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Clinical Application of Genetic Testing in Heart Failure

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Abstract

Purpose of review—The purpose of this review is to present our current understanding of the genetic etiologies that may cause or predispose to heart failure. We highlight known phenotypes for which a genetic evaluation has clinical utility.

Recent findings—The literature continues to demonstrate and confirm a genetic basis for conditions that cause heart failure. Evidence suggests a genetic model involving rare and common variants of strong or weak effect, in combination with environmental factors that may manifest as familial or simplex disease. Clinical genetic testing is available for several phenotypes, which can aid in the diagnosis and identification of at-risk family members.

Summary—The evaluation of heart failure should include investigating etiologies with a genetic basis. Conducting a genetic evaluation in patients with heart failure requires the ability to identify possible genetic etiologies in an individual's phenotype, obtain relevant family history, and clinically interpret genetic testing results.

Keywords

heart failure; genetics; cardiomyopathy; coronary artery disease; genetic counseling; genetic testing

Introduction

Heart failure, a pan-ethnic disease that is clinically manifest in more than 6.5 million individuals 20 years and older in the United States [1], is a whole body response resulting from inadequate cardiac output, most commonly a consequence of systolic dysfunction or impairment of ventricular filling. Approximately 960,000 new cases are diagnosed annually and the annual healthcare cost is estimated to be \$30.7 billion [1]. Americans ages 45–95 years old have a heart failure lifetime risk of 20–40% [1] and a 5-year mortality of approximately 53% [1].

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Conflict of Interest

Ana Morales and Ray Hershberger each declare no conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the author.

The most common etiologies that underlie heart failure arise from one or more pathological processes directly affecting the ventricular myocardium, termed cardiomyopathies (Table 1). The cardiomyopathies can be grouped into genetic (reviewed here), infectious (Chagas, HIV, Lyme disease, among others), environmental (radiation exposure, cobalt, selenium and other heavy metal intoxication, or thiamine deficiency, among others), and other causes (tachycardia-mediated cardiomyopathy, ischemic cardiomyopathy, valvular cardiomyopathy, drug-induced from agents such as adriamycin, trastuzumab, and endocrine, including hyper- or hypothyroidism, pheochromocytoma, and Cushing's disease). The degree of genetic or genomic influence on cardiomyopathies that are not known to be genetic have been minimally explored, although some preliminary evidence suggests gene environment interactions (e.g., Chagas disease, [2, 3]).

A genetic predisposition should always be considered in the evaluation for the etiology of heart failure, as a Mendelian (single gene) basis has been demonstrated for several cardiomyopathies, usually with specific phenotypes, that can lead to heart failure (Table 1). For these phenotypes, clinical genetic testing is available to confirm a diagnosis and identify at-risk individuals. With dilated cardiomyopathy (DCM) of unknown cause (sometimes referred to as idiopathic or non-ischemic cardiomyopathy), for instance, systematic clinical screening of first-degree family members of probands diagnosed with idiopathic in single center studies has shown familial disease in 15–35% [4, 5]. Genetic analysis of these individuals suggests that variants may be identified in 30–40% [6]. Because genetic testing makes it possible to identify underlying etiologies, the opportunity of prevention and treatment exists for at-risk family members who can benefit from periodic cardiovascular monitoring.

We recognize that most cases of DCM of unknown etiology (i.e., meeting rigorous criteria for idiopathic DCM) present as simplex disease. While clinical screening (history, exam, echocardiogram, ECG) of their first degree relatives will show familial disease in a fraction of these, most will appear to have sporadic disease, and the etiology of these cases remains uncertain. In a preliminary single center study, genetic analysis of such cases has identified variants in DCM genes in similar proportions to those observed in familial DCM [7, 8]. A NHLBI- and NHGRI-funded multisite study is now underway to test the hypothesis that most of idiopathic DCM has a genetic basis, regardless of family history [9].

While a number of conditions that lead to heart failure are not known to have a single gene basis, we recognize, however, that relevant genetic variation may be at play in a greater number of cases than currently understood. For example, preliminary data suggest that chemotherapy cardiomyopathy and heart failure can be mediated by DCM variants [10–12]. In addition, common conditions such as hypertension, diabetes, and body mass index, which can, in part be mediated by genomics and predispose to heart failure, can aggregate in families and have been postulated as contributing factors to the increased prevalence of heart failure in offspring of affected individuals [13]. Association studies also suggest that variants may influence patient mortality [14, 15] as well as influence treatment response [16–18]. Furthermore, genome-wide association studies have also reported relevant regions, including the 9p21 locus in coronary artery disease and myocardial infarction risk [19], and a common deletion in *MYBPC3* (a gene associated with DCM, HCM, and RCM), which can influence

risk of heart failure [20, 21]. Thus, the development of an underlying etiology of heart failure, or a variable treatment response to heart failure, may also result from a combination of environmental factors and one or more rare or common variants of strong to weak effect in a single gene or a combination of genes (Figure 1).

Human genetics has only begun to tap into the potential of clinical genetics applications to heart failure. This manuscript highlights the currently known Mendelian phenotypes for which a genetic evaluation, including genetic testing or cardiac surveillance of at-risk family members, can be of clinical utility. Cardiovascular disease risk assessment offers the opportunity to implement lifestyle, drug or device interventions that can decrease morbidity and mortality. This forms the rationale for surveillance of at-risk family members, so that relevant interventions may be taken prior to the onset of late phase disease (e.g., heart failure, major arrhythmias including sudden cardiac death, stroke and related issues). As an active area of research in which clinical applications are limited due to lack of replicability, common genetic variation and the pharmacologic response modulating the onset or progression of heart failure is outside the scope of this manuscript.

Left-Sided Heart Failure

Cardiomyopathy most commonly results from chronic left ventricular systolic dysfunction. Symptoms of both left sided and right sided heart failure may accompany significant systolic dysfunction and lead to the diagnosis of Heart Failure with Reduced Ejection Fraction (HFrEF). The clinical presentation of left sided heart failure involves symptoms of exercise intolerance (dyspnea, fatigue, and shortness of breath) and/or congestion (orthopnea, and paroxysmal nocturnal dyspnea) from salt and water retention. Left sided heart failure can also present with preserved ejection fraction, usually from impaired relaxation and ventricular filling (diastolic dysfunction). The presentation of heart failure with preserved ejection fraction is characterized primarily by volume overload.

Guidelines for the medical management of heart failure have been published [22]. Treatment includes lifestyle changes, including dietary modification, smoking and alcohol cessation, and avoidance of excessive activity. Prescription drugs, including diuretics, ACE inhibitors, beta blockers, and aldosterone antagonists are used. Invasive and advanced therapies, such as pacemaker and/or implantable cardiac defibrillator, left ventricular assist device, and heart transplantation, are also available.

Approximately 50% of left sided heart failure results from non-ischemic cardiomyopathy [23]. Included here are the primary cardiomyopathies, all of which have a genetic basis: idiopathic dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC). Guidelines for the genetic evaluation of cardiomyopathy have been published by the Heart Failure Society of America [24].

Many studies cite coronary artery disease (CAD) as the most common cause of heart failure [25–27], where ischemic cardiomyopathy may occur following myocardial infarction. CAD is considered a condition mediated by several factors, including lifestyle (lack of exercise, tobacco use) and comorbidities (obesity, diabetes, hypertension, and hyperlipidemia). While

the genetic basis of CAD remains complex, this phenotype can also result from a single gene predisposition to either severely elevated LDL cholesterol, termed Familial Hypercholesterolemia (FH) or lipoprotein A, both of which lead to early onset coronary artery disease, myocardial infarction, and stroke.

Right-Sided Heart Failure

Right sided heart failure can occur as a consequence of progressive left sided heart failure. The classic signs of right sided heart failure include abdominal and lower extremity edema. Right sided heart failure can also be secondary to right ventricular infarction due to CAD, or it can also result from pulmonary arterial hypertension, both of which can have a genetic basis.

Mendelian Conditions Leading to Heart Failure

A Mendelian condition is that in which a pattern of inheritance results from alteration in a single gene pair. Mendelian disease can be autosomal or X-linked, dominant or recessive. Most known cardiovascular genetic conditions that can present with heart failure are primarily autosomal dominant. In autosomal dominant disease, a single variant in a gene pair is sufficient to cause disease. The chance of transmitting the variant, and thus, a predisposition to disease, is 50% with each pregnancy. An individual who inherits a cardiovascular genetic disease-causing variant is born with an age-dependent predisposition for disease. Disease may or may not manifest (reduced penetrance), and manifestations are variable among affected individuals, including those belonging to the same family (variable expressivity). Usually variants of moderate to strong effect that cause autosomal dominant disease are rare or absent in the general population. Heart failure resulting from primary cardiomyopathy, as well as some forms of right-sided heart failure and CAD, have a Mendelian basis (Table 1).

DCM

DCM is the most common cardiomyopathy causing heart failure [6]. In addition to heart failure, DCM can also present with arrhythmia or stroke. When arrhythmia is the presenting feature, it ranges from minimal to severe, including syncope and sudden cardiac death. The DCM phenotype of left ventricular enlargement and reduced left ventricular ejection fraction can be caused by myocardial infarction from CAD, or from toxic, or infectious exposure. DCM can also be idiopathic. The prevalence is estimated to be 1/200, and there is no known racial or ethnic predilection. Onset is usually between ages 40–60 years, but it can occur in infants and children and older individuals. DCM also occurs in pregnancy, known as peripartum or pregnancy-associated cardiomyopathy [28–30].

Research on idiopathic cases suggests that familial DCM (more than one affected individual) is identified in 20–25% of cases [4]. Affected individuals may be symptomatic or asymptomatic. The latter can only be identified by cardiovascular screening, as recommended by the Heart Failure Society of America Guideline for the Genetic Evaluation of Cardiomyopathy [24]. These guidelines recommend that for DCM, screening be repeated every 3–5 years, as onset is age dependent, and a new case occurrence will support familial DCM, and thus, a genetic etiology. The pattern of inheritance is primarily autosomal

dominant. Cases of recessive and X-linked DCM are rare. More than 30 genes of diverse ontology have been associated with DCM [6]. Approximately 30–40% of familial cases have DCM-causing variants. Preliminary data suggests that a genetic basis is present in similar proportions in individuals who report a negative family history (simplex idiopathic DCM) [5–8].

Because DCM presents late in its course, in most cases with heart failure, the clinical screening of at-risk relatives has been advocated, and in fact has been recommended as a guideline by the Heart Failure Society of America [24]. This provides the basis to intervene, minimally with conventional medical therapy, with early DCM to mitigate late phase disease.

HCM

With a prevalence of 1/500 [31], HCM, a panethnic condition, has long been studied and recognized as a cardiovascular genetic phenotype. The key diagnostic feature is left ventricular hypertrophy in the absence of severe, uncontrolled hypertension, aortic stenosis, or physiologic adaptation due to athletic training. The clinical presentation may include chest pain, or presyncope or syncope from left ventricular outflow tract obstruction, which increases the risk for heart failure and sudden cardiac death [32–34]. Signs and symptoms may present in puberty, but infant and later onset HCM also occurs [35]. Symptoms of heart failure can be present late in the disease process.

The proportion of HCM that is familial, based on recent literature and observational clinical experience, appears to be approximately 30% [36]. More than 20 genes, most sarcomeric, have been reported in association with HCM [37]. Autosomal dominant inheritance is most common, but X-linked inheritance occurs with *LAMP*-related HCM and *GLA* variants. Digenic forms are observed in 3–5%, and are usually associated with severe, early onset disease [38, 39]. Founder HCM-causing variants in *MYBPC3*, one of the main HCM genes, are responsible for 35% of HCM in the Dutch population [40].

The likelihood of a positive genetic testing result is higher with young age of onset (< 45 years old), severe hypertrophy (>20 mm), and with a family history of HCM and sudden cardiac death. The proportion of genetically confirmed sporadic cases is approximately 30% [36].

ARVC – Arrhythmogenic Right Ventricular Cardiomyopathy

ARVC is a genetic condition characterized by right ventricular myocyte loss that leads to right ventricular enlargement, fatty infiltration, and wall thinning. Task Force diagnostic criteria have been developed [41]. Left ventricular involvement with heart failure can occur, which can precede right ventricular manifestations or even be the presenting feature [42, 43].

Estimates suggest a prevalence of 1/2000 [44]. The clinical presentation includes arrhythmia and sudden cardiac death. Onset usually occurs between ages 10–50 years old. Exercise is a known risk factor for arrhythmia [45] and clinical features have been reported to be more common in men [46].

Approximately 50% of individuals with ARVC have an affected family member [47]. To date, 7 genes have been reported with ARVC, five of which encode desmosomal proteins. Variants in these 7 ARVC genes account for 40–50% of cases (including sporadic cases) [48]. Most cases are autosomal dominant, and multiple variants in the same or multiple genes have been reported to mediate the phenotype [49].

RCM – Restrictive Cardiomyopathy

Idiopathic RCM is rare, but it affects individuals from all races and ethnic backgrounds. RCM is characterized by elevated ventricular filling pressures from reduced diastolic compliance, usually in the setting of relatively preserved systolic function. A variety of genetic factors may be involved, although all of RCM does not fit into a genetic paradigm. Of the most common causes, amyloidosis, iron overload, and sarcoidosis, the first two may have a genetic basis (e.g, *TTR*-based amyloid, and hemochromatosis) and are part of a genetic evaluation [50]. Cardiac arrest and skeletal myopathy [51, 52] can also rarely be observed with RCM.

Family history of cardiomyopathy has been reported in approximately 30% of children with idiopathic RCM [53]. In these families, autosomal dominant inheritance is most commonly observed. Genetic data on RCM is slowly emerging. While an accurate estimate of the proportion of genetically confirmed familial and non-familial cases remains unknown, approximately 10 genes have been identified in association with RCM, accounting for 30–50% of cases [53]. There is remarkable overlap between the genes causing HCM and those causing RCM. In fact, a restrictive physiology is observed in some HCM patients [54].

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) leads to right sided heart failure from abnormal constriction of the pulmonary microvasculature and compensatory pulmonary artery hypertension. The clinical presentation includes symptoms of right-sided heart failure, as well as chest pain, palpitations, and syncope. Data from the Primary Pulmonary Hypertension Registry showed that enrolled patients had a mean age at diagnosis of 36 years, with a male:female ratio of 1:1.7 [55], however, these trends have not been uniformly observed [56]. The phenotype is identified by right heart catheterization and exclusion of other causes of pulmonary hypertension, namely, disease arising from left-sided heart failure, lung disease, pulmonary embolism, hereditary hemorrhagic telangiectasia, and pulmonary veno-occlusive disease, among others [55–57]. Clinical under recognition has confounded an accurate assessment of PAH, but the incidence has been estimated at 1–2/ million population per year [58].

Familial PAH is classically autosomal dominant [59] with an estimated overall penetrance of 27% [60], although higher penetrance figures have been reported in females [61]. Six genes have been identified to date, five of which are involved in the TGF-beta signaling pathway [62–66]. Variants in *BMPR2* are by far the most common, accounting for approximately 75% of familial and 15% of non-familial cases [67].

Familial Hypercholesterolemia

Elevated LDL cholesterol is associated with an increased risk for CAD, which in turn causes angina, myocardial infarction, ischemic cardiomyopathy, or cardiac arrest. Severely elevated cholesterol (LDL-C >190; >160 mg/dL in children and adolescents) [68, 69] promotes early-onset CAD (usually < 60 years of age) and in some, clinical findings such as xanthomas and corneal arcus [70]. These cases may be explained by familial hypercholesterolemia (FH), a Mendelian condition [71].

Approximately 1/200 individuals of European descent have been found to have FH [72–74], but higher prevalence figures have been reported in some ethnic groups: 1/67 in individuals of South African Ashkenazi Jewish descent and 1/85 in Lebanese Christians [75].

FH is suspected when an individual presents with untreated, severely elevated LDL-C or total cholesterol with or without a family history of heart and vascular conditions associated with elevated cholesterol. To date, variants in 4 genes involved in lipoprotein processing or transport have been reported to cause FH [76]. Most FH-causing variants are found in the LDL receptor (*LDLR*). The condition is mostly recognized as autosomal dominant [76], but co-dominant (in which an alteration is found in both members of the gene pair, leading to severe disease) and recessive inheritance (with *LDLRAP1* variants) is also observed [76]. Cholesterol levels > 500 mg/dL with severe, early onset disease, usually around age 20, suggests homozygous and compound heterozygous forms [77]. Several models have been developed to assess the possibility of FH, namely, the US MEDPED Program, UK Simon Broome Familial Hypercholesterolemia Registry, and the Dutch Lipid Clinic Network [78, 79]. When diagnostic criteria for these models are met, the probability of identifying a FH-causing genetic variant is approximately 80% [80], however, in our clinical practice we have identified relevant variants in individuals who do not meet diagnostic criteria. Up to 3% of individuals with FH have variants in the *PCSK9* gene [81]. The molecular mechanism of this gene, whose normal function is to regulate the number of LDL receptors, has been leveraged in the development of *PCSK9* inhibitors, a promising drug class that can be effective in patients with FH [82, 83].

Elevated Lipoprotein A

Elevated (>25–30 mg/dL) lipoprotein A, or Lp(a), is an independent risk factor for CAD, stroke, myocardial infarction, and familial hypercholesterolemia [84–90]. The molecule consists of an apo(a) glycoprotein, apo-B100, and an LDL-like particle [91]. The apo(a) component (coded by the *LPA* gene), has homology to plasminogen and includes a variable number of kringle-IV repeats that show inverse correlation with Lp(a) levels [91]. While elevation of Lp(a) can coexist with and possibly be triggered by FH (warranting direct monitoring for optimal risk reduction), elevated Lp(a) can be present in patients without FH with normal cholesterol levels and absent CAD risk factors. These individuals and their family members are at risk for heart disease, and should be monitored appropriately.

Although Lp(a)'s role in CAD risk has been known for some time, there is limited literature guiding a clinical genetics approach to this biomarker. A 1992 study reporting on 48 Caucasian families showed that the *LPA* gene accounts for 91% of the variability seen in

Lp(a) levels. Another study reported that elevated Lp(a) appears to be inherited in an autosomal co-dominant pattern [92]. Affected family members have CAD, myocardial infarction, and stroke. While repeat kringle-IV repeat length and specific variants (rs10455872 and rs3798220), have been reported to influence Lp(a) levels and CAD risk [84, 85], there does not appear to be clinical utility for *LPA* genetic testing at this time: gene product testing is equally informative and more affordable than a molecular genetic test.

Genetic Evaluation

For patients with heart failure, we recommend a genetic evaluation to identify the phenotypes reviewed here, even if the family history is negative. Besides careful phenotyping, a genetic evaluation includes gathering family history, genetic testing, and at-risk relatives' evaluation in the setting of genetic counseling.

Family History

A three-generation family history should be obtained in any individual with HF in an attempt to identify an underlying heritable cause. Family history reports may include specific diagnoses (such as idiopathic DCM) or descriptions suggesting a particular phenotype (such as "thickened heart muscle" in HCM).

During family history intake, risk factors suggesting a non-genetic or multifactorial etiology (cigarette smoking, high blood pressure) must be assessed, as their absence suggests the presence of a genetic defect. Non-specific reports require further inquiry, including questions aimed at investigating the type of heart failure (right sided heart failure can be a clue to the presence of PAH), systolic dysfunction versus restrictive physiology (restrictive physiology may suggest RCM), ischemic versus non-ischemic disease (reports excluding an ischemic cause can help to narrow down the investigation to primary cardiomyopathies). Asking about procedures in relatives and their timing in relation to the onset of DCM can be informative. For instance, coronary bypass and angioplasty suggest CAD as the underlying etiology in these cases, but only if the CAD occurred before the identification of DCM.

In our experience, most patients report a negative or uninformative family history. We suggest screening for heart disease in family members by asking about a history of heart failure signs/symptoms (sleeping with more than one pillow, recurrent coughing/wheezing, fatigue, painful breathing), stroke, palpitations, dizziness, and or chest pain, or evidence of procedures clearly linked to cardiovascular disease (heart transplant, ventricular assist device, implantable defibrillators, pacemakers, coronary artery bypass grafting, valve repair or replacement or other cardiac operations).

While familial disease may manifest clear evidence of autosomal dominant disease (disease in every generation, similar numbers of affected males and females, and male-to-male transmission), these features may be absent due to reduced penetrance, variable expressivity, bilineal and *de novo* disease. Obtaining detailed family history information, ideally in pedigree format, is important to assess these features [93].

Cardiovascular Screening

The genetic evaluation also includes making recommendations for cascade, periodic cardiovascular screening in family members (Table 1). This screening may identify a phenotype, forming the basis for familial disease in a simplex case. Discussing the indication and rationale for family members' cardiac screening before discussing genetic testing can be a helpful strategy. Doing this can help avoid confounding the conversation about the proband's likely genetic etiology based on clinical evaluation (and need for relatives' screening) with the benefits of genetic testing (which is often misunderstood to inform if an individual's condition is genetic). Once the rationale for cardiovascular screening of family members has been established, genetic testing may be presented as a tool to identify who, among the family members for whom screening has been recommended, can be discharged from cardiac surveillance.

Genetic Testing

Table 1 summarizes available genetic testing for the conditions reviewed here. For all conditions, except Lp(a) elevation, genetic testing of a group of genes (panel testing) is most useful. Both the Genetic Testing Registry (<https://www.ncbi.nlm.nih.gov/gtr/>) and GeneTests (<https://www.genetests.org/tests/>) list commercial and research laboratories offering genetic testing. This testing is most informative when ordered in the most clearly affected individual in the family first. If a disease-causing variant is identified in the affected individual, periodic screening of family members is no longer recommended for the at-risk family members who test negative for the family variant. Thus, the key utility of genetic testing is to predict risk in relatives.

In clinical genetics, the evidence supporting a genetic etiology may be masked by several factors: asymptomatic disease may be present in relatives (which, if detected, would form the basis for a familial diagnosis, and thus, supporting a genetic basis); most cardiomyopathy shows age-dependent penetrance (a relative with negative cardiovascular screening may develop disease over time); and, in our experience, disease may result from the combination of multiple variants which alone are insufficient to be pathogenic; and finally, the sensitivity of genetic testing is far less than 100%, which means that an affected patient may have a variant in gene that is not yet discovered. For all of these reasons, genetic testing should be offered to individuals with the phenotypes listed in Table 1, regardless of whether familial disease is present. Furthermore, in some patients genetic testing can be useful to clarify a diagnosis when confounding factors are present. For example, finding a HCM-causing variant in an individual with a history of severe hypertension has clinical utility for the patient and his/her family.

Significant overlap is present between HCM, DCM, and RCM genes. Clinical overlap between these entities may also be observed, including, for instance, left ventricular hypertrophy (characteristic of HCM) with a low ejection fraction and left ventricular enlargement (features of DCM). Similarly, in our experience, the restrictive phenotype (characteristic of RCM) may be observed with features also suggestive of HCM or DCM. For these reasons, in our practice, we offer a comprehensive cardiomyopathy panel (which includes genes for all forms of cardiomyopathy) for both DCM and RCM. For HCM without

features of other cardiomyopathies, we restrict testing to only HCM-associated genes, owing to the fact that most variants are found in three genes: *MYH7*, *TNNT2*, and *MYBPC3*. Providers ordering genetic testing must be well equipped to interpret the results of a genetic test performed in an affected individual. Variants may be classified as pathogenic, likely pathogenic, of uncertain significance, likely benign, or benign. The strength of evidence favoring disease causation for a variant is mainly driven by available case and family data [94]. While genetic testing laboratories provide an interpretation, providers should be aware that laboratories may incorrectly adjudicate a variant because of, for example, suboptimal interpretation criteria or limited access to case data, which can lead to medically significant discrepancies. Therefore, the following should be considered when interpreting genetic testing results: comprehending the rationale that the laboratory provided to classify a variant, understanding the data associated with the variant (including any published literature, as cited in the laboratory report), accessing ClinVar (a repository of variants identified by laboratories and their clinical significance, www.ncbi.nlm.nih.gov/clinvar/)[95] to identify any conflicts in variant interpretation, and contacting the reporting laboratory to clarify information or reconcile any discrepancies.

In cardiovascular genetics, a non-negligible number of results will be returned with variants of uncertain significance. Providers ordering this type of testing must be able to discuss these findings, including the need, if applicable, for family segregation studies in an attempt to solve the variant. With new data or updated variant analysis algorithms, laboratories may reclassify a variant and release an updated report to the ordering provider. After verifying the basis for reclassification, these updates should be reported to the patient. The need and indication for variant testing of family members may also be revisited in these cases.

Genetic Counseling

A cardiovascular genetic evaluation should always be conducted in the context of genetic counseling [96]. Advanced genetic counseling practice involves understanding family dynamics to promote communication and adaptation to genetic risk. In genetic counseling, the family is the unit of care, and preventive care for at-risk family members is an essential goal. Genetic counseling is a patient-centered process that demands the ability to effectively communicate with children and adults of all cultural backgrounds and literacy levels. The process may require repetition and review over the course of multiple interactions. In every case, relationship-building should be prioritized, which can in turn increase trust, and, eventually compliance.

Conclusion

Heart failure causes significant morbidity and mortality, and is the culmination of varied forms of inherited or acquired heart disease. This complex syndrome may result from myocardial infarction and resultant ischemic cardiomyopathy or from non-ischemic disease resulting from a primary cardiomyopathy. In the majority of cases, genetic information is not currently useful for prognostic or therapeutic decisions. However, in those cases with possible genetic cause, a genetic evaluation that identifies specific genetic cause in many cases has implications for the family. This then can lead to cardiovascular surveillance to

avoid the onset or development of heart failure in at-risk family members. Experience suggests that a team-based approach to the genetic evaluation of heart failure, including both cardiology and medical genetics professionals, is most clinically useful. A genomic approach to heart failure research is essential to move the field ahead with novel gene discovery and mechanistic insights that enable better treatment for heart failure.

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Figure 1. Disease Model: Dilated Cardiomyopathy and Heart Failure

This figure portrays DCM and HF as separate entities. The causative hit, depicted by a thick blue arrow, includes genetic cause, depicted here as one high probability Mendelian mutation although other genomic models are possible, if not likely (9, 12). The causal pathways from normal heart to DCM and from DCM to HF are shown by the two other blue arrows. The causal pathway to DCM may take years and is asymptomatic until very late in its causal pathway when HF, arrhythmia or embolus (from mural thrombus) present. Because of the biological complexity and epidemiological impact of HF, its causal pathway from DCM is shown, although pathways from DCM to arrhythmia and embolus are also relevant. Factors that may accelerate these causal pathways are depicted with green arrows for DCM (A) or HF (B); environmental examples include hypertension, alcohol use, etc, while genomic factors include unfavorable genotypes (risk alleles). Other factors that may delay or arrest progression to DCM or HF are shown in red (C, D); such factors could include favorable environmental factors, e.g., good nutrition, a low salt diet, low blood pressure, drug therapy with ACE inhibitors or β -blockers, or genomic factors such as a protective alleles. Acute HF, e.g., from a large anterior wall myocardial infarction, is shown with a dotted line (E); in this situation the acute onset of HF may cause DCM subacutely (F), although the degree that genomics plays a role in DCM resulting from acute HF is uncertain, as most studies have focused on chronic HF. Also, whether chronic HF modulates or exacerbates the DCM causal pathway (A) itself remains poorly defined. The disordered HF physiology also feeds back onto itself, the so-called vicious cycle of HF (G). Reprinted from Journal of the American College of Cardiology, Vol 60, Issue 4, Authors: Sanaz Piran, Peter Liu, Ana Morales, and Ray E. Hershberger, in: Where Genome Meets Phenome: Rationale for Integrating Genetic and Protein Biomarkers in the Diagnosis and Management of Dilated Cardiomyopathy and Heart Failure, Pages 283–289, Copyright (2012), with permission from Elsevier.

Table 1

Etiologies of Heart Failure with a Known Genetic Basis.

Condition	Prevalence	Onset	Presentation	Key cardiac tests and procedures	Inheritance	# of genes, detection rate	Known genes	Cardiovascular screening of family members ⁷ if genetic testing is not performed, reveals a VUS or is negative in the proband	2 Cardiovascular screening of family members when positive for a known likely pathogenic or pathogenic family variant
Non ischemic, left sided heart failure									
DCM	1/200	20–60 y	Heart failure, sudden death, stroke	Echo/MRI: left ventricular enlargement, low ejection fraction; angiogram: negative; other causes excluded	AD, AR, XL	>30, 40%	LMNA, MYH7, TNNT2, RBM20, TTN, BAG3, SCN5A, TPM1, PLN, TNNC1, TNNT3, EYA4, MYPN, MYBPC3, MYH6, LAMA4, VCL, LDB3, TCAP, PSEN1, PSEN2, CRYAB, ABCC9, ACTC1, PDLIM3, ILK, SGCD, DES, CSRP3, ANKRD1, NEXN, NEBL, FLNC	Echocardiogram and ECG every 3–5 years	Echocardiogram and ECG, every year
HCM	1/500	puberty	Sudden death, chest pain	Echo: left ventricular hypertrophy; no hypertension or athlete's heart	AD, XL	>20, 40–70%	ACTC1, ACTN2, ANKRD1, CSRP3, FXN, GLA, JPH2, LAMP2, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYOZ2, MYPN, NEXN, PLN, PRKAG2, PTPN11, RAF1, TCAP, TNNC1, TNNT3, TNNT2, TPM1, VCL	Echocardiogram, ECG, Holter, stress test every 3–5 years	Echocardiogram, ECG, Holter, stress test every year
RCM	rare	>30 y	SCD, heart failure, skeletal myopathy	Echo: diastolic dysfunction; biopsy: no amyloidosis,	AD	10, 30–50%	TNNI3, TNNT2, MYH7, ACTC1, TPM1, MYL3,	Echocardiogram and ECG every 3–5 years	Echocardiogram and ECG, every year

Condition	Prevalence	Onset	Presentation	Key cardiac tests and procedures	Inheritance	# of genes, detection rate	Known genes	Cardiovascular screening of family members ¹ if genetic testing is not performed, reveals a VUS or is negative in the proband	² Cardiovascular screening of family members when positive for a known likely pathogenic or pathogenic family variant
ARVC	~1/2,000	~30 y	SCD triggered by (athletic) activity, ventricular arrhythmia, heart failure; symptoms	Echo/cMRI: RV dilation, motion abnl; cMRI/biopsy: RV fibro-fatty replacement; ECG: ventricular tachycardia, inverted T waves; ICD placement, heart transplant	AD, AR (rare)	7, 40–50%	<i>DSC2, DSC2, DSP, JUP, PKP2, TGFB3, TMEM43</i>	Echocardiogram, ECG, signal averaged ECG, and Holter evaluation every 3–5 years	Echocardiogram, ECG, signal averaged ECG, and Holter evaluation every year
Non ischemic, right sided heart failure									
PAH	rare	late 30s	heart failure signs and symptoms, chest pain, palpitations, syncope	Right heart catheterization: 25 mmHg PA pressure at rest; > 30 mmHg during exercise	AD	6, 78%	<i>BMPR2, CAV1, KCNK3, CAV1, SMAD9, BMPR1B</i>	Echocardiogram every 3–5 years	Echocardiogram, possibly every year
Ischemic, left sided heart failure									
FH	1/200	< 65 years	CAD, myocardial infarction, heart failure, stroke, peripheral vascular disease, xanthomas, corneal arcus	total cholesterol > 300 mg/dL and LDL-C > 190 mg/dL in adults.	AD, codominant	4, 80%	<i>POB, LDLR, PCSK9, LDLRAP1</i>	Cholesterol evaluation before age 10. Lp(a) should be monitored as well.	
Elevated Lp(a)	Not known	Not known	CAD, myocardial infarction, heart failure, stroke	Lipoprotein A > 25–30 mg/dL, normal cholesterol	AD	1, not known	<i>LPA</i>	Lp(a) evaluation starting in adolescence.	

Abbreviations: VUS, variant of uncertain significance; DCM, dilated cardiomyopathy; AD, autosomal dominant; AR, autosomal recessive; XL, X-linked; HCM, hypertrophic cardiomyopathy; SCD, sudden cardiac death; ARVC, arrhythmogenic right ventricular cardiomyopathy; RV, right ventricular; PAH, pulmonary arterial hypertension; FH, familial hypercholesterolemia; CAD, coronary artery disease

¹ Cardiovascular screening may begin in childhood, or as concerns arise

² Cardiovascular screening of family members when negative for a known likely pathogenic or pathogenic family variant is not recommended.