Announcer: Hello, my name is Paul Friedman. I'm chair of the Department of Cardiovascular Medicine at Mayo Clinic in Rochester, Minnesota. And I'm delighted to be joined by my colleague, Dr. Naveen Pereira, professor of medicine and genetic cardiologist with expertise in circulatory failure. Naveen, thank you for joining me,

Dr. Naveen Pereira: Paul. Thank you for having me. And this is obviously a topic of great interest to me and I'm happy to try and shed some light.

Dr. Paul Friedman: Yeah, I think it's a topic of great interest to all of us, and it's really a dramatically and importantly changing field. So let's jump in with some very basic fundamental questions. Who should get genetic testing if you identify somebody with ventricular dysfunction?

Dr. Naveen Pereira: Right, so, so that's actually a very important question. And the published guidelines by the American College of Cardiology, the American Heart Association, the Heart Rhythm Society, et cetera. And I would urge the listeners to read those guidelines, but in from a broad perspective. So heart failure with reduced ejection fraction is broadly classified as we know, into ischemic heart failure, those who have coronary disease. And then there's this whole entity of non ischemic cardiomyopathy. And within non ischemic cardiomyopathy, dilated cardiomyopathy is the most important cause of the non ischemic cardiomyopathies under heart failure reduced ejection traction. And so in my opinion that if there is no secondary cause of heart failure reduced ejection fraction, which is by definition dilated cardiomyopathy. And when you search for secondary causes, we are talking about making sure iron study is okay, thyroid is okay that this is an amyloid and such inflammatory causes, and we'll go to inflammatory causes in a minute. But, so if there are no obvious secondary causes, then doing genetic testing is useful. Now, genetic testing yield in these type of cases varies. So getting a family history actually is helpful, but it's not absolutely predictive that a genetic test would be positive. So a positive family history in a person with dilatative cardiomyopathy, the yield of genetic testing could be up to 40%. So up to 40% people have a positive result. And if there's no family history, then 20 up to 20% may still have a positive genetic test result. And this may occur because maybe family members are not screened. There may be some other family members who may have cardiomyopathy and they're asymptomatic. And we certainly seen that it'd may also occur because of what are known as de noble genetic variant. So genetic variance that occur not necessarily inherited from the parents, but a carino, but then the patient's genetic footprint.

Dr. Paul Friedman: So someone with reduced injection fraction heart failure with reduced ejection fraction and no clear pathogenic. Cause genetic testing is a pretty reasonable next step, which gets us to what is the process of genetic testing? How do you go about doing it?

Dr. Naveen Pereira: Right? So traditionally the model has been, so first of all, you can get DNA from the patient either by getting a blood test, or you can also spit saliva in a cup and send it to the genetic testing

company. Traditionally, when we've done genetic testing, we have always involved a genetic counselor. So we say one genetic testing this patient, we refer them to a genetic counselor. And that's ideally the best thing to do because the genetic counselor can tell them basically what to expect from the genetic results with whether it's pathogenic, likely pathogenic variant, or there's something called variant of uncertain significance, which I call a gray zone variant, where we are not sure whether it's pathogenic or likely pathogenic or benign. So proper preparation of the patient as to what to expect from genetic testing implications regarding insurance, et cetera. That is part of genetic counseling. So we've traditionally asked patients to see genetic counselors and then they arrange for the genetic testing, it's either blood draw or survivor sample. It takes approximately two plus weeks for the genetic results to come back. The commercial entities that do what is known as gene sequencing, they actually outline the letters of the DNA, and remember, they only look at certain genes that have been implicated in cardiomyopathy. So they don't look at all the, your whole genome or whole exome as we call it. So it's possible that you may get a, a negative genetic test because they're looking at 81 genes, et cetera, that are known to be a socio cardiomyopathy. But we have some patients where the family members basically are also affected. It's clearly a familial disease. The standard cardiomyopathy panels may be however you can do more advanced testing, but that's for more advanced centers. If that becomes an issue, the genetic counselors know that. Now, what we found in our practice is patients didn't wanna come back. So they came and saw the doctor and they said, and we said, well, can you, do you wanna go genetic testing? Well, do I have to come back for another appointment for this? And I'm not really interested. Also, in the old days, implications of genetic testing only meant that it gave you a molecular diagnosis for your cardiomyopathy, but there were no clear prognostic or therapeutic benefits of doing genetic testing. And so what we did, since patients don't wanna come back for a separate appointment, is we streamlined the process of genetic testing within the heart failure clinic. And I believe we are one of the first centers to do this. And it became so easy. So we actually preemptively put the order for genetic testing in the patient, new heart failure patient who came to see us, and then it was up to the practitioner to opt out. And so the, the practitioner, the physician clinician said, well, this patient has coronary disease, I don't want genetic testing. But it made the clinician threaten think that, well, maybe we should get genetic testing. So our genetic testing re uptake, I mean performing genetic testing doubled with introduction of this opt-out system. And then the patients, if they have agreed, after talking to their clinician, they basically, the heart failure nurses helped them and the heart failure nurses would show them a video that was prepared by a genetics counselor. So all the elements of genetic counseling were described in detail to the patient. And then the heart failure nurse filled out the paperwork and the patient had a blood test and the results would come back in two weeks to a cardiovascular physician who has expertise in genetics. And so it really came back to me and we would review the results and if they were positive or there were questions, I would call patients and let them know the results. So that's kind of how the process to really

Dr. Paul Friedman: Make it happen. Then you have to set up your practice in a way to integrate it or refer the patient to a center of excellence where it's part of their standard back. But - the test is hard, but the counseling to do it properly requires some measure of well, training and thoughtfulness so that people know the implications of the test.

Dr. Naveen Pereira: Right? And Paul, also, the insurance coverage becomes an issue. So I think the, there are some companies that assure a fixed deductible. So that was very helpful for our patients because the uncertainty whether insurance would pay or the copayment by the patient also created some angst with patients. And so working with a company that had an assured deductible for the patient, if it exceeded that deductible, that company would call patients and let them know if it was okay to proceed. So partnering with the patient, understanding the financial obligations was also an important component of the success of this process,

Dr. Paul Friedman: That clearly we don't wanna un have an unanticipated financial burden for our patients. Right? Really important that all angles are looked at. How does it benefit the patient? So someone presents with heart failure with reduced ejection fraction and you offer genetic testing, what benefit might they or their families get from that?

Dr. Naveen Pereira: Right? And that's really, you know, an important question that patients ask. And so, so couple of things. So one is I tell patients if you have a positive genetic test result, it gives you a molecular diagnosis for your condition. So usually we say idiopathic or maybe you had a myocarditis in the past and now you have a weak heart, et cetera. So some patients really like the certainty of their diagnosis. A second thing is that if that patient has family members, so we generally recommend first degree family members then to be screened for that pathogenic, likely pathogenic variant. And if any of them have the variant, then there is some, they add higher risk of developing cardiomyopathy. So there really should be high vigilance and periodic echoes. You know, depending every year or three to five years, depending on what the echo shows would be, surveillance would be instituted for the positive genetic quote unquote carriers of, of the family members among the family members. But if someone's gene negative, it takes away that whole, you know, cloud or the patient patient's, family members that, well, my father or mother had a genetic test that's positive. I may have it. Well, you can sort out that uncertainty by the family member getting the genetic test. So they don't, they at this, what we call this population risk of developing cardio, they're not at an increased risk. So that's I think very helpful. The second real benefit, Paul, and you are familiar with these, there's certain types of cardiomyopathies that are extremely arrhythmic. And we traditionally put ICDs when your ejection fraction is less equal to 35%. That's what the guidelines say. But there's some cardiomyopathies, like FLNC for example, filament C cardiomyopathy, highly arrhythmogenic, LMNA highly arrhythmogenic people with normal ejection fraction with LMNA could be at risk for arrhythmias. And so their criteria now established, but the genetic diagnosis will guide you whether to put an ICD earlier in these patients to prevent sudden death. And we all have heard of seen patients who, even though you have not low enough, have had sudden death. And so, so genetics can solve that. In fact, you know, when I think about any arrhythmia trial, the device trial, really I think genes should be the first kind of screening process in at least patients with cardiomyopathy. The third thing is sometimes diagnostic dilemmas. So for example, in our sarcoid clinic, we had patients presenting with inflammation on PET imaging and MRI and fortunately physician, the sarcoid clinic started ordering genetic testing and became part of their routine. And what we found was some of these patients actually had a genetic cardiomyopathy and they didn't have sarcoid. And it's well known that some genetic cardiomyopathies have inflammation as a presenting feature. So that became really, really interesting. And we are not sure, like unlike sarcoid, if it's a genetic cardiomyopathy that

lights up on a PET scan or MRI, we are not sure whether immunosuppression will work for them because it could be that it's the genetic driver causes cell death and results in inflammation and it's not a primary inflammatory process. So, so, so the whole diagnosis, I mean I've, I've had patients who were scheduled for heart biopsies and I've called the physician and said, we know why this patient shows inflammation or Pet imaging, it's a genetic cardiomyopathy. So you, you don't need to do a heart biopsy in these patients. And now Paul, most importantly, we have therapeutics directed against a specific genetic cardiomyopathy. So we are in a phase two trial testing a certain drug for certain types of genetic cardiomyopathies. There's now a gene therapy trial that's in human phase two that's testing gene therapy.

Dr. Paul Friedman: So just to be very clear about this. Then a specific genetic diagnosis will determine which specific drug might be used. Very different than the general concept of beta blockers, ACE inhibitors, et cetera, for all low EF patients. These are very specific agents and I may ask you to give a little more detail there. And we're now seeing CRISPR technology to actually change the DNA in patients with some genetic cardiomyopathies being tested, right? Not yet approved, but as part of a clinical trial.

Dr. Naveen Pereira: Absolutely. And Paul, I can predict that over the next decade that's gonna be standard of care. And so, you know, the system we set up has put us at a great advantage because we have so many patients who've had their genetic etiology identified. So now if there's a certain therapy that's approved for that specific genetic cardiomyopathy, we can identify those patients. We don't need patients to now come in and get genetic testing as they're being seen in heart failure clinic. We already have a pool of patients who we know have specific genetic cardiomyopathies. And so say filamin c again, if there's a gene therapy that's available, we can approach that patient and say, Hey, there's a gene therapy available, or CRISPR Cas9 treatment available for your underlying condition. And also them over and above, because remember, data indicates that people have a genetic cause of cardiomyopathy, have a worse prognosis. So if you do genetic testing in patients who are awaiting heart transplant, who have undergone transplant, the, the, that population is enriched with genetic cardiomyopathies indicating that genetic cardiomyopathies of worse prognosis land up with more advanced short cell therapy. I see. And it makes sense, right? I mean, standard therapy will only attenuate the disease so much, but you're not changing the fundamental underlying genetic driver of the cardiomyopathy.

Dr. Paul Friedman: Yeah, no, I wanna go back to one thing you mentioned earlier. 'cause I think for many people listening who may not have a big depth in genetics, the kinds of results you might expect when you get it, walk us through what they are, what they mean, and what it means to the patient.

Dr. Naveen Pereira: Right? No, that's very important. So, you know, if a physician sees a genetic test result, patient is seeing a physician, they need to understand. And so in general, there are three types of results. One result would be benign, meaning that there is no or negative, so actually four types of results. Negative meaning that as there was no genetic variant identified in any of the cardiomyopathy related genes. And so that's a negative gen gene test. But again, we always tell patients we may have

not, we may have missed a gene, at least in the genes tested, this is negative. And therefore it's always useful if there's a strong suspicion that there's a genetic cause to consider repeating genetic testing, say five years down the line because the gene panel keeps on changing actually. So,

Dr. Paul Friedman: So you're not expecting the patient to change, but the panel to change. And because it is genetic on the other hand, what about the role of whole exome sequencing that is non-commercial at this time? Do you want to comment on that a little bit? What is it and when do you use it?

Dr. Naveen Pereira: Right. So institutions can offer whole exome sequencing and what it, what that, so we have approximately 23,000 genes. And of those 23,000 we are testing 80 plus that may be associated cardiomyopathy. So there are genes out there that we may not know of. And so we can do whole exome sequencing. So the Center for Individualized Medicine at Mayo Clinic offers that service. And in fact, we have had many undiagnosed, or what we call as diagnostic odyssey cases where people don't know what the diagnosis is. And they've had holding some sequencing, and we've had answers, and I don't wanna go into details of a case, but there was a patient, a hyper, so-called hypertrophic cardiomyopathy, heart biopsy. So the great clinician who saw the patient said, this doesn't look like hypertrophic did biopsy. There were laminar bodies within the cardiomyocyte. So it looked like type, some type of storage disease had all standard genetic testing done. It wasn't fabry it wasn't danon and other types of inter glycogen storage, et cetera. So finally that patient underwent whole exome sequencing. And what we found was, I mean this is very rare, right? But what we found was that this patient had mucopolysaccharidosis type three A, a sanfilippo syndrome, which occurs only in infants and most of them are dead in their teens. But this patient was in our forties and had Sanfilippo syndrome. And the only clue that we got to test her for sanfilippo, you can do urine and blood tests, was through wholesome sequencing. Interesting. So it's very useful diagnostic test in difficult cases.

Dr. Paul Friedman: Sure. But again, only in academic centers as opposed to the much smaller commercial test. But you were starting to tell us, and we'll conclude with this on the four possible results from gene testing.

Dr. Naveen Pereira: Yeah, negative, so negative. And then you have some variants that we call this benign variants that, that there's a change in the letters of the DNA, but we don't think it's causing a, a problem with the gene function or the function of the protein or its structure of the protein. So those are benign. The third is a pathogenic or likely pathogenic variant. And so the company that reports these is highly certain that this is causing the disease process and calls it pathogenic, likely pathogenic. And the American collagen medical genetics have come out with very strict criteria as to when you can call a variant pathogenic, likely pathogenic. And so those companies reported as per ACMG criteria. So then you can confidently tell the patient you have a genetic cause for your cardiomyopathy. And the last is the gray zone, the variance of uncertain significance. And what happens with these is there's not enough evidence. It may affect protein structure function, but it's a guess. It may be very rare and rarer the variants more likely they are that they're causing disease. Otherwise, if it's common, then the disease

would be very common, right? So, so it's kind of a selection process. So, so the, and interestingly enough, our patients sometimes, okay, most of the times I would say I've talked to them, okay with this uncertainty. And if there are variants of uncertain significance over time, they get sorted out. It could be they go into the benign bin or they go into the pathogenic, likely pathogenic variant as more evidence comes in regarding that variant. So those are the four types of results we've seen.

Dr. Paul Friedman: Well, Naveen, fascinating space rapidly changing and transforming medicine and how we practice it. The more we understand our biology with precision, obviously the better we'll be and identifying the right treatment for the right patient. So thank you so much for educating me and all of us on this exciting field and we'll look forward to updates.

Dr. Naveen Pereira: Thanks Paul. You summarized that beautifully and that great questions and I appreciate the opportunity.