

Integrative Multi-Omics in Cardiovascular Genomics: From Molecular Mechanisms to Precision Cardiology

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ABSTRACT

Background: Cardiovascular diseases (CVDs) remain the major cause of illness and death worldwide, significantly and continuously increasing the strain on global healthcare systems. While genome studies helped discover many genetic factors associated with a higher risk of CVD, the single-omics approaches are still far from capable of mapping the entire complex and multifaceted causative nature of cardiovascular diseases.

Methodology: This article brings together existing data on the use of multi-omics ways to study heart health and implement precision medicine. We reviewed literature to check for ways molecular information is combined to find biomarkers, risk prediction, get a deeper understanding of disease mechanisms.

Output: By bringing together different layers of molecular data, multi-omics can give a more comprehensive picture of molecular heterogeneity and the elaborate regulatory networks that lead to heart-related diseases at the molecular level. Analysing together different types of molecular data has helped researchers to discover new markers of disease, patient stratification in a more accurate manner, enhanced prediction of disease susceptibility and clinical outcomes and has also revealed new potential therapeutic targets.

Conclusion: Integration of the data obtained from different molecular layers, lead to the detection of previously unknown biomarkers, exposure of dynamic regulatory networks, and promotion of the identification of therapeutic targets for different cardiovascular diseases. The progress that has been made in the high-throughput technology arena combined with AI and machine learning has ramped up the capacity to process very complex and huge datasets, risk stratification and the development of precision cardiology.

KEYWORDS: Cardiovascular Genomics, Multi-Omics, Metabolomics, Precision Cardiology, Transcriptomics.

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INTRODUCTION

Still the major cause of disease and death globally, cardiovascular diseases (CVDs) lead to around 17.9 million deaths every year, which is almost 32% of all worldwide deaths according to the World Health Organization (20,23). Across the globe, the increase in CVD is mainly due to the aging of the population, people moving to cities, and the growing number of people with risk factors like high blood pressure, diabetes, and lack of physical activity. Countries with low and middle income are the ones getting mostly affected by these diseases; it's a big example of health inequalities and shows that these countries are in a dire need of better ways for prevention, diagnosis, and treatment.¹ Even with the progress made in managing patients and health promotion, due to the intricate and many-sided nature of cardiovascular diseases, it is very difficult to accurately predict the risk and identify the right treatment targets.

Genome-wide association studies (GWAS) have played an important role in unravelling the genetic basis of CVD over the last twenty years. Such studies revealed many genetic

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loci linked to coronary artery disease, atrial fibrillation, and cardiomyopathies.² Unfortunately, genomics by itself can explain only a small portion of disease heritability, and it cannot identify the complex gene-environment and gene-lifestyle interactions. Besides, genomics tell us little about the downstream biological processes such as gene expression, protein function, and metabolic changes which are very important for understanding how diseases develop and are manifested.³ A focusing too much on just one or two aspects limits the understanding of the complexity of cardiovascular pathophysiology.

Multi-omics methods were conceived to break through the constraints in the biology and medicine research sectors. These methodologies combine different layers of biological data. Multi-omics can pinpoint the main regulatory networks, molecular markers, and disease mechanisms by taking into account the interactions at various biological levels, something single-omics methods are not capable of.² Developments in high-throughput sequencing technologies, mass spectrometry, and computational biology have aided the generation and integration of large multi-omics datasets, thus advancing the field of cardiovascular research. Besides, multi-omics data integration is at the core of systems biology, a field that interprets biological operations as interconnected networks of components rather than isolated elements. Such a systems view is essential in deciphering cardiovascular diseases since it is well established that multiple pathways co-operate to influence the onset, development, and final manifestation of a disease. Furthermore, the deployment of cutting-edge analytical techniques like artificial intelligence and machine learning not only strengthens our ability to identify meaningful patterns from very complicated datasets but also helps in translating these patterns to useful clinical information.^{4,5}

Overview of Omics Layers in Cardiovascular Genomics

To understand the complexity of CVDs it is necessary to thoroughly investigate biological systems at different molecular levels. Every "omics" field offers a distinct viewpoint and combining them results in a significantly detailed description of the disease processes. The main omics layers associated with cardiovascular genomics are genomics, epigenomics transcriptomics, metabolomics and proteomics.

Genomics

Genomics is the base of multi-omics studies as it provides the means to analyse the genome comprehensively along with its variations that cause susceptibility to CVD. Improvements in sequencing technologies that allow processing of a large number of DNA base pairs in a short time have paved the way for the identification of hundreds of genetic loci involved in major cardiovascular conditions such as coronary artery disease, atrial fibrillation, hypertension, and cardiomyopathies.^{2,6} These research findings have not only deepened our knowledge of the genetic make-up of CVD but also led to the emergence of methods like polygenic risk scores (PRS) which consider the effects of multiple variants to estimate the disease risk of an individual. However, by itself, genomics tells only a part of the story of disease biology. Many of the risk variants that have been found are in the non-coding areas of the genome, where the variants affect gene regulation without directly changing the protein structure.⁶ Therefore, there is still a big hurdle in figuring out how these variants are tied to the changes in function. Some time, Genomics fails to reflect the changes in biological processes that happen over time, such as the variation in

gene expression, the ways proteins interact, or the changes in metabolism, all of which play a vital role in disease-related changes in the body. Also, a point worthy of mention is that the lack of representation of different populations in genomic studies results in the findings from these studies having limited applicability worldwide and could also potentially lead to disparities when these findings are applied clinically. The majority of GWAS have been performed with European descendant populations, this might reduce the accuracy of genetic risk prediction in the other populations.⁷ Consequently, genomics plays an indispensable role in providing information on inherited risks but it has to be combined with other omics levels in order to be able to fully understand the mechanisms of cardiovascular diseases and to make precision medicine in cardiology possible.

Transcriptomics

Transcriptomics plays a key role in revealing the functional consequences of the genome by profiling RNA transcripts, thus indicating gene expression under particular physiological and disease states. While genomics offers a static map of the genome, transcriptomics monitors fluctuating gene expression levels, which helps to pinpoint molecular mechanisms of CVD development. Modern high-throughput methods including RNA sequencing (RNA-seq) and single-cell RNA sequencing (scRNA-seq) have significantly changed cardiovascular study, giving researchers tools for very detailed gene expression measurement in tissues as well as at the level of single cells.^{8,9,19} Transcriptomic analyses in cardiovascular genomics have identified important pathways that get disrupted in the heart, such as those involved in inflammation fibrosis oxidative stress, and remodelling of the heart tissue. For example, a large-scale transcriptomic study of human heart tissue has shown that there is significant diversity among cells and that gene expression patterns differ according to disease in heart failure and cardiomyopathies.⁶ Furthermore, combining this with genomic data through expression quantitative trait loci (eQTL) mapping allows us to interpret the function of genetic variants by connecting them to changes in gene expression.⁹ This combined challenge helps see how variations in one's genes can be the cause of differences in their physical features. Transcriptomics, in particular, encounters several challenges, including temporal changes, different tissues, and the problem of obtaining good quality heart samples, among others. Besides that, the level of mRNA is not always a good indicator of the amount of protein because of post-transcriptional regulation.

Proteomics

Proteins are considered the main agents through which most cellular functions are carried out. They are also major players in both normal heart functioning and heart diseases. Unlike transcriptomics, where mRNA is the main focus for gene expression studies, protein expression levels can't always be predicted by mRNA levels. This is due to the added layers of regulation after transcription, the process of protein

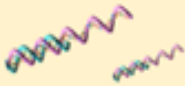
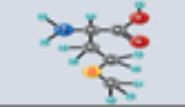
OMICS layer	Measures	Key examples	Integration and Impact
Genomics 	DNA sequence variation i.e. SNPs, indels	- GWAS loci for CAD, HF, AF. - Polygenic risk scores - Rare pathogenic variants (<i>MYH7</i>, <i>LDLR</i>)	 ↓ Disease Risk (CAD, HF, AF) ↓ Mechanistic insights ↓ Precision Medicine ↓ Improved outcomes
Epigenomics 	Histone modifications, DNA methylation, chromatin accessibility	- Histone marker in heart failure - Chromatin Accessibility	
Transcriptomics 	Gene expression levels	- Differential gene expression - Alternative splicing - Non-Coding RNA	
Proteomics 	Protein abundance, isoforms	- Altered protein - Phosphorylation changes - Biomarkers	
Metabolomics 	Metabolite concentration and metabolic pathway activity	- Lipid signatures in atherosclerosis - Metabolic remodelling - Energy metabolism	

Figure 1: Overview of OMICS layers in cardiovascular genomics

turnover, and also protein modifications after translation like phosphorylation, glycosylation, and ubiquitination.¹⁰ As a result, proteomics can offer a closer look at the changes in biological activities and the mechanisms of diseases. The developments in the resolution of mass spectrometry and quantitative proteomics methods, such as tandem mass tags (TMT) and label-free quantification, profiling of protein expression in the heart and other biological fluids has become extensive. Proteomic studies have revealed important markers affiliated with heart attack, heart failure, and the buildup of plaques in arteries, for instance, natriuretic peptides, troponins, and inflammatory mediators.¹¹ Besides, proteomics has played a major role in uncovering intricate pathways of heart tissue changes, the formation of scar tissue, and the dysfunction of the lining of blood vessels thereby leading to potential drug targets. Proteomics is often integrated with genomics and transcriptomics to supply a more detailed understanding of the function of genetic variants and gene expression. Protein quantitative trait loci (pQTL) studies, for instance, can demonstrate the link between genetic variation and protein level, which is the most crucial point that connects genotype to phenotype.¹²

Metabolomics

Metabolomics is the study of small-molecule metabolites, which are the byproducts of biological activity and provide a clear picture of the pathological and physiological conditions of a cell or organism. As metabolites reflect the combined effects of genetics transcription proteomics,

and environmental factors, metabolomics is a particularly insightful and sensitive method for studying CVD. Nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS) are two of the most advanced analytical methods. These methods allow for the rapid measurement of a wide variety of metabolites, including lipids, amino acids, and energy metabolites.¹³ Metabolomics in cardiovascular sciences has identified metabolic signatures characteristic of coronary artery disease, heart failure, and hypertension. Changes in lipid metabolism like increased low-density lipoproteins and fatty acids oxidation defects are majorly atherosclerosis. Also, changes in amino acid metabolism, especially branched-chain amino acids, have been linked to insulin resistance and higher cardiovascular risk.¹⁴ These findings highlight the potential of metabolomics for early disease detection, risk stratification, and evaluation of therapeutic effectiveness. Notably, metabolomics not only capture the biological processes happening inside the body but also expose the external factors such as diet, lifestyle and environmental exposures which are very crucial elements of precision medicine.

Epigenomics

Epigenomics is the study of the changes that can be inherited and can alter or reverse gene expression, without affecting the actual DNA sequence. DNA methylation, histone modifications, and regulatory non-coding RNAs are the primary epigenetic mechanisms that are essential for altering gene expression in response to various environmental and

physiological signals. Epigenetic regulation has been shown to be an important factor that connects genetic inheritance and external factors such as diet smoking stress, and aging in CVD. DNA methylation is the best-studied epigenetic modification, and it is usually associated with gene silencing (i.e. preventing the gene from being made into RNA). Changes in DNA methylation have been associated with atherosclerosis, hypertension, and heart failure, among other things, by affecting the expression of genes involved in inflammation, endothelial function, and vessel remodelling.¹⁵ The dysregulation of histone-modifying enzymes has been shown to contribute to pathological cardiac hypertrophy and fibrosis, which underlines their disease progression role.¹⁶ Epigenomic changes are not only highly flexible but also very dependent on the situation, which enables cells to change their behaviour very quickly when the environment around them changes. The ability to change so easily is one of the reasons why epigenetic changes can be ideal as biomarkers and therapeutic targets. When epigenomics data is combined with other types of omics data, it results in an improved understanding of gene regulatory networks, disease mechanisms, and so on.

Multi-Omics Integration Strategies

Combining multi-omics data is essential for taking cardiovascular genomics not just to the level of descriptive studies, but to a systems understanding level and ultimately to clinical applications. On their own, single omics layers provide valuable bits of information, but it is their integration that enables us to reveal the complex molecular interactions and regulatory networks underlying CVDs. Nevertheless, the integration of diverse data sets results in major computational and methodological problems, as the data differ in structure, scale, and biological meaning. In order to solve these problems, a number of integration methods have been created, which can be mainly divided into horizontal, vertical, and network-based approaches in addition to latest data fusion and machine learning methods.

Horizontal Integration

Horizontal integration, also known as the aggregation of datasets from the same omics layer but different studies, cohorts, or platforms, is a way of increasing statistical power, enhancing reproducibility, and revealing robust molecular signatures. In the field of cardiovascular genomics, this approach is most often used in large-scale genome-wide association study (GWAS) meta-analyses, which have led to the identification of thousands of genetic variants linked to coronary artery disease, blood pressure, and lipid traits. Recent multi-cohort GWAS meta-analyses have greatly increased the number of cardiovascular risk loci by using data from different populations, thus enhancing the understanding of genetic architecture and allowing genetically different populations to be compared.^{17,18} Similarly, the integration of transcriptomic datasets from

different studies has resulted not only in the identification of gene expression changes shared between heart failure and atherosclerosis but also these findings have obtained the strong biological support, which is reflected in increased biological plausibility of the results. However, horizontal integration remains an incredibly potent means of generating cardiovascular research outputs with high certainty and reproducibility. By leveraging large-scale collaborative datasets and improving the standardization of methodologies, this route has become a major factor driving the advancement of biomarker discovery, enhanced genetic risk prediction accuracy, and the development of precision cardiology that is population-specific.

Vertical Integration (Multi-Layer Integration)

Vertical integration refers to studying different kinds of omics data gathered simultaneously such as genomics transcriptomics proteomics, metabolomics, and epigenomics to follow how biological information is transmitted from genotype to phenotype. This approach is an important feature of systems biology since it allows us to identify the real molecular reasons of CVDs rather than merely linking them to markers. Through connecting genetic variations with their impacts at the molecular levels, vertical integration provides us with a detailed insight into the mechanisms of disease development and progression.

One major use of vertical integration is the mapping of quantitative trait loci, which includes expression quantitative trait loci (eQTL) and protein quantitative trait loci (pQTL) that highlight the connection between genetic variants and the expression levels of genes and proteins.^{9,13} These techniques have greatly helped in identifying the genes that cause disease by focusing on the loci found in GWAS for CAD and heart failure. Additionally, techniques such as Mendelian randomization use multi-omics data to establish causality between molecular features and disease, thus making the findings more directly applicable to medicine.²⁰ Vertical integration in cardiovascular research has led to the discovery of major pathways-related to lipid metabolism, inflammation, and vascular remodelling by the combination of genomic variants with transcriptomic and proteomic signatures. Metabolomics data integration in recent studies helped understand how genetic variation affects metabolic pathways associated with atherosclerosis and cardiometabolic risk.²¹ All things considered, vertical integration is an excellent strategy for connecting genetic variation and clinical phenotype, which is leading to the evolution of association-based studies into mechanistic and predictive models in precision cardiology.

Network-based integration is a systems biology approach that considers the whole living organism when studying biological processes. This is done by building a model of genes proteins metabolites, and regulatory elements acting as networks and interacting with each other. It is well known

that diseases are very complex phenomena involving many components and interactions, so modelling based on the analysis of single molecules only is usually of limited use. Therefore, the idea behind the network-based strategy is to be able to depict disease mechanisms in a much more realistic way by including all components that influence them directly or indirectly. For multi-omics studies, this type of methods, which are able to deal with different kinds of data, are used to derive unified interaction diagrams that can then be exploited for discovering major regulatory hubs, functional groupings, and pathways underlying disease phenomena.²²

Network-Based Integration

Gene co-expression network analysis is one of the main branches of this research field. It is aimed at discovering modules of genes whose expression levels correlate in a way that is coherent with known biological phenomena (physiological/pathological). One of the most popular variants of this method is weighted gene co-expression network analysis (WGCNA). In the case of cardiovascular diseases, WGCNA has been successfully utilized to identify gene groups that correlate with heart hypertrophy, fibrosis, and heart failure development at molecular level.²³ On the other hand, PPI networks integrate proteomics and capture physical interaction but also functional partnerships among proteins, thus enabling the identification of key signalling pathways associated with inflammatory responses, endothelial dysfunction, and myocardial remodelling. Overall, network-based integration continues to be an effective approach in uncovering the complex molecular structure of cardiovascular diseases and promoting precision medicine.

Pathway Enrichment Approaches

Pathway enrichment analysis offers a functional basis to analyze multi-omics data. The technique involves linking molecular entities (e.g. genes proteins, or metabolites) to known biological pathways. Instead of zeroing in on individual molecular variations, these techniques highlight that alterations of biological processes are coordinated. That is how the knowledge of mechanisms of CVD is deepened. Thus, tools like Gene Set Enrichment Analysis (GSEA), Kyoto Encyclopaedia of Genes and Genomes (KEGG) and Reactome help in locating the pathways that are the most enriched in the disease states.^{24,25} Pathway-based strategies that combine transcriptomic, proteomic, and metabolomic data help to reveal biological mechanisms that are shared across multiple omics layers, which can be trusted and understood better.²⁶ A major benefit of pathway enrichment is that it effectively reduces data dimensionality and highlights biologically relevant signals in high-throughput datasets. However, pathway enrichment has remained one of the main methods for multi-omics data integration, and it can help to turn complex molecular information into biologically meaningful insights in cardiovascular research.

Data Fusion Models

Data fusion models act as a fundamental aspect of multi-omics integration; they allow combining systematically heterogeneous datasets into cohesive analytical frameworks. Such models are very helpful in cardiovascular genomics, where the complexity of interactions across different molecular layers determines disease initiation and development.²⁷ Generally, data fusion tactics are dividable into three types: early, intermediate and late integration. Early integration methods (also known as concatenation-based methods) merge datasets at the feature level into a single matrix before proceeding with the analysis. This tactic, though easy to apply, might be exposed to performance deterioration due to high dimensionality and noise. Intermediate integration methods, e.g. multi-omics factor analysis (MOFA), extract common latent factors from different datasets, which represent biological processes and at the same time help in dimensionality reduction.²⁷ Late integration, or model-based integration, first perform the analysis of each omics dataset separately and then combine the results, thus providing more flexibility and robustness. In cardiovascular science, data fusion models have been effectively utilized to discover multi-omics biomarkers for coronary artery disease, heart failure, and cardiometabolic disorders. Integrative clustering techniques such as iCluster and Similarity Network Fusion (SNF) are examples of methods that can separate patients into molecular subtypes by combining omics profiles. Such advances have brought the possibility of personalizing treatment plans based on patient's molecular profiles.²⁸

Artificial Intelligence and Machine Learning Integration

Artificial intelligence (AI) and machine learning (ML) have emerged as important avenues for the addition and analysis of multi-omics data in cardiovascular genomics. Multi-omics datasets feature high dimensionality, heterogeneity, and complexity that go beyond the possibilities of traditional statistical methods. This situation requires advanced computational frameworks capable of identifying nonlinear relationships and revealing hidden patterns. AI/ML methods enable the integration of different omics layers such as genomics transcriptomics proteomics, metabolomics, and epigenomics into one predictive and mechanistic model, which have been very instrumental in speeding up research into cardiovascular disease CVD.^{29,30} Clustering and dimensionality reduction techniques, as part of unsupervised learning, enable the discovery of molecular subtypes and hidden structures in complex data. More lately, deep learning models such as neural networks and autoencoders have been incredibly beneficial in the integration of multi-modal data and in understanding the complex cross-layer interactions.³¹ AI-powered multi-omics models have become a powerful tool in cardiovascular

genomics. They have not only helped to predict risks by adding genetic information to the traditional clinical factors but also have led to the discovery of new gene-environment and pathway-level interactions. Attention should be given to ethical issues which include data privacy and the bias included in the algorithms. In general, the merger of AI and ML is a major breakthrough in multi-omics research, providing a means to translate complicated biological data into clinically useful information. Developing models that are not only interpretable and robust but also scalable will be key in the future to unlocking the greatest benefits of AI-powered precision cardiovascular medicine.

Applications of Multi-Omics in Cardiovascular Disease

Multi-omics approaches integration has deeply increased understanding, diagnosis, and treatment of CVDs. When combined genomics transcriptomics proteomics, metabolomics, and epigenomics, scientists can reveal complicated molecular pathways, discover reliable biomarkers, and facilitate precision cardiology. The use of multi-omics covers the main cardiovascular diseases, such as coronary artery disease, heart failure, cardiomyopathies, and arrhythmias.

Coronary Artery Disease (CAD)

Coronary artery disease, the primary cause of mortality globally, has been extensively studied utilizing several biological data layers. Studies of genomes have found many new genes that make people more likely to get CAD, whereas studies of transcripts and epigenomes have shown changed scenes of pathways that are responsible for inflammation, lipid metabolism and endothelial dysfunction.¹⁸ The profiling of proteins and metabolites came to the rescue to back up these discoveries by detecting circulating biomarkers, like inflammatory cytokines and lipid metabolites, which reflect the disease's progress. Integrative analyses that combine genetic variants with metabolite profiles have not only enhanced risk prediction but also pointed out new therapeutic targets, especially in the lipid and inflammatory pathways.

Heart Failure

Heart failure (HF) is a complicated syndrome involving both the structure and the function of the heart being significantly compromised. Multi-omics research has uncovered the molecular basis of cardiac remodelling, fibrosis, and changes in metabolism. Transcriptome studies have found the changes in gene expressions that correlate with different stages of the disease, whereas proteomics has detected modifications in signalling pathways related to heart muscle stress and remodelling of the extracellular matrix.⁹ Metabolomics studies have pointed to alterations in the way the heart metabolizes energy, especially fatty acid

oxidation and mitochondrial function that are impaired. By combining all these types of data, researchers are able to find markers that can indicate the presence and progression of the disease, and also discover new targets for treatment.

Cardiomyopathies

Genetic mutations in sarcomeric and cytoskeletal proteins underlie cardiomyopathies, such as hypertrophic and dilated, most commonly. The integration of multiple omics has led to better knowledge of the links between genotype and phenotype in such diseases. Genomic sequencing detects the mutation responsible, whereas transcriptomics and proteomics help understand the changes in gene expression and protein function as a result. On the other hand, epigenome studies point out the regulatory mechanisms which lead to disease variability and progression.¹⁶ These combined approaches make diagnostics more precise and pave the way for targeted therapeutics.

Arrhythmias

Atrial fibrillation is the most common type of cardiac arrhythmias and its development is a result of the interplay between hereditary factors, impairment of the ion channels, and the environment. Multi-omics approaches have uncovered a number of genetic polymorphisms associated with ion channel genes and neuronal conduction pathways which thus contribute to the arrhythmogenic potential. Transcriptomic analyses have indicated aberrant gene expression patterns of calcium homeostasis and cardiac excitability, whereas protein-level studies have explained changes in post-translational modifications of ion channel proteins which directly affect electrophysiological stability. Furthermore, metabolomics provides evidence of the metabolically disturbed state of cardiomyocytes, e.g. inefficient energy metabolism and increased oxidative stress, in the pathogenesis of arrhythmias. Altogether, these multi-omics findings shed a new light on risk assessment and pave the way for the implementation of tailored anti-arrhythmic drug treatments.^{31,33}

Biomarker Discovery and Risk Prediction

On the topic of biomarker discovery and risk prediction, multi-omics integration has opened up a new era of biomarker discovery by uncovering molecular signatures not only in genomics but also in proteomics and metabolomics. This has led to the identification of much stronger and reliable drug targets. In contrast to single-omics biomarkers, multi-omics disease signatures reflect the complexity of diseases more comprehensively and increase the ability to predict the risk of outcomes such as cardiovascular diseases. For instance, polygenic risk scores derived from genomic data combined with profiles for circulating proteins and metabolite have been shown to be excellent predictors of coronary artery disease as well as heart failure.^{34,35} Biomarkers are also of

paramount importance as they not only help in identifying the disease early but also assist in predicting the course of the disease and monitoring the response to the treatment. Further, integrated proteomics and genomics approaches have been instrumental in discovering new and clinically significant biomarkers for cardiovascular risk stratification and paving the way for precision medicine that is highly personalized.^{11,17}

Therapeutic Target Identification and Precision Medicine

Multi-omics strategies are a great resource for the identification of therapeutic targets and understanding disease-associated molecular networks and pathways. The combination of genome, transcriptome, and proteome data will allow the discovery of crucial regulatory nodes that will be responsible for the development of cardiovascular diseases. Such nodes frequently serve as potential drug targets for intervention. Moreover, metabolomics profiling is instrumental in identifying disrupted metabolic pathways for therapeutic interventions. Along the same lines, multi-omics precision medicine opens new avenues for drug repurposing and treatment strategies tailored to individual patients through molecular profiling. Personalized cardiology is on its way, utilizing molecular information to enable more targeted and effective interventions.^{13,22}

Challenges and Limitations

While multi-omics technologies and computational frameworks have improved dramatically, significant challenges remain that prevent their widespread use as research tools or in the clinic for cardiovascular diseases. Data heterogeneity is among the top issues since omics datasets can differ greatly across various characteristics such as scale dimensionality levels, and experimental platforms. A combination of genomes with additional omics dimensions like as transcriptomics, proteomics, and metabolomics necessitates intricate normalization and harmonization procedures. Besides, alignment of different datasets to a common reference may pose challenges and even lead to bias and non-reproducibility.³³ Also, if not corrected adequately, batch effects and technical differences between laboratories and different sequencing platforms may become confounding factors that mask true biological changes. On top of that, one of the main problems is the absence of standardized integration frameworks. There are multiple statistical and machine learning-based methods, but there is no single best one for multi-omics integration. This brings forth variability of analysis results and hampers comparability of independent studies. Moreover, most integrative models run the risk of overfitting and have low interpretability, especially deep learning methods, which are considered as "black-box" systems and challenging to use as clinically informative tools.³⁰ A main biological limitation is that the coverage of

different omics and sampling are not fully matched. Besides, data from different omics types are often generated from different individuals, different tissues or time points, and that renders it impossible to accurately reconstruct causal molecular pathways in cardiovascular disease.

Future Directions in Multi-Omics Cardiovascular Research

The integration of multi-omics data in cardiovascular genomics is most likely to see the development of very detailed, time-dependent, and practical systems-level models. One of the most revolutionary changes is single-cell multi-omics, which allows one to study the genomic transcriptomic epigenomic, and proteomic aspects of individual cells all at once. In contrast to bulk methods, single-cell techniques disclose the existence of different cell types in the cardiovascular tissues; the rare cell populations responsible for inflammation, fibrosis, and cardiac remodelling can be characterized in great detail. This is especially true of diseases that involve multiple factors, like heart failure and atherosclerosis, when the changes in the disease are due to certain subpopulations of cells rather than the entire tissue reacting in the same way.³⁶ The merging of single-cell data is likely to change the way diseases are classified and help to better identify therapeutic targets that are specific to certain cell types. An exciting development very closely related to this is the launch of spatial transcriptomics. This technique keeps tissue architecture intact at the same time as it maps gene expression patterns at spatial coordinates. Focused on the cardiovascular field, spatial methods allow to see how molecules change inside the heart muscle, blood vessel walls, and atherosclerotic plaques. The idea behind digital twins in cardiology is a quite revolutionary concept. Basically, a digital twin is a type of computer simulation of a patient that is made by integrating multi-omics imaging physiological, and clinical data to reflect a patient's health, simulate disease progression, and predict treatment outcomes. Such virtual models can potentially transform precision cardiology as they allow in silico simulation of therapeutic interventions even before patient treatment, thus cutting down on trial-and-error methods in patient care.^{37,38} In a genetically diverse country like India, which also happens to be experiencing a rapid rise in cardiovascular diseases, there is a great necessity to develop multi-omics datasets specific to the population. This will not only lead to the generation of more accurate polygenic risk scores but also help in discovery of biomarkers and ensure the fair implementation of precision cardiology in all ethnic groups.

CONCLUSION

Integrating multi-omics data is turning out to be a game-changing factor in cardiovascular genomics that not only leads to a change in single-layer molecular studies but also provides a systems-level understanding of disease.

Through the combination of different layers of omics layers, the researchers have the chance to analyse the complex networks of gene regulation both in cardiovascular functioning and in the disease process. Implementing this holistic approach to uncovering disease-associated pathways, identifying biomarkers, and understanding the molecular bases of coronary artery disease, heart failure, cardiomyopathies, and arrhythmias has greatly contributed to the field. One critical step towards achieving precision medicine for all is to carry out more multi-omics research in the populations that are currently least represented, like those in India and other low- and middle-income countries. Moreover, innovative methodologies such as multi-omics, transcriptomics, longitudinal profiling, and digital twin modelling are poised to transform cardiovascular research. These tools will open the door to the creation of disease models based on patients in real time and will do much to promote cardiology that is predictive and preventive.

REFERENCES

- Giovanni A, Enrico A, Aime B, et al. Global burden of cardiovascular diseases and risk factors, 1990–2019: update from the GBD 2019 study. *Journal of the American College of Cardiology*. 2020;76(25):2982-3021.
- Khera AV, Chaffin M, Aragam KG, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nature genetics*. 2018;50(9):1219-24.
- Hasin Y, Seldin M, Lusis A. Multi-omics approaches to disease. *Genome biology*. 2017 May 5;18(1):83.
- Karczewski KJ, Snyder MP. Integrative omics for health and disease. *Nature Reviews Genetics*. 2018;19(5):299-310.
- Johnson KW, Shameer K, Glicksberg BS, et al. Enabling precision cardiology through multiscale biology and systems medicine. *Basic to Translational Science*. 2017 Jun 1;2(3):311-327.
- Visscher PM, Wray NR, Zhang Q, et al. 10 years of GWAS discovery: biology, function, and translation. *The American journal of human genetics*. 2017;101(1):5-22.
- Martin AR, Kanai M, Kamatani Y, et al. Current clinical use of polygenic scores will risk exacerbating health disparities. *Nature genetics*. 2019 Mar 29;51(4):584.
- Tucker NR, Chaffin M, Fleming SJ, et al. Transcriptional and cellular diversity of the human heart. *Circulation*. 2020 Aug 4;142(5):466-482.
- GTEx Consortium. The GTEx Consortium atlas of genetic regulatory effects across human tissues. *Science*. 2020; 369(6509):1318–1330.
- Aebersold R, Mann M. Mass-spectrometric exploration of proteome structure and function. *Nature*. 2016 Sep 15;537(7620):347-355.
- Lind L, Sundström J, Ärnlov J, et al. Impact of proteomics on cardiovascular research. *Circulation*. 132(21), 209-221.
- Sun BB, Maranville JC, Peters JE, et al. Genomic atlas of the human plasma proteome. *Nature*. 2018 Jun 7;558(7708):73-79.
- Johnson CH, Ivanisevic J, Siuzdak G. Metabolomics: beyond biomarkers and towards mechanisms. *Nature reviews Molecular cell biology*. 2016;17(7):451-459.
- Shah SH, Kraus WE, Newgard CB. Metabolomic profiling for the identification of novel biomarkers and mechanisms related to common cardiovascular diseases: form and function. *Circulation*. 2012;126(9):1110-1120.
- Greco CM, Kunderfranco P, Rubino M, et al. DNA hydroxymethylation controls cardiomyocyte gene expression in development and hypertrophy. *Nature communications*. 2016 Aug 4;7(1):12418.
- Papait R, Greco C, Kunderfranco P, et al. Epigenetics: a new mechanism of regulation of heart failure? *Basic research in cardiology*. 2013 Jul;108(4):361.
- LeBlanc M, Zuber V, Andreassen BK, et al. Identifying novel gene variants in coronary artery disease and shared genes with several cardiovascular risk factors. *Circulation research*. 2016 Jan 8;118(1):83-94.
- Aragam KG, Jiang T, Goel A, et al. Discovery and systematic characterization of risk variants and genes for coronary artery disease in over a million participants. *Nature genetics*. 2022;54(12):1803-1815.
- Ritchie ME, Phipson B, Wu DI, et al. limma powers differential expression analyses for RNA-sequencing and microarray studies. *Nucleic acids research*. 2015 Apr 20;43(7):e47.
- Hemani G, Tilling K, Davey Smith G. Orienting the causal relationship between imprecisely measured traits using GWAS summary data. *PLoS genetics*. 2017;13(11):e1007081.
- Würtz P, Wang Q, Soininen P, et al. Metabolomic profiling of statin use and genetic inhibition of HMG-CoA reductase. *Journal of the American college of cardiology*. 2016 Mar 15;67(10):1200-1210.
- Barabási AL, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. *Nature reviews genetics*. 2011 Jan;12(1):56-68.
- Langfelder P, Horvath S. WGCNA: an R package for weighted correlation network analysis. *BMC bioinformatics*. 2008 Dec 29;9(1):559.
- Kanehisa M, Furumichi M, Sato Y, et al. KEGG for taxonomy-based analysis of pathways and genomes. *Nucleic acids research*. 2023 Jan 6;51(D1):D587-D592.
- Subramanian A, Tamayo P, Mootha VK, et al. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proceedings of the national academy of sciences*. 2005 Oct 25;102(43):15545-50.
- Fabregat A, Jupe S, Matthews L, et al. The reactome pathway knowledgebase. *Nucleic acids research*. 2018 Jan 4;46(D1):D649-55.
- Argelaguet R, Velten B, Arnol D, et al. Multi-Omics Factor

- Analysis-a framework for unsupervised integration of multi-omics data sets. *Molecular systems biology*. 2018;14(6):MSB178124.
28. Wang B, Mezlini AM, Demir F, et al. Similarity network fusion for aggregating data types on a genomic scale. *Nature methods*. 2014 Mar;11(3):333-7.
29. LeCun Y, Bengio Y, Hinton G. Deep learning. *nature*. 2015 May 28;521(7553):436-44.
30. Libbrecht MW, Noble WS. Machine learning applications in genetics and genomics. *Nature Reviews Genetics*. 2015 Jun;16(6):321-32.
31. Choy MK, Darbar D, & Yadav AV. Integrative omics approaches to atrial fibrillation mechanisms. *Circulation Research*. 2021;128(11):1757-1775.
32. Roselli C, Chaffin MD, Weng LC, et al. (2018). Multi-ethnic genome-wide association study for atrial fibrillation. *Nature Genetics*, 50(9), 1225-1233.
33. Verma S, Verma S, Abbas M, et al. Genetic Biomarkers in the Risk Assessment of Sudden Cardiac Events: A Personalized Approach. *iNew Medicine*. 2026:e70060.
34. Corral-Acero J, Margara F, Marciniak M, et al. The 'Digital Twin'to enable the vision of precision cardiology. *European heart journal*. 2020 Dec 21;41(48):4556-64.
35. Agbaedeng TA, Noubiap JJ, Mato EP, et al. Polygenic risk score and coronary artery disease: A meta-analysis of 979,286 participant data. *Atherosclerosis*. 2021 Sep 1;333:48-55.
36. Bersanelli M, Mosca E, Remondini D, et al. Methods for the integration of multi-omics data: mathematical aspects. *BMC bioinformatics*. 2016 Jan 20;17(Suppl 2):S15.
37. Kelsey G, Stegle O, Reik W. Single-cell epigenomics: Recording the past and predicting the future. *Science*. 2017 Oct 6;358(6359):69-75.
38. Verma S, Verma S, Abbas M, et al. Genetic Biomarkers in the Risk Assessment of Sudden Cardiac Events: A Personalized Approach. *iNew Medicine*. 2026:e70060.

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