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Authors:
Patricia Munroe (Queen Mary University of London)
Mihir Sanghvi (Queen Mary University of London)
William Young (Queen Mary University of London, Barts and The London School of Medicine and Dentistry)
Hafiz Naderi (Queen Mary University of London)
Richard Burns (William Harvey Research Institute, Queen Mary University of London)
Julia Ramírez (University of Zaragoza)
Christopher Bell (Queen Mary University of London)

Using Genomics to Develop Personalized Cardiovascular Treatments

Mihir M. Sanghvi[1,2,3], William J. Young[1,2,3], Hafiz Naderi[1,2,3], Richard Burns[1,2], Julia Ramírez[1,2,4,5], Christopher G. Bell[1,2], Patricia B. Munroe[1,2]

1. William Harvey Research Institute, Queen Mary University of London, London, United Kingdom
2. NIHR Barts Biomedical Research Centre, Queen Mary University of London, Charterhouse Square, London EC1M 6BQ, United Kingdom
3. Barts Heart Centre, Barts Health NHS Trust, London, United Kingdom
4. Aragon Institute of Engineering Research, University of Zaragoza, Zaragoza, Spain
5. Centro de Investigación Biomédica en Red, Biomedicina, Bioingeniería y Nanomedicina, Zaragoza, Spain

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Corresponding author:
Prof. Patricia B. Munroe
William Harvey Research Institute, Queen Mary University of London, Charterhouse Square, London, EC1M 6BQ
p.b.munroe@qmul.ac.uk

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 discuss how genomic data can resolve diagnostic uncertainty, support cascade screening, and inform treatment strategies. The role that genome-wide association studies have had in identifying thousands of risk variants for polygenic cardiovascular diseases, and how these insights, harnessed through the development of polygenic risk scores, could advance 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 promise of being a curative intervention for cardiovascular conditions.

Key words: Cardiovascular disease; Genome-wide association studies; Polygenic risk scores; Personalized medicine; Pharmacogenomics; Gene therapy

Abbreviations

AAV – adeno-associated virus
ACM – arrhythmogenic cardiomyopathy
APOB – apolipoprotein B
ASO – antisense oligonucleotide
ATTR – transthyretin amyloidosis
CAD – coronary artery disease
Cas9 – CRISPR associated protein 9
CVD – cardiovascular disease
CRISPR – clustered regularly interspaced short palindromic repeats
DCM – dilated cardiomyopathy
EMA – European Medicines Agency
FH – familial hypercholesterolemia
GWAS – genome-wide association study
HCM – hypertrophic cardiomyopathy
HMGCR – 3-hydroxy-3-methylglutaryl-coa reductase
ICD – implantable cardioverter-defibrillator
LNP – lipid nanoparticles
LDL – low-density lipoprotein
LDLR – low-density lipoprotein receptor
LQTS – long QT syndrome
MHRA – Medicines and Healthcare Products Regulatory Agency
mRNA – messenger ribonucleic acid
MYBPC3 – myosin binding protein c3
MYH7 – myosin heavy chain 7
NYHA – New York Heart Association
PCSK9 – proprotein convertase subtilisin/kexin type 9
PKP2 – plakophilin-2
PRS – polygenic risk score
QRISK2 – QRISK cardiovascular risk score version 2
RNA – ribonucleic acid
SERCA2a – sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase 2a
siRNA – small interfering RNA
TGA – therapeutic goods administration

1. Introduction

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. Whilst 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.

This review seeks to provide an overview of how genomic information is driving change across three main areas of CVD therapeutics and management (Figure 1/Graphical Abstract). Firstly, how genomic information can clarify diagnostic conundrums, guide treatment and inform risk prediction. Secondly, 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 hold promise of being a curative intervention for CVD.

2. Cardiovascular genomics: a brief overview

Cardiovascular diseases in a genomics context have been broadly split into two 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. Examples of monogenic CVDs include cardiomyopathies (e.g. hypertrophic cardiomyopathy [HCM], dilated cardiomyopathy [DCM], arrhythmogenic cardiomyopathy [ACM], channelopathies (e.g. catecholaminergic polymorphic ventricular tachycardia, long

QT syndrome), aortopathies and familial hypercholesterolemia.[3] Whilst 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 co-inheritance 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.

Polygenic disorders arise from multiple common genetic variants across the span of the genome. Whilst these variants individually have modest effects, when taken together they increase susceptibility to disease. Most polygenic variants are found in non-protein 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. Although the polygenic nature of these conditions has been appreciated for many decades, it has only been in the last twenty years that unbiased, high-resolution examination of the genome through genome-wide association studies (GWAS) have 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, two parallel approaches are being utilized to further our understanding of CVD: firstly, increasing the power of genome-wide studies by expanding cohort sizes, including under-represented populations and ancestries, and interrogating rare variants using data from whole-exome and whole-genome sequencing.[19–21] Secondly, leveraging GWAS findings to pursue personalized medicine approaches. Examples of this include highlighting therapeutic targets for CVD or drug repurposing opportunities[22,23] and development of polygenic scores to highlight individuals at potentially increased risk of disease development[24], which we will discuss in further depth.

3. Using genomics in clinical diagnosis and management

3.1 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 (e.g. long QT syndrome) whereas a broader analysis may be used where there is more clinical uncertainty with respect to the diagnosis (e.g. 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]

3.2. 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, thrombo-embolic 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 two main categories: acquired or genetic (often syndromic). Diagnostic left ventricular hypertrophy due to hypertensive heart disease or athletic training are acquired phenotypic mimics which 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 marked elevation in plasma low-density lipoprotein (LDL) cholesterol from birth, accelerated rates of atherosclerotic plaque deposition and premature ischemic heart disease.[35] It most often arises due to mutation in the LDL receptor (*LDLR*), apolipoprotein B (*APOB*), or proprotein convertase subtilisin/kexin type 9 (*PCSK9*) 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 reducing the impact of PCSK9 inhibition. Additionally, 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]

Long QT syndrome (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 (e.g., alarm clocks), and those with LQTS3 typically experience events during sleep.[39] Pharmacological therapy is key in reducing arrhythmic events. Beta-blockers serve as a cornerstone treatment for LQTS1 and LQTS2, commonly averting the need for an implantable cardioverter-defibrillator (ICD), though 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 in order 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 greater than 40 mm.[43]

3.4. 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.

3.4.1. Antiplatelets

Antiplatelet therapy forms the cornerstone of managing atherothrombotic conditions such as coronary artery disease 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 stroke patients, 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 is the hepatic enzyme responsible for the conversion of clopidogrel via a two-stage oxidation process, and is encoded for 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 two *CYP2C19* loss-of-function alleles is 13% in South Asian individuals compared to 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 as 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 3,037 enrolled acute coronary syndrome patients, 1,333 (43.9%) were prescribed clopidogrel. Of these, 68% of 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.

3.4.2. Beta-blockers

Metoprolol, carvedilol, and propranolol are among several beta-blockers metabolized by CYP2D6. This drug-metabolizing enzyme is responsible for the metabolism of 20–25% 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 70–80% of an oral dose undergoing CYP2D6-mediated metabolism.[55] By contrast, other beta-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. While 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 co-prescribed potent CYP2D6 inhibitors (e.g. 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 an 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 patient's underlying genetic makeup.

3.4.3. 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 crossbridges 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. Whilst mavacamten is licensed for adults with obstructive and symptomatic heart failure (New York Heart Association Class II-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 two loss-of-function variants potentially being at increased risk of systolic dysfunction as a result of mavacamten therapy at standard dosing regimens. This is as a result of reductions in ejection fraction being associated with mavacamten plasma concentrations and individuals with two loss-of-function alleles having a significantly longer mavacamten elimination half-life (533 hours) compared to normal (150 hours) or extensive metabolizers (72 hours), respectively.[62]

The European Medicines Agency (EMA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA) 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 a 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 EMA and the Australian Therapeutic Goods Administration (TGA) have recognized that certain conservative regimens in poor metabolizers achieve pharmacologic exposures comparable to higher regimens in normal metabolizers.[63,64]

3.5. Drug discovery and repurposing

While 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 development of therapy (e.g. 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: approximately 80-90% of variants lie in non-coding 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 FDA 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 coronary artery disease 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 agents and incident cardiovascular events studying agents such as cankinumab[74] and colchicine.[75,76]

4. 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 since the absolute risk reduction achievable by a given therapy is directly related to a person's baseline risk: individuals with higher predicted risk gain more benefit than those at lower risk. As such, the intensity of preventive interventions are 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 consider 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] Coronary artery disease (CAD) is a CVD for which dozens of PRS have been developed. Aragam et al. have published the most recent CAD GWAS findings.[15] In a study of 1.16 million ancestrally diverse individuals, a CAD PRS for coronary artery disease (CAD) comprised of 2.1 million genetic variants. In an independent sample, those in the top decile of the CAD PRS had a 5.7x greater risk of CAD compared to 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. has shown that CAD PRS with similar population-level performance do not provide consistent individual risk estimates.[92] 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 endpoint.[93]

Additional concerns around PRS include the datasets which they are derived; present biobank datasets 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 employed with the aim to improve trans-ancestry 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 beside 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 i.e. 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 very limited numbers of studies in this guise. Recently, however, a nested case-control study utilizing PRS has been published. Samani et al. 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.[102] In the study, of the 195 individuals who had a cardiovascular event, the QRISK2 10-year CVD risk score identified 61.5% of individuals as high risk compared to 68.7% when combining QRISK2 with the PRS. Whilst the study had some limitations, particularly that <1% of the entire cohort experienced a cardiovascular event which is not inkeeping with the baseline rates in the general population, one may hope that this mode of PRS study becomes more commonplace. Additionally, comparing PRS efficacy against updated CVD risk calculators such as QR4[103], as well as evaluating its added value relative to other contemporary biomarkers that are not currently included in these validated tools but show promise (e.g., 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 upon routine clinical practice.

5. 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. Whilst 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.

5.1. Gene therapy strategies

The molecular mechanisms by which pathogenic variants may result in disease may be classified as firstly, loss-of-function whereby presence of a pathogenic variant leads to the production of partially or totally non-functional protein resulting in insufficient protein for normal functioning or secondly, 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]

In order to combat these, three main categories of gene therapy have been developed: gene replacement therapy, gene silencing therapies and clustered regularly interspaced short palindromic repeats (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 in order to mitigate against the disease phenotype. Gene silencing employs antisense oligonucleotides (ASO) or RNA interference methods such as short interfering RNA (siRNA) (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 ASO-based strategy is exon skipping whereby is an ASO-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] Whilst 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 one 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, whilst 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 that widest choice including introduction of a stop codon to render the pathogenic gene copy non-functional, 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 in order to govern cellular processes.[113] CRISPR activation (CRISPRa) and inhibition (CRISPRi) 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]

5.2. 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 which enables ensuring cells receive therapeutic concentrations, demonstrates high tissue specificity, 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 employed vectors for cardiac gene therapy. This is due to AAVs rarely integrating into the genome of a cell meaning they can persist in organs for considerable periods and due to having a strong preference (tropism) for non-dividing, post-mitotic 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 prior to administration as pre-existing 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 a number of 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 (LNPs) 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 LNPs 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]

5.3. Current status of gene therapy in CVD

A number of 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 (ATTR) 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 ATTR amyloidosis in the form of transthyretin stabilizers (tamifidis)[121] and gene silencing approaches using siRNA (vutrisiran, patisiran).[122,123] Recently, a genome editing approach for ATTR amyloidosis has been 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 twelve months. A phase 3 study has been launched aiming to enroll 765 participants and will report in 2028. In familial hypercholesterolemia, the siRNA inclisiran designed to target *PCSK9* mRNA has received approval from regulators worldwide and is administered at six-monthly 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 one participant.[127] It is notable that these approaches have employed an LNP approach, and benefit from the fact that transthyretin and cholesterol are both produced in the liver thereby taking advantage of LNP's inherent hepatic tropism.

In the cardiomyopathy sphere, human trials have been occurring across a broad range of phenotypes. These include HCM, ACM and a number of HCM phenocopy conditions: Pompe disease, Friedreich's 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] TN201 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 three patients have received therapy to a follow-up of up to twelve months with increased RNA expression and improvements in NYHA classification for patients one and two. In ACM, three 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 plakophilin-2 (*PKP2)* gene which encodes a desmosomal protein, mutations in which are responsible for up to 40% of ACM cases.[132]

Moving towards polygenic CVD, the areas where gene therapy is being deployed include hypertension and heart failure. Zilebesiran is a siRNA 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 blood pressure at three- and six-months compared to baseline against placebo.[133] A phase 3 study is currently ongoing enrolling individuals with mean clinic systolic blood pressure between 140-170 mmHg on stable therapy with two-to-four antihypertensive medication and a ten-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 (I-1c) to restore cardiomyocyte intracellular calcium homeostasis, it is administered by percutaneous intracoronary infusion. It is enrolling adults with non-ischemic cardiomyopathy and NYHA Class II 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 pre-clinical 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 end-stage heart failure patients and controls demonstrating 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.

5.4. 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 trial design itself. Firstly, 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. Secondly, evaluation of genome delivery to target cells requires biopsy in order to perform RNA expression to determine the number of transcript copies per cell. In the case of cardiomyocyte, endomyocardial biopsies would be needed with non-trivial 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.

6. Conclusions

The understanding of the genetic basis of rare and common cardiovascular diseases 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 polygenic risk scores is permitting delineation of novel biological pathways of disease, drug discovery and refinement of risk stratification. The promise of genome editing technologies to effectively cure diseases represent 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 cardiovascular disease, albeit with the challenge of ensuring that this is an equitable and accessible option for all.

Figure Legends

Figure 1/Graphical Abstract: 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 precision medicine in cardiovascular health.

Figure 2: Diagnostic, prognostic and clinical management of the three main Long QT syndrome subtypes.
Overview of genotype specific differences in Long QT syndrome. LQTS: Long QT syndrome

Figure 3: Mechanism of action of mavacamten in hypertrophic cardiomyopathy (HCM).
In the HCM cardiac sarcomere, excessive myosin-actin crossbridges 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 crossbridges 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.

Figure 4: Mechanism of RNA interference (RNAi) 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 post-transcriptional gene silencing.

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 cardiomyocytes but also for 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.

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, variable conduction abnormalities; often more severe in males.	X-linked
Lysosomal glycosphingolipid catabolism	Fabry disease	Alpha-galactosidase A	*GLA*	Characterised by left ventricular hypertrophy, acroparesthesias, angiokeratomas, renal impairment; may cause “pseudo-HCM” with distinctive extra-cardiac 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 (e.g. Noonan syndrome)	RAS/MAPK signalling molecules (e.g. 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; can also cause carpal tunnel syndrome, peripheral neuropathy.	AD
Mitochondrial energy metabolism	Mitochondrial cardiomyopathies	Multiple	Various mitochondrial genes/variants	Often present with multisystem involvement, including neuromuscular deficits, sensorineural hearing loss, diabetes mellitus; can show LV hypertrophy and conduction abnormalities.	AD, AR, or matrilineal

Mitochondrial iron homeostasis / metabolism	Friedreich's ataxia	Frataxin	*FXN*	Neurological disorder (ataxia, dysarthria, neuropathy), diabetes mellitus, and frequent hypertrophic cardiomyopathy that can be a major cause of early mortality.	AR

AD (autosomal dominant), AR (autosomal recessive), ATTR (transthyretin amyloidosis), FXN (frataxin), GAA (lysosomal acid α-glucosidase), GLA (alpha-galactosidase A), HCM (hypertrophic cardiomyopathy), KRAS (Kirsten rat sarcoma viral oncogene homolog), LAMP2 (lysosomal-associated membrane protein 2), LV (left ventricular), MAPK (mitogen-activated protein kinase), PRKAG2 (protein kinase AMP-activated non-catalytic subunit gamma 2), PTPN11 (protein tyrosine phosphatase non-receptor type 11), RAF1 (Raf-1 proto-oncogene, serine/threonine kinase), RAS (rat sarcoma viral oncogene homolog), SOS1 (SOS Ras/Rac guanine nucleotide exchange factor 1), WPW (Wolff-Parkinson-White syndrome).

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 ClinicalTrials.gov reference. AAV (adeno-associated virus), LNP (lipid nanoparticle).

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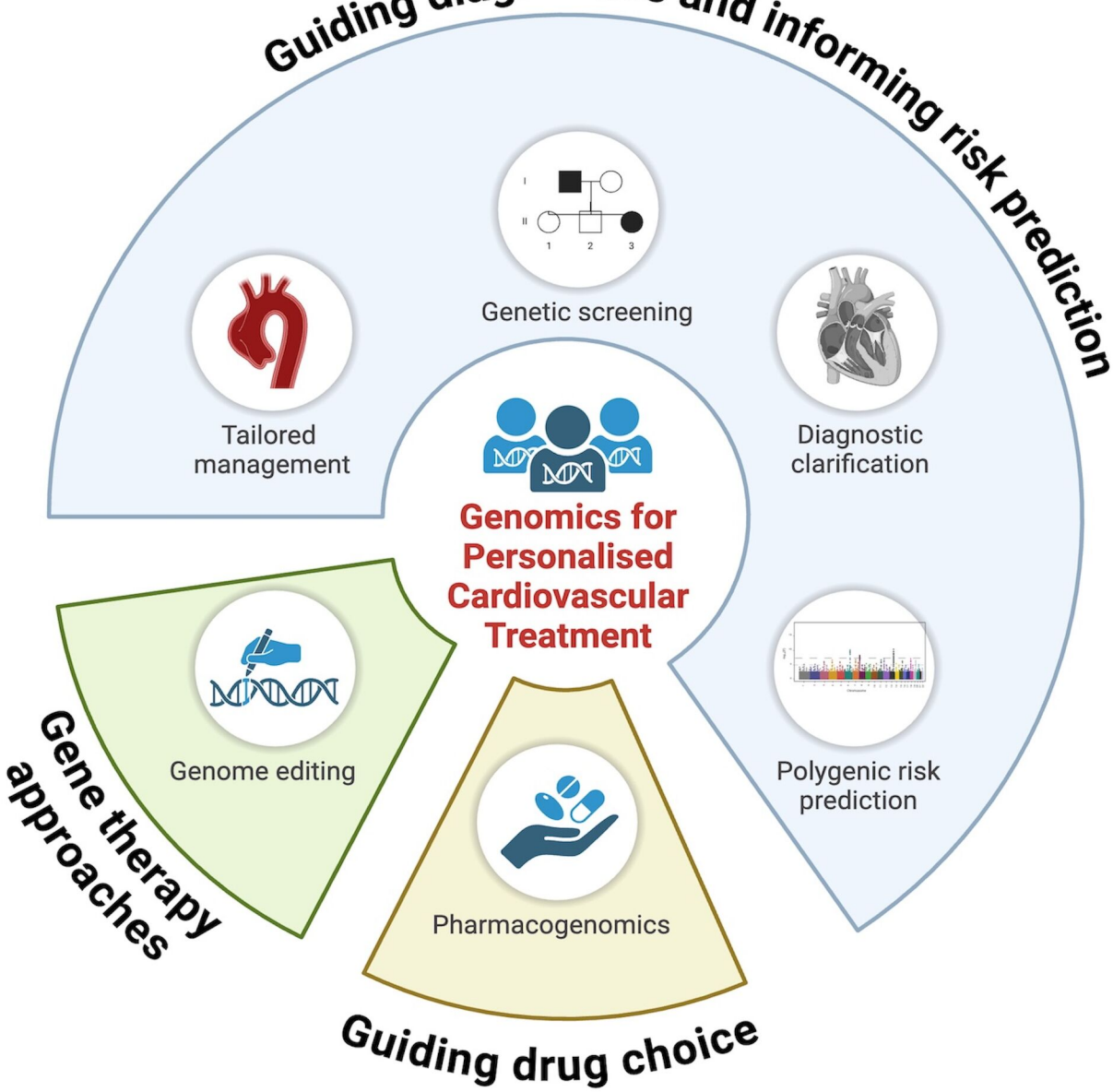
Highlights

- 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.

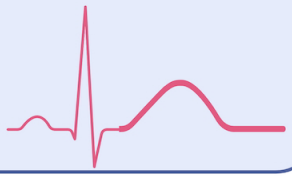
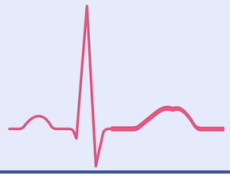
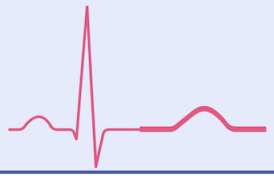
- Despite advancements, challenges remain in translating genomic insights into routine clinical practice, particularly around leveraging the breadth of genome-wide association study findings, ancestry-based disparities and real-world clinical integration of polygenic risk scores, as well as equitability of access.

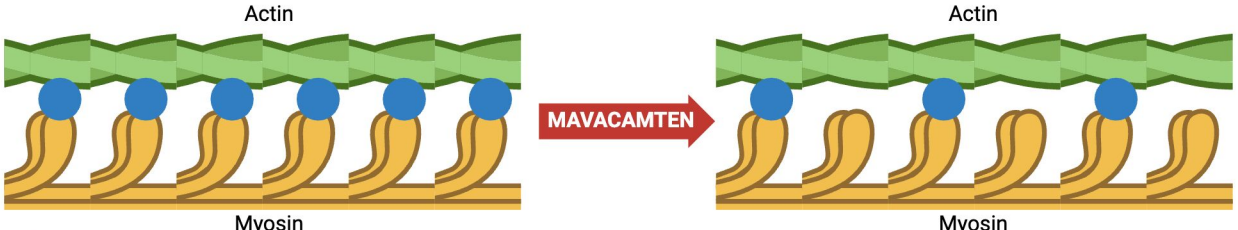
- Gene therapy, including RNA-based and CRISPR/Cas9-mediated gene editing approaches, have shown promising outcomes in a range of cardiovascular conditions. These technologies provide hope for durable, curative treatments but require careful management of safety, delivery, and clinical trial design challenges.


Guiding diagnostics and informing risk prediction
Genetic screening
Tailored management
Diagnostic clarification
Genomics for Personalised Cardiovascular Treatment
Polygenic risk prediction
Gene therapy approaches
Genome editing
Pharmacogenomics
Guiding drug choice

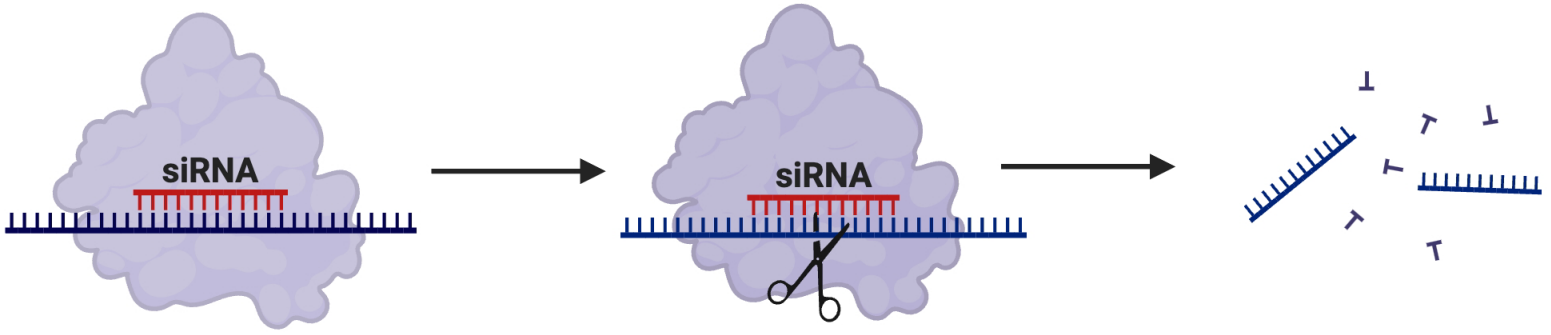
Clinical diagnosis of Long QT syndrome

Genetic testing

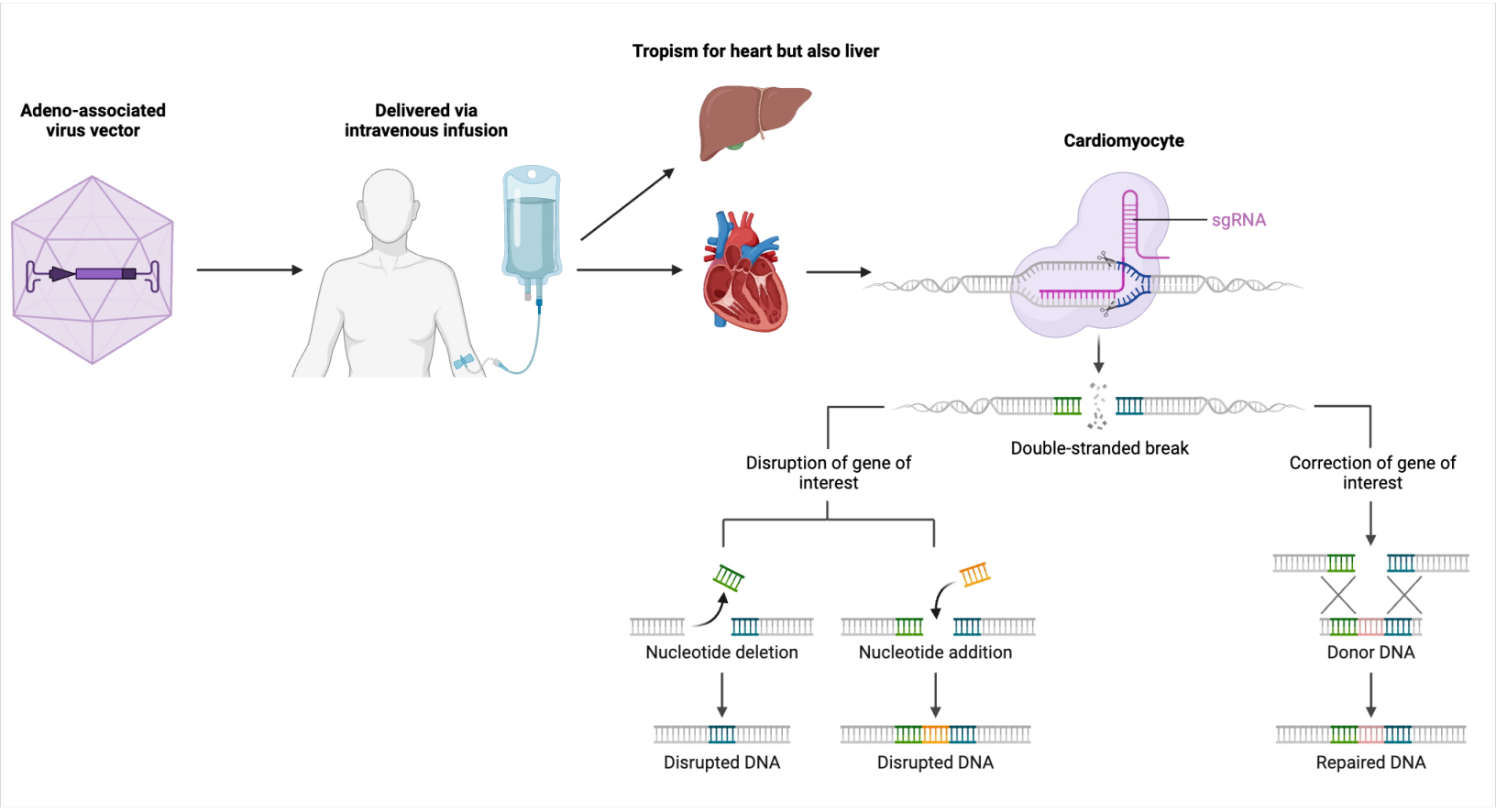
	LQTS 1 *KCNQ1*	LQTS 2 *KCNH2*	LQTS 3 *SCN5A*
Pathogenic genotype effect	Loss-of-function slow repolarising (I_{Ks}) current	Loss-of-function rapid repolarising (I_{Kr}) current	Gain-of-function fast depolarising I_{NA} current
Characteristic ECG features	Broad based T-waves 	Low amplitude or bifid T-waves 	Late peaking T-waves 
Arrhythmia mechanisms	Non-pause dependent. Impaired QT adaption to adrenergic activation	Pause dependent early afterdepolarisations	Amplification of inward Na+ current at low heart rates
Lifestyle advice	Avoid strenuous activity and stress 	Avoid sudden auditory stimuli 	
Risk stratification	Lower risk (vs LQTS 2 & 3), no sex differences	Females higher risk	Males higher risk
Medical therapy	Beta blockers e.g., Nadolol / Propranolol	Beta blockers, Spironolactone ?Mexiletine	Beta blockers, Mexiletine



- In the HCM cardiac sarcomere, there are too many myosin-actin crossbridges resulting in hypercontractility
- Mavacamten, a selective allosteric inhibitor of cardiac myosin, reduces the number of myosin heads in the active, ATP-hydrolyzing state thereby decreasing crossbridge formation
- Reduces: hypercontractility, outflow tract gradient and ejection fraction
- Improves: physical functioning, quality of life



- RISC + siRNA binds to a complementary mRNA.
- mRNA is cleaved at a specific site
- Cleaved mRNA is degraded in the cell ultimately resulting in decreased protein production


Tropism for heart but also liver
Adeno-associated virus vector
Delivered via intravenous infusion
Cardiomyocyte
sgRNA
Double-stranded break
Disruption of gene of interest
Correction of gene of interest
Nucleotide deletion
Nucleotide addition
Donor DNA
Disrupted DNA
Disrupted DNA
Repaired DNA