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Precision Cardiovascular Medicine: State of Genetic Testing

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Abstract

In the 15 years following the release of the first complete human genome sequences, our understanding of the ability of rare and common genetic variation to determine cardiovascular disease susceptibility, prognosis, and therapeutic response has grown exponentially. As such, the use of genomics to enhance the care of patients with cardiovascular diseases (CVDs) has garnered increased attention from clinicians, researchers, and regulatory agencies eager to capitalize on the promise of precision genomic medicine. However, owing to a large burden of “complex” common diseases, an unrelenting desire for evidence-based practice, and a degree of unfamiliarity/discomfort with the language of genomic medicine, the development and implementation of genomics-guided approaches designed to further individualize the clinical management of a variety of cardiovascular disorders remains a challenge. In this Review, we detail a practical approach to genetic testing initiation and interpretation as well as review the current state of cardiovascular genetic and pharmacogenomics testing in the context of relevant society and regulatory agency recommendations/guidelines.

INTRODUCTION

Since the sentinel discovery of the first heritable monogenic cardiovascular disease (CVD)-susceptibility genes in the early-to-mid 1990’s, genetic testing for familial aortopathies,[1, 2] cardiomyopathies,[3, 4] cardiac channelopathies,[5, 6] and hypercholesterolemia[7, 8] has transitioned rapidly from early research-based endeavors to a full complement of

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reimbursable commercially-available genetic tests. Furthermore, following the release of the first complete human genome sequences in 2001,[9, 10] ensuing genome-wide association studies (GWAS) have identified a plethora of common genetic variants that underlie risk of developing common CVDs such as coronary heart disease (CHD)[11] and atrial fibrillation (AF)[12] as well as inter-individual variability in cardiovascular drug-response. Collectively, genetic testing for rare monogenic CVDs, ongoing development of genetic risk scores (GRS) for common polygenic CVDs, and the implementation of pharmacogenomics testing to predict individual response to cardiovascular drugs represent the spectrum of genetic tests that currently impact the diagnosis, risk-stratification, and clinical management of patients with rare and common CVDs.

With the announcement of the Precision Medicine Initiative in early 2015, interest in precision genomic medicine has intensified, and the stage has been set for an unprecedented proliferation of genetics- and genomics-guided approaches. Although cardiovascular providers stand to benefit immensely from these advances, the rapid pace of genomic discoveries, gaps in genomics education/literacy, and paucity of data from randomized controlled trials (RCTs) designed to determine the clinical utility of genomic-aided approaches have left many overwhelmed and thereby ill prepared to deliver high-quality, genomics/genetics-guided care. As such, this Review aims to summarize the current clinical utility, commonly encountered pitfalls, and areas of emerging interest pertaining to the use of genetic and pharmacogenomic testing to individualize the clinical management of an array of CVDs.

Basic Principles Governing the Initiation and Interpretation of Cardiovascular Genetic Tests

With each passing year, cost-lowering technological advances, improved payer reimbursement, and legislation aimed at eliminating genetic discrimination make genetic testing increasingly accessible and appealing. However, as the pendulum has swung from inaccessible to more readily available, the increased, and at times, inappropriate utilization of genetic testing has brought with it a new set of obstacles.[13] As such, the ensuing paragraphs aim to help providers avoid common pitfalls associated with the inappropriate use of genetic testing, namely poor phenotyping, inappropriate genetic test selection, and misinterpretation of results, by outlining common indications, expected results, and basic interpretative strategies when considering CVD genetic testing.

At present, CVD genetic testing is reserved typically for one of three clinical indications: 1) comprehensive genetic testing to aid in or confirm the diagnosis of a heritable CVD in which there is a strong index of clinical suspicion (class I recommendation for many, but not all monogenic CVDs),[6] 2) mutation-specific cascade screening of appropriate relatives (class I recommendation for all monogenic CVDs),[6] and 3) the selected use of pharmacogenomics testing to aid in the selection and or dosing of certain cardiovascular medications (variable society and regulatory agency recommendations). It is important to note that due to variable expressivity and incomplete penetrance of monogenic CVDs coupled with significant background genetic variation in many monogenic CVD-causative genes, diagnostic genetic testing should be viewed as probabilistic rather than binary/deterministic in nature.[5, 14, 15]

As such, the clinical utility of a given genetic test is dependent highly on the pre-test probability of disease (i.e. strength of clinical phenotype/diagnosis) and disease-specific genetic test performance metrics (diagnostic yield, signal-to-noise ratio, etc.). In other words, in patients with weak/non-equivocal clinical phenotypes, the diagnostic yield of genetic testing declines, the signal-to-noise ratio rises, and the risk of encountering false-positives increases exponentially. Therefore, a "one-size-fits-all" mentality to genetic testing is ill-advised and genetic testing should only be undertaken if significant suspicion for an underlying genetic CVD remains following a thorough clinical evaluation, including but not limited to a detailed family history, comprehensive cardiovascular work-up, and assessment for multisystem syndromes. Given these nuances, the initiation and interpretation of cardiovascular genetic tests requires a multidisciplinary approach involving the coordinated efforts of general practitioners/general cardiologists, genetic counselors, medical geneticists, and cardiovascular sub-specialists with expertise in the CVD of interest. When feasible, the ordering, interpretation, and communication of monogenic CVD genetic test results should be done under the guidance of a genetically-oriented cardiologist and/or medical geneticist with expertise in heritable CVDs in conjunction with a cardiovascular-oriented genetic counselor. Regardless of the responsible provider, the patient and his or her family should receive genetic counseling. By assisting the multidisciplinary team with 1) the generation of multigenerational pedigrees and identification of the most appropriate individual(s) to initially test, 2) the selection of appropriate genetic tests, 3) the accurate interpretation and continued reassessment of genetic test results, and 4) assuring that psychosocial ramifications of genetic testing are adequately addressed, such genetic counseling provides additional assurance that genetic testing will be utilized appropriately and that high-quality, cost-effective care is delivered.[16]

Once a decision is made to pursue genetic testing and the patient apprised of the potential risks, benefits, and limitations of genetic testing (ideally by a genetic counselor), including the fact that a negative test cannot definitively rule out disease (except for the case of mutation-specific cascade screening) and variants of unknown/uncertain significance (VUS) without sufficient supporting evidence to be deemed pathogenic may be encountered, the work is far from over. First, the genetic test results should be interpreted in light of established criteria set forth by the American College of Medical Genetics (ACMG)[17] and other organizations as summarized in Figure 1. In some instances, a *bona fide* pathogenic mutation meeting one if not all of the ACMG's very strong/strong evidence of pathogenicity (i.e. null, established, and *de novo* variants as outlined in Figure 1)[17] is unearthed making interpretation straightforward.

However, in many cases, the commercial genetic test reports will return "positive" results with cryptic language such as "possible deleterious mutation" or "VUS" next to the identified variant(s). In this scenario, it is important to realize that "positive" is not synonymous with "disease-causative" as the identified VUS, in many circumstances, has a nearly equal chance of being a pathogenic mutation as it does a rare innocuous variant. When there is insufficient evidence to tip the scale in either direction, an agonizing situation for patients and providers develops recently referred to as "genetic purgatory".[13, 18] Although genetic purgatory is a situation all providers hope to avoid, once there, it is imperative to resist the temptation to act on a VUS by 1) escalating clinical management of

the index case and/or 2) initiating mutation/variant-specific cascade screening as these can lead to potentially harmful diagnostic miscues. Rather, providers need to closely scrutinize available clinical data and intermittently reassess the potential pathogenicity of the VUS in light of any new clinical, molecular, or computational data that may elevate or downgrade its status based on the ACMG's fluid evidence of pathogenicity framework (Figure 1).[17]

Genetic Testing for Commonly Encountered Monogenic (Mendelian) Cardiovascular Disorders (CVDs)

Classically, monogenic or Mendelian disorders arise from a rare mutation(s), passed from generation-to-generation in defined inheritance patterns (autosomal dominant, autosomal recessive, X-linked, etc.), that perturb the intended biological function of a single, disease-causative, gene-encoded protein (Figure 2).[19] In the subsequent sections, we summarize the current state of diagnostic clinical genetic testing for four commonly encountered classes of monogenic CVDs (aortopathies, cardiomyopathies, cardiac channelopathies, and familial hypercholesteremia) and how the judicious utilization of genetic testing can enhance and in some cases individualize the diagnosis, risk-stratification, and/or clinical management of patients afflicted by these potentially life-threatening disorders.

Aortopathies—The thoracic aortopathies include a spectrum of heritable connective tissue disorders such as Marfan syndrome (MFS), Loeys-Dietz syndrome, and vascular Ehlers-Danlos syndrome, that largely arise secondary to dysregulated transforming growth factor-beta signaling and predispose affected individuals to aortic dilatation/aneurysm, premature death secondary to aortic dissection/rupture, and a host of variable overlapping cardiac (arrhythmia, valvular dysfunction, etc.) and extra-cardiac (ophthalmologic, orthopedic, etc.) manifestations.[1, 2] In addition, thoracic aortic aneurysm and dissection without evident systemic connective tissue abnormalities can occur in families often in an autosomal dominant fashion. Mutations in several genes have been implicated in such syndromes of familial thoracic aortic aneurysm and dissection (FTAAD). Current commercially-available genetic testing panels cover ~16 aortopathy-susceptibility genes responsible for at least six distinct clinical entities as detailed in Table 1.

Although a relative paucity of clinically relevant genotype-phenotype correlations exist for the aortopathies, mutations within exons 24-32 of the MFS-causative *FBN1* gene that encodes fibrillin-1 gene are associated with a form of atypically severe, early onset MFS classically referred to as neonatal MFS.[25] Emerging evidence also suggests that MFS patients with haploinsufficient *FBN1* mutations (truncating/frameshift mutations that fail to produce a protein product) are at greater risk for premature aortic events/cardiovascular death[26, 27] and may be more responsive to angiotensin-receptor blockers[28] than counterparts with dominant-negative *FBN1* mutations (missense/exon-skipping mutations that yield an aberrantly functioning protein). As such, the clinical utility of genetic testing for these disorders is confined to 1) diagnostic confirmation in patients with a high pretest probability of disease (e.g. *FBN1* testing in MFS patients that meet revised Ghent criteria), 2) cascade genetic screening starting with first-degree relatives to determine those who would benefit from imaging surveillance and those who can be dismissed potentially, and 3) to allow for differentiation between clinical entities given the degree of phenotypic overlap particularly

since the current American College of Cardiology (ACC)/American Heart Association (AHA) Thoracic Aortic Disease recommendations regarding surveillance imaging and timing of surgical intervention differ between MFS, Loeys-Dietz, and vascular Ehlers-Danlos.[20] An overview of available society recommendations and clinical utility of genetic testing for the heritable thoracic aortopathies are summarized succinctly in Table 1.

Cardiomyopathies—The inherited cardiomyopathies are a group of phenotypically and genetically heterogeneous heart failure- and sudden cardiac death (SCD)-predisposing CVDs that arise secondary to mutations in genes that encode key cardiomyocyte structural components (myofilaments, Z-disc, desmosome, etc.) and are classified by functional and morphologic features as arrhythmogenic cardiomyopathy (ACM; previously referred to as arrhythmogenic right ventricular cardiomyopathy/dysplasia), dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), left ventricular non-compaction (LVNC), or restrictive cardiomyopathy (RCM).[3] Given the considerable phenotypic and genetic overlap between these cardiomyopathies, the use of commercial pan-cardiomyopathy gene panels has gained favor, particularly in cases where the addition of molecular insights afford an opportunity to further refine the clinical diagnosis. However, the use of large gene panels is likely best reserved for those individuals who have exhausted conventional cardiomyopathy-specific genetic testing as 1) nearly half of the > 60 cardiomyopathy-susceptibility genes identified to date lack sufficient evidence to be considered as *bona fide* disease-susceptibility genes and are considered "limited evidence genes",[29, 30] 2) next-generation sequencing (NGS)-based panels further complicate the already difficult task of differentiating rare benign genetic variation from disease-causative mutations by enhancing the detection of low frequency benign variants, and 3) current society guidelines recommend comprehensive/targeted diagnostic screening of only those genes (e.g. myofilament-only for HCM, desmosome-only for ACM, etc.) commonly and or very strongly associated with the clinically suspected cardiomyopathy (Table 1).[6, 23, 31]

In general, the lack of disease-modifying therapies limits the clinical utility of cardiomyopathy genetic testing to diagnosis and prognostication/risk-stratification. However, there are some situations where genetic testing for patients with suspected cardiomyopathies does have direct and immediate therapeutic implications. For example, in HCM, phenocopies such as Fabry disease, a lysosomal storage disease responsible for up to ~3% of familial HCM in some populations, [32] are amenable to treatment with enzyme replacement therapy. In addition, patients with DCM secondary to mutations in either *LMNA*-encoded lamin A/C or DES-encoded desmin are at much higher risk for conduction disease and/or malignant arrhythmias/SCD.[33-35] Here, genetic testing may guide the use of implantable cardioverter-defibrillators as primary prevention.

Unfortunately, due to a relative paucity of clinically relevant genotype-phenotype correlations, the clinical impact of genetic testing for ACM, DCM, LVNC, and RCM is confined largely to diagnostic confirmation for the proband and facilitation of cascade testing for the relatives at this time (Table 1). Although few clinically relevant gene- or mutation-specific genotype-phenotype correlations exist in HCM, multiple studies have demonstrated that those individuals with genotype-positive HCM (i.e. a positive genetic test), particularly those with mutations in the cardiac myofilaments, have a more severe

clinical phenotype (younger age at diagnoses, more hypertrophy, higher rate of progression to New York Heart Association class III/IV heart failure, and risk of cardiovascular death) compared to patients with HCM but a negative genetic test (i.e. heretofore genotype-negative HCM).[36–39] Furthermore, in comparison to individuals with thin-filament HCM (*ACTC, TNNI3, TNNT2* and *TPM1*), those with thick myofilament HCM (*MYH7* and *MYBPC3*) have more severe hypertrophy as well as higher rates of left ventricular outflow tract obstruction and progression to New York Heart Association class III/IV heart failure, but no difference in the risk of arrhythmia/SCD.[40] Lastly, ~5–10% of individuals with HCM and ACM harbor >1 disease-causative mutation resulting in so-called compound or digenic heterozygosity that is associated typically with a more severe clinical phenotype.[41–44]

These observations, coupled with the massive discordance between the genotypic and phenotypic prevalence of many inherited cardiomyopathies unearthed by analysis of recent large-scale exome sequencing studies,[45] suggest that 1) many genetic variants in cardiomyopathy-susceptibility genes, previously believed to be pathogenic, may be merely disease-modifiers or non-pathogenic altogether and/or 2) the classic monogenic/Mendelian autosomal-dominant mode of inheritance may be an oversimplification, particularly for ACM where a significant number of patients harbor >1 putative ACM-causative mutation, [41, 42] suggesting that an oligogenic model, whereby > 2 hits in genes encoding the same functional unit (i.e. desmosome, sarcomere, etc.) are required to produce overt disease, may prove ultimately to be the best fit for even these “monogenic” forms of genetic heart disease (Figure 2).

In summary, mutation-specific cascade testing of appropriate relatives remains a class I recommendation for all inherited cardiomyopathies once a *bona fide* disease-causative mutation is identified in an index case. In contrast, owing to the genetic complexity of these disorders, the challenges associated with evaluating the pathogenicity of rare variants, and the paucity of clinically useful genotype-phenotype correlations at present, diagnostic genetic testing of the index case is a class I recommendation only for patients with either HCM or those with DCM and significant cardiac conduction disease (Table 1).[6] It is anticipated that ongoing and future longitudinal studies that couple NGS-aided genotyping with in-depth clinical phenotyping may yield the additional insights necessary to further define the optimum role of genetic testing for patients with suspected ACM, DCM, LVNC, and RCM. Until then, recommendations for genetic testing for patients with these cardiomyopathies are class IIa/IIb (Table 1).[6]

Cardiac Channelopathies—The term cardiac channelopathies is used colloquially to describe a set of clinically and genetically diverse heritable cardiac arrhythmia syndromes, including Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and long QT syndrome (LQTS). These channelopathies collectively arise from defects in either critical cardiac ion channel macromolecular complexes or proteins critical for intracellular calcium-handling. Patients with a channelopathy typically have a structurally normal heart but are predisposed to arrhythmic syncope/seizures and SCD.[5, 46] In excess of 40 channelopathy-susceptibility genes have been described to date with the majority of commercially-available genetic tests covering at least 20 of these genes through

the use of disease-specific tests or comprehensive pan-channelopathy gene panels as outlined in Table 2.

Similar to the cardiomyopathies, the first-line use of commercial channelopathy panels should be approached with great caution as the inclusion of channelopathy-susceptibility genes without definitive clinical association and the enhanced detection of low frequency benign variants can confound the already difficult task of rare variant interpretation. Although the clinical utility of genetic testing in the diagnosis of cardiac channelopathies is well established and evidenced by recent Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA) recommendations,[6] LQTS, with its particularly robust genotype-phenotype correlations, represents one of the few monogenic CVDs where genetic testing facilitates a genomic/genetic-guided approach to both risk-stratification and treatment and is therefore the focus of the ensuing paragraphs.

Amongst clinically definitive LQTS cases (i.e. heart rate-correct QT interval > 480 msec and Schwartz score > 3.5),[49] ~75% have a mutation in one of the three canonical LQTS-susceptibility genes, the *KCNQ1*-encoded Kv7.1 potassium channel (LQT1, ~35%), the *KCNH2*-encoded Kv11.1/hERG potassium channel (LQT2, ~30%), or the *SCN5A*-encoded Nav1.5 sodium channel (LQT3, ~10%), with an additional ~5–10% expected to harbor mutations in the remaining 14 “minor” LQTS-susceptibility genes.[50, 51] Even among the three major LQTS-susceptibility genes, there is a significant rate of background genetic noise (~2.7% of 60,000-plus individuals in Exome Aggregation Consortium cohort harbor rare amino acid-altering genetic variation in the major LQTS genes).[13, 14] This complicates LQTS genetic test interpretation to the extent that occasional calls for universal LQTS genetic testing must be deemed ill-informed. However, when viewed in the context of an individual’s entire clinical picture (e.g. non-genetic risk factors such as age, gender, and degree of QT prolongation) and the established genotype-phenotype correlations (e.g. genotype-specific triggers and genotype-dependent responsiveness to primary therapy, i.e. beta blockers), the identification of a putative mutation in one of the major LQTS-susceptibility genes enables genotype-specific approaches to risk-stratification and clinical management.[49] Unfortunately, a seemingly positive genetic test for a minor LQTS gene, with the notable exception of exceedingly rare multisystem forms of LQTS such as Timothy syndrome (*CACNA1C*), Andersen-Tawil Syndrome (*KCNJ2*), the Calmodulinopathies (*CALM1–3*), and Triadin Knockout Syndrome (*TRDN*),[49, 52] does not carry the same weight as the major LQTS subtypes and thus contributes little-to-no significance on risk-stratification and clinical management.[13]

Current HRS/EHRA guidelines recommend (class I) LQTS genetic testing for any individual with a strong clinical suspicion of LQTS based on clinical/family history and electrocardiographic phenotype OR an asymptomatic individual with unexplained, serial QT prolongation (> 480 msec before puberty and > 500 msec after puberty.).[6] Similarly, under current HRS/EHRA guidelines, comprehensive or targeted genetic testing for individuals with a strong clinical suspicion for CPVT is recommended, whereas targeted screening of the *SCN5A*-encoded $Na_v1.5$ sodium channel in BrS can be useful in establishing a diagnosis in individuals with a strong clinical suspicion of disease based on clinical/family history and electrocardiographic phenotype.[6] Lastly, given that many genotype-positive LQTS, BrS, and

CPVT patients fail to manifest clinical/electrographic evidence of disease at baseline, mutation/variant-specific cascade screening of all at-risk relatives is recommended by HRS/EHRA following the identification of a *bona fide* channelopathy-susceptibility mutation in an index case.[6]

Familial Hypercholesterolemia—Familial hypercholesterolemia (FH) is a relatively common[47, 53, 54] predominantly autosomal dominant disorder of lipid/lipoprotein metabolism characterized clinically by elevated low-density lipoprotein cholesterol levels (LDL-C), tendon (xanthoma) and corneal (corneal arcus) cholesterol deposition, and if untreated a high risk for premature atherosclerotic CVD.[7] Due to the relatively high prevalence of FH across all racial/ethnic groups and devastating complications of unrecognized/untreated disease, FH is the only monogenic CVD that currently meets World Health Organization criteria for universal, population-based screening.[8, 55] Although current National Heart Lung and Blood Institute (NHLBI) expert guidelines strongly recommend universal lipid screening for children ages 9 to 11 [56], the rate of pre-pubertal lipid screening in the United States is low (~10%)[57] and the optimal approach to universal FH screening remains undefined (i.e. lipid screening alone vs. lipid screening followed by family-based cascade genetic screening).[8,57]

In recent years, the recognition of a significant overlap in LDL-C levels between mutation-positive and mutation-negative relatives [58] as well as between individuals with heterozygous FH (single mutation in a FH-susceptibility gene)[47, 53] and homozygous/compound heterozygous FH [>1 mutation in FH-susceptibility gene(s)][59] has led to an increased reliance on genetic testing. Specifically, the World Health Organization [60] and European Atherosclerosis Society[47] both recommend family-based, genetic cascade screening to enhance diagnostic precision in FH once a mutation-positive index case is identified. The role of genetic testing in FH is further highlighted by the incorporation of genetic test results into the two most commonly employed sets of validated FH diagnostic clinical criteria, the Dutch Lipid Clinic Network [61] and Simon Broome Registry criteria.[58]

Although six FH-susceptibility genes have been discovered to date (Table 2), most commercially-available panels and expert recommendations focus on initial sequencing and deletion/duplication analysis for three key genes (*LDLR*, *APOB*, and *PCSK9*) that account for ~>90% of mutation-positive, clinically definite FH cases.[47] Similar to other genetic disorders, the overall diagnostic yield of FH is dependent on the pre-test probability of disease (e.g. 63% for definite, 35% for probable, and 22% for possible FH based on Dutch Lipid Clinic Network criteria)[62] and the major FH-susceptibility genes are also subject to an inherent rate of background genetic variation. Thus, it is imperative that FH genetic test results are cautiously interpreted in light of the aforementioned ACMG guidelines.[17] As such, the primary clinical utility of FH genetic testing is 1) to confirm diagnosis/identify FH-causative mutation in those individuals with a definite/probable clinical diagnosis of FH (e.g. adults with LDL-C >190 mg/dL and children with LDL-C >160 mg/dL and personal/family history of premature atherosclerotic CVD or tendinous xanthomas) and 2) to facilitate cascade screening of first-, second-, and third-degree relatives of mutation-positive FH index cases.

Lastly, despite the identification of several potentially clinically relevant genotype-phenotype correlations shown to influence phenotypic severity [59, 63] and statin-responsiveness,[64] risk-stratification and clinical management decisions in FH are driven currently by LDL-C levels and therapeutic response. As our understanding of the genetic architecture of FH continues to evolve, particularly with regards to the ability of cholesterol-raising and cholesterol-lowering genetic variants with modest effect sizes to modulate the phenotypic expression of primary FH-causative mutations, it is anticipated that the role of genetics in tailoring individualized approaches to the risk-stratification and management of patients with FH will continue to grow.

Genetic Testing for Cardiovascular Diagnostic Odysseys

The term “diagnostic odyssey” refers to any patient or family with a suspected genetic disorder whereby the precise underlying clinical entity remains undifferentiated following standard genetic testing.[65] With its ability to detect changes throughout the coding regions of the human genome and increasingly cost-effective nature, whole exome sequencing (WES) is proving to be an indispensable diagnostic clinical tool for elucidating the genetic etiology of diagnostic odysseys.[66–68] In fact, WES has been successful in elucidating an underlying genetic basis for ~25% of diagnostic odysseys[65, 69–71] and in numerous cases has led to the identification of novel monogenic/Mendelian CVD-susceptibility genes/genetic loci in patients with seemingly genotype-negative disease.[66–68]

In addition to the use of clinical WES to investigate cardiovascular diagnostic odysseys in the living, several groups have explored the utility of WES-based molecular autopsies (WEMA)[72–77] as a cost-effective means of screening cases of sudden unexplained death in the young (SUDY) for previously undiagnosed SCD-predisposing monogenic/Mendelian CVDs, such as the cardiac channelopathies and cardiomyopathies, that are often undetectable on autopsy and known to underlie ~25%-35% of SUDY cases.[73, 76, 78] Although the majority of these studies, including a recent population-based prospective trial that utilized a 55 cardiac gene panel,[76] identified clinically actionable variants and increased the overall diagnostic yield in SUDY,[73-76] the use of large cardiac gene panels to probe ambiguous phenotypes such as SUDY needs to be approached with caution. Not only do these gene panels contain a significant number of polymorphic genes that collectively have the ability to produce an overwhelming amount of background genetic noise, but SUDY phenotypes are often poorly defined making it next to impossible to interpret suspected SUDY-causative variants in the context of the pre-test probability of any single heritable CVD. As a result, the use of WEMAs is likely to unearth many ultra-rare VUS in potential SUDY-susceptibility genes and the bulk of these variants will lack the supporting evidence needed to definitively ascertain pathogenicity. One can envision how the results of a 50-100 gene WEMA could be misinterpreted easily by well-intentioned clinicians triggering the misguided cascade screening of at-risk relatives that ultimately may result in harmful diagnostic miscues. As such, a tiered approach to WEMA starting with those genes (*KCNQ1*, *KCNH2*, *SCN5A*, *RYR2*, *PKP2*, *CALM1–3*, etc.) most likely to harbor clinically actionable variants based on prior SUDY studies [74, 75] is advisable and consistent with current HRS/EHRA recommendations when performed in conjunction with a

comprehensive postmortem examination and clinical/cardiologic evaluation of first degree relatives.[6]

Genetic Risk Scores (GRS) in the Prediction and Prevention of Polygenic (Non-Mendelian) Cardiovascular Disorders (CVDs)

In contrast to monogenic/oligogenic CVDs that typically arise from a rare, single gene mutation(s), many common CVDs, including AF, CHD, and hypertension, have a clear heritable component attributable to the collective contribution of multiple independent or interacting variants that in isolation account for a miniscule fraction of the complex trait or disease in question resulting in a so-called polygenic inheritance pattern (Figure 2).[79, 80] Although no commercial genetic tests are available currently for so-called "polygenic" CVDs, the following paragraphs briefly examine ongoing efforts to translate *bona fide* CVD-associated single nucleotide polymorphisms (SNPs)/genetic loci discovered through GWAS into a clinically useful aggregate genetic risk score (GRS) that, in conjunction with traditional clinical risk factors, can enhance risk-stratification and prevention of polygenic CVDs.

Over the past decade, multi-cohort GWAS meta-analyses led by transatlantic consortia such as the AF Genetics (AFGen),[12] Global Blood Pressure Genetics (BPgen),[81] and Coronary ARtery DIsease Genome wide Replication and Meta-analysis (CARDIoGRAM)[11] consortia, have yielded a large number of CVD-associated SNPs/genetic loci that reach genome-wide significance. However, owing to the small effect size of each individual SNP, the clinical utility of individual SNPs to predict disease likelihood is modest.[82] As a result, the concept of a "genetic risk score" (GRS) was conceived.[83] Here, a panel of weighted or unweighted diseasemodifier SNPs is used to generate a single aggregate score that undergoes subsequent predictive modelling (i.e. area under the receiver operator curve or net reclassification improvement index) to determine if the GRS improves predictive capacity, and therefore may have clinical utility, incremental to traditional clinical risk factors.[83]

To date, several GRS studies have demonstrated a relatively modest, but statistically significant incremental predictive ability for incident AF [84, 85] and adverse CHD events.[86-91] Furthermore, the recent Myocardial Infarction Genes (MI-GENES) clinical trial demonstrated that the incorporation of a CHD-GRS into a conventional risk prediction algorithm and subsequent disclosure of genetic risk for CHD to study participants led to lower LDL-C levels in comparison to disclosure of clinical risk factors alone.[92] Furthermore, disclosure of CHD genetic risk did not induce significant patient anxiety.[92] As such, the knowledge of an underlying genetic predisposition to common polygenic CVDs may lower the overall burden of CVD by prompting providers and patients to more aggressively address modifiable risk factors before disease onset (Figure 3). However, as the majority of CVD GWAS meta-analyses were conducted in cohorts of European ancestry, ongoing studies are needed to ascertain whether the current CVD-GRSs can be generalized to other racial/ethnic groups. Lastly, large prospective clinical trials are needed to determine if the use of a CVD-GRS can improve clinical outcomes, decrease disease burden, and lower healthcare costs.

Cardiovascular Pharmacogenomics

Drugs used in the prevention and treatment of CVD, including β-blockers, flecainide, clopidogrel, statins, and warfarin, account for manyof the most widely prescribed pharmacologic agents worldwide. Although these drugs are highly effective and safe at the population-level, individual patients occasionally display variability in the degree of efficacy and/or rate of adverse drug reactions. This clinical conundrum birthed the field of Pharmacogenomics, which aims to enhance the utility of available pharmacologic agents by linking variation in genes that govern a drug's pharmacokinetic (effect of the body on drug concentration/tissue distribution) and pharmacodynamics (effect of the drug on body molecular/cellular/organ function) properties to inter-individual variability in drug response. Furthermore, the concept of pre-emptive pharmacogenomics, wherein individuals are genotyped for relevant pharmacogenomic genes/variants and actionable results are then placed in the electronic health record, with linkage to clinical decision support, is being pursued actively.[93]

Due to a relative paucity of RCTs aimed at defining the clinical utility of pharmacogenomics testing and the availability of alternative agents with decreased or no known pharmacogenomic liability, current society and regulatory agency recommendations/ guidelines are variable in regards to the use of pharmacogenomics testing in clinical practice (Table 3). Although a thorough discussion of cardiovascular pharmacogenomics is outside the scope of this Review, current professional society and regulatory agency recommendations/guidelines pertaining to the use of pharmacogenomics testing when prescribing β-blockers, clopidogrel, statins, and warfarin are outlined in Table 3 and an expanded discussion of how pharmacogenomics data may be used to individualize cardiovascular drug and dosage selectionis contained within the online supplement.[94-139]

CONCLUSION

Although this Review details many examples of how genetic and pharmacogenomics testing has already led or will one day lead to genotype-guided approaches to the diagnosis, risk-stratification, and management of patients with an array of CVDs, the full promise of precision genomic medicine is far from being realized. As echoed throughout this Review, a number of significant barriers currently limit and complicate the use of genetic and pharmacogenomics testing in clinical practice. As such, it is imperative that innovative, well-designed, and adequately powered studies are undertaken to 1) elucidate genotype-phenotype correlations utilized in the development of individualized genotype-guided approaches to the risk-stratification and management of monogenic CVDs, 2) enhance the ability to distinguish pathogenic mutations from rare, benign, background genetic variants, 3) better define the genomic architecture of common CVDs, inter-individual response to common cardiovascular drugs, and the phenomena of incomplete penetrance and variable expressivity in monogenic CVDs, 4) determine the clinical utility of established GRSs and pharmacogenomics tests through prospective RCTs, and 5) implement precision cardiovascular genomic medicine at the point of care by integrating genetic/genomic testing results into the electronic health record with linkage to clinical decision support.[140] When coupled with the development of educational resources to ensure that current and future

cardiovascular providers are prepared to utilize evidence-based genetic/genomic approaches and ongoing support from broad proposals such as Precision Medicine Initiative, tackling these barriers should assure the future of precision cardiovascular medicine remains bright.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms:

ACC	American College of Cardiology
ACMG	American College of Medical Genetics
AF	atrial fibrillation
AHA	American Heart Association
ACM	arrhythmogenic cardiomyopathy
BrS	Brugada syndrome
CHD	coronary heart disease
CPVT	catecholaminergic polymorphic ventricular tachycardia
CVD	cardiovascular disease
DCM	dilated cardiomyopathy
EHRA	European Heart Rhythm Association
FH	familial hypercholesterolemia
GRS	genetic risk score
GWAS	genome-wide association study
HCM	hypertrophic cardiomyopathy
HRS	Heart Rhythm Society

LDL-C	low-density lipoprotein C
LQTS	long QT syndrome
LVNC	left ventricular non-compaction
MFS	Marfan syndrome
NGS	next-generation sequencing
PCI	percutaneous coronary intervention
RCM	restrictive cardiomyopathy
SCD	sudden cardiac death
SNPs	single nucleotide polymorphisms
SUDY	sudden unexplained death in the young
VUS	variant of unknown significance
WEMA	whole exome molecular autopsy.

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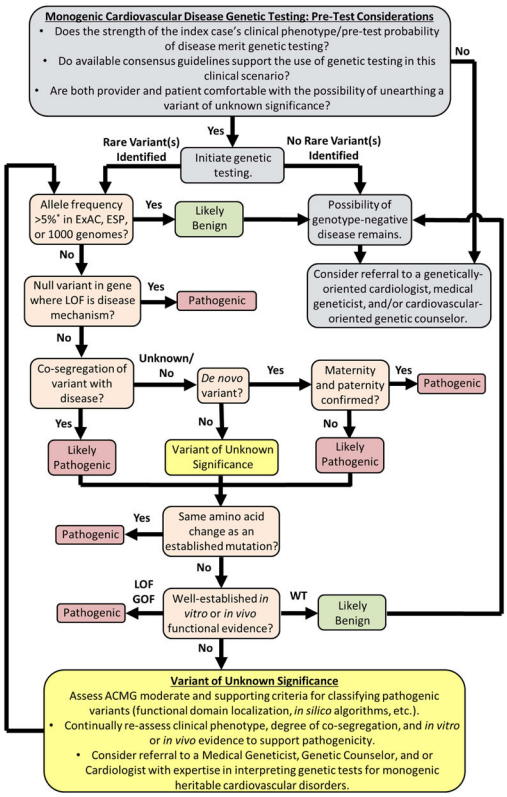

Figure 1 |.

A rational approach to genetic test initiation, rare variant interpretation, and the fluid re-assessment of variants of unknown/uncertain significance. Gray boxes denote basic considerations pertaining to the initiation of genetic testing. Beige boxes denote key steps in the classification of rare genetic variation based on widely acceptable American College of Medical Genetics criteria. Yellow boxes denote basic considerations pertaining to the identification of a rare variant of unknown/uncertain significance that currently lacks sufficient evidence to either up or down grade its probability of pathogenicity. *Allele frequency > 5% or greater than widely accepted estimates of disease prevalence in the Exome Aggregation Consortium, Exome Sequencing Project, or 1000 genomes serve as stand-alone or strong evidence of pathogenicity, respectively. ACMG = American College of Medical Genetics; ESP = Exome Sequencing Project; ExAC = Exome Aggregation Consortium; GOF = gain-of-function; LOF = loss-of-function; VUS = variant of unknown/uncertain significance; WT = wild-type.

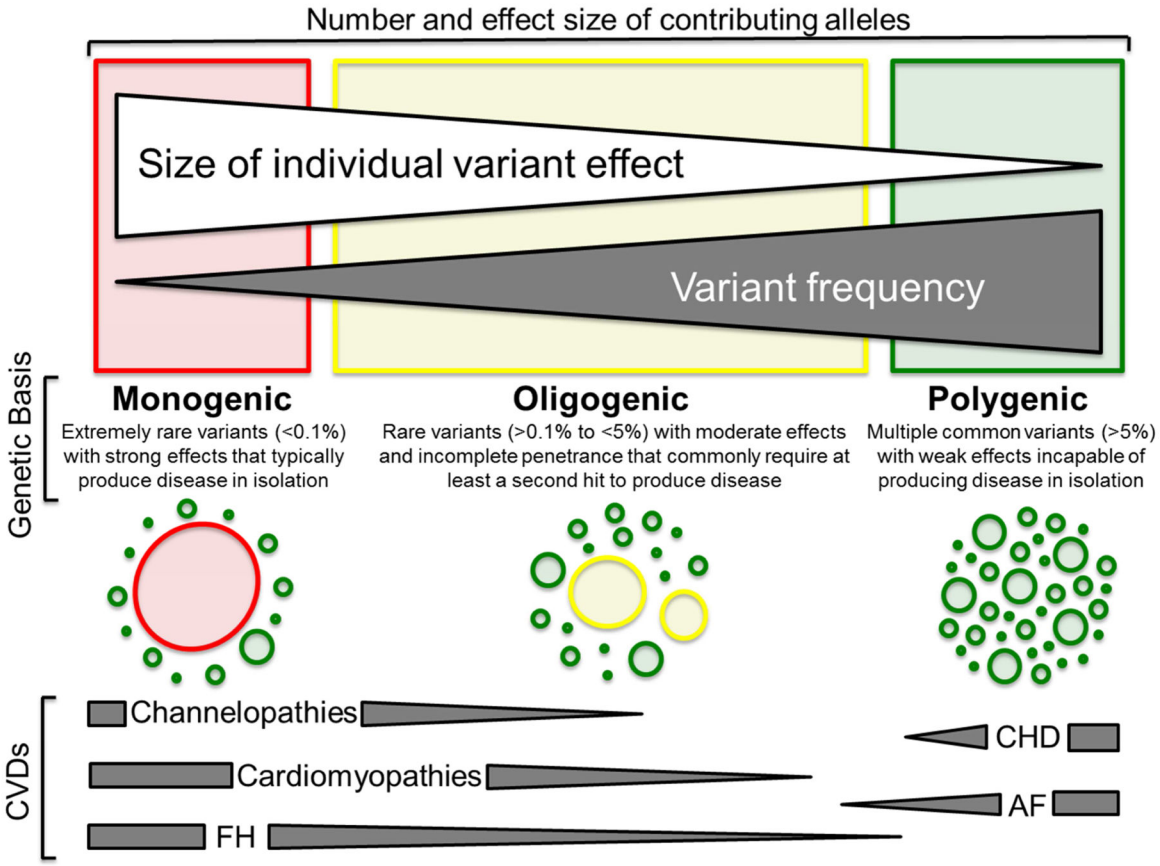

Figure 2 |.

The spectrum of genetic variation underlying the heritable component of commonly encountered cardiovascular disorders (CVDs). At the severe (red) end of the spectrum are extremely rare disease-causative mutations with strong effects on gene function that typically result in monogenic disorders such as long QT syndrome, hypertrophic cardiomyopathy, and familial hypercholesterolemia. In the middle of the spectrum (yellow) are rare variants with moderate effects on gene function that rarely produce disease in isolation, but in the presence of one or more second hits result in disease as seen in some instances of arrhythmogenic cardiomyopathy. Lastly, at the benign (green) end of the spectrum are common variants with weak effects on gene function that are incapable of producing disease in isolation, but may confer disease risk when multiple risk-associated common variants are present within the genome of an individual with environmental risk factors for disorders such as coronary heart disease and atrial fibrillation. In recognition that the genetic basis of most heritable CVDs is variable, dark gray triangles denote the spectrum of genetic variation underlying each CVD or class of CVDs. ACM = arrhythmogenic cardiomyopathy; AF = atrial fibrillation; CHD = coronary heart disease; CVD = cardiovascular disease; FH = familial hypercholesterolemia; HCM = hypertrophic cardiomyopathy; LQTS = long QT syndrome. Adapted from Giudicessi, J.R., and Ackerman, M.J. Determinants of incomplete penetrance and variable expressivity in

heritable cardiac arrhythmia syndromes. *Translational Research* 161(1), 1–14 (2013) with permission from Elsevier.[19]

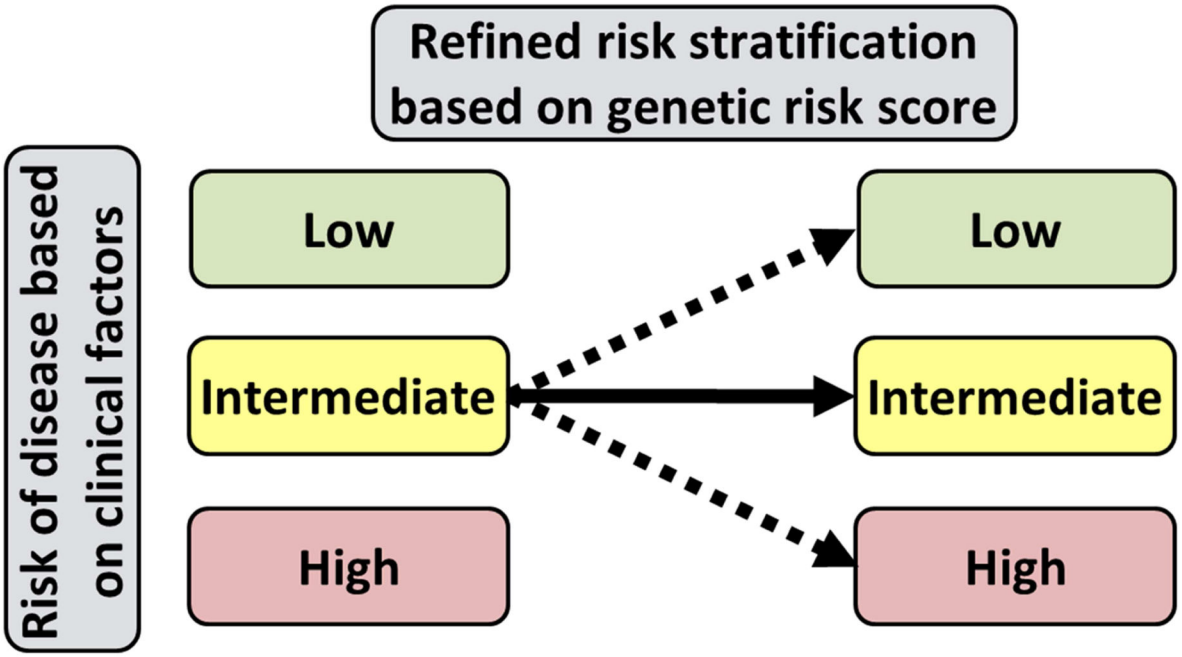

Figure 3 |.

Refinement of clinical disease risk estimates with the use of genetic risk scores (GRS). Generalized schematic displaying how the use of an aggregate GRS can be used to refine the risk assessment in individuals at intermediate risk for disease based on clinical risk factors leading to earlier identification of individuals at increased risk of developing disease. GRS = genetic risk score.

Table 1:

Current Recommendations and Clinical Utility of Commercially-Available Genetic Tests for Commonly Encountered Heritable Aortopathies and Cardiomyopathies

Class	Disorder	Genes	Clinical Impact	Society Recommendations[b]	Ref.
Aortopathies (systemic)	vEDS	*COL3A1*[c]	Diagnosis	ACC/AHA/AATS and ESC guidelines: 1) Patients with suspected vEDS based on clinical criteria should be referred to a geneticist to facilitate diagnostic genetic testing for *COL3A1* mutations (class I). 2) Mutation-specific cascade screening recommended if a bona fide disease-causative mutation identified (class I).	20, 21
	LDS	*TGFBR1*[c], *TGFBR2*[c], *SMAD3*, *TGFB2*, and *TGFB3*	Diagnosis	ACC/AHA/AATS and ESC guidelines: 1) Patients with suspected LDS based on clinical criteria should be referred to a geneticist to facilitate diagnostic genetic testing (class I). 2) Mutation-specific cascade screening recommended if a *bona fide* disease-causative mutation identified (class I).	20, 21
	MFS	*FBN1*[c]	Diagnosis Risk-stratification Management	ACC/AHA/AATS and ESC guidelines: 1) Patients with suspected MFS based on revised Ghent nosology should be referred to a geneticist to facilitate diagnostic genetic testing (class I). 2) Mutation-specific cascade screening recommended if a bona fide disease-causative mutation identified (class I).	20, 21
Aortopathies (non-systemic)	FTAAD	*ACTA2*, *MAT2A*, *MYH11*, *MYLK*, *PRKG1*, and *TGFB2*	Diagnosis	ACC/AHA/AATS and ESC guidelines:break 1) Known syndromic FTAADs (vascular EDS, LDS, and MFS) should be ruled out and the index case referred to a geneticist for consideration of diagnostic genetic testing (class I). 2) Mutation-specific cascade screening recommended if a bona fide disease-causative mutation identified (class I).	20, 21
Cardiomyopathies	ACM	**Major:** *DSC2*[c], *DSG2*[c], *DSP*[c], and *PKP2*[c] **Minor:** *JUP*, *RYR2*, *TGFB3*, and *TMEM43*	Diagnosis Risk-stratification	HRS/EHRA guidelines: 1) Genetic testing can be useful in patients who satisfy 2010 ESC task force diagnostic criteria (class IIa). 2) Mutation-specific cascade screening recommended (class I). 3) Genetic testing can be considered in patients with possible ACM based on 2010 ESC task force diagnostic criteria (class IIb).[d]	6, 22
	DCM	**Autosomal DCM:**~60+ genes identified to date. DCM with conduction disease: *LMNA*[c] and *SCN5A* X-linked DCM: *DMD* and *TAZ*	Diagnosis Management	HRS/EHRA guidelines: 1)Comprehensive or LMNA/SCN5A targeted genetic testing is recommended for all patients with DCM and significant cardiac conduction disease or family history of SCD (class I) 2) Mutation-specific cascade screening recommended (class I). 3) Comprehensive genetic testing can be useful in confirming the diagnosis of familial DCM and establishing a molecular target for cascade screening (class IIa).[d]	6
	HCM[e]	**Major:** *MYBPC3*[c] and *MYH7*[c] **Minor:** *ACTC*, *ACTN2*,	Diagnosis Risk-stratification Management	ACC/AHA. HRS/EHRA. and ESC guidelines: 1) Genetic testing recommended in patients fulfilling diagnostic criteria for or with signs/symptoms suggestive of HCM (class I). 2) Mutation-specific cascade screening recommended (class I). 3) Genetic testing should be considered in	6,23,24

Class	Disorder	Genes	Clinical Impact	Society Recommendations[b]	Ref.
		ANKRD1, *CSRP3*, *JPH2*, *LBD3*, *MYH6*, *MYL2*, *MYL3*, *MYOZ2*, *PLN*, *TNNC1*, *TNNI3*, *TNNT2*[c], *TPM1*, *TTN*, *TCAP*, and *VCL*		borderline cases after assessment by HCM specialist (class IIa).[d] 4) Genetic testing should be considered in deceased patients with pathologically confirmed HCM to facilitate cascade screening (class IIa).	

[a] AATS = American Academy of Thoracic Surgery; ACC = American College of Cardiology; AHA = American Heart Association; ACM, arrhythmogenic cardiomyopathy; DCM = dilated cardiomyopathy; EHRA = European Heart Rhythm Association; ESC = European Society of Cardiology; FTAAD = familial thoracic aortic aneurysm and dissection; HCM = hypertrophic cardiomyopathy; LDS = Loeys-Dietz syndrome; MFS = Marfan syndrome; and vEDS = vascular Ehlers-Danlos syndrome.

[b] Class of evidence indicated when available.

[c] Denotes commonly encountered genes with strong evidence that disease-causative mutations within these genes contribute directly to disease pathogenesis.

[d] Use of large gene panels in weak/borderline clinical cases substantially increases the risk of encountering a non-diagnostic VUS.

[e] Denotes the most clinically useful monogenic cardiovascular genetic tests.

Table 2:

Current Recommendations and Clinical Utility of Commercially-Available Genetic Tests for Commonly Encountered Heritable Cardiac Channelopathies and Familial Hypercholesterolemia

Class	Disorder	Genes	Clinical Impact	Society Recommendations[b]	Ref.
Channelopathies	BrS	**Major:** *SCN5A(BrS1)*[c] **Minor:** *ABCC9*, *CACNA1C*[c], *CACNA2D1*, *CACNB2*, *FGF12*, *GPD1L*, *HCN4*, *KCND2*, *KCND3*, *KCNE3*, *KCNE5*, *KCNJ8*, *PKP2* *MOG1*, *SCN1B*, *SCN2B*, *SCN3B*, *SCN10A*, *SLMAP*, *SEMA3A*, and *TRPM4*	Diagnosis Risk-stratification	HRS/ERHA guidelines: 1) Mutation-specific cascade screening recommended (class I). 2) Genetic testing can be useful when there is clinical suspicion (class IIa).[d]	6
	CPVT[e]	**Major:** *RYR2(CPVT1)*[c] and *CASQ2 (CPVT2)*[c] **Minor:** *CALM1*, *CALM2*, *CALM3*, *KCNJ2*, and *TRDN*	Diagnosis Risk-stratification	HRS/EHRA guidelines: 1) Genetic testing recommended when there is clinical suspicion (class I). 2) Mutation-specific cascade screening recommended (class I).	6
	LQTS[e]	**Major:** *KCNQ1(LQT1)*[C], *KNCH2(LQT2)*[C], and *SCN5A (LQT3)*[C] **Minor:** *AKAP9*, *ANKB*, *CACNA1C*, *CALM1*, *CALM2*, *CALM3*, *CAV3*, *KCNE1*, *KCNE2*, *KCNJ2*, *KCNJ5*, *SCN4B*, *SNTA1* and *TRDN*	Diagnosis Risk-stratification Management	HRS/EHRA guidelines: 1)Genetic testingrecommended when there is either clinical suspicion or in asymptomatic patients with unexplained QT prolongation (QTc > 480 ms pre-puberty or QTc > 500 ms post-puberty, class I). 2) Mutation-specific cascade screening recommended (class I). 3) Genetic testing may be considered in asymptomatic patients with otherwise unexplained QT prolongation (QTc > 460 ms pre-puberty or QTc >480 ms post-puberty, class IIb)[d]	6
Familial Hypercholesterolemia	FH[e]	**Major:** *LDLR*[C], *APOB*[C], and *PCSK9*[C] **Minor:** *APOE*, *LDLRAP*[C], and *STAP1*	Diagnosis Risk-stratification	AHA, EAS, and NLA statements/ guidelines: 1) Genetic testing strongly recommended for individuals with a definite or probable diagnosis of FH based on validated clinical scorecards (DLCN, Simon-Broome, etc.). 2) Mutation-specific cascade screening provides a diagnostic gold-standard in families with an identified disease-causative mutation(s).	8,47, 48

[a] AHA = American Heart Association; BrS = Brugada syndrome; CPVT = catecholaminergic polymorphic ventricular tachycardia; DLCN = Dutch Lipid Clinic Network; EAS = European Atherosclerosis Society; EHRA = European Heart Rhythm Association; FH = familial hypercholesterolemia; HRS = Heart Rhythm Society; LQTS = long QT syndrome; and NLA = National Lipid Association.

[b] Class of evidence indicated when available.

[c] Denotes commonly encountered genes with strong evidence that disease-causative mutations within these genes contribute directly to disease pathogenesis.

[d] Use of large gene panels in weak/borderline clinical cases substantially increases the risk of encountering a non-diagnostic VUS.

[e] Denotes the most clinically useful monogenic cardiovascular genetic tests.

Table 3:

Expert Guidelines Regarding Utilization of Genotype-Guided Drug/Dose Selection in Cardiovascular Disease

Class	Medication(s)	Gene(s)	Clinical Concern	Relevant Society/Regulatory Agency Recommendations	CPIC Strength	Ref.
Anti-platelet	Clopidogrel	*CYP2C19*	Clinical efficacy in ACS patients undergoing PCI	AHA/ACC recommendations: Due to lack of RCTs, the evidence base is insufficient to recommend routine CYP2C19 genotyping, but can be considered on a case-by-case basis for individuals at high-risk for poor outcomes. CPIC Dosing Guidelines: Ultra-rapid - Standard dosing Extensive - Standard dosing. Intermediate - Alternative agent. Poor - Alternative agent. FDA recommendations: Due to the estimated 2–14% of individuals who are poor metabolizers alternative dosing or anti-platelet agents should be considered. Clinical CYP2C19 genotyping is available to identify poor metabolizers	Moderate-to-strong	113, 141
β-blockers	Carvedilol Metoprolol Propranolol	*ADRB1* *CYP2D6* *GRK4* *GRK5*	Therapeutic response	No recommendations have been made by CPIC, AHA/ACC, or regulatory agencies.	N/A	N/A
Statins	Simvastatin	SLCO1B1	Statin-induced myopathy	AHA/ACC recommendations: No formal recommendations. yCPIC Dosing Guidelines: Normal function - Standard starting dose. Intermediate function - Consider alternative. Low function - Consider alternative; CK surveillance. FDA recommendations: Simvastatin 80 mg should not be started in patients with a new clinical indication for a statin.	Strong	123
Vitamin K antagonist	Warfarin	CYP2C9 and VKORC1	Clinical efficacy and toxicity	AHA/ACC recommendations: No formal recommendations. CPIC Dosing Guidelines: Recommend use of pharmacogenetic-guided warfarin dosing algorithms that account for CYP2C9 and VKORC1 genetic variation (e.g. http://www.warfarindosing.org). FDA recommendations: Recommend use of electronic (e.g. http://www.warfarindosing.org) or table genetic-guided algorithms that account for CYP2C9 and VKORC1 genetic variation to establish initial dosing when possible.	Strong	142

[a]ACC = American College of Cardiology; ACS = acute coronary syndrome; AHA = American Heart Association; CK = creatinine kinase; CPIC = Clinical Pharmacogenomics Implementation Consortium; FDA = Food and Drug Administration; and PCI = percutaneous coronary intervention.