

Genetic testing in cardiovascular disease

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Cardiovascular disease (CVD) is the leading cause of morbidity and mortality globally and is responsible for an estimated 32% of deaths.¹ An effort over many decades targeting modifiable risk factors has resulted in significant improvements in mortality and age-adjusted prevalence. However, the improved medical management and decreased mortality have also resulted in a 193% increase in overall CVD prevalence globally over the past 30 years. New approaches to prevention and early disease detection are greatly needed. Genetic testing has been incorporated into routine management of monogenic CVD, such as hypertrophic cardiomyopathy and primary arrhythmic syndromes. Advances in sequencing and computational biology now additionally provide unprecedented insights into the genetic contribution to common complex conditions, including coronary artery disease (CAD) and atrial fibrillation. Maximising the use of these genetic tools for the identification and prediction of CVD will require innovative prospective implementation studies and a rapid upskilling of our health workforce beyond the traditional clinical genetic pathways.

This narrative review seeks to provide an overview of the current evidence and recommendations for genetic testing in CVD, as well as evidence behind emerging platforms (eg, polygenic risk scoring). We searched the online databases PubMed and MEDLINE between September 2022 and April 2023 for expert consensus guidelines, consensus opinions, systematic reviews, meta-analyses and review manuscripts in English language published since 1 January 2010. Search terms included “cardiovascular disease[MESH Major Topic]” or “cardiovascular diseases[MESH Major Topic]” and/or “genetic test”, “genetic risk”, “genetic risk score”, “polygenic risk score”, “genome-wide association study”, and “guidelines”. Manuscripts included in these documents were individually reviewed and included as appropriate based on authors’ experience.

Monogenic conditions

Monogenic disorders with Mendelian inheritance patterns are characterised by the presence of a single genetic variant with large effect size that is sufficient to lead to a disease phenotype (Box). Monogenic diseases can have dominant, recessive or x-linked inheritance patterns, and are categorised according to their autosomal or mitochondrial gene location. Despite well characterised examples in the CVD space, spanning from severe derangements in lipid metabolism to myocardial conditions associated with arrhythmias and early sudden cardiac death, these make up only a small proportion of the burden of CVD. Some important examples are described below based on inclusion in expert consensus guidelines.

Lipid metabolism

Familial hypercholesterolaemia is an autosomal dominant condition characterised by significantly elevated concentrations

Summary

- Cardiovascular disease (CVD) is the leading cause of morbidity and mortality globally and is responsible for an estimated one-third of deaths as well as significant morbidity and health care utilisation.
- Technological and bioinformatic advances have facilitated the discovery of pathogenic germline variants for some specific CVDs, including familial hypercholesterolaemia, cardiomyopathies and arrhythmic syndromes. Use of these genetic tests for earlier disease identification is increasing due, in part, to decreasing costs, Medicare rebates, and consumer comfort with genetic testing.
- However, CVDs that occur more commonly, including coronary artery disease and atrial fibrillation, do not display monogenic inheritance patterns. Genetically, these diseases have generally been associated with many genetic variants each with a small effect size. This complexity can be expressed mathematically as a polygenic risk score. Genetic testing kits that provide polygenic risk scoring are becoming increasingly available directly to private-paying consumers outside the traditional clinical setting.
- An improved understanding of the evidence of genetics in CVD will offer clinicians new opportunities for individualised risk prediction and preventive therapy.

of circulating low-density lipoprotein (LDL) cholesterol (LDL-C) and is the most common monogenic condition in humans, affecting an estimated one in 300 people.² Nearly 1500 pathogenic variants have been identified across the three main causative genes (*LDLR*, *APOB* and *PCSK9*) affecting components of plasma lipoprotein cellular uptake and these collectively have a population prevalence of 0.32%.³ Case-control studies have demonstrated a nearly tenfold increased familial hypercholesterolaemia prevalence in people with CAD and more than 20-fold increased prevalence in people with premature CAD compared with the general population.³ Familial hypercholesterolaemia is most frequently diagnosed clinically using the Dutch Lipid Clinic Network and/or Simon Broome tools.^{4,5} However, these clinical diagnostic algorithms have limitations, particularly when diagnosing children and adolescents. Identification of pathogenic variants can facilitate cascade testing, allowing for earlier diagnosis and aggressive LDL-targeting pharmacotherapy for biological family members, thus having a substantial impact on medical management.

Thoracic aortic disease

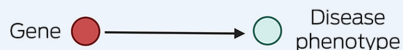
Heritable thoracic aortic disease is defined as aortic aneurysms and/or dissection with strong genetic association and no other discernible features. This, therefore, often results in catastrophic clinical presentation, as only about 5% of patients with thoracic aortic aneurysm and dissection are symptomatic before dissection.⁶ The lack of physical features results in difficulty in assessing true prevalence and heritability, with a predicted incidence of 2.9–4.3 cases per 100 000 person-years and suspected autosomal dominant inheritance pattern.^{7,8} Eleven

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Basic overview of genetic contribution to disease*

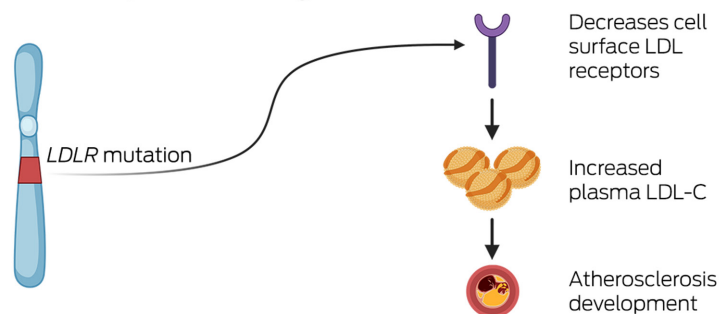
Monogenic disorder

A condition determined by a rare variant in a single gene



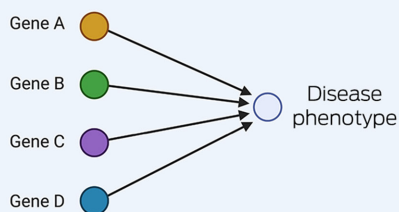
Example: familial hypercholesterolaemia (FH)

Mutation in *LDLR*, *APOB* or *PCSK9* gene can result in FH



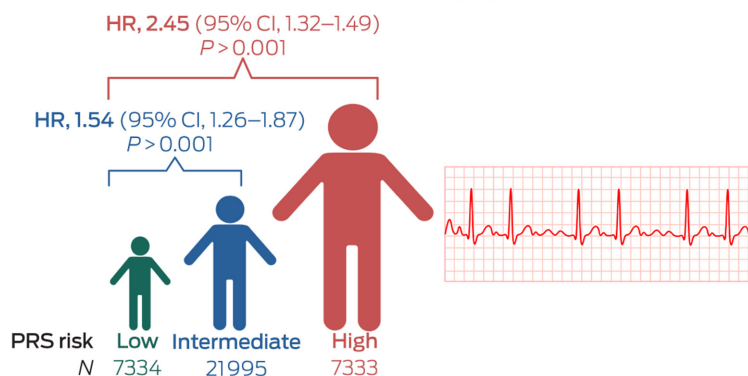
Polygenic disorder

A condition associated with the combined action of many common genetic variants



Example: atrial fibrillation (AF)

Top 20% polygenic risk score (PRS), calculated from 6.7 million SNPs, was associated with 2.45-fold increased risk of developing AF



CI = confidence interval; HR = hazard ratio; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; SNP = single-nucleotide polymorphism. * This can be simplified into monogenic and polygenic disorders, recognising that genetic contribution is a spectrum and many diseases display patterns from both. These patterns are additionally affected by comorbid conditions, lifestyle factors and environmental exposures. Source: Image created with [Biorender.com](https://www.biorender.com). The data included in the atrial fibrillation example were from Marston et al.⁵⁰

genes have been identified as definitively or strongly associated with heritable thoracic aortic disease, with most of them relevant to maintaining vascular wall integrity. The role of vascular smooth muscle cell dysfunction in the development of thoracic aneurysms has been well characterised,⁹ and, indeed, these genes can be grouped based on the role of the coded protein in smooth muscle cell contractile function, extracellular matrix adhesion, and transforming growth factor- β (TGF- β) signalling.¹⁰ A variant in *ACTA2*, encoding α -2 actin with smooth muscle cell-specific contractile function, is the most common genetic variant associated with heritable thoracic aortic disease, with a penetrance of about 50% and identified in 12–21% of cases.^{11,12} Genetic screening programs have been proposed due to their potential impact on surgical intervention and familial case identification, especially in patients with early onset, a positive family history of dissection, and no history of hypertension.¹³

In addition, causative pathogenic gene variants have been identified in syndromes with vascular manifestations; for example, vascular Ehlers–Danlos (*COL3A1*),¹⁴ Loeys–Dietz (*TGFBR1/2*),^{15,16} and Marfan (*FBN1*) syndromes.^{17,18} Genetic testing in these settings aids identification of the syndrome and can play an important role, as there are substantial differences in how the vasculature is affected in each syndrome. Genes associated with vasculopathies, including *COL3A1* and

TGFBR2, have additionally been implicated in other forms of arterial dissection, including spontaneous coronary artery dissection.^{19,20}

Inherited cardiomyopathies

Inherited cardiomyopathies are a spectrum of cardiac diseases broadly classified into hypertrophic, dilated, arrhythmogenic and restrictive phenotypic subtypes, which are not explained by the presence of ischaemic, congenital, hypertensive or valvular disease. Although epidemiological data are scarce due to underdiagnosis, at least 0.6% of the population are estimated to be affected by this spectrum of diseases, with significant differences in clinical presentation depending on sex and race.²¹

Hypertrophic cardiomyopathy is a primary myocardial disorder that is characterised by asymmetric ventricular hypertrophy and distinctive histopathological features, including myofibril hypertrophy, disarray, and interstitial fibrosis. Hypertrophic cardiomyopathy is generally caused by deleterious variants in sarcomere genes, with variants in *MYH7* and *MYBPC3* identified in nearly 70% of cases.²² It is important to differentiate hypertrophic cardiomyopathy from other heritable disorders that mimic this condition, some of which have specific therapies, including glycogen

storage disorders, Fabry disease and cardiac amyloidosis.²³ Despite decades of research into the genetic underpinnings of hypertrophic cardiomyopathy, a subset of patients will have negative results on genetic testing. Although this may reflect undiscovered monogenic forms of disease, it has been proposed that ventricular hypertrophy, in some cases, might result from combinations of common variants.

Dilated cardiomyopathy is a disorder with prevalence estimates of up to one in 250 persons and has numerous causes, which can be genetic or acquired.^{24,25} These distinctions are increasingly blurred, with evidence of rare genetic variants in patients with environmental causes of dilated cardiomyopathy and vice versa. A genetic basis for disease is often not apparent in the index case, and a positive family history may only emerge after successive relatives are diagnosed.²⁶ Although more than 250 disease genes have been reported, recent gene curation efforts have shown that only ten to 20 genes currently have robust evidence for dilated cardiomyopathy causation ([Supporting Information](#), table 1).^{26–28} Truncating variants in the gene *TTN* (*TTN*tv), which encodes the sarcomeric protein titin, are the most common genetic cause of dilated cardiomyopathy, present in up to 20% of cases.²⁹ Interpreting the clinical significance of *TTN*tv may be challenging, as these variants are also present in up to 3% of the general population.³⁰ It has been proposed that a “second hit” might modify severity in *TTN*tv carriers, which is currently an area of active research.^{31,32}

Arrhythmogenic cardiomyopathy is an umbrella term that refers to a group of highly arrhythmic cardiomyopathies that variably affect the right and/or left ventricles.³³ This includes arrhythmogenic right ventricular cardiomyopathy that mainly affects the right ventricle, but frequently has left ventricular involvement, and arrhythmic forms of dilated cardiomyopathy, such as those associated with *LMNA*, *FLNC*, *RBM20* and *SCN5A* variants.³⁴ Arrhythmogenic right ventricular cardiomyopathy exhibits autosomal dominant inheritance in most cases, with pathogenic variants identified in desmosomal genes.³⁵ There is often incomplete penetrance with variable expressivity. Truncating variants in *PKP2* are most frequently implicated and typically give rise to the right-sided phenotype.³⁶ In addition, pathogenic variants have been identified in non-desmosome encoding genes, albeit all with less frequency.

Inherited arrhythmic disorders

Inherited arrhythmic syndromes include monogenic conditions such as long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, and familial forms of atrial fibrillation. LQTS is one of the most common inherited cardiac conduction diseases, which can lead to sudden cardiac death and is believed to occur in about 50 infants per 100 000.³⁷ Nearly 80% of patients with a prolonged corrected QT interval, in the absence of structural heart disease and exposure to QT prolonging drugs, have an identifiable LQTS-associated genetic variant,³⁸ which mostly demonstrates an autosomal dominant inheritance pattern. Three genes have been definitively associated with LQTS. *LQT1* and *LQT2* have been associated with potassium channel protein-encoding genes *KCNQ1* and *KCNH2* respectively.^{39,40} Genetic association with *LQT3* is more complex, with gain-of-function variants in *SCN5A*, which encode a sodium channel subunit, associated with disease and identified in about 10% of LQTS cases.⁴¹ Mutations in *SCN5A* have additionally been associated with Brugada syndrome, cardiac conduction abnormalities and dilated cardiomyopathy.

Complex genetics and cardiovascular disease

Advances in sequencing, computational power, analytical approaches, and global collaborations have been central to unlocking the contributions of genetic variation to commonly occurring complex CVD, such as CAD and atrial fibrillation.

Genome-wide association studies (GWAS) using large case-control studies have identified common variants associated with disease without surveillance bias to specific biological pathways or genes of interest. Due to the substantial overlap between cases and controls, the prognostic significance of a single-nucleotide polymorphism (SNP) in an individual patient is limited. Polygenic risk scores (PRS) have been derived to increase the clinical utility of these data by assessing the collective effects of SNP profiles in individual subjects. Emerging research in certain complex CVD suggests that patients with very high scores have an increased risk of disease several-fold higher than that of the population average, and indeed a risk level equivalent to risk conferred by some monogenic disorders.

CAD heritability is classically estimated to be about 40–60%,^{42,43} a proportion not fully explained by causal rare variants in genes associated with monogenic lipid disorders. More than 200 significant GWAS loci have been identified in European populations and incorporated into multiple CAD-PRS algorithms. Only about half of included SNPs have previously been associated with traditional CAD risk factors, including lipid metabolism and blood pressure. In a pivotal study in 2016 that included data from more than 55 000 participants from four separate cohorts, the relative risk of incident CAD events was increased by 91% in participants with a top quintile CAD-PRS compared with those in the bottom quintile.⁴⁴ Importantly, the detrimental effect of a high CAD-PRS was able to be offset by adopting a healthier lifestyle, with an observed 46% relative risk reduction of CAD events. In another study using CAD-PRS of 1.7 million genetic variants, the relative risk of CAD was 4.17-fold higher in participants with top versus bottom quintile scores, a result independent of traditional risk factors.⁴⁵

Atrial fibrillation is the most common cardiac arrhythmia in Australia and affects about one in 18 Australians aged over 55 years.⁴⁶ It confers an increased risk of stroke and heart failure and constitutes a growing health care and economic burden. Although atrial fibrillation can occur as a familial condition, it is more commonly a complex trait in which age, sex, genetics, comorbid conditions, and lifestyle factors are key components. Nearly 200 chromosomal loci that influence atrial fibrillation susceptibility have been identified by GWAS, and several atrial fibrillation-PRS have been devised. Several prospective cohort studies suggest that atrial fibrillation-PRS are predictive of incident atrial fibrillation ([Box 1](#)) and that addition of atrial fibrillation-PRS improves predictive ability into models that include age and sex,⁴⁷ as well as into a model including clinical data such as anthropometrics, blood pressure, smoking status, blood pressure-lowering medication, diabetes, and history of myocardial infarction and heart failure.^{48–51} Atrial fibrillation-PRS may also be useful for predicting the risk of atrial fibrillation recurrence after ablation procedures.⁵²

Guidelines and screening recommendations

An exponential expansion of technical and analytical capacity has contributed to an increase in genomic research and associations with CVD. However, there is a distinct lack of trial data measuring the impact of genetic test implementation.

Broadly, current guideline recommendations for genetic testing in the clinical setting support its use to confirm causation of a clinical diagnosis for a CVD with established, monogenic inheritance patterns, and to guide cascade genetic and clinical testing in at-risk family members. Cascade genetic testing refers to a process wherein targeted genetic testing is offered to at-risk first degree biological relatives of an individual with a germline pathogenic variant; this is typically an iterative process, with further testing of first degree relatives of newly identified probands to reduce incidence, morbidity, health care utilisation, and mortality from certain diseases or conditions.^{53,54} Individuals should be considered for genetic testing if they have a confirmed or suspected heritable CVD, who are at high *a priori* risk for a pathogenic variant, and typically following collection of a three-generation family history and pre-test genetic counselling.⁵⁵ A multidisciplinary team with competencies in CVD management and clinical genomics is ideally placed to offer cardiac genetic testing in this setting, considering emerging evidence, recommendations from both medical and clinical genomic societies, and legal or regulatory implications for the patient. Pragmatically, the presenting patient is typically the individual referred for genetic testing; however, the multidisciplinary team should consider proband genetic testing of another affected relative with a more severe phenotype, if available, to increase the chance of identifying a pathogenic variant.

The multidisciplinary team should consider the clinical applicability of genes selected for screening, resisting the inclination to use larger, broader genetic panels due to the more limited clinical application, higher number of variants of unknown significance, and opportunity for incidental secondary genetic findings. The Clinical Genome Resource (ClinGen, <https://clinicalgenome.org>) provides an up-to-date resource for evaluating the contribution of a gene and variant to a disease. Variant classification is a process of considering whether there is sufficient evidence to identify a variant as the cause of disease (ie, pathogenic, likely pathogenic [P/LP]) or not (ie, benign, likely benign). Where there is insufficient or conflicting evidence, an uncertain variant of unknown significance classification will be made. Regular review of variant classifications is necessary, with flow-on impact to at-risk relatives who may have used this information in cascade genetic testing.

Pre- and post-test genetic counselling by a trained genetic counsellor is important in ensuring individuals have made a sufficiently informed decision to proceed with testing and have considered potential implications for themselves and their family.⁵⁶ A summary letter directed towards the relatives, delineating the genetic finding, may be provided to support family communication and the opportunity for at-risk relatives to consider for cascade clinical and/or genomic testing as appropriate for the condition.

An example of guideline recommendations for genetic testing, and genes currently receiving a “definitive” or “strong” clinical validity classification by ClinGen, is outlined below and presented in the [Supporting Information](#), table 1.

Lipid metabolism

Genetic testing should be considered in patients with total cholesterol of 6.5 mmol/L or greater in the absence of secondary causes, or an LDL-C of 5–6.5 mmol/L in the context of past medical or family history of premature CAD (Medicare Benefits Schedule [MBS] item 73352).⁵⁷ Cascade screening of first degree biological family members — involving LDL-C measurement, targeted variant testing, or both — is also advised (MBS item 73353).

Thoracic aortic disease

Genetic testing for heritable thoracic aortic disease is recommended in individuals with disease diagnosed under 60 years of age or if a positive family history has been identified.⁵⁸ It should be noted that only 20–30% of causative genes for heritable thoracic aortic disease have been identified. Genetic testing is additionally recommended in patients with suspected Marfan, vascular Ehlers–Danlos, or Loeys–Dietz syndromes to support accurate genetic counselling and screening of at-risk family members.⁵⁸ However, no tests are currently Medicare-rebated and should be completed in the context of specialist clinics.

Inherited cardiomyopathies

Genetic testing is recommended in all patients meeting clinical criteria for hypertrophic cardiomyopathy, dilated cardiomyopathy and arrhythmogenic cardiomyopathy, especially when used to enable cascade screening.^{59–61} Where a patient does not meet the clinical diagnostic criteria, genetic testing is not routinely recommended; however, there may be value for those in whom a monogenic cause is strongly suspected and the testing is performed in a centre with high level expertise, given the high prevalence of variants of unknown significance.^{56,62} Cascade genetic testing for these conditions in first degree biological family members is recommended if a disease-causing variant is identified.

Specialists or consultant physicians can request Medicare-rebated genetic testing for hypertrophic cardiomyopathy, dilated cardiomyopathy or arrhythmogenic cardiomyopathy in patients with a clinical presentation, family history, or laboratory findings consistent with the inherited cardiomyopathy (MBS item 73392). Targeted genetic screening of first degree biological relatives may be requested by specialists or consultant physicians if a P/LP variant is identified (MBS item 73393). Genetic testing may additionally be requested for reproductive partners of the proband to determine reproductive risk (MBS item 73394).

Inherited arrhythmic disorders

Genetic testing is recommended in individuals with known or suspected LQTS based on clinical presentation, family history, and electrocardiogram; genetic testing is additionally recommended in asymptomatic adults with a QTc greater than 500 ms in adults and greater than 480 ms pre-puberty, in the absence of conditions expected to result in QT prolongation.⁶¹ Importantly, genetic testing in LQTS is unique in that results can allow for independent risk prognostication and inform therapeutic decision making.⁶³ Cascade, variant-specific genetic screening of first degree relatives is recommended if a confident genetic variant is identified in the proband.⁶¹

Medicare-rebated genetic testing for inherited cardiac arrhythmic syndromes or channelopathies may be ordered by specialists or consultant physicians for patients whose clinical presentation or family history indicates a greater than 10% risk of a pathogenic variant (MBS item 73416). If a P/LP variant is identified, specialists or consultant physicians may order variant-specific testing in first degree biological relatives (MBS item 73417) or reproductive partners (MBS item 73418).

CVD without Mendelian inheritance patterns

Genetic testing in polygenic forms of CVD, including common CVD such as CAD and atrial fibrillation, is still evolving and not currently recommended in a clinical setting.⁶⁴ Despite strong

association of PRS with the relevant disease state, prospective studies collecting evidence on use of these tools are still required for clinical translation. Currently, the role of PRS in patient management remains an active area of research. Close observation of PRS implementation for other non-cardiovascular conditions, including cancer, will be beneficial.

Medicolegal, insurance and workforce implications

There are several insurance, medicolegal and workforce implications remaining in law and practice which warrant consideration. Globally, consumers report genetic discrimination for insurance coverage as a leading cause of concern when considering testing.⁶⁵ In Australia, under the *Disability Discrimination Act 1992 (Cth)*,⁶⁶ genetic information is legally permitted to be incorporated into non-health insurance policy underwriting, including disability, income protection, life and mortgage insurance.⁶⁷ The standards and policy framework are self-regulated by the insurance industry through the Financial Services Council, a members' association representing more than 100 financial services firms. Since 2019, following a Parliamentary Joint Committee recommendation that genetic discrimination be banned in the life insurance underwriting process,⁶⁸ the Financial Services Council issued a moratorium on the request for, or use of, genetic information during policy underwriting.⁶⁹ However, the legal position and ability of insurance providers to use this information during future policy underwriting remains unchanged. Australians have been fortunate for the recent listing of several genetic tests for monogenic cardiac diseases on the MBS, making these accessible at no cost to the patient; clinicians should refer to the MBS Online tool (www.mbsonline.gov.au) for an up-to-date list of rebated genetic tests and eligibility criteria. The need for specialised services and genetic counselling to support broad access will greatly increase as more specialists and families wish to pursue this testing.⁷⁰

Future directions

Incorporation of genomic testing into CVD assessment offers a unique opportunity to further personalise diagnosis and treatment for the individual patient, and, in some cases, target cascade clinical and genomic screening in family members. However, significant gaps remain which impede incorporation of these powerful tools into more routine clinical practice.

Diversity and inclusion in genomic research increase both the groups of individuals benefitting from these novel tools and our scientific understanding of the genetic basis for CVD. Efforts at a regulatory level have sought to increase the diversity and inclusivity of research participants in genetic research. However, validation studies in historically under-represented ancestry groups frequently demonstrate attenuated or non-significant results,^{71,72} and substantial gaps remain in patients from poorly represented ancestry groups, perpetuating health disparities. Numerous studies have shown individuals from diverse ancestry groups have a lower diagnostic yield from

genetic testing, due to the higher rate of variants of unknown significance compared with individuals of European ancestry.⁷³

Furthermore, prospective studies and implementation research are necessary to measure the efficacy, health economic, and psychosocial impacts of incorporating genetic testing for CVD diagnosis and management. Networks of academic researchers, primary care and specialty clinicians, clinical geneticists, payers, and health policy experts need to be organised and supported, providing a platform for efficient, prospective clinical implementation studies of emerging tools. One such network, the Partnership for Precision Prevention in CAD, has been formed in Australia, supported by a National Health and Medical Research Council Partnership Grant (GNT2005790). This network has developed a primary care-based clinical network and launched the first prospective study testing implementation of a PRS-triaged coronary calcium scan for the diagnosis of subclinical CAD in individuals at low to moderate five-year CVD risk (Trial No. ACTRN12622000436774).

Conclusion

Substantial advances have been made in the past three decades associating CVD to markers of genetic risk. In some conditions, implementation of genetic testing has improved risk prediction in individual patients, guided treatment decisions, and facilitated cascade screening in at-risk biological family members, leading to earlier diagnoses and intervention. However, further implementation studies and clinical trials are needed to develop evidence for effective incorporation into the medical practice.

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Competing interests: Gemma Figtree reports personal fees from CSL; she reports grants from Abbott Diagnostic, Janssen Pharmaceuticals and Sanofi; she is a founding director and Chief Medical Officer of Prokardia; she has a patent for biomarkers and oxidative stress awarded — United States, May 2017 (US9638699B2) — licensed to Northern Sydney Local Health District, a patent Use of P2X7R antagonists in cardiovascular disease (PCT/AU2018/050905) licensed to Prokardia, a patent Methods for treatment and prevention of vascular disease (PCT/AU2015/000548) licensed to the University of Sydney/Northern Sydney Local Health District, and a filed provisional patent application Methods for predicting coronary artery disease (Ref. 2022-009-PRO-0; 2022902660) to the University of Sydney/Northern Sydney Local Health District; she has received personal fees as Executive Committee Member of CPC Clinical Research Jodie Ingles serves as the chair of the ClinGen Hereditary Cardiovascular Disorders Gene Curation Expert Panel.

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Supporting Information

Additional Supporting Information is included with the online version of this article.