Dr. Kendall Discusses "Is It Really Mito?"

Dr. Fran Kendall of VMP Genetics discusses "Is It Really Mito? When an Alternative Diagnosis should be Considered." Talking points include:

- **Clinical red flags that suggest an alternative diagnosis should be considered**
- **Why that option should be entertained**
- **Tools utilized to re-analyze patients classified with mitochondrial disease.**

Slide 1:

When an Alternative Diagnosis should be considered

Good afternoon everybody, happy Friday. Today I am going to talk a little bit about when an alternative diagnosis to a presumed mitochondrial disease diagnosis should be considered. So the first thing I want to outline is just my overall objectives.

Slide 2:

Disclaimer: *Dr. Kendall and VMP Genetics have no financial interest in any laboratory.*

Slide 3:

Objective: T*o review the approach to mitochondrial disease diagnosis, clinical red flags that suggest a non-mito diagnosis should be considered, why an alternative diagnosis should be entertained, and the tools utilized to reanalyze patients classified as mito.*

I am going to start to by reviewing the approach to mitochondrial disease diagnosis in general and some clinical red flags that suggest to me that a non-mitochondrial diagnosis should be considered. I will talk a little bit about why alternative diagnoses should be entertained, and some of the tools that I utilize when I reanalyze m patients. I will be making my points utilizing actual cases, due to HIPAA and privacy regulations there is no identifying information in regards to these cases, but they are actual cases. There are a few that I thought highlighted some specific points

but I have many many others cases, some of which I am going to mention to emphasize other points as we go through this.

Slide 4:

Mitochondrial Energy Disorders

- *Found in 1 in 4,000 individuals*
- *Carrier rate of common mtDNA mutations may be as high as 1 in 200*
- *Caused by an alteration in our inherited blueprint (gene mutation) or "toxic" affect of external factor such as medication*
- *Results in decreased energy production and localized or widespread problems*

Let me just segway into information that most of you in the community are already familiar with but there may be some of those who are relatively new to the community and it never hurts to just reemphasize some major points so that we are all on board and functioning from the same perspective. As we know mitochondrial energy disorders are found in about 1 in 4,000 individuals, and that number changes a little bit depending on the reference and resource you utilize but that certainly there are much greater incidence than when I started in this field in the early 90s at Boston Children's when we thought the incidence was 1 in 520,000 so that is obviously far more common than we believed in the past.

There is also a carrier rate of some of the common MTdna mutations, maybe as high as 1 in 200, now this study is now 5 to 10 years old but it was a study done out of the UK where they looked at newborn screening samples and analyzed them for some of the common MTdna mutations. Those are the maternally inherited mutations. They found them in as high as 1 in 200 individuals. There have been no other studies on that data to my knowledge that showed whether all of those individuals developed clinical symptomatology which I doubt they did. Or they may develop it later of course as well. So they may carry for example a MERRF mutation

but they may not come to clinical presentation until much later. I have several patients with MERRF who did not present until well into adulthood. So they may not have any clinical disease in this point in time but it is still interesting from a broad perspective to know that these mutations have a far greater impact than what was initially anticipated.

Of course, mitochondrial energy disorders are called by an alteration in our inherited blueprint, in our gene mutation, or they can be due to a toxic effect of external factors such as medication. For the emphasis of this discussion, I do not get into any of the external factor toxicity issues such as the form and toxicity of the medications. Certainly they do exist and they do cause problems for patients but my focus is really on primary mitochondrial disease today, those that actually alter specific gene or genes that result in mitochondrial disease. Again as we all know mitochondrial energy disorders result in decreased energy production and a broader cascade of clinical findings in the cell that I won't go into. But it results in localized or widespread problems in multiple organ systems for affected individuals.

Slide 5:

Common Problems in Mito

- *Central Nervous System (Brain) problems such as developmental delays including autism and autistic features, loss of function, seizures, hypotonia, weakness, muscle pain, ptosis, and CPEO, hearing loss.*
- *Failure to thrive, short stature*
    - *Chronic fatigue*
    - *Gastrointestinal issues such as gastroparesis, chronic constipation, and dysmotility and liver failure*
    - *Autonomic dysfunction such as irregular heart rate and blood pressure and temperature instability with heat intolerance*
    - *Endocrine problems such as diabetes or hypothyroidism*

- *Cardiomyopathy and heart rhythm abnormalities*

The next slide outlines some of the more common problems that those of us in mitochondrial medicine see on a day to day basis so of course particularly in children you have a lot of central nervous systems or brain problems, not that adults don't struggle as well but of course the earlier onset in kids will often translate into developmental delays including autism. Certainly neurodegeneration or loss of functions, seizures, muscle pain and weakness, in adults a common problem I see is ptosis which is droopy eyelids and CPEO, which is an acronym for Chronic progressive external ophthalmoplegia. That means that people can't look up, down, or sideways due to eye muscle weakness. And then of course hearing loss.

Some of the other things we see again primarily in kids, failure to thrive and short stature, but adults can also have extreme weight loss and fatigue, fatigue occurs very frequently in both adults and children. Gastrointestinal issues are very widespread and can range from things like chronic constipation to far more severe, dysmotility, resulting it tp and dependence and even liver failure in some subsets of mitochondrial disease like alport syndrome for example. Autonomic dysfunction is again a very common problem that I deal with all the time, and that can cause a temperature instability, many people with mito overheat quite readily. They can also have irregular heart rates and blood pressure problems so when they get the cardiovascular issues, that tends to be more significant in the sense that they need other interventions other than just cooling vests and those type of things to help manage those symptoms. Certainly you can see endocrine problems like diabetes and hypothyroidism and while we don't see it that frequently, things like cardiomyopathy and heart rhythm abnormalities do occur as well.

Slide 6:

How to Diagnose Mitochondrial Disease

- *Several tiers of testing are utilized to diagnose mitochondrial disease*
- *Constellation of clinical features*
- *Biomarker studies - lactate and pyruvate levels, CSF lactate, CPK, urine organic acids, carnitine levels.*
- *Radiographic studies - identification of mito related imaging abnormalities.*
- *Functional testing - examining the OXPHOS energy pathway*
- *Gene testing - evaluation of mtDNA and nuclear mitochondrial genes*
- *Utilization of published Criteria such as the Bernier Criteria*

The next slide talks about the diagnosis of mitochondrial disease, and so for those of you have been in the community for awhile and are familiar with these diseases and certainly you have gone through the process yourself, you recognize that this is not an easy diagnostic journey. So if you go into your physician and you say “I think I have diabetes” for whatever your reasons, you have a family history, or you are losing weight or you are urinating a lot. It is relatively easy to sort that out, people will check your fasting blood sugar and something known as hemoglobin A1C and will know whether you have diabetes or not and that is kind of that journey.

In terms of mitochondrial disease we usually have to use multiple tiers of testing. Usually the first diagnostic clues are the constellation of clinical findings and features, and the hallmark of that is multi-system problems, and you are all probably familiar with that terminology. That means things that are seemingly unrelated and affect a wide swatches of the body. So if somebody comes in an has a lot of central nervous system problems, and then has cardiomyopathy and muscle weakness and an enlarged liver that doesn’t work very well, that unusual constellation of findings is often the first clue. Then we will use again, a number of different tiers of testing, biomarker studies, they look for biochemical abnormalities in the blood, urine, and cerebrospinal fluid, that can

be out of whack in mitochondrial disease.

The thing to keep in mind though is that not all patients with mitochondrial disease will have elevated lactate or any of these other abnormalities for example, many do, but not everybody does. I happen to have an adult patient with MELAS, and those of you who know that disease and that acronym, part of the disease description is elevated lactate levels and she has never had any elevated lactate levels, and she has the mutation, and her mother had the mutation, so there is no question about her diagnosis, but despite the name of her disease she does not have elevated lactate levels, so if somebody has just looked at that, it would have been dismissed. So again, biomarkers are very helpful, but they are not always 100% diagnostic.

Radiographic studies, we utilize particularly in the kids with developmental delays and seizure disorders, and you can certainly see things like white matter disease, in leigh disease for example, there is very distinctive, symmetrical, lesions in the brain, usually affecting parts of the basal ganglia and the brain stem, so some other motor coordination and vital function centers. But that is not particularly useful tool, in adults for the most part, but again it can be very helpful. The exception to that is MNGIE, which is another one of our famous acronyms in mitochondrial medicine. Those individuals with that subtype of disease usually have white matter disease. The remaining studies we have are a combination of functional testing and gene testing. Functional testing, is referring to enzymatic analysis of the mitochondrial electron transfer or chain pathway, so that is what muscle biopsies are, and what they were utilized for. So again, we are looking and measuring that biochemical pathway. Then of course we have gene testing, which took a backseat to muscle biopsies for many years just because we didn't have such advanced tools that allowed us to look at such a broad spectrum of genes, but that has markedly improved in the last 5 to 10 years and that has kind of eclipsed muscle biopsy, as your kind of go to diagnostic tool.

Then of course the last categorization that I have listed here in terms of how to evaluate patients is utilization of published criteria, such as the Bernier criteria. There are number of diagnostic criteria out there they are relatively old, meaning they haven't

been updated recently, but they are at least 10 plus years old, but what these criteria do is trying to assign point sto various aspects of findings of mitochondrial disease, to give you some sense whether or not you think this patient definitely has mitochondrial disease, probably, so there is a little bit of gradientaion there, so that again can be a little problematic so it certainly helps us, particularly in cases where we feel perhaps that you have mitochondrial disease based on some, not definitive finding but actual gene diagnosis, but you have other things. We as the mitochondrial clinicians refer to those criteria to say “Yes, I understand doesn’t meet all of this ritera but they probably have a mitochondrial disease based on utilizing these published criteria.” And that certainly helps in some cases where you are dealing with other physicians who are perhaps skeptical about a diagnosis.

Slide 7:

Before Embarking on an Evaluation...

Make sure you screen for other disorders like…

-Chromosome abnormalities

-Other inborn errors of metabolism

-Any other disorders that could explain the clinical presentation

Now, one thing that I tell folks all the time, and sometimes I need to do it when I see patients myself, is that before embarking on an evaluation, you should make sure that you screen for other disorders before really considering mitochondrial disease. For example, and most people do have these some of these studies done before they present to somebody like me but sometimes they don’t. Things like chromosome abnormalities or other inborn errors in metabolism, or any other disorders that could potentially explain some of the clinical presentation. For example, I see a good number of adults who, one of their presenting symptoms is fatigue, as it is for most mito patients, but fatigue can be kind by other problems, anything from hypothyroidism, even to autoimmune disease, so if somebody comes in and have not have those screenings or studies for some of those other disorders, I will make sure I will look at those, before I

embark on extensive studies like gene testing or biopsies. So that is just a few things that you can keep in mind before you consider some of this more advanced and complex testing is to make sure you have had some of the basics looked at.

Slide 8:

Clinical "Red Flags"

- *Predominately a seizure disorders*
- *Developmental delay syndrome, particularly with dysmorphic features, without multisystem involvement*
- *Isolated myopathy*
- *Static disease process*
- *No biochemical abnormalities*
- *"Gut" feeling of practitioner*

Have said all of this in terms of, this is mitochondrial disease, and these are the common problems and how we routinely diagnosis, the true topic today is to focus on, cases whereby I diagnosed and what my thought process was in regards to why I felt strongly that these patients had some other diagnosis. These are clinical red flags for me, I can't speak for any of my other colleagues, of course, I'm sure that some of them would concur with many, if not all of these, but nonetheless, these are not published red flags, these are what I have generated and identified as red flags in my clinical practice.

The first one is if a patient has predominantly a seizure disorder. This can be a little bit challenging because of course some mito kids have predominantly seizures as the big primary focus of their disease process, but we have identified over the past 5-10 years, many, many, seizure disorders syndrome gene mutations. So if a child has severe seizure disorder, has had severe seizures his or her entire lifetime, and most of the problems are linked to having severe neurological impairment due to intractable seizures, such as developmental problems, such as brain atrophy on brain MRI, then

you really need to think that perhaps this could be a seizure disorder mutation and not mitochondrial disease.

The next red flag is certainly developmental delay syndrome, particularly if it has dysmorphic features, and they don't have multi system involvement. So again, many kids with mitochondrial disease will have a host of developmental problems, but with rare exceptions they usually don't have dysmorphic features, and for those of you not familiar with that terminology that means facial features and other body features that are identifiable by looking at them on the outside of their bodies, that are different from you would expect based on their family. A common dysmorphic syndrome that we are all familiar with is down syndrome. You might not be able to tell me in medical terms, what the features are in that particular disorder, but you certainly know a down syndrome child when you come across them, so those are the kind of features I am talking about, and again without multisystem involvement. So if you have a child that has dysmorphic features and developmental delays, but they don't have any other organ system problems, then you definitely need to think about some of these neurodevelopmental syndromes.

The next is isolated myopathy. Myopathy is muscle disease. Again, many mitochondrial patients have myopathy, there is a subclass of occasions known as mitochondrial myopathy, but once again most mitochondrial patients will have other features other than just purely muscle weakness. That can be wide ranging, for example, kearn sayre syndrome has a lot of muscle weakness but those patients, mtDNA deletion syndromes will also have muscle weakness, one of which is kearn sayre syndrome, but they often has ptosis, and ophthalmoplegia and even other body system problems. So, having said that, again mitochondrial patients often have more widespread body problems, so isolated myopathy should be a red flag.

The next is a static disease process, so even though mitochondrial can have a slower, smoldering, course as I describe it to some of m y patients, meaning they progress over time but it isn't a rapid progression. If you are looking at a patient who has had no changes over years to decades, then that is considered static encapalothy

or a static process, it is considered extremely stable, maybe they have a little muscle weakness, but nothing else and nothing else got worse. Maybe they have some developmental delays but nothing else, and nothing gets worse. So that is when you have to say, this is a very static process, maybe this is not a mitochondrial disorder.

The next is, no biochemical abnormalities, that to some degree conflicts with what I said earlier about my MELAs patient that doesn't have an elevated lactate level, so you do have to take this with a grain of salt, but certainly if I see a patient who is very static in terms of their disease process and they have no biochemical abnormalities at all, not elevated lactate, no low carnitine, no elevated CPK, any of those findings, and again that does become a red flag for me.

The last one is the gut feeling of the practitioner. That is a vague statement of course and I can't really quantify it any more for you but, like we all do as parents, or as physicians, nurses, or whatever our chosen profession is, we develop and understanding of disease process, and we have gut feeling. It doesn't really matter what your background is in terms of your career but we all sometimes say, "No, I really don't feel like that is the case" and that is intuition based on sometimes unconscious understanding of things that we can't necessarily express, but we just know that something is not quite right.

Slide 9:

Seizure Disorder Syndrome

- *Patient presented at 6 months of age with infantile spasms*
- *Chromosomes, lysosomal enzymes, biotinidase assay, metabolic studies, all negative EXCEPT for a mildly increased lactate on one occasion*
- *Brain MRI, CSF testing negative; muscle biopsy complex I defect*
- *Clinical course notable for predominant seizure disorder and delays with no other system involvement*
- *All follow-up metabolic studies consistently negative*

- *Patient identified to have an SCN2A de novo gene mutation*

So having said all of that in terms of the red flags that I utilize in my practice, and what I have come to see as findings that make me want to reanalyze somebody, what I wanted to do now is segway into discussing several cases. And so, the first one, is slide number 9, and it is a seizure disorder syndrome so I am going to talk about the highlights of how this patient presented and what some of the abnormalities are, and why I decided to pursue some other diagnoses. I have three cases that I am going to talk about and then I am going to segway again into some other comments about testing and my approach and what I do.

The first one again is the seizure disorder syndrome, this patient presented at 6 months of age with infantile spasms which is a significant seizure disorder. At the time that the patient was first investigated for the possibility of a mitochondrial disease the child had already had chromosomes, lysosomal enzymes, biotinidase assay and a number of metabolic studies, everything was negative except for a mildly increased lactate on one occasion. Just as quick aside, for those of you who are not as familiar, lactate is a marker for mitochondrial disease, but it is very finicky in terms of its collection and processing. It is not uncommon to have some false positives. So that is something to keep in mind.

After the initial studies that this child underwent was a brain MRI and some spinal fluid studies and a muscle biopsy. This little one was found out to have a complex 1 defect, so it was labeled as a mitochondrial disease. In terms of following the patient, this kid's clinical course was notable seizure disorder and delays, linked again, to having an intractable seizure disorder and loss of brain matter due to that. So remember, keep in mind, as most of you understand, if someone is seizing constantly their brain can not really focus on learning and developing. So kids with severe seizure disorders typically have severe developmental problems. But this child had no other systemic involvement. I followed her and did a number of metabolic studies and they were consistently negative, so that elevated lactate that was seen initially was not

repeated, meaning it was not found to be abnormal on multiple occasions, subsequent to the initial diagnostic evaluation. So I was concerned given the clinical course and the findings that this child may have a seizure disorder syndrome.

Interestingly I did a smaller gene panel initially for some of the more common seizure disorder mutations which ended up being negative and then I expanded my workup and found that this little kid had a de novo SCN2A known seizure disorder syndrome mutation. De novo means that it is just in the child, so even though it is genetic, meaning it alternating this child's genetic blueprint, it was no inherited or passed down through this child's parents.

Again this is one example and I have many, many, many, examples of seizure disorder syndrome patients that had undergone similar evaluations with biopsies, told they had mitochondrial disease and turned out to have seizure disorder mutations. Most often seizure disorder mutations are de novo which means there are no recurrence risks for a couple. Sadly I do have one family who underwent a biopsy and were told the child had mitochondrial disease and the father proceeded to have a vasectomy, and it turned out that the child had a de novo seizure disorder mutation. So there would have been no recurrence had the family elected to have other children.

Slide 10:

Neurodevelopmental Gene Syndrome

- *Patient presented at 12 months of age with hypotonia, DD and elevated lactate level*
- *Chromosome studies, telomeric FISH studies, metabolic studies, CSF testing all negative EXCEPT for a lactate of 14 with nL up to 12*
- *Muscle biopsy notable for complex I and IV defects*
- *Clinical course notable for static encephalopathy with no other system involvement and dysmorphic features*
- *Follow-up metabolic studies negative*

- *Patient identified to have de novo mutation in the ZEB2 gene associated with Mowat-Wilson syndrome*

The next case is a neurodevelopmental gene syndrome patient. Again, I am going to walkthrough what was initially identified and particular reasons which I decided to investigate further. This child presented at 1 year of age, with low tone and development delays and I think one or two elevated lactate levels, so this kind underwent chromosome studies and telomeric FISH studies, metabolic testing, CSF testing, all of which was negative except for a lactate of 14 with nL up to 12. Just looking at this, that makes it a little ambiguous but it was not the CSF testing that was abnormal, it was the blood lactate which was 14 with normal up to 12. A muscle biopsy was completed and identified complex 1 and 4 defects. The clinical course for this child was that he demonstrated a static encephalopathy and he had no other organ system involvement and he had dysmorphic or unusual facial features. On follow up, on a number of occasions, his metabolic studies were negative.

So because again he had static encephalopathy, no other body system involvement, no positive metabolic screening studies over time, I was concerned that again he likely had a neurodevelopmental gene syndrome mutation. Indeed, investigation found that he had a de novo, again, this was isolated to him, so no recurrence for his parents or his siblings weren't going to be carriers or anything along those lines, and he was found to have a very rare disease called Mowat-Wilson syndrome due to a defect in the ZEB2 gene. So again, this disorder, not a common disorder by any stretch, it is rare, but it is a neurodevelopmental gene syndrome, it is associated with dysmorphic features and again it typically has a static course and that is exactly what this child had. His clinical facial features were consistent with that disease as well.

Slide 11:

Myopathy

- *Patient presented at 6 years of age with congenital axial and proximal muscle weakness with several mildly increased CPK levels*
- *Metabolic studies unremarkable*
- *Muscle biopsy notable for chronic, stable myopathy affected core and extremities without other system involvement*
- *Follow-up metabolic labs consistently normal*
- *Patient identified to have a de novo mutation in the C0L6A2 gene associated with the Ullrich/Bethlem muscular dystrophy spectrum of disorders*

So the last case on slide 11, which I am going to specifically discuss in a lot of detail, is a myopathy case. Again myopathy is a muscle disease and gain we have many mitochondrial patients have mitochondrial myopathy, but quite often they will have other findings or features. So this patient presented at about 6 years of age, with axial (core) muscle weakness and proximal muscle weakness. Proximal muscles are those that are closest to the center of the body. Proximal would be hip girdle, and shoulder girdle muscle weakness, so his trunk was weak and his shoulder girdle and hip girdle, and he did have a couple of elevated CPK levels. In this particular case he never had any elevated lactate or other markers under than his CPK levels. So he had a muscle biopsy at once point for to changes that you can see due to chronic myopathy, now keep in mind that when these biopsies are done, of course we measure the electron transfer chain, but we also look at the muscle under the microscope. We look at its structure, look for other abnormalities, so in this case it showed signs of a myopathy or muscle disease but they were not specific, meaning it did not say “Aha it is this particular muscle disease”. And then he had complex 1 defect.

So he was again, like the other patients labelled with a mitochondrial disease, but clinically he had a very chronic, stable, myopathy that affected his core and extremities, and again he had no other system involvement and his metabolic labs were also consistently normal. He turned out, on further evaluation to also have a de novo mutation (so all three of these cases had mutations isolated to them without recurrence risk to their extended family or for the parents) in something called the C0L6A2 gene associated with the Ullrich/Bethlem muscular dystrophy spectrum of disorders. So there is a broader spectrum where they can present in infancy all the way up to adolescence and order and it is essentially isolated myopathy. So again, he was confirmed to have a different diseases.

Slide 12:

Even If It REALLY Looks like Mito…

- *Presented at 4 years of age with ataxia and subsequently developed seizures and developmental delays*
- *EMG and initial brain MRI were normal; ataxia studies for Friedreich's ataxia and ataxia telangiectasia were normal*
- *Muscle biopsy noted complex I defect; all other biochemical studies were negative*
- *Follow-up brain MRI at age 7 years noted cerebellar atrophy*
- *Follow-up metabolic studies were negative*
- *Patient identified to have an autosomal recessive form of spastic ataxia, affecting the SACs gene*

So these are three cases specifically that presented with some symptoms that made me concerned that they may have another disease, and it turned out in all of those cases that indeed they did. Now just to make it more complicated, the last case I am going to present on slide 12, it says “Even if it REALLY looks like mito, it still might

not be” and that is where it gets a little scary from your perspective as parents, and families, and patients, and even for those of us who are clinicians, so this one was a little bit tougher, but there were some red flags for me regardless even thought this patient really looked like a mitochondrial patient. This child was 4 years of age when she presented with unsteadiness or ataxia, and subsequently developed seizures and developmental delays. So there was some disease progression and it was not a static case, again, that is why it looks more like mitochondrial disease. EMG and initial brain MRI were normal. She underwent some ataxia studies for a couple of more common causes of unsteadiness like Friedreich's ataxia and ataxia telangiectasia and those studies were normal.

She ultimately made her way to consideration of mitochondrial disease and she was found to have a complex 1 defect, although all of her other biochemical studies were negative. When she was seven years old she underwent a subsequent brain MRI, in part because she was developing other clinical symptoms, including seizures. She was found to have cerebellar atrophy, that can occur in mitochondrial disease but it also occurs in a number of other neurometabolic disorders. Now, this child, I think the thing that was most telling to me, was that in follow up her metabolic studies were negative, now why was that a red flag for me? Well this was a child who was showing some progressive clinical signs, and often when that happens with people, even if their baseline metabolic studies are negative, usually with time, as their body is struggling and they are showing progressive symptoms, then there cells will also show signs of faltering, so their lactate, their CPK, those types of markers will start to become elevated, and hers were solidly normal.

As a result, I investigated her further, and I was concerned about one of many different types of ataxia. There are many, many ataxia syndromes out there and she did have spasticity, so again as part of her progression, she developed some spasticity and she was found to have an autosomal recessive form of spastic ataxia affecting the SACs gene. Now of course in this case, this was an inherited disorder, both of her parents were identified to be carriers, so there were recurrence risks and carrier risks

for her siblings and of course for her parents as well. So again, this is a difficult case because by all means it certainly looked like a mitochondrial disease in terms of progression, both clinically and based on brain MRI but again, there were some hallmarks to me, particularly the metabolic studies that made me concerned, that perhaps I really did need to look for something else.

Slide 13:

Implications of the Correct Diagnosis

- *Allows for implementation of appropriate treatment modalities*
- *Prevents unnecessary interventions and testing*
- *Provides eligibility for clinical treatment trials, if available*
- *Provide accurate prognostic information*
- *Allows for accurate recurrence risks for subsequent pregnancies and other family members*

So, here are four cases, three that exemplify some very specific points, in seizures or isolated myopathy, and the last one, was again, a little more challenging, but if we go to slide 13 and I have just a few more slides and I guess we will have some time for some questions. What are the implications of the correct diagnosis? I just wanted to emphasize this in part, not just so much for most of you I think you go through this process and you are dealing with chronic disease, you understand that, but I certainly have patients who have had physicians tell them, 'Well, what does it matter?', well in my opinion it matters a lot, and here are some reasons why having the correct diagnosis and why continue to look for the appropriate answer is important.

So the first comment is, allows for implementation of appropriate treatment modalities, and that is kind of a no brainer for those of us in this community but keep in mind, not that there is necessarily a cure all, definitely not for mitochondrial disease or for some of these other disorders, but there can be some appropriate treatments. Now,

one case that I didn't present today, but I will bring up is a young girl who had initially presented with hypotonia and she had had a biopsy and was told she was told she had mitochondrial disease and she did not have lots of follow up because she was relatively stable. She came to me as a young adult of many years of again, not really being in the community, as a college student, and she had developed a movement disorder. Now again, mitochondrial patients can have movement disorders, but there was something about her presentation that made me concerned, and I determined that she did have a movement disorder, and she happened to have a treatable movement disorder.

Had she been treated much earlier, she would not have had to contend with the clinical symptom and problems she had been dealing with for many, many years, but nonetheless, she was found to have a treatable disorder, and appropriate treatment was implemented with improvement. So that is the first point, the second is that it prevents unnecessary interventions and testing. I routinely do follow up studies on my mitochondrial patients to study things like lactate and those types of things, and even at times I will do brain MRIs or other studies, depending on the patient and their clinical symptoms. While they are not overly aggressive or invasive, it is still intervention and testing and if you don't have a mitochondrial disease and you have a static disorder that doesn't require specific monitoring on a yearly basis, than you are undergoing unnecessary interventions and testing that are not required.

The next provides eligibility for clinical treatment trials if they are available and you are eligible for them. But again those people in the community know that part, with treatment trials, you have to have a clear cut gene diagnosis and certainly if you have some other disorder, and perhaps there are clinical treatment trials available for those, if you don't know you have the disorder then of course you are not going to know that you are eligible.

Next is it provides accurate prognostic information. Again, being classified as one disease and thinking you have that disease versus something else that has a completely different outcome is extremely important. The young boy that I described with the myopathy, he was a very, very bring young man, and when he discovered he

said to me ‘Now I can think about my future’. This boy had spent his entire young life thinking that he was never going to make it to adulthood. Now he is going to have to problems with his myopathy, but he is going to survive his illness and he will thrive through it. So that is obviously is an incredible moment for that young boy to have to understand that he had a full life ahead of him. So of course accurate prognostic information is obviously important.

The last point I wanted to make is that it allows for accurate recurrence risks in other pregnancies and other family members. So again as you noted through the four cases that I presented, three out of the four were de novo, or isolated to the presenting patient, which meant for their parents, their siblings, their extended family, there was really no issue. There is something called germline mosaicism which I am not going to get into for the purposes of today’s talk, and that can make people face a small risk, but your genetic counselor would talk to you about that. But for the most part these are de novo which means there are not going to be recurrence risks, and that has huge implications for families considering other children or siblings that may wonder as they get into their own reproductive years, what kind of recurrence risks they would have or what they would have to worry about. So if it is de novo of course they don’t have to.

Slide 14:

Diagnostic Tools

-Genomic studies

Careful, whole does not mean 100%

-Biochemical tissue assays

-Metabolic Studies

So what are the diagnostic tools that I utilize for the purposes of evaluating patients? It is very similar to when I investigate people on the front end, but I will talk a little bit more about it and bring up some points. So of course genomic studies are out there, genomic is looking at our genetic blueprint and there is a whole host of gene testing available to us. So we can have isolated gene testing if at the clinician you are

worried about a specific disease you can look at that one gene. There are panels of specific, genes, so there are neurodevelopmental panels out there, and there is more broad testing like whole exome or whole genome testing. The one point I wanted to bring up about the genomic studies is just to be careful about the world ‘whole’ in terms of whole exome and whole genome, that doesn't mean that 100% of genes will be evaluated and that if you walk away from that test that there is a way you couldn’t have a genetic disorder or a mitochondrial disease even. Let me bring up a few points about that in terms of my personal experience.

Whole exome sequencing looks at about 3-4% of our genetic blueprint. If you look at some of the published data they talk about 35-45% of people walk away with a definitive diagnosis. Another 35% or so are found to have candidate genes which means their genes are highly suspicious, but we don’t have the medical information now to say that they absolutely do. The rest of course we just don’t know, we just didn’t find anything that we can hang our hat on. Again, the point is that is not 100%.

Now keep in mind there was a study this summer, at least the information was released this past summer in 2017, where research group looked at a number of mitochondrial patients who had negative studies like exome and mtDNA and those type of things. They found that 10% of the patients that they evaluated turned out to not have a problem in their genetic code, but in the actual transcription and translation of that code. So remember, think of your genetic code as a blueprint for a house, you might get a blueprint that looks perfectly fine but if the contractor takes that blueprint and instead of your kitchen puts in a garage, then that was a problem after the code, there was nothing wrong with the code it was just the way they interpreted or the way it was transcribed or translated from there.

The last things of course in terms of re-diagnosis, or clarifying are biochemical tissue studies and metabolic studies. Again, biochemical tissue assays have taken a backburner to the genomic studies, but keep in mind sometimes they are necessary because those genomic are not 100%. I have a case of a child who I was strongly suspicious had pyruvate dehydrogenase complex deficiency based on a number of

findings. The child had undergone some gene testing through an institution in New York and it was negative and the family was told that she doesn't have this PDH deficiency. So I reverted to basic biochemical studies like we used to do 20 years ago and indeed she does. So again, there are a number of diagnostic tools that are used to initially classify or reclassify patients.

Slide 15:

Who Arrives at the Diagnosis

-Labs do not diagnose patients, clinicians do

-Clinical acumen/experience of the doctor matters

-We are not all the same

The last comment I want to bring up is who arrives at the diagnosis. A couple of points, labs do not diagnose patients, clinicians do, so that is something to keep in mind. So it is actually with these advanced genomic studies you can get a report back that says you have a variant of unknown significance, which is the bane of all of our existence in terms of these big findings. But it is not the lab who is going to determine if that is diagnostic or not, it is is the clinician who is interpreting the data.

So I will give an example of how that impacted a patient. I had a child a number of years ago who came to see me for a mitochondrial disease evaluation and I thought that the child had something called cornelia de lange syndrome something I had seen during my training and time in Boston in particular. So I did a couple of the common gene mutation studies looking at common genes, and lo and behold they were negative so I said 'I don't know, this kid still looks like de lange'. So I did some additional more extensive studies and I found a variant in a very uncommon cornelia de lange gene. That gene caused the disease in less than 1% of the patients. My point is is that it was variant but because the child had every clinical feature seen with this disease, even though it wasn't documented as a clear cut mutation, I as the clinician said this is the cause for this child. So it is the clinician who is going to make that final diagnosis. Now if something is clearly pathogenic, of course, most physicians are going to utilize what the

lab tells you but there can be this variability as you know.

The last thing is really that the clinical experience and acumen of the doctor does matter. Again, a comment is, we are not all the same, and that is based on our experience. So keep in mind if you came to me and you asked me how to treat colon cancer, well I'm just like you I can google it and tell you something, I can certainly temper it with my baseline medical knowledge, but I am not an oncologist and I wouldn't be the best choice to go to for that issue. Having said that, when you are looking at rare disease, when you are looking at mitochondrial disease, you need to go to someone who understands that subset of medicine. That is critically important for many reasons, and I see many patients who come in from all over the country and I do international consults as well, and people who are labeled with and told they have certain diseases based on whatever studies that were partial studies or not even appropriate studies, the evaluating physicians really didn't have the experience and didn't know the diseases. So you have to be aware of that because that can have a profound impact and people can walk around with the incorrect diagnosis for many months to years, again if they weren't evaluated by somebody who really understands the disease. So again, there is a reason for some specialists, just like I said, if you came to me for cancer counseling, I would advise you not to, because I certainly do not have the knowledge base to do something like that.

So those are the points I wanted to make today. I know this can certainly be overwhelming to some degree, particularly from the perspective that in a community that often gets targeted for child medical abuse or fictitious disease, having anything that kind of shows that foundation a little bit, and having one of the specialists say, 'Wait a minute you may not have the disease', this can be a little bit disconcerting. But as I indicated, this is not about anything other than making sure that people have the facts, they have treatments available to them if they are available, and that they have the right diagnosis. I am not wedded to a diagnosis, I am wedded to the right diagnosis. Thank you all very much for your attention today, and I appreciate the opportunity to talk to you about this topic because it is an important one I think, and I talked about a few cases

today but I have probably 50-100 cases on my desk that I have re-diagnosed, so it is an important topic for the community. So thank you very much and I am happy to entertain a few questions before we finish for today.

MaryBeth Hollinger:

Thank you Dr. Kendall, that was a very informative presentation and I received many comments through email with people thanking you and just saying that they have learned so much from just listening today. I do think you bring up very good points about seeking the right diagnosis, and not feeling, owned by a particular diagnosis or feeling like that will be a loss if that particular diagnosis, so hopefully people can disassociate from the diagnosis, and just view the person themselves. I also love your point on the gut feelings, because I think many parents, have those same gut feelings, so they understand that there is some value to a parent saying 'I know my kid just doesn't look right or there is something off, this is my 4th kid of my 2nd kid, I kind of get this' and saying that yeah, the doctors have those same gut feelings that they need to trust as well. There are so many awesome points I could go through the whole thing. We do have many questions.

Dr. Fran Kendall:

I just wanted to bring up a couple of things MaryBeth to enforce things, so for me personally, I know that parents and families get anxious, but in my practice for example I know in other places, if they do some for example some gene testing on someone who had a biopsy and it is negative, people are taking the diagnosis. I don't do that, I don't take away a diagnosis until I have something to replace it with. Now, I am not saying that if someone comes into my office and the only thing wrong with them is a hangnail, and somebody told them they have a mitochondrial disease, I will tell them I really don't think you have that. But in terms of, if you have kid that has a seizure disorder and developmental delays and the only thing that has been abnormal to date has been a biopsy, I won't remove the diagnosis. I might continue to look, as tools expand, but I

won't remove that diagnosis. So for my population personally they don't have to fear and I will always tell them that, and they know that, the patients that I follow know that I will not do that if they do because some of these biopsies it doesn't mean the biopsies are always incorrect, but it just means that they may have been detecting some secondary abnormalities but it is not the primary of the cause of the child's problems or the adult's problems.

MaryBeth Hollinger:

I just think that point of a more correct diagnosis can bring you better and more effective therapies and treatments, it has to be shouted from the rooftops, because that is a huge difference.

Questions:

This one comes up very often in my phone calls, we all know that genetic testing is now coming to the forefront, as it becomes more accurate and sophisticated, how accurate and comprehensive is genetic testing for mitochondrial disorders?

Dr. Fran Kendall:

Well it does have its limitations, and I have seen different data, but some of the labs will report that it is only about 60% of gene mutations are identified, and again I brought up that study from this past summer where they looked at a bunch of patients who didn't have a gene diagnosis, and they like are kids with leigh disease, who clearly had a mitochondrial disease, and they are showing that there are other abnormalities. Meaning it is not necessarily the code, it is another point. But that is the data that I have seen, 50-60%, and that is why in part why we sometimes have to user multiple different tiers of testing, and sometimes I have to hold on to different things, like this patient has chronically elevated lactate, but their DNA testing was negative, but they have a neurodegenerative course. Well, that is probably mitochondrial disease. It is a good question because again, in a world where people will say 'Well you don't have a gene

mutation, you don't have it', you can't really say that with 100% accuracy and certainty.

MaryBeth Hollinger:

Another person is asking how far out you are booking appointments? I think just listening to you today you may be getting a plethora of calls.

Dr. Fran Kendall:

It depends on the time of year, of course at the end of the year when everybody met their deductible, we get a lot in, because genetic testing they have copays and that kind of stuff. It varies usually, a month or two. Sometimes we will have, people get sick of course and they have to reschedule or cancel an appointment for a later time, so sometimes we even have openings as soon as a couple of weeks, so it really just depends, when you are calling in and what we might happen to have, but generally we can get people in, and if there are certain emergency situations, I probably shouldn't say that Mike will probably kill me, but we can try to make accomodations for people as quickly as we can.

MaryBeth Hollinger:

And the cost I know is dependent on too many factors to get into on this call and they should call you for more information about that.

This one is interesting, from the slide that showed the common symptoms, the caller wanted to know if there was a certain number that you need like referring to an ADD scale where you need 10 points on a scale in order to be diagnoses. So they were wondering if there was anything like that that was offered for mitochondrial disease.

Dr. Fran Kendall:

That is a good question, I don't think so but I could bring up the bernier criteria, it is usually multi system problems, so if it is 2 or 3 organ system involvement or 2 of these 3 features it is usually what most people consider enough to consider a multi

system process.

MaryBeth Hollinger:

This one came in, what makes for a strong clinical diagnosis for those who can not afford genetic testing?

Dr. Fran Kendall:

The things that are probably, and again sometimes it depends on the patient, if it is a child or an adult, but certainly if it is a child and they have a neurodegenerative disease, that is certainly worrisome, and again if they have a multisystem problem. For example if they have a seizure disorder and they have progressive/regression of developmental skills and they have for example, liver disease/failure or progressive liver dysfunction, that would be a big red flag for alpers syndrome for example. In children that is the kind of clinical feature.

Now of course if folks can't afford genetic testing or they can't get it covered, usually you can get some basic biochemical studies so if you have those markers as well, then that is helpful. Then in an adult, it is a little bit more challenging in adults because some of the chronic features are things like fatigue and autonomic dysfunction and that can be caused by a lot of different things. For example if someone has an autoimmune connective tissue disorder, they may develop secondary autonomic nerve damage and then have symptoms similar to mito.

But some of the things that I keep in mind in adults in particular that are big red flags are ptosis and certainly ophthalmoplegia. So if you have really droopy eyelids and you don't have myasthenia gravis, you don't have ehlers-danlos syndrome, you don't have those things, and if you develop external ophthalmoplegia, those are really good clinical symptoms and certainly again, as an adult, if you have a neurodegenerative disorder, some of the first mitochondrial diseases back in the 30s and 40s, when they first described were actually in adults who had neurodegenerative disease. So of course the are not the things anybody wants clinically, but they are some of the big red flags

from a clinical perspective. But you know again keep in mind, that is reflective of the more severe cases scenarios, so those signs are going to miss people, but those are some of the things people are going to look at to say this is more likely than not.

MaryBeth Hollinger:

There is that big distinction between the children and the adults which is quite frustrating to the adults, but I try to tell them, “Think of a 50 year old car, it had a couple car accidents, it drove through that deep puddle, it can have a little stressors, on so many levels that are giving out all sorts of symptoms whereas with a baby that history is so much shorter, it is sometimes a little more clear cut to get to the root of their issues.

Dr. Fran Kendall:

And that is a very good descriptive analogy to use, and the other thing is that keep in mind as well, is that most often the adults are at least in part, functional, so what I mean by that, and that is not meant to diminish anyones symptoms whatsoever, but an adult, especially if you are a parent and you are worried about taking care of your kids, or going to work to put food on the table, you will kind of dismiss things for a long time, or it might start to come to your concern, but you do in to see a physician and you say I am always tired and they say ‘Well you are a parent and you work a lot’ so things will get dismissed because in part you do continue to function at some level. So that is the other problem with adults, a lot of times people don’t take a some of the adults seriously until they are so impacted that they are so far along in their disease problems, that it is sad that they didn’t get any relief or assistance up until they really present with significant problems.

MaryBeth Hollinger:

It is very true, I have a very special place in my heart for the adults.

Dr. Fran Kendall:

I do think they struggle more because a parent is a bulldog advocate for a kid, whereas they are doing it on their own.

MaryBeth Hollinger:

Well I know that it is after 1:00 pm and I so appreciate the time and the depth of this presentation, I know that it will bring up a lot of discussion, and I hope that it opens some eyes so if someone notices that maybe they haven't had progressive symptoms, or aren't quite following that mito pattern, that maybe there is another answer for them that could bring them a lot more relief. I appreciate it, I know that our community is cheering for you!