

Announcer: Welcome to Medical Breakthroughs from Penn Medicine, Advancing Medicine Through Precision Diagnostics and Novel Therapy.

Dr. Caudle: This is Medical Breakthroughs from Penn Medicine on ReachMD. I'm your host, Dr. Jennifer Caudle, and joining me on this episode, is Dr. Anjali Owens, Medical Director at the Center for Inherited Heart Disease at Penn Medicine. Dr. Owens, welcome to the program.

Dr. Owens: Thank you. It's a pleasure to be here today.

Dr. Caudle: So, to start us off, Dr. Owens, what can you tell us about inherited cardiomyopathy? How prevalent is it within our country? And what kind of burden does this have on patients?

Dr. Owens: There are several types of inherited cardiomyopathy. We usually classify them by how they affect the structure of the heart. For example, one of the most common types, which affects at least 1 in 500 people worldwide is called hypertrophic cardiomyopathy or HCM. In this form of inherited cardiomyopathy, the walls of the left ventricle are abnormally and usually asymmetrically thick, resulting in stiffened and hypercontractile left ventricle. Another form of inherited cardiomyopathy is dilated cardiomyopathy or DCM, in which the ventricles are weakened and enlarged, usually with a reduced systolic function. There are also more rarely seen inherited forms of cardiomyopathy, including right ventricular form, noncompaction cardiomyopathy, where the walls of the ventricles are highly trabeculated, and even restrictive cardiomyopathy where the atria become enlarged as a result of thick ventricles. Importantly, symptoms vary tremendously amongst patients who have these cardiomyopathies and their family members. Some patients who have cardiomyopathy are totally asymptomatic and others have severe symptoms.

Dr. Caudle: So how can we, as clinicians, detect patients with inherited cardiomyopathy?

Dr. Owens: The best way to detect patients who are at risk for inherited cardiomyopathy is to start with a detailed multigeneration family history. Questions that we ask include direct questions such as, 'Do you have a family member who's been diagnosed with heart disease, cardiomyopathy, or heart failure?' and also less direct questions such as, 'Do you have a family member who died suddenly of either unknown or cardiac causes?', 'Is there someone who died at a young age?' 'Or someone who's had a heart transplant or a defibrillator or a pacemaker implanted?' If someone has that suddenly, it's important to inquire whether an autopsy or postmortem genetic testing has been performed, which can be useful. If concerning family history or symptoms are present, we then take the next step of an office visit with a cardiologist for an exam and EKG and an echocardiogram to evaluate the structure and function of the heart. In some cases, if we need additional information, we perform a stress test, a cardiac MRI, or a Holter monitor.

We know that, uh, inherited forms of cardiomyopathy can arise at any point in your lifespan, from infancy all the way to elder years. And for that reason, we suggest that patients have periodic cardiac imaging and exams throughout their lifetime if they have a known family history of inherited cardiomyopathy. We also now use genetic testing to risk stratify patients who are at risk for familial cardiomyopathy. We start by doing the genetic testing on the person in the family who is known to have cardiomyopathy. If we sequence the genes that we know cause cardiomyopathy and find the change in their DNA that causes disease, what we call a pathogenic or disease-causing variants. Then we can test any interested blood relative for that specific change in DNA. And the inherited cardiomyopathy, we know are inherited for the most part in the autosomal dominant manner, meaning that each child has a 50% chance of inheriting the pathogenic variant from the affected parent like the flip of a coin. If someone has the pathogenic variant, but their heart is currently normal on echocardiogram, they're still at risk for developing cardiomyopathy at some point in the future. And these are the people that need to have ongoing follow-up and ongoing testing. If, on the

other hand, the child did not inherit the pathogenic variant and their heart is normal by echo, then we do not think they're increased risk in the future to develop the cardiomyopathy, and they can be dismissed from needing routine lifelong follow-up. The caveat to using genetic testing is that it's not perfect, and in order to re-stratify family members, you really need to be confident that you found the disease-causing variant.

Dr. Caudle: So, Dr. Owens, what are the current therapeutic approaches physicians implement in practice when treating patients with cardiomyopathies?

Dr. Owens: One of the challenges of treating patients with genetic cardiomyopathy is that we have very few, if any, targeted therapies. We use medications that have been designed to treat other cardiovascular conditions such as hypertension or arrhythmias and use them for theoretic and symptomatic benefits.

We tailor the therapy that we use based on how the heart is structured and how it's functioning. For example, for hypertrophic cardiomyopathy where the heart muscle is thick and stiff, it can be difficult for the heart to relax and fill, and also difficult when the heart empties because there can be obstruction to blood flow. So we tend to use medications that slow the heart rate and relax the heart, like beta blockers and calcium channel blockers. For patients with dilated forms of cardiomyopathy where the heart is enlarged and weakened with reduced systolic function, we use medications that vasodilate the peripheral blood vessels in order to reduce actual load on the heart. And we sometimes use diuretics to manage volume overload. Importantly, none of these medications are targeted to treat the underlying genetic cause of cardiomyopathy.

Dr. Caudle: Dr. Owens, you were part of a team that recently completed exome sequencing at the Perelman School of Medicine on the LMNA gene to evaluate its link to cardiomyopathy. So, what did your team discover? And what will it mean for patients with this LMNA cardiomyopathy?

Dr. Owens: We know that pathogenic changes in the gene, Lamin-A, can cause a number of medical problems throughout the body, including cardiomyopathy and arrhythmia. What was novel about this study was that we were able to utilize what's called a genotype first approach, so looking at Lamin-associated cardiac disease. We did this by using the large population enrolled in our Penn Medicine Biobank to find patients who have disease-causing changes in Lamin-A, looking at the gene first, and then looking in our electronic health records to see what their hearts look like. We found that many patients who have Lamin-related heart disease and perhaps disease in other organ systems have not yet been clinically diagnosed with genetic disease. This means we need to have a higher suspicion of genetic disease to make the correct diagnosis, and hopefully the right treatment.

Dr. Caudle: So could you share a few of the recent innovations in the management of the genetic cardiomyopathies?

Dr. Owens: Yes, there are a number of groundbreaking clinical trials investigating targeted treatment of genetic cardiomyopathy. Our group has participated in clinical trials, investigating the role of mycin inhibitors, novel compounds for hypertrophic forms of cardiomyopathy, and mycin activators for dilated forms of cardiomyopathy, and a compound to treat Lamin-related cardiomyopathy, as well. There are also drugs in clinical trials which treat infiltrative forms of cardiomyopathy, like amyloids, which can run in families, and storage disorder, like Fabry disease that affects men more than women, and is inherited. It's absolutely an exciting time to be a genetic cardiologist.

Dr. Caudle: And before we close, Dr. Owens, how and when should physicians refer our patients to Penn Medicine?

Dr. Owens: If you are seeing a patient in your office and you elicit that important family history of cardiomyopathy, sudden death, young age of transplant or defibrillator/pacemaker placement, then it is important to start with the clinical screening of that patient, including echo, EKG, and exam. And then if they're interested in pursuing genetic testing, counseling, or targeted therapies, it is important to refer them to an academic center that's able to do that.

Dr. Caudle: Excellent. Well, that's a great way to wrap up our discussion. I – I'd really like to thank my guest, Dr. Anjali Owens, for shedding some light on the connection between inherited cardiomyopathies and genetics. Dr. Owens, it was great having you on the program today.

Dr. Owens: Thank you so much.

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