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Clinical Screening and Genetic Testing

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Clinical screening lies at the heart of preventive medicine, because identification of a disease in its earliest form offers an opportunity to intervene and disrupt its expected deleterious course. In cardiovascular medicine, clinical screening is most effective in diseases such as hypercholesterolemia, where the disease in its earliest form may not have symptoms or signs but can be readily diagnosed with an inexpensive, noninvasive test. Other aspects of a disease like hypercholesterolemia also make a systematic screening program successful: it is relatively common, it has serious consequences such as myocardial infarction, and it is treatable, with the likelihood of adverse sequelae being reduced significantly by treatment. These and other criteria are used by groups, such as the US Preventive Task Force, to develop recommendations for screening programs (http://www.ahrq.gov/clinic/USpstfix.htm).

Genetic screening is a form of screening used for diseases with a significant heritable component. It involves searching for a one or more DNA variants in individuals believed to be at risk for a disease, where the DNA variant is believed to contribute to disease incidence or progression. Before comparing genetic and clinical screening, it would be helpful to review some aspects of the genetic basis of disease.

Genetic diseases lie along a continuum ranging from mendelian disorders to complex diseases, which arise from the interaction of a number of genetic and environmental factors. Mendelian disorders typically arise from a mutation in a single gene and have a sufficiently dramatic effect in that those who inherit the genetic mutation typically inherit the disease. The concept of penetrance captures the distinction between genetic variants contributing to Mendelian disorders and complex disease traits. Penetrance for a genetic mutation is defined as the proportion of individuals carrying a particular genetic mutation who also demonstrate the disease phenotype. The mutations that lead to Mendelian disorders have very high penetrances (approaching 100%); whereas, for most variants contributing to complex

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disease, the penetrance is quite low. This concept has significant relevance in the discussion of the utility of genetic screening.

The concept of genetic architecture describes the number of genes contributing to a disease trait, the number of variants per gene, and the magnitude of effect that each variant has on development of the trait. Although Mendelian disorders usually arise from inheritance of a single genetic mutation, many different individual genes may, when mutated, lead to a common disease phenotype (genetic heterogeneity). Furthermore, for any gene, many different mutations may also lead to the same disease phenotype (allelic heterogeneity). Both genetic and allelic heterogeneity introduce complexity when one goes about designing a genetic screening program for cardiomyopathies. Furthermore, although the penetrance of a disorder may be high, the exact manifestation of disease may vary from individual to individual, despite inheriting the same mutation (variable expressivity). A final level of complexity arises from the fact that multiple distinct diseases may share a common “low-resolution” phenotype, but in fact have a different pathologic basis (termed phenocopies), with potentially different disease course and treatment.

Genetic screening differs from clinical screening in several regards. Rather than serving as a way of diagnosing disease in asymptomatic individuals, the identification of a risk variant in an individual can give the probability of disease risk in individuals who may not yet have disease. Acting on this information may not only allow prevention of disease progression, but also the prevention of disease incidence, the “holy grail” of medicine. A second difference is that discovering that individuals with subclinical disease have a genetic risk variant may provide insight into the biologic basis of disease for that individual. For clinically heterogeneous diseases, such as atherosclerosis or hypertension, understanding the driving pathophysiologic progress may allow targeted therapy that may surpass the efficacy of the “one treatment fits all” approach commonly used. Moreover, with some limitations, knowledge of the causal process may permit a more accurate prognosis of catastrophic outcomes, such as sudden cardiac death or stroke, and allow the focused implementation of screening or preventive therapeutic procedures that may be too costly or risky for the general population, but have high likelihood of benefit for a limited number of high-risk individuals.

When should genetic screening used? An example may help illustrate the approach used for potentially heritable disorders. Consider an individual with a disease that does not appear to be arising from any known environmental cause—in genetic studies, this individual is called the proband. An initial step should be to establish whether the disease is familial, as this has relevance to pursuing a genetic diagnosis for the individual and on managing risk within family members. In addressing familiality, one must construct a careful family pedigree, asking about the health and manner of death of every relative. One needs to be careful to distinguish two apparently similar situations with considerably different ramifications: one where detailed pedigree information is available and no disease is apparent versus another where there does not appear to be any other relative with the disorder but inadequate family history is obtained. Only in the former case could one conclude that the disease is not familial but, instead, sporadic or attributable to environmental factors. If the proband has multiple relatives with the disorder, one would consider it to be familial and consider genetic screening.

The next considerations are related to the likelihood of identifying a causal variant in the proband. If the genetic architecture of the disease is such that there are a relatively small number of genes (low genetic heterogeneity) involved and there are causal genetic variants of moderate-to-high penetrance, genetic screening can be useful. Because many Mendelian disorders show significant allelic heterogeneity, screening for a single mutation tends to be unsuccessful and sequencing of portions of the gene (exons, splice junctions) tend to be required to find likely causal variants. Several limitations exist with genetic testing of a single proband. Sequencing errors can occur, resulting in false positives and false negative results. Even with careful sequencing, a variant may be found in one of the candidate genes but not actually be causal for the disease. To establish a sequence variant as a potential mutation requires that it have the potential to have a deleterious effect (missense or nonsense) and lie within a protein domain previously attributed functional significance. A mutation that is falsely assigned causality and used for genetic screening in family members would lead to both false reassurance and false alarm, as the inheritance of the variant would have no bearing on the likelihood of developing the disease. This situation may be ameliorated if a large number of family members are available for genetic testing, as cosegregation of mutation with disease can be used to infer causality.

How useful would the identification of a genetic variant be? Because of the bewildering genetic and allelic heterogeneity of most Mendelian disorders, the individualized prognostication and treatment that was once hoped to follow genetic diagnoses has not materialized. There is simply not enough prognostic information for individual mutations to provide mutation-specific predictions with any accuracy. As a result, the current utility of identifying a causal mutation in a proband is almost exclusively limited to facilitating screening of family members. In particular, with the help of genetic screening, it can help identify affected individuals at a preclinical phase or those with ambiguous clinical screening results.

A “cascade screening” approach allows an efficient method of evaluating which family members carry the causal allele. Once a genetic diagnosis of the proband is made, all of the first-degree relatives of the proband are screened. One can limit further genetic screening to first-degree relatives of the proband’s affect first-degree relatives. This process continues until no further affected individual is identified. Genetic diagnosis allows a considerable degree of reassurance to family members who are genotype-negative, as they no longer need clinical surveillance and need not worry that disease will be passed on to their progeny. Conversely, a positive diagnosis in a clinically unaffected individual may lead to initiation of more frequent surveillance, avoidance of high-risk behavior, implementation of preventive treatment, and potentially it may affect reproductive choices. Of course, as discussed above, the success of such an approach depends fully on confidence that the mutation used for screening is actually causal.

If a causal genetic variant cannot be definitively established for the proband, clinical screening should then be considered, as it can be useful in many of the same ways as genetic screening. Cascade screening, described above, cannot work for clinical screening because of incomplete age-dependent penetrance, which may lead to premature termination of screening if any individual failed to display features of the disease. Thus, all relatives of the proband should be screened, typically at least one level beyond the last affected generation. The age of screening typically depends on the range of age of onset for the disease.

One can apply the above considerations to any disease with a heritable component. Below, the authors will address the screening approaches to dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular dysplasia (ARVD), and restrictive cardiomyopathy (RCM), highlighting how the known genetic architecture of the trait guides a genetic screening approach and how clinical characteristics of the disease influence a clinical screening approach.

HCM

The genetic architecture of hypertrophic cardiomyopathy (Table 1) makes it amenable to genetic diagnosis. HCM appears to be familial in approximately 50% of cases and the inheritance pattern in documented cases is almost always autosomal dominant with high penetrance.[1,2] There are 12 known genes responsible for this disorder (not including several phenotypic mimics),[3] and mutations in the exons or splice junctions of one of eight sarcomeric genes explain approximately 50% to 60% of cases.[4] There are now several academic or commercial tests available for genetic screening. The Center for Genetics and Genomics at Harvard Medical School offers a $3000 screening test for 106 exons and splice sites of five sarcomeric genes (MYH7, MYBPC3, TNNT2, TNNI3, TPM1), and an additional $1150 screening test for 19 exons and splice sites in three other genes (ACTC, MYL2, MYL3) (http://www.hpcgg.org/LMM/comment/HCM%20Info%20Sheet.htm). Similarly, several companies offer comparable services for a range of genetic conditions. Despite the availability of commercial sequencing services, the prevalence of HCM, which is 0.2% to 0.5% of the general population, is too low to justify screening of the general population.

The allelic heterogeneity of HCM, which includes over 400 causal mutations, makes individualization of treatment and prognosis based on genetics implausible. It is highly unlikely that for any mutation adequate samples will ever be assembled for a reliable estimate of risk. Furthermore, incomplete penetrance and variable expressivity within families further erode confidence in the predictive utility of mutations. Attempts to prognosticate on the basis of genetic mutations have been difficult to replicate and designations of mutations as benign or malignant are often based on observational studies in small numbers of families.[5] It is, of course, expected that some mutations will have a more deleterious impact on protein function than others—but to extrapolate the clinical impact of a single mutation from a small number of individuals to others with different genetic and environmental backgrounds should only be undertaken with caution.

Thus, at present, a genetic diagnosis is most useful for screening relatives of the proband, with a cascade-type approach, as described above. If a genetic diagnosis is not pursued or made, clinical screening can be performed using ECG and echocardiography.

Echocardiography has greater specificity, although ECG findings may precede changes in left ventricular (LV) thickness. ECG abnormalities, even in the absence of LV hypertrophy on echocardiography are suggestive for affected status, especially given the high pretest probability of disease in first-degree relatives.

There is uncertainty as to the age at which clinical screening should be initiated or terminated. Given the concern for sudden death in child athletes, an early diagnosis of HCM in children has clear relevance to mitigating risk. Furthermore, as multiple HCM variants can show clinical onset late in life,[6] it is unclear if screening can be stopped confidently at any age. Maron and colleagues[6] have recommended optional screening for age less than12 years (unless family history of premature sudden death, symptoms, or plan to pursue strenuous sporting activity), 12 to 18 month screening intervals for children between 12 and 18 to 21 years old, and screening every 5 years for ages greater than 18 to 21 years. Although representing a rational approach, there have been no efforts to validate this strategy in any large population for cost-effectiveness or influence on morbidity or mortality.

A preclinical diagnosis of HCM, either through genetic or clinical screening, leaves one with the opportunity to make clinical decisions before disease onset. Unfortunately, there are no clear options for treatment to alter the course of disease. Sudden death in HCM is certainly the most dreaded sequelum and the possibility exists of implanting a defibrillator for primary prevention. Unfortunately, one cannot be confident which HCM patients will benefit most from this therapy. At present, just as with ischemic cardiomyopathy, the best predictor of sudden death in HCM patients is a personal history of cardiac arrest: 59% of individuals with one episode of cardiac arrest have a second one within 5 years.[7] However, in the absence of a prior cardiac arrest, the criteria for risk prediction become less clear. A personal history of unexplained syncope or a family history of sudden cardiac death[8] has modest additional predictive utility. The caveats described above that apply to establishing familiality also apply to establishing a family history for sudden death—one must be concerned if there are simply not enough family members on which to base a negative conclusion. In other studies, features such as LV wall thickness, nonsustained ventricular tachycardia, and abnormal blood pressure response in exercise have been implicated as potential predictors of sudden death, but these studies did not account for familiality and no formal validation of any of these prognostic models has occurred.

DCM

DCM is considerably more complex than HCM, both in terms of genetic architecture and known contributing environmental factors. Coronary artery disease, nutritional deficiency, viral infection, and toxins such as alcohol can cause DCM, though familial predisposition may continue to play a role in many of these cases. The prevalence of DCM may be as high as 1 in 2500 adults.[9] Given that the histologic findings of DCM are nonspecific with myocyte loss and interstitial fibrosis, a diagnosis of idiopathic DCM requires an extensive work-up to exclude other causes, some of which may prove to bereversible.[10]

Over 20 genes have been implicated in the pathogenesis of DCM, with autosomal dominant, recessive, and X-linked patterns of inheritance (see Table 1).[11] Penetrance is often low, and expressivity varies considerably from individual to individual. Dilated cardiomyopathy can be syndromic, with other accompanying systemic abnormalities such as the skeletal muscle dystrophies and retinal disease.[12] Given the fact that mutations in DCM are distributed widely over a large number of different potential causal genes, there is usually too low a likelihood of success to recommend genetic sequencing or genetic screening. It is the associated cardiac and noncardiac findings that can help narrow the diagnosis. For example, in one small study, if atrioventricular block accompanied DCM, there was a mutation found in the lamin A/C gene in one-third of cases.[13]

As with all cardiomyopathies, it is challenging to predict risk for particular mutations. One exception may be a tendency for DCM caused by lamin A/C mutations to demonstrate a high rate of malignant arrhythmias in patients with conduction abnormalities.[14] This finding has not been replicated.

Although the complexity of DCM precludes genetic screening, clinical screening can often be very useful. Moreover, an early diagnosis in asymptomatic family members of the proband allows the initiation of potentially disease-modifying agents such as angiotensin-converting enzyme (ACE)-inhibitors (see below). Clinical screening is performed by echocardiography and ECG. Individuals with ECG abnormalities or mild echocardiographic abnormalities (mildly depressed systolic ejection fraction or mild LV enlargement) should be followed with screening that is more frequent. As with HCM, there are no explicit evidence-based guidelines for screening, although it would be reasonable to begin in childhood and continue at periodic intervals into late adulthood. For every affected individual, care must be taken to exclude age-appropriate, potentially reversible causes (eg, tachyarrhythmia, coronary artery disease, alcohol) as these may contribute to disease even in the context of an inherited tendency.[15]

The forbidding genetic and phenotypic heterogeneity of DCM makes genotypebased treatment unlikely. Clinical guidelines recommend ACE-I and beta blocker use for all dilated cardiomyopathies, independent of cause,[16] and automatic implant-able cardio-defibrillator implantation in symptomatic individuals with severe LV dysfunction. It is unclear if early initiation of ACE-I or beta blockers mitigates the disease course in individuals with mild echocardiographic abnormalities, or exclusively ECG abnormalities. The authors tend to favor the use of ACE-I in such cases, given the efficacy in asymptomatic LV dysfunction of all types.

ARVD

ARVD is a genetically heterogeneous disorder, with 12 current genetic loci (ARVD1–12) identified through linkage studies (see Table 1).[17] Causal genes corresponding to eight of these loci have been found, with five encoding desmosomal proteins. The prevalence of ARVD is unknown but has been estimated at 1:1000 to 1:5000 individuals.[18] ARVD is familial in nearly 50% of cases[19] and inheritance is usually autosomal dominant, with variable expressivity and incomplete penetrance.

The routine diagnostic workup of a patient suspected to have ARVD includes ECG, Holter monitor, signal-averaged ECG, echocardiogram, and potentially cardiac magnetic resonance.[20] If the clinical and family history and these initial studies raise a high suspicion for ARVD, endomyocardial biopsy can be performed for confirmation and an electrophysiology study may be useful to exclude benign right-ventricular outflow-tract tachycardia. The above diagnostic tests have been incorporated into task force criteria (TFC) for the diagnosis of ARVD (see Table 1).[21]

The frequency distribution of causal genes appears to vary with geography and demography although a large percentage (up to 43%) of cases can be explained by mutations in the plakophilin 2 (PKP2) gene.[22,23] As with HCM, allelic heterogeneity is present, with over 50 PKP2 mutations currently known.[17] The penetrance of ARVD mutations appears lower than HCM, potentially due to the insensitivity of the TFC.[19,24] Sequencing of the most commonly mutated genes may be useful in identifying family members of the proband who require long-term clinical follow-up, especially since correct identification of affected individuals may be useful in prevention of sudden cardiac death. Toward those ends, the Center for Genetics and Genomics at Harvard Medical School also offers sequencing of 69 exons and splice sites for the four most common genes mutated in ARVD (PKP2, desmoplakin, desmoglein 2, and desmocollin 2), for $3000. It is unclear what percentage of probands will be identified through this assay. Once a mutation is found, additional family members can be screened at a cost of $250 each.

As with HCM, the relevance of genetic diagnosis to prognostication or individualiza-tion of therapy is limited by the fact that most mutations identified to date are rare and “private” to individual families.[25] Futhermore, given incomplete penetrance and variable expressivity within families, it is unclear to what extent one can extrapolate the sudden-death risk from one family with a given mutation to another, even if they share the same mutation. Given the wide range of effects that mutations can have on protein function, ranging from little to no change in activity to severe dominant negative action, it is highly unlikely that investigators will be able to define a common risk profile for all mutations of a single gene, such has been proposed for desmoplakin[26] and PKP2.[27,28]

If a genetic diagnosis cannot be made for the proband, clinical screening of family members would occur initially by ECG and echocardiogram. Abnormalities on either of these would result in further testing as described above, with a low threshold for declaring a positive diagnosis even if formal TFC are not met, given the high prior probability of disease. As a result of early onset of disease and the potential hazards of exercise on disease progression, screening for ARVD should begin in childhood. For genetic screening, all first-degree relatives should be screened initially, with cascade screening, as described above. If clinical screening is being performed, individuals who appear “negative” for disease should continue to be screened at some regular interval.[29] The late appearance of ARVD in some individuals[30] requires that screening should continue throughout adult life. Nava and colleagues[29] used a systematic (but uncontrolled) screening and prevention approach in 37 families with ARVD and demonstrated that frequent screening, initiation of anti-arrhythmics as needed, and avoidance of exercise led to very low mortality among affected individuals.

A similar approach could be extrapolated to asymptomatic individuals harboring a potential ARVD mutation.

Implantable cardio-defibrillator (ICD) implantation in patients with the diagnosis of ARVD remains an area of uncertainty. Piccini and colleagues[31] recommend ICDs for all ARVD patients meeting TFC, given the high risk of ventricular tachycardia, even in patients with no prior history of syncope or cardiac arrest. As with HCM, attempts have been made to identify high-risk diagnostic features with high positive predictive value for sudden cardiac death, such as right ventricular (RV) dysfunction, LV dysfunction and recurrent ventricular tachycardia.[32,33] A consensus on criteria for ICD implantation has yet to appear.

RCM

RCMs demonstrate several rare hereditary variants, including familial idiopathic restrictive cardiomyopathy and hereditary amyloidosis. Familial idiopathic RCM is extremely rare, with reports only in small case series.[34,35] No gene has yet been identified. Furthermore, in some families with HCM, individual members can show a pattern of restrictive filling with little or no LV hypertropy.[36,37] In a systematic analysis of 1226 relatives of HCM probands, this “restrictive phenotype” of HCM was seen in 1.5% of individuals and the diagnosis was accompanied by a high rate of dyspnea and mortality.

Hereditary amyloidosis represents a more common form of heritable RCM and typically involves a genetic defect in the transthyretin (TTR) protein or Apo AI protein leading to misfolded proteins and infiltration of the myocardium with amyloid fibrils. RCM shows allelic heterogeneity, with over 100 TTR mutations identified to date.[38] The inheritance pattern is usually autosomal dominant.

An RCM patient with evidence of a familial inheritance pattern should undergo right heart catheterization with RV biopsy to evaluate for infiltrative disease. If amyloid deposits are found, hereditary amyloidosis should be presumed and TTR sequencing performed to identify the causal variant. The identified variant can be used for genetic screening. If no amyloid deposits are seen, one should suspect an idiopathic variant, and clinical screening of family members by echocardiography and ECG should be performed.

Unfortunately, none of the treatment measures for RCM have shown to impact mortality. Loop diuretics, calcium channel blockers, beta-blockers, and ACE-inhibitors are commonly used for relief of symptoms.

SUMMARY

General principles of genetic disease architecture can guide screening and diagnostic approaches for all of the cardiomyopathies and, in fact, for all inherited diseases. At present, the primary benefit of identifying a causal mutation in a proband is to facilitate screening in family members. A preclinical diagnosis achieved through screening programs can allow initiation of further monitoring programs for disease development, avoidance of high-risk behaviors, and potential implementation of disease-mitigating therapies. Although there is considerable incentive to offer genotype-based forecasting for patients, allelic and genetic heterogeneity and variable expressivity have rendered such individualization of care highly unlikely. The ultimate desire for tailored prognostication and therapy is likely only to be realized when phenotypic profiles are generated that can integrate individual genotypic and environmental information, yet be common enough to allow accuracy in prediction and classification.

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Table 1

Genetic architecture of hypertrophic and dilated cardiomyopathies and arrhythmogenic right ventricular dysplasia

	HCM	**DCM**	**ARVD**
Prevalence	1/500	1/2500	1/1000–1/5000
Number of known causal genes	12	20	7
Number of known variants	>400	>50	>70
Familiality	50%	35%	30%–50%
Predominant patterns of inheritance	Autosomal dominant	Autosomal dominant, autosomal recessive, X-linked	Autosomal dominant, autosomal recessive
Potential preventive treatment	AICD	ACE-I, beta-blocker, AICD	Avoidance of exercise, AICD

Abbreviations: ACE, angiotensin-converting enzyme; AICD, automatic implantable cardio-defibrillator.