At the heart of genetic testing

Genetic testing for rare heart conditions might someday expand to more common cardiac ailments. Already there are signs testing is dramatically changing how some conditions are treated and doctors' definition of who a patient is. Stephen Strauss reports.

It has not been a very happy year for those hoping that genetic testing was going to revolutionize our ability to predict who was and who wasn't going to come down with major heart diseases. Not to mention using that knowledge to do something about the conditions. In February, an article in the *Journal of the American Medical Association* found that when 19,000 American women were followed an average of 12 years, an analysis of their genetic differences "did not improve cardiovascular risk prediction"[1]. The catchline of an article in *Science* magazine in June declared "So far, genome-wide association studies have not found common genes with a big impact on heart health"[2]. And *The New York Times* also in June declared "after 10 years of effort, geneticists are almost back to square one in knowing where to look for the roots of common disease"[3].

Camaroon soccer star Marc-Vivien Foe collapsed and died of hypertrophic cardiomyopathy at the age of 28.

Buried beneath the gloom is what might be termed a good news asterisk. It reads: none of the above is true if we shift our gaze from common heart conditions to a wide range of less common, but genetically linked, cardiac diseases. Over the past five years or so, testing for gene mutations connected to them has been transforming how doctors diagnose illnesses, treat patients and expand that treatment to include family members.

It has also given birth to a commercial gene testing industry that believes it is perched on the brink of a major leap forward.

Preventing early death

The difference between what is happening in two domains is so acute that David Margulies, cofounder and CEO of Correlagen, a Waltham, Massachusetts–based genetic diagnostics company (now a LabCorp subsidiary), is absolutely tart in his criticism of any linkage between what is called genome-wide association studies in heart disease and monogenic sequencing tests for gene-specific heart conditions. "It's like comparing apples to zebras," he says.

A classic example of a testing apple can be seen in the use the Canadian province of Newfoundland and Labrador has been making of a genetic screening for the heart disorder known as arrhythmogenic right ventricular cardiomyopathy (ARVC). ARVC causes a fatty buildup in the heart, which often without warning generates a highly irregular heart beat and then, no heartbeat at all. ARVC has become infamous in the world of sport as one explanation for why previously ostensibly healthy athletes suddenly collapse after a competition.

"ARVC often goes undetected until a person drops dead," says Kathy Hodgkinson, a geneticist and clinical epidemiologist at Memorial University in St. John's, Newfoundland, who wrote her PhD thesis on ARVC genetics in the province. "And it appears in Newfoundland families more often than it does elsewhere."

Although it is estimated that ARVC worldwide afflicts roughly 1-in-5,000 people, that number may be as high as 1-in-1,000 people in Newfoundland. The high incidence is the fruit of a highly penetrant mutation, which a study of old records and family bibles suggests first appeared in the late 1700s in descendents of a British immigrant.

After ARVC was first clinically described in the 1980s, researchers at Memorial University in St. John's, Newfoundland began to study the genetics of the early and unexpected heart attacks occurring in the province. In 1997, the group initiated a formal search for the gene that gives rise to the condition. They first localized it to chromosome 3 and then in 2007 uncovered the exact gene where the Newfoundland-rooted mutation occurs. This research has off the top allowed scientists to get a more precise measurement of Newfoundland's ARVC's deadly demographics.

When 18 extended families carrying the mutations were studied—the largest one comprising 1,200 people with records of heart deaths extending over ten generations—it turned out that the median age of death for men is 41. Women, probably because of the mitigating effect of estrogen, on average die at 71.

But equally important, when you know who carries the gene defect, there is something you can do about it. Newfoundland doctors are now counseling family members with the mutation to have a cardiac defibrillator implanted. The recommendation is being made to boys in their late teens and girls in their late 20s, even if there is no overt sign of any heart disease.

With their families' history of early deaths on their minds, the cardioverter defibrillator (ICD) implantation is an option that Newfoundlanders are seizing upon. By 2009, 104 adults who carry the mutation have been offered an ICD, and only nine refused to be implanted. And the intervention is working. Last year the Memorial researchers reported that the five-year mortality rate in men who had an ICD implanted in them was zero. This compares with a death rate of 28% for men who didn't have the implantation.

"We have been able to take a heart attack, which in the past was seen as an act of God, explain it as an act of genetics, and then do something to keep their genetics from prematurely killing people," says Terry-Lynn Young, a professor of molecular genetics at Memorial University, who has been spearheading the study of the mutation in the province.

Spawning diagnostics

The gene became part of a generalized ARVC screening test that Newton, Massachusetts based-PGxHealth offers for five genes associated with variants of the condition. But more significantly, it has now become part of PGxHealth's suite of heart disease gene screening. Beginning in 2004, with a test for long QT syndrome (LQTS), which is also a sudden and unexpected heart killer, PGxHealth now tests for six separate heart conditions. In total, upwards of 100 genes associated with genetically linked heart conditions are being screened for by various companies (**Table 1**).

The tests have become increasingly sophisticated and can now quantify the percentage of cases that can be linked to each individual gene mutation. The differences are rather striking.

Table 1 Genetics of rare heart conditions

Disease	Number of genes	Approximate frequency	Treatments
Hypertrophic cardiomyopathy	17	1 in 500	Beta blockers, implantable cardioverter-defibrillator, lifestyle changes
Dilated cardiomyopathy	23	1 in 2,500	Avoidance of alcohol, lowered salt intake, various heart failure drugs, Implantable cardioverter-defibrillator, heart transplants
Long QT syndrome	12	1 in 5,000–7,000	Beta blockers, implantable cardioverter-defibrillator, avoidance of strenuous activities
Brugada syndrome	6	1 in 2,000–10,000	Implantable cardioverter-defibrillator
Arrhythmogenic right-ventricular cardiomyopathy	7	1 in 1,000–-10,000	Beta blockers, implantable cardioverter-defibrillator, avoidance of strenuous activities
Catecholaminergic polymorphic ventricular tachycardia	2	1 in 10,000	Beta blockers

Thus, whereas in dilated cardiomyopathy (one of a group of diseases in which the heart muscle wastes away) 12 genes associated with the condition account for no more than 6% of the cases, in hypertrophic cardiomyopathy (a thickening of the heart, particularly of the left ventricle) two of nine associated genes used by several companies in gene testing account for as much as 40–60% of the cases.

The growing number of genes associated with these disorders is important, not simply because it leads to a deeper understanding of the biological pathways involved, but because for certain genes, the specific mutation a person carries may have profound clinical significance. Effectively, conditions that before genetics testing were seen as singular illnesses have in the past few years been grouped into closely related conditions, each of which may manifest itself, and be treated, differently.

For example, the genetic tests for LQTS differentiate several varieties of the condition associated with different genes. Type 1 LQTS accounts for 35% of the cases, type 2 for 30% and type 3 for 10%. The other ten genes currently associated with the condition collectively account for only about 2% of the cases.

The triggers for the variants can be quite different. Strenuous exercise, particularly swimming, has been associated with attacks and deaths in type 1 LQTS. However, Peter Schwartz, a cardiologist at the University of Padua in Italy, who has been studying the condition since the early 1970s, says "we found, and that was a surprise, that [those with] type 2 and 3 are at very low risk during exercise, as it is not a trigger for them." What triggers type 2 LQTS are loud noises, think a telephone suddenly ringing or an alarm clock bell. Conversely, in type 3 LQTS, the most important trigger is depression and sleeping.

What has also followed from the splitting of the condition into three genetically differentiated disorders is a partial realization of the dream of personalized medicine. Doctors now recommend that people with type 1 LQTS limit strenuous activities but those with type 2 or type 3 need not.

What's more, there are implications for drug prescription. Schwartz has shown that beta blockers, which typically were given to everyone diagnosed with LQTS, are significantly more protective for those with type 1 LQTS than for those with type 2, and perhaps not at all effective for type 3.

"Screening is, in variance what with a lot of people think, not just a research tool; it is a clinical tool. There is no doubt that cardiac genetics is allowing us to modify disease management," remarks Schwartz.

Screening exercises

Another part of screening's clinical significance is that it has added a significant new tool to cardiologists' diagnostic armatorium. Many of the classic diagnostic technologies that indicate heart disease fail when it comes to conditions in which the heart suddenly stops beating because of a genetic abnormality.

"Many times people with these conditions can have a normal EKG [electrocardiogram], because your EKG is just a spot look," says Sherri Bale, co-president and clinical director of GeneDx, a gene screening diagnostics company in Gaithersburg, Maryland. "It is a minute-and-a-half, or three minutes, or whatever, snapshot of your heart. If an arrhythmia doesn't occur during that time, you don't see anything."

One marker of the significance of gene screening for diagnosis is that professional organizations are beginning to recommend that screening for disease-causing gene mutations become a normal part of the diagnosis process. For example, the European Task Force on Diagnosing ARVC recently recommended that the diagnostic criteria be revised to include "identification of a pathogenic mutation categorized as associated or probably associated with ARVC/D in the patient under evaluation"[4].

Who's your patient?

The diagnostic reach of cardiac disease testing is doing more than improving diagnoses, it is now forcing physicians to reconfigure their view as to whom their patients are. "Traditionally cardiologists are good at seeing the disease in front of them and then nailing it, attacking it, treating it. They are hardwired to treat an individual patient well," says Michael Ackerman, a pediatric cardiologist, who is director of Mayo Clinic's Long QT Syndrome Clinic in Rochester, Minnesota.

"What we are not good at in cardiology historically is thinking of these as genetic diseases and reflecting 'I now have to think like a family medicine doctor. I now have to take care of all the family,'" he says.

Some of the changes require an organizational reconfiguration. Ackerman points to the LQTS clinic he set up at Mayo in 2000 that is geared to evaluate, counsel and treat all affected family members, regardless of age rather than having the children seen in one medical facility and the adults seen in another across the city. This is important because potentially quite a lot of family members might come in to be treated, particularly if the gene is dominant and therefore could have been passed on to half of close blood relatives.

Heidi Rehm, a geneticist at Harvard Medical School and director of the Laboratory for Molecular Medicine at Partners HealthCare Center for Personalized Genetic Medicine in Cambridge, Massachusetts, is preparing a paper on the genetic testing of over 2,000 people with hypertrophic cardiomyopathy at her facility from 2004 to 2010. Of the first 533 individuals who tested positive for the mutation, 255 subsequently brought in at least one family member to be tested. All told, an average of 3.4 people per family were tested with the range being a single family member to 33 members of one huge extended family.

Even so, expanding these practices to include gene-carrying family members has proven

daunting to doctors, in part because, as Schwartz remarks, "a large majority of physicians grew up not knowing a thing about genetics." As a consequence, gene diagnosis companies are trying to bridge the information gap by having genetic counselors on staff whose specific job it is to counsel not patients but the doctors who must treat them.

The issues are both complex and varied. For example, family testing means cardiologists must now confront a new emotional element in their practices. "There is a lot of sudden anxiety when people have to deal not only with the death of a family member but with something that now can affect the rest of the family. There is an emotional overload for a lot of people coming to get this type of testing," says Amy Daly, a genetic counselor with GeneDx.

At the same time, cardiologists must deal with family members' refusing genetic testing for themselves—and the dire consequences of that ignorance. The Newfoundland group wrote in a recent paper of a 31-year-old man who declined to be tested, even though ARVC had been detected in his family. He subsequently died while golfing from what turned out to be ARVC[5].

"There sometimes is total denial, people just saying 'this isn't going to happen to me,'" Memorial University's Young explains.

A different, and happier result, was reached when it was discovered that a young Newfoundland man training to become a commercial pilot carried the ARVC mutation with its risk of sudden death. "We just talked things through," says geneticist Hodgkinson, "and he decided to change careers." An interesting conundrum for physicians is what to do if subjects at high risk of sudden death choose to ignore the information and continue in a profession where their condition might put other lives in danger. Parents must also decide whether or not to test their potentially at-risk children for the mutations.

The difficulties that these and other genetic screening and diagnosis issues introduce into a medical practice have fed into what is seen as a general reluctance by many cardiologists to expand their treatment to include gene testing and gene counseling for family members. Some feel only a legal impetus is going to change this.

In a recent editorial in the *Journal of the American College of Cardiology*, Schwartz has argued that only the threat of malpractice will produce a general acceptance of what is being termed 'cascade screening'[6]. "I am afraid the turning point will be when someone will be convicted in court for not having recommended genetic screening and someone died," he says.

The mutational conundrum

Whereas the rapid expansion and almost immediate applications of genetic screening for less common heart conditions clearly has been beneficial, it has brought with it several unresolved issues. One is the meaning and the multiplicity of mutations. Rehm points to data she analyzed several years ago, where she found that out of more than 1,000 mutations in her database "850 of them were pathogenic, 150 were not."

What is unclear in the extreme is how to differentiate the dangerous from the benign when it comes to mutations. "When you scan a large group of healthy volunteers … rare variants pop up in them, pop up right next door to amino acids in which there is no doubt about disease mutations," says Ackerman.

Not to mention the effect of multiple mutations. About 7% of the people in Rehm's study have at least one additional mutation. "The significance of the second mutation isn't always clear," says Rehm. This is confusing to doctors. "Physicians have a lot of questions about what we call 'variants of unknown significance'," says GeneDx's Daly. But it may be even more confusing to patients and family members who have to decide if they are going to initiate treatments or actions to reduce their risks. In a soon-to-be-published paper, Rehm and her associates describe how, when a positive mutation result came in, one mother decided to severely reduce the activity of one of her children, only to be informed a year later that the laboratory that screened for the disease had decided the mutation was benign.

The money game

And then there is the question of who pays and how much they pay for the testing. Indeed, people point out that the differences between countries when it comes to paying for gene testing is almost a litmus test for that country's medical system. Ackerman says that when the tests for LQTS genes first became commercially available in 2004, there was a great deal of excitement because it was felt that the tests were finally going to be of clinical significance.

This was in part driven by the fast turnaround time of the commercial tests—6 to 8 weeks as opposed to months or even years when university laboratories alone oversaw testing. "But guess what? What we learned —our patients' insurance was not paying for it," Ackerman notes.

It has only been in the past couple of years that many US payers have been picking up most, generally about 75%, of the price of the testing. Part of what has convinced them has been the economics of a negative screening. In place of conducting yearly magnetic resonance imaging or EKGs on patients whose susceptibility to the disease is unknown, noncarriers can be excluded from the testing lists.

Others point out that governments in places like New Zealand and Canada are more willing to pay for the screenings because it is in their long-term economic interest. "The payer who is paying for the test is same [one] who pays for the treatment of heart disease two decades later," says Correlagen CEO Margulies.

Because this is not the case in the US, gene test prices are not so much what actually get paid, but the opening level at which negotiations between payers and gene screening companies begins. "We are paid very different amounts by different payers on different days," says Margulies.

Moving the technology forward

Ask people involved what the future holds for heart gene testing and the first words that come out are "more, better, cheaper."

Using what are called next-generation or third-generation sequencing platforms, companies are racing to increase the number of genes being tested and decrease the costs of the tests. Ackerman foresees the day in five or ten years when everyone gets a test for their gene variations for less than $1,000.

That might mean that today's specific tests for specific heart genes may be folded into a generalized gene screening. "I believe we are in a ten-year window for disease-specific genetic testing," Ackerman says. GeneDx's Bale on the other hand doesn't believe gene-specific diagnostic tests for inherited heart failure are going to cease to be conducted. With more genes will come more complexity and "unfortunately we will identify tons of stuff we don't know how to interpret," she says.

Nonetheless change is happening now. Rehm says Partners HealthCare is working on a heart screening test for 65–70% of the most frequent mutations associated with rare heart conditions. "I think we will catch half of all positives with this screening test. You never will get an inclusive result, because we will only test for variants we know the significance of."

That change won't be five or ten years away and cost $1,000. "The goal is to do that testing for under $500. We hope to have such a test available by the end of the year," Rehm says.

Stephen Strauss, Toronto

1. Paynter, N.P. *et al. J. Am. Med. Assoc.* **303**, 631–637 (2010).
2. Couzin- Frankel, J. *Sci.* **328**, 1220–1221 (2010).
3. Wade, N. *The New York Times*, 12 June 2010 <http://www.nytimes.com/2010/06/13/health/research/13genome.html?_r=1&ref=general&src=me&pagewanted=all>
4. Marcus, F.I. *et al. Circulation* **121**, 1533–1541 (2010).
5. Hodgkinson, K. *et al. Genet. Med.* **11**, 859–865 (2009).
6. Schwartz, P.J. *J. Am. Coll. Cardiol.* **55**, 2577–2579 (2010).