

Review

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# Genetics in the diagnosis and treatment of cardiovascular diseases

Kevin Bliden<sup>1,#</sup>, Sahib Singh<sup>1,#</sup>, Roni Shanoada<sup>1</sup>, Isha Kalia<sup>2</sup>, Udaya Tantry<sup>1</sup>, Alyssa Zimmerman<sup>1</sup> , Aravind Dilli Babu<sup>1</sup>, Lekshminarayan Raghavakurup<sup>1</sup>, Taylor Stude<sup>1</sup>, Damian Sidorski<sup>1</sup>, Paul Gurbel<sup>1</sup>

<sup>1</sup>Sinai Center for Thrombosis Research and Drug Development, Sinai Hospital, Baltimore, MD 21215, USA.

<sup>2</sup>Department of Genetics, The GW Medical Faculty Associates, Washington, DC 20037, USA.

#Authors contributed equally.

**Correspondence to:** Dr. Paul Gurbel, Sinai Center for Thrombosis Research and Drug Development, Sinai Hospital, 2401 West Belvedere Avenue, Baltimore, MD 21215, USA. E-mail: pgurbel@lifebridgehealth.org

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## Abstract

Cardiovascular diseases (CVDs) remain one of the leading causes of morbidity and mortality worldwide, with genetics being a major risk factor. Genetic cardiovascular disease can occur either because of single variant (Mendelian) or polygenic influences and has been linked to inherited cardiovascular conditions (ICC) such as arrhythmias, cardiomyopathies, dyslipidemias, and aortopathies which are significant factors leading to sudden cardiac death in young adults. Timely screening, diagnosis, and management of ICC can not only provide life-saving treatment to a patient, but also identify at-risk family members. The field of pharmacogenomics (PGx) helped to understand the variable action of medications such as clopidogrel, aspirin, warfarin, and statin according to genotype. Newer technologies such as multi-omics can combine data from multiple sources such as genomics, epigenomics, transcriptomics, proteomics, metabolomics, and microbiome. These advancements can contribute to the development of polygenic prediction scores and precision medicine tailored to individual genotypes. Substantial strides have been made in genetic-based therapeutics, gene editing technologies, and drug delivery systems, which have significantly expanded treatment options for patients with acquired or inherited CVDs. Although variable, the country- and society-specific guidelines on genetic testing for ICC and PGx and treatment are being continuously updated to keep up with ongoing research in the field. Along with appropriate knowledge, other factors including cost and availability of genetic testing play a vital role in the usage by both physicians and patients. With the advent of newer genetic testing for CVDs, a key factor is the availability of genetic counselors



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(GCs) who are specifically trained in cardiovascular genomics. The current review provides a concise summary of the major influences of genetics in the diagnosis and treatment of CVDs.

**Keywords:** Cardiovascular genetics, pharmacogenomics, inherited cardiovascular diseases, genetic counseling

## INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide. Nearly one-third of all global deaths were due to CVDs, of which 85% constituted heart attacks and strokes<sup>[1]</sup>. This trend is seen despite the innovations and improvements in pharmacotherapy such as antiplatelet and cholesterol-lowering agents, likely influenced by underlying variations in genotypes which lead to variable treatment responses<sup>[2]</sup>. Exploring the underlying genetic mechanisms of CVD has led to developments in the field of precision medicine, wherein tailored therapeutic options can be presented to individual patients for the best possible outcomes<sup>[3]</sup>. Tailored options have included cytochrome P450 (CYP) 2C19 genetic testing to personalize a P2Y12 inhibitor class of antiplatelets, microRNA (miRNA) biomarkers that diagnose medication-induced cardiotoxicity, and polygenic score to identify increased risk for the development of coronary artery disease (CAD)<sup>[4-6]</sup>. Although beneficial, concerns remain pertaining to the cost of genetic testing, limited access to genetics healthcare professionals, and a lack of knowledge regarding the interpretation of genetic testing results, which may hinder the utilization of genetics in clinical practice<sup>[7-10]</sup>. The purpose of this manuscript is to provide a high-level overall review of the current role of genetics in the diagnosis and treatment of CVDs, including the benefits, limitations, and approved testing options and guidelines by society experts.

### Advances in genomic testing

There have been several advancements in genomic testing recently, especially for CVDs. These range from targeted sequencing of the genome to multi-omics approaches<sup>[4]</sup>. Non-coding gene fragments such as microRNAs (miRNAs or miRs) have emerged as potential biomarkers of CVD development and prognosis<sup>[11]</sup>. These serve as regulators of many genes involved in inflammation and fibrosis, thus controlling CVD evolution. Animal models have shown the downregulation of miR-181a as the mechanism behind decreased myocardial fibrosis seen with sacubitril/valsartan<sup>[12]</sup>. As biomarkers, the upregulation of some miRNAs has been reported to correlate with heart failure (HF) (miR-122), atrial fibrillation (miR-483-5p), myocardial complication in diabetes (miR-1 and miR-133a), ischemic myocardial injury (miR181c), and ischemic stroke<sup>[13-17]</sup>. Others are involved in myocardial hypertrophy and cardiac remodeling, thus controlling progression to HF<sup>[18]</sup>.

Long and circular RNAs (circ RNAs) are other types of non-coding RNAs that affect gene regulation via epigenetic mechanisms, thereby playing a role in plaque formation and chronic HF<sup>[19]</sup>. Like miRNAs, several circ RNAs could be used as biomarkers for CAD (hsa\_circ\_0001879, hsa\_circ\_0004104, hsa\_circ\_0005540, hsa\_circ\_0124644), myocardial infarction (MI) (circRNA\_104761), hypertension (hsa\_circ-0005870, hsa\_circ\_0105015 combined with hsa-miR-637), and rheumatic valvular heart disease (hsa\_circ\_0000437)<sup>[20-22]</sup>. In the field of cardio-oncology, circFOXO3 and circITCH were shown to affect anthracycline-induced cardiotoxicity<sup>[23]</sup>. Despite the potential benefits, the clinical application of testing for long non-coding miRNAs and circ RNAs remains limited due to the lack of adequate human studies and trials<sup>[24]</sup>.

Combining data from multiple sources such as genomics, epigenomics, transcriptomics, proteomics, metabolomics, and microbiome, the multi-omics technologies provide a comprehensive diagnostic approach and are the latest upcoming genetic technologies<sup>[4]</sup>. Multi-omics technologies are being developed

and utilized for various CVDs. In a study of healthy subjects, Sánchez-Cabo *et al.* used blood multi-omics to show the association between subclinical atherosclerosis and epigenetic age acceleration, the latter being defined as the difference between epigenetic age (assessed by the effect of DNA methylation on genome) and chronological age<sup>[25]</sup>. They reported several inflammatory genes and pathways such as IL1B and IL6 to be responsible for this association. Similar applications of multi-omics in platelets revealed unique phosphopeptides and proteins, helping to better understand platelet activation<sup>[26]</sup>. Ferrucci *et al.* performed transcriptomic and proteomic analyses on muscle biopsies in patients with peripheral artery disease and showed alteration of mitochondrial respiratory proteins and glycolytic enzymes, which could be targeted in the future to change disease course<sup>[27]</sup>. Current atherosclerotic CVD (ASCVD) risk prediction scores are being enhanced with additional input from proteomics and lipidomics such as sphingolipids and fatty acids<sup>[28]</sup>. In a study of cardiac tissues from patients with hypertrophic cardiomyopathy (HCM), Garmany *et al.* showed upregulation of rat sarcoma-mitogen-activated protein kinase activation via multi-omic analysis<sup>[29]</sup>. Similarly, Moore *et al.* reported distinct mitochondrial homeostasis mechanisms and metabolic pathways in patients with HCM using multi-omics<sup>[30]</sup>. Other current ongoing applications of multi-omics are being studied for thoracic aortic aneurysms, cardiovascular regeneration, hypertension, and CVD subtyping<sup>[31-35]</sup>.

Single-cell RNA (scRNA) sequencing and transcriptomics provide information from a single cell instead of combined information from multiple tissue cells<sup>[36,37]</sup>. Currently being extensively tested for use in other fields such as oncology, single-cell sequencing is being explored now for CVDs as well. Single-cell sequencing is being used to understand the pathophysiology of cardiac fibrosis in HF, the role of vascular smooth muscle cells in atherosclerosis, and differences in markers such as ANKRD1 and NPPB according to the site of myocardial ischemia, *etc.*<sup>[36,37]</sup>. While most of the work has been done on animal models, replication in human cardiomyocytes is technically challenging due to different cellular structures<sup>[37]</sup>.

Several other new genetic testing modalities are upcoming. Small RNAs derived from transfer RNAs (tRNAs) can function as biomarkers for atherosclerosis, pulmonary hypertension, and MI<sup>[38]</sup>. Similarly, epigenetic changes in RNA, such as m5C methylation, can lead to CVDs via dysregulated expression<sup>[39]</sup>. Alteration of apoptosis via the mammalian sterile 20-like kinase 1 (MST1) has been linked with various CVDs such as MI, HF, cardiomyopathy, and aortic vascular diseases<sup>[40,41]</sup>. Specific galectins such as galactose-specific lectin-3 (galectin-3) have been shown to participate in vascular calcification<sup>[42]</sup>. These genetic findings would also potentially serve as therapeutic targets for CVDs<sup>[43-46]</sup>.

### **Advances in genetic-based cardiovascular therapeutics**

Advances in genetic-based therapeutics, gene editing technologies, and drug delivery systems have significantly expanded treatment options for patients with acquired or inherited CVDs. Gene therapy presents three new areas of exploration for future application: RNA therapeutics, cardiac regeneration, and cardiac gene editing. RNA therapeutics can now target previously “undruggable” pathways by silencing the expression of proteins involved in pathogenesis or by providing an exogenous message to generate a therapeutic protein<sup>[47]</sup>. Several RNA therapeutics have proven to be beneficial for treating both rare and highly prevalent CV-related disorders such as atherogenic dyslipidemia<sup>[47-49]</sup>.

In theory, RNA molecules such as antisense oligonucleotides (ASOs), microRNAs (miRNAs), and small interfering RNA (siRNAs) can target any interest gene’s mRNA and non-coding RNAs (ncRNAs). Antisense oligonucleotides (ASOs) selectively bind via complementary base-pairing to mRNA through two mechanisms: occupancy-mediated and occupancy-only. Both binding mechanisms can alter mRNA to modulate protein expression. The occupancy-mediated mechanism of ASOs enhances the downregulation

of target transcripts, while the occupancy-only mechanism can control the down-/upregulation of target transcripts. ASOs provide a unique characteristic of steric blocking to allow the regulation of pre-mRNA and mRNA without degrading the RNA itself. Both small interfering RNAs (siRNAs) and microRNA (miRNAs) utilize the RNA-induced silencing complex (RISC) to stop the expression of a targeted protein. siRNAs instigate mRNA degradation, leading to suppression of gene expression at a post-transcriptional level, while miRNAs utilize this pathway to repress translation<sup>[47-49]</sup>.

Preclinical evidence has supported the use of gene therapy, specifically with cytokines, growth factors, and miRNAs, to promote cardiac tissue remodeling for the treatment of conditions such as CAD, PAD, and HF. While multiple animal studies have succeeded in demonstrating angiogenesis, stimulating the regeneration of cardiomyocytes, and reducing oxidative stress and apoptosis, it has not translated into success in clinical trials<sup>[50]</sup>. However, with advances in gene editing technologies (CRISPR-Cas9, base editing, and prime editing) and direct delivery systems using adeno-associated virus (AAVs), lipid nanoparticles (LNPs), such as liver siRNAs, and virus-like particles (VLPs), the likelihood of success is promising in the near future<sup>[50]</sup>. There are currently several ongoing clinical trials (ranging from Phase I to III) investigating the use of gene therapy treatment for cardiac regeneration, specifically analyzing gene vehicles and route administration for successful nucleic acid delivery<sup>[50]</sup>.

## GENETIC TESTING FOR INHERITED CARDIOVASCULAR DISEASES

Inherited cardiovascular diseases (ICVDs) such as aortopathies, arrhythmias, cardiomyopathies, dyslipidemias, and hypertension are important causes of morbidity and mortality with known pathogenetic mutations [Table 1]<sup>[1]</sup>. Although guidelines have recommended genetic testing for screening ICC, implementation remains low due to a lack of access to genetics healthcare professionals as well as genetic counseling and genetic testing services<sup>[51]</sup>. Timely screening, diagnosis, and management of inherited CVDs can not only provide life-saving treatment to a patient but also identify at-risk family members. Genetic counseling plays a vital role as a bridge between physicians and patients, helping both to understand genetic testing options and the implications of results<sup>[51]</sup>.

### Inherited aortopathies

Inherited aortopathies include Marfan syndrome, Loeys-Dietz syndrome, and Ehlers-Danlos syndrome (EDS). In a retrospective study of the UK National Diagnostic Service, Bowen *et al.* showed that angiotensin II receptor blocker and beta-blocker therapy can reduce adverse vascular events in Vascular EDS (vEDS), an inherited connective tissue disease which occurs due to *COL3A1* genetic variants<sup>[52]</sup>. Giuliani *et al.* reported that patients with genetic aortopathies such as Marfan syndrome and Loeys-Dietz syndrome have a higher risk of complications from an aberrant subclavian artery, including aneurysms and dissections<sup>[53]</sup>. Given the usual poor prognosis associated with ICVDs, there is a huge potential for ongoing and future studies on pharmacogenomics in this field.

### Inherited arrhythmia syndromes

Inherited arrhythmia syndromes (IASs) include conditions such as catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, and long and short QT syndromes, which occur due to genetic variants in genes affecting calcium and ion channels<sup>[54]</sup>. Clinical genetic testing panels have been created and incorporated into the International Consortium (Clinical Genome Resource)<sup>[54]</sup>. Even though there exists a significant level of incomplete penetrance among rare mutations in conditions like long QT syndrome and idiopathic atrioventricular conduction disease in young patients, the upcoming therapeutic techniques such as CRISPR/Cas9 technologies may offer a treatment for such disorders by splicing the genetic arrhythmogenic substrates<sup>[55-57]</sup>. Atrial fibrillation (AF) is the most common cardiac dysrhythmia, with an estimated prevalence from < 0.5% in young adults to > 8% after the age of 80. The heritability of AF is

**Table 1. Genetic testing for inherited cardiovascular diseases with definitive, strong, and moderate clinical validity classification**

CVD	ICVD and gene-disease classification*	Prevalence [Ref.]
Aortopathies	<b>Thoracic aortic aneurysms and dissections</b> Definitive: <i>TGFβ2, SMAD 3, FBN1, TGFβR1, TGFβR2, ACTA2, MYH11</i> Strong: <i>MYLK, PRKG1, LOX</i> Moderate: <i>EFEMP2, SMAD2, MFAP5, FOXE3</i>	1.3%-8.9% men; 0.1%-2.2% women [183]
	<b>Ehlers-danlos syndrome</b> Definitive: <i>COL1A1, COL1A2, COL3A1, COL5A1, COL5A2</i>	0.002% [52]
	<b>Loeys-dietz syndrome</b> Definitive: <i>TGFβR1, TGFβR2</i>	Unknown
	<b>Marfan syndrome</b> Definitive: <i>FBN1</i>	0.005%-0.01% [184]
Arrhythmias	<b>Long QT syndrome</b> Definitive: <i>CALM1, CALM2, CALM3, SCN5A, KCNH2, KCNQ1</i> Strong: <i>TRDN</i> Moderate: <i>CACNA1C</i>	0.05% [185,186]
	<b>Short QT syndrome</b> Definitive: <i>KCNH2</i> Strong: <i>KCNQ1</i> Moderate: <i>SLC4A3</i>	0.05%-0.4% [187,188]
	<b>Catecholaminergic polymorphic ventricular tachycardia</b> Definitive: <i>TRDN, RYR2, CASQ2, TECRL</i> Moderate: <i>CALM1, CALM2, CALM3</i>	0.01%-0.02% [189]
	<b>Arrhythmogenic right ventricular cardiomyopathy</b> Definitive: <i>CASQ2, RYR2, TECRL, TRDN</i> Moderate: <i>CALM1, CALM2, CALM3, CASQ2</i>	0.02%-0.05% [190]
	<b>Brugada syndrome</b> Definitive: <i>SCN5A</i>	0.05% [191]
	<b>Hypertrophic cardiomyopathy</b> Definitive: <i>TNNC1, ACTC1, TPM1, TNNI3, CSRP3, TNNT2, MYH7, MYL3, MYL2, MYBPC3, ALPK3, PRKAG2</i> Moderate: <i>JPH2, TRIM63, CSRP3, KLHL24</i>	0.2%-0.5% [192]
Cardio myopathies	<b>Dilated cardiomyopathy</b> Definitive: <i>BAG3, DES, FLNC, LMNA, MYH7, RBM20, SCN5A, TNNC1, TNNT2, TTN</i> Moderate: <i>ACTC1, JPH2, NEXN, TNNI3, TPM1, VCL</i>	0.4% [193]
	<b>Arrhythmogenic right ventricular cardiomyopathy</b> Definitive: <i>DSG2, PKP2</i> Moderate: <i>DES, PLN</i>	0.04% [194]
	<b>Congenital heart disease</b> (congenital structural, conductive, myopathic) Definitive: <i>GATA4, SMAD2, NKX2.5, NR2F</i> Moderate: <i>HAND1, HAND2, ETS1</i>	0.69%-0.93% [195]
Dyslipidemias	<b>Familial hypercholesterolemia</b> Definitive: <i>APOB, LDLR, LDLRAP1, PCSK9</i>	0.32% [196]
	<b>Familial hypobetalipoproteinemia</b> Definitive: <i>ANGPTL3, APOB</i>	Unknown
	<b>Sitosterolemia</b> Definitive: <i>ABCG5, ABCG8</i>	0.0005% [197,198]
Hypertension	<b>Pulmonary arterial hypertension</b> Definitive: <i>SOX17, BMPR2, KDR, GDF2, TBX4, KCNK3, SMAD9, ATP13A3, CAV1</i> Moderate: <i>GGCX, TET2, ABCC8</i>	0.00106% [199]

\*Gene disease classification based on Clinical Genome Resource Gene Curation Expert Panel<sup>[200]</sup>.

estimated as high as 62%, indicating a strong genetic component<sup>[58]</sup>. While studies have implicated several pathogenic contributors to AF, there has been no definitive association established<sup>[59]</sup>.

### **Inherited cardiomyopathies**

Inherited cardiomyopathies (ICs) include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), left ventricular noncompaction cardiomyopathy (LVNC), and restrictive cardiomyopathy<sup>[60]</sup>. Most ICs are single-gene disorders with an autosomal dominant inheritance pattern and a 50% risk of transmission to a child<sup>[54]</sup>. There is also considerable overlap among the cardiomyopathies<sup>[61]</sup>. While the association of several genes in relation to HCM, DCM, and ARVC have been established (see [Table 1](#)), no genes have been validated in association with restrictive cardiomyopathy. This is despite the fact that numerous pathogenic mutations in almost 20 genes have been identified in patients with restrictive cardiomyopathy<sup>[61]</sup>. The usual testing strategy for ICs includes clinical genetic panels consisting of 30 to > 100 genes that are responsible for proteins found in cardiomyocytes. While most of the pathogenic variants do not have any disease-modifying therapies yet, few, such as truncating variants in the titin (*TTN*) gene, which account for 20% of ICs, have ongoing trials testing specific therapeutic options<sup>[62,63]</sup>.

### **Congenital heart disease**

Congenital heart diseases (CHD) include ventricular and atrial defects, patent ductus arteriosus, tetralogy of Fallot, pulmonary valve stenosis, and other developmental heart defects that occur in 1% of infants born each year. Like many diseases, CHDs have been associated with environmental and maternal risk factors including smoking, alcohol consumption, age, and obesity, and approximately 20% have been attributed to chromosomal anomalies or genetic defect underpinnings. Point mutations of cardiac transcription factor genes, SNPs, aneuploidy, and chromosomal copy number variants (CNV) are directly associated with CHD pathogenesis<sup>[64]</sup>. Accordingly, gene-editing technologies such as Zinc Finger Nuclease and CRISPR-Cas9 show the potential to correct genetic mutations that underlie inherited cardiac disorders, which has already been demonstrated in long QT syndrome<sup>[65,66]</sup>. By precisely targeting and modifying the affected genes, scientists can potentially reverse or mitigate the effects of these genetic abnormalities<sup>[67,68]</sup>.

Several challenges that providers face include identifying the person in a family to begin the genetic testing process, finding the most useful genetic testing panel, and interpreting the genetic testing results<sup>[60]</sup>. Hence, diagnosing cardiomyopathies and CHD at the earliest stage possible, from prenatal to postmortem diagnosis, has been proposed as it can help in prognostication and identifying other family members at risk<sup>[69-72]</sup>. While guidelines may recommend genetic testing, significant challenges remain in the operationalization of genetic testing in the clinical care of cardiology patients<sup>[73,74]</sup>. Another challenge pertains to the prevalence of extracardiac anomalies associated with congenital heart disease and its management. It is estimated that the rate of extracardiac anomalies coupled with CHDs is around 28% and extracardiac structural malformations around 25%<sup>[75]</sup>. Such cases are more common than isolated cardiac dysfunction and management is becoming increasingly complex. Coordination among different teams and specialists becomes even more imperative, and the role of surgical management in addressing phenotypic malformations is crucial<sup>[76]</sup>.

### **Dyslipidemias**

Genetic causes of dyslipidemia can be monogenic, caused by a rare DNA variant that has a strong impact on phenotype, or polygenic, with multiple common genetic variants. Familial Hypercholesterolemia (FH) is common among the general population, with a prevalence of 1 in 200 to 1 in 250 and remains vastly underdiagnosed and undertreated<sup>[77]</sup>. Untreated FH causes increased low-density lipoprotein cholesterol (LDL-C) levels, leading to an increased risk of premature coronary heart disease, which can manifest as

myocardial infarctions and sudden cardiac death<sup>[77]</sup>. Individuals with untreated FH have a 20-fold increase in risk of premature CHD and a 13-fold increase in CHD mortality as compared to the general population<sup>[78]</sup>. FH is associated with mutations in four proteins: low-density lipoprotein receptor (LDLR), low-density lipoprotein receptor adaptor protein (LDLRAP1), apolipoprotein B (APOB), and proprotein convertase subtilin/kexin 9 (PCSK9)<sup>[78]</sup>.

One of the most notable targeted drug treatments for LDL lowering and atherosclerotic CV disease (ASCVD) risk reductions is PCSK9 inhibitors. PCSK9 is an enzyme that marks LDL receptors for degradation, prevents LDL-C from being broken down intracellularly, and results in elevated levels of circulating LDL-C<sup>[79]</sup>. Gain of function mutations in the PCSK9 gene increases the activity of the PCSK9 enzyme; thus, treatment in the form of PCSK9 inhibitors, such as monoclonal antibodies, has been indicated in patients with heterozygous FH in which a pathogenic mutation in the PCSK9 gene has been identified. Currently, there are three approved PCSK9 inhibitors that have demonstrated a substantial reduction in LDL levels and reduced major adverse cardiovascular events (MACE) when used in conjunction with statin therapy. Alirocumab (Praluent; Regeneron/Sanofi) and evolocumab (Repatha; Amgen) are fully humanized monoclonal antibodies. Inclisiran (Leqvio; Novartis) is a small interfering mRNA that inhibits the intracellular synthesis of PCSK9. Mipomersen is an antisense oligonucleotide inhibitor that causes selective degradation of the apoB-100 mRNA and inhibition of protein translation, leading to substantial reductions in LDL-C and other lipoprotein levels<sup>[72]</sup>. In heterozygous FH patients with CHD, LDL-C levels were reduced by 28% when treated with mipomersen<sup>[80]</sup>.

Angiotensin-like 3 (*ANGPTL3*) has newly emerged as a target for the treatment of elevated levels of circulating LDL-C in individuals with homozygous familial hypercholesterolemia (HoFH). HoFH is caused by DNA variants in LDLR, and other genes associated with LDLR function, including *APOB*, *PCSK9*, and *LDLRAP1*<sup>[81]</sup>. Individuals with the rare genetic disorder display severely elevated LDL-C levels due to minimal or no residual LDLR (LDL receptor) function. LDLR-dependent cholesterol-lowering medications such as PCSK9 inhibitors, statins, ezetimibe, and bempedoic acid have minimal effect in lowering LDL-C in individuals with HoFH<sup>[82]</sup>. Inhibition of *ANGPTL3* reduces LDL-C independently of the LDLR potentially by controlling VLDL-C catabolism upstream of LDL-C. Presently, there is one approved *ANGPTL3* inhibitor, evinacumab (Evekeza; Regeneron), a fully humanized monoclonal antibody<sup>[81]</sup>.

Increased serum Lipoprotein (a) (Lp(a)) concentration is an important inherited risk factor for ASCVD and aortic stenosis progression and is independent of the serum LDL-C. Several studies investigating antisense oligonucleotides (ASO) pelcarsen (Ionis Pharmaceuticals/Novartis) and LY3819469, as well as small interfering RNAs (siRNAs) olpasiran (Amgen) and SLN360, have shown to be highly effective in lowering the serum Lp(a) concentration with a good safety profile<sup>[83,84]</sup>. Upcoming Phase III trial results will determine if these new RNA-based therapies will be a major player in the wide spectrum of lipid-lowering medication. Other genetic forms of FH where expression of some functional LDL receptors can be unregulated are included in [Table 1](#). Although the genetics of FH are well known, the integration of genetic testing into practice has been constrained due to limited knowledge of FH by providers, lack of consensus among FH diagnostic criteria, and time constraints in clinical encounters<sup>[85]</sup>.

## CARDIOVASCULAR THERAPY PHARMACOGENOMICS

Genetic variants have been identified as contributors to antiplatelet drug response and other cardiovascular medications [[Table 2](#)]. Sinai Center for Thrombosis Research (SCTR), in collaboration with the University of Maryland School of Medicine (UM), was one of the first to test the role of *cytochrome P450 (CYP) 2C19\*2* variant in the pharmacodynamic and clinical efficacy of clopidogrel therapy<sup>[86,87]</sup>. In a genome-wide study,

**Table 2. Cardiovascular medications, single nucleotide polymorphisms and drug response with guideline-based recommendations**

CV medication	Gene (SNP ID)	Drug response and guideline-based recommendations
Clopidogrel	<i>CYP2C19</i> *2 (rs4244285), *3 (rs4986893) <i>CYP2C19</i> *17 (rs12248560)	Response: reduced effectiveness in <i>CYP2C19</i> LOF carriers in homozygote (poor metabolizers) and heterozygote (intermediate) LOF carriers and increased or normal effectiveness in GOF carriers Recommendations: alternative P2Y12 inhibitors (Ticagrelor or Prasugrel) in poor/intermediate metabolizers if clinically indicated
Warfarin	<i>VKORC1</i> (rs9923231) LOF <i>CYP2C9</i> *2 (rs1799853) LOF <i>CYP2C9</i> *3 (rs1057910) Other: <i>CYP4F2</i> (rs2108622), <i>CYP3A4</i> (rs2242480), <i>CYP4F2</i> (rs2108622)	Response: increased effectiveness ( <i>VKORC1</i> A/G or A/A), Reduced effectiveness in <i>CYP2C9</i> poor metabolism (e.g., <i>CYP2C9</i> *3/*3, *2/*3, *3/*3). Other gene polymorphisms under investigation or weak evidence Recommendation: consider an alternative agent (DOAC) in individuals with <i>VKORC1</i> A/G or A/A genotype or <i>CYP2C9</i> poor metabolizers
Statin therapy	Statin Induced Myopathy <i>SLCO1B1</i> (rs4149056, rs4263657)	Response: common variants of the rs4149056 C allele are strongly associated with an increased risk of statin-induced cardiomyopathy. Increased risk for rhabdomyolysis with statin use (rs4263657) Recommendation: consider a tailored statin dose in individuals with the C allele. Advised to avoid statins (rs4263657)

healthy participants treated with clopidogrel for 7 days were evaluated for genetic associations with platelet aggregation in the Pharmacogenomics of Antiplatelet Intervention (PAPI) Study<sup>[86]</sup>. In response to clopidogrel, the presence of *CYP2C19*\*2 was associated with reduced inhibition of ADP-stimulated platelet aggregation. In the initial validation study that evaluated patients who underwent percutaneous coronary intervention (PCI), carriers of the *CYP2C19*\*2 alleles were found to have a significant increase in cardiovascular events at 1 year as compared to non-carriers (20.9% vs. 10.0%). This landmark study was among the first to open the gates to precision medicine, leading to the consideration of alternative antiplatelet therapy (not containing clopidogrel) in patients carrying the loss-of-function *CYP2C19*\*2 genotype.

In the ONSET/OFFSET and RESPOND genotype studies, our group performed the first correlation study between the *CYP2C19* genotype and the effect of clopidogrel vs ticagrelor in patients with CAD<sup>[88]</sup>. Irrespective of the *CYP2C19* carrier status, ticagrelor therapy was found to significantly reduce platelet reactivity compared with clopidogrel ( $P < 0.01$ ). Additionally, the presence of loss-of-function carriage of the *CYP2C19* genotype did not affect the antiplatelet action of ticagrelor but was associated with higher platelet reactivity in those on clopidogrel. A subsequent meta-analysis of 9 studies with 9,685 CAD patients treated with clopidogrel similarly reported a significant increase in major adverse cardiovascular events (MACE) and stent thrombosis among carriers of reduced-function *CYP2C19* alleles as compared to non-carriers<sup>[89]</sup>. Such genotypic studies were valuable in understanding experimental antiplatelet therapies as well<sup>[90]</sup>.

Going further, our group evaluated the effect of *CYP2C19* in patients on maintenance dual antiplatelet therapy (DAPT) with aspirin and clopidogrel<sup>[91]</sup>. While no difference was found in platelet reactivity between carriers and non-carriers of the \*2 allele in patients on aspirin alone, \*2 carriage was associated with higher platelet aggregation in patients on DAPT with clopidogrel. Similar findings were shown in a subset of East Asian patients with MI who inherently had a higher prevalence of *CYP2C19* loss-of-function allele carriage<sup>[92]</sup>. Following this, the guidelines for antiplatelet therapy were modified to incorporate genotypic testing in selecting high-risk patients undergoing PCI, where alternate antiplatelet agents may be selected based on the results<sup>[93-96]</sup>.



In addition to the *CYP2C19*\*2 allele, effects of other loss-of-function alleles such as \*3 were evident in the ACCEL-DOUBLE-2N3 study conducted in Korea by Jeong *et al.*<sup>[97]</sup>. East Asian patients who underwent PCI and were treated with clopidogrel (standard dose 75 mg or high dose 150 mg) demonstrated increased platelet aggregation with \*3 allele carriage as compared with \*2 allele. While conventional *CYP2C19* genetic testing is time-consuming and labor-intensive, our group was among the first to test and report a high accuracy of a novel point-of-care testing method that could analyze 11 *CYP2C19* variants within 3 h<sup>[98]</sup>. Similar to ticagrelor as above, we also showed no effect of *CYP2C19* LoF carriage on platelet reactivity in those treated with prasugrel<sup>[99]</sup>. Although trials such as TRILOGY ACS failed to show any significant difference in cardiovascular outcomes between prasugrel and clopidogrel based on genetically predicted *CYP2C19* metabolizer status in medically treated patients with acute coronary syndrome (ACS), genetic testing held importance for patients with high-risk characteristics<sup>[100-102]</sup>. This was later confirmed by the genome-wide association study (GWAS) in patients on clopidogrel, which showed a significant association of *CYP2C19*\*2 with platelet reactivity, with the subsequent development of pharmacogenomic polygenic response score showing predictive value for cardiovascular outcomes<sup>[103,104]</sup>. The work in pharmacogenomics of antiplatelet therapies has recently been conducted in other countries as well, along with studies showing their cost effectiveness as compared with the standard of care<sup>[105-111]</sup>.

Like clopidogrel, resistance to aspirin has been associated with genetic variants. For example, resistance has been linked to variants in the genes encoding GPIIIa and COX<sup>[4]</sup>. A recent systematic review of 21 studies with 10,873 patients reported 3,014 to be aspirin-resistant<sup>[112]</sup>. This resistance was attributed to polymorphisms of various genes such as *P2RY1*, *MDR1*, *PLA2G7*, *HO1*, *TBXA2R*, *ALOX12*, *ALOX5AP*, and *PON1*. Furthermore, a variant in endothelial aggregation receptor-1 (PEAR1) has been linked to residual platelet aggregation following aspirin treatment<sup>[113]</sup>. However, in a study of 13,547 healthy older individuals without a history of atherothrombotic CVD, Lewis *et al.* found no effect of PEAR1 genotype and aspirin use on cardiovascular and bleeding events<sup>[114]</sup>. A recent healthy volunteer study evaluated 62 pro-thrombotic gene transcripts included in the Aspirin Response Signature (ARS) score and reported that a higher score is associated with increased platelet inhibition and bleeding risk. These findings suggest that ARS scores may be used to guide aspirin treatment<sup>[115]</sup>. As the evidence for any specific gene involved in aspirin resistance remains low and heterogeneous, future studies will play an important role in precision medicine with aspirin<sup>[4]</sup>.

Anticoagulant medications are used for various indications, including prevention of stroke in the setting of atrial fibrillation, to treat venous thromboembolism, *etc.*<sup>[4]</sup>. Warfarin was previously the most common anticoagulant used and was replaced later by direct oral anticoagulants (DOACs). Although genetic studies revealed a variation in the effectiveness of warfarin due to genotypic variants in *CYP2C9* (warfarin metabolism), *VKORC1* (target enzyme), and *CYP4F2* (vitamin K metabolism), the subsequent clinical trials reported conflicting results on the role of implementing genotype-guided algorithms for warfarin<sup>[4,116,117]</sup>. This was likely due to the geographical, racial, and dosing heterogeneity in patient groups<sup>[4]</sup>. Similar studies have also been recently conducted to assess the role of pharmacogenomics for DOACs, which could be used to predict the risk of bleeding in the future<sup>[118,119]</sup>.

For statins, the *SLCO1B1* gene variant is the most studied and has been shown to be associated with statin-induced myopathy due to decreased clearance by the liver<sup>[4,120,121]</sup>. *ABCG2* encodes an efflux transporter (BCRP) that modulates the absorption and disposition of rosuvastatin with carriers of A allele experiencing a greater reduction in LDLc. However, many genetic variants, such as rs2231142 in *ABCG2*, have wide variation in prevalence in different patient populations, as evidenced by recent studies<sup>[122,123]</sup>. Another genotype (LILRB5 Asp247Gly) was found to cause an increase in creatine kinase (CK), which could possibly

contribute to precision therapy in the future<sup>[124]</sup>. The potential of pharmacogenomics in prescribing statins is vast, given that almost 40 variants of 23 genes were found to be linked with dyslipidemia in a recent genomic study<sup>[125]</sup>.

Glucagon-like peptide-1 receptor agonists (GLP-1 agonists) are one of the latest therapeutic options that have been shown to reduce adverse cardiovascular outcomes in addition to being used for diabetes<sup>[126]</sup>. A genomic study recently reported a greater reduction in HbA1C with GLP-1 agonists in the presence of *ARRB1* genetic variants, which would be important to assess for cardiovascular risk reduction in the future<sup>[126]</sup>. Such advances in pharmacogenomics coupled with other medications with an indirect effect on CVDs show a promising future for precision medicine<sup>[127-130]</sup>.

The development of clinical trials that include PGx information may help to improve our understanding of the mechanism of action of drugs used for the treatment. Furthermore, there is growing evidence, primarily from oncology trials, that the incorporation of PGx within study design leads to lower drug development costs and increased safety and efficacy<sup>[131]</sup>. A growing number of clinical trials with PGx information are appearing in the field of cardiovascular medicine. As an example, Tardif *et al.* performed a retrospective GWAS study of the overall neutral placebo-controlled dal-Outcomes trial and found that the effect of the cholesteryl ester transfer protein (CETP) modulator dalcetrapib on the composite of cardiovascular death, myocardial infarction or stroke was influenced by a polymorphism in the adenylate cyclase type 9 (*ADCY9*) gene<sup>[132]</sup>. Although patients with the AA genotype at position rs1967309 experienced fewer cardiovascular events with dalcetrapib, those with the GG genotype had an increased rate and the heterozygous AG genotype exhibited no difference from placebo. The role of dalcetrapib in reducing the occurrence of MI in patients with recent ACS and AA genotype at variant rs1967309 (*ADCY9* gene) is under investigation in the dal-GenE trial [Supplementary Table 1]. Additionally, PGx is currently utilized to evaluate pharmacogenetic interactions of RNAi therapeutics in development, including PCSK-9 and Lp(a) inhibitors.

## IMPLEMENTATION INTO MEDICAL PRACTICE

Various country- or society-specific guidelines exist on genetic testing for CVDs and pharmacogenomics. The American Heart Association (AHA) and American College of Cardiology (ACC) guidelines recommend genetic testing for patients with suspected or confirmed diagnosis of inherited CVD along with cascade testing for family members of patients with HCM, other forms of inherited cardiomyopathies, arrhythmias, familial hypercholesterolemia, heritable thoracic aortic aneurysm, or dissection, and left ventricular noncompaction with shared decision making, pre and post genetic counseling<sup>[133,134]</sup>. For pediatric patients, special consideration was advised for predictive genetic testing due to the incomplete penetrance of most CVDs, thereby providing a patient with a genetic diagnosis that may not manifest clinically in their lifetime<sup>[135]</sup>. Additionally, while the Genetic Information Nondiscrimination Act protects an individual's genetic information from health insurance discrimination and employer discrimination, it does not provide protection for life insurance and long-term disability insurance<sup>[134]</sup>. Given the implications of positive genetic results for asymptomatic individuals such as the pediatric population, the timing of such testing in the pediatric population was advised to be delayed till the patient reaches decision-making age, unless a disease-modifying treatment is available for the genetic condition being considered.

In 2022, the ACC/AHA released detailed guidelines for aortic diseases, specifically elaborating on the genetic testing, follow up, and management of hereditary thoracic aortic diseases (TAD)<sup>[136]</sup>. Key risk factors for familial TAD include the presence of syndromes such as Marfan syndrome, occurrence of TAD < 60 years of age, family history of TAD, or sudden unexplained death at a young age. As exome and genome sequencing become increasingly available for multiple indications other than CVDs, it is possible to

discover incidental genes that are linked to CVDs<sup>[137]</sup>. A recent scientific statement from AHA (2023) recommends that these incidentally found genes be properly reported along with an estimation of pre-test probability and pathogenicity of the genetic variants<sup>[137]</sup>. Additionally, the updated practical guidance for genetic testing for cardiomyopathies (2023) was released as well<sup>[59]</sup>. The European Heart Rhythm Association (EHRA) and Heart Rhythm Society (HRS) expert consensus statement expanded the guidelines to include genetic testing for patients with sudden cardiac death wherein there is a suspicion of genetic CVDs, and the cause is not found after pathological evaluation<sup>[138]</sup>. While private insurance and laboratories cover the recommended genetic testing, Medicare only covers testing for patients with disease-appropriate phenotypes but not routine screening for those with positive family histories<sup>[139-141]</sup>.

Like inherited CVDs, various committees have provided guidelines for pharmacogenomic testing. These include the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Dutch Pharmacogenetics Working Group (DPWG), the Canadian Pharmacogenomics Network for Drug Safety (CPNDS), *etc.*<sup>[142]</sup>. Based on the committee recommendations and the tables by the Food and Drug Administration (FDA) on pharmacogenetic biomarkers/associations, the American College of Medical Genetics and Genomics (ACMG) has provided guidance to the laboratories conducting the genetic testing<sup>[143,144]</sup>.

As opposed to inherited CVDs, routine pharmacogenomic testing is not advised. Although CPIC is recommending genetic testing to optimize medication use, their adoption in the clinic remains uncommon. If available, the CPIC guidelines advise therapeutic warfarin dosing based on the *CYP2C9* and *VKORC1* genotypes to maintain the target international normalized ratio (INR)<sup>[145]</sup>. For clopidogrel, only selective testing of the *CYP2C19* genotype was advised in high-risk patients undergoing PCI at the discretion of the treating physician<sup>[146,147]</sup>. Regarding statin-associated musculoskeletal symptoms, the CPIC recommended dosing based on the *SLCO1B1*, *ABCG2*, and *CYP2C9* genotypes<sup>[148]</sup>. While Medicare provides coverage for pharmacogenomic testing based on the FDA and CPIC guidelines, the inconsistencies between the genetic lists of these organizations need better corroboration<sup>[149,150]</sup>.

Genetic testing for affected patients can include single site testing once a specific genetic variant is identified within a family, phenotype-specific panels (i.e., Familial Hypercholesterolemia panel, Brugada syndrome panel, *etc.*), or expanded panels that include genes that are associated with multiple cardiovascular conditions. The utility of genetic testing is vast, including reproductive decision-making, surgical or pharmacological treatment, and management of cardiological and extra-cardiological symptoms.

The cost and accessibility of genetic testing have improved over the last 15 years due to technological advancements, an increase in commercial companies and university-based programs, and the incorporation of point-of-care (POC) genetic testing [[Supplementary Table 2](#)] However, there are important limitations to be considered regarding genetic testing for CVDs. First, obtaining insurance coverage for expanded testing can be a distinct barrier for some patients. In Dellefave-Castillo's (2022) study, comprehensive genetic testing was provided through a sponsored program at no cost for the patients<sup>[151]</sup>. However, in mainstream clinical practice, genetic testing is traditionally billed through insurance by the laboratory, with any remaining cost billed to the patient directly. Large deductibles and lack of insurance coverage for broader panels could lead to large out-of-pocket costs for patients. While many labs offer financial assistance plans and ways to bypass insurance, the prices patients must pay can still be prohibitive for many families. There are also many programs for patients who need to have genetic testing done, so that they can even do genetic testing free of charge in certain cases.

Second, as the number of genes tested increases, so does the possibility of receiving uncertain results such as Variants of Uncertain Significance (VUSs)<sup>[152]</sup>. VUSs are mutations with limited or conflicting evidence to support whether they are pathogenic or benign<sup>[153]</sup>. This ambiguity can lead to confusion among providers and patients alike<sup>[154]</sup>. While guidelines recommend that VUSs should not be used to guide medical decision-making or surveillance of at-risk family members, these types of results may lead to more questions than answers<sup>[155]</sup>. Over time, many of these variants are reclassified to either benign or pathogenic, but the timeline of reclassification spanning from months to years may lead to higher levels of concern, ambiguity in clinical and reproductive decision-making, and inappropriate discharge from follow up<sup>[152,156]</sup>. Providers should take special care in explaining the possibility of a VUS in pre- and post-test counseling.

Third, choosing a test that includes genes conferring risk for cardiovascular phenotypes beyond the patient's clinical diagnosis increases the risk for secondary findings. Secondary findings (i.e., incidental findings) are results unrelated to the diagnostic question or original purpose of the genetic test<sup>[156]</sup>. Whether one would classify a new molecular diagnosis of cardiomyopathy in a patient clinically diagnosed with an arrhythmia as a secondary finding is up to the frame of reference of whether the purpose of the test is to elucidate genetic changes that may contribute to their heart problems or is it to confirm/deny whether a mutation exists in genes only related to their cardiomyopathy. Our understanding of cardiovascular genotype-phenotype associations is evolving, and an unexpected result may be phenotypic expansion. Regardless, patients may experience surprise or anxiety when receiving a diagnosis that is different from their reason for referral. Similarly, providers may not feel equipped to disclose these results. For example, an electrophysiologist may not feel as prepared as a cardiomyopathy specialist to discuss the implications of an unexpected genetic test result conferring a risk for cardiomyopathy. Providers and patients should both be informed that new cardiovascular diagnoses may be revealed through comprehensive cardiovascular genetic testing. Pre-test counseling should include the benefits and risks of genetic testing so patients can make informed decisions about their health.

With respect to pharmacogenomics, there are chances of errors that may lead to false under or overdosing of the medication<sup>[145]</sup>. Unlike established forms of CVDs, the insurance coverage for genetic testing remains incoherent<sup>[139-141,149,150]</sup>. Additionally, medications such as warfarin have few indications left due to the era of DOACs, and INR monitoring is still needed after genetic testing is done<sup>[145]</sup>. Lastly, the clinicians, especially primary care physicians, may not be up to date regarding the indications and adequate referral for genetic testing, thereby further limiting the awareness among patients.

### Treatment and outcomes

The utility of genetic testing and appropriate counseling is predicated on improving patient understanding of their disease and psychological and emotional stress related to their diagnosis and informing treatment plans to increase the likelihood of positive outcomes. Implementing genetic testing in the clinic has already been seen in other fields. McKnight *et al.* utilized genetic testing to enhance epilepsy treatment, which included adding or beginning a new medication, referring to a specialist, or stopping a current medication. This was coupled with 75% of patients in the study citing positive outcomes and 65% reporting a reduction in seizure activity<sup>[157]</sup>. Positive outcomes and/or a greater understanding of disease associated with genetic testing have also been seen in the context of primary and preventative care<sup>[158,159]</sup>. Improved positive outcomes have been demonstrated pertaining to cardiovascular disease, namely reduced risk of MACE and major and minor bleeding during P2Y12 de-escalation<sup>[160]</sup>, significantly reduced LDL-C level in patients with familial hypercholesterolemia without CHD<sup>[161]</sup>, and event-free survival in patients with dilated cardiomyopathy<sup>[162]</sup>. Notably, gene therapy of mice with ARVC harboring a pathogenic mutation in the PKP2 gene has been shown to restore PKP2 protein levels, inhibit pathogenesis, and prolong survival<sup>[163,164]</sup>.

### Genetic counseling

With the advent of newer genetic testing for CVDs, a key factor is the availability of genetic counselors (GCs) who are trained specifically in cardiovascular genomics<sup>[165]</sup>. Cardiovascular GCs are vital in constructing a thorough and complete three-generation family history (pedigree), determining which genetic testing is most appropriate given an individual's personal and/or family history, discussing the benefits, limitations, and implications of genetic testing, providing psychosocial support, and coordinating proband (first-person in the family to undergo genetic testing) and cascade genetic testing (testing family members after a disease-causing mutation has been identified in the family)<sup>[165]</sup>. Additionally, given the nature of cardiovascular genetic testing, GCs also collaborate with regional and state medical examiner officers to coordinate postmortem genetic testing in order to identify the cause of death as well as determine if relatives are at risk for genetic disease and/or sudden death. GCs are well positioned to bridge the silos of the healthcare system and promote team science approaches and interdisciplinary collaboration. While there is not a one-size-fits-all model for the integration of cardiovascular GCs in a clinical practice setting, it is crucial that genetic counseling occurs simultaneously with genetic testing in order to promote patient-centered care and informed decision making. Although effective collaboration and communication are seen in the various practice models used by genetic counselors at different clinical practices, further development into a comprehensive and cohesive model may lead to improved outcomes<sup>[166]</sup>. Such models for counseling of inherited CVDs are being rapidly updated to keep pace with the evolving genetic testing<sup>[167-169]</sup>.

### Polygenic risk scores

Polygenic risk scores (PRSs) are a weighted average of the effects of all genetic variations across the genome contributing to a particular disease and condensed into a single score. The American Heart Association has outlined three categories to consider for implantation into clinical use: efficacy, harm, and logistics<sup>[170]</sup>. Studies have shown that utilizing genetic scoring can increase the accuracy of predicting risk<sup>[171]</sup>, identifying those who can benefit the most from statin use<sup>[172]</sup>, and estimating lifetime risk<sup>[173]</sup>. However, given the bias in the genetic databases that are used to construct these scores<sup>[174]</sup>, more research and increased diversity of the dataset would greatly benefit its implementation.

## ETHICAL, LEGAL, AND PSYCHOSOCIAL IMPLICATIONS

Given the sensitivity and personal nature of genetic testing, patients may be reluctant and concerned about generating such information. While previous documents address ethical concerns related to research involving human subjects, such as the Nuremberg Code and the Declaration of Helsinki<sup>[175,176]</sup>, they serve as a principal backdrop to build new parameters related to genetic testing. Fear of discrimination by employers and insurance companies, psychological impact of learning about genetic status, and decision-making have been shown as patient concerns<sup>[177,178]</sup>. Further, premature commercialization and conflict of interest have already been demonstrated<sup>[179]</sup>.

## FUTURE PERSPECTIVES

Genetic testing to diagnose CVDs and to guide pharmacotherapies, particularly for precision medicine, has a big potential to modify morbidity and mortality rates in these subsets of patients. The upcoming gene therapies, including targeted siRNAs, can contribute to a significant reduction in adverse CV outcomes in vulnerable populations. Additionally, novel therapies aimed at the sarcomere have shown promise in treating those with various cardiomyopathies<sup>[61]</sup>. Conspicuously, there is a dearth of information pertaining to pathogenic mutations in genes related to thrombosis and atherosclerosis. Characterizing and validating such genes would provide great insight into cardiovascular pathogenesis. Further, continuing to develop the use of genome editing with CRISPR-Cas9 and RNA editing with Cas7-11 holds great potential<sup>[180,181]</sup>. However, as previous research has shown, there is a significant gap between available evidence and

implementation into practice<sup>[182]</sup>. At the center of this all is the requirement for collaboration among physicians and the wider availability of genetic counselors.

## DECLARATIONS

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### Authors' contributions

Made substantial contributions to the conception and design of the study, prepared the initial draft, and provided edits to the paper: Singh S, Bliden K, Shanoada R, Kalia I, Zimmerman A, Stude T, Gurbel P  
Performed editing and critically reviewed the manuscript for important intellectual content: Tantry U, Babu AD, Raghavakurup L, Sidorski D

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All authors declared that there are no conflicts of interest.

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