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Panomics in metabolic dysfunction-associated steatotic liver disease: unravelling the drivers of disease heterogeneity

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The knowledge accumulated over the past two decades has revealed that the natural history of metabolic dysfunction-associated steatotic liver disease (MASLD) and the drivers of the disease severity are not only complex but also exhibit variation among patients. This intricate clinical scenario entails major therapeutic and management implications. In this review, we provide a comprehensive examination of recent advancements in our understanding of MASLD heterogeneity, drawing insights from multiomics and panomics studies. The discussion herein explores the instrumental role of panomics in MASLD research, elucidating the potential for the identification of molecular subtypes that exhibit divergent survival outcomes or heterogeneous responses to various treatments. Furthermore, we provide insights into the challenges in addressing disease heterogeneity and potential solutions. Finally, the most advanced technological advancements and prospective research directions in the domain of MASLD research are delineated, with the objective of facilitating the implementation of personalized diagnosis and interventions. (*Clin Mol Hepatol* 2026;32:156-169)

Keywords: MASH; OMICS; Genomics; Proteomics; Metabolomics

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), which has recently undergone a nomenclatural change,¹ represents the most prevalent chronic liver disease,^{2,3} with escalating incidence and prevalence rates.^{4,5}

Although the disease course is relatively benign at the earlier stages, the presence of fibrosis—a hallmark feature of the disease progression—increases the risk of several complications, including hepatic^{6,7} and systemic ones.⁸⁻¹⁴ This intricate clinical scenario entails significant therapeutic and management implications.^{15,16}

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CONCEPT OF MASLD HETEROGENEITY

The accumulated knowledge of the past two decades has demonstrated that the natural history and drivers of the disease severity are not only complex but also exhibit variation among individual patients. Patients with MASLD have the potential to evolve to metabolic dysfunction–associated steatohepatitis (MASH), and patients exhibiting advanced liver fibrosis may eventually progress to liver cirrhosis and hepatocellular carcinoma (HCC).^{2,6,17–20} Nevertheless, the course of the disease is dynamic and is influenced by main modifiers, including alcohol consumption,²¹ comorbidities,¹⁹ and genetic predisposition.^{22–24} Therefore, a distinctive feature of MASLD is its disease trajectory, which is characterized by substantial heterogeneity.^{25–27} Clustering to identify distinct MASLD subtypes based either on data driven or biological mechanisms of the underlying genetic drivers^{28–30} and latent class analyses have begun to identify the endogenous variables of patients behind this clinical characteristic heterogeneity, and reinforce the concept that MASLD is a central component of the metabolic syndrome.³¹ In this review, we provide a comprehensive examination of recent advancements in our understanding of MASLD heterogeneity, drawing insights from multiomics and panomics studies.

WHAT IS PANOMICS? DEFINITION AND SCOPE OF PANOMICS

The remarkable intricacy of the underlying mechanisms driving common human diseases, particularly those of multifactorial pathogenesis, such as MASLD, has prompted considerable challenges to biomedical research. Conventional single-omic analyses, while informative, frequently yield a partial representation of the complex molecular processes causing and triggering disease pathogenesis. In response to these challenges, panomics strategies have led to the development of a new era of systems biology, offering unprecedented insights into the molecular underpinnings of disease heterogeneity.

Each omic layer offers a distinct perspective on cellular and tissue function. Genomics examines DNA sequence variation, including single nucleotide polymorphisms (SNPs), structural variants, and copy number changes. Transcriptomics profiles mRNA expression and regulatory non-coding RNAs (ncRNAs) including small (microRNAs, isomiRNAs, and piRNAs), long ncRNAs, and circular RNAs, to indicate gene activity patterns. Epigenomics investigates modifications such as DNA methylation and histone modifications that regulate gene expression without changing the underlying DNA code.³² Proteomics measures proteins, their post-translational modifications, and interactions within cellular pathways. Metabolomics assesses small molecules and metabolites, the ultimate byproducts, indicating biochemical activity and metabolic state. In the last decades, to this layer of eukaryotic organismal complexity, other contributors were added. First, mitochondria with their own genome, transcriptome, proteome, and metabolome, study of which can be named “mito-omics”, played an essential role in health and disease, from heritable mitochondrial diseases to the contributions to complex diseases such as MASLD.^{33–37} Second, our body contains a myriad of ecosystems of microbial communities that co-exist in various parts, including skin, mucosa, gut, and internal organs, whose exact composition and function are being recognized very recently. Then, metagenomics, as an example, examines the composition and function of microbial communities, such as those found in the gut or other tissues, which can affect host physiology and disease susceptibility.

While “multiomics” and “panomics” are often used interchangeably, multiomics is generally defined as the integration of multiple datasets from diverse “omics” domains—such as genomics, transcriptomics, and proteomics, among others—to examine a biological system. In contrast, “panomics” can be regarded as a more refined and comprehensive form of multiomics, frequently involving a more profound, more integrated examination across multiple levels of biological organization.³⁸

Abbreviations:

MASLD, metabolic dysfunction-associated steatotic liver disease; MASL, metabolic dysfunction-associated steatotic liver; MASH, metabolic dysfunction–associated steatohepatitis; HCC, hepatocellular carcinoma; sc-omics, single-cell omics; scRNA-seq, single-cell RNA sequencing

PINPOINTING THE EDGE: PANOMICS' UNIQUE INTEGRATION OVER MULTI-OMICS

Panomics represents a more advanced and integrative methodology in biomedical research, characterized by the simultaneous and combined analysis of data from multiple distinct omics domains. Unlike traditional approaches that focus on single molecular layers, panomics seeks to transcend these boundaries by modeling the complex interactions and regulatory networks that collectively govern biological systems (Fig. 1).

The principal objective of panomics is to move beyond isolated molecular datasets and provide a holistic representation of biological processes. By integrating diverse single omics data, panomics enables researchers for instance, to examine how genetic information is translated into functional proteins and metabolites. This comprehensive integration facilitates a systems biology perspective, allowing for the exploration of intricate molecular relationships and regulatory mechanisms within cells and tissues.

Through this approach, panomics not only captures the individual contributions of each omics layer but also reveals

the dynamic interplay among them. The resulting insights are instrumental in understanding the broader biological context, supporting the identification of key molecular drivers, and elucidating the underlying mechanisms that shape disease progression and response to treatment. As such, panomics intend to understand how an organism orchestrates the myriad of simultaneous processes supporting life.

The panomics approach is defined by several critical characteristics: First, data integration and bioinformatics.³⁹ A fundamental requirement for panomics is the integration of diverse, high-dimensional datasets. This necessitates the use of advanced bioinformatics and computational biology tools to accurately align, normalize, and analyze data originating from disparate 'omics' methodologies.⁴⁰ The computational challenge lies in managing data heterogeneity while deriving biologically meaningful correlations.⁴¹ Second, holistic biological interpretation. Panomics enables a holistic view of biological systems. By functionally connecting genetic variation to resultant alterations in gene expression, protein abundance, and metabolite function, the approach provides a systems-level comprehension of

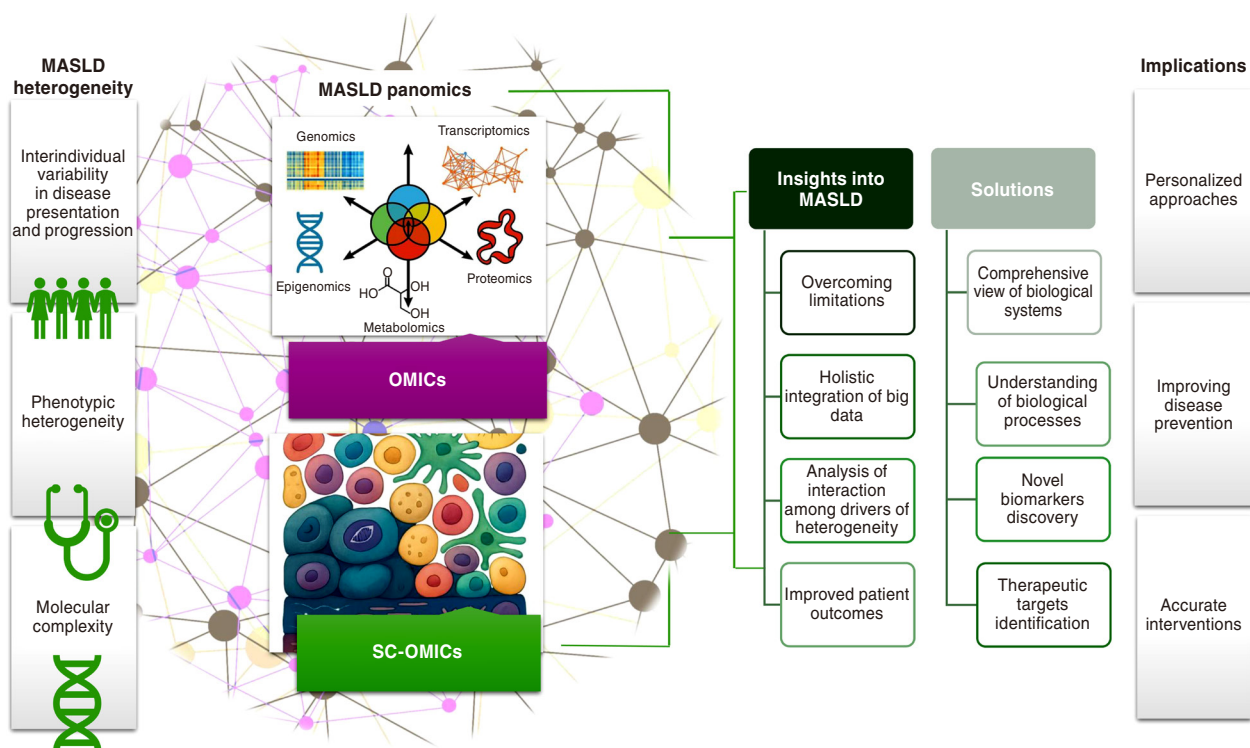


Figure 1. The use of panomics in MASLD research. MASLD, metabolic dysfunction-associated steatotic liver disease.

complex biological phenomena, including disease etiology, progression, and the mechanisms underlying therapeutic responses. Third, biomarker and drug discovery. The translational utility of panomics is crucial in precision medicine. The capacity to integrate multi-level molecular data from individual patients is vital for the discovery and validation of novel biomarkers and for the rational design of highly personalized therapeutic strategies.

In the case of MASLD, the overarching goal of integrative panomics is to yield actionable insights into the disease biology and solutions to address the drivers of disease heterogeneity. Consequently, integrative omics leads to the identification and utilization of novel markers and targeted therapeutic interventions, facilitating the implementation of precision medicine. This approach takes interindividual variability into account during the diagnosis, prognostication, and treatment of patients (Fig. 1).

Nevertheless, the integration of panomics into MASLD research remains in its nascent stages, indicating that substantial foundational and translational work is still requisite to fully elucidate the complex pathobiology of the disease and identify novel therapeutic or preventative targets.

THE RATIONALE OF OMICS IN MASLD RESEARCH. PART I: MOVING FROM SINGLE OMICS TO MULTIOMICS/PANOMICS TO UNCOVER DISEASE MECHANISMS

An overview of studies in MASLD that used integrative omics approaches is shown in Table 1. Each study presents different strategies and clinical applications. The fundamental premise underlying omics in MASLD research is that patient subgroups may exhibit novel molecular subtypes with divergent survival outcomes or heterogeneous responses to various treatments (Fig. 2). This potential disentanglement is now possible due to the advent of high-throughput omics platforms that are capable of molecular profiling of biological samples at a hitherto unimaginable level. First, single-omics approaches, including high-throughput DNA sequencing technologies, have served to define the genetic risk of MASLD and its progression.⁴²⁻⁴⁴ However, the application of epigenomics and transcriptomics in liver tissue samples led to significant advancements in our understanding of disease mechanisms and the dis-

inction between metabolic dysfunction-associated steatotic liver (MASL) and MASH, and tried to explain, at least in part, the “missing heritability”.³² For example, Murphy et al.⁴⁵ demonstrated that functionally relevant differences in liver methylation have the capacity to distinguish patients with advanced MASLD from those with mild disease. These methylation changes were observed in genes that regulate processes associated with disease progression, including inflammation, fibrosis, and carcinogenesis. Furthermore, earlier studies that explored the epigenetic modifications in the liver tissue of patients with MASLD demonstrated the importance of methylation changes in the transcriptional activity of master regulators of glucose and lipid metabolism, such as *PPARGC1A* (also known as *PGC1a*). These alterations in gene expression have been demonstrated to exert a significant impact on hepatic mitochondrial copy number and the development of insulin resistance,⁴⁶ a phenomenon that can be well programmed in the fetal life.⁴⁷

The use of array-based DNA methylation and mRNA expression profiling in liver samples from morbidly obese patients after bariatric surgery also exemplifies treatment-induced epigenetic organ remodeling in patients living with MASLD.⁴⁸ Most notably, a comparative analysis of liver biopsies before and after bariatric surgery revealed that MASLD-associated methylation changes are, at least to a certain extent, reversible.

Epigenetic changes involved in the disease progression are not limited to the genomic DNA. It has been shown that hepatic methylation and transcriptional activity of genes encoded by the mitochondrial DNA are associated with the histological severity of MASLD.³⁵ The advent of deep-coverage technology also enabled the comprehensive sequencing of the liver mitochondrial genomes, which led to the hypothesis that the variability of the mitochondrial genomes in patients with MASLD likely originates from a common germline source. This finding may offer another potential explanation for a proportion of the “missing heritability” of the disease.³⁶

On the other hand, the circulating metabolome has been demonstrated to reflect not only the systemic metabolic-inflammatory environment, but also the changes occurring in the liver of affected individuals.⁴⁹ Furthermore, metabolome-derived diagnostic and predictive panels have the potential to identify patients with an increased risk of seri-

Table 1. Overview of studies in MASLD that used integrative omics approaches

Omics approaches	Study design	Primary source of sample	Specific approach	Key results: insights into the disease biology, diagnostic strategies and potential applications	Reference
GWAS Proteomics RNA-seq	Population-based	Blood subcutaneous adipose tissue	Meta-GWAS High-throughput proteomics measurements (Olink and SomaScan)	Non-invasive evaluation of MASLD and new therapeutic options	52
WGS Proteomics Phosphoproteomics Lipidomics Metabolomics	Hospital-based	Liver tissue, blood, and urine specimens	LC-MS QTOF LC-MS/MS	Three molecular types of MASLD defined as how much liver fat or liver macrophages, and the risk of cirrhosis or liver cancer	53
Global DNA methylation RNA-seq snRNA-seq	Hospital-based	Liver tissue	Transcriptome and methylation array	Epigenetic modifications in complement genes correlate with MASLD severity	54
Proteomics RNA-seq	Hospital-based	Liver; blood	High-throughput proteomics measurements (SomaScan)	A novel non-invasive diagnostic model that prioritises at-risk MASH	55
Proteomics RNA-seq SC-RNAseq Cross-high-throughput proteomic platforms	Population-based Hospital-based	Blood; liver tissue	High-throughput proteomics measurements (Olink and SomaScan)	MASLD stratification into subclasses at risk of extrahepatic manifestations	56
High-throughput 16S rRNA HDACs-HATs total activity Global 5-hmC levels	Hospital-based	Liver tissue (nuclear extracts from fresh liver samples)	Gene sequencing ELISA	Liver epigenome in patients with MASLD is the target of microbial signals	57
High-throughput 16S rRNA Targeted genotyping SNPs	Hospital-based	Blood; liver tissue	Gene sequencing Polygenic risk scores	Genetic variation may influence the liver microbial DNA composition	58
Targeted genotyping SNPs RNA-seq Metabolomics	Population-based Hospital-based	Blood; liver tissue	Cluster analysis	Two distinct endotypes of at-risk MASLD (cardiometabolic and liver-specific MASLD) that have different underlying Biological profiles and distinct clinical progression patterns	28
snRNA-seq snATAC-seq	Hospital-based	Liver tissue	Gene expression and chromatin accessibility	Human hepatic stellate cells subpopulations	59
GWAS sc-eQTL	Hospital-based	Liver tissue	Single-nucleus transcriptome	Liver eQTLs influence gene expression and clinical outcomes in MASLD	60
Single cell multiome assays Targeted genotyping SNPs	Biobank samples	Liver tissue	ATAC+Gene Expression assays Cell-type specific chromatin architecture Spatial transcriptomics	High-resolution maps of liver cell types reveal cellular heterogeneity in hepatocytes Identification of transcriptional drivers of changes within hepatocyte zones and subtypes in MASH	61

Table 1. Continued

Omics approaches	Study design	Primary source of sample	Specific approach	Key results: insights into the disease biology, diagnostic strategies and potential applications	Reference
GWAS Transcriptomics Proteomics	Population-based	Blood	High-throughput proteomics measurements (Olink) Array genotyping Mendelian randomization	Identification of potential causal targets of MASLD	62
Proteomics Metabolomics	Population-based	Blood	Targeted high-throughput H-nuclear magnetic resonance metabolomics High-throughput proteomics measurements (Olink)	Proteomic subtyping in MetALD versus MASLD	63

MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; GWAS, genome-wide association study; WGS, whole-genome sequencing; SNP, single-nucleotide polymorphism; RNA-seq, RNA sequencing; eQTLs, expression quantitative trait loci; sc-eQTLs, single-cell eQTLs; HDACs, activity of histone deacetylases; HAT, acetyltransferases; 5-hmC, 5-hydroxymethylcytosine; snRNA-seq, single-nucleus RNA sequencing; snATAC-seq, single nucleus ATAC (single nucleus assay for transposase-accessible chromatin using sequencing); LC-MS, liquid chromatography-mass spectrometry; QTOF, Quadrupole Time-of-Flight; 16S rRNA, small subunit ribosomal RNA.

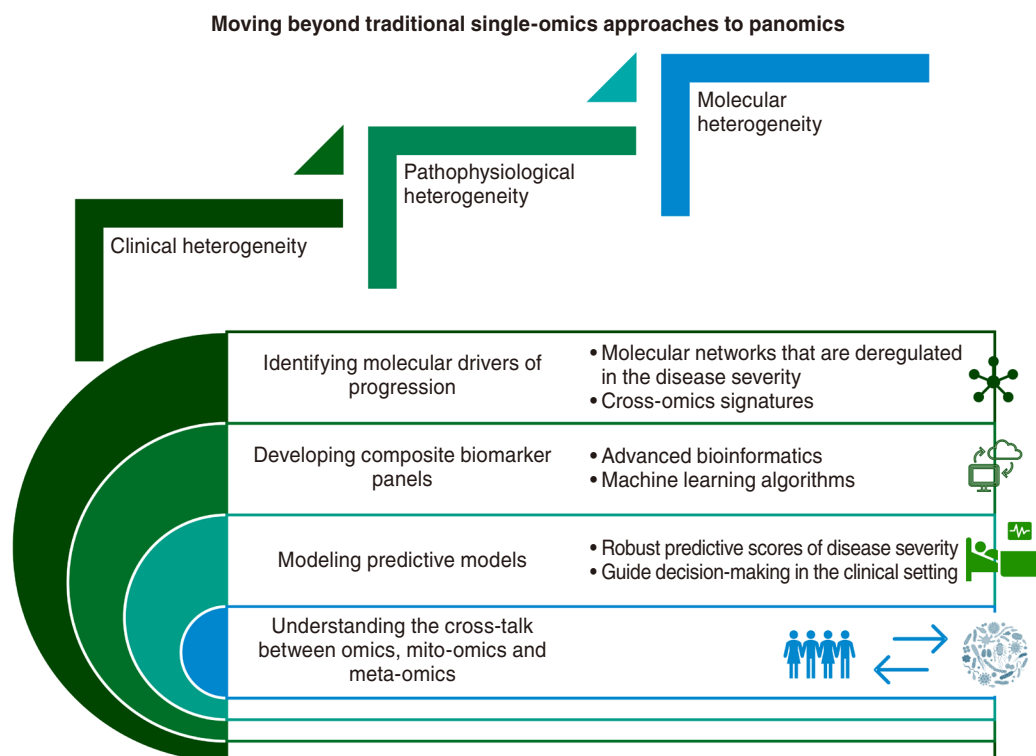


Figure 2. The concept of MASLD heterogeneity: Advantages of transitioning from conventional single-omics methodologies to panomics. MASLD, metabolic dysfunction-associated steatotic liver disease.

ous complications.⁵⁰ To illustrate, Huang et al.⁵¹ developed a prediction score employing machine learning (ML) and 250 metabolites to predict mortality from MASLD in the general population and Nouredin et al.⁵⁰ developed

MASEF score, a promising diagnostic tool for the assessment of at-risk MASH.

The integration of lipidomic approaches with data mining strategies facilitates the inference of networks and potential

pharmacological targets. Moreover, it elucidates the potential of lipidomic studies to provide insight into the interrelationships among metabolite clusters that modify the biology of MASLD, genetic susceptibility, diet, and the gut microbiome.⁶⁴

In recent years, the application of state-of-the-art methodologies in the investigation of the blood proteome in MASH has resulted in the gain of valuable insights,^{55,56,62,65–70} thereby facilitating the elucidation of disease mechanisms and the identification of optimal non-invasive biomarkers. It is of particular significance to highlight the applications of systems biology to the use of omics, including pathway-based approaches and gene-gene or protein-protein interactions.^{23,71} These applications serve to amplify the molecular characterization of the disease, as they are capable of escalating the results of gene expression to an unprecedented level of complexity. It is crucial to point out that a comprehensive study⁷² underscores the fundamental distinction between transcriptomic and proteomic analyses: while transcriptomics quantifies mRNA abundance as a proxy for gene expression, proteomics directly measures protein levels—the functional executors of cellular activity. Across 29 human tissues, including the liver, the authors reveal a widespread discordance between mRNA and protein abundance, with proteomic data showing greater stability and narrower dynamic variation. In the liver, key proteins such as phenylalanine hydroxylase (PAH) are abundantly expressed despite moderate transcript levels, illustrating the role of post-transcriptional regulation and protein stability. Moreover, the study identifies 37 proteins with no prior protein-level evidence, some validated by synthetic peptides, highlighting proteomics as a discovery tool beyond annotation. Notably, many highly expressed transcripts lack corresponding detectable proteins, suggesting translational inefficiency, rapid degradation, or technical limitations. These findings affirm that mRNA abundance alone is insufficient to infer protein presence or function, and that proteomic profiling is essential for uncovering hidden layers of tissue-specific biology—especially in metabolically active organs like the liver.

THE RATIONALE OF MULTIOMICS/PANOMICS IN MASLD RESEARCH. PART II: CLINICAL UTILITY OF MOLECULAR PATIENT SUBTYPING

The combination of omics strategies offers a substantive

benefit for not only MASLD research but also for broad molecular profiling in clinical practice (Fig. 2). The most compelling rationale for employing panomics approaches in MASLD research is the potential for integrating individual layers of omics data to generate a comprehensive molecular landscape. This landscape can be conceptualized as a multilayer map of biological events, originating in the DNA and exerting repercussions on all facets of cell and tissue biology. Nonetheless, the analysis of integrative omics data is not only complex in nature but also demands numerous statistical resources to guarantee an unbiased result. This integration should likely require artificial intelligence (AI) resources to deconvolve the complexity of the multi levels mentioned above.

The integrative multiomics strategy is at the cutting edge of patient care and provides a refined methodology for the precise stratification of patient cohorts. By drawing upon the comprehensive knowledge derived from these diverse data sources, this approach enhances the precision of disease diagnosis and facilitates the development of highly personalised treatment modalities.

A research study classified MASLD into three distinct molecular subtypes by analyzing whole-genome sequencing, proteomics, phosphoproteomics, lipidomics, and metabolomics data from a variety of biological samples.⁵³ These subtypes exhibit unique features, including a subtype associated with increased expression of specific enzymes, namely CYP1A2 and CYP3A4, which have been implicated in the reduction of liver fat by affecting key signalling pathways. Another subtype is characterised by a greater presence of both M1 and M2 macrophages in the liver, which is probably triggered by lipids and leads to inflammation. Finally, a third subtype has been shown to exhibit potential risk for HCC development by increased transcription of CEBPB- and ERCC3-regulated oncogenes.

Magdy et al.⁵⁴ utilised a combination of omics approaches to provide evidence that genes associated with the complement system are linked to the severity of MASLD. These findings provide new insights into the progression of MASLD and suggest that the blocking of the function of certain complement proteins could be a promising therapeutic approach for managing the disease.

The overarching objective of integrative omics is to translate these intricate molecular signatures into straightforward, non-invasive, and highly precise clinical instruments.

These instruments can accurately stratify patients, facilitating the implementation of personalised and preventative medicine for those at the highest risk of severe complications.

For example, Govaere et al.⁵⁵ constructed a proteo-transcriptomic model of progressive MASLD and identified a circulating proteomic expression profile for distinguishing patients at risk of MASH using a signature of 31 markers.

Another illustration of panomics is the integration of human omics data with meta-omics. In this regard, Pirola et al.⁵⁸ combined metagenomic data of the liver tissue in samples of patients covering the full spectrum of the disease severity with genetic variation at regions of the genome that provide either risk or protection against MASH. In this study, the authors demonstrated that genetic variations at specific loci, namely *PNPLA3*-rs738409, *TM6SF2*-rs58542926, *MBOAT7*-rs641738, and *HSD17B13*-rs72613567, along with a variant affecting macronutrient intake (*FGF21*-rs838133), are likely to exert an influence on the composition of liver microbial DNA. In a further study, Pirola et al.⁵⁷ showed that the host liver epigenome – encompassing the activity of enzymes that play an essential role in maintaining the balance between histone acetylation and deacetylation, along with the comprehensive DNA hydroxymethylation status – may function as a target for microbial signals. Consequently, the integration of data derived from human samples and the analysis of the host's omics, in tandem with meta-omics, may facilitate a more comprehensive understanding of the disease pathogenesis from a holistic standpoint.

TECHNOLOGICAL ADVANCES FUELLING MASLD PANOMICS: ADDRESSING CELLULAR HETEROGENEITY BY SINGLE CELL APPROACHES (SC-OMICS)

Conventional bulk omics methodologies, including bulk RNA sequencing, analyse a sample of millions of cells, thereby yielding an average molecular profile. Although bulk RNA sequences can be deconvoluted by a process that is not always straightforward. Therefore, bulk RNA sequencing may obscure significant cell-to-cell variations leading to an oversimplistic view, even when considering a particular cell type like hepatocytes. Conversely, single-cell

omics (sc-omics) employs a cell-by-cell analysis of the DNA, RNA, or proteins of each cell, thereby unveiling the molecular distinctions present within a tissue. The utilization of sc-omics confers numerous advantages, including the identification of hitherto concealed cell populations that are instrumental in the progression of the disease and indeed cell trajectories in the disease process. For instance, in the context of MASH, single-cell RNA sequencing (scRNA-seq) has been used to identify a minor subset of liver cells that exhibit distinctive gene expression signatures, thereby facilitating the understanding of the progression of the disease to fibrotic stages.⁷³ This insight is not attainable through the utilization of bulk sequencing or at least, not without certain bias. The identification of these specific populations enables researchers to develop targeted therapies that selectively eliminate these cells.

Elison et al.⁶¹ created a single-cell map that provided a high-resolution view of liver cell types, annotating 88% of the genetic regions linked to MASH. They found that one-third of these regions affect the regulation of hepatocytes, linking them to distant target genes. The study also characterized the diversity within hepatocyte populations, identifying specific groups enriched in MASH with altered gene expression, localization, and signaling.

On the other hand, the application of sc-omics facilitates the mapping of disease trajectories and microenvironments. For instance, through the implementation of quantitative, label-free proteomic analysis on the primary cell types of the human liver – comprising hepatocytes, liver endothelial cells, Kupffer cells, and hepatic stellate cells – Ölander et al.⁷⁴ have successfully identified 9,791 proteins, thereby confirming the existence of cell-type-specific proteins.

In a recent study, Hong et al.⁶⁰ conducted a single-cell expression quantitative trait locus (sc-eQTL) analysis on liver biopsies from patients with MASLD and control samples. This analysis identified over 3,500 sc-eQTLs across major liver cell types and cell-state-interacting eQTLs (ieQTLs), which exhibited significant enrichment for disease heritability.

Dealing with large panomics datasets requires specialised bioinformatics tools to integrate multiple “omics” layers (genomics, transcriptomics, etc.) and to address the issue of missing data, where low-abundance transcripts are not detected in a cell.

The future of single-cell omics lies in its integration with spatial omics,⁷⁵ which not only profiles individual cells but also preserves their physical location within a tissue. This approach will facilitate a more comprehensive understanding of the heterogeneity of the disease.

CHALLENGES IN ADDRESSING DISEASE HETEROGENEITY AND POTENTIAL SOLUTIONS FOR IMPLEMENTING CLINICAL TRIALS

The primary challenge in overcoming the hurdles associated with disease heterogeneity is the accurate diagnosis and subtyping of patients living with MASLD and diverse disease drivers and clinical trajectories.

The second challenge resides in the development of efficacious treatments for the heterogeneous subtypes of MASLD, given that a therapeutic agent that proves effective in one subtype may prove ineffective or even deleterious in another.

The third challenge emerges from the high degree of molecular complexity inherent to the disease. It is the result of intricate, cross-talk interactions involving multiple genes, proteins, and molecular pathways, compounded by environmental factors. While mapping these vast biological networks is a considerable analytical hurdle, achieving a comprehensive, systems-level understanding is indispensable for translating genomic and proteomic data into effective, individualized therapies.

Potential solutions to these challenges are provided by panomics approaches that focus on personalised medicine. The ultimate aim of these approaches is to identify endotypes (subtypes defined by a distinct biological mechanism, those mentioned above, “latent classes”) and subsequently design tailored therapies based on each unique genetic and molecular profile. Nevertheless, the implementation of panomics to address these goals is not only time-consuming but also costly for some healthcare systems.

To address the aforementioned obstacles and challenges, it is reasonable to implement a series of pragmatic solutions. In particular, it is necessary to ensure that the current clinical trials, which are either ongoing or scheduled to commence in the near future, are not delayed.

A potential example of a straightforward solution is the

implementation of adaptive clinical trials. The final point concerning the implementation of adaptive clinical trials involves the implementation of pre-planned strategies, for example, the identification of patients’ subgroups using genetic information or molecular biomarkers. This strategy is intended to ensure that endotypes of MASH, for instance, respond optimally to a given treatment. An interesting example of this strategy is the use of AZD2693, a potent GalNAc-conjugated ASO that targets *PNPLA3* mRNA in patients who carry the G-risk allele of rs7383409.⁷⁶

A more complex yet valid and attractive strategy is the implementation of seamless Phase II/III designs that allow for a randomised proof-of-concept stage before committing to the full cost of a Phase III trial.⁷⁹ Response-adaptive randomization can increase the probability that new patients will be assigned to the treatment arm with a better outcome. Nevertheless, statistical methods used for analyzing and interpreting data from adaptive trials present significantly greater challenges compared to those used in conventional trials.

INTEGRATING AI AND ML IN MASLD RESEARCH

The complexity and clinical heterogeneity of MASLD necessitate advanced computational tools. AI, specifically ML algorithms, is emerging as the essential technology for transforming large, high-dimensional datasets—particularly multiomics data—into clinically actionable insights. ML models (such as deep learning networks and random forests) are uniquely suited to integrate and interpret disparate data types (genomics, proteomics, metabolomics, and clinical records). This capability moves beyond simple statistical correlations to construct unified, systems-level biological models of the disease, identifying cross-platform regulatory networks that drive progression from simple steatosis to MASH.^{15,78-81} Furthermore, AI is rapidly being adopted to create predictive models that bypass the need for invasive liver biopsy. These models leverage combinations of clinical, radiological (e.g., ultrasound, MRI), and laboratory data readily available in electronic health records (EHR) to accurately diagnose MASLD in the general population; stratify patients by disease severity (e.g., distinguishing high-risk fibrosis/MASH from low-risk steatosis); and

discover novel biomarkers by finding complex patterns in molecular and clinical data. The goal of this integration is to achieve precision medicine in MASLD, ensuring that therapeutic interventions are tailored to an individual patient's unique molecular profile and risk trajectory.^{78,82,83} These procedures are greatly facilitated by the emergence of impressively improving Large Language Models (LLMs). LLMs are designed to understand and generate human-like text, leveraging large-scale patterns in data. They may facilitate (are facilitating) multiomics/panomics applications by integrating diverse data types (genomics, proteomics, and metabolomics) with clinical context (HER data) to support patient diagnoses and classification. As with any new and powerful technology, this growing field of applications needs close and careful monitoring and regulation.

FUTURE DIRECTIONS

Below are the key technological developments guiding future MASLD research. By providing the tools to unravel the molecular and clinical heterogeneity of the disease, these advancements are set to have a direct, transformative impact on the creation of superior diagnostic models and the discovery of innovative therapeutic targets.

For example, integration of patient-derived 3-D *in vitro* disease models coupled with panomics techniques is a pivotal strategy in the realm of drug discovery and precision medicine. This integration of omics with 3-D culture models, exemplified by 3-D organoids, now even with perfusion vessels, yields promises and advancements in the field of MASLD research.⁸⁴⁻⁸⁷

Developing transcriptome-proteome-based molecular classifications of MASH involves multiomics data fusion. This requires computational methods to analyze mRNA levels alongside the actually expressed functional proteins. By correlating these two critical layers of molecular information, researchers can identify functional discordances and network perturbations unique to MASH progression, thereby establishing mechanistically informed disease classifications rather than descriptive clinical groupings.

Furthermore, we anticipate a strong impact from two key methodological advances. First, the application of spatial proteomics using DNA-barcoded antibody libraries will enable highly multiplexed protein analysis while preserving

crucial tissue architecture.⁸⁸ Second, the use of fluxomics will provide essential insight into the functioning and dynamics of multiple deregulated metabolic pathways.⁸⁹

In parallel, the field will be significantly advanced by expanding the systemics (systems biology of systems or Sos)⁹⁰ in MASLD research. Specifically, the use of multi-tissue multiomics systems biology informs on molecular pathways deregulated simultaneously in multiple tissues, thereby dissecting cross-tissue mechanisms of disease pathogenesis. Likewise, drug-response clusters based on molecular sub-groups will enable precision medicine.⁹¹

The integration of single-cell panomics represents a crucial advance. By allowing researchers to dissect the complex cellular and molecular heterogeneity among hepatic resident and non-resident cells in MASLD, this technology creates a powerful predictive platform. This platform is essential for accurately forecasting individual treatment responses and enabling truly personalized therapeutic strategies.⁹²

In proteomics, further investigation is essential to map the variations in the proteome and phosphoproteome that underpin hepatic cellular dysfunction. Specifically, analyzing these molecular changes is critical for deciphering the mechanisms that drive key pathological processes, including inflammation, hepatocyte injury, and fibrosis progression. Likewise, analysis of the MASH secretome needs to be expanded by multiplexed immunoassay-based beads for measuring the concentrations of cytokines and fibrogenic factors in the supernatant of multicellular spheroid tricultures to uncover novel disease monitoring biomarkers ultimately reflecting the circulating secretome.

Finally, two parallel research avenues are set to transform the field. First, the application of epi-transcriptomics techniques—including N6-methyladenine (m6A) and other post-transcriptional RNA modification sequencing—will allow for the precise examination of RNA modifications in liver tissue and their influence on disease progression. Second, big-data analysis, in conjunction with AI, ML, LLMs, and panomics, is poised to become crucial for simulating potential clinical scenarios and accurately predicting therapeutic targets.

Authors' contribution

C J Pirola and S Sookoian are responsible for conception, design, analysis, interpretation, and drafting of the

manuscript. All authors approved the final version of the manuscript.

Conflicts of Interest

The authors have no conflicts to disclose.

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