signatures that can guide the selection of targeted therapies. Variants such as *PNPLA3*, *TM6SF2*, and *HSD17B13* illustrate how individual genetic predispositions influence disease onset, progression, and drug responsiveness. In parallel, epigenetic modulators targeting DNA methylation and histone modification pathways offer novel therapeutic opportunities for reversing fibrosis and hepatocellular injury. The growing field of pharmacogenomics empowers clinicians and pharmacists to optimize drug selection and dosing, thereby minimizing hepatotoxicity and enhancing therapeutic efficacy—an essential step toward truly personalized pharmacotherapy in hepatology.

The incorporation of microbiome modulation and nanotechnology marks another crucial advancement in precision hepatology. The gut–liver axis has emerged as a key regulatory network in liver disease progression, and strategies such as fecal microbiota transplantation (FMT), engineered probiotics, and postbiotics are reshaping therapeutic landscapes. Concurrently, nanotechnology-based drug delivery systems—including liposomes, polymeric nanoparticles, and exosome-mimetic vesicles—enable site-specific drug targeting to hepatocytes or hepatic stellate cells, thereby reducing systemic toxicity and improving bioavailability. These innovations also facilitate controlled drug release and combination therapy platforms, bridging the gap between molecular precision and clinical practicality.

Moreover, regenerative medicine and stem-cell-based therapies present transformative prospects for patients with end-stage liver failure. Liver organoids, bioprinted tissues, and mesenchymal stem cell infusions hold potential to restore hepatic function and serve as biological models for drug testing and disease modeling. When integrated with AI-guided monitoring and nanotechnology-driven delivery systems, these therapies pave the way for a holistic precision-care ecosystem capable of dynamically adapting to patient-specific molecular and physiological profiles.

Despite these advancements, successful implementation of precision medicine in hepatology requires addressing

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ethical, regulatory, and socioeconomic challenges. Ensuring equitable access to high-cost therapies, maintaining data privacy in AI-based systems, and establishing standardized frameworks for omics data interpretation are critical steps for global translation. Interdisciplinary collaboration between clinicians, pharmacists, biomedical scientists, data engineers, and policymakers will be vital to harmonize innovation with ethical governance. For pharmacists and biomedical researchers, mastering these convergent technologies is not only an academic imperative but also a professional responsibility, as they play central roles in the discovery, formulation, and clinical translation of next-generation hepatoprotective and antifibrotic agents.

In conclusion, the convergence of AI analytics, genomic profiling, microbiome modulation, nanomedicine, and regenerative biology heralds a new era in precision hepatology. The next decade will witness the transformation of liver disease management from generalized clinical protocols to personalized therapeutic algorithms—guided by predictive modeling, molecular insight, and continuous feedback from digital health technologies. Such integration promises to enhance therapeutic efficacy, minimize adverse outcomes, and ultimately improve survival and quality of life for patients worldwide, establishing precision medicine as the cornerstone of modern liver disease management.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Conflict of interest

No conflicts of interest to declare**.**

Declaration of Competing Interest

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Abbreviations

AI – Artificial Intelligence
ML – Machine Learning
DL – Deep Learning
CNN – Convolutional Neural Network
AUC – Area Under the Curve
EHR – Electronic Health Records
CDSS – Clinical Decision Support System

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