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Using Genomics to Develop Personalized Cardiovascular Treatments

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ABSTRACT: Advances in genomic technologies have significantly enhanced our understanding of both monogenic and polygenic etiologies of cardiovascular disease. In this review, we explore how the utilization of genomic information is bringing personalized medicine approaches to the forefront of cardiovascular disease management. We describe how genomic data can resolve diagnostic uncertainty, support cascade screening, and inform treatment strategies. We discuss how genome-wide association studies have identified thousands of genetic variants associated with polygenic cardiovascular diseases, and how integrating these insights into polygenic risk scores can enhance personalized risk prediction beyond traditional clinical algorithms. We detail how pharmacogenomics approaches leverage genotype information to guide drug selection and mitigate adverse events. Finally, we present the paradigm-shifting approach of gene therapy, which holds the promise of being a curative intervention for cardiovascular conditions.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: cardiovascular diseases ■ genetic risk score ■ genetic therapy ■ genome-wide association study ■ pharmacogenomics

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Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality globally, despite significant advances in both primary and secondary prevention strategies.[1] The traditional paradigm for CVD management relies upon standardized risk algorithms, population-based guidelines, and treatment protocols. Although these approaches have undoubtedly improved outcomes, they often do not encompass the substantial heterogeneity of CVD, which encompasses differences in genetic predisposition, comorbidities, and lifestyle factors. This heterogeneity can lead to distinct clinical presentations, varying rates of progression, and diverse therapeutic responses between individuals.

With the cost of genetic sequencing falling ever lower, access to genomic data for patients, clinicians, and investigators has never been greater.[2] In turn, it has ushered in an era of personalized medicine that seeks to tailor interventions based on individuals' unique genomic architecture.

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This review seeks to provide an overview of how genomic information is driving change across 3 main areas of CVD therapeutics and management (Figure 1/ Graphical Abstract). First, how genomic information can clarify diagnostic conundrums, guide treatment, and inform risk prediction. Second, the field of cardiovascular pharmacogenomics where genomic data can guide drug choice and predict adverse drug reactions. Finally, we highlight the paradigm-shifting approach of gene therapy which holds the promise of being a curative intervention for CVD.

CARDIOVASCULAR GENOMICS: A BRIEF OVERVIEW

CVDs in a genomics context have been broadly split into 2 main groups: monogenic disorders and polygenic disorders. Monogenic disorders are caused by pathogenic variants that affect the structure, function, or expression levels of the protein encoded by a particular gene.

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Nonstandard Abbreviations and Acronyms

AAV	adeno-associated virus
CAD	coronary artery disease
CVD	cardiovascular disease
GWAS	genome-wide association study
HCM	hypertrophic cardiomyopathy
LDL	low-density lipoprotein
LDLR	low-density lipoprotein receptor
LQTS	long-QT syndrome
PCSK9	proprotein convertase subtilisin/kexin type 9
PRS	polygenic risk score
SERCA2a	sarcoplasmic/endoplasmic reticulum Ca2+ ATPase 2a

Highlights

- Genomic approaches have the potential to transform cardiovascular disease management through improved diagnosis, refined risk stratification with polygenic risk scores, and targeted therapies.
- Cardiovascular pharmacogenomics allows personalized treatment decisions, reducing adverse drug events and improving therapeutic outcomes based on individual genetic profiles.
- Despite advancements, challenges remain in translating genomic insights into routine clinical practice, particularly around leveraging the breadth of genome-wide association study findings, ancestry-based disparities, and real-world clinical integration of polygenic risk scores, as well as equitability of access.
- Gene therapy, including RNA-based and CRISPR/Cas9–mediated gene editing approaches, has shown promising outcomes in a range of cardiovascular conditions. These technologies provide hope for durable, curative treatments but require careful management of safety, delivery, and clinical trial design challenges.

Examples of monogenic CVDs include cardiomyopathies (eg, hypertrophic cardiomyopathy [HCM], dilated cardiomyopathy, arrhythmogenic cardiomyopathy), channelopathies (eg, catecholaminergic polymorphic ventricular tachycardia, long-QT syndrome [LQTS]), aortopathies, and familial hypercholesterolemia.[3] Although the genes underlying these conditions were previously thought to determine disease development in a straightforward fashion following Mendelian (dominant, recessive) inheritance patterns, our understanding of this paradigm has changed, particularly with the advent of large-scale population-based biobank sequencing initiatives. Pathogenic variants have been identified in individuals without CVD (incomplete penetrance),[4,5] and in those with disease, a wide range of clinical phenotypes are expressed; this is potentially due to heterogeneity among pathogenic variants, additional contribution of clinical and environmental risk factors,[6,7] and coinheritance of other (common) genetic variants which may exacerbate or ameliorate the effect of the principal pathogenic variant on the phenotype.[8,9] Clinical screening for monogenic CVD disorders is now relatively commonplace, and we will discuss in the next section how this has facilitated improved diagnosis and earlier treatment.

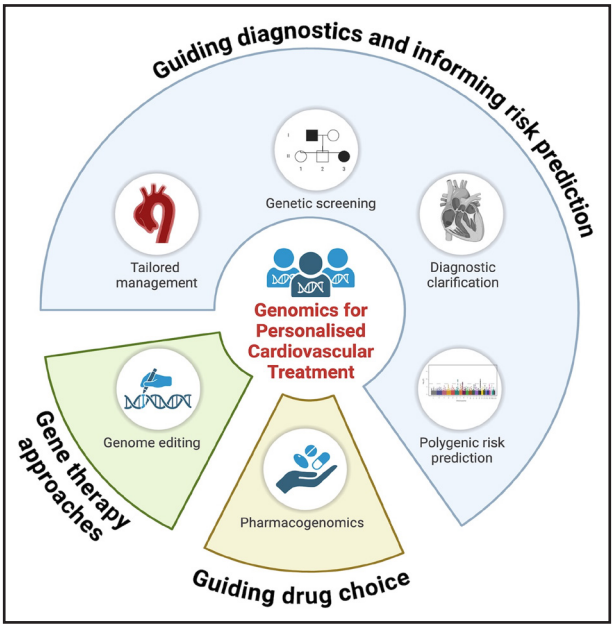


Figure 1. The role of genomics in personalized cardiovascular treatment.
Key areas where genomics is enabling development of personalized cardiovascular medicine include genetic screening for early detection of hereditary cardiovascular conditions, tailored management strategies to optimize patient-specific care, diagnostic clarification to refine disease categorization, pharmacogenomics to guide medication choices based on genetic profiles, polygenic risk prediction for assessing multifactorial disease susceptibility, and genome editing to correct or modify genetic defects. Taken together, these genomic approaches advance personalized medicine in cardiovascular health. Created with BioRender.

Polygenic disorders arise from multiple common genetic variants across the span of the genome. Although these variants individually have modest effects, when taken together they increase susceptibility to disease. Most polygenic variants are found in nonprotein coding regions of the genome[10] and are known to interact with each other as well as with lifestyle and environmental factors.[11,12] Examples of polygenic CVDs include hypertension, atrial fibrillation, and atherosclerosis/coronary artery disease (CAD). Although the polygenic nature of these conditions has been appreciated for many decades, it has only been in the last 20 years that

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unbiased, high-resolution examination of the genome through genome-wide association studies (GWAS) has been possible. To date, thousands of genetic variants have been demonstrated to be associated with a wide range of CVDs.[13–18] In this sphere, 2 parallel approaches are being utilized to further our understanding of CVD: first, increasing the power of genome-wide studies by expanding cohort sizes, including underrepresented populations and ancestries, and interrogating rare variants using data from whole exome and whole genome sequencing.[19–21] Second, leveraging GWAS findings to pursue personalized medicine approaches. Examples of this include highlighting therapeutic targets for CVD or drug repurposing opportunities[22,23] and the development of polygenic scores to highlight individuals at potentially increased risk of disease development,[24] which we will discuss in further depth.

USING GENOMICS IN CLINICAL DIAGNOSIS AND MANAGEMENT

Genomic Screening

Genomic testing of monogenic cardiovascular disorders has become a standard aspect of clinical management. Cascade screening refers to the process whereby after a genetic diagnosis has been made in a proband—usually the index presentation within a family—onward genetic testing can be offered to first-degree relatives and subsequently other family members who may be at risk of disease.[25,26] Relatives who do not carry the disease-causing variant can be released from lifelong clinical surveillance, whereas those who do carry the disease-causing variant may require clinical surveillance performed at regular intervals depending on the condition, age, and severity of their clinical phenotype.

First-line testing has usually centered on genes robustly associated with the presenting phenotype in the form of targeted gene panels. However, with falling costs of whole exome and whole genome sequencing, there is now the possibility to proceed directly to performing these analyses. The choice of approach mainly depends upon clinical presentation and most likely genetic etiology: a targeted gene panel is preferred if the condition is strongly associated with a small set of genes (eg, LQTS), whereas a broader analysis may be used where there is more clinical uncertainty with respect to the diagnosis (eg, pediatric syndromic cardiomyopathy).[27] Furthermore, there is also the option of a hybridized approach: application of virtual panels to data from whole exome sequencing whereby, although sequencing data are generated for all genes, only the genes in the virtual panel relevant to a patient's condition are subjected to downstream interpretation.[28] Resources such as the Genetic Testing Registry in the United States or the National Genomic Test Directory in the United Kingdom are examples of resources delineating what testing is available on a per-condition basis.[29,30]

Clarification of Diagnosis and Tailoring of Clinical Management

Genomic testing can be utilized to resolve diagnostic uncertainty and guide decision-making around clinical management. This is particularly useful in cases of suspected HCM. HCM is a heart muscle disease characterized by increased left ventricular wall thickness (hypertrophy). It is associated with increased risks of sudden (arrhythmic) cardiac death, thromboembolic disease, and progressive heart failure and has an estimated prevalence of 1 in 500.[31] It is most commonly caused by pathogenic variants in genes encoding sarcomeric proteins in the cardiomyocyte.[32] Importantly, a diagnosis of HCM can only be made in the absence of another cardiac, systemic, or metabolic disease capable of producing the degree of hypertrophy evident in a particular patient. As such, there are numerous conditions that mimic symptoms and signs of HCM but have different causes, known as phenocopies (Table 1).[33] Phenocopies fall into 2 main categories: acquired or genetic (often syndromic). Diagnostic left ventricular hypertrophy due to hypertensive heart disease or athletic training are acquired phenotypic mimics that will not show genetic markers for HCM. Genetic phenocopies often include storage and metabolic disorders, with distinct risks or clinical features that require specific treatment, such as enzyme replacement for Anderson-Fabry disease or transthyretin-silencers for cardiac amyloidosis. An accurate diagnosis through genetic testing that includes phenocopy screening enables tailored management strategies. Thus, genetic testing is recommended for all individuals newly diagnosed with HCM and in particular when extracardiac symptoms are present.[25,34] A list of HCM phenocopies is presented in Table 1.

Familial hypercholesterolemia is characterized by a marked elevation in plasma LDL (low-density lipoprotein) cholesterol from birth, accelerated rates of atherosclerotic plaque deposition, and premature ischemic heart disease.[35] It most often arises due to mutation in the *LDLR* (LDL receptor), *APOB*, or *PCSK9* (proprotein convertase subtilisin/kexin type 9) genes. Knowledge of the driving pathogenic variant has been shown to have implications for treatment efficacy in familial hypercholesterolemia. For example, individuals with pathogenic *PCSK9* variants may respond particularly well to PCSK9 inhibitors, whereas these therapeutic agents may demonstrate less potency in those who are homozygous for *LDLR* pathogenic variants.[36] This may be expected given that PCSK9 inhibitors bind circulating PCSK9 and prevent it from targeting LDLR receptors for degradation; in those who are homozygous for *LDLR* mutations, there are too few functional LDL receptors to recycle

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Table 1. Summary of Main Hypertrophic Cardiomyopathy Phenocopies

Cellular location/ biological function	Disease	Protein	Gene	Key features	Mode of inheritance
Metabolic regulation/ glycogen metabolism	PRKAG2 syndrome	AMP-activated protein kinase (γ2 subunit)	*PRKAG2*	Glycogen storage in myocytes and conducting tissue; may present with WPW syndrome and progressive conduction system disease in addition to LV hypertrophy.	AD
Lysosomal membrane	Danon disease	Lysosomal-associated membrane protein 2	*LAMP2*	Severe hypertrophy, skeletal myopathy, and variable conduction abnormalities; often more severe in males.	X-linked
Lysosomal glycosphingolipid catabolism	Fabry disease	Alpha-galactosidase A	*GLA*	Characterized by left ventricular hypertrophy, acroparesthesias, angiokeratomas, renal impairment; may cause pseudo-HCM with distinctive extracardiac findings.	X-linked
Lysosomal glycogen metabolism	Pompe disease	Lysosomal acid α-glucosidase	*GAA*	Can present with infantile-onset cardiomyopathy (often rapidly fatal if untreated) or late-onset limb-girdle phenotype with possible LV hypertrophy.	AR
RAS-MAPK pathway	Rasopathies (eg, Noonan syndrome)	RAS/MAPK signaling molecules (eg, KRAS, SOS1, PTPN11, RAF1)	*KRAS, SOS1, PTPN11, RAF1*	Systemic involvement with characteristic facial features, short stature, variable developmental aspects; hypertrophic cardiomyopathy is a common cardiac manifestation.	AD
Other	Hereditary (ATTR) amyloidosis	Transthyretin	*TTR*	Amyloid deposits in the myocardium can mimic HCM, often with restrictive features, and can also cause carpal tunnel syndrome and peripheral neuropathy.	AD
Mitochondrial energy metabolism	Mitochondrial cardiomyopathies	Multiple	Various mitochondrial genes/variants	Often present with multisystem involvement, including neuromuscular deficits, sensorineural hearing loss, and diabetes; can exhibit LV hypertrophy and conduction abnormalities.	AD, AR, or matrilineal
Mitochondrial iron homeostasis/ metabolism	Friedreich ataxia	Frataxin	*FXN*	Neurological disorders (ataxia, dysarthria, and neuropathy), diabetes, and frequent hypertrophic cardiomyopathy that can be a major cause of early mortality.	AR

AD indicates autosomal dominant; AR, autosomal recessive; ATTR, transthyretin amyloidosis; HCM, hypertrophic cardiomyopathy; KRAS, Kirsten rat sarcoma viral oncogene homolog; LV, left ventricular; MAPK, mitogen-activated protein kinase; PRKAG2, protein kinase AMP-activated noncatalytic subunit gamma 2; PTPN11, protein tyrosine phosphatase nonreceptor type 11; RAF1, Raf-1 proto-oncogene, serine/threonine kinase; RAS, rat sarcoma viral oncogene homolog; SOS1, son of sevenless homolog 1; and WPW, Wolff-Parkinson-White syndrome.

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reducing the impact of PCSK9 inhibition. In addition, genomic testing may reveal causal variants in *ABCG5* or *ABCG8*, which encode sterolin transporters responsible for regulating the absorption and excretion of dietary sterols (plant-derived compounds structurally similar to cholesterol). Pathogenic variants in these genes cause sitosterolemia, a rare autosomal recessive lipid disorder characterized by elevated plasma levels of plant sterols due to impaired sterol excretion. Unlike familial hypercholesterolemia, sitosterolemia has a distinct treatment protocol focused on eliminating dietary sterols and using ezetimibe, rather than statins.[37]

LQTS is an inherited arrhythmia characterized by prolonged ventricular repolarization and an elevated risk of ventricular arrhythmia and, in turn, sudden cardiac death (Figure 2).[38] Most cases are associated with loss-of-function variants in *KCNQ1* (LQTS1) or *KCNH2* (LQTS2) or gain-of-function variants in *SCN5A* (LQTS3). Each genotype influences not only the underlying arrhythmia mechanism but also the circumstances of triggering events. For example, patients with LQTS1 are more prone to arrhythmias during exercise, those with LQTS2 are triggered by sudden auditory stimuli (eg, alarm clocks), and those with LQTS3 typically experience events during sleep.[39] Pharmacological therapy is key in reducing arrhythmic events. β-Blockers serve as a cornerstone treatment for LQTS1 and LQTS2, commonly averting the need for an implantable cardioverter defibrillator, although their efficacy is somewhat lower in LQTS2 than in LQTS1.[40] In contrast, mexiletine, a sodium channel blocker, has been designated a class I indication for LQTS3 and may also confer QT-shortening benefits in LQTS2.[41] As such, preventive strategies and treatments to minimize arrhythmic burden can be tailored to individuals by leveraging genotype-specific insights.

Thoracic aortic disorders (aortopathies) can be evident in individuals with Marfan syndrome, Loeys-Dietz syndrome, and vascular Ehlers-Danlos syndrome, which are inherited conditions. It can present with thoracic aortic aneurysm or dissection. Identification of a causal pathogenic variant will have a direct impact on management to present aneurysmal formation and dissection with a lower threshold used to recommend surgical intervention (aortic root diameter <50 mm compared with 55 mm in the general population).[42] There are also genotype-specific recommendations for those with pathogenic variants in *TGFBR1* or *TGFBR2* (Loeys-Dietz Syndrome) in the presence of additional risk factors; these individuals should be considered for aortic surgery if the aortic root diameter is >40 mm.[43]

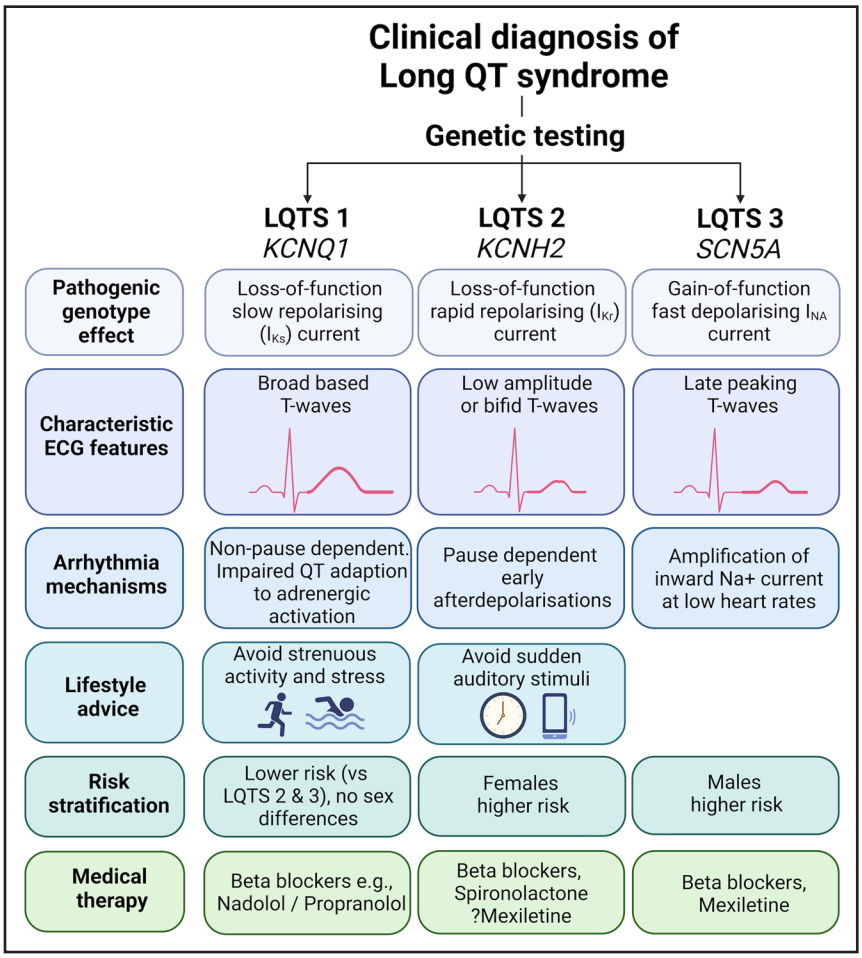


Figure 2. Diagnostic, prognostic, and clinical management of the 3 main long-QT syndrome (LQTS) subtypes. Overview of genotype-specific differences in LQTS. I_{Ks} indicates slow repolarizing potassium current; I_{NA}, fast depolarizing sodium current; and K_r, rapid repolarizing potassium current. Created with BioRender.

Pharmacogenomics

Pharmacogenomics describes the use of specific genomic information with the aim to optimize therapeutic prescription and decrease toxicity.[44] Here, we summarize pharmacological agents used in a variety of CVDs for which genomic data might better personalize treatment and lead to improved outcomes.

Antiplatelets

Antiplatelet therapy forms the cornerstone of managing atherothrombotic conditions, such as CAD and stroke. In cases of acute coronary syndromes or when patients undergo percutaneous coronary intervention, dual antiplatelet therapy with aspirin and a $P2Y_{12}$ receptor antagonist is generally recommended.[45] Available $P2Y_{12}$ inhibitors include clopidogrel, prasugrel, and ticagrelor. Among these, prasugrel and ticagrelor are typically favored for high-risk patients due to their superior cardiovascular outcomes, but clopidogrel is often routinely used in those with higher bleeding risk or on anticoagulation.[46] For patients with stroke, long-term secondary prevention commonly involves single-antiplatelet therapy with clopidogrel alone.[47,48] Importantly, unlike prasugrel or ticagrelor, clopidogrel is a prodrug that requires conversion to an active metabolite.

CYP2C19 (Cytochrome P450 family 2 subfamily C member 19) is the hepatic enzyme responsible for the conversion of clopidogrel via a 2-stage oxidation process and is encoded by the highly polymorphic *CYP2C19* gene. Individuals with a loss-of-function variant in *CYP2C19* are at increased risk of ischemic events due to reduced activity of the enzyme. Of note, the prevalence of loss-of-function variants is variable across ancestries: the prevalence of carriage of 2 *CYP2C19* loss-of-function alleles is 13% in South Asian individuals compared with 2.4% in European individuals.[49] A meta-analysis of randomized controlled trials of individuals undergoing percutaneous coronary intervention demonstrated that there were fewer major adverse cardiovascular events in individuals assigned to having genotype-driven treatment.[50] Performing pharmacogenomic testing in patients considered for clopidogrel therapy is recommended across international guidelines.[51,52] Despite these guideline recommendations, its translation into prescribing patterns is not straightforward. This was demonstrated in a secondary analysis of the GEMINI-ACS-1 trial which examined physician behavior in response to mandatory reporting of CYP2C19 clopidogrel metabolizer status.[53] Of the 3037 enrolled acute coronary syndrome patients, 1333 (43.9%) were prescribed clopidogrel. Of these, 68% of

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patients with reduced metabolizer status continued to receive clopidogrel after CYP2C19 status results were provided to physicians indicating a degree of reluctance in altering pharmacotherapy despite pharmacogenomic information.

β-Blockers

Metoprolol, carvedilol, and propranolol are among several β-blockers metabolized by CYP2D6. This drug-metabolizing enzyme is responsible for the metabolism of 20% to 25% of commonly prescribed medications, such as antidepressants and opioids.[54] The gene encoding CYP2D6 is highly polymorphic, contributing to variability in drug response. Among these agents, metoprolol is particularly reliant on CYP2D6 for its elimination, with 70% to 80% of an oral dose undergoing CYP2D6-mediated metabolism.[55] By contrast, other β-blockers, such as atenolol and bisoprolol, are either not metabolized by CYP2D6 or only minimally so.

Multiple studies have explored how CYP2D6 metabolizer status affects the clinical response to metoprolol in patients treated predominantly for heart failure or hypertension. Although some investigations indicate that poor metabolizers can tolerate lower maintenance doses compared with normal metabolizers, this finding has not been consistently reproduced.[56,57] More consistently, several studies have noted an increased incidence of mostly asymptomatic bradycardia (heart rate <60 bpm) in poor and intermediate metabolizers.[58] Prescribers should be aware that when patients with specific *CYP2D6* genotypes are coprescribed potent CYP2D6 inhibitors (eg, selective serotonin reuptake inhibitors, such as paroxetine or fluoxetine), their effective drug metabolism profile can shift, a process known as phenoconversion. This shift can move a patient from a normal or intermediate metabolizer status toward a poor metabolizer phenotype, thereby altering drug concentration, therapeutic efficacy, and side effect risk. The extent of this phenoconversion depends on both the strength of the CYP2D6 inhibitor and the underlying genetic makeup of the patient.

Cardiac Myosin Inhibitors

Mavacamten is a first-in-class, novel therapeutic option for individuals with obstructive HCM. Myosin inhibitors inhibit cardiac myosin ATPase which reduces the formation of myosin-actin cross-bridges and decreases myocardial contractility (Figure 3).[59] As a result, it can reduce left ventricular outflow tract obstruction and symptom burden. Mavacamten therapy is given via dose uptitration based upon echocardiographic monitoring of left ventricular ejection fraction and outflow tract gradient, the latter of which should reduce in a dose-dependent fashion.[60]

Mavacamten is mainly metabolized by CYP2C19 with smaller contributions from CYP3A4/5 and CYP2C9. Although mavacamten is licensed for adults with obstructive and symptomatic heart failure (New York Heart Association class II and III), left ventricular systolic dysfunction is a recognized adverse sequela, occurring in 5% of treated individuals in the phase 3 study.[61] As discussed earlier, there is variation in the occurrence of loss-of-function *CYP2C19* alleles across ancestries, with individuals who carry 2 loss-of-function variants potentially being at increased risk of systolic dysfunction as a result of mavacamten therapy at standard dosing regimens. This is a result of reductions in ejection fraction being associated with mavacamten plasma concentrations and individuals with 2 loss-of-function alleles having a significantly longer mavacamten elimination half-life (533 hours) compared with normal (150 hours) or extensive metabolizers (72 hours), respectively.[62]

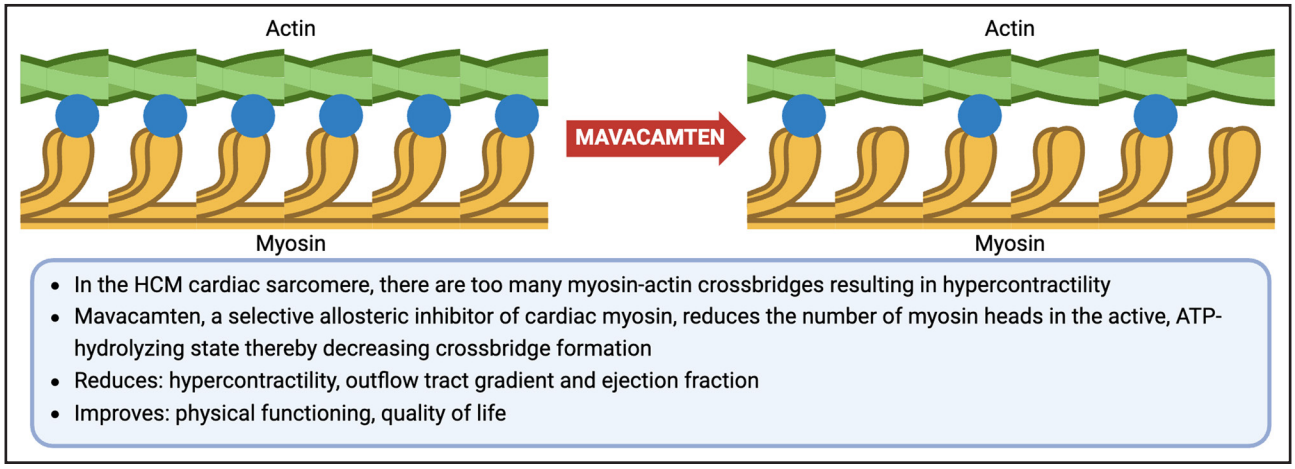


Figure 3. Mechanism of action of mavacamten in hypertrophic cardiomyopathy (HCM).
In the HCM cardiac sarcomere, excessive myosin-actin cross-bridges lead to hypercontractility, increased left ventricular outflow tract obstruction, and impaired cardiac efficiency. Mavacamten, a selective cardiac myosin inhibitor, binds to the myosin heads in their off state, reducing the number of myosin heads available for interaction with actin. This results in fewer cross-bridges forming during contraction, thereby decreasing hypercontractility and restoring normal myocardial relaxation. Consequently, mavacamten reduces left ventricular outflow tract gradient and improves ejection fraction, enhancing cardiac function, physical performance, and quality of life for patients with HCM. Created with BioRender.

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The European Medicines Agency and the UK Medicines and Healthcare Products Regulatory Agency recommend determining a patient's *CYP2C19* genotype before initiating therapy to ensure appropriate dosing.[63] If genotype information is not available, treatment can be initiated using a more conservative dosing approach generally advised for individuals who are likely to have reduced CYP2C19 function. Conversely, those not classified as poor metabolizers can typically begin therapy at standard dosing, with scope to adjust as needed. Dose modifications may also be required when administering concomitant medications that affect CYP2C19 or CYP3A4 activity. Notably, both the European Medicines Agency and the Australian Therapeutic Goods Administration have recognized that certain conservative regimens in poor metabolizers achieve pharmacological exposures comparable to higher regimens in normal metabolizers.[63,64]

Drug Discovery and Repurposing

Although pharmacogenomics focuses on testing individuals for specific variants in particular genes involved in drug metabolism, and genes identified as causal for monogenic diseases leading to the development of therapy (eg, PCSK9 inhibitors), there was hope that the multitude of GWAS findings could be translated into novel or repurposed CVD treatments—progress in this domain has, however, been relatively slow. The overarching challenge stems from the complex biology underlying most genome-wide significant variants: ≈80% to 90% of variants lie in noncoding regions, and even variants within known genes have modest effect sizes, making it challenging to discern causal genes and clear therapeutic targets.[65] Nevertheless, evidence suggests that selecting genetically supported targets can double the success rate of drug development.[66] Indeed, a retrospective analysis of Food and Drug Administration drug approvals in 2021 demonstrated that two-thirds of new drugs were supported by human genetic evidence.[67] Together, this has ensured continued enthusiasm for exploiting GWAS for drug discovery and repositioning strategies.

The utility of GWAS in these domains can be demonstrated by the identification of genetic variants influencing pathways targeted by existing therapies. For example, lipid trait GWAS have highlighted loci related to *HMGCR* and *NPC1L1*, the therapeutic targets of statins and ezetimibe, respectively.[68] GWAS of glycemic traits have pinpointed variants in *KCNJ11/ABCC8* and *PPARG*, targets for sulphonylureas and thiazolidinediones.[69] As is typically the case in GWAS, the variants identified in these studies often have small effect sizes, emphasizing the idea that even if a locus has a statistically small effect, it need not undermine or detract from the clinical relevance of the mapped gene, target protein or identified pathway.

CVD conditions have also benefitted from repurposing opportunities highlighted by GWAS. In a large-scale GWAS of stroke, a locus was mapped to the *F11* gene which encodes the protein targeted by conestat alfa, a C1-esterase inhibitor used in the treatment of hereditary angioedema.[70,71] Conestat alfa is currently being investigated in a phase 2 trial enrolling patients with ischemic stroke, with the GWAS finding providing supportive evidence for this repositioning attempt.[72] GWAS of CAD have frequently identified loci associated with genes primarily related to inflammatory disease, lending further evidence to the importance of inflammation as a driver of atherosclerosis.[73] In recent years, several trials have examined the role of anti-inflammatory therapies and incident cardiovascular events studying agents such as cankinumab[74] and colchicine.[75,76]

GENOMICS IN RISK PREDICTION USING POLYGENIC SCORES

Given the financial and healthcare burden of CVD-associated mortality and morbidity, primary prevention of CVD is a cornerstone of public health strategy all across the world.[77–79] These strategies are predicated upon the principle that the absolute benefit of a preventive therapy is proportional to an individual's baseline risk: those at higher risk gain more benefit than those at lower risk. As such, the intensity of preventive interventions is usually aligned with an individual's absolute risk. Given this paradigm for primary prevention, improving the precision and reliability of risk prediction is an area of great interest.[80]

Polygenic risk scores (PRS) aggregate the effects of risk variants to determine the genetic component of an individual's disease risk.[81] PRS emerged soon after GWAS for CVD-associated traits with an observation that participants with a greater number of risk alleles had a significantly increased number of clinical events.[82,83] Early PRS simply combined risk alleles across loci achieving genome-wide significance having been robustly validated in large-scale GWAS.[84,85] Modern PRS approaches incorporate millions of variants and integrate linkage disequilibrium patterns and effect size distribution assumptions to improve predictive accuracy.[86,87] More recently, a novel generation of PRS methodologies has begun to leverage functional genomic information to enhance prediction.[88]

The purported applications of PRS in CVD include incorporating PRS with currently utilized primary prevention risk models, to considering using a PRS when an individual has been shown to be at borderline risk, or as a standalone risk predictor.[89] Indeed, generation of PRS is no longer an academic pursuit and has given rise to a multimillion-dollar commercial market.[90] CAD is a CVD for which dozens of PRS have been developed. Aragam et al[15] have published the most recent CAD GWAS findings. In a study of 1.16 million ancestrally diverse individuals, a CAD PRS for CAD comprised 2.1 million

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genetic variants. In an independent sample, those in the top decile of the CAD PRS had a 5.7× greater risk of CAD compared with those in the bottom decile. Similar PRS have been constructed for atrial fibrillation, hypercholesterolemia, and type 2 diabetes.[91]

These associations with CAD risk are in line with previous PRS that have been developed across a range of PRS methodologies. However, a recent study by Abramowitz et al[92] has shown that CAD PRS with similar population-level performance do not provide consistent individual risk estimates. That is, when testing the performance of different CAD PRS in an independent sample, there was significant discordance in risk percentile estimates for a given individual indicating that they are not interchangeable. The recognition that different PRS may generate discordant individual-level estimates necessitates that for clinical implementation, refinement of statistical methods to quantify this uncertainty, and novel strategies to communicate this uncertainty to stakeholders will be required. It is already widely recognized that population genetics literacy among both patients and clinicians remains limited. An acknowledgment of this in a PRS-based context is demonstrated by a recently published clinical trial specifically designed with feasibility and acceptability to patients and primary care professionals of incorporating PRS into clinical management as its primary end point.[93]

Additional concerns around PRS include the data sets from which they are derived; present biobank data sets are the source of the overwhelming majority of large-scale GWAS and meta-analyses. There is a widely acknowledged underrepresentation of individuals of non-European ancestry in these cohorts, with PRS tending to demonstrate suboptimal performance in these populations.[89,94,95] Novel PRS methodologies are being used with the aim to improve transancestry prediction.[96–98] Most recently, PRS approaches leveraging haplotype information (groups of genomic variations that tend to be inherited as a set) have been shown to perform more robustly across diverse populations.[99] Other concerns besides ancestry are that there is compelling evidence that large-scale volunteer databases tend to be older, female, less urban, better educated, live in areas of less deprivation, have higher household incomes, and require fewer medications.[100,101] This may have implications for the portability of PRS in the general population: the genomic data upon which PRS calculation is predicated are in the main external to healthcare systems, that is, taken from and validated within research biobanks or direct-to-consumer testing products.

In light of these concerns, it is possible that evaluating the value of PRS in real-world clinical settings where it affects management decisions may provide the best barometer as to their utility. To this end, it has been surprising that there have been limited numbers of studies in this guise. Recently, however, a nested case-control study utilizing PRS has been published. Samani et al[102] implemented a CVD framework for individuals undergoing their National Health Service Health Check and evaluated its ability to better discern those at high risk of CVD. In the study, of the 195 individuals who had a cardiovascular event, the QRISK cardiovascular risk score version 2 ten-year CVD risk score identified 61.5% of individuals as high risk compared with 68.7% when combining QRISK cardiovascular risk score version 2 with the PRS. Although the study had some limitations, particularly that <1% of the entire cohort experienced a cardiovascular event which is not in keeping with the baseline rates in the general population, one may hope that this mode of PRS study becomes more commonplace. In addition, comparing PRS efficacy against updated CVD risk calculators, such as QR4,[103] and evaluating its added value relative to other contemporary biomarkers that are not currently included in these validated tools but show promise (eg, lipoprotein[a])[104] will be important benchmarks. Performing prospective studies and trials in real patients and patient settings will help determine where PRS sits in the armory of risk assessment and how it impacts routine clinical practice.

GENE THERAPY

Gene therapy is a potentially paradigm-shifting approach in the treatment of CVD. Utilizing individual genetic insights, it offers the prospect of being truly curative and alleviating the requirement for long-term pharmacotherapy. Although there are substantial challenges, which will be further discussed, ongoing trials in humans demonstrate how far the field has progressed and demonstrate that we are on the cusp of understanding the feasibility of gene therapy for the treatment of both inherited and acquired cardiovascular disorders.

Gene Therapy Strategies

The molecular mechanisms by which pathogenic variants may result in disease may be classified as first, loss-of-function whereby the presence of a pathogenic variant leads to the production of partially or totally nonfunctional protein resulting in insufficient protein for normal functioning or, second, whereby a pathogenic variant results in sufficient protein production but with either deleterious functioning (gain-of-function) or with interference with the normal protein produced by the wild-type allele (dominant negative).[105]

To combat these, 3 main categories of gene therapy have been developed: gene replacement therapy, gene silencing therapies, and CRISPR/Cas9–based direct genome editing.[106] Gene replacement is the process of provision of a functional copy of a defective gene, enclosed in a vector, to the target organ thereby increasing protein levels to mitigate against the disease phenotype. Gene silencing employs antisense oligonucleotides

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or RNA interference methods, such as small interfering RNA (Figure 4).[107] These interventions aim to attenuate or abolish the transcriptional and translational activity of the pathogenic allele preventing production of the deleterious protein. A further antisense oligonucleotide–based strategy is exon skipping whereby is an antisense oligonucleotide–based strategy that modifies mRNA splicing by masking specific exon-inclusion signals in pre-mRNA. This selective skipping of targeted exons can restore the reading frame or otherwise alter the encoded protein to alleviate the effects of pathogenic mutations.[108] CRISPR/Cas9 gene editing approaches continue to develop but current tools being utilized are the nuclease system, base editors, and prime editors.[109] Although these individual techniques vary, all include a guide RNA molecule encoding for target DNA. The CRISPR/Cas9 nuclease system approach creates a double-stranded break of DNA. Subsequently, intrinsic repair mechanisms within a cell will act to repair the break, during which random bases may be inserted or deleted frequently resulting in a de facto stop codon thereby terminating gene transcription prematurely and leading to a truncated protein (Figure 5). Base editing is considered an improvement on the nuclease system because a double-stranded break in the DNA is not required; instead, it converts 1 nucleotide (cytosine to thymine or adenine to guanine) within a small editing window. Given that no repair is required, the resultant change is more controlled and predictable. Prime editing moves beyond base editing as it permits insertion, deletion, or substitution of multiple nucleotide bases, again without introducing double-stranded DNA breaks.[110] Prime editing, therefore, offers a more versatile array of therapeutic options. Gene replacement therapy can be utilized in cases of loss-of-function pathogenic variants, whereas gene silencing therapy can be utilized where there is production of deleterious protein. Gene silencing is not as durable approach as the others and, therefore, requires repeat dosing. Gene editing provides the widest choice including the introduction of a stop codon to render the pathogenic gene copy nonfunctional, restoring normal DNA sequences, or even introducing promoter sequences to induce increased gene expression.[111] There have also been gene editing approaches to tackle nucleotide expansion repeat disorders in in vitro experiments.[112] Looking forward, there also is the promise to harness the role of the epigenome, which encompasses the precise and flexible biochemical regulation of chromatin status and gene expression to govern cellular processes.[113] CRISPR activation and inhibition approaches offer powerful tools to modulate the epigenome by targeting specific regulatory elements to upregulate or silence gene expression without altering the DNA sequence.[114,115]

Gene Therapy Delivery Strategies

Gene therapy must be delivered to specific cell types via a vector. Successful delivery of gene therapy is one of the primary challenges in its clinical translation: developing a vector that enables ensuring cells receive therapeutic concentrations, demonstrates high tissue specificity, and permits repeat dosing all with minimal adverse effects is a significant challenge.

Viral vectors consist of genetic material surrounded by a viral capsid. Adeno-associated viruses (AAVs) are the most commonly used vectors for cardiac gene therapy. This is due to AAVs rarely integrating into the

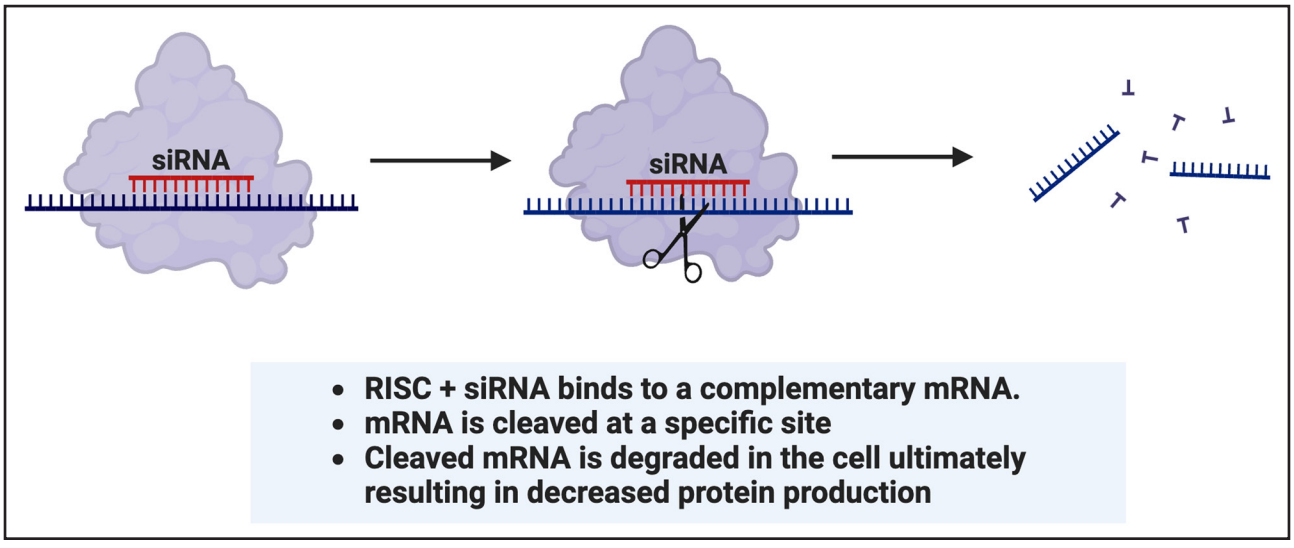


Figure 4. Mechanism of RNA interference mediated by small interfering RNA (siRNA).
The RNA-induced silencing complex (RISC) incorporates siRNA, which then binds to a complementary mRNA sequence. The mRNA is cleaved at a specific site, as directed by the siRNA sequence. The cleaved mRNA fragments are subsequently degraded within the cell, leading to a reduction in the corresponding protein production. This process demonstrates the role of siRNA in posttranscriptional gene silencing. Created with BioRender.

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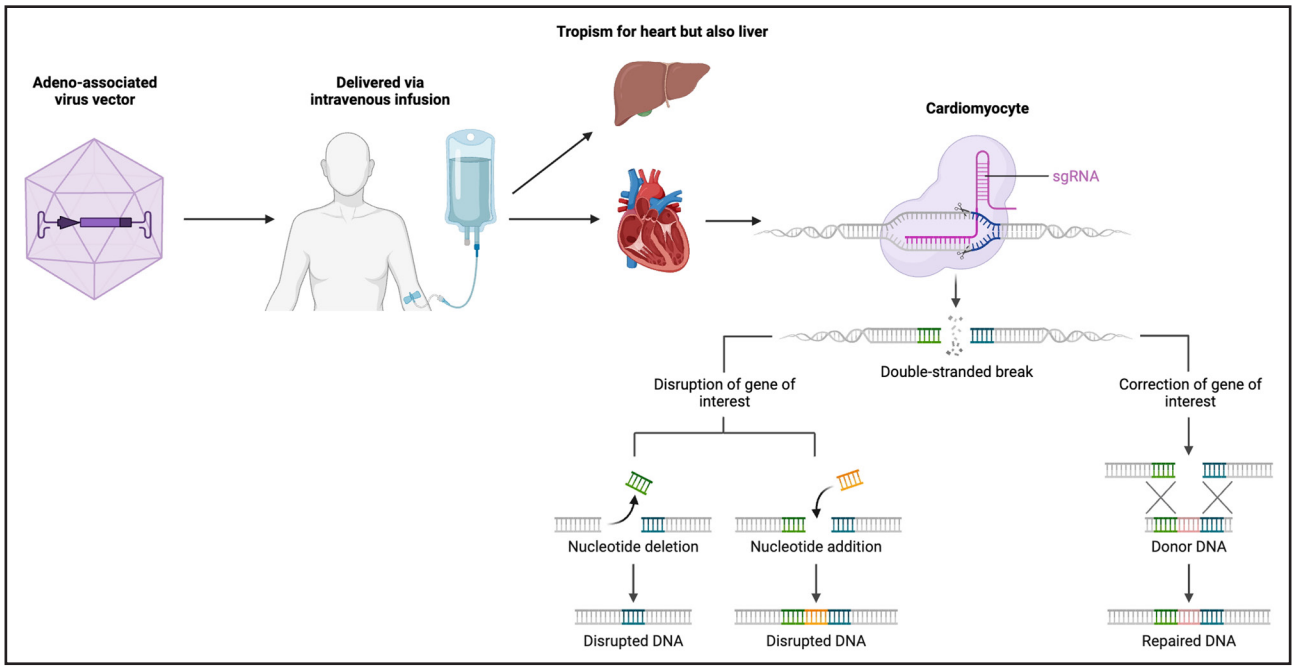


Figure 5. Schematic of CRISPR/Cas9 genome editing mechanism in cardiomyocytes.
An adeno-associated virus (AAV) vector delivers the CRISPR/Cas9 system, including the single-guide RNA (sgRNA), into the cardiomyocyte. This is administered via intravenous infusion. AAV vectors demonstrate high affinity for not only cardiomyocytes but also hepatic cells. The Cas9 protein, guided by the sgRNA, induces a site-specific double-stranded DNA break at the gene of interest. This can result in either disruption or correction of the gene. Disruption occurs through nucleotide deletions or insertions, leading to frameshift mutations and loss of gene function. Correction involves the introduction of donor DNA to repair the gene via homologous recombination, restoring normal function.

genome of a cell meaning they can persist in organs for considerable periods and due to having a strong preference (tropism) for nondividing, postmitotic cells, such as cardiomyocytes.[116] The AAV8 and AAV9 serotypes possess the most superior tropism for cardiomyocytes but additionally, demonstrate strong liver tropism. This not only affects safety due to the potential for liver inflammation but also limits the effective dose reaching the heart.[117] Hepatotoxicity is the most common adverse effect of AAV vectors. With viral vectors, once a patient is exposed to a specific vector, the immune system can form neutralizing antibodies, and as such antibody testing must be performed before administration as preexisting antibodies significantly inhibit AAV delivery efficacy. A further sequela of this is that repeat administration of specific gene vectors is not possible at present. Another key limitation of AAV vectors is that they can only accommodate sequences up to 4.5 kb, which when considering gene replacement strategies, makes them unsuitable to deliver several genes: for example, *MYH7, MYBPC3* (encoding sarcomeric proteins β-myosin heavy chain and myosin-binding protein C), *DSP* (encoding desmoplakin, a key component of cardiac desmosomes), and *RBM20* (encoding an RNA-binding protein involved in splicing of titin, a structural sarcomere protein) when considering cardiomyopathies.[118]

Lipid nanoparticles consist of lipids, phospholipids, cholesterol, and polyethylene glycol and have advantage over AAVs due to their reduced immune response and ease of manufacturing. They have been used routinely in clinical practice including in the SARS-CoV-2 mRNA vaccines.[119] The main drawback of lipid nanoparticles is that they have relatively low tissue specificity with preferential liver tropism resulting in the therapy accumulating primarily in the liver and limited effective delivery to cardiomyocytes, although, as discussed in the next section, this can be advantageous when developing therapies for certain conditions.[120]

Current Status of Gene Therapy in CVD

Several gene therapy trials have been performed or are currently ongoing across a variety of cardiovascular disorders. A summary of these is provided in Table 2.

The most advanced areas in which gene therapy is being investigated are amyloidosis and familial hypercholesterolemia. Transthyretin amyloidosis is an infiltrative cardiomyopathy resulting from transthyretin deposition within the myocardium; this leads to left ventricular hypertrophy and a progressive decline in cardiac function with symptoms of heart failure. Significant progress has been made in the treatment of transthyretin amyloidosis in the form of transthyretin stabilizers (tamifidis)[121] and gene silencing approaches using small interfering RNA (vutrisiran and patisiran).[122,123] Recently, a genome editing approach for transthyretin amyloidosis has been

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Table 2. Overview of Current Cardiovascular Disease Gene Therapy Trials

Trial identifier	Therapeutic compound	Disease	Gene target	Approach	Delivery vector	Trial phase
NCT05885412	RP-A601	Arrhythmogenic cardiomyopathy	*PKP2*	Gene replacement	AAV	1
NCT06109181	LX2020	Arrhythmogenic cardiomyopathy	*PKP2*	Gene replacement	AAV	1, 2
NCT06228924	TN-401	Arrhythmogenic cardiomyopathy	*PKP2*	Gene replacement	AAV	1
NCT05836259	TN-201	Hypertrophic cardiomyopathy	*MYBPC3*	Gene replacement	AAV	1b, 2
NCT05445323	LX2006	Friedreich ataxia	*FXN*	Gene replacement	AAV	1, 2
NCT05302271	AAVrh.10hFXN	Friedreich ataxia	*FXN*	Gene replacement	AAV	1a, 1b
NCT04174105	AT845	Pompe disease	*GAA*	Gene replacement	AAV	1, 2
NCT03533673	ACTUS-101	Pompe disease	*GAA*	Gene replacement	AAV	1, 2
NCT04093349	SPK-3006	Pompe disease	*GAA*	Gene replacement	AAV	1, 2
NCT00976352	AAV-GAA	Pompe disease	*GAA*	Gene replacement	AAV	1, 2
NCT02240407	AAV-GAA	Pompe disease	*GAA*	Gene replacement	AAV	1
NCT04046224	ST-920	Fabry disease	*GLA*	Gene replacement	AAV	1, 2
NCT04519749	4D-310	Fabry disease	*GLA*	Gene replacement	AAV	1, 2
NCT06092034	RP-A501	Danon disease	*LAMP2*	Gene replacement	AAV	2
NCT06128629	NTLA-2001	Transthyretin amyloidosis	*TTR*	Gene editing	LNP	3
NCT05598333	AB-1002	Ischemic cardiomyopathy and heart failure	*PP1*	Protein inhibition	AAV	2
NCT06125847	NGGT006	Familial hypercholesterolemia	*LDLR*	Gene replacement	AAV	1
NCT00891306	LPLS447X	Familial hypercholesterolemia	*LDLR*	Gene replacement	AAV	2, 3
NCT06293729	NGGT006	Familial hypercholesterolemia	*LDLR*	Gene replacement	AAV	1
NCT06112327	VERVE-101	Familial hypercholesterolemia	*PCSK9*	Gene editing	LNP	1 (paused)
NCT06164730	VERVE-102	Familial hypercholesterolemia	*PCSK9*	Gene editing	LNP	1
NCT06451770	VERVE-201	Familial hypercholesterolemia	*ANGPTL3*	Gene editing	LNP	1
NCT05860569	GC304	Hypertriglyceridemia	*LPL*	Gene replacement	AAV	1

Trial identifier denotes https://www.clinicaltrials.gov reference. AAV indicates adeno-associated virus; GAA, GAA, lysosomal acid α-glucosidase; and LNP, lipid nanoparticle.

developed aiming to provide an even more durable reduction in transthyretin using the CRISPR/Cas9 approach called nexiguran ziclumeran.[124] Phase 1 results were recently published in 36 patients demonstrating a mean change in serum transthyretin of −89% at 28 days and −90% at 12 months. A phase 3 study has been launched aiming to enroll 765 participants and will report in 2028. In familial hypercholesterolemia, the small interfering RNA inclisiran designed to target *PCSK9* mRNA has received approval from regulators worldwide and is administered at 6-month intervals.[125] The VERVE-101 molecule is a CRISPR/Cas9 approach designed to alter a single base in the *PCSK9* gene. Interim results from a phase 1b trial in familial hypercholesterolemia patients indicated that a single treatment with high-dose VERVE-101 resulted in a 55% reduction in LDL cholesterol which persisted at 6 months.[126] As of April 2024, however, the trial was paused due to safety concerns arising from liver injury and thrombocytopenia in 1 participant.[127] It is notable that these approaches have used a lipid nanoparticle approach and benefit from the fact that transthyretin and cholesterol are both produced in the liver thereby taking advantage of inherent hepatic tropism of the lipid nanoparticles.

In the cardiomyopathy sphere, human trials have been occurring across a broad range of phenotypes. These include HCM, arrhythmogenic cardiomyopathy, and several HCM phenocopy conditions: Pompe disease, Friedreich ataxia, Anderson-Fabry disease, and Danon disease. In HCM, the TN-201 is being studied in the phase 1b/2 My-PEAK-1 clinical trial.[128] TN-201 is a gene replacement strategy delivering a functional copy of *MYBPC3* using an AAV vector. Interim data from the trial has reported that the first 3 patients have received therapy to a follow-up of up to 12 months with increased RNA expression and improvements in New York Heart Association classification for patients 1 and 2. In arrhythmogenic cardiomyopathy, 3 phase 1 trials are ongoing investigating RP-A601, LX2020, and TN-401 compounds.[129–131] All of these trials are gene replacement trials targeting the *PKP2* gene, which encodes a desmosomal protein, mutations, which are responsible for up to 40% of arrhythmogenic cardiomyopathy cases.[132]

Moving toward polygenic CVD, the areas where gene therapy is being deployed include hypertension and heart failure. Zilebesiran is a small interfering RNA molecule that targets the production of angiotensinogen in the liver. Angiotensinogen is the most upstream precursor in the renin-angiotensin-aldosterone system. In the phase 2 study (KARDIA-1), a single administration of zilebesiran reduced ambulatory blood pressure and clinic systolic

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blood pressure at 3 and 6 months compared with baseline against placebo.[133] A phase 3 study is currently ongoing enrolling individuals with mean clinic systolic blood pressure between 140 to 170 mm Hg on stable therapy with 2 to 4 antihypertensive medications and a 10-year CVD risk of >15%.[134] In heart failure, AB-1002 is being studied as part of the GenePHIT phase 2 study.[135] It is a gene replacement strategy delivering a constitutively active form of protein phosphatase inhibitor-1 (I-1c) to restore cardiomyocyte intracellular calcium homeostasis; it is administered by percutaneous intracoronary infusion. It is enrolling adults with nonischemic cardiomyopathy and New York Heart Association class III heart failure symptoms. As well as ongoing trials in common CVD, it is also instructive to consider previous trials which did not meet their end points, highlighting that the translation from promising preclinical findings to patient benefit is not always straightforward. One such example was the CUPID 2 trial of SERCA2a (sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase enzyme, responsible for calcium handling) overexpression for patients with advanced heart failure with reduced ejection fraction.[136] This phase 2b randomized trial did not show any benefit despite promising support from preclinical and pilot data.[137] Interestingly, the gene encoding SERCA2a, *ATP2A2*, has not been implicated in GWAS for heart failure or ventricular phenotypes.[16,17,138,139] Furthermore, a recent proteomics analysis of cardiac tissue from patients with end-stage heart failure and controls demonstrated no difference in SERCA2a protein abundance.[140] This serves to highlight how genomic evidence, as well as incorporating detailed knowledge of tissue-level changes, can be critical when it comes to selecting targets to pursue in the context of gene therapy.

Challenges Facing Gene Therapy

Gene therapy is the most advanced frontier of CVD management incorporating genomics. In addition to the challenges surrounding toxicity, tropism, and repeat dosing, there are relatively complex issues around the trial design itself. First, it is not straightforward to identify the right patient to partake; those with mild disease may not be able to demonstrate significant therapeutic benefit during the trial follow-up period, whereas those with more severe phenotypes, given that it is unclear as to whether gene therapy can improve or revert disease its advanced stages, may not derive any benefit whatsoever. Second, the evaluation of genome delivery to target cells requires a biopsy to perform RNA expression to determine the number of transcript copies per cell. In the case of cardiomyocytes, endomyocardial biopsies would be needed with nontrivial complications from the procedure. A further consideration is cost; given the degree of research that is required to bring a gene therapy to market, the cost to the healthcare system or patient will inevitably be high. As an example, SRP-9001, recently approved for use in young pediatric patients with Duchenne muscular dystrophy, has been priced at $3.2 million per patient.[141] It has been well documented that significant health inequality exists in the implementation of genomics and personalized medicine.[142] Now that the use of genomics is growing beyond screening, diagnosis, and risk prediction and into therapeutics, there is potential that this gap will widen; it would be prudent to address these challenges before they become too firmly entrenched.

CONCLUSIONS

The understanding of the genetic basis of rare and common CVDs has advanced substantially over the last 25 years. Evaluating genomic information now forms part of routine clinical workflow for inherited cardiac conditions in improving diagnostic decision-making, screening of relatives, and guiding decisions on therapy. In common cardiovascular conditions, new insights borne from genome-wide data and PRSs are permitting the delineation of novel biological pathways of disease, drug discovery, and refinement of risk stratification. The promise of genome editing technologies to effectively cure diseases represents an application that may revolutionize our approach to certain conditions and is attracting large amounts of investment. All of these taken together highlight the role of genomics in bringing personalized medicine to the forefront of the management of CVD, albeit with the challenge of ensuring that this is an equitable and accessible option for all.

ARTICLE INFORMATION

Received February 04, 2025; accepted April 7, 2025.

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Acknowledgments

Figures created in BioRender.

Sources of Funding

M.M. Sanghvi recognizes his British Heart Foundation Clinical Research Training Fellowship (FS/CRTF/22/24353). W.J. Young and H. Naderi recognize the National Institute for Health and Care Research (NIHR) Integrated Academic Training program, which supports their Academic Clinical Lectureship posts. J. Ramírez acknowledges support from the European Union–NextGenerationEU fellowship under grant RYC2021-031413-I funded by MCIN/AEI/10.13039/501100011033 and from the European Union NextGenerationEU/PRTR under grants PID2021-128972OA-429 I00, CNS2023-143599, and PID2023-148975OB-I00 funded by MCIN/AEI/10.13039/501100011033. C.G. Bell is supported by Barts Charity (G-002372) and Impetus Grants from the Norn Group and Hevolution Foundation (Round 2). P.B. Munroe acknowledges the support of the National Institute for Health and Care Research Barts Biomedical Research Centre (NIHR203330) and a delivery partnership of Barts Health NHS Trust, Queen Mary University of London, and St George's University Hospitals NHS Foundation Trust and St George's University of London.

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Disclosures

None.

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