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Genomic Medicine Revolutionizes Heart Care: A New Standard of Practice

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Abstract

The integration of genomic and precision medicine into cardiovascular healthcare represents a transformative advancement in addressing the global burden of cardiovascular diseases (CVDs). Precision medicine leverages genomic, proteomic, and metabolomic data to provide personalized care, optimizing treatment outcomes while minimizing adverse effects. Over the past decade, extensive research has highlighted its potential to revolutionize the management of major CVDs, including myocardial infarction, hypertension, and heart failure, which significantly contribute to global morbidity and mortality. Genomic tools, such as polygenic risk scores (PRS) and single nucleotide polymorphisms (SNPs), enhance cardiovascular risk prediction, enabling early interventions and targeted therapies. For example, PRS has demonstrated utility in stratifying individuals with a heightened genetic predisposition to coronary artery disease. Advances in the identification of monogenic variants have also enabled personalized interventions for familial hypercholesterolemia. Furthermore, biomarkers, like cardiac troponins, copeptin, and genetic variants in CYP2C19, have refined diagnostic and therapeutic strategies for acute myocardial infarction. Genomic insight into hypertension have unveiled critical pathways, offering potential targets for innovative treatments. Despite the promise, challenges, such as ensuring diverse study populations and addressing ethical considerations remain. This evolving paradigm underscores the transformative impact of genomic and precision medicine, heralding a new era of individualized cardiovascular care.

Keywords: Genomic medicine, precision medicine, cardiovascular diseases (CVDs), polygenic risk scores (PRS), single nucleotide polymorphisms (SNPs), coronary artery disease, familial hypercholesterolemia, genetic variants, genomic insights

INTRODUCTION

The emergence of genomic/precision medicine holds significant promise in transforming the future of cardiovascular disease (CVD) healthcare by leveraging the power of "omics" in cardiology (Figure1).

Genomic medicine is a medical discipline that uses a patient's genomic information to guide their care, while precision medicine is a marketing term for genomic medicine

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Precision medicine has emerged as a transformative approach in cardiovascular healthcare, offering tailored treatment strategies based on an individual's unique biological profile through advancements in "omics" technologies. Over the past decade, extensive research has been conducted to explore its clinical applications in cardiology, with reviews highlighting its potential to revolutionize disease management. Comprehensive analyses have been documented, including omic-specific insights for major cardiovascular conditions, such as myocardial infarction, hypertension, and heart failure. These

diseases, which contribute significantly to global Disability-Adjusted Life Years (DALYs), represent priority areas for precision medicine interventions. By integrating genomic, proteomic, and metabolomic data, precision medicine enables personalized care, improving treatment outcomes and minimizing adverse effects.

Progress in this field (Figure 2) demonstrates a significant shift toward more individualized and effective cardiovascular care, mirroring its success in other disciplines like oncology.

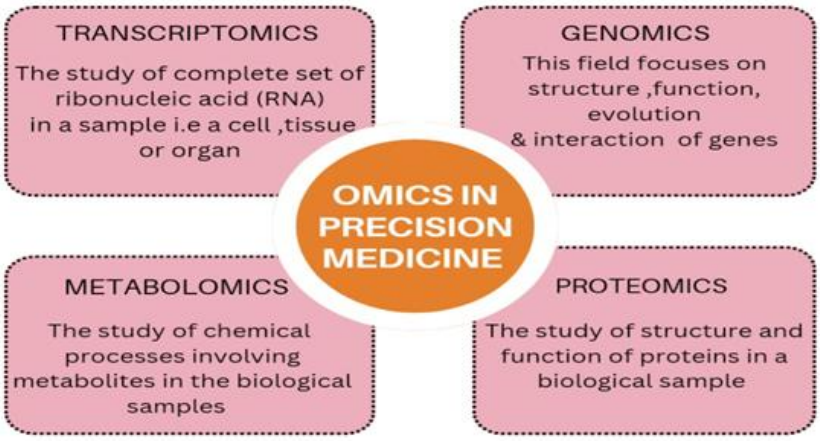

Figure 1. Omics in precision medicine.

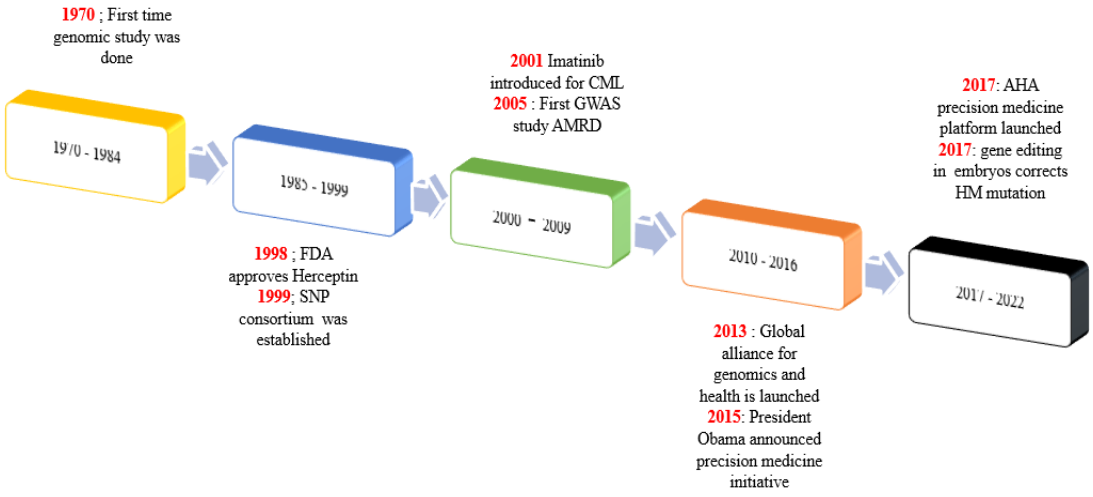

Figure 2. Timeline of evolution in precision medicine in cardiovascular care.

MORBIDITY AND MORTALITY RATE AND CVD COMPLICATIONS

Morbidity and mortality are the most common terminologies used for the epidemiological investigations in determining severity, progression, to compare the health and risk factors of diseases in given population. There is often confusion in morbidity and mortality because of similarities but they are completely distinguishable. Morbidity is used to describe symptoms or unhealthy conditions for any diseases. In a more coherent term, it is presented as prevalence rate and incidence rate. Prevalence is the frequency of the disease happening in given area and the incidence is the incoming of the new cases of symptoms or illness in that population in given time. Both these terms, when divided into the total number of populations of the area taken, will give an estimate of prevalence rate and incidence rate. The morbidity rate is calculated as total no. of diseases, symptoms or affected individuals divided by the total population. Percentage is the unit [1–3].

On the other hand, mortality is the absolute number of deaths that occurred under the condition which is investigated. It is also considered as death rate. The given formula for mortality rate is the deaths per year due to underlying conditions divided by the total population whole entity multiply to 1000 (for ease of measurement in smaller units) [3]. CVD Complications: complications are unintentional conditions cause during procedure, treatment or disease. Arrhythmias, stroke, chest pain, angina, myocardial infarction, heart failure and peripheral artery disease considered as cardinal complications in patients with CV disorders [4, 5].

THE ROLE OF GENOMIC/PRECISION MEDICINE IN CARDIOVASCULAR RISK PREDICTION

Genome-Wide Polygenic Risk Scores (PRS)

Polygenic risk scores (PRS) have emerged as a powerful tool in genomics, combining the effects of numerous genetic variants across the genome to estimate an individual's genetic predisposition to a particular disease. In cardiology, PRS for coronary artery disease (CAD) have been extensively studied. These scores aggregate the risk conferred by multiple common genetic variants, each contributing a small amount to the overall disease risk.

Several studies have demonstrated the clinical utility of PRS in predicting cardiovascular events. For example, Khera et al. found that individuals in the highest quintile of a CAD PRS had a threefold increased risk of coronary events compared to those in the lowest quintile, underscoring the potential of PRS to identify high-risk individuals who may benefit from early intervention [6].

Single Nucleotide Polymorphisms (SNPs)

Single nucleotide polymorphisms (SNPs) are the most common type of genetic variation among humans and play a crucial role in the genetic basis of many diseases, including CVDs. Certain SNPs have been robustly associated with increased cardiovascular risk. One of the most well-known is the SNP rs10757274 on chromosome 9p21, which has been consistently linked to a higher risk of coronary artery disease [7]. This SNP is in a genomic region that does not code for proteins but may influence gene regulation, providing insights into the mechanisms underlying CVDs.

Monogenic Variants

While PRS captures polygenic risk, certain monogenic variants can also have a profound impact on cardiovascular risk. Mutations in genes, such as LDLR, APOB, and PCSK9 are known to cause familial hypercholesterolemia, a condition characterized by high levels of low-density lipoprotein (LDL) cholesterol and a markedly increased risk of premature coronary artery disease [8]. Identifying these mutations can lead to targeted interventions, such as aggressive lipid-lowering therapy, which can significantly reduce cardiovascular risk in affected individuals.

CLINICAL APPLICATION OF GENOMIC MARKERS

The integration of genomic markers into clinical practice has the potential to revolutionize cardiovascular risk assessment and management. Some of the key applications include:

Enhancing Risk Prediction Models

Combining genomic data with traditional risk factors can improve the predictive accuracy of cardiovascular risk models. For example, Abraham et al. demonstrated that adding PRS to conventional risk factors significantly improved the prediction of coronary artery disease events [9]. Such integrated models can help identify individuals at high risk who may not be recognized by traditional risk factors alone.

Guiding Therapeutic Decisions

Genomic markers can also inform the choice and intensity of preventive therapies. In the ODYSSEY OUTCOMES trial, patients with high PRS for CAD were found to derive greater clinical benefits from

alirocumab, a lipid-lowering therapy [10]. This finding suggests that genomic risk stratification could guide personalized treatment decisions, optimizing the balance between treatment benefits and risks.

Personalizing Lifestyle Recommendations

Individuals identified as having a high genetic risk for CVDs through PRS or specific genetic markers may benefit from more intensive lifestyle interventions. Personalized recommendations, such as stricter dietary control, increased physical activity, and more rigorous smoking cessation efforts, could be particularly beneficial for these high-risk individuals [1–4].

MYOCARDIAL INFRACTION

Acute myocardial infarction (AMI) occurs when the blood flow to the myocardium is persistently obstructed, resulting in tissue necrosis and cell death [11]. It is a non-communicable condition with a significant global burden, affecting individuals across all regions of the world [12]. The prevalence of AMI is estimated at 3.8% in people under 60 years of age and rises to 9.5% in those over 60 years of AMI is multifactorial, involving diverse causal mechanisms and genetic predispositions that vary widely among individuals [13].

Accurate diagnosis through sensitive biomarkers, timely therapeutic interventions, and effective strategies to prevent complications remain critical in managing this condition. Research highlights the pivotal role of time in determining the extent of myocardial damage, emphasizing that "time is myocardium." Advances in pharmacological and mechanical reperfusion therapies have underscored the importance of early restoration of coronary blood flow. However, no single parameter, including ischemia duration, can fully capture the complexity of the pathophysiological processes in AMI or guide optimal management strategies [14].

Coronary main-stem stenosis is a heritable condition. That results in tapering at the ostia or in the first centimetres of the right or left coronary artery is vulnerable to a stronger genetic influence than more distally located stenosis. So, the siblings and other first-degree relatives of affected population are more prone to develop the coronary heart disease [15].

Gene Identification and Personalized Medicine in Acute Myocardial Infarction

The discovery of genes linked to acute myocardial infarction (AMI) has significantly advanced the field of personalized medicine, improved risk stratification and enabling the development of more precise therapeutic strategies. Genetic studies have identified several genes associated with AMI, shedding light on their role in disease progression. For example, the genetic region on *chromosome 9p21.3* exhibits the strongest association with myocardial infarction risk [16]. Other implicated genes and alleles include PAI-1, Stromelysin-1 (5A-1171/6A), LTA, LGALS2, AT2 (-1332 G/A), RS671, LDLR, AKAP12, OR8D2, GLRA2, and the nitric oxide synthase gene regions, which further elucidate the molecular mechanisms contributing to AMI [17]. These findings not only enhance our understanding of the pathogenesis of AMI but also open pathways for targeted therapies.

Advancements in genomics have also improved AMI management, particularly using dual antiplatelet therapy (DAPT) following percutaneous coronary intervention (PCI)**.** Traditionally, DAPT involves the combination of aspirin and clopidogrel**,** reducing the risk of thrombosis and recurrent AMI. However, individuals with CYP2C19 mutations exhibit reduced clopidogrel metabolism, leading to a higher risk of ischemic events [18]. To address this limitation, genotype-guided therapy using alternative P2Y12 inhibitors, like ticagrelor, has demonstrated better outcomes by reducing both ischemic events and bleeding risks [19].

PRECISION MEDICINE IN LONG QT SYNDROME

Precision medicine is also instrumental in managing cardiovascular conditions like long QT syndrome (LQTS**)**. LQTS, a genetically heterogeneous disorder, is primarily associated with mutations in KCNQ1, KCNH2, and SCN5A, which correspond to LQT1, LQT2, and LQT3 subtypes, respectively.

These mutations account for approximately 70% of genotype-positive LQTS cases, with each subtype requiring tailored clinical interventions. For instance, the sodium channel blocker mexiletine has proven effective in reducing arrhythmic events in patients with LQT3 [20].

Role of Biomarkers in AMI

Biomarkers are measurable biological parameters that serve as indicators of disease presence, severity, or risk. An ideal biomarker is easily measurable, highly specific, and sensitive. For instance, myeloperoxidase and hyaluronidase-2 have been identified as markers of plaque erosion in acute coronary syndrome (ACS) patients [21]. Similarly, the CD44v6 splicing variant of the hyaluronan receptor has been shown to aid in the detection of silent myocardial infarctions, being higher in cases of plaque erosion compared to plaque fissures [22].

Decisions around extending DAPT therapy have also been increasingly personalized. Prognostic models incorporating factors, such as demographics, cardiovascular history, biomarkers, and medications help optimize treatment duration and reduce adverse outcomes [23].

Oxidative stress-induced cardiomyocyte injury is another critical factor in AMI pathogenesis. The Akt/GSK3β/Fyn pathway**,** activated by bFGF (basic fibroblast growth factor)**,** has been shown to reduce cardiomyocyte apoptosis and infarct size, highlighting its potential as a preventive therapeutic target. Similarly, epoxyeicosatrienoic acids (EETs) exhibit anti-inflammatory, vasodilatory, and cardioprotective effects, demonstrating promise in AMI management [24].

DIAGNOSTIC TOOLS AND BIOMARKERS

Various diagnostic modalities – such as ECG, cardiac enzymes, biomarkers, echocardiography, coronary angiography, and intravascular imaging techniques – are essential for optimizing AMI diagnosis and treatment through precision medicine. Two widely used biomarkers in AMI diagnosis are creatine kinase-MB (CK-MB) and cardiac troponins. By 2000, cardiac troponins replaced CK-MB as the gold standard for detecting myocardial infarction, as they are released exclusively during irreversible myocardial tissue damage [25]. Other emerging biomarkers include copeptin, a stable surrogate marker for arginine vasopressin (AVP). Elevated AVP levels post-AMI are associated with vasoconstriction, ventricular stress, and coronary artery narrowing. Copeptin, when combined with a negative troponin test, aids in the early exclusion of AMI. Another promising marker is H-FABP (Heart-type fatty acid-binding protein)**,** which is rapidly released during myocardial ischemia and necrosis, making it a sensitive indicator of early cardiac injury [26].

Hypertension

Hypertension, commonly known as high blood pressure, occurs when the force of blood against the walls of the arteries remains consistently high. This condition significantly raises the risk of severe complications, such as heart attacks and strokes. Globally, it is a leading cause of mortality and disability, accounting for approximately 9.4 million deaths annually [27]. Hypertension prevalence varies based on geographic region, age, and gender. An estimated 1 billion people worldwide – approximately 40% of the general population – live with hypertension. The occurrence increases with age, affecting 22.4% of adults aged 18–39, 54.5% aged 40–59, and 74.5% of individuals aged 60 and above [28]. Among individuals aged 15–59, the prevalence is slightly higher in men than women. However, in older populations, it is about 6% higher in women than in men [29]. Hypertension is more prevalent in urban areas, with one-third of urban adults affected compared to one-fourth of rural adults [30]. Despite advances in understanding its pathophysiology, hypertension remains a significant public health concern due to its role as a critical risk factor for cardiovascular diseases (CVDs). Risk factors include unhealthy lifestyle choices, medical comorbidities, certain medications, family history, age, and race, among others [31]. Often referred to as a “silent killer,” hypertension frequently goes undetected, contributing to preventable deaths. Its development is influenced by a combination of genetic, biochemical, physiological, and environmental factors.

ROLE OF GENOMICS IN HYPERTENSION

Genomic studies have identified several genes associated with hypertension. The GWAS catalog highlights seven key genes (ACE1, ACE2, ADRB1, ADRB2, MME, CACNA2D2, and UMOD) with established pathophysiological mechanisms linked to hypertension [32]. Hypertension is a multifactorial condition influenced by interactions, such as gene–obesity, gene–physical activity, gene–sodium, gene–alcohol, gene–smoking, and gene–diet (Nature Genetics). Over 1,000 blood pressure-related loci have been identified, with five loci (PKD2L1, SLC12A2, CACNA1C, CACNB4, and CA7) serving as targets for antihypertensive medications (PubMed). Epigenomic research has pinpointed patients who respond well to aldosterone-based therapies targeting the sodium channel epithelial 1α subunit (SCNN1A) [33]. Hypomethylation of the Atgr1α promoter, leading to increased angiotensin 1α receptor (AT1aR) expression, is another potential mechanism in hypertension. Similarly, the Na+/K+/2Cl- cotransporter 1 (NKCC1), regulated by the Sic2a2 gene, exhibits increased expression due to promoter hypomethylation in hypertensive individuals. Single nucleotide polymorphisms (SNPs) in lncRNA CDKN2B-AS1 have also been linked to blood pressure fluctuations [30]. At least 70 genes with variations play a role in human blood pressure regulation. Studies, such as the Framingham Heart Study, have identified phenotypes contributing to severe hypertension or offering protection against it, serving as potential targets for individualized therapies. For instance, a single SNP in the uromodulin gene (UMOD) is associated with hypertension and is expressed in the kidney's thick ascending limb of the loop of Henle. This discovery has led to the recommendation of furosemide as a first-line therapy for patients with this mutation [34].

Role of Biomarkers in Hypertension

Currently, no specific biomarker has been identified to predict responses to antihypertensive treatments reliably. Prospective randomized studies are essential for identifying and validating biomarkers. In one such study involving a Chinese population, 11 biomarkers were assessed for predicting hypertension progression with promising results [34]. The GENRES trial, a placebo-controlled, randomized cross-over study, demonstrated that the angiotensin receptor blocker losartan is influenced by NPNS1 gene variants, while hydrochlorothiazide is linked to PRKCA gene variants, both affecting blood pressure regulation [34].

CHALLENGES AND FUTURE DIRECTIONS

Despite the promise of genomic markers in cardiology, several challenges remain. These include the need for large, diverse study populations to ensure that PRS are applicable across different ethnic groups and the ethical considerations surrounding genetic testing, including concerns about privacy and potential discrimination [35, 36]. Additionally, the integration of genomic data into electronic health records and routine clinical practice is still in its early stages and requires further development [37].

Future research should focus on optimizing PRS models for different populations, exploring the utility of genomic markers in predicting other cardiovascular outcomes, and addressing the ethical and logistical challenges of integrating genomics into clinical care [38, 39]. As the field advances, it is likely that genomic markers will play an increasingly important role in the personalized management of cardiovascular diseases.

CONCLUSIONS

In conclusion, leveraging biomarkers and genetic insights significantly enhances the precision of AMI diagnosis and management. These advancements not only improve patient outcomes but also reduce complications associated with conventional treatment approaches, emphasizing the transformative impact of precision medicine on cardiovascular care.

Author Contributions

- *Conceptualization and design:* Dr. Vishwa Mehta.
- *Acquisition of data:* Foram Shah, Vidhi Bhatt, Astha Parekh, Richa Shah.

- *Writing original draft of manuscript:* Richa Shah, Foram Shah, Vidhi Bhatt, Astha Parekh.
- *Review and editing of the manuscript:* Dr. Vishwa Mehta.

Competing Interests

There are no conflicts of interest.

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