What You Should Know About Genetic Testing for Mitochondrial Disorders

About the Speaker: Amanda Balog is a board-certified genetic counselor and is the lead genetic counselor for the Mitochondrial and Metabolic Testing Programs at GeneDx. Prior to joining GeneDx, Amanda worked for several years as a clinical and research genetic counselor specializing in immune and lysosomal storage disorders.

MaryBeth Hollinger: My name is MaryBeth Hollinger, I am the Director of Education, Support, and Advocacy at MitoAction and I help to gather speakers and put together these presentations along with the rest of our crew so I am just happy to give you guys experts so we can all increase our knowledge base, share with our physicians and our PTs and our OTs and everyone involved so we can just raise awareness and education and help our mito community along as best as we can. I have generations of ties to neuromuscular and mitochondrial disorders so I am quite interested to hear what Amanda has to say even the impact of family history on these results.

Amanda Balog: Thank you MaryBeth and thanks to MitoAction for letting me speak to you all today about mitochondrial genome and genetic testing for mitochondrial disorders. It is a very confusing and complicating and fast moving part of genetics and so I am happy to provide a little background information and answer some questions from you guys.

9:46
Slide 1:

So the title of this presentation is Not Just Your Mother's Genome because when we talk about mitochondrial disorders we talk about a lot about the mitochondrial genome but we want to take a step back and look at all aspects of mitochondrial genetics and have a broader overview for this talk.

10:22
Slide 2:

So the first thing I want to say is that I want to disclose that I am an employee of GeneDx, we are a diagnostic genetic testing laboratory and subsidiary of OPKO and that we do mitochondrial genome testing and mitochondrial genetic testing here. I also want to let you know that the information that I am presenting today is our experience at GeneDx and the testing experience can vary from lab to lab.

11:01
Slide 3:

I know a lot of this information will be very familiar to you all but I want to make sure that everyone has a good background. Let's start with the basics: What are mitochondria? Mitochondria are sub compartments that are in almost every cell within you body. The mitochondria is what turns the food you eat into the energy that your cells need. So it turns that food into chemical energy that your cells can use to do all of their work: keeping your heart pumping, your brain cells firing, your muscles working, and your body growing and developing, mitochondria really are the source of energy for those parts of your body.

Slide 4:

So now that we kind of know what mitochondria are, what can happen when you have concerns with your mitochondria? Individuals with mitochondrial disorders have symptoms in almost every part of their body. The symptoms that they have particularly occur in organs or tissues that need the most energy since mitochondria are responsible for providing that energy. Things like your muscles, your heart, your liver, your brain, those are where we see the symptoms. So they can have cardiomyopathy, or muscle weakness, or vision concerns and individuals that have a mitochondrial disorder may have symptoms in just their heart, or just their muscles, or they can have symptoms in all of these organ systems, they can have problems with seizures and digestive issues and having anemia. It is also important to note that they symptoms can change over time. So some individuals might just start out with muscle weakness and then later develop seizures or heart problems. It is not just a snapshot at one point in time, we are looking at a patient's symptoms over time when we are suspecting a mitochondrial disorder.

Slide 5:

If you look at Slide 5 you will see a picture of human chromosomes. When we talk about genetics most of the time we are talking about things called nuclear genes. These are the genes that you inherit from both of your parents, you get one copy from mom, one copy from dad. Most of your genetic information is in your nuclear genome. This is the information that makes you, you. Your hair color, your eye color, how tall you are, whether you have long fingers or short fingers, this is what makes you, you. Again there are 46 chromosomes and 23 pairs and you inherit one copy from each parent.

Slide 6:

So if you look at the next slide, we will see that the genetics the mitochondria are a little different. Mitochondria are unique, because they have their own separate genome. Unlike the nuclear genome, instead of being in a long string, mitochondrial genomes are in a circle. Another unique thing about mitochondrial disease is that you don't get it from both mom and dad, it is only from mom. So if mom has a mitochondrial genome mutation, all of her children could be at risk for inheriting that versus if dad is the one that has the mitochondrial genome mutation none of his children are at risk for inheriting that. There are some other particular unique aspects of mitochondrial genomes that make testing and evaluating for mitochondrial disorders a challenge sometimes and we will discuss those a little later in the presentation.

Slide 7:

So when we discuss mitochondrial disorders, how do we diagnose these? In the genetics realm mitochondrial disorders are particularly difficult to diagnose and I am sure a lot of you are very familiar with that fact. This particular cartoon shows blind men trying to figure out what an elephant is by examining its different parts. Depending on the part that they are looking at, they are all coming up with different conclusions. The fellow investigating his tusks thinks "Oh! It's a spear." The man holding his ear thinks "Oh! It's a fan." So depending on how you are looking at it you have a different perspective of what it is. And this is true for many individuals with mitochondrial disorders. If they have heart concerns and they see a cardiologist, the cardiologist may just look at the heart symptoms that they are having. If they see a neurologist they make think about the seizures the particular child his having. If they are seeing an ear nose and throat doctor, they may just look at the

hearing loss. But it is not until you take a step back, take a look at the entire medical history and the whole picture of the patient do you begin to suspect a mitochondrial disorder. This is what genetics is particularly good at is taking a step back and looking at the whole presentation of a patient to try and find a diagnosis.

Slide 8:

So if you look at the table on Slide 8, you will see a very large table with a very large number of chains. This is a table from 2012 and it shows the nuclear genes that we knew at the time caused the primary mitochondrial disorder. This list is very large and it is already outdated. Currently there are over 250 genes known to cause primary mitochondrial disorders, and more are being discovered on a regular basis as we continue to do genetic testing on more patients and have more sophisticated tools, both in data analysis and computers and with genetic testing itself to discover genes and to discover different variants. If you have a physician that thinks you have a primary mitochondrial disorders, they might order a mitochondrial disorder testing panel which looks at the kind of genes that cause this. One of the big advantages of doing a panel test versus other types of test, its makes sure that we look at those genes really closely. It may include different type of analysis on testing those genes.

Slide 9:

If we look at the next slide Slide 9, your physician may also consider something called whole exome sequencing (WES). Instead of looking at a targeted set of 250 genes, or 100 genes, or 50 genes, whole exome sequencing sequences the coding part of about 20,000 genes, so almost all of the genes in your genome. Not all of these genes are associated with a human disease, only about a quarter of them are, if you look at that pie wedge there. But most of the genetic changes that we look at with that cause a human disease are going to be in the exome. So the exome is the coding part, it is the part of genes that get turned into protein, which is not your whole genome, it is only about 2% of it but like I said when we are looking for things that cause human disease, most of those genetic variance are going to be within the exome. So whole exome sequencing is a more broad look at genetics, so because we are looking at so many more genes, you are not going to find all of your variance in the report. We are just going to report things that look like it could be the cause of the symptoms that a particular patient is having.

Slide 10:

Regardless of the type of genetic testing an individuals has, whether it is a panel type test or whole exome sequencing, one of the most important steps in that testing is the analysis component. Whether you are sequencing one gene or 20 genes or 20,000 genes, you are going to find genetic variation, you are going to find variants that are different than the standard set. Most genetic variation is normal. If we go back, it is what makes you, you. It is what makes your facial features, your eye color, these minor differences are caused by normal genetic variation. The analysis process is trying to determine if a variant that we find it part of that normal genetic variation, or could it possibly cause the symptoms the patient is having.

Slide 11:

On Slide 11 you will see the spectrum that we look at when we are trying to decide if a variant could be causing a patient's symptoms. When we do whole exome sequencing (whole

exome sequencing) or when we do panel testing we look at those variants and try to put each of those variants on this spectrum. Is it pathogenic or disease causing? Or is it benign, a normal part of variation. We use lots of different types of evidence to see where a particular variant falls on this spectrum. For nuclear genes we follow a set of published guidelines that one of our cofounders Sherri Bale helped develop in 2015. These guidelines are used by not just us at GeneDx, but many other laboratories, and the goal of having these guidelines is to have a set of rules and objective criteria that we can use to improve the quality of our variant interpretation, and to increase the consistency from laboratory to laboratory. Our goal is to see if it is a pathogenic variant or if it is of uncertain significance that we have agreement between those different laboratories. For mitochondrial genome variance, the previously published set of guidelines don't apply to those variants.

But we look at much the same information that those guidelines put out. We look at published genomes that are from healthy individuals. So we see is this variant present in healthy individuals. We look at the type of genetic change, isn't one that chops a protein in half. Is it in part of a gene that is really really important and that we know can cause diseases in that region. Has this ever been published before? Has this ever been reported in somebody that has a mitochondrial disorder. I will say that of the biggest pieces of information that we use, especially for mitochondrial disorders is detailed clinical information. It helps us identify patterns. Do we see the same variant in multiple unrelated patients who look a lot like clinically, who have the same set of seizures symptoms, vision problems, and heart problems.

The other major criteria and evidence that we use for mitochondrial genome variance is parental testing. When we have the parental information in our testing, we are much more likely to come to a diagnosis or to be able to interpret these variants accurately. So we look at was this particular variant inherited from a parent who doesn't have any symptoms? Then it is more likely to fall on the benign side than the pathogenic side. Versus a variant that is de novo or only in the child and wasn't inherited from either parent, that is more likely to fall into the pathogenic end of the spectrum. Another thing that is important to note about variant interpretation is that it is not static. Every time we see a variant we gain additional information that can move this variant along the spectrum. Just because a variant was of uncertain significance in 2014, doesn't mean that it is still a variant of uncertain significance in 2017.

At GeneDx we think that it is important for us to contribute to the genetics community and we submit our variant classifications to a database called ClinVar. Where we say we found this variant and this is how we classified it and it says the date of the classification and we are one of the top submitters for laboratories in that database. So individuals who had testing at GeneDx or at other laboratories can look at ClinVar and see what the current classification is for the variant. But overall it is important for patients who have had genetic testing in the past especially if it didn't provide a clear diagnosis, or if there were some variants of uncertain significance found, to follow up with their physicians. To see if that variant of uncertain significance in 2014 is still a variant of uncertain significance in 2017.

Slide 12:

So we often get the question 'Which test is best for patients who are suspected to have a mitochondrial disorder?'. Unfortunately, the simple answer is, there is no single test that is best for all patients. What test is the most likely to come to a diagnosis really does depend on the patient's specific symptoms and family history. And it should be a discussion between you and your doctor to

see which test is best for you, and which one is most likely to lead to a diagnosis.

Slide 13:

So we had talked about panel testing and whole exome sequencing and what happens when we compare those two. And if you look at Slide 13 you will see two pie charts with the diagnosis rate of panel testing vs. whole exome sequencing which are the two most common types of genetic tests for mitochondrial disorders. So when we compare panel testing for these patients who are suspected of having a mitochondrial disorder we found that whole exome sequencing had a higher chance of finding a diagnosis. whole exome sequencing identified a diagnosis in about 29% of our patients vs panel testing found a diagnosis in about 20%. Both of these tests are just the nuclear diagnoses. When you add in the mitochondrial genome it adds in about 3% to that total diagnosis.

With this data, why wouldn't you always do whole exome sequencing? When we looked at our panel testing, we found that when we looked at the types of symptoms that the patient was having, if the patient was having symptoms that were classic for a mitochondrial disorder, those things like Leigh Syndrome where they have very specific findings on brain MRI. Or if they have something call progressive external ophthalmoplegia which is a very specific type of eye muscle weakness. So these are patients who not only look like they have a mitochondrial disorder, it really really looks strongly like they might have a mitochondrial disorder. And these individuals had a diagnosis rate higher than 20%, whereas those who have symptoms that were a little less specific, so things like isolated muscle weakness, or isolated seizures, where it could be mito, but it could also could be other type of genetic disorders. Those patients had a much less lower rate than 20% with panel testing.

We will dive more into the whole exome sequencing positive results in the next slide, but I also wanted to take this minute to talk about negative results. Even with whole exome sequencing we are looking at 20,000 genes, but a negative result doesn't mean that there isn't' a genetic cause for the symptoms the patient was having. There are multiple reasons why you could have a genetic disorder and have negative genetic test results, it could be because there is a type of variant that you have that wouldn't be detected by this test. So fragile x syndrome wouldn't be detected by whole exome sequencing, and that is one of the most common types of intellectual disability in boys. Or you could have a variant in a gene that we just don't know the function of yet, so if we remember back to the beginning, only about a quarter of the 20,000 genes in our exome are known to have caused any genetic disorder. So it can be that we just don't know what that gene does yet to accurately link that variant to a patient's symptoms.

Slide 14:

So if you look at Slide 14 you will see a little bit closer examination of the whole exome sequencing results for patients who were suspected of having a mitochondrial disorder. When we look at that 20% that had a positive result, or diagnostic result, when we break that down, we found that over half of the diagnoses we made using whole exome sequencing, were not primary mitochondrial disorders. So when we talked about the elephant before, we talked about mitochondrial disorders are particularly challenging to diagnosis, and one of the reasons is that mito disorders look like a lot of other disorders, and a lot of other disorders look like they could be a mito disorder. So a child with seizures could have an epilepsy gene mutation, or they could have a

primary mitochondrial disorder. Or patients who have muscles weakness could muscular dystrophy or they could have a mitochondrial disorder. So that makes it particularly difficult to figure out which test is best. In addition some of these conditions that were not primary mitochondrial disorders, in the grey wedge, can indirectly cause mitochondrial disorders, so again making them look even more like primary mitochondrial disorders. This just reinforces that testing for mitochondrial disorders is difficult, and it is difficult to decide which test is best. But we have some data to say which ones based on our internal data are most likely to yield a diagnosis.

Slide 15:

If we move on to Slide 15, if you remember from earlier, we had talked about having two copies of most nuclear genes, one from mom, and one from dad, so if we are looking at a particular specific variant you generally can have zero copies, one copy, or two copies. However with mitochondrial genomes, each cell can have hundreds of mitochondria and this can lead to something called heteroplasmy. Heteroplasmy is the percent of mitochondrial genomes that have a particular variant, and this number can be 0%, it can be 1%, and it can be anywhere in between 1% and 100%. With that, another added level of difficulty with mitochondrial genome heteroplasmy is that this percentage that you see of a particular variant can vary from tissue to tissue.

Slide 16:

One of the classic mitochondrial genome mutations is the A3243 genome mutation - MELAS syndrome. That particular MELAS mutation happens quite often with that variant. So many patients with MELAS syndrome may have the pathogenic variant in blood, but it is at a low level, so maybe 3% or 4%. When we look at an affected tissue, or a tissue where they are having symptoms like muscle, we will find a significantly higher heteroplasmy level, like 50% or 60% in muscle. Another important aspect of heteroplasmy is that his percentage can vary with age. If we go back to that common MELAS mutation, the level of heteroplasmy for affected individuals, tends to go down in blood over time, so at age 12 they may have 40% heteroplasmy versus at age 40, they may only have 15% heteroplasmy. Even if the heteroplasmy in a muscle sample for that same patient remains at 40% or remains high.

Additionally, when we talk about mitochondrial genome variants and heteroplasmy we see something called the threshold effect. So if an individual has 2% heteroplasmy for a slam dunk pathogenic variant which we know is pathogenic and causes classic mitochondrial disorder 2% may not be enough to cause symptoms in that individual. So you need a certain level of heteroplasmy in order to show symptoms. This particular level of the threshold can vary from variant to variant. So there is a classic mitochondrial genetic variant for antibiotic induced hearing loss and for leber's hereditary optic neuropathy, for individuals who have pathogenic variants related to those two conditions generally we see symptoms when 100% of the cells have the pathogenic variant or close to 100% of cells have that pathogenic variant. Whereas that common MELAS mutation you can show symptoms at just 25% heteroplasmy. So it is important to look at not just the heteroplasmy level but the particular variant that is identified in a patient.

Slide 17:

Since heteroplasmy can vary from tissue to tissue we get a lot of question about sample type, and which sample type is best for mitochondrial genome testing. It general our philosophy is that we want to look at the tissues where we are most likely to identify a variant if it is there. For

individuals who have a mitochondrial genome pathogenic variant, generally there is a higher percentage of that variant in places where they have symptoms. So if they have liver dysfunction, it is generally higher in liver, or if they have muscle weakness it is generally higher in muscle. So if a patient has those particular symptoms, then a lot of times muscle may be best. Sometimes it is not just which sample is best, but which sample is critical, to making a diagnosis. There are some specific types of disorder where having a particular sample type is really really important and can make or break a diagnosis.

Slide 18:

If we look at Slide 18, you will see pictures of an individual who has something called chronic progressive external ophthalmoplegia (CPEO). CPEO is a symptom that is highly specific for mitochondrial disorders so it is a very specific type of muscle weakness of the eyes. Most of these patients have a primary mitochondrial disorder. It is important to note that half of these patients have a large mitochondrial genome deletion so you will see half or a quarter of the mitochondrial genome is just missing in the patients. But it is important to note that if you test the blood of these patients you won't find that deletion. Even if it is present in a high level in muscle, it is only detectable in muscle. So you can test blood all you want for patients who have a deletion that causes CPEO you won't find it in the blood, only in the muscle sample.

Slide 19:

If you look at page 19 you will see a bone marrow biopsy from a patient who has Pearson Syndrome. Which is an infantile onset sideroblastic anemia and pancreas dysfunction condition. So it is a very specific type of anemia and a very specific type of pancreatic disease that really makes you think this patient has a mito disorder. So patients with Pearson Syndrome they also have these large mitochondrial genome deletions. But in this case, you don't want to send muscle because generally the deletions in these patients is confined to blood. So for these two particular conditions, sample type is extremely important and can make or break the diagnosis of the patient.

Slide 20:

We also get a lot of questions about other sample types for mitochondrial genome testing. While muscle is a good type of tissue to test for many patients, muscle biopsies are invasive. We would rather not biopsy a baby if we don't have to. Even blood draws can be hard to get for some patients. We have looked at other sample types that we get questions about. But the question of which sample type is best is similar to what type of test is best and is one you should with your physician based on your specific clinical symptoms and your specific clinical history.

We offer testing with oral rinse and buccal swabs and find that if we find a heteroplasmic variant, it is similar in blood. For skin cells we generally don't want those cells because if a mitochondrial genome variant, sometimes they will be selected against. So the sample may start at 40% but over time if you culture those cells or cause them to reproduce, you will find that heteroplasmy level goes down. So it may start at 40%, but it my go down to 30% or 20% or 10% and become undetectable even if a variant was there to begin with. One that we get frequent questions about is urine sample testing so because some studies have found that the heteroplasmy variant in urine is similar to those of muscle. However, DNA from urine, the quality is extremely poor, so most of the time you don't get results. So here at GeneDx or most other laboratories won't be able to offer at this time. Another question we get is hair follicles, and again, it has the same problem as urine

cells, where you get very very poor DNA quality. In addition to that, heteroplasmy can vary greatly from follicle to follicle so just because you are testing one hair sample does not mean that that it is representative of the heteroplasmy is present in other hair samples.

Slide 21:

So if you look at Slide 21 you will see a list of some of the limitations of genetic testing, because we have gone a very long way in the field of genetics to be able to offer testing that is able to find diagnoses in more patients but it is important to know the limitations of that testing. So knowledge about the function of all of the genes in the genome is incomplete at this time. So like I said a quarter of the genes have been associated with a human disorder, which means that three quarters of the genes, we are not all the way sure they cause human disease.

Additionally, in testing we may find a variant, but we may not know enough about the gene, or the function of the variant, to be able to link it to the patient's symptoms. Not all types of genetic testing can detect all types of genetic variants known to cause disease. Such as repeat expansion, which if I go back to fragile x syndrome, which is one of the more common forms of inherited intellectual disability, that wouldn't be detected by whole exome sequencing because it is a repeat expansion, it is not a sequencing variant unlike most other genetic changes. Additionally for mitochondrial genome variants, heteroplasmy can vary from tissue to tissue, so depending on the sample type that you send or the particular spot of the muscle biopsy, a variant may not be detected in one tissue but may still be present in other tissues. So while genetic testing can be a great service and can provide a lot of information to patients, it is important to realize that there are limitations. There may still be a diagnosis that testing can't identify at this time.

Slide 22:

I would like to thank MitoAction for inviting me here today to present to you all, I'd like to GeneDx mitochondrial testing team (see slide) as well as mito patients and their families that allow us to provide this testing and provide diagnoses and who have been through a diagnostic odyssey a lot of times, and we are really thankful for the information we are willing to provide and the services we are able to provide for them too.

Questions and Answers

MaryBeth Hollinger:

What a great presentation! My mind is swirling and you have clarified things for me, and I did not realize how specifically CPEO can only be found in one sample type but not in another, I didn't realize that it would not show up at all. You have increased my knowledge base, and I so appreciate it. MitoAction in general gets many questions about genetics. People have some raw results but just don't know what they mean. I so appreciate you clarifying many of questions that come to us and I can use your presentation when they reach out to us to explain some of these find tune differences between sample types and testing types and why this and not that. So thank you so much Amanda.

If a patient comes in and has one allele, one copy of a homozygous mutation, meaning that they need two to qualify as having that disease, is there in mitochondrial disease a partial expression give that they don't have both genes, or is it 'nope you are carrier and you really don't have this disease'.

Amanda Balog:

The answer is, it depends. In genetics, especially mitochondrial genetics, we end up with that answer a lot. Most of mitochondrial disorders are something called autosomal recessive, which like you said you have two copies of the gene and both copies need to have something in order to cause the disease. It is a question we get a lot because when we test a lot of genes we find a lot of variants and there are multiple reasons that you can have that. It could be that you are just a carrier of a recessive disorder and that this is unrelated to your symptoms, that there is a diagnosis still out there, and I will say for most of the VUSs that we find that are heterozygous, that is likely the answer, that you are just a carrier.

But depending on the particular genes sometimes carriers have symptoms, and depending on the type of testing and the coverage and how well they were able to sequence that gene, it could be that they have a second variant that we are not able to detect at this time. We talked about whole exome sequencing, it only looks at the protein coding parts of genes, so it does not evaluate every part of every gene, it just looks in those places where we are most likely to find a variant, so they could have something that is outside of that region, or a type of variant like I said that wouldn't be detectable by sequencing. Unfortunately, it depends, if it is a variant of uncertain significance it is unlikely to be the diagnosis for that patient but it really depends on the specific variant, the specific gene, and the specific patient.

MaryBeth Hollinger:

Very helpful thank you. There is another question about VUSs and they did note that you use ClinVar to track these, but they were wondering how best should these VUSs tracked personally? Do you just trust that your diagnostic company will continue to track that VUS and let you know if 'Oh, other people have this and it is disease causing,' or is there something more active that the patient population should be doing with their VUSs?

Amanda Balog:

They should be consulting with the order physician on a regular basis to see if the variants have been updated over time. At GeneDex we will look at the variant the next time it is seen, so if we saw a variant in 2014, and then we saw it again in 2017, we will reevaluate the evidence that is available for that variant. But if we don't see it again we won't necessarily be able to update the classification of the variant with the additional data that may be available.

MaryBeth Hollinger:

If there has been a progression of symptoms?

Amanda Balog:

Right, or if it has been published. So that is something to talk to your physician about, and they can reach out to us directly if they had testing with us to see if we have updated the classification. Because evidence does accumulate over time, both to make things move towards the pathogenic end and the benign end. So definitely that relationship with your physician is the most important with reminding them to see if any of those classifications have updated.

MaryBeth Hollinger:

As well as clinical registries that may help with that tracking as well. A caller asked “What if a presentation looks like mito, but nothing seems to be showing on genetic testing.

Amanda Balog:

So that is one of the limitations of genetic testing. It depends on the type genetic testing, if they have had just mito genome testing alone, versus panel testing, versus whole exome sequencing, it may be that additional genetic testing would be a good idea and may be likely to lead to a diagnosis. It could be that the patient has the most comprehensive testing that is available at this time, but in the future testing may be offered.

When I was in school whole exome sequencing was not clinically available, it was only on a research basis, and it was very new and very very very expensive and so we could only offer it for research studies. Now it is a standard of care for a lot of different patients so our panel of genes has increased from 24 genes to 139 genes to now 319 genes, so the testing that is available changes over time so maybe additional testing might be warranted, maybe not right now, maybe in the future. It may be that this isn’t genetic, that there is something else going on that is causing mitochondrial dysfunction, but that is a good conversation to have with your physician.

MaryBeth Hollinger:

Perfect, that is very reasonable.

Joy:

This is Joy, I just wanted to see if I understood this, did you say that if I had genetic testing a year and a half ago and so you are saying that in 6 months, after two years of whatever talking to the doctor about if there are any changes in that genetic testing?

Amanda Balog:

Yes, just to see if the classification of those variants has changed over time.

Terry:

My name is Terry, you were talking about different specimen types for the testing, if had the blood sample used, but also had the muscle biopsy, and I guess I never asked, what was best to use at that time, would it be advantageous then to also have the muscle biopsy put through for genetic testing and do people do that?

Amanda Balog:

That is not unusual to do actually, if we go back to that case example of PEO, that testing muscle really is important, it can also be important for patients who have muscle weakness, with PEO we know the number of increased diagnoses that are made with muscle biopsies versus blood alone. With other types I don’t think there is a good number on how many patients have negative mito genomes with testing in blood who would then get a diagnosis on muscle. So it depends on your particular symptoms, it may be worthwhile to repeat it, and depending on the type of muscle biopsy sample that is left, it has to be frozen it can’t be paraffin embedded it can’t be slides, so some samples aren’t appropriate for mito genome testing because of DNA quality. So that is something to discuss with your physician.

MaryBeth Hollinger:

There is another question that came in that is a bit more specific, so I'm not sure if it is in your realm. They had some gene diagnostic testing that came back with a likely pathogen for GST type 2, some enzymatic testing came from the low end of normal, but some pulmonary testing has shown neuromuscular respiratory weakness. So the person is wondering if that is enough evidence for it to be diagnosed as GS2 or should they be looking elsewhere.

Amanda Balog:

That is a tough one. GST type 2 is actually one of my subspecialties prior to coming to GeneDx. That would really depend on your specific variance, your specific enzyme levels, I would definitely go back to your physician, or have a consultation with an expert in GST type to see what or not this is low end of normal or more diagnostic then that.

MaryBeth Hollinger:

Right, because I can see how the enzymes coming back, even low end of normal is still in that normal range, some people dismissing that without not weight your symptoms quite enough. It is obviously not a big line in the sand, it is a little grey area in there.

Amanda Balog:

As we do more genetic testing, the spectrum of symptoms that are associated with a particular disorder is increasing. Even stuff that we have known about for a long time we are still learning about known disease causing genes. So it is definitely a learning experience for all of us in genetics.

MaryBeth Hollinger:

What would be the cost if you have no insurance?

Amanda Balog:

It depends on the testing.

MaryBeth Hollinger:

Can you give us a range or something to contemplate?

Amanda Balog:

It really depends, and there are some financial assistance programs available at different laboratories, so it is really really difficult to give that range.

MaryBeth Hollinger:

Fair enough. So people should be looking into what testing is best for them, whether it is whole exome or a panel and then start to see what financial assistance is available. I know many state run insurance doesn't cover it because it is considered experimental.

Amanda Balog:

And a test may be cheaper, if it so unlikely to yield a diagnosis, even though it is a lower amount of money, it isn't likely to yield a diagnosis. So that is something to consider in that calculation.

I have a question, I was wanting to find out, it kind of leads into the one that was just asked, about how to find out about the programs where you may be able to receive assistance, I have been diagnosed with mitochondrial myopathy and a genetic variance and they found two main defects in my genes, so I was referred to a metabolic specialist but I lost my health insurance. So I am wanting to find out, how do you find the information about programs where you may be able to receive assistance and go ahead and get the proper testing and care.

Amanda Balog:

That is a tough one, MaryBeth, you are more tied into the resources in the mito community I think than I am on the laboratory end.

MaryBeth Hollinger:

I would say it would be best to contact me after the call, at mito411@mitoaction.org and I will try and compile a list of those resources for anyone who would like then. Mito Action has some access to those lists so that would probably be the best way to go. Is that okay with the caller?

Yes, thank you so much I appreciate it, and wonderful call today, thank you.

Fred:

My name is Fred, I just don't know how to get started. I have symptoms like hypothyroidism but that is not it, I have low temperatures in the 95 and 96s, and all of my doctors are clueless. I don't even know how to get started with genetic testing, I don't know what test to get.

Amanda Balog:

Have you seen a genetic specialist or a geneticist at this time?

Fred:

No I have not.

Amanda Balog:

If you have a myriad of symptoms or you are concerned about a mitochondrial disorder, that is a really good place to start. Like I said, genetics are really good at taking a step back and looking at the whole of the patient to try and see if a genetic diagnosis can link those symptoms. You can find a genetic counselor if you are in the United States, NSGC.org and there is search function where you can put in your zip code and the subspecialty of genetic counseling you are looking at and see if that counselor is seeing patients to find a genetic counselor in your area, and that is a really good place to start.

Fred: Alright, thank you.

MaryBeth Hollinger:

I have a question here, again it is specific, "Which genetic test might be best to detect a mitochondrial disorder that would explain neutropenia and leukopenia when they are pretty severe?

Amanda Balog:

That is a specific one. That is a good one to discuss with your physician.

MaryBeth Hollinger:

I agree and they would really need a bigger picture and a bigger historical timeline. And I think you do bring up this point Amanda, when you go to a counselor or a very good metabolism, that family tree, even your personal history, things that you have never connected in the past, suddenly come to life and you can start to see patterns emerge that maybe you didn't notice, and I find that fascinating and such a key component, to this whole diagnostic path. Even if you think you have your whole history down, sometimes talking it out, putting it on a timeline with the help of genetic counselor or a physician or whoever you think, can really bring patterns to life that you didn't notice before because you are so close to it, you live it.

Amanda Balog:

Exactly, and with mito disorders that is especially true because you can have symptoms in all these organ symptoms or just one, and individuals in the same family can have symptoms in different symptoms, even if they have the same pathogenic variants. With that MELAS variant sometimes they have isolated hearing loss or diabetes or just cardiomyopathy and no seizures but somebody else has seizures. So family history is extremely important in the context of mitochondrial disorders.

MaryBeth Hollinger:

Let me throw one more at your here, if someone had testing done in 2014 and it did not yield much diagnostic information, would you suggest that they redo that testing at some point and what time frame do you like that retesting to be done.

Amanda Balog:

It is not good to repeat the same genetic test that you had done in that past so if you had a specific panel that had 24 nuclear genes, it generally doesn't make sense to repeat the specific genetic test again. It's not like a complete blood count where that changes over time. Your nuclear genetics is pretty static. It may be worthwhile to see what is now available for genetic testing, it may make sense to do a different type of genetic testing. If you had a panel in the past, maybe whole exome sequencing is better, or may now you have different symptoms that make you think, oh maybe it is not this range of disorders it is this range of disorders. So having genetic evaluation or neurological evaluation, not just once but periodically, is just a good idea to be updated on the test offerings that are available and might be appropriate for you as well as tracking new symptoms that may make you go down a different path on that diagnostic odyssey.

Caller:

I'm the patient that had the testing done by GeneDx in 2014, at that time, the analysis was 139 nuclear genes, now that you have a more expanded panel of genes that you look at, could this testing be repeated? I don't have new symptoms, it is the same symptoms I have had for decades and decades, there is nothing new about this but I know the testing is improving.

Amanda Balog:

We get that question a lot, ‘I had version 1 of this panel and now you offer version 3, is it a good idea to do version 3’? Depending on your symptoms it may or may not, the diagnostic yields from doing version 3 when you had version 1 in the past, the increase in diagnostic yields, the additional patients who gain a diagnosis by testing those genes is pretty low because the first panel had the heavy hitters, it had the ones that were most likely to yield a diagnosis, so most of the genes that we add to panels are some of the more rare types. It may or may not depending your clinical symptoms, different genetic testing may be worthwhile as well.

MaryBeth Hollinger:

I would like to close by thanking you for sharing your expertise, and taking some of these specific questions as well as general ones, the questions have been wonderful questions and in depth, and it just shows the knowledge base of our community and how they know well how to use their time with an expert to get more information or clarification when needed. Thank you so much, we all in this community that are in our corners and fighting for our diagnoses and working to improve the technology every single day. IF you have any lingering questions you can send them to me at mito411@mitoaction.org email and I will either see if I can get Amanda to jump on board and help me out to answer them or I will answer myself.