SHARON CRESCI: Thank you very much. I think that this symposium is just fantastic. And I really appreciate being invited to speak at it. I have no financial interests to disclose.

So this is a question that my colleagues often ask me, when they are taking care of their patients with hypertrophic cardiomyopathy. And as I think you'll see from this talk, it's often a pretty complicated answer. And as you've been hearing, I think if there's one theme tonight, it's shared decision making. And when you approach genetic testing in patients with hypertrophic cardiomyopathy and their family members, it definitely is a shared decision.

So what to the guidelines say? I think it's important to review these, because I think that these points are extremely important. Class one indication to take a family history, and perform genetic counseling as part of the assessment in all patients with hypertrophic cardiomyopathy. And what I think is the most important part of this guideline is that persons who undergo genetic testing should also undergo counseling by someone knowledgeable in genetics of cardiovascular diseases. And this counseling and discussions should occur before the genetic test is sent.

Genetic testing is recommended when patients with an atypical clinical presentation of HCM, or when another genetic condition is suspected to be the cause of the LVH. And we won't get into this too much, but I will cover this very briefly.

And clinical screening, with or without genetic testing, is recommended in all first-degree relatives of patients with HCM. So let's just review what that clinical screening entails. It's an echocardiography and a 12 Lead ECG for detection of HCM. If the family member is less than 12 years of age, it's optional unless any of the following are present: a family history of early HCM-related death, early development of LVH, or other adverse complications. If they're a competitive athlete in an intense training program, if they have symptoms, or if they have other clinical findings that suggest early LVH, you should start screening earlier than 12 years old.

In others, you will screen every 12 to 18 months, from the ages of 12 to approximately 21. And we just tell our families to schedule that echocardiogram once a year, just is easier to do. And then once they're 21 years of age, it's recommended at least every five years to repeat the echo and the ECG. And obviously, more frequently if there's a family history of late-onset LVH or HCM-related complications, and absolutely if the patient family member has onset of symptoms or a change in symptoms.

Now, you've heard about this before from some of the other speakers. I secondarily work in the echo lab. And at Wash U we perform a very comprehensive screening with echocardiography. We're looking for the obvious findings that are consistent with HCM, such as asymmetric LVH, or systolic anterior motion of the mitral valve.

But we're also looking for very subtle findings, such as abnormal tissue Doppler patterns for age, abnormal peak systolic strain, which is shown here in the anterior wall and anteroseptum of this patient. And also, the crescent shape of the left ventricle is often very useful.

The guidelines state that genetic testing is reasonable in the index patient, to facilitate the identification of first-degree family members at risk for developing HCM. It's a two-way guideline. And as you know, HCM is caused by more than 1,400 individual mutations in more than 11 genes. The sarcomeric genes that are most often involved are mutations in myosin-binding protein C, and beta-myosin heavy chain, followed by those in alpha-tropomyosin and troponin T.

I won't, in the interest of time, spend too much time on this. But I just want to remind you that there are HCM phenocopies that most of the genetic tests will identify. These phenocopies are found in less than 1% of patients who are sent for genetic testing. But these are critically important to identify.

I show three of the most common ones here. And they're important to identify because, for example, Fabry's response to enzyme-replacement therapy, and so you would not want to miss that diagnosis. And mutations in the LAMP2 gene typically follow a very rapidly-progressive course. And so you are going to be thinking about possibly considering that patient for heart transplantation earlier on.

Some clinical findings that might suggest these phenocopies to you, you may see Wolff-Parkinson-White pattern on an EKG with the first two, and you may see symmetric LVH and late gadolinium enhancement in the posterior basal wall on an MRI for Fabry's.

We should look at how, if you send a genetic test, what are you going to get back? Well as I said, there are more than 1,400 mutations that are currently known to be causative mutations for hypertrophic cardiomyopathy. And if your patient has one of these, it will come back to you on the report as definitely pathogenic or likely pathogenic.

Now as you know, we all have genetic variation in our genes. And so there might be a variant that's identified that is not known whether or not it's a causative, pathogenic mutation. And so that might be classified as an uncertain, or a variant of unknown significance, or a VUS. And that's exactly what it sounds like. It's not known. There may be some disparate information about whether or not that runs in families with hypertrophic cardiomyopathy, and whether that is truly a causative variance. And then, there might be other variants that are identified in your patient that are thought to not be pathogenic, or to have little clinical significance, or to definitely not be pathogenic.

So there are two categories of genetic testing for hypertrophic cardiomyopathy: diagnostic, in which you are comprehensively sequencing a patient's genes to identify a disease-causing mutation in a patient who has hypertrophic cardiomyopathy, and predictive, where you're performing focused genetic testing to determine if a family member has a previously-identified mutation.

If you're doing your diagnostic it is also, as I said in the guidelines, that that could help discriminate between HCM and other causes of LVH, including hypertension, in an athlete's heart. However, this is only helpful if the pathogenic or likely pathogenic mutation is found. If you have a mutation identified that is, for example, a VUS, or if no pathogenic variant is found, you cannot conclude that the patient does not have hypertrophic cardiomyopathy. And you're essentially left with your clinical impression and continued uncertainty about what to recommend to the family members.

There are similar requirements if you're going to try and do a predictive testing for a family member. So you are required to have a pathogenic or likely-pathogenic mutation identified in the index family member before you start genetic testing their family members.

And let me just take you through this. So if you identify a family member who phenotypically has classic findings consistent with hypertrophic cardiomyopathy, and of course, they have to be willing to be tested. So this is obvious, but the family member cannot require the person with hypertrophic cardiomyopathy to be clinically tested. They have to be willing to do it. And no pathogenic variant is identified. Well, that happens fairly often, because current state-of-the-art genetic testing across the country will only identify a pathogenic mutation about 50% of the time in someone who clearly has hypertrophic cardiomyopathy from a clinical point of view.

So if no pathogenic variant is identified, or if a variant of unknown significance is identified-- which you know may be reclassified later to be a pathogenic variant, but currently at the time of your testing, is a variant of unknown significance-- you have to continue to clinically follow the first-degree family members and repeat the echocardiography and the ECG's as I described previously.

So you essentially are left back in the same boat as you were before you undertook the genetic testing. I've had some physicians say to me, is that good news? It's really no news. It's not good news. It doesn't mean that the index patient who clinically has hypertrophic cardiomyopathy doesn't have hypertrophic cardiomyopathy. It essentially means that at this time, we're unable to identify a pathogenic variant in that patient. And in fact, the guidelines say, as a class three indication, that genetic testing is not indicated in relatives when the index patient does not have a definitive pathogenic mutation.

So what if you identify a likely-pathogenic variant, or a pathogenic variant? Well, then you can go on and test the first-degree family members who wish to be tested. And there are definite cases where certain members of the family wish to be tested, and certain don't. But you can test those that wish to be tested for that specific identified mutation in their family member. So it's targeted genotyping.

But there are still some issues. So if they have the mutation present, you have to explain to them what that means. And again, I think all of these discussions need to happen before you send the genetic test. Because we know that hypertrophic cardiomyopathy is a disease with incomplete penetrance. And this is shown really nicely on the slide by AJ Marian.

This is a truncated pedigree of a family who has the same one mutation for hypertrophic cardiomyopathy. And as you can see here, all of the circle and square people, filled in boxes and circles, carry that mutation. And yet, if you look at their degree of left ventricular thickness, with the normals shown here on the left, you see that there are certain patients, certain individuals, who have very profound disease, very profound degree of LV mass.

However within the same family, as shown by the green circles, there are some people who have normal hearts, normal LV mass indices, carrying the same mutation. And some of these people will never, ever get the cardiac manifestations of the disease. So people who get genetically tested have to understand that even if they are mutation-positive, they may always be phenotype negative. And they have to be willing to live with that, if you will, with that knowing that they may develop the disease, but they may never develop the disease.

So what if you test a family member and the mutation is not present? Well, the guidelines state that ongoing clinical screening is not indicated in genotype-negative relatives in families with HCM. And I think that those guidelines should be followed, but there is a caveat that I tell the patients. And this is what it is. We know from several studies that double mutations are present in 5% to 8% of patients with hypertrophic cardiomyopathy.

So I just want to take you through just a couple of pedigrees, here. So in this case, your index patient is phenotype-positive and has been tested, and has two mutations. They have a mutation in myosin-binding protein C, and a mutation in troponin T.

And the children, as you see, one of them has one of the mutations, and one has another. So currently, with current genetic testing, if you test both of those children each of them will come back with a positive genetic test. And it will show that they are truly mutation positive.

However, what if your index patient has a double mutation, but one of those mutations is in troponin T, and the other one is in that 50% that have not yet been identified? Well following the same logic, if there are two children, each inherit one of those mutations. The child on the left will have a genetic test, and that will be positive for the troponin T mutation. However, the one on the right will still be mutation positive, but our test will not be able to identify that. And so their genetic test will come back negative.

So if a patient is mutation negative there is still a minimal, but not 0%, chance of them eventually being phenotype positive. So these two issues make the conversation very difficult. The patients understand this. They are very knowledgeable and very intelligent. But it really has to be a personal decision about what they would prefer to do, which information that they would like to have, and how they would like to proceed.

I just want to make one further point. Several investigators have shown that double or compound mutations are potentially more frequently associated with worse phenotypes, worst disease, including sudden death. However, at the current state of our knowledge, it is a 2 B indication that the usable-ness of genetic testing and the assessment of risk of sudden cardiac death in [INAUDIBLE] is uncertain, although this may be modified in the next set of guidelines.

So I hope that I've shown you the potential benefits, but also the potential harm, in doing genetic testing, and why it really is essential that you have a very extensive conversation with each member of the family to decide whether or not they would prefer to undergo genetic testing or not. Thank you.