Role of Genetic Analyses in Cardiology
Part I: Mendelian Diseases: Cardiac Channelopathies
Silvia G. Priori, MD, PhD; Carlo Napolitano, MD, PhD

Abstract—Genetic analysis can be performed to identify the molecular substrate of inherited arrhythmogenic diseases; however, the role of this information in helping the management of patients is still debated. Here, we support the view that the practical value of genetic analysis is different in the various inherited conditions and that it is strongly influenced by the amount of information available in each disease about genotype-phenotype correlations. In some diseases, clinical management of patients is profoundly affected by the type of the underlying genetic defect; therefore, in these conditions, there is a high priority to introduce genetic analysis into clinical practice. In the absence of genotype-phenotype correlations, genetic testing still can be very useful when there is a clinical advantage in establishing presymptomatic diagnosis or when screening of family members may point to reproductive counseling. Finally, there is a high priority for introducing genetic testing for those genetic diseases in which a limited number of genes allow a high yield of successfully genotyped patients. We have developed a “score” to compare the value of genetic testing in arrhythmogenic diseases and to convey our view that the clinical role of genetic analysis is different in the various inherited cardiomyopathies and channelopathies. Healthcare authorities should become responsive to the advancement of knowledge in this field and should help facilitate access to genotyping for families affected by those conditions in which genetic analysis provides useful information for clinical management. (Circulation. 2006;113:1130-1135.)

Key Words: cardiomyopathy ▪ death, sudden ▪ genetics ▪ hypertrophy ▪ ion channels ▪ myocardium

In the last 20 years, the identification of the genes responsible for cardiomyopathies and ion channel diseases has opened the “molecular era” in the understanding of the pathophysiology of inherited arrhythmogenic diseases. A great deal of expectations arose the first few years after these discoveries. Along with the excitement for silencing the debates on the origins of diseases such as the long-QT syndrome (LQTS) or hypertrophic cardiomyopathy (HCM), identification of causative genes raised the expectation for a rapid transition of genetic testing “from bench to bedside” and the hope that it would result in a simplified method for diagnosing these cardiac diseases that frequently puzzle the clinician.

It is clear that a rapid penetration of genetic analysis into clinical cardiology has not yet occurred even for those diseases in which the benefit of knowing the genetic substrate is established. It is therefore important to understand the reasons for these unmet expectations to assess the present and future roles of genetic analysis in clinical practice and how to facilitate the transition of genetic screening from “research” to “practice.”

Were the Initial Expectations for Applicability of Genetic Testing Appropriate?
In the development of innovations in medicine, it is common that, after the initial widespread skepticism about the merit of a discovery, the initial positive results are applauded with an enthusiasm that often turns into high expectations for its rapid transition from the research arena to the clinical setting. In most instances, this is not what happens. Just as the discovery process may take decades of work, the introduction of any innovation into practice requires several “trial-and-error” attempts first. However, although the achievement of a new discovery occurs in the protected environment of the research laboratory and is ignored by the media, the transition from laboratories to clinics occurs under the spotlight and attracts the observers ready to call on the failure of the innovation if the speed of its development does not fulfill their expectations.

Both supporters and detractors of genetic analysis have contributed to the confusion among clinicians about the realistic expectations for the clinical applicability of genetic testing for cardiomyopathies and ion channel diseases.

In this article, we present our view and support the concept that, for some of the diseases discussed here, genetic analysis is ready for clinical use. To support our opinion, we have developed a score system that allows the role of genotyping to be compared in different cardiomyopathies and ion channel diseases. Finally, we comment on the reasons underlying the long time required to move genetic screening from research to the clinic.
TABLE 1. Criteria to Define Applicability of Genetic Testing in Clinical Practice

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
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<tbody>
<tr>
<td>Technical aspects</td>
<td></td>
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<tr>
<td>Percentage of genotyped patients</td>
<td></td>
</tr>
<tr>
<td>≥50</td>
<td>3</td>
</tr>
<tr>
<td>30 to 49</td>
<td>2</td>
</tr>
<tr>
<td>10 to 29</td>
<td>1</td>
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<tr>
<td>Unknown or ≤10</td>
<td>0</td>
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<tr>
<td>Size of the genomic region to screen, kb</td>
<td></td>
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<tr>
<td>≤1</td>
<td>1</td>
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<tr>
<td>&gt;1 to 3</td>
<td>0</td>
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<tr>
<td>&gt;3 to 8</td>
<td>-0.5</td>
</tr>
<tr>
<td>&gt;8 to 13</td>
<td>-1</td>
</tr>
<tr>
<td>≥13</td>
<td>-1.5</td>
</tr>
<tr>
<td>Clinical aspects</td>
<td></td>
</tr>
<tr>
<td>A, Presymptomatic diagnosis is clinically relevant</td>
<td>0.5</td>
</tr>
<tr>
<td>B, Identification of silent carriers is clinically relevant</td>
<td>0.5</td>
</tr>
<tr>
<td>C, Results influence risk stratification</td>
<td>0.5</td>
</tr>
<tr>
<td>D, Results influence therapy/lifestyle</td>
<td>0.5</td>
</tr>
<tr>
<td>E, Reproductive counseling is clinically justified</td>
<td>0.5</td>
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</tbody>
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What Is the Role of Genetic Analysis in the Management of Ion Channel Diseases and Cardiomyopathies?

A single answer to this question does not exist. Undoubtedly, genetic testing for cardiomyopathies and channelopathies should “eventually” be regarded as a mandatory examination, but deciding on when genetic testing is ripe for introduction into the clinics is an important matter for discussion.

Here, we provide our view on the role of genotyping in cardiomyopathies and ion channel diseases. We have used an approach similar to that used by the American Heart Association/American College of Cardiology (http://circ.ahajournals.org/manual/index.shtml) and European Society of Cardiology (http://www.escardio.org/initiatives/guidelines/?hit=related) to develop guidelines.

We have performed a careful and systematic analysis of the literature to collect the relevant studies on the topic and have ranked the evidence on the performance of genetic screening and the impact of molecular data on clinical management. When data were not available, we have used experts’ opinions.

We have developed a “score” system (Table 1) to express a cost/benefit assessment of genetic analysis in each disease. The score is obtained by taking into consideration different parameters, including the success rate of genotyping (yield of genetic screening), an indirect estimate of its cost (expressed as the size of the coding regions of the genes implicated in each disease), and the clinical benefits that it provides (impact of the identification of the genetic defect on the patients and their families). This score allows comparison of the clinical value of genetic testing in cardiomyopathies and ion channel diseases and provides an “evidence-based” answer to the question addressed in this debate (Table 2).

Conditions in Which Genetic Analysis Is Indicated (Score ≥3)

Timothy Syndrome, Romano-Ward Long-QT Syndrome, Jervell and Lange-Nielsen Long-QT Syndrome, and Andersen Syndrome

Timothy syndrome6 is the most lethal form of the long-QT syndrome (LQTS). In this condition, the advantage of genetic testing is hard to dispute. Timothy syndrome is characterized by prolonged repolarization associated with a variable number of abnormalities: syndactyly, language developmental delay, paroxysmal hypoglycemia, altered immune response, and cardiac malformations. All patients identified so far carry the same mutation in the KCNQ1 gene. Genetic analysis is expensive (≈100 Euros) and fast (turnaround of ≈1 week), and its accuracy is close to 100%. Identification of the mutation has a prognostic implication (adverse outcome); the absence of the mutation excludes the presence of the syndrome; prenatal diagnosis can be performed; and screening of family members is important for reproductive counseling. In this disease, there is no doubt that genetic analysis needs to be available to the clinician.

Genetic testing in the other forms of LQTS also can be considered ready for introduction into clinical cardiology. Screening of the genes associated with Romano-Ward LQTS4,5 allows us to identify the genetic defect in 50% to 70%6–8 of clinically affected individuals. This estimate is based on the screening of 5 LQTS genes: KCNQ1, KCNE1, KCNE2, KCNH2, and SCN5A. The ANK2 ankyrin gene that so far has been associated only with a handful of individuals with an atypical form of LQTS is excluded, and the screening of the very large gene ANK2 therefore is not justified outside the research arena.

Because not all the genes for Romano-Ward LQTS have been discovered, the lack of identification of a genetic defect cannot rule out the presence of the disease. Screening of family members of a genotyped proband allows presymptomatic diagnosis and the implementation of therapy when appropriate; it allows the clinical status (affected versus non affected) to be defined in borderline cases.

Of major relevance and rather unique to LQTS is the fact that identifying genetic defects contributes to risk stratification,9 therapy selection,10 and prevention of factors that precipitate arrhythmias.11 Because up to 90% of genotyped patients8 carry mutations on 2 genes, limiting genetic screening to those 2 genes may provide an even higher score in favor of the introduction of genotyping by reducing the workload and the time to diagnosis. From the above-mentioned considerations, it seems logical to promote the implementation of genotyping for Romano-Ward LQTS at affordable costs within the reimbursement plan of insurances and healthcare systems.

The recessive form of LQTS (Jervell and Lange-Nielsen disease)12 is characterized by homozygous or compound heterozygous mutations in 2 genes (KCNQ1 and KCNE1) that account for at least 80% of cases (unpublished data). Heterozygous mutations on the same genes are responsible for allelic variants of Romano-Ward LQTS.
Genetic analysis is relatively rapid and has high yields, and once the mutation is identified, it is possible to extend the screening to family members. Interestingly, homozygous carriers of mutations on the KCNQ1 gene and in KCNE1 are affected by Jervell and Lange-Nielsen LQTS, and their family members who are heterozygous carriers of the same mutations are affected by Romano-Ward LQTS; thus, their identification is very important and has clinical implications.

In Andersen syndrome, identification of the genetic defect is achieved in ~70% of clinically affected individuals by screening a single small gene. Genetic analysis carries clinical relevant implications such as the possibility to perform presymptomatic diagnosis, to identify silent carriers, and to encourage reproductive counseling.

### Hypertrophic Cardiomyopathy

HCM is characterized by large genetic heterogeneity; 19 genes and 2 loci have been associated with the disease, and hundreds of different mutations have been identified. As a consequence, searching for mutations in so many genes is unlikely to become the preferred approach for the introduction of genetic screening for HCM in clinical practice. Because the prevalence of mutations in some of the genes is very low, it may be logical to recommend screening of those genes that allow higher yields of positively genotyped individuals. It has been suggested that screening of the entire open reading frame of 9 HCM genes (MYH7, MYBPC3, TNNT2, TNNI3, MYL2, MYL3, TPM1, ACTC, and TNNC1) allows genotyping of >60% of HCM patients and that >80% of them carry mutations in the MYH7 and MYBPC3 genes. As discussed for Romano-Ward LQTS, limiting genetic screening in HCM to those genes that account for most of the successfully genotyped patients may confer an even higher priority to genetic testing in HCM.

Genotype-phenotype studies have suggested that genetic analysis may contribute to risk stratification; however, these data are still preliminary and have not been incorporated into our assessment of the role of genetic analysis in HCM. It has been suggested that carriers of MYBPC3 mutations tend to have late onset and severe prognosis mainly because of frequent sudden arrhythmic death. Delayed onset may unexpectedly pose a risk of sudden death in adults and middle-aged individuals who were defined as unaffected at early age.

Among the mutations identified in the MYH7 gene, some may carry prognostic indication. It has been suggested that the R403Q, R719W, and R453C mutations may confer an adverse prognosis, whereas nearly normal life expectancy may be anticipated for carriers of other allelic variants such as V606M, L908V, G256Q, and P513C. If these data are confirmed in larger series of patients, the priority of genetic screening in HCM will rise even more.
As of today, genetic analysis in HCM allows identification of the genetic defect in a high percentage of patients. Molecular data contribute to the management of patients because they allow presymptomatic diagnosis and identification of silent mutation carriers and patients for whom reproductive counseling may be appropriate.

**Catecholaminergic Polymorphic Ventricular Tachycardia**
Screening of the 2 genes (RyR2 and CASQ2) associated with the autosomal dominant and autosomal recessive forms of catecholaminergic polymorphic ventricular tachycardia (CPVT) allows the identification of mutations in 70% of patients.\(^{19}\) Even if only 2 genes are responsible for most of the CPVT cases, genetic analysis is this disease is complicated by the fact that RyR2 is one of the largest genes associated with channelopathies, and the time required for its screening offsets the advantage of having to screen “only” 2 genes.

The clinical diagnosis of CPVT is rather elusive because affected individuals show an unremarkable ECG and lack structural abnormalities of the heart, so genetic analysis often is very helpful for diagnosing the disease. This is especially important because, if left untreated, CPVT is a highly malignant disease, but prognosis improves substantially once the disease is correctly identified and therapy is implemented.

Presymptomatic diagnosis, diagnosis in silent carriers, and reproductive counseling are additional important benefits of successful genetic analysis. Overall, the indication for DNA screening in CPVT is high.

**Dilated Cardiomyopathy Associated With Conduction Defects**
Although the complex scenario provided by the genetics of idiopathic dilated cardiomyopathy (DCM) is discussed later, we introduce here a subgroup of DCM patients in whom genetic analysis can be considered a part of patient management. DCM associated with conduction defects has been associated with mutation on the LMNA/c gene.\(^{20}\) Arbustini et al\(^{21}\) reported that 30% of patients with DCM and cardiac conduction defects harbor mutations in this gene. Genetic analysis in this subgroup of DCM patients is therefore rather simple and effective. Because the disease shows an age-dependent penetrance and eventually all carriers of the defect develop a full-blown phenotype, early identification of carriers and silent mutation carriers among family members may be very important for early implementation of therapy and reproductive counseling.

**Conditions in Which Genetic Analysis Could Be Considered (Score ≤1)**

**Right Ventricular Cardiomyopathy**
Recently, it has become evident that arrhythmogenic right ventricular cardiomyopathy (ARVC) is a disease of the desmosome. It is estimated that the PKP2 gene encoding for plakophilin 2\(^{22}\) allows identification of mutations in 25% of patients with the disease. Because all other genes account for a very small proportion of genotyped patients with ARVC, we consider it appropriate to estimate from current knowledge that <30% of clinically diagnosed ARVC patients can be genotyped and most of them on the PKP2 gene. We have excluded from our evaluation of the value of genetic analysis in ARVC the atypical form allelic to CPVT that is associated with mutations of the RyR2 gene. Screening of RyR2 should be limited to the small subgroup of ARVC patients with polymorphic ventricular tachycardia elicited by stress and emotion.

It is anticipated that the priority of genetic screening for ARVC will increase as more information is collected about genotype-phenotype correlations. As of today, the importance of knowing the genetic defect relies very much on the possibility of evaluating family members to establish the diagnosis in clinically borderline cases, silent carriers, and asymptomatic individuals and to allow reproductive counseling.

**Brugada Syndrome**
Only 1 gene has been so far associated with the Brugada syndrome: the gene encoding for the cardiac sodium channel. Screening of this gene allows the identification of mutations in 15% to 20% of patients.\(^{22}\) Because Brugada syndrome is a disease that manifests in adulthood with a very incomplete penetrance and a high proportion of mutation carriers remain asymptomatic,\(^{23,24}\) the value of genetic analysis for reproductive counseling is less obvious than in other conditions associated with sudden death during childhood or adolescence. Additionally, because there is no pharmacological therapy for Brugada syndrome, the identification of silent carriers of SCN5A mutations cannot benefit from prophylactic therapy to reduce the risk of cardiac arrest. Genetic analysis is useful in nonpenetrant mutation carriers and in family members of genotyped probands to detect early manifestation of the disease.

**Conditions in Which Genetic Analysis Is Still Performed as a Research Activity (Score ≥1)**
Identification of the genetic basis of DCM has proved particularly complicated. Among idiopathic DCM, the proportion of inherited forms is still poorly quantified. Several genes have been implicated in DCM, but most of them cause DCM in the context of syndromes that involve other manifestations such as skeletal myopathies.

Dissection of the molecular basis of DCM without extra-cardiac manifestations remains a big challenge in the genetics of cardiomyopathies. This goal should be achieved before genetic analysis in DCM is given higher priority and its introduction is advocated in clinical practice.

No studies have systematically assessed the relative prevalence of the various DCM subtypes. The genetic screening of relatively large series of patients with idiopathic DCM\(^{25}\) suggested that only a small proportion of idiopathic DCM can be genotyped.

Diseases such as myocardial noncompaction,\(^{26}\) familial atrial fibrillation,\(^{27,28}\) progressive conduction diseases,\(^{29}\) inherited sick sinus syndrome,\(^{30}\) and short-QT syndrome\(^{31–33}\) have been described in few patients. Some of these conditions represent a subset of genetic forms of acquired diseases (atrial fibrillation, sick sinus syndrome, Lev Lengre disease). Current understanding of the genetic basis of these conditions is...
Is the Scientific Community Prioritizing the Introduction of Genetic Testing in Clinical Practice?

It is clear from what we have presented so far that the identification of a disease gene is not enough to introduce the screening of that gene into clinical medicine. Additional and important information has to be collected before genotyping can be moved to the clinics. It is necessary to assess the percentage of clinical cases that can be successfully genotyped and the workload required to genotype them. It is important to determine the common DNA variations (polymorphisms) present in each gene to avoid false-positive diagnosis. This process may be complex because it requires the screening of large series of individuals from different ethnic backgrounds. Furthermore, because even uncommon DNA variants can be functionally silent, it is important to have some additional evidence that a mutation has a high probability of being the cause of the disease before a molecular diagnosis is established. For example, it is valuable to demonstrate that a mutation is present in multiple families with a given phenotype and that it is not present in a large number of control individuals. Finally, it is important to conduct genotype-phenotype studies that allow defining the impact of genetic analysis on the clinical management of a disease. Only when all this information becomes available is it possible to move genetic analysis outside the domain of research activities.

It is important to ensure that the scientific community gives adequate priority to the collection of this critical knowledge to ensure a rapid transition of genetic screening to the clinics. Unfortunately, however, several factors limit the progression of the type of knowledge needed to promote translation of research into practicing medicine.

The discovery of new disease-related genes is usually applauded with great enthusiasm by the scientific community and is chased by the most prestigious journals. On the contrary, identification of additional mutations in the same gene is regarded as a “less innovative” research, so expanding the knowledge of the number of genetic variations and their link to the clinical phenotype has not been adequately promoted. Unfortunately, too much of this type of research has been discouraged and perceived as having a lower priority for both publication in leading journals and funding. As a consequence, fewer investigators have been involved in these areas of research, and it has become progressively more difficult to find financial support for collecting this “orphan knowledge.”

Because it is clear that the transition of genotyping from research to clinics can be promoted only if the scientific community has an incentive and a genuine interest to pursue the collection of the data that make genetic analysis reliable and helpful in the management of patients, action is needed to correct the current trend.

We believe that once the need for genotyping can be based on solid scientific evidence and the contribution provided by genetic analysis to the management of patients can be demonstrated, it will become much easier to achieve the goal of reimbursable and widely available genetic analysis. It is not a coincidence that in the field of LQTS, in which risk stratification and management of the disease benefit from genetic data, commercial genotyping enterprises have rapidly become involved and will partner with patients to achieve reimbursement for genotyping by governments and insurances.

Conclusions

We have provided evidence to support the concept that the priority and value of genetic analysis for the management of patients with cardiomyopathies and channelopathies are specific to each diseases. It is also evident from the data presented here that for many of these diseases there are compelling medical reasons to consider genetic testing an important component of clinical management of affected individuals and their relatives. The lack of availability of genetic testing is related largely to the absence of appropriate reimbursement policies; thus, it is important that the scientific communities involved in researching these diseases feel committed to prioritize the collection of data that will facilitate transition of genetic analysis for cardiomyopathies and channelopathies into clinical practice. Partnering with stakeholders such as patients’ associations, governments, insurance, and private companies involved in genotyped may be an effective approach to achieve these goals.

Disclosures

None.

References


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