

HCM is a major cause of death in young athletes, but can be diagnosed in people of all ages. Because HCM is often asymptomatic, some patients may be unaware of their condition until it is detected during routine medical screening.



WINDY

to intervene

SUDDEN CARDIAC DEATH KILLS AS MANY AS 300 YOUNG ATHLETES EACH YEAR. THE ROOT CAUSE IS OFTEN GENETIC. BUT NOW A NEW TEST OFFERS ANSWERS AND INSIGHT.

♥♥♥ GROWING UP, Wendy Borsari had reason to believe she had escaped the genetic heart condition that wreaked havoc on her family, killing three uncles and sending her mother into congestive heart failure. Borsari's regular childhood echocardiograms found no problems. When she was 18, doctors concluded Borsari was perfectly healthy. They were wrong.

In 1993, shortly after Borsari graduated from college, her doctor heard an irregular heartbeat during a routine exam. This time, an echocardiogram confirmed Borsari's fears: hypertrophic cardiomyopathy (HCM). A genetic abnormality that enlarges muscle cells in the heart's left ventricle, HCM can cause a sometimes-fatal irregular heartbeat, heart failure, exercise intolerance, and chest pain. With an HCM diagnosis in hand, Borsari began to actively manage her health, with frequent medical checkups and more careful health-related decisions. Today, as a 39-

BY KATHRYN BROWN

year-old mother of two, she leads a pleasantly ordinary life in the Boston suburbs.

HCM is the primary cause of sudden death in people under 30. Young athletes in particular, researchers say, suffer sudden cardiac death at two to three times the rate of others of their generation. Although estimates vary, as many as 300 young athletes may die from sudden cardiac death every year in the United States alone—collapsing at soccer games or swim meets, for example, or simply during practice. One of Borsari's uncles died as a teenager, heading to the football field, roughly 50 years ago. (The other two died at ages 26 and 33.)

For patients and families, dealing with this uncertainty is costly, emotionally draining, and fraught with physical danger.

If HCM is detected in time, doctors can manage the condition with surveillance, lifestyle changes, and, sometimes, an implantable defibrillator. But young adults are not universally screened for heart conditions, and early HCM symptoms—such as shortness of breath—may easily be mistaken for more common conditions such as asthma. Although a family history of HCM suggests the need to test children, many—like Borsari—develop clinical symptoms later. For patients and families, dealing with this uncertainty is costly, emotionally draining, and fraught with physical danger.

Now, a new genetic test may allow early identification and diagnosis of those at greatest risk for developing HCM. The test can confirm an HCM diagnosis in patients who show clinical symptoms of the disease and can provide further information for individuals at risk for the condition. Administered by the Harvard Medical School–Partners Healthcare Center for Genetics and Genomics, the test detects mutations in eight genes that account for up to 70 percent of HCM in patients with clinical symptoms.

MOLECULAR MECHANICS

♥♥♥ **HHMI INVESTIGATOR** Christine E. Seidman and her husband, HHMI alumni investigator Jonathan G. Seidman, both of Harvard Medical School, developed the HCM test. The Seidmans have spent the past two decades identifying and explaining the molecular mechanics behind HCM. They tracked its incidence through families, analyzed the genomes of affected family members, mapped relevant disease genes, and, ultimately, pinpointed many of the telltale mutations that cause the condition. The couple currently is working to understand how these mutations trigger signaling molecules that cause heart muscle cells to grow abnormally.

Cardiovascular geneticist Jonathan Seidman brings a long-standing interest in the molecular causes of hypertrophy to the hunt for HCM genes. In particular, he has analyzed the mutations linked to the disease and currently heads efforts to determine how HCM genes may contribute to the risk of hypertrophy in other cardiac conditions.

Meanwhile, Christine Seidman sees HCM from the perspective of both researcher and physician. As director of the Cardiovascular Genetics Service at Brigham and Women's Hospital, she sees patients several days each month. Most days of any given week, however, she can be found at the lab bench. Her research efforts on HCM and other cardiac conditions, such as dilated cardiomyopathy, were recently recognized with her election to the National Academy of Sciences.

Christine Seidman's interest in heart disease emerged early in her career. After graduating from medical school in 1978, she spent roughly a decade in medical and research fellowships at Johns Hopkins and Harvard, specializing in internal medicine. She became intrigued by the research and clinical implications of the heart's unique biology. For example, she says, the cells of the mature heart don't divide, as cells in other tissues do. In another quirk, the heart can be caused to change shape by a diversity of disorders, from HCM to hypertension to coronary artery disease. But the change actually occurs in only two ways—hypertrophy, in which the heart walls thicken, or dilation, whereby the heart's volume increases. Either change limits the heart's blood-pumping ability, threatening to stop it completely. "Here you have a variety of pathogenic stimuli, and they all activate one of these two pathways to disease," Seidman says. If we could prevent these changes from occurring, she adds, "we could really help patients."

Christine Seidman established her lab at Harvard Medical School about 20 years ago, and began recruiting families with a history of cardiac hypertrophy or dilation for research studies. The lab homed in on HCM, painstakingly mapping disease genes to specific chromosomes and then fingering the genes themselves.

PROMISES AND PITFALLS

♥♥♥ **WORKING TOGETHER** and with colleagues, the Seidmans have linked HCM to mutations in structural proteins—such as the cardiac B myosin heavy chain and cardiac myosin binding protein C—found in heart muscle cells. These proteins help form the sarcomere, the pumping part of heart muscle cells. When mutated, the proteins apparently short-circuit the cells' normal flow of calcium that is needed to regulate cellular activity. As a result, the muscle cells grow unchecked, swelling into dramatically thickened heart walls.

Among individuals carrying an HCM mutation, however, it's impossible to know just when—or if—a heart actually will become hypertrophic. "You're born with an HCM mutation, but its clinical signs could take years to evolve," Christine Seidman says. Yet on the positive side, she notes, "we have a huge window to intervene. That's why I'm keen on gene-based testing."

The Seidmans developed a test, based on direct DNA sequencing, that screens a patient's blood sample for mutations of the genes most commonly implicated in HCM. Made available to the public last year, the test is offered in two panels. The first, HCM-A, includes the five most common genes for HCM. Among patients with existing clinical symptoms, HCM-A offers

Although the gene mutation responsible for causing HCM is inherited at the time of conception, it may take decades before there is clinical evidence of impaired heart function. The clinical spectrum of HCM ranges from asymptomatic individuals to those with exercise intolerance, chest pain, or disabling symptoms of heart failure.





HARVARD PHYSICIAN AND RESEARCHER CHRISTINE E. SEIDMAN DEVELOPED A DIAGNOSTIC TEST FOR HYPERTROPHIC CARDIOMYOPATHY (HCM), A GENETIC HEART ABNORMALITY THAT IS FREQUENTLY THE CAUSE OF SUDDEN DEATH IN YOUNG ATHLETES.

THE HCM TEST

The HCM test sequences DNA from a patient's blood sample, detecting mutations in the genes most commonly associated with HCM. The test is offered in two panels, HCM-A and HCM-B, for the following genes:

HCM-A

GENE	NAME
MYH7	myosin, heavy chain 7
MYBPC3	myosin-binding protein c, cardiac
TNNT2	troponin t2, cardiac
TNNI3	troponin i, cardiac
TPM1	tropomyosin 1

HCM-B

GENE	NAME
ACTC	actin, alpha, cardiac muscle
MYL2	myosin regulatory light chain
MYL3	myosin essential light chain, cardiac

Source: www.hpcgg.org/lmm

a roughly 50 to 60 percent detection rate of a pathogenic mutation. The second panel, HCM-B, targets three other genes, adding another 5 to 10 percent to the detection rate of a pathogenic mutation. When both panels are analyzed, a disease-causing mutation is identified in 55 to 70 percent of individuals. The detection rate is highest among families in which clinical diagnosis is well established.

After developing the test, the Seidmans transferred the technology to the nonprofit Harvard Medical School–Partners Healthcare Center for Genetics and Genomics. The center's laboratory of molecular medicine actually performs the test, as one of many genetic tests—including a different test for unexplained cardiac hypertrophy—available to the public. (The Seidmans do not receive any profit from these tests.) But the center has a broader mission: to incorporate genetics and genomics into clinical medicine. To that end, the center maintains a computer database with the medical records, including HCM test results, of patients in the Partners Healthcare system, which includes Massachusetts General and Brigham and Women's hospitals.

Tapping this database, participating cardiologists can easily weave a patient's HCM diagnosis into his or her clinical care. Ultimately, the center's goal is to learn whether genetic test results improve that care. "Many labs provide genetic testing, but we're different because we're also interested in incorporating the knowledge of genetics and genomics into the practice of clinical medicine," explains Raju Kucherlapati, scientific director of the center and a geneticist at Harvard. "This same attitude is what makes Christine's work special. She not only discovers genes, but also understands patients and clinical outcomes. So she's in a good position to assess how genetic tests for cardiovascular conditions can change the practice of medicine."

Already, the HCM test illustrates the promises and pitfalls of applied genetics. Among its promising points, the test can provide critical information. Families with an HCM history, for instance, often want to know whether a child carries a mutation linked to the condition. If so, parents may steer him or her toward sports and hobbies that are not overly strenuous. In addition, patients previously diagnosed with general cardiac hypertrophy can take the test to identify, or possibly downplay, HCM as the cause. Finally, patients with suspected HCM can learn which mutation they carry—useful knowledge, as several of the mutations can result in more severe forms of the condition.

However, like any other test for a complex genetic condition, the HCM test has gaps. "It's good at finding mutations in eight key genes,

and that probably accounts for most cases of unexplained cardiac hypertrophy,” says Allison Cirino, a genetic counselor at the Cardiovascular Genetics Center of Brigham and Women’s Hospital. “But there are still other HCM genes out there, and a negative test result cannot rule them out.”

Cost is another drawback. Because the comprehensive HCM test screens for more than 250 possible mutations across 14,188 base pairs of nucleotides, it is highly technical and thus expensive. Panel A alone costs \$3,000 and Panel B costs \$1,150. Alternatively, checking family members for a known mutation costs \$250. Major insurance companies have covered the test for patients who received preapproval, Cirino notes.

Finally, some people may fear that the HCM test—or any genetic test—could publicly label them as vulnerable or diseased, leading to genetic discrimination from health- and life-insurance companies, or even employers. That’s one reason, Christine Seidman suspects, why some who’ve taken the HCM test since last year have done so by mail—downloading test forms from the Internet and then quietly sending in blood samples with payments—as opposed to working with a cardiologist, who would keep permanent medical records. Still, Kucherlapati notes that most test takers are referred by physicians. So far, he adds, at least several hundred people have taken the HCM test.

Despite the challenges, many other medical scientists consider the HCM test—the only such test currently available—to be a step forward. “This test is an important advance, and the Seidmans deserve credit for creating something needed and new,” says Barry J. Maron, director

of the Hypertrophic Cardiomyopathy Center at the Minneapolis Heart Institute Foundation. “As is the case with any test, there are limits—particularly cost and false negatives—that must be overcome. But now we can at least aspire to having an HCM diagnosis in a timely fashion.”

TO USE A NEW TOOL WISELY

♥♥♥ **BORSARI, WHOSE FAMILY** has long participated in the Seidmans’ research, agrees. “Any scientific progress in HCM testing is a move in the right direction,” she says. “We now have something else available to help us make wiser decisions in the future.” Borsari adds that when her own son and daughter were born—in 2000 and 2003, respectively—she immediately had researchers test their blood for HCM mutations. (She prefers to keep the results confidential.)

As the Seidmans’ research evolves, their findings could improve future versions of the HCM test—or, possibly, lead to therapies that treat the condition. For example, in studying the genetically engineered mice that the Seidman lab uses to unravel HCM’s molecular mechanisms, the researchers could discover molecular signals that kickstart abnormal growth in heart muscle cells, leading to hypertrophy. The ability to block such signaling could form a major therapeutic advance.

Looking ahead, Christine Seidman says that society—from doctors and patients to employers and insurers—must learn how to deal with genetic information as an emerging medical tool. “Genetic tests can be enormously informative and potentially life-saving,” she says. “At the same time, this is very personal and powerful information, with all the issues that brings.” ■

HOW DO PATIENTS GET AN HCM TEST?

There are two basic routes to the HCM test: The first, and most widely recommended, is through a cardiologist. The patient gives a blood sample at the doctor’s office, which is then sent to the molecular medicine lab at Harvard Medical School–Partners Healthcare Center for Genetics and Genomics. About 6 weeks later, the cardiologist receives the results and reviews them with the patient. ♥ Alternatively, individuals can download test forms directly from the center’s Web site (www.hpcgg.org), submit a 7-milliliter blood sample in a test tube by overnight mail, prepay for their test, and receive results in 6 weeks. ♥ Although formal genetic counseling is not part of the HCM test—it is available but not required—the center does have a staff counselor to answer specific questions by telephone. Meanwhile, independent genetic counselors work in all major urban areas nationwide (to find one, see the Web site of the National Society of Genetic Counselors www.nsgc.org). Many patients benefit from speaking with a qualified counselor, who can explain how a test works and what results mean, as well as answer questions.

The center’s laboratory of molecular medicine performs the test as one of many genetic tests available to the public.

In May 2005, HHMI researchers published research in *Genes & Development* showing that they had induced adult heart muscle cells to proliferate in adult animals. Researchers said the studies provide a framework for exploring the molecular mechanisms that might one day make possible clinical regeneration of damaged heart muscle. According to Mark Keating, an HHMI alumni investigator at Harvard Medical School and Children’s Hospital Boston and senior author of the paper, “These findings represent the first step toward showing that drugs that eliminate p38 activity could reduce scar tissue formation and enhance cardiac regeneration after cardiac injury.” Keating said the formation of scar tissue in damaged hearts is the major reason myocardial infarctions lead to subsequent abnormalities and compromised heart function.

[MORE INFORMATION AT HHMI NEWS ONLINE](http://www.hhmi.org/news/keating8.html)

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