PERSPECTIVES

GENETIC RISK IN CARDIOVASCULAR DISEASE: HOW CLOSE ARE WE TO CLINICAL TRANSLATION?

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Abstract

Cardiovascular disease (CVD) remains the leading global cause of morbidity and mortality, influenced by a complex interplay of genetic and environmental factors. By many, medicine is entering the era of personalized management approach, in one direction because of the advances in genomics, particularly genome-wide association studies (GWAS). Monogenic disorders such as familial hypercholesterolemia, driven by mutations in *LDLR*, *APOB*, and *PCSK9*, illustrate the profound impact of single-gene defects on lipid metabolism and coronary artery disease (CAD) risk. In contrast, polygenic risk scores aggregate multiple variants to refine individual risk prediction for multifactorial diseases such as CAD, though their predictive utility remains modest when added to conventional clinical models. Beyond protein-coding genes, non-coding RNAs (miRNAs, lncRNAs) and endothelial nitric oxide synthase (eNOS) polymorphisms have emerged as key regulators of vascular function and inflammation, offering novel insights into disease mechanisms. However, the clinical translation of genetic testing is hindered by limited predictive accuracy, ethnic bias in genomic research, and challenges in interpreting variants of uncertain significance. Ethical considerations, including psychological impact and data privacy, further complicate its application. Future directions emphasize integrating multi-omics data, diversifying genetic studies, and advancing gene-based therapies such as CRISPR-mediated *PCSK9* editing and RNA silencing approaches. Ultimately, while genetic testing holds promise for precision medicine in cardiovascular care, its implementation must be accompanied by improved risk modeling, equitable population representation, and rigorous clinical validation.

Key words*: Atherosclerosis, Cardiovascular disease, Genomic medicine, Precision cardiology.*

Introduction

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide, with complex interactions between genetic predisposition and environmental factors driving its development and progression. By many, medicine is entering the era of personalized management approach (1), in one direction because of the advances in genomics, particularly genome-wide association studies (GWAS). Over the past few decades, advances in genetic research have significantly improved our understanding of the inherited components of CVD,

identifying numerous genetic variants that contribute to disease susceptibility, modify its clinical course, and shape the individual response to therapeutic interventions. GWAS and large-scale sequencing efforts have uncovered both common and rare genetic variants that play key roles in critical biological pathways such as lipid metabolism, inflammation, vascular homeostasis, and thrombosis.

A major advancement in cardiovascular genetics has been the identification of polygenic risk scores, which aggregate the effects of multiple genetic variants to predict an individual's overall risk of developing conditions such as coronary artery disease (CAD). While these scores enhance risk stratification, particularly when combined with traditional risk factors, their predictive power remains limited by factors such as population-specific genetic variability and the complex interplay between genes and lifestyle. Additionally, monogenic disorders such as familial hypercholesterolemia (FH) have provided insights into the impact of single-gene mutations on CVD risk, highlighting the role of genes such as *LDLR*, *APOB*, and *PCSK9* in cholesterol metabolism and atherosclerosis.

Beyond protein-coding genes, non-coding elements of the genome, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), have emerged as critical regulators of gene expression in cardiovascular health and disease. These non-coding RNA molecules modulate processes such as lipid metabolism, endothelial function, and inflammation, offering potential therapeutic targets for precision medicine. Furthermore, genetic variability in endothelial nitric oxide synthase (eNOS) has been linked to vascular dysfunction, further underscoring the molecular complexity underlying CVD.

Despite these achievements, challenges regarding the full clinical translation of genetic discoveries remain. The functional outcomes of many identified genetic variants often remain unclear, and the majority of GWAS studies have been conducted in populations of European ancestry, limiting their applicability across diverse groups. Moreover, there is concern about the clinical utility of genetic testing, as some studies question whether genetic risk prediction significantly improves upon traditional risk models based on lifestyle and clinical factors.

Future research efforts must focus on refining genetic risk prediction through multi-omics approaches, expanding studies in underrepresented populations, and developing targeted therapies that harness genetic insights for personalized treatment strategies. As our understanding of the genetic architecture of cardiovascular diseases continues to evolve, integrating genetic data with environmental and lifestyle factors will be essential for advancing precision medicine and improving patient health outcomes.

The aim of this literature review is to provide a concise overview of the current status of genetic research in cardiovascular diseases, highlighting both its potential and its limitations. This review will examine key genetic associations with CVD, including polygenic risk scores, monogenic disorders such as familial hypercholesterolemia (FH), and the role of non-coding RNAs in disease regulation. In addition, it will explore the impact of endothelial nitric oxide synthase (eNOS) on vascular function and discuss how genetic variations contribute to cardiovascular risk stratification, disease progression, and therapeutic response.

Furthermore, this review will critically assess the clinical utility of genetic testing in cardiovascular diseases, addressing concerns regarding its predictive power, applicability across diverse populations, and integration into existing clinical risk models. By incorporating findings from recent genome-wide studies (GWAS) and functional genomics, this analysis aims to clarify the advantages and limitations of genetic testing in improving patient health outcomes. Finally, future directions in cardiovascular genetics will be explored, including the potential of multi-omics approaches, the expansion of genetic studies to underrepresented populations, and the development of targeted genetic-based therapies. The expected outcome of this review is to provide a balanced perspective on the role of genetic research in cardiovascular disease, guiding future studies and informing clinical decision-making in the era of precision medicine.

Familial Hypercholesterolemia (FH) and Monogenic Disorders

Familial hypercholesterolemia (FH) is one of the best-characterized monogenic disorders that affect lipid metabolism. FH is primarily caused by mutations in the *LDLR* (low-density lipoprotein receptor), *APOB* (apolipoprotein B), and *PCSK9* (proprotein convertase subtilisin/kexin type 9) genes, which lead to significantly elevated levels of LDL cholesterol and an increased risk of premature atherosclerosis and CAD (coronary artery disease). Individuals with heterozygous FH (1 in 250 people) have a lifetime risk of CAD that is up to 20 times higher than that of the general population, while those with homozygous FH (1 in 160,000 to 1 in 300,000 people) often develop severe CAD in childhood (2). Genetic testing for FH has been successfully implemented in clinical settings, enabling cascade screening of family members and the early initiation of lipid-lowering therapy, which significantly reduces cardiovascular events (3).

Hypertrophic and Dilated Cardiomyopathy

Cardiomyopathies, including hypertrophic cardiomyopathy and dilated cardiomyopathy, also have a strong genetic basis. Hypertrophic cardiomyopathy is primarily caused by mutations in sarcomeric genes such as *MYH7* (beta-myosin heavy chain) and *MYBPC3* (myosin-binding protein C), which account for approximately 80% of genotyped cases (4). Dilated cardiomyopathy, on the other hand, shows greater genetic heterogeneity, with pathogenic variants identified in *TTN* (titin), *LMNA* (lamin A/C), and *DSP* (desmoplakin), among others (5). Genetic testing for cardiomyopathy has helped refine diagnosis and identify relatives at high risk, but its ability to guide therapeutic decisions remains limited (6).

Mutations in non-sarcomeric genes, such as *FHOD3*, are considered to be associated with hypertrophic cardiomyopathy in 0.5–2% of patients with a known genetic etiology of hypertrophic cardiomyopathy (7). However, the study by Vodnjov (8) determined that a common variation of *FHOD3* c.1646+2T>C is responsible for genetically confirmed hypertrophic cardiomyopathy in 16% of the subjects of Balkan origin. This variation has been confirmed as the second most common cause of hypertrophic cardiomyopathy among individuals tested with Balkan ancestry, after the c.913_914del variant of *MYBPC3*.

Polygenic Risk Scores and Coronary Artery Disease

Unlike monogenic disorders, CAD (coronary artery disease) is a polygenic disease, which means that it is influenced by the cumulative effects of multiple genetic variants, each having a small individual impact.

At present, through GWAS, 350 genetic loci have been associated with CAD (9). Of these, one locus stands out with significant and consistently replicated associations, located on the short arm of chromosome 9, specifically at 9p21.3 (10).

Interestingly, most of the polymorphisms at 9p21.3 are located in non-coding regions and show the strongest association with altered expression of the antisense long non-coding RNA (lncRNA) in the INK4 locus, *ANRIL* (see below in the text). The association between 9p21.3 variants and CAD appears to be independent of conventional risk factors for atherosclerosis (11). Pechlivanis et al. (12) found that polymorphisms of the 9p21.3 chromosome have a more significant association with coronary artery calcification in men compared to women.

Polygenic risk scores aggregate multiple variants to provide a quantitative estimate of an individual's inherited risk for CAD. Patel et al. (13) introduced *GPS Mult*, a multi-ancestry polygenic risk score that incorporates genetic data from over 1.4 million individuals. *GPS Mult* demonstrated strong associations with both prevalent and incident CAD, identifying individuals with up to three times higher risk compared to those with an average genetic risk.

However, although the polygenic risk score improves genetic risk stratification, its additional predictive value beyond traditional risk models remains a subject of further investigation. Tada et al. (14) and Natarajan et al. (15) found that the polygenic risk score only modestly improves risk prediction when added to clinical algorithms based on age, LDL cholesterol levels, hypertension, and smoking status.

Given that lifestyle and environmental factors also play key roles in the development of CAD, the clinical impact of polygenic risk scores remains a topic of ongoing research.

Atrial Fibrillation (AF)

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and genetic studies have identified a strong hereditary component in its development. Genome-wide association studies (GWAS) have identified more than 100 loci associated with AF, many of which involve genes linked to ion channel function, atrial structure, and cardiac development (16). Mutations in genes such as *PITX2* and *ZFHX3* have been particularly strongly associated with AF susceptibility.

Although AF is a complex disorder influenced by both genetic and environmental factors (such as hypertension, obesity, and sleep apnea), genetic testing is beginning to contribute to risk stratification and the identification of individuals predisposed to early-onset or familial AF. However, the translation of genetic insights into therapeutic strategies remains in its early stages, with current clinical management still relying primarily on traditional risk factors and rhythm-control strategies.

Telomeres and Cardiovascular Disease

Telomeres, the repetitive nucleotide sequences at the ends of chromosomes, play a critical role in maintaining genomic stability. Shortening of telomeres has been associated with cellular aging and the pathogenesis of various cardiovascular diseases. Studies have shown that individuals with shorter leukocyte telomere length have a higher risk of developing coronary artery disease, heart failure, and stroke (17).

Genetic studies have identified variants in genes involved in telomere maintenance, such as *TERT* and *TERC*, that are linked to telomere length and cardiovascular risk (18). However, whether telomere shortening is a causal factor in cardiovascular disease or merely a marker of cumulative exposure to environmental and biological stress remains a subject of debate.

While telomere biology offers an intriguing link between aging and cardiovascular disease, its clinical application as a biomarker for risk prediction is still limited. Additional research is needed to clarify the causal mechanisms and to determine whether therapeutic interventions targeting telomere maintenance could provide benefits in cardiovascular disease prevention and treatment.

Nitric Oxide and Endothelial Function

Nitric oxide (NO) is a key regulator of vascular tone, platelet aggregation, and endothelial function. Genetic variations in the gene for endothelial nitric oxide synthase (*eNOS*), also known as *NOS3*, have been associated with cardiovascular disease risk. Polymorphisms such as Glu298Asp (rs1799983) and 4a/4b VNTR in intron 4 have been linked to altered NO production, endothelial dysfunction, and increased susceptibility to conditions such as hypertension, atherosclerosis, and myocardial infarction (19). Additionally, genetic variations that affect the bioavailability of nitric oxide (NO) may interact with traditional risk factors such as hypertension and smoking, further increasing the risk of atherosclerosis and thrombosis.

In a study by Macedonian researchers involving 36 young individuals with coronary artery disease, variants of the gene encoding eNOS 786 T>C were found in 42%, eNOS 894T in 39%, while eNOS 786 T>C variants were rare, with a frequency of 19% (20).

Non-coding RNA and Cardiovascular Regulation

Non-coding RNAs (ncRNAs), including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), have emerged as critical regulators of gene expression in cardiovascular diseases, influencing key biological processes such as cholesterol metabolism, endothelial function, and inflammation.

Among the various miRNAs, specific molecules such as *miR-33* and *miR-92a* have shown a significant role in the modulation of cardiovascular health. *miR-33*, for example, inhibits cholesterol efflux by targeting the ATP-binding cassette transporter A1 (*ABCA1*), which is a key transporter in reverse cholesterol transport, thereby contributing to dyslipidemia and the progression of atherosclerosis (21). *MiR-92a* is associated with endothelial dysfunction and the

promotion of atherosclerosis through its influence on vascular integrity and inflammatory responses.

Long non-coding RNAs (lncRNAs) also contribute to the pathogenesis of cardiovascular diseases, and *ANRIL* is one of the most extensively studied. *ANRIL* is associated with the risk of coronary artery disease (CAD) due to its regulatory effects on the proliferation of vascular smooth muscle cells and inflammatory pathways (22). Dysregulation of lncRNAs such as *ANRIL* affects atherogenesis by altering cellular homeostasis within the arterial walls, leading to the formation and progression of atherosclerotic plaques.

Although the therapeutic potential of ncRNA-based interventions is being explored increasingly, their clinical application remains in its early stages. While preclinical studies suggest that targeting specific ncRNAs could offer new strategies for the treatment of CAD and other cardiovascular conditions, significant challenges regarding delivery mechanisms, adverse effects, and validation in large human populations remain.

Further research is necessary to fully understand the mechanistic roles of ncRNAs and to develop safe and effective therapies that harness their regulatory functions for precision medicine in cardiovascular diseases.

Limitations of Genetic Testing in Cardiovascular Diseases

Despite the significant achievements in genetic research and their application in cardiovascular diseases, genetic testing still faces several important limitations that hinder its wide clinical acceptance.

One of the main concerns is the incomplete predictive power of genetic testing, especially in the case of polygenic risk scores (23). Although polygenic risk scores have shown certain usefulness in identifying individuals with increased genetic risk for conditions such as coronary artery disease (CAD), they cover only a part of the total risk. Cardiovascular diseases are influenced by a complex interaction between genetic, environmental, and lifestyle factors, including diet, physical activity, smoking, and socio-economic conditions. The current risk models, which include traditional factors such as cholesterol level, blood pressure, and family history, already provide strong predictive power. Research suggests that adding genetic testing often offers only marginal improvement in risk stratification. This raises concerns about the real usefulness of polygenic risk scores, especially when considering the costs and accessibility of genetic testing for large populations.

Ethnic Bias in Genomic Research

Another significant limitation is the ethnic bias in genome-wide association studies (GWAS). Most large genetic studies have been conducted mainly in populations of European origin, which has led to the development of genetic risk scores that are less applicable to individuals of non-European descent. Since allele frequencies and genetic risk variants can differ significantly among populations, applying risk scores based on European data to individuals of African, Asian, or Latin American origin can lead to errors and misclassification of risk. This problem not

only reduces the accuracy of genetic predictions but also worsens existing health inequalities, as individuals from underrepresented populations may receive less accurate assessments of genetic risk.

Although there are efforts to include diverse populations in genetic research, there still exists a significant gap in ensuring that genetic findings are equitably applicable to various ethnic groups.

Variants of Uncertain Significance (VUS) and Challenges in Interpretation

Additionally, the presence of variants of uncertain significance (VUS) represents a major challenge for the interpretation of genetic testing. Many genetic variants identified through sequencing still lack well-established functional consequences, which makes it difficult to determine whether they contribute to disease risk or are merely benign variations.

In clinical settings, identification of VUS can create uncertainty for both patients and healthcare providers, leading to difficulties in making informed decisions about treatment and preventive measures.

The lack of standardized guidelines for VUS interpretation, as well as the constantly evolving nature of genetic databases, further complicate this issue. Until more research is conducted to clarify the functional impact of these variants, clinicians must be extremely cautious when integrating genetic findings into patient management (24).

Ethical and Psychological Aspects

The psychological burden of genetic risk information must not be overlooked. Individuals who are identified as high-risk based on polygenic risk scores may experience anxiety, stress, or a false sense of inevitability regarding disease development. Additionally, concerns about genetic discrimination and data privacy represent an ethical challenge that must be addressed (25).

Concerns Regarding Direct-to-Consumer (DTC) Genetic Testing

The emergence of DTC genetic tests has made genetic risk information more accessible. However, their reliability and clinical utility remain subjects of debate. The American College of Medical Genetics and Genomics has warned against the unregulated use of DTC genetic testing, emphasizing the need for professional genetic counseling (26). Given these limitations, genetic testing in cardiovascular diseases should be viewed as a complementary tool, rather than a replacement for traditional methods of risk assessment. Although genetic insights can offer valuable information, they must be interpreted in the context of existing clinical risk factors and the overall medical history of the patient. Integration of genetic testing into clinical practice will require continuous refinement of risk models, improved representation of diverse populations in genetic research, and stronger validation of genetic markers before they can be confidently used for clinical decision-making in prevention and treatment of cardiovascular diseases.

Future Directions in Cardiovascular Diseases Genetic Research

To improve the clinical use of genetic testing in cardiovascular diseases, future research must address current limitations and explore new approaches that integrate genetic data with other molecular and clinical factors. One promising direction is the refinement of polygenic risk assessments through integration of multi-omics data. By including not only genetic variants but also proteomic, metabolomic, and epigenomic data, researchers can develop more complex risk models that provide deeper understanding of disease mechanisms (27). Multi-omics approaches have the potential to improve the predictive accuracy of genetic testing by identifying dynamic interactions between genes and biological pathways that contribute to cardiovascular diseases (28).

Another critical area for future research is expanding genetic studies to include more diverse populations. As discussed earlier, the overrepresentation of European ancestry in GWAS limits the applicability of current genetic risk assessments to other ethnic groups. Increasing the representation of African, Asian, and Indigenous populations in genetic research is essential for developing risk models that are more broadly applicable. Large international collaborations and biobanks that prioritize diversity, such as the "All of Us Research" program in the U.S., are already taking steps to bridge this gap. However, continued efforts are needed to ensure that future genetic discoveries benefit all populations equally.

Additionally, the development of targeted therapies based on genetic profiles represents an exciting perspective in cardiovascular medicine. Advances in gene-editing technologies such as CRISPR-Cas9 have opened new possibilities for direct modification of disease-causing genetic variants (29). For example, current studies are exploring how CRISPR-based interventions could be used to inactivate genes such as *PCSK9*, with the aim of lowering LDL-cholesterol levels and reducing atherosclerosis risk (30). Similarly, RNA-based therapies, including siRNA (small interfering RNA) and antisense oligonucleotides, are being investigated as potential tools for modulating gene expression in cardiovascular diseases. Inclisiran was developed; it reduces the production of PCSK9 through messenger ribonucleic acid (mRNA) silencing. The inclisiran administration twice a year reduces LDL-C by over 50% in a range of patient groups. (31).

Although these approaches are still in early stages of development, they hold significant potential for precision medicine strategies tailored to individual genetic profiles.

In conclusion, the future of genetic research in cardiovascular diseases will depend on the ability to overcome current limitations while leveraging new technologies to improve risk prediction, expand population applicability, and develop innovative therapeutic approaches (32).

As research advances, genetic testing has the potential to evolve from an academic tool into a routine part of cardiovascular risk assessment and personalized medicine. However, realizing this potential will require continuous interdisciplinary collaboration among geneticists, cardiologists, bioinformaticians, and public health experts to translate genetic innovations into meaningful improvements in patient care.

Conclusion

While genetic testing has potential in the field of cardiovascular medicine, especially for certain hereditary conditions, its limitations require a careful and informed approach. It is crucial to emphasize that accurately interpreting genetic findings is essential for reliably distinguishing between pathogenic mutations, benign variants, and variants of uncertain significance. To support wider adoption in the population, standardized protocols may be necessary. Healthcare professionals should provide comprehensive counseling for patients to understand the possible outcomes, benefits, and limitations of genetic testing. Continuous research and refinement of genetic testing methods are essential for increasing their predictive accuracy and clinical usefulness in the treatment of cardiovascular diseases.

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