Managing Cardiomyopathies in Lysosomal Diseases

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Hello everyone. Welcome to the second session of the CME series of Lysosomal disorders for this year. As you may recall, we are focusing on different systems on this series. And the subject of today's talk, is going to be the cardiovascular system.

I want to do an introduction before I start introducing our speaker. So when we are teaching students or fellows of about Lysosomal storage disorders, obviously we emphasize the fact that the lysosomal disorders are multi-system diseases. So every single system is involved in a lysosomal disorder of varying degrees. So what you're seeing in a slide as the ones that are highlighted are the lysosomal disorders that may present with cardiovascular vascular involvement as the initial presentation. So obviously we have the glycogen storage disease or the Danon type-2 or Pompe disease or Danon disease.

The LAMP2 deficiency, which we call as lysosomal myopathies, can primarily present as a cardiomyopathy. The telltale, the poster disease for adult onset cardiomyopathy in lysosomal disorders, is obviously Fabry disease. However, I included other disorders, like valve involvement or myopathy has been reported in other conditions, either primarily or secondarily in the disorders that are listed here. So when we say cardiomyopathy, it can be hypertrophic, more comes to mind, but it can be dilated as well. The cardiovascular disease or coronary artery involvement, rhythm disturbances or valvular disease are commonly encountered in a lysosomal disease patient. So the importance of the age of presentation and when we are seeing a patient also may help to differentiate some of the phenocopies. So if we are evaluating a neonate or an infant in the emergency room, so the first thing that comes to mind that in more areas of energy metabolism, that may include obviously the mitochondrial cytopathic, but this also can include a Pompe disease infant.

So if you are as old as I am, and then if you practice in the emergency room, the typical presentation of these babies with some hypotonia, but major respiratory distress, and then if you do an x-ray, they have very, very large heart. They actually almost fill the whole entire chest. As the patient ages during the childhood or later adulthood, obviously we need to think about the other myopathies including Danon disease and late onset Pompe disease, Fabry disease, and also the other conditions, the MPS with the valvular involvement, especially if they do not have a significant facial phenotypic presentation. So cardiovascular system, what are the theories, how is involved in a lysosomal disease? So basically we're taking this from the animal models and multiple lines of evidence that heart is involved or the cardiovascular system is involved either primarily or the secondary during the inflammatory process.

So basically, in the animals, when there is impairment of lysosomal acidification or lysosomal dysfunction, they have seen that there is left ventricular enlargement that accompanies contractile dysfunction. So this is a animal model. And then these animals do have actually TFEB abnormalities. So how the TFEB, obviously this is the master of the molecule that regulates the lysosomal pathway. There are multiple signaling pathways including the immune and other cytokines interact with TFEB leading to the accumulation of autophagosome. So basically this is in addition to the impaired lysosomal acidification. So there is impaired degradation secondary to death or the TFEB dysfunction. So as we know that the multiple animal models also demonstrated augmentation of autophagy, it worsens cardiomyopathy in animal models. Actually, the good example for that is actually Pompe disease where we had autophagic vacuoles. The dysfunctional lysosomes actually are accompanied by the cardiac hypertrophy and cardiomyopathy.

So as we said, the downstream activation of the inflammatory pathways may lead to rhythm disturbances in wild type CKD mouse. So this is the secondary involvement in Fabry disease. So we know that the worsening of the kidney function also accompanies the worsening of the cardiac involvement.

This is another evidence why we're seeing this Fabry disease. Obviously there is the inflammasome activation also associated with electrical remodeling, enlarged atria, atrial fibrosis and atrial fibrillation. So we discussed this figure quite a bit, but I just want to remind the audience about the presentation of lysosomal disorders. So these are mostly enzyme deficiencies and then there is a threshold where the patient is not symptomatic and then the mild symptoms start and the phenotypes can range from mild to severe.

So Fabry disease is a good example for that and we know that the cardiomyopathy or Fabry disease associated cardiomyopathy actually can start even at the milder phenotypes. And then if you could remember what we called, was a cardiac phenotype or cardiac type of Fabry disease. We know that this is a misnomer because these patients do also have the other systems involved, but obviously it seems like cardiac tissue actually seems to be more vulnerable at presentation with the Alpha-gal deficiency.

So this concludes my very brief introduction to this session, but it is my pleasure to introduce Dr. Jefferies today. John Jefferies holds an MD and MPH and he comes with multiple accolades and multiple very prestigious titles. One of them is he's the governor of the American College of Cardiology at the Tennessee chapter. He's also a research associate at the St. Jude's Children's Research Hospital. And to his portfolio, he is also the team cardiologist for the NBA team, Memphis Grizzlies. Dr. Jefferies has published close to 300 peer reviewed research papers. He edited multiple cardiology textbooks and he also wrote manuscripts and book chapters on cardiomyopathy, cardiovascular genetics, advanced heart failure, and his research interests include obviously the cardiovascular genetics. We're going to be hearing from him cardiomyopathy with an emphasis on Fabry disease, obviously with the management of the cardiomyopathy and inheritable disorders. So Dr. Jefferies, it is my pleasure to give the podium to you. Thank you.

John Jefferies, MD

Thanks and a pleasure to speak to everyone today and I'll try and stay on time and we'll have opportunities at the end for questions. And then obviously if there are things that flow over from the discussion, I'd be happy to field questions or have one-on-one conversations. So you just heard a great synopsis of some of the cardiovascular implications of LSDs. We'll focus mostly on Fabry today. But that being said, most of what we're going to talk about is translatable to different types of genetically triggered disease. These are my disclosures. I'm involved in a lot of the research, mostly in the Fabry space, but also in Pompe and Goucher as well. So this is a bit about some of the information we hope to cover today, and you heard a great intro that LSDs and the heart, we really do need a lot of guidance. As you heard, almost all of these diseases have some sort of cardiovascular implication.

Most of the time, that just boils down to how aggressively you're looking for it. And we'll talk a little bit about how to phenotype patients. What does the cardiologist's role in this multidisciplinary team? Just some ideas, some examples of what we see in the Fabry and Pompe space, what we consider best practices, and then some of the research trends in this area. And then obviously, hopefully some time for some Q and A. So our objectives today, one, will hopefully describe what the role of the cardiologist is in the team approach to care of very complex patients as you all know. Some of the best practices to managing the cardiomyopathies and not just the cardiomyopathy, but the concurrent sort of phenotypes that go along with myopathic disease. And then what we would say some of the best practices are. So as you all know, very heterogeneous group of conditions and you just saw a wide display of different diseases where we're talking about MPS sort of based diseases more in the Fabry space, which is what we'll talk about. Very heterogeneous at the genetic level, but some of the phenotypes are overlapping.

And we'll talk more about just how do you leverage available diagnostic tools to really sort of what I would call deeply phenotype these patients. As you all know historically, oftentimes these were grouped more on the storage or the kind of deposits as you heard about. But more recently we're kind of thinking more about on the nature of the protein defect itself. And obviously these protein defects inevitably have some sort of downstream implications for the cardiovascular system. So we know the implications can be significant. I'll tell you ahead of time, we know for Fabry this is currently the leading cause of mortality is cardiovascular disease and it's a significant driver not only of mortality but of morbidity. So this is something that really should be important to providers and obviously is important to patients.

And so how is it that cardiologists are involved? And a lot of this has to do not only with the treatment, but really our strategy on this has been more about active surveillance. So our view on cardiovascular implications is usually the earlier you can find disease, the earlier upstream, greater opportunity to offer intervention and maybe bend that curve of involvement over time. So our approach is that a proactive and very durable longitudinal approach is needed for the cardiovascular surveillance. I won't spend time on this because you guys all know this already, but obviously a disease of deposition, which leads to obvious phenotypic changes over time. And just to reiterate some of the things that you've heard, but we know this idea of sort of presymptomatic ideas exist. In the Fabry, for example, we know deposition is occurring in utero.

So once again, if you really, really look aggressively, how early can you find the phenotype of cardiovascular involvement in Fabry, for example? And we've done a lot of the work on the pediatric side, and you don't necessarily see things like LVH as you heard about or these kinds of HCM phenocopy idea, but you do see other things and they're not always muscle. Usually they're related to the electrical system. So the earliest phenotypic evidence we would see in pediatric patients would actually be sinus bradycardia or some other rhythm or electrical disturbance. So you think, "Well, I'm doing surveillance, I'm doing an echo that's more than enough." It actually isn't enough because that's not actually the earliest place you're going to see disease. But then we know these are progressive diseases, the burden continues to increase every day. And so there eventually becomes a tipping point where there will become overt phenotypic changes and then ultimately symptomatic disease.

And you've probably seen this specific to Fabry for example. We know a lot of the findings that precede cardiovascular disease, the things like heat and cold intolerance and anhidrosis and all those sorts of things, fatigue, which we see across the spectrum of a lot of these diseases. But we say cardiac dysfunction is in adulthood. And what I'm trying to tell you is that that actually is a bit of antiquated thinking. It actually turns out that we see involvement much earlier than adulthood, and it's incumbent on us as providers to actually use the right tools to look for that cardiovascular involvement. And these are some of the spectrums just for Fabry, but these can be found across a myriad of these sorts of diseases and phenotypes.

So what I would advocate for you is when you think about these diseases is that we really don't know as much as we think we do. I can say that confidently about Fabry and Pompe and Gaucher, at least with a cardiovascular disease, because we learn more and more every day. And most of that is because of the tools we use to look at the heart and the vascular system. But this is a list that would be generic to almost any kind of disease, a genetically triggered disease that you might see involvement.

So obviously in Fabry we do see systemic hypertension. Some of that is from vascular disease and endothelial dysfunction and thickening of the musculature, but it also involves the kidney as you heard. And so we obviously know kidney disease can drive systemic hypertension. You do see LVH, we see rhythm and conduction disease as I was just saying. We do see valvular disease, it's usually left sided and Fabry for example. So it would typically be mitral and aortic, not so much tricuspid or pulmonic. We do

see vasculopathy as I was alluding to. Interestingly, we see ischemic heart disease, so premature coronary disease. Sudden death of course is something we try and avoid and we'll talk a bit about maybe some ways to think about that in these populations. And then we can see dilation of the aorta and not typically progressing to the degree of a true dissection. But we do see aneurysmal disease in a few patients. It's rare, but it's increasingly being seen, especially with some of the imaging modalities that we leverage currently.

So part of my goal was to tell you what I think the role of the cardiologist is, and obviously in centers that really do this at a high level, there's usually going to be a multidisciplinary approach. And I know that sometimes that's a limitation of resource and space and providers. But ideally, the way to deal with this is a multidisciplinary team because these are complex patients with multiple organs being involved. And so the cardiologist is one member of that team. And the biggest component of that is just good communication. But remember, cardiologists have little sub-subspecialties within. And what I do is heart failure, cardiomyopathy, transplant, genomics, but we have people that put stents in obviously, so interventional cardiologists. We have people that do rhythm disturbances, more of electrophysiology.

And so within cardiology, there are sub-disciplines that also may be involved in the care of the patients over time. And these patients can manifest with any of these problems. We talked about coronary disease, we talked about rhythm disturbances, we talked about bradycardia, we talked about aortic disease. Maybe in having a surgeon involved in these patients may be a part of the pathway because these phenotypes are very, very complex. No one patient is the same compared to another, and their dynamic. They change over time. So the role of cardiologist is actually to be thoughtful about the different types of cardiology that needs to be implemented to take the best care of the patient. Just for Fabry, but this is also translatable across other diseases is the idea of, "Okay, what's going on at the cellular level?" And we heard a little bit about that, exactly what are we doing? And from a deposition perspective.

We see changes in hypertrophy from the cellular level. I'll show you some data. It's not just cellular. We actually see changes in the extracellular matrix as well, which is an important prognosticator of disease. See changes in the endothelium, which is obviously important when we talk about vasoconstriction and vasodilatation. And then we talk a little bit also about the valve disease. And usually the valve disease out of all of these things is probably the least implicated in most of the patients that we manage. So here is also sort of a broader idea of what's going on. And as I say, it's actually even a little more complicated than this, but we do see changes at the myocyte level, and that's driving some of this hypertrophy that we see on ECHO or MRI. And we know that that causes this classic idea of diastolic dysfunction.

Diastolic dysfunction can be a part of a larger sort of moniker of disease called heart failure with preserved ejection fraction. And we'll talk briefly about that in a second. But obviously this can drive apoptotic mechanisms and cell death, which also can lead to systolic dysfunction, so the squeeze component of everything. We see changes with the vasculature as we've talked about in myocardial ischemia, and then obviously the conduction system, remembering that conduction system tissue is different than cardiomyocytes. We're talking about Purkinje fibers and other things, which also can be subject to deposition and disease. And this is kind of a large approach to looking at Fabry and some of the things that you might see. And you can imagine that when you overlap this with common diseases, this can become a little complicated.

So we have a Fabry patient who comes in and maybe they have chest pain, and the question is, are they having an MI? Because we know they're predisposed to myocardial infarction, but it actually turns out they also have baseline elevated high sensitivity troponins, which is the biomarker we use to look for myocardial ischemia. So these are all things that make the care of patients with Fabry, for example, or

any LSD very complicated because some of the biomarkers we may use in the normal or general population are automatically potentially abnormal in some with Fabry. And so Fabry patients we saw are turning over cardiomyocytes just as in hypertrophic cardiomyopathy. You heard alluded to sarcomere based disease. They're constantly turning over cardiomyocytes, which means they're releasing troponin. So if their troponin is a little bit elevated, that's just normal for them. It doesn't mean they're having an acute coronary syndrome. So it just is a complex thing and you have to really have some understanding of all this if you're going to take good care of the patients.

This is a sort of a longitudinal timeline or a horizon, if you will, about how things change over time. And these are some of the end endpoints that you can look at along this progression of disease, if you will. And as I said, from my perspective, we try and be as far to the left as we possibly can. Some of that's because the question is maybe does the patient have cardiac involvement because we won't consider a therapy specific to the LSD. Maybe we want to start ERT, something like that. Does the patient have cardiac involvement? Well, that in part depends on the tests that we use. And I'm going to show you some data about that in just a second. But these are some of the nomenclature that you see floating around how we look at cardiovascular phenotyping in these cohorts.

You'll think this GLS, which stands for global longitudinal strain. We'll talk a little bit about that Low T1, so T1 mapping. We'll talk a little bit about that. Troponin, we talked about. NT-proBNP is a natriuretic peptide which we can look at. So all these things are available, but the question is how do you interpret them? And so we'll try and spend a little bit of time talking about that. The main takeaway on the cardiology side, and this is true of anyone, especially when it comes to cardiomyopathy and heart failure, once someone becomes symptomatic with heart failure, their trajectory has changed for the worse. Period. And if you get admitted with that heart failure, your trajectory has dramatically changed.

So anything you can do to detect the disease and avoid that heart failure decompensation or the admission is obviously a big deal. Similarly, obviously if you incur a stroke, the opportunity to get back to normal or baseline becomes really challenging. So everything that we do should really be about trying to anticipate these potential problems and avoid them if at all possible because obviously they can be lethal. As I said, cardiovascular complications, now leading cause of mortality used to be kidney disease. You've gotten a little bit better in that direction. Most people have symptoms if you ask carefully about it, and these ideas of chest pain, shortness of breath, which are relatively nondescript. The point is if you're starting to have symptoms, the horse is probably already out of the barn from the phenotype perspective.

And so what can we do to move further up? And you've heard me talk a little bit about this already. Most of the data that we reference in these diseases, if you do any searches, really are on adults and usually older adults, which is unfortunate because if you have damaged enough myocardium to have cysto-dysfunction, so your ejection fraction is low, you really have gone through a few doors that we can't come back through anymore. When you start seeing that kind of impairment and when you're starting to have symptoms, you have damaged a lot of your heart. So the ability to recover that is really, really hard. Even in the current era with a lot of the different medications that we have.

We've talked a little bit about this and you heard this in the intro, is that there's a lot of different mechanisms that are going on. You heard a bit about autophagy and some other things, which interestingly in most heart failure populations is a good thing. So the presence of autophagy actually in heart failure is a predictor of better outcomes in traditional kind of heart failure. But in something like Fabry or genetically triggered disease, it's actually can be a different kind of pathway. And a lot of this is still ultimately driving inflammation. If you look at inflammation, it is behind everything that I do as a cardiologist, whether that's atrial fibrillation, whether that's a stroke, whether that's heart failure, whether that's coronary disease, inflammation plays a role in all of that, and how can we sort of squelch

or mitigate that inflammation in a way that doesn't have deleterious effects on the patient, which is something we're still trying to figure out, at least in adult heart failure.

So I know we're talking about cardiomyopathy, but I wanted to bring in the idea of arrhythmias because for me, this talk is really about telling you what you need to be looking for in your patients. And as I said, usually the earliest manifestation is sinus bradycardia with or without symptoms. So remember, a low resting heart rate in the general population actually predicts longevity. That's a good thing. But in Fabry, it's actually telling us that maybe the sinus node has deposition, right? So there's some sort of disease there, or maybe even in the conduction system, distant to the sinus node. And we know arrhythmias are a big driver of disease, both brady and tachy. So slow and fast, and sometimes we'll do electrophysiologic testing, but this is one of those things you get through the conduction disease based on a simple electrocardiogram. Rhythm disturbances, you can get through monitoring devices and we'll talk a little bit about some of that.

But this is just kind of where you might see evidence of a slow heart rate where we're seeing some AV problems. So conduction along the electrical system. And this is commonplace and this is where we might think about a pacemaker in someone. And these are the kinds of things you might see on a routine electrocardiogram. And you might ask yourself, well, what else can I look on an ECG? The QRS and all these other kinds of things, all these little measurements that I get on an EKG, is there anything on there that might tell me that I need to be thinking more intentionally about the patient in front of me? And this is one of those things. So every ECG has a cure restoration. So you look at the top, it's already measured for you. You can measure it again if you so like. But when that QRS exceeds normal limits, so remember we measure those in milliseconds, if it gets beyond 110 milliseconds, that actually tells you that your conduction system is impaired in some way.

So the ability of electricity to propagate down through the electrical system is impaired. You see that by a lengthening of the QRS. And you can see here clearly once the QRS starts getting longer, that outcomes are worse. So you don't have to do any fancy crazy electrophysiologic testing to see this kind of stuff. This is on every EKG that you order. And this might prompt you to think, well, if this is going on, are they prone to any other problems like rhythm disturbances? And so that requires doing a little bit more testing, right? So you see on the left is a conventional ECG, but that's like three seconds. Then on the top right, you would see more of a traditional, like a Holter monitor. So how you could wear a monitor for 24, 48, 72 hours.

Patients aren't big fans of these. They're uncomfortable. And obviously showering and all that kind of stuff becomes an issue, but it gives us real time data over some protracted period of time. Down the bottom left is a wearable. So that is a device that adhesive to the chest wall, and there's a little button on there that when you have symptoms, you can push it and it'll actually timestamp it and tell you the patient had palpitations. And those usually are good for about seven days, and you can change those out every seven days. And so that means you could get four of those. You could get a month's worth of data, which is helpful. But sometimes patients don't always read the textbook and they decide to have a palpitation or rhythm disturbance the day after they take one of these devices off, which is not uncommon.

Then you can actually go to the bottom, which is an implantable device. That's called implantable loop recorder. So that lives under the skin and the subcutaneous tissue, and that will give you up to about five years of rhythm data. So that's pretty impressive. And we started using these more in our Fabry patients. And what's interesting, I used it on a patient of mine, is a female, interestingly enough, and this is what we found she was having what's these presyncope symptoms. So she was getting dizzy, never passed out, never captured anything on conventional monitoring. We put a loop in, and this is what we saw. This is ventricular tachycardia. She had a defibrillator placed and then had two subsequent

appropriate shocks. So this is just about doing diligence when it comes to rhythm monitoring. And I would tell you strongly that this is the one area we pay the least amount of attention to in patients with LSDs, is rhythm monitoring.

We get captivated by MRIs and CTs and echoes, which is great, but this is what leads to sudden death, right? Heart failure doesn't usually lead to sudden death. That's a dwindling disease. This is what kills you immediately. So just something to keep in mind. So now we can move over more to the myocardium and what are we worried about or what are we paying attention to? This is an old slide. It's been around a long time, but it still has the same sort of impact. So when you talk to a cardiomyopathy doctor like me, we care about ejection fraction, but we actually care more about the shape of the ventricle. And so when the ventricle starts getting thick or big or enlarged, that's called remodeling, pathologic remodeling. And what you see in the top right and the top going from left, you see a normal heart and then the heart becoming diseased and becoming big and boggy.

So what I explain it to patients is that on the far left, a normal heart is kind of conical like a football. So if you cut a football in half, the end of that football is like a cone shape. When you have pathologic remodeling, it becomes more like a basketball, so it becomes more spherical. And that's actually what we measure on things like echo and MRI. When we look at the end-diastolic diameter and the axis measurements and the sphericity and all this kind of stuff, we are looking for remodeling. Similarly, in the bottom, you see what we see more commonly in Fabry or any other kind of storage disease is where the heart becomes thickened. So that's the idea of hypertrophy. People don't always recognize that a fair amount of the time, maybe one in 10 or something like that. That thick heart actually will turn into a thin heart, so it won't just stop it becoming thick. It will continue to become dysfunctional. And as opposed to being thick and muscular, it'll actually become thin walled and big and boggy.

And so that's going from a hypertrophic phenotype to a dilated phenotype. And all these things can be assessed with imaging. And so we'll talk a bit about some of the imaging. So when we talk about best practice from my perspective, the first step is accurate diagnosis. So we've talked a little bit about some of the rhythm and conduction disease, but the myopathic disease is really informed by imaging, and that's usually where things fall down in my opinion. Most people would leverage echo echocardiography because it's widely available and easy and cheap and all that kind of stuff, but unfortunately it'll miss a lot of the disease that we're talking about this early phenotypic disease. But the phenotype is important because it actually dictates which therapy you're going to use. And we'll talk a little bit about that in just a second.

We heard a little bit about hypertrophic and dilated. There are actually five types of genetically triggered cardiomyopathy, so phenotypes if you will, and you see four of them here. So that means we can see any of these in the setting of a disease like Fabry. The one that is not on here is arrhythmogenic. Cardiomyopathy is a very different disease. It's a disease of the desmosome. We don't usually see that in the setting of Fabry, but all of these other ones we can. And the management of these is all different. So just something to keep in mind and we'll talk a little bit about that in just a second. So as I said, echoes kind of what we typically leverage, mostly because people have access to it. And this is a still frame. This is a four chamber view.

Along the left, you see a normal heart and you see the sort of wall that separates the two chambers. That's the interventricular septum. And you see it in the right frame, someone with diseases is a Fabry patient where that is thickened and bright and white. That is left ventricular hypertrophy, and that's something that we're paying attention to. On the short axis here, even easier to see, this is where you're cutting a heart like a donut. Looking down on the left is normal, on the right, you could probably see that from the parking lot, obviously much thicker than the normal patient on the left, and that's conventional echo. We do two-dimensional imaging. We'll do three-dimensional imaging to look for the

chamber sizes in the e-ejection fraction. We look for color flow to look for regurgitation and whatnot. But it actually turns out you can do more advanced imaging with echo.

And this is this idea of strain and strain rate imaging. And basically what we're talking about is looking at a specific area of the heart muscle to see if it's squeezing and relaxing. So usually a heart, we're looking at the whole body of the left ventricle. What I'm talking about is a specific area of the heart. And you can see that here, is that all these little red dots under A, that's a normal heart that we're putting a dot on the heart muscle and we're tracking that.to see how much it moves. So how much it moves with contraction and then does it return and how quickly does it return with relaxation? So that's strain and strain rate imaging. And on the left that all red is completely normal, but you see on the right when we track someone with Fabry, for example, they have pockets of areas of heart that is not squeezing or relaxing well.

So you see areas of red would indicate things are pretty normal, but then you see different colors. You see some yellows and greens and blues that tells you those are areas of myocardium that are abnormal. And remember, you could have this abnormal strain rate in the setting of a normal ejection fraction. If you just glance the report and it says, "Well, the EF is 55, the patient is fine." But then you look at the strain rate imaging and it is actually abnormal that patient has a cardiac phenotype. Period. So a lot of this is just how deeply do you dig to diagnose the disease or cardiac involvement. This is the test of choice in cardiomyopathy clinics is to do CMR. Obviously there's some limitations in younger kids because of sedation, anesthesia, heart rate, that kind of stuff. But this is the test of choice if at all possible because it's very reproducible.

It gives you very exact things. But the biggest thing is it gives me the opportunity to look at the heart muscle itself. So if you've ever seen an echo, it's just a black and white image that's squeezing on a screen. That's what it looks like. With MRI, we can actually look at the heart muscle specifically and look for areas that have been damaged or even more so changes in the extracellular space around those cells. And we're going to talk about that in just a second. And importantly, there is no radiation exposure. People sometimes get confused. CT, there is radiation. MR there is none. So that is a safety thing. And here is someone also with Fabry disease. And so you can appreciate this is us looking at the heart that, I don't know if you can see my pointer, but that big gray blob in the middle there is the interventricular septum, which is much thicker than it should be.

But then you see the little arrows on the right picture pointing out to the area that should all be black. So that represents the muscle, that's the free wall of the left ventricle. And what you're seeing there is white instead of where it should be black. And that's evidence of gadolinium enhancement. Okay? So if you ever do an MRI, and you see this report says, "No evidence of late gadolinium enhancement or evidence of late gadolinium enhancement." So gadolinium is a contrast agent. We inject intravenously. In normal hearts, gadolinium is up. The uptake to the heart is quick, but it is cleared quickly. Okay? So when it's cleared, it's all black in this picture. But when it gets hung up in the heart, which is indicative of scar tissue for example, what should be black then becomes white. And what you are seeing here is late gadolinium enhancement. That is exactly what that represents.

But as you all know, some Fabry patients have kidney disease and sometimes can be pretty dramatic. And there's a cutoff that most labs would use a GFR less than 40 or less than 30, where they will not administer gadolinium because of potential negative impacts on the kidney itself. So the question is how could we look at the heart muscle without giving gadolinium? And that's where this cool technique called native T1 imaging comes in. So this is a pre contrast image to look and see basically at the health of the myocardium. And it's more important than just giving contrast. It actually gives you sort of a roadmap of the entire heart and it's all color coded, which is good for people like me who are not

imaging docs to tell what is normal and what is abnormal. And you can change these colors based on your preferences and all the different screens and the vendors and all this kind of stuff.

But you can see here on this particular slide, if you look at slide A, that's a completely normal heart. So the green circular thing is the left ventricle, and then in that is the blood, obviously the red, and where it's all nice and green and homogeneous, that is a normal heart. But then you look at someone with Fabry disease, one, it strikes you as the heart is much thicker. So this is left ventricular hypertrophy. It's what's called concentric because it's the entirety of the heart muscle. But you also see, as opposed to being nice and green, it's a dollar shade of green. And there are specs of blue and red. And this actually is abnormal T1 imaging. And this actually comes out as a number. And interestingly enough, Fabry disease is the only disease we know of where the number actually goes down.

Most diseases like aortic stenosis or coronary disease, hypertension, our T1 numbers actually go up, but Fabry, it actually goes down. So if you had an MR report and gave you a T1 value and it was below the reference range for your lab, let's say it's below 900, then that would tell you the patient actually has an abnormal value and has a cardiovascular phenotype. But then to corroborate that this is actually doing what we think it is, we give the patient gadolinium to say, "Well, it looks like in this area where there's kind of these red dots where there should be green that probably represents scar." How can we validate that? So we give gadolinium and then once again where it should be black, we see white in panel C. So it gives us very similar information without the exposure to the contrast agent.

And then lastly, this is something that I think is fascinating is how can we look at extracellular volumes? So we know that the cardiomyocytes are implicated here, but we also know if you expand the extracellular matrix, that is also a bad thing in the setting of most cardiomyopathies. And as that number goes up, as the extracellular volume goes up, mortality goes up. So your Kaplan-Meier curve is impacted negatively. You can get the same bit of information from an MRI. And high level centers leverage MRI in things like Fabry are doing these sorts of studies to see if the ECB is expanding. So it's not just about cardiomyocytes the milieu that it lives in.

And this is just sort of a nice kind of area showing us some of the things, all the different modalities that we've talked about. I guess you see some echo, you see MRI, and then you see some T1 imaging here, obviously with an electrocardiogram consistent with left ventricular hypertrophy. So just some nice sort of ways to bring it all together and remembering that these are things that can change over time. So the most common thing I see that is really depressing to me and avoidable is that maybe you send your LSD patient to a cardiologist, they get an echo and an EKG, both of which are red as normal, and the patient's told you don't ever have to come back because you don't have heart disease. Well, we all know that that's not true, and eventually the patient probably will have heart disease and maybe they weren't using the right modality to look at the heart.

So this isn't just a snapshot thing, even if it's normal, you got to keep looking, but also people that have abnormal disease, you're going to potentially see changes over time, so you just got to keep paying attention. So we'll divert a little bit in the last few minutes just into the way we look at heart failure in the adult world as is applicable to what we're talking about today though, and I'll try and go quickly in the interest of time. When you look at guideline statements in cardiology, this is how we talk about heart failure. We talk about stage A, which means you're at risk. So let's say you have a history of hypertension or you have a dyslipidemia, but we also remember that anyone with a genetic trigger by definition is stage A. So anyone that harbors a mutation for any of the diseases we've talked about today is stage A. So you have to think about them differently.

Stage B is when you start seeing phenotypic changes, but no symptoms when you go to stage C is when you have phenotypic disease plus symptoms. And stage D is really pretty far down the path. In the United States and adult world, we think about coronary disease as a primary driver of heart failure, but

it actually turns out that's only about 50, 55% of the time. A lot of it actually are nonischemic causes of cardiomyopathy, many of which are genetic. And so that's where being more thoughtful in how we look at the genome in patients with heart disease is becoming more and more commonplace. And you see things on here like infiltrative disease, which we talked a little about like amyloid. Peripartum cardiomyopathy is actually genetically triggered. Those are typically titin mutations. So most of the things we're talking about here actually have a genetic underpinning. And so that means 40, 45% of the heart failure, at least some of that is being driven by genetic disease, some of which may be LSDs for example. So there's things that we have to pay attention to.

When you talk to adult cardiologists this is the way that we speak. And so you'll understand what we mean. There are four different sort of classifications We used to talk about systolic dysfunction, diastolic dysfunction that progress into a thing called HFrEF, which is heart failure with the reduced ejection fraction and HFpEF, which is heart failure failure with preserved ejection fraction. Now we've come up with two additional categories and those are shown here. So HFrEF is someone with an EF less than 40, and HFpEF is usually someone with an EF greater than 50. And then you kind of have this no man's land in between, which is the mid-range injection fraction. But how we treat patients is very much implicated by what these numbers show. So just so you're familiar with the terminology.

And this is kind of the conventional way we would treat reduced ejection fraction heart failure in the United States today is with a pillar of four drugs, classes of drugs, beta blockers, think either ACE inhibitors, ARBs, or I think called Arnie, which is a drug called Entresto in the U.S., SGLT2 inhibitors, which were classically diabetic drugs, and then MRAs or mineral or corticoid receptor antagonists like spironolactone would be sort of the four mainstays of therapy.

And then we can progress these over time depending and sometimes evens on race. So for African-Americans, we think about different kinds of drugs, a drug called Bidil, which is hydralazine plus nitrates. And then we move along the progression to things like biventricular pacemakers, what's called CRT, or maybe we were talking about LVADs and transplants. And that's beyond the scope of this conversation, but at least you understand this is kind of mechanistically how we approach someone with heart failure. And these that [inaudible 00:46:20] are adults. We do have pediatric guidelines, but they're not as well established, but absolutely happy to talk about that if people are interested in learning more. And our big thing in adult cardiology when it comes to these patients or even in pediatric patients, is about picking the right drug and then up titrating those drugs as much as possible, but also looking for other diseases that could be causing the problem.

And in our Fabry patient, this is a big deal. So things like atrial fibrillation are actually quite common in Fabry, and they're a big driver of the stroke that we see. So we used to think that a lot of the stroke in Fabry was just because of deposition and vascular narrowing. It actually turns out a lot of that is embolic, meaning they have AFib, they develop a clot, clot flips off to the brain, causes an ischemic stroke. Similarly, we see a lot of sleep apnea, which is a driver of myocardial dysfunction. All these things are important when you're trying to think about how to manage someone with an LSD, for example. This is a big question that we get in Fabre, and you heard a little bit about in the beginning, this idea of HCM phenocopies. So true hypertrophic cardiomyopathy is a sarcomeric disease, okay?

So troponins and tropomyosins and all those other sorts of genetic defects, MY7, MYBPC3. And this is the algorithm for how we decide who's at risk for sudden deaths. So remember in hypertrophic cardiomyopathy, two big things we need to do. One is to treat any symptoms of obstruction or other related symptoms, but the second is that we know that those patients are at risk of sudden death. And so it's paramount on us to identify those patients and potentially put in a defibrillator in those patients. This is the screening mechanism we use in the United States to establish risk factors for people with hypertrophic cardiomyopathy to decide if they need a defibrillator. And you can see a lot of things on

here like family history of sudden death, massive left ventricular lipotrophy. Also, a completely different lecture, but just to give you a framework that if you had someone with an LSD and the question was whether they were at risk of sudden death, we typically apply these same guidelines even though they haven't been corroborated in diseases like Fabry.

We usually would translate these particular criteria onto the Fabry population. So just so you're familiar with all of this, because as I showed you, we do have patients that if you look hard enough, you will find substrate for disease like ventricular tachycardia and you may want to intervene in the form of a defibrillator. So just so you're conversing in the things that we are looking for, and a lot of these things you can look for in your own clinics, things like family history of sudden Death, obviously it's just good history taking massive LVH, things like echocardiography, MRI, all these things can be looked at in your clinics and it may help you to decide what the best treatment pathway is for your patient.

This is something that I think when we talk about cardiovascular disease, and this is specific to Fabry, but we see patients that come in, and this is just a report that we published last year about the findings of lymphedema. And so as you know, lymphedema can sometimes you might think it's peripheral edema, not truly lymphedema. So maybe it's from congestive heart failure for example. And I put this in simply as an example to understand that I see patients like this, and the first thing that folks look at is that, "Well, this patient must be in heart failure." Must be. Right? And so I'm going to give them lots and lots of diuretics and give them compression stockings and hope that they get better. Well, lymphedema is not responsive to diuretics. Actually, it will potentially make things worse and you will make things worse because the intravascular volume will be lower.

You're going to induce acute kidney injury and actually hurt an already failing kidney, at least in the setting of Fabry. So this is a completely different phenotype that you need to think about in patients, at least with Fabry where the treatment here has nothing to do with diuretics for right heart cath or anything like that. It's actually about mobilizing this fluid. So I just put this in to help you to understand, as I said at the onset, we think we know a lot about cardiovascular implications of Fabry and Pompe and Gaucher. I would confidently argue we don't know very much. We're starting to, but we still don't know very much, so be agnostic when it comes to looking at patients with LSDs and cardiovascular disease.

The other thing that I think that we wanted to talk about was just some of the research ideas, and I'll talk about that in just a second, but just remember is that the presentation of these patients can be widely variable. Siblings in the same family can look very different. So don't always assume that everybody is a predictable timeline in these kinds of patients. We know a lot of this stuff already. We've talked about this. All these things you can assess with the technologies we've talked about today. The one thing we did not talk about on the cardiovascular side is the idea of autonomic dysfunction, which we see pretty commonly now in storage disorders in general. Part of that's at the heart level, part of that's at the vascular level, but a very hard thing to manage. But it is increasingly common that we see autonomic dysfunction or dysautonomia in patients with LSDs.

I was asked just to briefly mention about research trends and what I would say is that you probably hear a lot in your other lectures about gene therapies and new ERTs and all these other sorts of things, and there's no doubt that is important. And the first thing you should do is if you see someone with LVH, and the question is do they have hypertrophic cardiomyopathy versus Fabry versus amyloid? Is that you need to figure out what the disease is because there may be a disease specific therapy. In the setting of Fabry or an amyloid, those disease treatment options are very different than in someone with conventional hypertrophic cardiomyopathy. But the other thing we're seeing is just the repurposing of existing therapies. And so we've talked about some of those therapies today, meaning can I use Entresto in someone with Fabry and an ejection fraction of 25%? Probably. We don't have clinical data to that, but would it make sense that we could potentially use it in that population? Yes.

Would we need to be a little more thoughtful in how we do surveillance of things like kidney function potentially. But could you repurpose those drugs that are already available to potentially treat our more rare disease populations? And the answer is yes, you absolutely can. For me, that's really where a lot of the research is going. It's great to do the multi-billion dollar the and gene therapies and we're involved in those trials, but we also know there's a lot of learnings and that's probably off in the future. How can we use things that are available to us today to treat patients? And this is one of them is repurposing existing therapies. So in conclusion, broad spectrum of Fabry, but in LSDs in general, and what I want you to take away is that all of the techniques we've talked about today can be applicable to any different diagnosis. It is not unique to Fabry. It is not unique to LSDs. You can apply this concept to any patient with genetically triggered cardiovascular disease.

Our view on this is really about the evaluation of patients of all ages is critical because we still just don't know what the earliest phenotypic involvement could be at this point. Obviously in the setting of Fabry, some people go down the wrong path of thinking that a carrier may not manifest disease. We all know that's not true. So we're pretty agnostic to that too. We look at our females just as we would look at our males, maybe not as early, but we do look at them with the same set of tools. And then, as I said, promoting the use of existing technologies. Our comprehensive approach I do think allows us an opportunity to identify disease earlier upstream. Usually earlier intervention leads to better outcomes. I didn't talk about this today, but we have a few publications in this area about using artificial intelligence to diagnose disease that currently may not have been diagnosed.

So how could we leverage artificial intelligence to identify people at an adult onset Pompe or a Fabry patient who otherwise have just escaped conventional diagnostics, right? No one has put two and two together and say, "Maybe this is what this patient has." We're starting using artificial intelligence in the diagnostic component, but also using AI to a lot of the images that you saw earlier, looking at echo data and MRI data using artificial intelligence to better interpret that information and also arrive at an earlier diagnosis. But that's like a three-day symposium if we wanted to talk about that. But just be in mind that I think things are progressing in all of these diseases and it's an opportunity for us just to do a better job. So with that, this is my contact information. If anybody wants to reach out, please feel free, and I'll stop sharing now and we can take any questions if there are any out there. And I apologize if we're kind of close to time.

Dr. Goker-Alpan:

I would like to personally thank Dr. Jefferies for this very comprehensive presentation. And this was much needed for not only for Fabry patients. There are a few questions. I'm going to lump them together for the sake of time, and I do have actually a few questions myself for general management of patients with Fabry disease. Before I do, we may run over time, but some of the audience may would like to stay for some few questions. So just a comprehensive evaluation. We have been discussing, obviously cardiomyopathy is the prototype for patients with Fabry disease. What about the patients with LOPD, late onset Pompe disease? Could you just briefly discuss, because we have been seeing these patients too.

Dr. Jefferies:

Absolutely. And it's the same kind of mechanism. As you guys know, some of our foci are a little bit different, maybe more on the electrical side than as much on the cardiomyopathy side. What I try and think about is that you can use exactly the tools that we've been talking about to evaluate that. The late onsets very similarly is that good imaging is always the cornerstone. And if all possible, doing MRI think is a great idea, and it at least gives you a baseline. If you have access to the advanced technologies that

we talked about, like T1, like ECV, definitely take advantage of that. But anytime you can do an MRI over the echo, that's always advantageous because the measurements are just more precise, whether it's just the size of the ventricles or if it's the size of the atria or the wall thickness or whatever. Always, always, always a better option.

And you want to know kind of where you're starting from. But as I said, the thing that we under-explore the most in all of cardiology, whether it's adult or pediatric, whether it's common or rare, is the rhythm side. And so I would urge you to be really thoughtful and intentional about how you look for rhythm disturbances and taking really good histories about dizziness, about syncope, all those other sorts of things, because at the end of the day, those are the things that are going to kill the patient. That's the sudden death opportunity. So just keep that in mind.

Dr. Goker-Alpan:

So we discussed the ICD guidelines with the hypertrophy and previous VTAC. So this is given. So what we are getting challenged is with the degree of the fibrosis and what is the degree of fibrosis that drives for an ICD? And putting this, actually, I want you to comment on the differences in a female patients versus male with Fabry disease. As we see fibrosis almost always first before the concentric hypertrophy happens. And these patients may not have concentric hypertrophy, may just have the posterior role involvement. So I have many questions in one for you.

Dr. Jefferies:

She's doing great. She's going to be a cardiologist I think. They very appropriate questions. So the conventional thinking on fibrosis, at least in the true sarcomeric population, doesn't mean it translates directly into Fabry, for example, is 15% of the left ventricular mass. So if it's above 15%, that is an independent risk factor for sudden death.

Dr. Goker-Alpan:

So what about the patchy involvement though?

Dr. Jefferies:

Exactly.

Dr. Goker-Alpan:

Yeah. Okay.

Dr. Jefferies:

The problem is, and this is a bit conceptual, so I apologize. Those criteria are based mostly on an ischemic population. So you think about a heart and you have an LAD coronary that gets occluded. We know that the distribution of heart muscle's going to be affected there, and it's easy. We can differentiate normal from abnormal on an MRI very, very easily. Here's necrotic tissue, here's a per necrotic region, and here's normal, and we can draw a line around that, and that's 12%, 18%, whatever. The problem with a genetically triggered disease is, in theory, every cell is impacted. So that's where the value of LG actually starts to go down because you get these patchy little areas. But it could be that what looks normal could be completely abnormal, right? We really don't know. That's where the T1s come in is to give us a little bit better idea.

The problem is no one's established a cutoff on the T1 value for an ICD, for example. So those are future questions we'll have to ask. But you're exactly right in that LG has its place, but it's usually for very discrete areas of abnormalities, and that's not in genetically triggered disease. Genetically triggered disease, the entire myocardium is impacted. I had a patient with a genetically triggered restrictive cardiomyopathy. The patient had an MY& mutation, I think, if I remember right. On MRI, completely normal, no LG burden. Patient died, did a postmortem, the entire myocardium was fibrous. So it just tells you for LGE to work, you have to be able to compare an abnormal area to a normal area.

Dr. Goker-Alpan:

So it's everything.

Dr. Jefferies:

You may not have a normal area.

Dr. Goker-Alpan:

Exactly. Interesting.

Dr. Jefferies:

Yeah.

Dr. Goker-Alpan:

So females?

Dr. Jefferies:

You mean as far as how would I approach them?

Dr. Goker-Alpan:

Yeah. How would we approach? I mean this is actually general. So we were actually working on a project and we compiled some of the literature. So it looks like actually heart disease is different in a female than a male patient. So in general, and this becomes more actually important in a patient with Fabry disease, obviously.

Dr. Jefferies:

Yeah. Like I say, I grew up in the school of thought that the males were always going to be more affected, and that's just the way it is. In my own experience, some of my most severe cardiac phenotypes are females.

Dr. Goker-Alpan:

I agree with that.

Dr. Jefferies:

And the patient I showed you with the VT, that was a female. And so by conventional wisdom, "Well we don't need to be as aggressive and maybe we only see them every three years and maybe echo is sufficient." Once again, I think we don't know enough to make those sorts of comments. And so for me, I

approach everyone relatively the same male female, if it's someone with this diagnosis, this is the battery of tests that we're going to employ, obviously including genetic testing if they already come to me with a diagnosis. We're still going to look at rhythm stuff. And our Fabry, the other thing we didn't talk about is sometimes we will do stress testing and or coronary CT angiography to look for the coronary disease that we alluded to. So that's another layer of imaging [inaudible 01:03:16].

Dr. Goker-Alpan:

I will actually ask a question. I am interrupting you for the sake of that. So the troponins, okay. So basically actually we do have very young patients with increased troponins. Obviously it is not increased as in a myocardial infarction, but how do we work these patients up? So all the patients who have increased troponins, do they need to have a stress test? Obviously there may be obstructive cardiovascular disease, but there may be non-obstructive as well because of the cardiac muscle enlargement.

Dr. Jefferies:

That's a great question. The reason this is become an issue is because we started doing high sensitivity troponins. So in the past they may have had a troponin, it was elevated, but it was still in the upper limits of the normal range for conventional troponin. Now when we do high sensitivity, everybody, even a car wreck will have an elevated troponin. And so in my view, those are patients... I do sometimes think about a coronary CT angio. You have to understand the limitations of conventional stress testing can be significant, right? It all depends on your pretest probability. And the problem with Fabry or some of these other disease, they may not be able to exercise. They may have joint pain, other things where can they really perform an adequate stress test? And the answer is most of the time, no they can't. So if my question is really about obstructive disease angiography is still the best question.

Now, if I have a different question about autonomic dysfunction or something else, then I may think about stress testing, tilt table, all the other kinds of stuff that we talked about. But if I'm really worried about coronary disease or ischemic disease, I've traditionally now been going more down the CCTA path than stress testing. It's easier for the patients and I think it gives me more valuable information. The other place though is looking at the MRI. If you're seeing areas of scar or fibrosis or changes in T1 that could easily explain the troponin anemia. So just something else to keep in mind.

Dr. Goker-Alpan:

And then while we're talking about the biomarkers, so obviously almost actually our experience, the high troponin is almost universal with when a cardiomyopathy is involved. But what about NTBPH? Actually we don't see this until the very late stages of patients with Fabry disease. And I'm going to actually piggyback again another question to that. So the ejection fraction doesn't decrease during rest even a patient has severe cardiomyopathy. And then this has been recognized actually recently and we ended up actually sending three patients to cardiac transplant with reasonable ejection fractions. So obviously we exercise them. Then how do you work these patients up that you may suspect that they will be candidates for transplant?

Dr. Jefferies:

That's a long discussion. Part of what we would do would be typically a right and left part catheterization. So you'd look for the pressures, you look for the trans pulmonary gradients, the PVR, all these things that you may not care so much about. And then you're obviously looking for things that are reversible. So still the biggest cause of heart failure preserved ejection fraction in the U.S. is going to be

coronary disease, usually with diabetes, hypertension. So the question is there anything if you revascularize that could the heart muscle function get better over time? And so that would be part of the evaluation. And as you alluded to, oftentimes we would do a thing called cardiopulmonary exercise testing, not just conventional stress testing to look at MVO2 levels. And that also sometimes is a good indicator of when someone which should be considered for a transplant.

Fabry is just a little more complicated because of some of the non-cardiac limitations to doing that sort of stuff. And there are guidelines out there that we can circulate about how to work up for a transplant. The first thing is that you would send them to a cardiologist with expertise in transplant medicine and they would evaluate all of that. But you were asking about natruretic peptides like BNP. Remember BNP is a stretch hormone, so it's really dictated by the pressure in the left ventricle. But there are situations where NT-proBNP can be falsely low. Usually older people and obese people as you may get a BNP that reads normal when in actuality it should be high. Flip is BNPs are cleared by the kidney. So people with kidney disease may have elevated natruretic peptides when in actuality it's just because they're not clearing the hormone.

Dr. Goker-Alpan:

And we have one more observation. People who wait, we have seen few of those actually have increased BNPs. I guess it's coming from the lungs, is that right?

Dr. Jefferies:

That's right.

Dr. Goker-Alpan:

Yeah. And so I have two more questions and then we probably need to go. One is the stroke prophylaxis and role of stroke prophylaxis in patients with Fabry disease.

Dr. Jefferies:

Great question. So a little bit of background, as I said, a lot of the stroke has actually being driven by AFib. The only way we know about AFib is to diagnose it. So that's where the loop recorders or watches or other things come into play. What we typically use would be a thing called a CHADS2 VASc score, which is once again, not validated specific to Fabry, but it's the best tool that we have. And that's informed by things like a history of hypertension and whether you're male or female and you have vascular disease. And you can actually go on the AHA website. There's a CHADS2 VASc calculator, and if you get a two or higher, then you should be considered for systemic anticoagulation. In the current era, we would usually use DOACs, something like Allegis or Xarelto. You could use something like Coumadin, but obviously a little bit harder to deal with. But that's typically how we would do it. And conventional adult cardiology, the use of aspirin as a prophylactic therapy has pretty much gone away. So you either get nothing or you get systemic anticoagulation.

Dr. Goker-Alpan:

So what about the anti-platelets or platelet inhibitors?

Dr. Jefferies:

Yeah, that's what we say. Now, if you had an existing stroke or carotid disease, different discussion. But purely for atrial fibrillation and that's your risk for stroke, we usually have abandoned the idea of using

something like aspirin and antiplatelet therapy because it doesn't seem to make a difference and the side effects seem to outweigh any kind of benefit. So usually you would get nothing or you would get systemic anticoagulation. But remember that can change over time, the need for that anticoagulation.

Dr. Goker-Alpan:

Right. I mean I had some patients with the vascular ectasia and they did actually have significant vertebral artery strokes even on full commoditization. That is not easy to predict what is the value and how it's going to be effective. So one last question that's from the audience. And the people are still staying, which is very unusual.

Dr. Jefferies:

Amazing

Dr. Goker-Alpan:

Yeah, exactly. So the treatment, obviously that is disease specific treatment. So when can we start or when can we expect to reverse the pathology? So obviously for every disease there's a point of no return. So when are you going to be talking to your patient? Either you start now or we are going to be dealing with the complications.

Dr. Jefferies:

Yeah, I think it depends on how you think about it. There's always an opportunity, unless someone is in multi-organ failure and whatnot. But even those end stage patients, we're now starting to transplant Fabry patients. So we do heart transplants in patients with Fabry. So you're not always out of the discussion. The question about is there some point of no return for medications is probably more apropos. And usually if you see someone has full thickness scar, for example, that ain't coming back. We even use that for revascularization criteria. But things like valvular disease, hypertrophy, relaxation, abnormalities, we do see some changes in those with things like ERT. So there are always possibilities, right? And you start layering on things like gene therapy and other sort of regenerative therapies. Is there a possibility to at least get some normal myocardial function back or normal electrical conductivity or whatever?

I think the answer is yes, but I'm still a proponent if we can catch it upstream, we're still way, way, way better off. But you don't think the beauty of all this now is that people with Fabry do get transplants. They are considered for cardiac resynchronization, which has been a big milestone because in the past it was, "Well you're not a candidate because you have Fabry." It's like, "Well, that's not true., That's not true." So a lot of it revolves around increased literature, a lot of more publications and people just being more aware of the disease. That's obviously what you guys are doing is greatly helping that. Thank you.

Dr. Goker-Alpan:

Actually, absolutely. What we recommend these patients to start treatment at any stage, obviously if they have valvular disease or really severe myopathy, we don't really expect this to correct itself. Even at some earlier stages, maybe improvement, but it's the wellbeing of the patient. I know we see the Fabry disease like any other disease, heart disease, kidney failure becomes very inflammatory. So actually this further probably drives the disease forward. So I thank you very much and looking forward to your AI lecture during our grid symposium and we are advertising our audience too. This material, there is some audiences asking whether they're going to be shared. This material is going to be available online for a

year after a month. So basically that the slides can be viewed again. Thank you very much Dr. Jefferies. It's greatly appreciate it. Thank you.

Dr. Jefferies:

All right, take care everyone.