MEETING TRANSCRIPT

Energy in Action

Mitochondrial Disease Externally-Led

Patient-Focused Drug Development Meeting

Friday, March 29, 2019

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Remote CART Captioning

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SPEAKER: Hello I'm a volunteer, Hailey, and this is Lilly. On behalf of all patients, welcome to this externally led patient-focused drug development meeting.

As a patient, I'm very excited about this meeting. For the first time, our community is coming together to share our unique experiences. We're able to talk about our pain, our struggles, and our simple joys in the context of how mitochondrial disease affects us all. Our voices are truly being heard here today. I encourage you to participate today as we continue our journey to advance treatments, cures, and hopefully very soon a treatment for mitochondrial disease. Thank you.

(Applause).

MR. HARMAN: Well, thank you to Hailey and to Lilly for such a warm welcome this morning. Ultimately, what today is about is those patient families that are leaders in this fight. It is more kisses from puppies like Lilly that we're going for every day. So, Hailey, we're grateful to have you here with us today, and thank you for the warm welcome.

Good morning. My name is Brian Harman. I'm the president and CEO of the United Mitochondrial Disease Foundation. Today, on behalf of my friends at MitoAction, the Muscular Dystrophy Association, and our friends here today, I am glad to be with you during this momentous occasion for our community.

The Energy Action Patient-Focused Drug Development meeting for mitochondrial disease aims to set the groundwork toward creating effective therapies for mitochondrial disease. This is truly a milestone for our community. It also serves as a testament to the power of individual patient advocacy groups to come together to benefit our disease community. We are grateful for the leadership of our friends at MitoAction and Muscular Dystrophy Association, who helped us pull this tremendous meeting together today. Please join me in a round of applause.

(Applause.)

We're grateful for the opportunity to amplify our collective voice for our distinguished guests from the U.S. Food and Drug Administration. Thank you for your time and support in bringing this meeting to fruition. Please join me in welcoming our friends from the FDA today.

(Applause.)

Our efforts today, though, are truly driven by one significant force, and that is the patients and families that we serve -- mito champions like Hailey who you saw on the screen this morning.

Today, they're going to present to you both a voice and a choice. Our patient families will bring their voice to help us better understand their experiences, their struggles, their hope. These courageous panelists have already made their choice -- a choice to put their energy in action, a

choice to share their perspective of certainty, amidst a path of often uncertainty. For that, we are most grateful.

(Applause.)

But, most importantly, today I present to you all a choice -- a choice to engage and join us in bringing the patient voice to life. Whether you are with us today in person or online, your involvement in this meeting is paramount to our success. We thank you in advance for your support.

This special support that we have runs very deep. Our network of clinicians, researchers, and industry professionals have been lockstep with our patient families on this journey.

Of course, our work can't advance without the unwavering support of our corporate partners and family foundation partners. I want to extend a special recognize to out platinum sponsors, Stealth Biotherapeutics, Bio Electron, and Edith L. Trees Charitable Trust. Thank you so much for your support.

(Applause.)

They are joined by nine additional partners who have made our patient families and this important meeting a priority. Please join me in recognizing all today's meetings sponsors.

(Applause.)

So I would like to take a moment just to outline this morning's agenda. I will be covering the morning, but of course we have two panels that we will be having this afternoon, two that we'll hear from this afternoon. But this morning, we are going to be showcasing the adult patient perspective on mitochondrial myopathy.

Our first panel will share the burden of the disease that relates to symptoms and daily impacts, followed by a panel that will share perspectives on current and future treatments. Here is what is really important though, for everyone in the room and following us online today.

After each panel this morning, we'll ask you to share your voice and make your choice to engage with us. We will kick this off with audience remote polling questions, which will be explained later in the program. If you haven't already, please refer to your program book, look at the applications, and you can participate in this important part of this meeting. Following the polling, we'll have a live moderated discussion with the audience.

For our friends who are joining us online today, at the close of the meeting we'll be sending a survey of everyone online so they can continue to provide feedback and information. It's really important as we wrap up this meeting providing a really strong report as a result of this meeting.

We're grateful that Dr. Lucas Kempf is with us today to give us closing remarks at the end of the session. He will be wrapping up the session.

But first, to kick us off this morning, I am pleased to introduce a true champion at the mitochondrial disease community. Dr. Michio Hirano personifies that deep bench of expertise and support that I talked about earlier. Dr. Hirano is Professor of Neurology at Columbia of University in New York, Director of the H. Houston Merritt Clinical Research Center, Chief of Neuromuscular Division, and Associate Director of the Adult Muscular Dystrophy Association Neuromuscular Clinic. Dr. Hirano also serves as the principal investigator for the North American Mitochondrial Disease Consortium.

Here with us today to share a clinical overview of mitochondrial myopathy in adults, please join me in welcoming Dr. Michio Hirano.

(Applause.)

DR. HIRANO: Thank you for that very kind introduction. If my father were here, he would be proud. If my mother were here, she would say I deserved it.

Okay. So, it is truly an honor and pleasure to be here today to represent the clinicians and investigators in mitochondrial disease. There are many of us who could have spoken, and I feel very privileged to be able to do this on behalf of the group.

I would say that I would like to just mention that I've been studying mitochondrial diseases for nearly 30 years, both clinically seeing adults and children with mitochondrial disease, but also in clinical studies I think this meeting is particularly important, because we are on the cusp of many exciting therapies, and to have the patients speak out to this point is really critical in guiding how we're going to assess the efficacy of these therapies in the pipeline.

I would like to begin by reminding everyone about the mitochondria that you learned about in high school biology and maybe college as well. We learned about pathways to mitochondria and how it creates energy. mitochondria take the fats and carbohydrates that we ate this morning -- the bagels and cream cheese, for example -- and then converts it into energy in the form of ATP. They are truly the powerhouses of the cell. We produce nearly our bodies weight in ATP, in energy currency, every day. That's why the title of the session is Energy in Action. We depend on that energy for all of our functions. Without it, we have lots of problems.

The mitochondria came from bacteria that formed this symbiotic relationship, 1 or 2 billion years ago. They came in as a separate cell, and they brought with them their own DNA and the capacity to make energy called through this process called oxidative phosphorylation . I'm not going through the biochemistry, but I will just say a few principles about mitochondria and how that makes mitochondrial diseases so complicated.

As I mentioned, mitochondria is present in virtually every cell in the body. The only cell that lacks mitochondria is red blood cells, but the precursors to make red blood cells have

mitochondria. So they play very important functions. Beyond just making energy, they have to replicate the mitochondrial DNA to translate that DNA to RNA, translate that RNA to proteins, and includes many other functions as well. As I mentioned, they have their own DNA. So, they're the function of two DNAs, the nuclear DNA and mitochondrial DNA, and that means mutations of either of these two genomes adds complexities to these diseases. So mitochondrial disease is not one disease but rather many diseases.

Just to illustrate how dynamic these organelles are, they are not the static kidney beans that you see in the textbooks. They're very dynamic. They move up and down the cells on these microtubular rails, and you'll see they come together, fuse, and then they divide again. So they are very dynamic, constantly active.

Because mitochondria are required to make energy in all parts of the body, virtually any part of the body can be affected, but particularly brain and muscle, because these are two organs that have high energy requirements. We often call these encephalomyopathies. This morning's session is focused on the myopathy, the muscle part, that manifests weakness and fatigue in exercise intolerance. Other parts of the body, including the heart,the extraocular muscles, the muscles around the eyes, controlling eye movements and lifting up the eyelids, are frequently affected as well. Liver, kidneys, and gastrointestinal system are all frequently affected in these disorders. So, they're very complex clinically, and they're frequently multi-system in disease, involving three or more organ systems.

This was a paper written by one of our colleagues, Zarazuela Zolkipli-Cunningham, published last year, in which she conducted a survey on patients to ask them what kind of symptoms they experience and what particularly motivates them to participate in clinicals trials. I want to take one point from that paper, that is, that mitochondrial disease patients reported an average of 16 symptoms. That's a lot of symptoms that people are experiencing. So we'll hear more about that this morning.

I mentioned that the mitochondria have their own DNA, and that DNA could be mutated that cause a variety of diseases. Over 270 different point mutations of mitochondrial DNA have been associated with human diseases, as well as single and multiple relations of this genome and even lack of mitochondrial DNA and completion of mitochondrial DNA can cause mitochondrial diseases.

I'm just going to highlight some principles about these diseases that are caused by mitochondrial DNA mutations. Mitochondrial DNA is transmitted strictly from mothers to their children, maternally inherited. So, the inheritance pattern is very different from the standard genetic diseases we all recognize. The mitochondrial DNA is present in hundreds to thousands of copies in each cell. So, you can have a variable amount of mutation. You can have 1 percent or 99 percent mutation. And depending on the level of mutation, you could have very severe disease, mild disease, or you can even be asymptomatic. And this could happen within a single family, where there are people who have the mutation who are completely healthy and others

who are devastated by the same mutation, because the load of mutation is higher and those are more severely affected. And distribution of cells as they divide, as shown in the bottom, the distribution and mutation can differ from cell to cell in different parts of the body, and that affects the presentation of these diseases.

As I mentioned, brain and muscle particularly are vulnerable because they have high energy requirements, and the threshold for developing symptoms in those organs is lower than any other parts of the body.

Just to illustrate a few of these diseases, this is one called Kearns Sayre Syndrome. The woman on your left has the disease, standing next to her mother and her son. This is to show that this is typically a sporadic disease. Usually, only one person in the family has this particular disease which is characterized by ptosis, droopy eyelids. You can see that in this lady. If you look really carefully, you'll see she's wrinkling her forehead. She's lifting up her eyebrows to pull up her eyelids because she has such droopy eyelids. And she has inability to move her eyes, known as progressing ophthalmoplegia. She has degeneration in the back of the eye called pigmentary retinopathy, which causes difficulty seeing at night. And she has a pacemaker because she has a cardiac conduction block, and myopathy causing weakness, as well. So, this is the Kearns-Sayre Syndrome, and that's typically caused by a single deletion of mitochondrial DNA. It's typically sporadic, but in women with this disease, 4 percent of their children may inherit that mutation, and they may end up with a completely different disease called Pearson sideroblastic anemia, a severe anemia that requires transfusions, and can even be fatal, and thus, the same mutation causes two completely different diseases within a familyThis is a disease called MERRF, which stands for myoclonus epilepsy and ragged red fibers. You can see the ragged red fibers here on your right side. This is a muscle biopsy. You take a piece of muscle and slice it really thin like prosciutto, and you can stain it, and normally the muscle has the greenish color. But these areas are full of mitochondria, and they're on the edge of the muscle fibers so we call them ragged red fibers. That's one of the hallmarks of many of these mitochondrial diseases. This patient has myoclonus epilepsies, and he also has myoclonus as part of this. He has fatty tumors, you can see a little above his clavicle and on his back. So, this is another one that's typically internally inherited.

Another disorder that you see frequently is MELAS, mitochondrial encephalopathy lactic acidosis. The clinical hallmark of this disease is the stroke-like episodes. These are not typical strokes, because they frequently affect young people often before age 40, and they don't conform to vascular territories. They're not due to occlusions or clots in large blood vessels in the brain but rather affect the surface of the brain, what we call the cortex, and often in the back of the brain, causing visual problems. These are three of the common permutations of mitochondrial mutations.

In addition, we have the other genome, the nuclear genome which contains 20,000 or so genes, and roughly 1 to 2,000 of those genes are required for various mitochondrial functions. We now know over 250 different nuclear genes that, when mutated, can cause mitochondrial disease. And the number is expanding. Every month there are one or two new genes that are

identified as causes of mitochondrial disease. This is a growing list, could end up with over 1,000 different nuclear mitochondrial diseases.

I just want to highlight a couple of these. One of these is called Thymidine Kinase, TK2, deficiency, which means the parents are carriers and are completely healthy but one in four children from these parents ends up with a disease that presents as a myopathy with weakness. And the first report from Israel from Saada openly describe these very young children who develop weakness and early respiratory failure, and they typically die, unfortunately, very early in life due to progressive weakness. As I said, a nuclear gene that becomes a protein TK2, goes to mitochondria and is required to make the building blocks to make mitochondrial DNA. So, this is a depletion or lack of mitochondrial DNA. Predominantly, as I said, a myopathy. It starts in young children. But as we often see with many of these disorders, when we initially see them in children we find out the clinical spectrum is actually wider and the development of the disease sometimes begins in childhood or even in adulthood, and sometimes is associated with other problems like seizures, encephalopathy, and other organs, but predominantly myopathy. You can see a curve which shows survival of patients over time. Infants, showing in the blue line, unfortunately pass away early from this condition, where those later on can live longer but still can be very affected by this disease.

Another disease where it is a nuclear gene defect affecting mitochondrial DNA replication is pol gamma mutations. Pol gamma is the protein that is responsible for replicating the mitochondrial DNA, and is required to make mitochondrial DNA. Mutations in this gene can cause a spectrum of the diseases, ranging from just extraocular muscle weakness causing droopy eyelids and inability to move the eyes, known as progressive. Or it can be part of a multi-systemic disease like sensory ataxic neuropathy, and it even presents in children as Alper disease which is a severe birth disease of brain and liver. So, this is a wide spectrum disease associated with this particular gene.

I talked about several of these diseases being quite complex, and they are certainly a group considered rare but not that rare. There's a study from the northeast of England. They studied the epidemiology of these diseases. 1 in 5,000 adult patients were symptomatic for mitochondrial DNA mutation, 1 in 34,000 was affected by a nuclear gene defect function. So overall 1 in 4,300 people in the northeast of England were affected by mitochondrial disease. If you do the math, that means approximately 75,000 people in the United States are estimated to have mitochondrial disease. That's quite a significant number.

One of the ways in which we try to understand this and develop therapies is through this NIH-funded initiative called the North American Mitochondrial Disease Consortium called NAMDC, comprised of 16 science and partners with UMDF and MDA. We are working to collect information about patients through registry, with educational programs, through training mitochondrial disease clinicians, investigators, and we have funded studies and other studies through this network. I think this is going to be the most effective way to address these

diseases, which are rare, but if we form a network and work together, we can work at understanding these diseases and developing and administering therapies for clinical trials.

I want to emphasize that in our registry, which now have almost 1500 patients, about three-quarters of them have myopathy. So, myopathy is a very common feature in these mitochondrial diseases and is the focus of this morning's session. So, we'll hear more about patients what they experience with these myopathies.

We on the academic side are trying to explore this in parallel with you. We had a group that met a couple of years, three years ago, to discuss primary mitochondrial myopathy. That is genetically-defined disorders in which the mitochondrial energy production is affected, leading to either exclusively or predominantly myopathy or muscle weakness or other symptoms related to muscle dysfunction. So, we came up with this definition of primary mitochondrial myopathy, and we proposed some outcome measures that we could use to try to measure this. But I think having input from patients today will allow us to refine these outcome measures and perhaps develop new ones. So, we look forward to hearing more from all of you.

With that, I will end. I thank you for your attention, and I will bring Phil Yeske, who needs no introduction here.

(Applause.)

DR. YESKE: Thank you, Dr. Hirano, for that excellent overview of the clinical perspective on primary mitochondrial disease with a particular emphasis on mitochondrial myopathies. The key takeaway there is some three quarters, 75 percent, of mitochondrial disease patients have some form of myopathies. So, this is a really important time to gather this patient perspective.

I am Phil Yeske. I'm the Science and Alliance officer at UMDF. I have been in this role for five years now, but I've been involved with the mitochondrial disease community for nearly 15. I think some or most of you know, my introduction was when my first daughter Natalie was diagnosed with mitochondrial disease in 2004. She had a pediatric form called NARP, on the Leigh Syndrome spectrum. Unfortunately for Natalie, she lost her battle just passed her first birthday. But I knew I wanted to stay involved with this community, and there were no therapeutic opportunities, to speak of, in 2004. So, it's incredibly exciting to be here now, in 2019, and see this important next step of gathering patient perspective taking place. I really looked forward to this day and in partnering with all of you to gather that perspective.

But now, it's my honor to introduce one of our key external collaborators on this. This was a meeting all about collaboration and partnering. For us, we knew that to be successful with this we were going to have to partner extensively to pull this meeting off.

So now, it is my honor to introduce our meeting moderator for the day, James Valentine. James is an attorney at the firm of Hyman, Phelps & McNamara. While that is interesting, I think what is really interesting in his background is that James worked for six years at the FDA. He understands the FDA. He worked on the patient engagement side and was intimately

involved in the creation of patient-focused drug development. His perspective is clearly going to be critical.

This is the 15th meeting that James has facilitated. So we are not getting a rookie hereby any means. James' experience and insights are clearly going to be invaluable throughout the day and post-meeting.

So with that, I will turn it over to James to moderate our morning session, focused on adults with myopathies.

(Applause.)

MR. VALENTINE: Thank you, Phil, for that kind introduction. I would like to join in welcoming all of you to the externally-led patient-focused drug development meeting on mitochondrial disease and, of course, our morning session, which is focused on adult patients with myopathies. For those of you that are in the room and are representing pediatric patients with neurologic manifestations, we welcome you to attend and participate or observe this session. We will be reserving the afternoon to hear from you all.

I would also like to welcome all of our attendees on the web, and echo what Brian said that your participation in today's meeting is absolutely important. You'll be able to participate in our live polling as well as share your experiences via that survey that will be launched.

So with me being here on the stage, this is kicking off the patient voice part of our meeting. We have great clinical overview, and I want to walk us through how I'll be working with each and all of you to help learn about your experiences with mitochondrial disease and your preferences for treatments for mitochondrial disease. I think to help understand that, it is worth speaking a little bit to the history of this program, the patient-focused drug development initiative.

Back leading up to 2012, at the FDA there was an understanding that the agency really needed to develop a more systematic way of gathering patient perspective on their condition and on available treatment options. Given the tools that existed at the time, the brainstorming ways to do this, knowing the patient perspective would be very helpful for informing the agency's understanding of the context for their assessment of benefits and risks of investigational therapies, and in their decision making for approving new drugs. And there's recognition as well that this input really informs FDA's oversight, not only at that approval decision, but also during the drug development. Dr. Hirano mentioned the value that your voices will have in doing things like selecting outcome measures that can be utilized during clinical development to actually measure treatment benefit in clinical studies. And that is certainly within the thought process of where that PA was thinking with these meetings.

In 2012, FDA launched its patient-focused drug development initiative -- or PFED, as we call it -- and over the course of five years hosted over 20 of their own FDA-led meetings across a number of different individual disease areas. These were very successful meetings and very informative to the agency. But the agency recognized that it couldn't keep up with the demand

for these meetings, and that it would be able to more fully benefit from these meetings and attend more of these meetings if they were not planning them but instead attending them. So in 2015, FDA launched the parallel effort, the externally-led patient-focused drug development program, which allows patient organizations like UMDF and MDA and MitoAction to submit letters of intent, and express their interest in putting on one of these meetings that FDA as well as other stakeholders like drug developers can attend and benefit from.

So today I believe marks -- at least by my own account -- the 25th externally-led patient-focused drug development meeting. We are very excited to have you all be a part of this very important meeting.

With regard to the actual agenda and what we are setting out to do, within each of our two sessions today we are going to be breaking out our discussion into two main topics. Our first topic, we're going to explore the symptoms that matter most to you. So, we're going to be exploring the symptoms and health effects that have the most significant effects and burdens on your life. We're going to be exploring how those symptoms and burdens impact your ability to do activities in daily life. We want to know how those different impacts may vary from day to day, week to week, month to month even, as well as how your symptoms have changed over time.

We'll then build on that discussion moving into our second topic, where we're going to discuss current approaches to treatment. We're going to want to know, you know, what are the things that you're doing to try to help treat or manage your mitochondrial disease? Certainly, this includes any drugs or medical procedures that you might realize. But we're really casting a broad net there, and we want to focus not only on kind of traditional medical treatment but other things that you might utilize, whether that be diet, exercise, or even lifestyle modifications that you employ in your life. We want to hear how well those things are working for you as well as what are the biggest downsides of those different approaches to treatment. And then, at the end of that session on topic two, we're going to turn to the future and we want to hear from you what you would like, short of a cure, for your mitochondrial disease from an ideal treatment for your disease. So, we'll have a discussion about that.

You heard from Brian that for each of those two sessions, each of those two topics, we're going to explore and hear from you in a number of different ways. We're going to first hear from a panel of your peers of patients and caregivers. The purpose of this panel is to set a good foundation for discussion that will follow. And the panelists, I would note, were selected to reflect a range of experiences with mitochondrial disease, which we hope to then round out more fully with our discussion with all of you here in the room.

At the conclusion of our panels, we'll have polling questions. If you turn to page 5 in your booklet, you can see there's a page that says "how to." You can get a head start on logging into the polling system. These polling questions will give us a chance live here in person today to collect some information from all of you, both here in the room as well as those of you

following along online. The responses to those questions are intended to help us aid in our discussion, and you will be able to follow along using your phones, computers, tablets, any web-enabled device that you have. We do ask that only patients and family members respond to those polling questions, and we'll give you further instruction about participating when we get to our first set of polling questions here in a minute.

After we work through those polling questions together, get everyone thinking about those topics, we're then going to move to a facilitated audience discussion with our patients and family members here in the room. Here, we're trying to build on the experiences shared by the panel and expressed in those polling responses. I will be asking you to raise your hand and answer our discussion questions, which are also provided in your booklet on page 6, if you want to go ahead and get a sneak peek at what we'll be exploring together.

I just ask that when you are called on, that you please state your name, and if you know your mito diagnosis, as well before answering. That will help us when we go back to look at the transcript and put together the summary report of the meeting.

And then, as has already been mentioned a couple times and you'll hear several more times throughout the day, we also have the Webster Bay, which will be sent around to all of our registrants. So, for those of you following along online as well as for those in the room that may not have a chance to share everything that you want to today, we will be collecting that and incorporating that into our summary report. Which is my next topic, the report is called The Voice of the Patient Report. This is a very important report that following this meeting, the meeting hosts in this case UMDF and its collaborators will publish, summarizing all the testimony that is provided today, as well as the perspective shared in that survey, and also the views that are provided through the different polling questions that we asked.

These reports are very important. They serve the function of communicating both to FDA's review staff as well as the regulated industry what improvements patients would like to see in their daily life. I know our colleagues at FDA will be -- in the long run, the impact that this program has served, better served, with the more understanding of how they might find ways to develop new treatments for these diseases. And that report will certainly serve as an important reference for them in doing so.

So, finally, before we move to our polling questions, I want to just lay out a few discussion ground rules for today.

First and foremost, again, we encourage all our patients and family members to contribute to the dialogue. Please don't be shy. I'm sure you won't. Included in that, I said family members, but that is important. Even if the patient, the individual with mitochondrial disease, is here in the room today, we also do want to hear from the caregiver or family member perspective. So please feel free to share your perspective on the burdens and treatment for mitochondrial disease.

We also have in the room with us FDA officials and representatives from companies that are developing products as well as clinicians and researchers. I just remind all of those stakeholders that they are here to listen, and also for our audience members that we will not be asking any of those stakeholders questions today. They are here to hear from you, the experts in your own disease.

Our discussions will focus on symptoms and treatments. We know that there's many other important aspects of living with mitochondrial disease that may be important to you. But for the purposes of today and the limited time that we have, we do ask that you keep your remarks focused on the discussion questions at hand. We certainly know that your views and what you will be expressing are very personal and may be emotional, so we ask that you please be respectful of one another. To that end, if you do raise your hand and participate, we do ask that you try to be as concise in your response, because given the time that we have we want to try to hear from as many different voices as possible.

With that, let's go ahead and get started. And we'll move into our first set of polling questions which are demographic questions.

Again, I will point you to page 5 in your booklet, the how to, or you can look at the top of the screen here, to see the ways that you can participate in this. If you have a mobile phone, you can download the poll everywhere app. Or on your phone tablet or computer, you can just go to the URL in your web browser, poll ED.com/energy in action.

There's also opportunity if you don't have mobile access but you have text access, that you can text to the number 22333 in the message, type out energy in action, and that will put you into the polling process. Then you can then text in your responses to the questions.

So whichever of those ways works best for you, we encourage you to go ahead. And for those that are representing adults with myopathies, please go ahead and log into the system. Raise your hand if you are having trouble and someone will come and assist you.

So I see we are getting a head start here on our first question, which is great. Hopefully they are comfortable with this.

This first set of demographic questions, we're asking all of our patients and caregivers representing individuals with adult myopathies to respond.

Our next two sets of polling questions we're going to ask that if there's more than one person here today representing an individual with mitochondrial disease, if the patient is here and willing, that they be the one person to respond to the remaining polling questions. If not, then the caregiver can take that place. But we would just like to, for the second and third sets of polling questions, have one response for each individual with mitochondrial disease represented today.

So, our first polling question:

Which of the following best describes you? This is for all of our patients and caregivers. A, you are an affected adult with a mitochondrial myopathy; B, you are a caregiver for an affected adult with mitochondrial myopathy; or, C, you have lost a loved one who was an adult patient with mitochondrial myopathy. Please select that which best represents you.

We'll give you just a few more moments. Raise your hand if anyone in the room is having problems getting into the polling system. For those following along on the web, remember you can go to that same URL and answer these questions as we follow along online.

Okay. So, it looks like about two thirds of our participants today are individuals themselves affected with mitochondrial myopathy; then another a third are caregivers of individuals affected with mitochondrial myopathy. We do not have any individuals represented, who have lost a loved one who is an adult patient with mitochondrial myopathy.

Our second demographic polling question is: Where do you currently reside? Your options are A, the U.S. Pacific, which includes California; B, the U.S. West and Mountain region; C, U.S. Midwest; D, the U.S. South which includes Texas; E, the U.S. Northeast and New England; F, Canada; G, Mexico; H, outside of North America; I, other.

We'll give you a few moments to give a response here. These early ones should be pretty easy. The later questions we have will get into it a little more.

It looks like nearly half -- probably not surprising given the location of this meeting -- are participants representing the U.S. Northeast and New England. A little over a quarter represent the U.S. South. We also have representation from the U.S. Pacific, West and Mountain region, and the Midwest. And then we have no representation from outside of the United States, and one other.

So, we move on to our third demographic polling question, which is: Do you live in, A, a city; B, a rural area; or, C, a suburban area?

All right. Final responses are coming in. It looks like right now we have over half of you live in suburban areas, a little over a quarter in cities, and then the remainder living in rural areas.

The next question: We would like to know how old the patient is that you're representing here today, whether that's yourself or your loved one, how old they are now. The options are A, 18 to 20 years old; B, 21 to 30; C, 31 to 40; D, 41 to 50; or, E, greater than 50 years old.

Any final responses that might be coming in? About a third of our individuals represented today are over 50 years old. After that we have about a quarter that are represented from the 31 to 40 year-old-age range, about a fifth in the 21 to 30 year-old-age range, also representation in the 41 to 50 and 18 to 20 age range. So a good representation across our age ranges of individuals affected with mitochondrial myopathy.

Finally, for our demographic polling, we want to know: At what age was the patient diagnosed with mitochondrial disease? The age options here are: A, 0 to 10 years; B, 11 to 17; C, 18 to 20;

D, 21 to 30; E, 31 to 40; or, F, greater than 40 years old. The age that the patient was diagnosed with mitochondrial disease.

It looks like just under a third of our patients represented today were diagnosed at age greater than 40. We have good representation across the age region, the next greatest being the 31 to 40-year-old category, the 11 to 17, 0 to 10, and then a small amount of you that were diagnosed in the 18 to 20-year-old age range.

So that concludes our polling questions. Keep your phones and tablets and computers close by. We're going to be moving to our next set of polling questions in not too long. But before we do that, I want to introduce our first topic of discussion, which is burdens of mitochondrial disease. I would like to invite our first panel to the stage.

This first topic again is focused on the symptoms and daily impacts of mitochondrial disease. So here through our panel, our polling, our audience discussion, we're going to explore what are the symptoms that you experience because of your condition that have the greatest impact on your life. We're going to build on that, what are the specific activities that are important to you that you cannot do at all or as fully as you would like because of your condition. We want to know how that might vary on your best days versus on your worst days. We would like to know also how those things have changed over time. Do your symptoms come and go? Do you know if there's anything that makes it better or worse? Finally, we would like to know what worries you most about your condition.

And to get us started on all these questions, we have a great panel that will kick us off. For our first panel we have, Laura, Devin, Debbie, Rachel, and Alyssa. And I'll ask Laura to kick us off.

MS. PRUDHOMME-GAUPP: "What part of dead do you not understand, Mrs. Gaupp?" Andrew, then 8 years old, quickly responded: "The part about dying. I refuse to talk to anyone unless they're going to talk to me about how I'm going to live." This was the first of many rare disease specialists we would consult, as she reviewed his brain lesion MRI films. Andrew is now 28 and he's still fighting.

I am Laura Prudhomme-Gaupp. I was five months pregnant with my youngest son when Andrew was diagnosed with complex 1, 3, and 4, in Atlanta, at the age of eight after years of searching for answers.

All of my four biological children have hit genetic lotteries and have some symptoms of mitochondrial disease, starting with immune system dysfunction. The worst part of about mitochondrial disease is whatever we're fighting that day, and often it is a surprise; the unpredictability of symptoms, constant demand to adapt to a new level of care and need, and most importantly, as the family unit, manage the needs of every family member while explaining to the entire world around us mitochondrial disease. The worst symptoms that reduces Andrew's quality of life is fatigue, the unexplainable brown and blackouts where he has literally no energy and partial to total brain fog. An otherwise intelligent young man with

autism spectrum becomes dysfunctional, slurring his words, staring into space, flattening his hands just to stay awake and cognizant of the world around him. Sadly, the world sees this and they think he's mentally challenged rather than a college graduate. The direct result of these two symptoms is unemployment and the inability to stay independent living, which carries the burden not only socially for this mito patient but also for the supporting family and society as a whole.

Andrew's list of symptoms come and go and affect almost every bodily system, hand tremors making it often hard for him to eat, weakness particularly eccentric muscle weakness which is critical for going downstairs, overall tremors including his tongue and lips as fatigue sets in, his eyelids droop, he looks high sometimes; pulmonary dysfunction -- he uses an assisted ventilator -- swallowing problems, seizures, hypothyroid, hypogonadism, diabetes, and bipolar with schizophrenia.

Andrew was very sick as a young mito patient. But as each symptom was treated, he began to stabilize and we began to see a future for Andrew. We never thought that he could grow up, much less finish college. But Andrew did graduate from college in December of 2015 with a 3.8 GPA as an honor graduate. He lived independently with an assistant for a full semester, and for the first time we really thought Andrew was going to be independent. We thought he might live independently as a young adult. But that didn't work out for Andrew. He was preparing for his graduate entrance exam shortly after he secured an assistantship when he had a brief two- or three-day illness. Just a mild virus. No one thought he needed to be in the hospital. Just a slight fever, mild vomiting, no dehydration. He began to refuse his meds, however, and then food. Within days, he spiraled into madness. I called his local doctor repeatedly and explained what was going on. We tweaked his medications, but to no avail. He just kept purging himself as, surely, in his mind, I was poisoning him.

Andrew's story takes a really sad twist then as the emergency room team mistook him for another typical 25-year-old while I was picking up his ventilator at home. During this time, none of his life-sustaining mito therapies were given while he was in a small-town mental hospital. He was returned to us approaching death, catatonic, and 30 pounds lighter.

The absolute worst part about mitochondrial disease is that we never know when everything is going to change. It is a slow form of drowning. Just when you catch your breath, another big wave just washes over you and you're thrown under, and each time gets a little bit harder to get back up.

The activities that Andrew cannot do that are most missed are social independence, just being a young adult. Because of fatigue and predictability, it's really hard to plan to stay out late partying, being able to safely drive a vehicle, sports of any kind, anything that requires planning ahead and knowing that you will be able to stay awake and attend a function is always limited. Packing medicines, a wheelchair, a ventilator, and an assistant is just really not sexy at 28. It is really hard to hit on a girl like that.

And this is a message from Andrew: My greatest fear is having to hire doctors locally who know nothing about mitochondrial disease and they can't treat me, and that I will never find a doctor who can treat me to help me manage these critical life-changing symptoms long term. And, most importantly, I have watched my friends with mitochondrial disease slip into madness and/or die. I'm afraid that the next time that I'm sick , it will be my last.

(Applause.)

MS. SHUMAN: My name is Devin Shuman. I'm 26 years old, I'm from Las Vegas, Nevada, and I have mitochondrial DNA depletion syndrome. I was diagnosed my junior year of high school, but I first developed symptoms when I was 13 and I had mono that just never seemed to go away. You could track the onset of my symptoms in high school as my mile time in PE slowly increase from 8 minutes to 10 minutes, to finally it became impossible for me to run at all. I have had countless dreams running on a beach or running soccer that I wake up from crying because I just miss the simple act of movement.

When I was in sixth grade, I can remember being in the neighborhood pool and trying to figure out why everyone else found swimming to be such fun. It was the top activity in the summer. Except, to me, swimming meant trying not to drown, and there's nothing fun about that experience. At the time, I didn't realize it, but that was my first experience with exercise intolerance.

When you're a teen developing a medical condition, honestly it can all just feel so normal at times. Everything else in your life is changing, too. And yet, you somehow realize that this particular experience is unique. Your friends can understand when you have to go to the doctor sometimes. But when you're missing 80 out of 180 days of school, that's when it becomes a little harder to relate to. Just going to a school dance for a couple of hours, or when I went off to college just packing up my dorm room at the end of the year, would trigger a rhabdomyolysis episode. This is when I pushed my muscles so past their point that they actually started to break down on me. It is a pretty serious complication just going to a school dance since it can lead to kidney failure. When I go to the ER, I'm constantly reminded that what it would take for a normal 26-year-old to trigger that is something like cross-fit or running a marathon. But it's one of those things that you learn as you go. If I had known what this was in high school, I probably would have gone to the ER at least once a month. But luckily, for the sake of my memory and sadly for the sake of my health, I didn't realize what these episodes were until a friend at a conference told me: These aren't normal. You have to tell your doctor. Now I mostly avoid the ER by tailoring my life so I don't put myself at risk.

Every year brings a new challenge, a new norm to adapt to. In college, it was migraines that hurt so much I used to cry out in pain in the middle of lectures. In grad school, it was dysautonomia that caused me to pass out while doing my clinical rotations. I spent hours of my undergrad education pacing my dorm room, unable to sit down because of the pain I was in, and I spent countless nights in grad school in the ER having cardiology workups. These are just

a couple of examples of what it is like when you're a mito young adult living within a norm that you can't predict because it always shifts. And when it does, you're stuck trying to figure out, is this life-threatening, or is this just the latest annoyance that I have to deal with?

Mito has impacted every hour of my day, every day of my life, as much as my mother hates to hear me say that. Choosing a college that would allow me to take a reduced course-load, I considered mito. Choosing a career that I could someday do from home, I considered mito. Before I do the dishes, before I vacuum, go on a walk, plan a trip, I have to go through and think, will this activity trigger a migraine? Will I even have the energy to finish this plan that I'm making? And, do I have time to block off days afterwards to rest in bed or maybe go to the ER? On my best days, though, I can ignore the pain, rest between every activity, and mostly ignore my mito. I'm very happy that way. On the worst days, though, I will be crying in frustration. Going to the kitchen seems equivalent to climbing a mountain, and just trying to process what others are saying to me takes all of the energy and concentration that I have.

But you know what? With mito in the end what I most worry about is not myself. The burden from this disease that keeps me up at night is my concerns for my mito friends and for my brother. March and April are the anniversary of at least five or six of my good friends' deaths. So it's kind of an opportunity. Many of our friends are extremely isolated. Mito's energy weakness, the fatigue from it, it can restrict their lives so that they're stuck in their homes, and it can even steal their voice from them. Every six months, at least one of our great friends dies, someone that we know personally, not just some stranger that you hear about. And until we have treatments, until we have something that can help, this is going to keep happening. I mean, we're not stupid. We know there's not one cure for mito. We know there's not one thing that will help us. But if there's anything that we can do to give these children -- to give these brothers, these sisters, these friends -- futures instead of funerals, we need to do it. Anything to ease the daily burden to let these people go back into their lives, to have a life, for that to happen to bring hope to families is worth our time. And I hope you guys will help us, because this is our life, for better or worse. Thank you.

(Applause.)

MS. PARSONS: Hello. My name is Debbie Parsons and I'm 49 years old, from Marietta, Georgia. In 2011, I had a muscle biopsy confirming mitochondrial disease complex 1 and 3 deficiency and a spinal tap confirming a cerebral folate deficiency. Additional testing showed dysautonomia, myopathy, amplitude changes on fingers, connective tissue disease, cardiac issues, and a multitude of other diagnoses. I have significant difficulty with multiple levels of pain, fatigue, and muscle weakness.

Growing up, there were random things that seemed to be connected including pain, bleeding issues with cycles, surgery, and childbirth. I remember finishing last in high school during the mandatory PE runs and not being able to keep up due to extreme pain in my legs and I was

exhausted. In college and afterwards I tore my ACL multiple times and question the viability of my muscles and ligaments.

I earned my bachelor's degree in educational psychology, a master's degree in rehabilitation counseling with an emphasis in sign language, and a teacher certification for special education. I enjoyed my career working with people with special needs.

In 2001, while I was pregnant with my second child, I had significant issues with pain and fatigue which I thought was due to caring for a very energetic two-year-old who had medical issues. Throughout the pregnancy, I became sicker with multiple infections. As soon as it was safe, my daughter was born via C-section at 36 weeks. She was 7 pounds, 11 ounces and was healthy, but her journey with mito began a couple months later.

In 2008, issues were worsening and I began experiencing full body and needle-like pain that I could not explain away. It was hurting to walk, to grip things, and on one of my hands my fingers would get white and cold. I started falling for no reason. I went to the ER on several occasions for right-sided numbness, chest pain, issues with my vision, and difficulty being able to say words I was thinking. The neurologist indicated complex migraines can mimic stroke-like episodes.

I began working part-time, but that still proved incredibly difficult. I worked one day, and slept that afternoon and the whole next day. At work, I typed with a glove on to try to keep my fingers warm. After sitting for even 30 minutes I was in pain, and when I would stand up I would have chest pain, dizziness, and felt I was losing my balance and passing out. I began having difficulty remembering basic things, like my password to get in my e-mail and my route to work. I started missing work because I was too exhausted to even get up to use the rest room, and the intense full body pain and visual blurring continued. In 2015, I had to stop working. This was beyond devastating because I loved my students and my career, and it was a part of my being. I kept telling myself that it will help slow the progression, but it did not.

My balance and weakness continue to be unpredictable. There are times when I walk out the front door and fall into the bushes because my legs aren't working right. I know I am going to have to think really hard about every step that I'm taking to make sure I pick up my feet all the way. I typically use some type of adaptive device, whether a cane or a walker or even a wheelchair. I'm really struggling with losing my independence, especially on the days when I cannot get out of the house.

My memory/brain fog is worsening and it is frightening to me. My daughter was sick at school, and I pulled up to her elementary school, parked to go in, only to realize I was in the wrong school because she was at high school. She had not been to that school for five years. I was prescribed medication, ironically, for issues with memory and didn't realize until an appointment months later that I had forgotten about the prescription. I had been confusing my meds and even have difficulty remembering my age. One of my worst mom moments was when my daughter went to take her pills and realized they looked different. Thankfully, she

told me, because I had put the wrong pills in her pill case and had confused her meds. It was the worst feeling to know that things are slipping away and I could have harmed my daughter. I am frightened because I feel like I'm losing my identity and sense of being.

I'm missing milestone events with my family. Whether it is a band performance, track meets, or even medical appointments for my kids, I have frustratingly had to miss some due to severe fatigue and pain. I think it is tough for folks to understand the depths of what is happening because I look fine on the outside, but on the inside there's not enough energy to keep everything running properly.

The pain, fatigue, weakness, depression, and anxiety are always present, but the intensity is a moving target. What worries me most about mitochondrial disease is how unpredictable it is and the unknown. Will my daughter and I be here in five years? Will we keep getting worse? Will they find the gene causing what's happening? And I'm also worried about how misunderstood mitochondrial disease is, but I'm so forever thankful to people who are dedicating their lives to us. Thanks.

(Applause.)

MS. SCHANZENBACH: I'm Rachel Schanzenbach. And I would like you to imagine, you've just celebrated your 25th birthday. You're a vibrant, strong, young adult living life to the fullest as you pursue your dreams. Even better, you're getting to see your dreams become a reality. And then -- you swiftly become very old. Not chronologically old, you're still in your 20s, but functionally your stamina and strength are now as fragile and limited as your own grandmother's.

What I've asked you to imagine sounds like a fantastical tale, but it isn't, as impossible as Rip Van Winkle or Dorian Grey? I wish this were fiction, but for those of us with mitochondrial disease, this frightening state of at once experiencing both youth and advanced age is the reality we face each day.

2006 was the year I turned 25. Before then, the only special needs that had really affected my life were my pervasive developmental delay and its accompanying sensory and attention disorders. But those didn't keep me from living an active life as a young adult. Back then, during any given week, I could easily commute to college five days in a row, keep up with four classes, make good grades in each, work a part-time job and stay on my feet for an entire five-hour shift, then in my free time I could volunteer for community service, join my bowling league, go to concerts with friends, or hiking in the mountains with my family.

That was me, the way I used to be. But those days have vanished. My life now is painfully different. Listen to how my doctor recently described me for a research study: "Rachel has very low exercise tolerance which make it impossible for her to do even basic housework, cooking, or cleaning on most days. Her cognitive function has also declined. She would like to

be more active and involved, without becoming exhausted and in pain from minimal activities. She is only 37 years old but many days she functions like she is in her 80s."

Now, rather than being able to volunteer my time and energy caring for children, the elderly, and the homeless, as I used to, I'm the one requiring others to care for me. I'm the one needing people to make my food, drive me places, and be my company as I am shut-in at home. Forget mountain hiking and bowling. I'm thrilled now when I can conquer a flight of steps or lift bags of groceries, or even do both in the same day.

If you get a good night's sleep, do you wake the next morning refreshed? I used to, before 2006. Now, though, as the line from my favorite songs says, "I'm worn even before the day begins." No matter how much sleep I get, my brain keeps right on feeling as sluggish and overwhelmed as the night before. Having such relentless mental fatigue is like having a brain that tops out at 20 miles an hour in a 65-mile-per-hour world. I can't tell you how much I would love for my brain to be able to keep up with loads of college-level reading, writing, and socializing as it once did. But for now, I am just grateful for days when I can compose my family's grocery list, check e-mail, or read a chapter of a book to my children. These are simple abilities, but I don't have them every day. And, honestly, most of the time even listening to music, making phone calls, or watching TV drain my mental energy so much that I have to avoid them.

While most of my peers are out and about living busy, busy lives surrounded each moment of the day by people and activities and responsibilities, I instead live with a tremendous amount of social isolation. I have to spend most of my days at home, alone, very quietly, and with little activity or accomplishment. Some people think this sounds like a dream life -- not going to work, and having other people care for me, my kids, my home -- and some have accused me of malingering to avoid normal life. As cruel as those accusations are, I've sometimes wished they were true. Because if my own problems were psychological, I could have a medical path toward freedom out of the captivity of this relentless illness.

I would like for you to imagine with me now what my life would look like without mitochondrial disease. I would finish my college degree, work in science, become a foster parent, and have energy to give back to others. I am looking forward to that day.

(Applause.)

MS. DELOTTE: I've come to learn that describing what mitochondrial disease feels like is a hefty task because words can't fathom what we endure on a daily basis. The simplest explanation is that everyone is a phone battery. By the end of the day, we're all plugged in and expected to be on 100 percent in the morning. While the majority are, mitochondrial disease patients are stuck at 25 percent. We continually get plugged in, yet we never fully charge.

Good morning, my name is Alyssa DeLotte. I'm an 18-year-old student and was diagnosed with mitochondrial disease at the age of 14. I deal with debilitating symptoms every day that range

from mild to severe. The most crippling are fatigue, pain, and dysautonomia. The fatigue is almost impossible to describe because it seems otherworldly. It feels as though someone has taped cinder blocks to my eyelids some mornings and there's no way to keep them open. It can make it impossible to chew because I simply don't have the energy to keep opening and closing my mouth. Sometimes it can even make walking feel as though I'm trapped in four feet of quicksand. Mito seems to reinvent the word fatigue. The symptoms vary day to day, and when I go to sleep at night I never know what symptoms I'll have the next day. I might wake up and be able to walk with little pain and have more energy than usual. Another day I might wake up unable to move, paralyzed by pain, fatigue, and weakness. It's like my body is playing Russian Roulette.

I never knew how many types of pain there were until I started experiencing them firsthand. Joint and muscle pain can be overwhelming at times. It is an achy pain that can range from a dull feeling or can escalate into an intense stiffness. Nerve pain feels as though parts of your body are on fire and burning. It feels like a tingling feeling that can feel like you're being poked by a thousand needles. GI pain is like having a stomach virus every day of your life, and it's usually accompanied by other things like nausea, vomiting, and diarrhea. These different kinds of pain affect me on an almost everyday basis. I've found that my pain goes up after exerting myself. I try to take breaks from some activities to prevent the crippling pain the next day. I almost never have pain-free days.

Dysautonomia is like a drunk relative at a holiday party -- it doesn't leave. It is the misregulation of the autonomic nervous system and for me causes a high heart rate, low blood pressure when changing position, dizziness, fainting, and tremors to name a few. I experience these symptoms every day, all day. Dysautonomia can be quite a hindrance with my quality of life depending on the day.

Mito affects the activities I love, yet I don't let it stop me. Most teenagers hate having to go to school, but I thrive in a learning environment. When I was 14, I could no longer go to school. I was in a wheelchair because of the debilitating symptoms of mito. Most days, I couldn't even open my eyes, eat on my own, or sit upright because I couldn't hold my head up due to the fatigue. I had to constantly be monitored because I was too weak to do anything. I became enrolled in hospital homebound and virtual school until I was rehabilitated enough to make the transition back to in-person classes. This took almost two years. I am now able to split my time half and half. I have completely lost my ability to run, surf, and skateboard, which were my favorite hobbies at one point. I hope to one day return to those things. Being sick affects social events with my school friends, too. There are days when I wake up with severe symptoms and have to cancel plans to meet up with them. I've even had to miss school dances that all of my friends attended. The best thing is that I am lucky enough to have friends who understand and support me. If I am too sick to do anything, they bring the fun to me.

Good days and bad days are complete opposite sides of the spectrum. On good days, I usually have little pain and less fatigue. I might be able to go out with friends, get extra schoolwork

done, or even go on a fun adventure. I can't exert myself, though, because the more I do, the sicker I will be the next couple of days. Bad days can be pretty straining as well. I might have a hard time doing anything. I struggle to open my eyes and do basic tasks without help, like brushing my hair, sitting up, or taking a shower. On bad days, I can't even get out of bed. I rest as much as I can. I used to have bad days pretty much every day, but since starting the mito cocktail the bad days have become less frequent.

I have come a long way since my diagnosis. While still bad, my symptoms are a drastic improvement from that point. My biggest concern is the fact that there are no treatments that target the root of the problem which are gene mutations and mitochondrial dysfunction. Right now, we're chasing around symptoms, but eventually these symptoms will worsen and we need a plan of attack. These concerns are on the minds of every patient and caregiver who suffers from or experiences the horror we call mitochondrial disease. I hope that someday in the future this will change. Thank you.

(Applause.)

MR. VALENTINE: Thank you for those very moving testimonies. I ask everyone to please join me in a round of applause for our whole family.

(Applause.)

So now we have an opportunity to expand the discussion, expand on what we've just heard from our panel, and hear from all of you in the room and online through our next polling questions which are on this topic of symptoms and burdens of your mitochondrial disease.

So to go ahead and jump right in. Our first question for all of you is to: Please select the answer that best describes the stage of disability for you or the person for whom you care. Your options are, A, minimal disability, ability to run and jump; B, symptoms are present or mild, able to walk and capable of leading an independent life; C, symptoms are significant and require regular or periodic holding on the wall or a person for stability in walking; D, walking requires a walker or other aids, such as a service dog, and abilities vary from day to day; E, you're not able to walk, confined to a wheelchair, and perform some activities of daily living that do not require standing or walking; or, F, severe disability, dependency on others for assistance with all activities of daily living. Please select the answer that best describes you or your loved one's current stage of disability.

I'll give you a few more minutes to give your response. As it stands, it looks like the largest portion of you are representing individuals most are symptoms present but mild, where you're able to walk and capable of leading an independent life. After that, it looks like a number of you are representing individuals with symptoms that are significant, requiring regular or periodic holding onto a wall or another person or walking requiring a walker or other such aid; abilities vary from day to day. However, we do have some representation from individuals that are not able to walk or have such severe disability that they depend on others for assistance

with all activities of daily living; as well as some with experience with minimal disability, able to run or jump.

Moving to our next polling question. Please select the mitochondrial disease symptoms that most impact your daily quality of life. Here, you're able to select up to five responses of those things that are most impacting your life. Your options here are chronic fatigue and pain; B, muscle weakness; C, GI problems; D, exercise intolerance; E, sleep difficulties; F, dysautonomia; G, headaches or migraines; H, peripheral neuropathy; I, eye muscle problems and/or vision impairment; J, mood disorder; or, K, some other symptom that's not here that most impacts your daily quality of life. Again, please select up to five that most impact your daily quality of life.

On this, the percentages that you're seeing are the percent of responses, not the percentages of individuals. Because people can report more than one of their disease symptoms, they can report up to five, it's reporting here percentage of those responses, total number of responses. We'll give you a few more moments to give response to this question. Again, it looks like the greatest disease symptoms that has the most impact on your daily life are chronic fatigue, followed closely by muscle weakness, also fairly is high exercise intolerance; however, all of the other disease symptoms that are listed have been rated as top five, most impacting symptoms, and then as well as "other" having a fair number of responses. So, when we get to the audience discussion, we certainly want to explore these different disease symptoms and how they're impacting your daily life. And for those that selected "other," we'd be very eager to hear which symptoms that we did not have listed are most impacting your life.

Our next question, you will see we have the same responses. Here, our question is a little different. The question: As mitochondrial disease progresses, development or progression, which of the following symptoms worries you the most? Again, select up to five. So here we're asking you to select those things that as your disease continues to develop or progress, which of these things worry you the most. Your options again are: A, fatigue; B, muscle weakness; C, GI problems; D, exercise intolerance; E, sleep difficulties; F, dysautonomia; G, headaches or migraines; H, peripheral neuropathy; I, eye muscle problems or vision impairment; J, mood disorder; or, K, some other symptom that is not listed on this slide.

We'll give you a few more moments to give your responses here. Please select up to five disease symptoms that most worry you.

We're seeing a similar pattern to the response of those things that are currently having the greatest impact as is our last question. Here, we're seeing our top three responses as chronic fatigue, muscle weakness, exercise intolerance. However, all of the different disease symptoms listed here have been selected as the top five, including a fair amount of "others," which again we want to explore in audience discussion.

Our next polling question for you is: What specific activities of daily life are most important to you that you or the person for whom you care are not able to do because of mitochondrial

disease? Please select those top three things that are important to you that you are not able to do. Your options here are: A, speaking with others and being understood, especially in noisy settings; B, driving; C, personal hygiene, such as taking a shower, dressing independently; D, walking, moving around independently and safely; E, writing and typing; F, feeding one's self, including cutting food and handling utensils; G, manipulating small objects such as keys, or picking up items; H, reading books, seeing a computer screen or phone; and, I, some other specific activity of daily life that's important to you that you are not able to do. And we're picking the top three things that you're not able to do that are important to you.

A few more results are trickling in. By and large, it looks like walking, moving around independently and safely is that activity which is important to you that you're not able to do that create the top three such activity. However, after that, a fair distribution across, speaking with others, driving, feeding one's self, manipulating small objects, and other important activities of daily living. Only a few of you responded that writing and typing is something that you're not able to do that's important to you.

Our final polling question for this topic is: As a result of living with mitochondrial disease, which of the following social, emotional, or economic consequences are most significant to you? Please select up to four here. Your options are: A, loss of hobbies or activities; B, social isolation; C, frustration; D, depression and/or anxiety; E, financial difficulties; F, loss of job or inability to get a job; G, trouble building or maintaining relationships; H, a lack of hope for the future; I, loss of independence; J, having modified work or school hours; K, other communication issues; or, L, some other result of living with mitochondrial disease that has a significant impact on you in terms of social, emotional, or economic consequences. And we're selecting up to four.

We'll give a few more moments to get in your responses selecting your top four of these different social, emotional, or economic consequences that are most significant to you. It looks like the loss of hobbies or activities is at the top of the list, followed by loss of independence and social isolation; however, each of these different consequences those represented in the room are reporting as being significant, including a couple of you that have selected "others," which of course we'll want to hear about.

With that, that concludes our topic one polling through our discussion questions. Now we're at the part of the agenda for our topic on symptoms and burdens of your disease that have impacts on daily life. We want to hear from those of you in the audience. As I mentioned at the beginning of this morning, through this session we want you to raise your hand if you have something to share. If I call on you, please state your name and, if you know it and are willing to share it, your mitochondrial disease diagnosis. And then please share your responses to the questions.

To get us started, I want to use some words from Devin's statements; which she said that there's certain activities that she has to consider for mito. She gave a nice list of all of those

things. So, I want to expand upon that and ask those of you here in the audience: What are the activities that are important to you where you have to consider your mito before you do that? Raise your hand. We have mics that can come to you so that way, you can share. What activities that are important to you when you are planning your day perhaps that you have to consider your mito? The question is, what activities that are important to you do you have to consider your mitochondrial disease before setting out to do? What activities? Okay. We're going to pass for now. Okay. We have a hand.

SPEAKER: My son has MERRF. He's 34 years old. We not only have to consider daily. We have to consider several days before and several days after. So, if he wants to go fishing for two hours, we have to make sure that two days before he doesn't do anything because he won't have enough energy to even sit for two hours to fish. And then we have to figure, he can't have a doctor's appointment, he can't have anybody come visit, because he won't have energy for the next two days.

MR. VALENTINE: So, this is all energy dependent.

SPEAKER: Yes.

MR. VALENTINE: Is it pretty consistent over time? That is, he needs two days of rest for a two-hour activity?

SPEAKER: Yes.

MR. VALENTINE: Are there ever things that change that in any way, either you need a longer period of time or a shorter period?

SPEAKER: It just depends on what the activity you're going to do is. Like if we have to go to the hospital or a doctor's appointments, you know, we're 40 minutes away and he can wait a couple hours and come back then, he'll take more recovery time. So, we don't plan anything before or after for a couple of days for something as simple like go for a doctor's appointment.

MR. VALENTINE: So, it's kind of two days off, part of a day on, two days off.

SPEAKER: Yes. And that's pretty common. He's only 34 years old. He should be able to do more, but he can't.

MR. VALENTINE: So what things? You mentioned fishing. What are things that he can do?

SPEAKER: That's about it. That's about it. He just can't do much else.

MR. VALENTINE: Is there anything that's really important to him that he has not been able to continue doing?

SPEAKER: Go to concerts, watch games. Because of neurological problems, he can't be in the environment -- he would have to be around people,noises, and talking.He can't be in those environments with neurological issues. So, he misses concerts. He can't even be, honestly, in a

room where there's a lot of people at our house. When we have company, people have to come in and visit him in his room, like, one or two at a time at the most, and give him a break. Because of mental fog issues, too, it takes more to process what they're saying. And then he gets exhausted just from the processing, and the talking and the listening and coming up with the thoughts and then having them come out of his mouth.

MR. VALENTINE: Mental.

SPEAKER: Yes, it's also mental, too.

MR. VALENTINE: Thank you very much for sharing.

A hand over here.

SPEAKER: Hi. I'm speaking on behalf of my brother who is 44 years old. He was diagnosed with an adult onset mitochondrial disease at 36. So in eight years, he now has no feeling below his knees, so walking is a continuous issue. It's even a day-to-day discussion of what he can do during the day. It's looking at: I have to go down the stairs, and how am I going to make it down the stairs? I have to take a shower, and I'm worried I'm going to fall out of that shower. I have to make dinner. And some of his neurological issues have extended to his hands, so things like cutting a piece of bread, he has to continually watch what his hands are doing so he doesn't hurt himself. And it has progressed significantly in the last eight years.

MR. VALENTINE: So, you're speaking to the peripheral neuropathy that he has?

SPEAKER: Yes.

MR. VALENTINE: He's experiencing numbness from the knees down and also from his hands.

SPEAKER: And it's spreading. The numbness started in his feet and now it's extending up. And in the last two years, he experienced it in his hands.

MR. VALENTINE: Has he also experienced pain related to that, or is it just numbness?

SPEAKER: Yeah, pain, says his step-dad. Yes, pain as well. And I think overall, it's become a day-to-day living condition, and just keeping him safe, honestly.

MR. VALENTINE: You said it's progressed pretty significantly over the last eight year. Can you give me an example comparing how much?

SPEAKER: Ryan was a great skier. He did a program called the National Outdoor Leadership School where he hiked through the Windriver Valley in Wyoming. He used to crew for Gonzaga. And now, he's on SSI and walks with a walker.

MR. VALENTINE: Thank you.

SPEAKER: He was always a great kid.

MR. VALENTINE: Thank you so much for sharing that.

SPEAKER: Thank you.

MR. VALENTINE: So regardless of which symptoms is driving -- we've heard about the energy and fatigue, we've heard about peripheral neuropathy. But what other activities that are important to you do you have to consider your mito or your mito impact? If you would share with us.

Yes.

SPEAKER: Every single thing. I'm really lucky that I have my own apartment. But I only have that because my parents live right next door. But day-to-day life activities, like showering and washing my hair and drying my hair, I can't do alone. I have to plan every single part of my life days ahead, hours ahead. When I get really sick, I can't manage my own medications or IVs by myself because my brain is just not functioning. And it's gotten to the point where if I have to walk long distances, I have to use a wheelchair.

But the bottom line is, every single moment of your life is affected by this disease. I am missing multiple big family events this summer because I can't travel that far. But the bottom line is, every moment of your life is impacted by the disease, even if it's just taking a shower.

MR. VALENTINE: You said a lot of important things, and I have a few follow-up questions. First is you started talking about personal hygiene, even that kind of daily activities, not being able to do that alone. What is driving your inability to do that?

SPEAKER: Fatigue. I lose all the feeling in my arms at a certain point. I've passed out in the shower before. And usually after I take a shower, I immediately have to lay down and can't get up for 30 minutes to an hour.

MR. VALENTINE: You said that so you need help doing that. Is that from another person?

SPEAKER: Usually my mom is the one. The caregivers do not get enough credit. I wouldn't be able to do it on my own. But it's hard, as a 30-year-old, to have to ask your mom to help you dry your hair.

MR. VALENTINE: What is it that makes it difficult to travel long distances? What aspects of mitochondrial disease?

SPEAKER: I usually get incredibly ill after a certain amount of time in the car even. I start vomiting, I get migraines or either pass out and crash. And then there's the part about finding out if there's a hospital nearby? Is there a doctor that can take care of you? My cousin's getting married in the middle of some island in Italy. So that's not something that we can even think about, let alone the financial burden, because we're having to pay so much out of pocket for medications, that medications are not an option.

MR. VALENTINE: Thank you very much.

What other activities? We have a hand here.

SPEAKER: Hi. My name is Valerie. I just thought I would tag on to what was just said, that there isn't an area of my life that is not affected by mitochondrial disease. That even just basic personal hygiene or walking around the house. Before I'll walk across the house I'll make a calculation or check a list to see what else can I do. So planning the trip, because I don't have enough energy to be going downstairs or whatever to get food- to take care of anything I need. Because even on a great day I might not have all the energy that I need to do all the things that I want to do. I just wanted to echo that there isn't an area of life that isn't affected by mitochondrial disease.

MR. VALENTINE: We're going to talk about managing the energy that you do have. Do you, say when you wake up on a given day, have a sense of how much energy that you have that day? Do you know if it's going to be a good day or bad day, or is that unpredictable?

SPEAKER: In my case, I would say it's somewhat unpredictable. I have an idea of how much I'm starting the day with, but within half an hour I know that's going to change drastically.

MR. VALENTINE: Thank you very much.

SPEAKER: Hi. Liz here. So, the short answer is: Everything. But probably the biggest is the laundry. I live in a condo in DC. The laundry is downstairs on the lower level and I'm on the fourth. While there is an elevator, I typically go down and then come back up, switch it, go down, and then come back up. But that's just the thing about it should not take this much energy to plan an entire week and then it's exhausting. Just everything. Even just like cooking and whatever. I mean, sure, I can. But then I don't have the energy to cook again if I mess it up. I mean, you have to eat, so microwave.

MR. VALENTINE: Thank you, Liz.

So, I want to explore a little more of this idea of that's the worst days. We just heard from one person that it's a little bit unpredictable whether you're going to have a better or worse day. But I would like to know how often you have either good days, really good days, and what that actually means for you, or, how often do you have the worst days. And, again, give us a sense of what that looks like. Do you have a follow up for that? Yes.

SPEAKER: I wanted to add on the last note that, like Liz said, even planning for activities takes mental energy and can lead to brain fog. And even just planning ahead for how we're going to manage our energy takes energy. And then it's just an endless spiral of planning. To go up and down for laundry takes energy, and then we have less energy for the laundry. And it just keeps going. Even a basic thing like what we eat takes energy to digest. So even eating in order to get the nutrients we need to have energy takes energy, and that's just another spiral as well. Just things we can control takes the energy we have.

I'm sorry, would you remind me of your second question?

MR. VALENTINE: How far often do you have either those really good days or those worst days? Say, in a given week or maybe even more than that, every two weeks, how often do you have what you consider your personal worst days or best days?

SPEAKER: In my case, that is more variant over years.

MR. VALENTINE: Okay.

SPEAKER: My worst day, having been diagnosed years ago, was every day, not knowing how to manage it or what to do with it. And over the past two years of learning how to manage my day, I can very happily say that I rarely have a worst day from what that was. But it's taken years of managingit, without doctors who know how to help me navigate the process, without having a lot of people around me who have a similar diagnosis that know what to do, and just managing through trial and error.So I can happily say now I don't have many bad days, but that can always change clearly from some of these stories we've heard. So, it's very carefully managed.

MR. VALENTINE: How long has it been since you had your last one, the last time you had a worst day?

SPEAKER: Maybe a year.

MR. VALENTINE: Thank you very much.

Other thoughts on best and worst days? A hand here in the front, and then we'll come to the back.

SPEAKER: Hello. My name is Leslie. Best and worst days. I would say out of a week I might have two good days and five bad days. It all depends on how much sleep I get. If I get about nine hours of sleep, then I can usually feel as though I have a pretty good day. Sometimes when I start a new supplement, that really boosts my energy and that gives me like a really nice day, as far as I can describe it, because it allows me to exercise more. But if I don't get sleep, then it's a bad day.

MR. VALENTINE: Can you give me an example, maybe something that can help me understand the difference between that good day versus what that bad day looks like?

SPEAKER: So a bad day, brain fog, just really dragging, pushing myself. And I can't make it through the whole day. I have to take a nap and crash for an hour and a half, a couple hours, and then I feel somewhat refreshed after that. I feel better.

MR. VALENTINE: Is there an activity that on a bad day there's just no chance that you would be able to do it, and on a good day you can do it?

SPEAKER: I don't know. I mean, I just constantly push myself. I always try to get some exercise in. On a bad day, it would be 15 minutes maybe in the gym. On a good day, it can be about an hour.

MR. VALENTINE: I think you're probably beating me on exercise. But that's commendable. That's very helpful.

SPEAKER: It definitely helps me to maintain my strength. Because if I don't, then I feel like a drastic loss in my strength, my muscles start to cramp up. But if I maintain some exercise, then I feel as though that's what's really, really, really helped me.

MR. VALENTINE: That sounds like sleep and exercise are really driving feeling good.

SPEAKER: Yeah. And sometimes I just, I can't -- anxiety prevents me from getting a good night's sleep or I just don't sleep as well. So sometimes I take melatonin, I'll take some medications to help me to sleep. But if I could get nine, ten hours of sleep every night -- which doesn't always happen -- then I'm better off.

MR. VALENTINE: Sure. Thank you so much for sharing.

We had a hand towards the back. Right here.

SPEAKER: Hi. My name is Anisa. My genetic diagnosis is combined -- I'm -- I'm sorry, I have complete brain fog today. I can't even read my own writing. The difference between good and bad days is a good day for me, unfortunately, at this point is only happening once every few weeks. Bad -- really, really bad days would be asleep for 16 to 18 hours. When I am up, I can barely pull my head up. A variation of a good day is where I can get up, go to a concert, go do something fun that requires a lot of energy, to a day that you can't care for yourself, is quite a range.

MR. VALENTINE: Do you notice that there's either cycles, or is it pretty consistent over say over weeks or months of how many good and bad days you have?

SPEAKER: I would say it's become a cycle of I have one good day and use my energy to do go something, then two to three weeks of bad days. And the recovery time between has increased drastically over the years since diagnosis.

MR. VALENTINE: So, when you were first noticing that you needed some time to recover, how long would it take you to recover?

SPEAKER: Yeah, it could be a couple hours of recovery, and then slowly through the day, then several days. I would say, over the course of about seven years, it's increased from maybe an hour of recovery to a week to recover.

MR. VALENTINE: Thank you very much for sharing.

SPEAKER: Good and bad days are us doing the exact same thing every single day for weeks, and he could have a couple good days, a couple bad days. And there's no rhyme or reason or pattern of what makes why he's having a good day. And even if he was to do no activity whatsoever, he could eat the exact same thing, sleep the exact same amount, or do everything exactly the same every day, and you could have bad days and good days and there's no rhyme or reason or pattern at all of why he has good or bad ones.

MR. VALENTINE: And what do the good ones and bad ones look like for him?

SPEAKER: Well, for him, he's pretty affected. So, his bad ones are he can't barely even talk. He slurs his words, he's not hearing well. And good days are himspending two hours in his wheelchair and talking, doing some exercising, and going outside. So, he's pretty affected. He's a little different than a lot of the other people here.

MR. VALENTINE: Thank you.

SPEAKER: So, my husband is the one that's affected. My name Cindy, he's Tim. We just discovered his problem was GFM1, agenetic problem.

There's really not good days, but there's better days. And Tim recently told me that on a typical day three hours is about the most that's okay. He wakes up feeling horrible. I don't know, that it has been mentioned yet, but sleep for most people it's like let me take a nap and I'll feel better. He takes a nap and he feels horrible. So, when he wakes up in the mornings, it's as if he's been hit by a train in just excruciating pain, and it takes at least an hour just to feel semi back into the world with being okay. And then he wears out and takes a nap, and again you start all over with the train wreck feeling. So, you know, most of us go, well, let me take a quick nap and that will give me energy. Well, if he takes a nap, he's out for like three hours because you have to sleep and then the recovery from the sleep. It becomes extremely difficult.

And then the other thing is activities. Yeah, we can go do stuff but we have to be super flexible. Because we may go, oh, let's go out and go antiquing, and after that half an hour it's like, okay, I'm done, we go back home. So there's always flexibility, you know, when he's done, he's done, and he can't go any further.

And then another thing is the constant shifting of, like standing will hurt shortly after he stood for a while. So, then he'll sit down. But then after a little while of sitting, that's uncomfortable so he lays down. He lays down, after a while that's uncomfortable so he stands. I mean, there's never an ability to just --

MR. VALENTINE: What's driving that?

SPEAKER: The pain. Constant pain, constant muscle spasms. You know, it highly impacts day-to-day living.

MR. VALENTINE: Is that you start feeling pain, you're out antiquing, walking around. Is it that you get tired after 30 minutes and you need to rest, or you're starting to feel pain and you need to sit down?

SPEAKER: It's severe pain. The fatigue, I can usually push through but the pain is more difficult. And the pain and the stiffness never leave, but the pain levels can shift to the extremes. That's what scares me, is that.

MR. VALENTINE: Has the pain been getting worse over time?

SPEAKER Yes.

MR. VALENTINE: It's progressive?

SPEAKER Very much so. I was diagnosed in my late 40s, and I'm now in my late 50s and its significantly worse.

MR. VALENTINE: Is that something that worries you, that you'll keep getting worse?

SPEAKER Yes. Certainly. And then providing for retirement, of course, you know. But from a day in and day out basis, from a practical level, like everybody here has said, it's difficult to know what you can do, what you can't do, what will send you into a downspiral. And so, you have to live as much as you can, like cooking and doing laundry and various things, but the pain level that is a muscular neuropathy is most significant issue, the pain.

MR. VALENTINE: Thank you both so very much for sharing.

While we have other hands up throughout, think about including in your responses on this topic of worries. We do want to cover in a session, what is the aspect of your mitochondrial disease that you are worried most about. But please don't feel you need to answer that. I'm just throwing it out for consideration.

Let's move here. Let's take these two.

SPEAKER: So, on a good day I can work about five hours. I'm on disability but I work part-time. It has a lot to do with how well I take care of myself. I get nutrient IVs. That help me a lot, cocktails. On bad days, it can be an energy expenditure or a delay. Like I lose the ability to walk. And I get brain fog. As another woman said, exercise helps but it's kind of a double-edged sword. You want to keep the capability you have, but doing anything intense immediately just kills my abilities.

MR. VALENTINE: Thank you.

SPEAKER: I have complex 1, by the way. As James, Phil, and others have heard me say before, life is a like a box of chocolates, you're never know what you're going to get. That's mito life, too.

So, there's some days where earlier are good hours, and the rest is like I'm out of commission, either asleep or I can't do much other than just be on the couch. And then other times, where it's like you run as much as you can when you feel more energetic but at the same time you know that you'll have to pay some sort of price after it. And the worst day I had was mid-November, and I was so, so, so dizzy that I called 911. And I had sort of like -- I can't leave without forgetting, leaving my keys behind, so brain fog there. So, I couldn't let the ambulance people in the door. And then basically in to the emergency room and my temperature was 100.3. Granted for some it's not but for me it's a big deal. So, things like not being able to walk or think, and like not being able move really, that's a bad day. And then when you feel like that, it's like wow. My normal, what my best feels like. And then just brain fog is like well -- because some days I can have fog, and then I just forget, like write in a e-mail or text.

So mito's like a box of chocolates. You never know what you're going to get.

MR. VALENTINE: Thank you very much.

I think our final comments for this first discussion, right here.

SPEAKER: Hi. My name is Sharon. As everyone was talking, I wanted to say that the most consistent thing about mitochondrial disease is its inconsistency. I had one of my bad days yesterday, and today I feel different. I call where I'm at right now my normal crappy self. We really are warriors, because I don't think those of us that live with mitochondrial disease live with it. So, the perspective might be a little different, but this is my normal crappy self, which maybe to other people, it may be what I feel in my body might be wow. We're used to living with a normal, crappy level.

Yesterday all my symptoms were escalated, and that was because I was up at 4:00 a.m. and I had a nine-hour travel day. And I did sleep 14 hours, but that doesn't mean anything. Just because we rest doesn't mean that we're rested. And today I feel better.

MR. VALENTINE: I'm glad to hear that. Thank you for sharing.

Our final comments.

SPEAKER: Hi. I was diagnosed in 2014. I get my days and my sleeping -- my days and nights are mixed up. I sleep during the day and am awake at night. PT really helps me. I try to keep at a positive level. I have the shakes and a lot of fatigue. As long as I can do things in the kitchen and I find a lot of strength. So that really helps me. I just want to speak to worries. You asked what worries us.

MR. VALENTINE: Yes.

SPEAKER I have MERRF as well I think because my mom. And I find the best place is in the gym. I have mild symptoms, but I keep going. I worry, what's going to happen to me? I have no children, I have chosen not to as well because of MERRF and other reasons. So, I can help take care of my mom, but I really hope my stepsons love me when I'm older because they're all I

have. Who is going to help if I am in the situation that my mom is in? And the unknown is a major worry, the unknown of the mitochondrial disease, what's going to happen.

MR. VALENTINE: Thank you all for sharing. For everyone in the room, we'll have plenty more time to explore and build on what we've been talking about when we get back from our break. So now we're going to take a 10-minute break. We'll come back at 10:40 and we'll get started on topic two, talking about treatments.

(Break taken.)

MR. VALENTINE: Welcome back, everyone. We are still in our morning session here, discussing individuals with mitochondrial disease that are adults affected with myopathies. We're now moving into our second topic of the day, which is: What are the different current treatment approaches that you all as a community utilize to try to live with and manage your mitochondrial disease symptoms, as well as discuss what are your preferences for future treatments, short of a cure for your condition? In this topic, our panel discussion and polling and audience discussion, we're going to being exploring a number of questions. First, we want to know, what are those things that you're doing to try to help treat your condition? Not only drugs and other medical procedures, but what else you might be doing or using, like diet, exercise, or lifestyle modifications. And specifically, we would like to know what are the different symptoms that you are trying to manage or treat with those different treatment approaches, and how that regiment of treatments may have changed over time. When discussing those different treatments that you use, we're interested to know how well those different products or approaches are working for you, as well as what are some of the significant downsides of those treatments that affect your daily life. And that could be anything from side effects or having to go to the hospital receive treatment or restrictions on driving, et cetera.

Then finally, as I mentioned, we want to end our discussion on topic two looking more towards the future and knowing, short of a cure, what specifically you would be looking for from an ideal treatment.

To kick this off on this topic, we have another great panel for you. We have Luisa and Robert, Deborah, Michael, Sharon, and Nicole.

Luisa and Robert, take it away.

MR. MILLER: My name is Robert Miller, and I'm here to speak for my wife, Luisa Miller. The words I'm reading are hers. Luisa is a 59-year-old physician, practicing medicine full time in a state hospital in Rhode Island. She is a wife and mother of two healthy adult children.

In 2016, a mutation on the TK2 gene was identified, allowing a specific diagnosis of Thymidine Kinase 2, TK2, related mitochondrial DNA depletion syndrome. The identification of this specific mitochondrial disorder was life-changing for us. It allowed for the first time a treatment which addressed the underlying metabolic defect. After decades with little to do to

change the course of the disease, there was suddenly hope. Almost two years ago, Luisa began treatment with two nucleosides, deoxythymidine monophosphate and the deoxycytidine monophosphate, under a compassionate care waiver. These are the precursors of the enzyme TK2 which is needed for mitochondrial DNA synthesis. The following is a description of Luisa's illness and the treatments she has undertaken.

The first indication that something was wrong occurred in her mid-20s, when a routine blood test revealed an elevated CPK. Months of biopsy followed revealing ragged red fibers and a nonspecific diagnosis of mitochondrial myopathy. It was not until her late 30s that disabilities began to accumulate. She left her position as an emergency room physician because of impaired speech. She developed difficulties swallowing. It was difficult to handle nutrition or handle her own secretions. At five-nine, she weighed just over 100 pounds. Placement of a percutaneous gastric tube became necessary. As her respiratory muscles weakened, she required bypass ventilatory support. Shortness of breath worsened, fatigue was increasing, her ability to walk declined. She depends entirely upon her gastric tube for nourishment, for her medications, and upon BiPAP support to lie down upon exertion. Difficulty handling her secretions led to repeated aspiration pneumonias, several times requiring admission to an ICU. In time we became skilled at performing pulmonary suction so that she has not experienced a significant pneumonia in over five years. When she does still aspirate, we perform drainage and percussion followed by vigorous suction. She must have a portable suction machine always at hand, whether in her office, in the car, or at home. She uses an albuterol nebulizer and portable inhalers and employs incentive spirometry. Liquid albuterol and guaifenesin help keep her airways relatively clear.

In addition to the two nucleoside, Luisa takes a typical mitochondrial cocktail consisting of creatine, CoEnzyme Q10, Carnitor, vitamin C and vitamin E. The only adverse effect she has experienced is nucleoside therapy diarrhea which she manages by taking up to seven Imodium tablet's per day.

The following is a description of some of the adaptive measures she has employed. She finds her speech most disabling. She carries a notepad and pen wherever she goes. Our children and I generally understand her speech, but for everyone else she must write whatever she wishes to say an iPhone app called Big, in which is typed a sentence or two in large, easy-to-read lettering which can be held up for everyone at the table to read at once. Our family and friends have adapted to communication with her.

She takes a two- to three-hour nap each afternoon to rest her muscles after work and to eliminate the metabolic byproducts that accumulate during the day. When she does too much, weakness increases, aching muscles require Tylenol or Ibuprofen and bedrest for several hours or a day. Unsteady gait requires the use of a cane. Climbing stairs is very difficult. We installed a platform lift over the steps of our home, we rebuilt the steps on our front deck at half the standard height, and we have a chair lift for access to the second floor of our home.

Rising to stand from a chair is a struggle. The chair in her office is higher than standard and she carries a cushion in her car to use as a booster, as now, whenever chairs of only standard height are available.

Just three months into the nucleoside treatment, there were subtle but objective signs of improvement. While she still can't eat, she is able to drink an eight-ounce cup of coffee with less aspiration. Being able to drink coffee may not sound like much, but in terms of pleasure and quality of life it's important. She still requires BiPAP at night or when lying down, but she may now go days without being aware of her hunger. She believes she has more energy to approach daily life.

While improvements may be small, for the first time ever Luisa has not experienced a noticeable progression of her disease.

I will read the last paragraph of Luisa's words in the first person.

I was asked which symptom we wished to see addressed in new drug development. This is an impossible question. Would I rather breathe, eat, or sleep? Would I rather hear or speak? I can do none of these things. What do I want? I would like to see a cure for mitochondrial DNA deficiency syndromes. I write these words knowing how profoundly fortunate I am that this disease was not truly expressed until well into my 30s. I had an opportunity to become educated, fall in love, marry, establish a home and a career and have children, whereas some, especially babies and children, may never get a chance at the life that I have had. For this generation of children, I hope a cure or effective treatment will be found.

(Applause.)

MS. CARMEN: Hello. My name is Debbie Carmen. I'm 47 years old, and I live in central Illinois with my 20-year-old son, Alex, and my fiancé Derek. My journey began at the age of five years old when I ran with a funny gait, had severe muscle cramping after exercise, and would cry for hours from pain. At the age of 12, I ended up having an emergency appendectomy where I went into cardiac arrest and I was diagnosed with malignant hyperthermia. This is caused from a gene mutation. I am joining you through this recording today because I fell in December and have a tibial plateau fracture. Because people affected by mitochondrial disease heal more slowly, I'm still not well enough to travel and be with you in person.

At the age of 31, I woke up in bed one morning and was unable to move from my waist down. I was in excruciating pain in my low back, had low potassium, and a plethora of other problems. I was treated for a possible staph infection and sent home after nearly five months. After some research, I believe I had lumbar rhabdomyolysis caused by mitochondrial disease.

After my extended illness in 2002, I was on OxyContin, morphine, fentanyl patches, oxycodone methadone, and Avinza. I was hospitalized three times for pancreatitis as a side effect from the Avinza, which is a long-acting narcotic. I was put on Neurontin, which caused excessive swelling in my legs and hands, but that caused me to have the feeling that I was being zapped with a

stun gun in my lower legs. I developed pyelonephritis, which is an abscess of the kidneys, along with acute kidney failure, after taking arthritis medication called Vioxx. Because I did not have infection, I was later told this was caused from the mitochondrial disease due to autonomic dysfunction. I take Klonopin for orthostatic hypertension and restless leg syndrome, which causes excessive sleepiness.

I went to rehabilitation for five days after my extended illness for detoxification from the narcotics. They gave me an injection called buprenorphine, which worked well for my pain. I currently take Suboxone, which is buprenorphine and naloxone, taken in a sublingual film. However, it has side effects, such as my legs swelling and some mild memory loss. I have been on it for 12 years. Although it doesn't work for my pain completely, it does enable me to get up from bed most days and have some semblance of a normal life.

I take 400 milligrams twice a day of magnesium, which has helped with the chest pain I've had my entire life; however, it only helps a little with my leg pain and spasms. I have muscle spasms in any muscle. I can have them in my legs, toes, feet, arms, chest, diaphragm, and stomach. I have been taken by ambulance to the hospital for muscle cramping that would not stop. I have tried a TENS unit for pain, but it didn't help. I occasionally use lidocaine patches, which help temporarily.

I was put into physical therapy three times but released for failure to progress due to fatigue and other symptoms that would occur. I tried the mito cocktail and was taking coenzyme Q-10, but it didn't help. And although the prescribed levocarnitine did help my leg pain, I was unable to take 29 pills a day due to gastroparesis which is caused from the mitochondrial disease. I have to eat several small meals a day because I feel full very fast. I have a lot of nausea and I take 8 milligrams of Zofran.

I have severe allergies and used to take three shots a week. My allergy testing was off the charts. I woke up every day with headaches. I purchased an ionic room filter and have noticed an improvement in my headaches. Although I'm on Topamax as a preventative, I became unable to take migraine medication such as Imitrex due to a prolonged QT interval in my heart which is caused from the mitochondrial disease.

I live in a small, rural community. There are not any mitochondrial specialists in the state of Illinois; therefore, I have not seen one in 11 years. It would be a blessing to have medication available to have less pain, as well as increased energy and stamina would allow me to care for myself and improve my ability to be independent. As I am still mobile, if my primary symptoms were controlled, it is possible that I would be able to become employable. I would enjoy working at home performing medicine transcription. The simple things that others take for granted, such as walking the dog, vacationing with their child, swimming, would be a blessing if I could do them again by use of medication. However, as my life is right now, there is no way that I am able to perform any skills as I never know if I am able to get out of bed. The pain dictates my days and nights. It controls my life.

(Applause.)

MR. MONTERIO: Hi, everyone. Good morning. My name is Michael Monterio. I'm 44 years old and I'm from Leominster, Massachusetts. I was diagnosed with a mitochondrial complex III deficiency and a fatty acid oxidation disorder in 2012 after going undiagnosed for five years. An invasive cardiopulmonary exercise test, along with frozen muscle biopsies, suggested a mitochondrial issue. My doctors at Massachusetts General Hospital then referred me to the Center for Inherited Diseases of Energy Metabolism at Case Western Reserve University Hospital in Cleveland, for a biopsy, which then confirmed my diagnosis of myopathy.

The onset of my symptoms started when I was 34 years old. They include severe fatigue, muscle weakness, cramping, shortness of breath with light exertion, exercise intolerance, stomach dysmotility, abnormal body temperature regulation, muscle and nerve pain, sleep pattern disruptions, and a constant mental fog and fatigue.

Personally, I have integrated several treatment regiments throughout the course of my illness, whether due to my doctors suggesting lifestyle changes, prescribing additional or excluding medications, and also personal research on any supplements. In regards to conventional medicine, the mitochondrial vitamin cocktail with L-carnitine was the start of my initial treatment. Unfortunately, I did not experience any benefit from the cocktail even after the dosage was increased after three months. For pain management, it has been trial and error from most medications, from ibuprofen to Lyrica, Neurontin, tramadol, morphine, and fentanyl. None of these helped, but ultimately opiate oxycodone did provide some relief. I am also given Mestinon for neuropathy/mild preload failure, a stimulant to help with energy, supplemental oxygen for shortness of breath, and a bilevel breathing machine for nighttime.

I have also tried naturopathic therapies, notably IV ozone and IV laser treatment, chiropractic, massage therapy, and I also incorporate light graded resistance exercises, along with a strict vegetarian diet.

As far as symptoms are concerned, the extreme fatigue is definitely the most significant, a fatigue that doesn't go away with extra rest and regresses when doing any kind of exertion. For me, the most beneficial part of my current protocol is the stimulant I'm prescribed, Adderall. However, by no means does this medication give me the energy to do things without them still being a challenge. It simply provides me a little more energy to do daily living tasks, go to doctor appointments, do errands and exercise when I can. Being a former college athlete and an active person my entire life, exercise has always been extremely important to me to try to maintain a healthy lifestyle. Therefore, taking the stimulant has had a positive effect on my overall physical and emotional health.

As my illness has progressed over the past few years, I have felt that regardless of what changes I have made in regards to my treatment, it has had less of a positive impact on my quality of life and the result is a consistent decrease in energy. Everything is becoming more physically challenging to me, and I have found myself being bedridden more times than not. Receiving

the endless amount of support from my family and significant other has been tremendously helpful in coping with this illness.

Being from the Boston area, I have been fortunate enough to have access to excellent doctors and some of the best teaching hospitals in the entire country. However, due to this condition being so unpredictable and unstable, I have learned to understand that it will take additional research and clinical studies in order to find possible effective treatments. Due to my disabling symptoms, I am no longer able to work my position in law enforcement that I held for 13 years, which is very hard to accept. I chose to work in the gang unit because my passion is helping individuals in need. Ironically, now I'm the one who needs help due to my declining health. However, I still motivate myself, thinking that someday I'll come across some kind of treatment that will make me feel better so that I can return to work.

Management of this condition I feel is one of most important aspects of living with this. I try to avoid situations that can worsen my symptoms, such as exposure to cold and heat, fasting, not getting enough sleep, and knowing and accepting my limitations by not doing too much and pacing myself.

From a patient's perspective, when you lose your health it makes you realize some of the smallest things in life are actually the biggest ones. Someone who has their health may unintentionally take these things for granted. I'm so thankful for what I do have, but the reality is having a disease that leaves my future uncertain is still difficult to accept. But I do my very best not to let it define me or the person I am. Going forward, I can only anticipate in the near future medical advancement or drug development or clinical treatments can discover something that can optimize mitochondrial function and ultimately provide hope and improvement with quality of life in all those who suffer for mitochondrial disorders, because we desperately need help. Thank you.

(Applause.)

MS. SHAW: Hi, everyone. I'm Sharon Shaw. I'm 54 years old. I live in Tucson, Arizona. It really is my honor to be here today serving on behalf of my community.

I was diagnosed 19 years ago with Kearns Sayre Syndrome. Years later, and through better diagnostics, they were able to narrow it down to CPEEO++, which is in Kearns Sayre Syndrome spectrum of mitochondrial disease.

Living with mitochondrial disease means managing a long list of symptoms. Today, I will only talk about my top symptoms, which include: Head-to-toe pain in all my muscles, extreme weakness in my body, severe fatigue and exhaustion which translates into terrible inconsistent energy levels. My eyeballs are 75 percent paralyzed due to chronic progressive external ophthalmoplegia, which includes droopy eyelids, making it difficult to have a normal range of sight. I suffer from severe dry eye syndrome due to my eyelids not opening or closing all the

way, and extreme neck weakness, making it hard to hold my head up due to neck muscle atrophy.

The past 19 years has been a journey of trying anything I can find to help myself. Today, my self-help regiment consists of: Physical therapy three times a week; I use a TENS unit, which is electrical stimulation, on my muscles. I use Sore no More muscle cream. This brand helps to reduce my pain and soreness for a short time for about 50 percent.

For my severe neck pain, I have had two cervical ablations, a needle inserted between the discs of my spine, in my neck area, and it electrocutes and kills the nerves which, if it works, removes the chronic pain. The downside is that immediately after this procedure, my pain increased 75 percent until all the nerves died. It can be a dangerous procedure and it does not always work. I wear a soft cervical neck collar to relieve my neck strain and to help hold my head up. As of the last year, I am now developing drop head syndrome.

I have to use celluvisc extra thick eye drops every 15 minutes; otherwise, I get blurred double vision and am not able to read or drive at night. I had to have a frontalis sling surgery due to eyelids not closing or opening all the way. Silicon slings were surgically implanted into my forehead muscle attaching my eyelids to my eyebrow muscle. This helps to keep my lids from drooping completely closed. So, to raise my eyelids, I raise my eyebrows. Unfortunately, this procedure only lasts ten years. I am overdue to have a repeat surgery. I have to tape my eyes shut at night to prevent cornual ulcers. This acts like a fake lid to protect my eye environment. I have had not had cornual ulcers since taping my eyes shut each night for the last 19 years.

I carry a portable EKG device, Kardia brand, that works through my cell phone to monitor my heart arrhythmias and tachycardia. I can send the reports to my cardiologist as he assesses if my heart abnormalities are changing or if indeed I need some sort of intervention.

I have been on high dose of ubiquinol Co-Q for 18 years together with the standard mito cocktail, vitamin B, alpha lipoic acid. I used to take Carnitor, but had to stop because it caused stomach problems. I also had to stop creatine because it caused chronic diarrhea.

I was diagnosed with cerebral folate deficiency through a spinal tap. I immediately went on (garbled) which has made a major difference helping my brain fog and depression due to this condition.

Daily, I take matcha, collagen, bone broth protein, fish oils, greens, turmeric, magnesium -- the turmeric helps with inflammation -- and probiotics and aloe to help my gut. I've also been on a special water called Vivo for 10 years which helps my migraines and vertigo. It also helps my cells to eliminate free radicals and my body is better able to absorb all supplements I need to take.

I currently am in a clinical trial going on two years, specific to treat my mitochondrial myopathy. The first five months I noted inconsistent small improvement, a few days of feeling more energy than nothing. The last seven months, I have noted daily increase and consistency of my

energy, stamina, and endurance. So far, it's done nothing for my muscle weakness or pain. The downside is I have to inject each day into my stomach, which has caused welts and skin scarring at the injection sites.

When I look back over 19 years, the amount of money, time, and energy I have spent trying to help my condition, I know for sure that all my efforts have created an unbreakable resiliency within me. But I am also very worn out in a way fighting so hard on my own. I know that if I stopped trying to help myself, I will fall into hopelessness and this is not an option, and why I'm here today to ask for more treatment options to be available to me soon, like the clinical trial drug that I'm on, a drug to stop my muscles from wasting, a drug to help give me a better quality of life.

I am running out of options, and I need your help, please. Thank you.

(Applause.)

MS. DEJEAN: My name is Nicole DeJean. I live in Lafayette, Louisiana, and I was diagnosed with a mitochondrial disorder in 2010 at the age of 32. My symptoms include daily muscle and joint pain, muscle weakness, extreme fatigue, stomach pain and sluggishness, hypoglycemia, and disrupted sleep patterns.

I approach my treatment as a lifestyle and incorporate strategies throughout my day. As a foundation, I have labs drawn every 12 months to determine my vitamin and metabolic levels. The vitamin cocktail I take is determined by the results of these labs. I travel five hours round trip to see a mitochondrial disease specialist, one who can analyze the metabolic aspects of my condition. My diet consists of mostly fresh, raw, vegetarian meals prepared at home. I do yoga on a regular basis in order to increase my activity tolerance and decrease my muscle weakness. I incorporate daily rest or nap periods in order to transition from my morning to my afternoon routine. Oral hydration is also vital to the health of my muscles in limiting the pain and weakness.

Despite my attempts to address my treatment regimen as a lifestyle approach, the disease is so unstable and unpredictable the treatment takes a lengthy trial and error approach. At various points in my disease process, I have had to discontinue treatments that were previously effective. I have tried prescriptions that treat various individual symptoms, to include blood sugar instability and joint pain. However, these medications either had no effect or were more negative than therapeutic. Two of the prescriptions that I used the longest and eventually discontinued were Precose and Celebrex. Celebrex had absolutely no effect on the joint pain symptoms for which it was prescribed. I used Precose for a few years to address my hypoglycemic episodes. Eventually, though, Precose amplified my existing muscle pain to the point that it hurt to sit, vision decline that required frequent, more intense changes in eyeglass prescriptions, and erratic glucose readings. I felt like my body was shutting down. Once I discontinued taking the medication, I no longer have the debilitating muscle pain, no longer

needed eyeglasses, and am now able to control most of my hypoglycemic episodes with diet and exercise.

The vitamin regimen -- creatine, magnesium, and potassium -- that treats my muscle pain and weakness often becomes very hard on my stomach, causing extreme pain and irritation. I have had to take many breaks from the vitamins which then prompts the very symptoms I'm trying to manage. The process to find pharmaceutical grade vitamins that are reliable and effective has taken years and endless amounts of research. Because of the instability of the disease and the research involved to acquire appropriate treatment, my regimen is not efficient.

When my muscle pain becomes too challenging to treat with just the vitamin cocktail, I have experienced relief with IV saline infusions. I initiate this treatment when the pain interferes with both sleep and waking hours. This is generally short-lived because after too many infusions my veins begin to wear out and can no longer be accessed.

I'm extremely conservative with the use of pain medications because they exacerbate the fatigue and muscle weakness. In addition, I have an extensive family history of addiction, so I do not consider these medications an option. During the day, I use ibuprofen which often dulls rather than eliminates the pain. I am currently only using one prescription medication, Neurontin, and despite it being the most effective I can only use it at bedtime because it causes me to fall asleep.

Besides muscle and joint pain, my other, most significant symptom is pervasive fatigue. I'm continuing to become more limited in my ability to function effectively for the entire day in my roles as wife, mother, and professional because of this. I have found that the most effective treatment for the fatigue is rest, clean diet, and high doses of ubiquinol. However, I'm in a perpetual state of sleepiness and overall physical and mental fatigue.

There isn't a treatment I'm using that has eliminated my symptoms. At best, they are giving relief but not absence. Therefore, I've learned to work with the symptoms. I enjoy being outside in my garden and staying busy in our community. My ability to engage in those activities is limited and I am budgeting time and energy according to the day's priorities. I do believe that my current regimen is allowing me to participate at a limited level, and without any treatment my activity level would be even less.

Ideally, any treatment that would be developed from mitochondrial disorders would stabilize the muscles by minimizing or eliminating pain without the harmful side effects of the current medications on the market. Additionally, treatment for muscle myopathy would also aid patients in physical strengthening and recovery of lost ability. I'm a veteran of the Louisiana Army National Guard. At one time, I was physically active and felt strong. Now, I often have feelings of physical weakness and my activity level is low. I can visibly see that I am losing muscle mass. Recently, I've had to quit a job that I love in order to keep up with my own physical health and my responsibilities as a wife and mother. If a drug was developed that

would treat my condition, it would mean a return to balancing my work and personal life without having to forfeit one for the sake of the other. Thank you.

(Applause.)

MR. VALENTINE: Please join me in another round of applause for the whole panel.

So now we are at the point where we are going to extend this discussion of approaches to treatment, both current and future, to all of you here in the room and online, with our live polling questions. So, pull out your phones, tablets, and laptops. For those on the web, you can head back to the browser you're using to follow along.

Our first question for you is, we want to get a sense of which prescription medications that you take now to treat your symptoms of mitochondrial disease. Please select all that apply. I will note that we're going to have other questions that are going to discuss vitamins and supplements and other strategies that you might use. Here, we focus on prescription medications. Select all that apply. Your options are: A, pain medications; B, heart medications; C, antidepressant or antianxiety medications; D, muscle relaxants. E, IVIG; F, diabetes medications; G, experimental medications that are a part of a clinical trial; H, other prescription medications not listed; or, I, you are not taking any prescription medications to treat your symptoms of mitochondrial disease.

Just seeing the very large H that's showing up on the screen here, "other prescription medication," we had quite a long list that we had to pare down to fit onto a slide that we can actually see. So, we do expect that and do very much want to hear from all of you about what other prescription medications not listed.

We have a question. A clarifying question?

So the question is, levocarnitine, she gets it as a prescription but it is a vitamin. Do so do we want to count this as a prescription? She gets a prescription. Our table of experts have said that if you get it as a prescription, then put it in this category as a prescription medication. That's a great question. Thank you.

All right. So, while final results are trickling in, clearly there's a lot of other things we haven't listed that you have experience with. But of those things that we do have on the slide, there's a good range of experience, particularly with pain meds, anti-depressant and anti-anxiety meds, heart meds, and muscle relaxants. There's also some experience with experimental medications as part of trials as well as a little bit with IVIG, and diabetes medications. It looks like maybe a couple of people said that they are not using any prescription medications. If that's you and you're in the room, we certainly would like to hear more about why that may be, whether that's either where you are in your disease progression or if it's because of something else.

Our next question is on the topic of vitamins and supplements, nonprescription. So here, please select all the vitamins and supplements that you take now to treat your symptoms of your mitochondrial disease. Your options are: A, Co-Q10; B, carnitine; C riboflavin; D, creatine; E, vitamin E; FA alpha lipoic acid; G, vitamin B3, or nicotinamide, or niacin; H idebenone; I, other supplements or vitamins not listed on this side; or, J, you are not taking any vitamins or supplements now to help treat your mitochondrial disease.

The final results are coming in. Again, it looks like there's a great deal of other things that we weren't able to list, keeping the trend, on the slide that we want to hear from you all about how it's working, what the verdict is, and any of those supplements or vitamins that you're using. Of those we have listed, the greatest experience is with Co-Q10, but have a great deal of experience with all of the other vitamins and supplements. Idebenone seems to be a little experience in the room and online, however, and also a few people who have said that they are not taking any vitamins or supplements currently.

Moving right along. Our third category of different, we're calling treatments. These are the things you're currently doing to help manage your mitochondrial disease or your disease symptoms. They include things like, A, choice of diet; B, modifications or accommodations at work or in school or at home; C, physical therapy, including aqua or hippo therapy; D, stretching; E, use of adaptive devices; F, exercise such as cardio or strength training; G, mental health services; H, occupational therapy; I, speech therapy; J, you're not currently doing anything, besides perhaps prescription medications or vitamins and supplements to help manage your mitochondrial disease; or, K, some other strategy that's not listed on the slide that you use to help manage your disease symptoms. Again, please select all that apply.

It looks like the results are just finishing up, trickling in. It looks like there's nobody in the room that's not doing some kind of strategy to help manage their mitochondrial disease or symptoms. The selections with most experience that we have today are choice of diet, modifications and accommodations, and physical therapy. After that, it looks like the next kind of bunch are stretching, use of adaptive devices, and exercise. There's also experience with mental health services, OT speech therapy, and then of course other things that aren't listed which we do want to hear about.

This question is, when you take all three of those categories and broad categories of treatments -- so your medications, your vitamins and supplements, your different lifestyle changes -- in general, how much do all those things together, or all of those changes, how much do they improve your quality of life? A, there's no benefit; B, they help somewhat; C, they help a lot; D, they have a significant benefit; or, E, you're not sure of how much these things improve your quality of life. It's like that which represents your experience.

Okay. It looks like about half, a little over half of those that we have participating today say that all of these different approaches to treatment are helping somewhat, about a third are saying that they help a lot, and a little over 10 percent saying that there's significant benefit,

and then there's going to be a handful of people here today that are not sure. Nobody said that these things have no benefit in improving their quality of life.

So here we're asking about now future possible treatments, and what would be the most important possible outcome of a future treatment for you. Your options are, A, slowing or stopping the progression even if you have no gain in function or symptoms, just so things aren't getting worse; B, you do experience a gain in function, such as energy, strength, mobility, dexterity, cardiac function, or speech; C, you would prefer to have a possible treatment that prolongs life; or, D, some other outcome that is important to you, most important to you, for a possible drug treatment. Please select that outcome which is most important for you for a possible drug treatment.

It looks like about three-fourths of those of you participating today would like to see a gain in function, and a quarter of you believe that most important is to slow or stop progression of the disease, even if that did not mean a gain in function but your symptoms are at least not getting worse.

Going a little deeper on this idea of a future treatment, which of these abilities or symptoms would you rank as most important for a possible treatment today? You can select up to three of these different abilities or symptoms that you would like a treatment for. A is a reduced chronic fatigue; B, reduced muscle weakness; C, reduced GI problems; D, reduced exercise intolerance; E, reduced sleep difficulties; F, reduced Dysautonomia; G, reduced headaches or migraines; H, reduced peripheral neuropathy; I, reduced mood disorders; J, reduced eye muscle problems and/or improved vision; or, K, some other ability or symptom that you feel is most important for a possible drug treatment today. Please select up to your top three.

All right. We'll give you a few more minutes to get into your response to this question. As it stands, it looks like the greatest ability or symptoms that those of you who are participating today would like would be, A, reduction in chronic fatigue, followed closely by a reduction in your muscle weakness. It looks like there's no ability or symptom on this list that is not in somebody's top three. So, as we explore what it is that you're ideally looking for, I think we're going to have a range of things to hear about.

Okay. Our final question. We've asked you about what are the treatment benefits that you would look for. But we want to also ask you about some of the tradeoffs or factors that might go into deciding whether or not to take medication, or even before it's approved participate in a clinical trial or research study for a new medication. So, which of the following factors would influence your decision to do one of those things, to take new a medication or participate in a clinical trial. Here, select all that apply. A, significant risks of serious side effects, such as things like cardiac side effects or kidney issues; B, the cost and/or travel; C, the burden of administration, such as the need for anesthesia, radiation exposure, or surgical procedure; D, common side effects of the treatment, things like nausea, loss of appetite, or headache; E, the length of the treatment, if it requires hospitalization or requires numerous doctors' visits; F, if

you have to change your current treatment or management plans, such as stopping a medication, supplements, or exercise; G, the way the treatment is administered, whether it's oral, IV, or subcutaneous; H, none of these factors would influence your decision; or, I, some other factor. Select all of them that apply.

All responses are trickling in. It looks like the top factor that would influence your decision is significant risk of serious side effects. After that, perhaps the burden of the administration. But there's pretty much everything else listed, other factors on the slide are considerations that are important to the group, including some others that weren't listed. There may be only a couple or a few people maybe that they changed their mind, that none of these would be important. So maybe no one said that none of these would be important considerations.

Okay. So now we have a chance to explore these, now that we've heard from everyone in polling, to hear some of your specific experiences with some of these different treatment approaches. We'll start by talking about current treatments, and then we'll save few treatments for a little later towards the end of our discussion.

So, where I would like to start is, what are treatments or strategies, any of the things included in these questions that you have tried for what you reported to us in the first session as your top three burdens or symptoms of mitochondrial disease. I would like to hear how well those selection of treatments is working for those things that you told us are most impacting your daily life. So, whatever that might be for you. We have heard a lot about fatigue, we have heard about pain and peripheral neuropathy. We've heard about a whole wide range of issues. Whatever that pain point is for you, we would like to hear how well treatments are working.

SPEAKER: Hi. My name is Sharon. I enjoy a lot of things and I've been able to significantly improve my quality of life. I do a weekly IV nutrient cocktail, which is some of the standard mito cocktail but also customized to me based on extensive nutrient testing every nine months. I found increasingly glutathione and branch chain amino acids have been able to reduce my fatigue and kind of delay fatigue. I have done hyperbaric oxygen therapy which has helped me tremendously, trying to go after hypoxia. My immune system kind of failed, so I've been doing IVIG and then (garbled) for EPS Barr and herpes viruses. And I'm taking POTS medicines like (garbled), which has really helped, as well as paying attention to my hormones, adrenals, hydrocortisone, thyroid medications, and (garbled) hormones. So all of the above helped.

MR. VALENTINE: What would you say has been the biggest improvement you've seen from any of those different treatment regimens?

SPEAKER: Being able to increase my ability to function at a normal level. I still have bad days, but I can work -- like I was able to work two hours a day three or four years ago. Now, I can work, on a good day, five hours. And I can exercise for longer periods of time. Before, I was having to have a nap every two minutes to get a workout in, get a 15-minute workout, but now I can go for longer. It's been a gradual improvement, and there's setbacks and not every day is good, but overall. The biggest issue is the cost. My insurance doesn't cover most of it, and just

add it all together, treatment and have a doctor, you know, available can help. And then getting the -- one other thing I want to point out. I get most of my meds from compounding pharmacies. I'm allergic to corn and milk, so FDA approved don't do much good. I have to get them compounded.

MR. VALENTINE: How long does it take you to get to what is your at least current comprehensive plan?

SPEAKER: It's been over about an eight-year period.

MR. VALENTINE: And how long, of those eight years, you do you think you've been kind of at this point?

SPEAKER: I think the last nine months I've had probably the best improvement. Like two years ago, I was sleeping 13 hours a day and brain-fogged a lot of the time. The thing that I have done in the past nine months that I added was NAM or NA-plus and phospholipids helped.

MR. VALENTINE: Great. Thank you so much for sharing all of that.

Other experiences with treatment approaches?

SPEAKER: I'll speak for my brother again. So, his primary underlying condition is Parkinsonian symptoms, and so medications that he takes are Ropinirole and Sinemet to treat his Parkinson's on top of what's going on with his mitochondrial disease.

The primary concern that we have is that as his mitochondrial disease has evolved he becomes more dependent on those drugs, to the point that they changed his Sinemet to a generic version and after taking that he couldn't walk for three days. He has become very much dependent on those drugs in order to just keep a level of mobility as the mitochondrial disease has progressed.

MR. VALENTINE: So, it's kind as if you're balancing these very two different sets of disease issues at the same time.

SPEAKER: Right.

MR. VALENTINE: As his mitochondrial disease has progressed, have his Parkinsonian disease symptoms also progressed in parallel?

SPEAKER: Absolutely, to where you can tell. He takes his meds on a three-hour basis, and at two hours and 45 minutes, that looks much different than 15 minutes when he's taken the medication.

MR. VALENTINE: How has that need for that treatment regimen and that kind of confounding set of symptoms ,how has that impacted the way you manage the mitochondrial symptoms?

SPEAKER: I think it's that underlying fatigue,butthey kind of go hand in hand. Because there's no real medication to treat the mitochondrial symptoms, we're reliant on these Parkinsonian drugs that really don't treat the underlying problems.

MR. VALENTINE: Thank you very much. That's very helpful.

SPEAKER: I've been on an experimental treatment now. I've tried everything from mito cocktail. And my diagnosis is CPEO+, which I've had -- in the beginning I was homebound for an entire year. With the recent clinical trial, the medication, the injections, which I was given permission to use the thigh instead of the belly because of the pain-it's made significant improvement. The events in the evening were so difficult before. I went to one of my daughter's events, and I said: Listen to my voice. My voice is clear. My eyes were open. It was unbelievable. Sometimes your mind plays tricks on you as far as with your energy. Recently, I had my third ERG. The first two showed RP, the last one was normal. And that doctor said, you were so sick before. And I said, I don't ever want to be like that again. So, this progressing with treatments is everything and appreciated.

MR. VALENTINE: So, one of the biggest things you're noticing is your energy levels at the end of the day aren't dropping off.

SPEAKER: It's everything. The struggles are all the same. Everyone has had difficulty and agony. And to be more normal, it's just -- it's everything.

MR. VALENTINE: Sure. Thank you very much.

SPEAKER: I'm significantly more functional than a lot of folks in this room, but I made a list of everything that it takes for that to happen. I'm on 17 prescription medicines, four for dysautonomia, two for gastroparesis, three for migraines, one for nerve pain, one for fatigue, three for sleep, one for dystonia, and then two parts of the mito cocktail that are available by prescription, then I'm on four other over-the-counter supplements for the mito cocktail and one for sleep. And then every month I get -- every three months I get Botox injections in my legs for dystonia and in my head for migraines. Every night I do feeds through my feeding tube for gastroparesis and use a C-PAP for sleep apnea. I go to physical therapy once a week for balance issues. And then I have constant lifestyle modifications. Like sleep is really important, I take a lot of medicines for sleep because otherwise my body won't sleep and I get a lot sicker. I walk for exercise. I do frequent meals. And I'm managing this -- even for somebody that, like I'm able to work full time but it's only because I am managing this. Like, it takes a village and my whole life to coordinate my every day.

MR. VALENTINE: Has this been something that you've been able to use for a while now, or is this more recent, this treatment regimen?

SPEAKER: Yeah. It's kind of built up over time. Because it's not like any symptoms get better, it's just ones get added on, so then new treatments become necessary.

MR. VALENTINE: So, it's like you're constantly adding to manage that.

SPEAKER: Yeah. It's never taking away, because nothing ever gets fixed.

MR. VALENTINE: Right. Thank you so much.

SPEAKER: Thank you, Tania. So, sort of to first note is that Co-Q10, there are different brands. The brand I take now is the only brand that works over the one's I've tried. Like there's ubiquinone and ubiquinol. Co-Q10. Leucovorinhas given me my dexterity back.

For the dysautonomia, I use Pedialyte, which helps my brain fog so that I'm not walking on my knees and crawling.

MR. VALENTINE: Thank you. A comment here.

SPEAKER: Thanks. I guess I just want to give a shout-out for the mitochondrial cocktail. It's not a prescription and it is costly. When I was first probably two years diagnosed, I was at the point where I was potentially going to be on disability and then started the mitochondrial cocktail, and now am actually working full time. But I also have the opportunity to work at home. If I had to go into the office every day, that would be a different thing for me. But being able to work from home helps. Again, I can do my shower later in the day. But I do think the mitochondrial cocktail for me has been excellent. I've had to add other things now with the neuropathies and whatever prescription-wise. But the cocktail is great.

MR. VALENTINE: I know there's different combinations. The consistent cocktail -- and you don't have to go through your current whole list. But more kind of from the time before you started on the cocktail, which I think for a lot it's one of the first things people start taking. But what are the areas that you are most impacted, most benefited from starting on the cocktail?

SPEAKER: Probably the fatigue is much better and muscle weakness is better.

MR. VALENTINE: Do you have an example?

SPEAKER: Well, I was at one point having trouble really getting up in the morning. And when I do that, I have to feel like I have a restful night's sleep. Doing regular activities of daily living like doing your laundry, taking your shower, putting my hands up over my head was exhausting. Taking the laundry basket up the steps because I couldn't pick it up anymore because my muscles were weak. And going up the steps. Those are all things I can do now. Some of them still make me tired, and if I have the opportunity I will ask somebody else to do it. But I think that I can do all those things.

MR. VALENTINE: Sure. Thank you.

I know we heard from some of our panelists that some of the medications either that they were taking and stopped or maybe still are taking had some side effects, that either drove them to stop taking or they're still dealing with in order to get that trade-off or benefit. So, any

thoughts that you have about side effects or other downsides to any of these other treatments? We're interested.

SPEAKER: Hi. My name is Emily. I'm here for my mom who had a bad day yesterday on travel day, so she was unable to make the flight. But she is here in spirit, and I've been texting with her all morning. But for her, two sides of the same coin. She had kind of jokingly called it symptom “whack 'em all”, where something will come up and then we'll find a treatment for it; and then that comes with a side effect or something else will come up. For her also I think it's unique. She's very small, about 90-pounds, four-ten. She's a very small woman, but she's taking quantities of like a 200-pound man because she adapts to the drugs so quickly. And so we are constantly shifting between one to another to another because she may do a year-and-a-half of ratcheting up the dose until it stops being effective. For folks like her, finding similar drugs that do the same thing and then transferring back and forth between them for the same symptoms becomes a cycle and then it leads to more symptom “whack 'em all”. It’s sort of a constant cycle of trial and error with different medications and different levels and dosages, and then starts over again.

MR. VALENTINE: Thank you very much.

Yes.

SPEAKER: I think a large concern especially with the mito cocktail is nausea, with so many patients having other GI concerns, taking those large volumes of meds can be quite difficult. I found, as I started CPM, I was able to get certain aspects of the cocktail via IV. For the first time I found they helped. Unfortunately, very few components of the cocktail are currently available in an IV form. And if they are, they are plagued by constant shortages, which can change -- you have something that works and then you lose it for several months. It can be so disappointing to find a solution that goes away. So, I would say nausea and being unable to tolerate meds is probably a large concern for many patients.

MR. VALENTINE: Thank you.

Another.

SPEAKER: What I have found. My son has been on Co-Q10 folic acid for probably over 16 years. And we have up to a point -- and then add in things, and then you add in something else, but then it's taken away. You're almost afraid they'll be taken away. You're like: If I take away this one -- I'm not sure it's working. But -- it's not me. It's someone else I'm doing this for, and then it gets taken away because you don't know if it has been doing something that whole time. It gets to the point where you just keep adding things and adding things. And luckily, he's got a tube now, so everything has to go through the tube so he doesn't have to swallow as many pills. But he would get to the point where we would say, okay, on Sunday you don't take supplements today, because he took so many of them. But I'm just not willing to take anything away because I don't know what they're doing.

MR. VALENTINE: Thank you.

The final question that I want to spend the rest of our time on, is now looking to the future. We asked a couple polling questions about what it is that you might want from a future treatment. Of course, the ideal is a cure. But as we're thinking of things that might be the next thing that could become available for you, ideally, what would that look like? And I mean this could be we're talking about progression, this could be particular symptoms, this could be activities in your life that you would like some help with treatment. What would that look like for you?

SPEAKER: Hi. My name is Laurie, and I'm speaking for my mom. She's diagnosed with Parkinson's, and it is a mitochondrial disease to give the disease. And I think if you look back on the last 10 years, she's now at a place where she's not able to do as much. And if you can kind of go backwards in her journey, what really took away a lot of independence -- which I think is a big issue for the community -- is physical ability to do things. And it's not just fatigue. It's actual balance issues, ataxia, and just the simple movement of getting your body to do what you want it to do at the time you want it to do it. And even with the fatigue part, if your body was able to do what you wanted it to do from an ataxia or balance, or just connecting everything together, then possibly you wouldn't have as much, you know, the mental illness piece of depression and anxiety of being isolated and alone because you had all your physical abilities taken away. That creates a really hard balance.

So, I think, to sum it up, something that would help curb taking away those physical independent type activities beyond just fatigue.

MR. VALENTINE: Yes. Thank you.

Other thoughts on what you would like to see come up on future treatment? You have a lot of people in the room that are working on research and development and are regulators. So, it's your chance for them to hear from you what it is.

SPEAKER: I was just thinking about if some of the pain and problems are coming from free radical build-up, if there is a way -- is there a good way to attack it from that aspect? And maybe that would be, like, curing the pain from the cause source. So maybe that's a direction to look at, too. Since there's so many different disorders, you know, it might be hard to target each specific deficiency. But if we could tackle it from a broad spectrum, that might -- because of the pain and muscle spasms, and some of that I think is from free radical.

MR. VALENTINE: And on pain, what amount of pain or relief would be involved, too. You know, how much and what do you need to see to be able to go antiquing for an extra 30 minutes?

SPEAKER: Broadly, anything. But if you can get a couple points of pain level down a little bit would be one.

MR. VALENTINE: What would that mean for you? What would you be able to do?

SPEAKER: A little more mobility and independence. Leaving the house more. A little more activity.

MR. VALENTINE: Okay.

SPEAKER: Well, given what I've heard today from the various experiences we all have, I think there's got to be a toolkit of solutions that can be personalized for each of us, because I don't think it's going to be a magic pill that's going to cure all of us. And I think it's going to have to take different forms. Like the gastroparesis, you made the point where getting it into our blood stream somehow without having the right digestive system, some of us are on the go take pills. It's got to be a variety of solutions, and we're just not there yet.

MR. VALENTINE: Thank you.

SPEAKER: And this is shifting gears a little bit. But I hope that folks that have a clinical diagnosis of mitochondrial disease but not a genetic diagnosis have access to these treatments when they become available. Like I know in trials, of course, you're required to have a genetic diagnosis. But I've got a variant that's never been seen before. They can't prove formally, but it's the cause. I just hope, once treatments become available, the FDA and insurers realize that there are a lot of people in my position.

MR. VALENTINE: Thank you.

SPEAKER: Over the years I've lost, I don't know, 20, 25 pounds of muscle. And as I get older, it's getting hard to really know because you start to put on a little fat to replace it. But at least 25 pounds of muscle. Treatment that will help with my muscle physiology, because I feel as though my body and energy deprivation, losing weight, you know, just getting thinner and thinner. So, something that will help with the physiology. And I can usually tell what's going on Co-Q10, actually ubiquinone, seems to help me the most and helps with my recovery from workouts. If I didn't take that, then I would just be really, really wiped out and I wouldn't recover from anything. So, to put on some more muscle mass, that would be wonderful for me, and I think that would help with overall fatigue also and feeling less wiped out. Increase the energy capability of my muscles, and to put on some muscle mass.

MR. VALENTINE: Sure. Thank you.

I think this might be a good place to stop and end this session. Thank you, panelists.

(Applause.)

We have spent the morning together first exploring the burdens and impacts of your mitochondrial disease and your myopathy and how that's impacted your life, your daily life. And we just spent the remainder of this morning talking about the ways to try to treat and manage that. I think we've accomplished, that from my perspective. We've heard a great diversity of experiences, which I think is the benefit of having so many people here together. And as we're wrapping up the patient voice portion of this morning, I just want to say that I

commend all of you. We've spent the last three to four hours here in this room discussing all of those important, difficult, and very personal issues of living with mitochondrial disease. Certainly, you all put your energy into action today. And from what we've heard from each of you, certainly that is no small task staying in this room working with me over these last three hours. I want to thank you for that opportunity to work with each of you.

(Applause.)

So now as we move into our closing, it's my great pleasure to get to introduce to you Dr. Lucas Kempf from the Food and Drug Administration. I talked to you this morning about the important role that your input plays in FDA's role as a regulator of new drugs, and Dr. Lucas Kempf is the Acting Associate Director for the rare disease program in FDA's Office of New Drugs, which is the group that works across the drug center's different review divisions to consider the difficult aspects of developing products for rare diseases.

Prior to joining FDA in 2012, Dr. Kempf spent eight years at NIH with a focus on neuroscience research and working to understand the genetics of neuropsychiatric disease and developing translational approaches in therapeutics for these disorders. He was also trained at UC Berkeley in molecular biology and genetics. He received his MD from the University of Kansas and did his postgraduate training in psychiatry at Georgetown and Johns Hopkins before he moved to NIH. Please join me in welcoming Dr. Kempf.

(Applause.)

DR. KEMPF: I thank you for inviting me to this very important event. I think we need to give James a great round of applause.

(Applause.)

And the program that he put together for you. Like he said, there's 25th we know for rare diseases, we have about 7,000, so only 6,975 more to go, James.

To be in front of you is kind of an interesting thing for my career, because as you heard sort of the short biography I actually have been working in mitochondrial diseases for a while. When I was in medical school, I did a summer rotation at a research institute in Spain founded by Ochoa, who won the Nobel Prize for his work in RA. When they created this institute, the Henry Ford Institute was devoted to a different organelle. The organelle that I happened on was the mitochondrial one. It was in 2002. I helped with the sequencing of the trans-outer membrane mitochondrial protein 20, which took the months in the summer. So, I got to have the opportunity to work with a lot of folks whose pure career was devoted to the mitochondria. Then my research at the NIH, actually on one of the projects that was on was characterizing this gene called pro DH, which is in the mitochondria. So, it was very interesting to see the presentation at the beginning, because that was sort of the beginning of a lot of my work, the mitochondria and the gene, to work on. That enzymes to create glutamine and that exists

inside your mitochondria. Glutamine is a major neurotransmitter for it to activate most neurons. It's been associated with autism, bipolar disorder, and schizophrenia.

Just sort of beyond that, this has been a very enjoyable meeting for me. But we also had the opportunity recently to speak with the Heart Foundation, which did a patient-focused program for themselves. And I can tell you that the voice of the patient document that came out of there has been shared pretty widely at the FDA, which is influential in the way that people sit down and think about the advice that we give as regulators to drug companies about the practical applications of how to design drug studies for populations of patients with mitochondria.

I am just going to reiterate or summarize some of the things that stuck out to me as we had our meeting this morning.

One of the things that struck me -- and this is probably well known to all of you -- is that 16 symptoms per patient is the average. For drug developers, that could be a little bit daunting because they're sort of used to looking at the world through a little bit of narrow pinhole of symptoms; therefore, drug targets the symptom. So, when we talk about a syndrome, that's a much harder problem because everybody here has some different cluster of all those symptoms. And that's what we see also, in what you were just discussing about how many drugs every single person is on here. The largest category in all that was like more than one, multiple things not even listed here, which makes it -- those sorts of factors are very important when drug companies or regulators are trying to help people design clinical studies because they want to know what's going on in the background, what else are you all doing in order to improve your lives? So that if we see improvement that, you know, it may be due to some change in where you're getting your generic vitamins, that maybe that generic one doesn't work anymore. It wasn't manufactured in the quality way that we expect drugs to come to the market through the regular process.

The other thing that I think was probably pretty important is some of the stuff that we've heard that struck me that I hadn't appreciated was driving is such a huge issue with all of you. Sitting in the back, we noticed that many times when people made comments there was a lot of head-nodding. That probably also means that -- and this group is not necessarily super representative of all your community, which also makes all the folks who are at home -- that's really important for you all to be inputting your experience also into this process, because the drugs that are going to be developed are also for you all, too. Not just the folks who have the sustainability to be able to be here. The factors that we have, the people participating, there's a bunch of people getting the diagnosis 10 and under and then there's this big gap, and then it was 30 and above. That's probably not necessarily realistic, but it's also representative of where you are as a community. This is probably unrecognized. Probably, as many of you said, I was diagnosed when I was 30 or 40s, but I look back and I had symptoms my entire life. Which means there's a lot of work as far as the foundation to get that diagnosis before it's starts, making interventions that are going to be coming out of this at a period of time where people

will benefit the most. Because the things that you talked about towards the end, where what was more important, regaining function or preventing further deterioration, the majority of people want to regain function. But, in reality, a lot of these drugs, when it comes to your children, is going to be not deterioration. You want that to continue and to have a life and not be the entire focus of everything. Like many people were saying, you wake up and the first thought is: What is mito going to do to me today?

The other very important thing that you talked about that needs to be appreciated is how heterogeneric it is and how unpredictable it is. You have a sort of general vocabulary what a good day is, and that may be very individual for each of you but it's understandable by each one of you, which is also important for drug companies to understand how to make a metric that describes a good day. Because one of the conversations we were having after we met folks like in the hallway amongst themselves is, how do you create a measurement to tell if intervention is working if on one day the person performs fine and the next day they don't? And we ask you to come into a clinic one day out of every six months. If we catch you on a good day, maybe that drug is working; if we catch you on a bad day, we're going to assume the drug is not working. Maybe it is. You've had a lot of series of good days, and that getting in the car and traveling to the site wiped you out and you performed worse. So, a lot of that information that you are going to get out of this meeting is really important for folks working in this space.

So, I am not going to continue anymore with my comments. Have your lunch, and hopefully too many people don't have to take lots of pills then, too.

(Applause.)

DR. YESKE: Thank you, Dr. Kempf, for those really insightful comments and key takeaways from this morning's sessions. It was really impactful. The good news is we are halfway. The good news is we have two more sessions to go today. But we certainly earned a break. If I was going to try to put my quick summary to it, I think the thread that I heard from the opening comments from Brian to Dr. Hirano's clinical overview to the panelists and the discussions that took place, and including comments from Dr. Kempf: Hope. Right? That nobody is giving up, and there's real hope that treatments are in development and that the patient perspective is an important part of developing those treatments. So that's why we're here today. I would say mission accomplished for the first half. Now we look forward to an afternoon, where we're going to pivot from adults with myopathies to pediatric patients with neurological manifestations.

We'll reset the room. For those of you who have joined us online today, we are going to be back at 1:00. So please plan to tune back in. For those of you in the room for lunch, it is set across the hall. I believe it is called the Chesapeake Room, directly across the hall. Again, we're going to really try to stay on time here because we have a full program this afternoon as well. So please try to come back a little early before 1:00, so that at the strike of 1:00 we can get started with our pediatric sessions.

Thanks, everyone, for your involvement, and enjoy the break.

(Applause.)

DR. YESKE: Hello, again, everyone to those in the room, but also streaming and watching online. We need just a couple more minutes to get everybody seated for the afternoon session, so we just ask for your patience. We'll get started in a couple minutes. Thank you.

We're going to go ahead and get started. We have a full agenda for the afternoon. As I mentioned before the break, we're going to pivot now to another really important subpopulation of the mitochondrial disease community, and that's the pediatric patients that have neurologic manifestations of mitochondrial disease.

This afternoon we'll run the same format. I realize that many people in the room were not part of this morning's session, perhaps online as well. So, we're going to kind of quickly go through the agenda and orient everybody as to how we move this forward.

This morning, I mentioned in my introductory comments that partnering and collaboration were critical elements to putting this meeting together, and that was over 12 to 18 months. So, we would like to start the afternoon session by providing an opportunity for two close collaborating organizations and their representatives to briefly share with you their thoughts on this meeting but also share with you some of the details of the afternoon agenda.

Without further ado, I'm going to introduce from Kira Mann, the CEO of MitoAction.

MS. MANN: Good afternoon, everybody. I hope you had a great lunch. MitoAction is thrilled to be here with you today to help raise our collective voices as we work towards new therapies and treatments for mitochondrial disease.

Stronger together. That is what today is all about, our united voices all aimed toward a common goal and together affecting change and keeping progress moving forward. It is truly an honor that you allow us, the patient advocacy groups, to walk with you on your journey of mitochondrial disease. We're honored to be here and working so closely with UMDF and MDA.

This afternoon we'll shift our focus to the impacts of mitochondrial disease and the pediatric community. Starting us off, we'll have a clinical presentation by Dr. Amy Goldstein who will discuss the neurological manifestations in children with mitochondrial disease. Participants will then have the opportunity to provide demographical information for children with neurological issues using the platform. We will then move into our first parent panel who will share their perspective on symptoms and the daily impacts mite. Their presentation will be followed by a polling session and then a moderated discussion with the panel.

To provide a run-through of the afternoon sessions following a short break and introduce our clinical speaker, please join me in welcoming Brittany Hernandez. Brittany is the Director of Advocacy for the Muscular Dystrophy Association, and leads MDA government affairs and

patient advocacy work. Brittany previously handled federal affairs for the March of Dimes, and spent over eight years working on health policy for Representative Steve Cohen of Tennessee.

Please join me in welcoming Brittany.

(Applause.)

MS. HERNANDEZ: Thank you. Again, I am really pleased to be here today in partnership with UMDF and MitoAction on behalf of MDA. I would like to just echo everything said about the importance of advocacy and the partnerships between these groups. Our voices are strong and they're stronger together and MDA is thrilled to support the work of partner organizations and all of you in this important effort to inform the FDA about the patient perspective on mitochondrial disease.

I will go through the agenda. After the break, at 2:40 p.m. we're going to break and start our fourth panel session focused on current and future approaches to treatment, followed by another discussion facilitated by James before we wrap up the day's closing remarks by Larissa and Phil.

At this time, I would like to welcome Amy Goldstein, who is the Clinical Director of Mitochondrial Medicine Frontier Program. She is an associate professor at clinical pediatrics, and an attending physician in the Division of Human Genetics at the Children's Hospital of Philadelphia. Thank you.

(Applause.)

DR. GOLDSTEIN: Thank you so much. It is just an honor and privilege for me to be here, representing my patients but also the clinicians who help take care of these children and adults with mitochondrial disease. I am the clinical director of the mitochondrial clinic at CHOP in Philadelphia.

I have also been a longstanding member of the UMDF community and now with MitoAction, helping to really push forward education. This is an area of medicine that doctors do not always get exposed to, and if you ask any clinician who is currently taking care of mitochondrial disease patients, it is most likely that they somehow encountered a patient in their early training that made a true impact on their lives. I had the great fortune of taking care of a little boy named Kevin in my pediatric intern year and knew I needed to specialize in mitochondrial disease. You will also notice that although I'm a child neurologist, I live in the Department of Human Genetics, and many of the doctors who take care of these children and adults are either neurologists or genetics doctors, because this is a genetic disorder that does have a very large burden on the neurological system. So, again, we are going to focus on neurologic manifestations and pediatric patients.

I'm also the immediate past president of the Mitochondrial Medicine Society. Amel Karaa who is here is the current president of the MMS. This is a group of clinicans that we started so that

we really had an opportunity globally to speak with each other about care, to see if we could unite standards of care and develop practice parameters for our patients.

I am going to go ahead and get started.

I want to talk a little bit about the burden of disease, and you heard some this morning and you'll hear this afternoon, these are very complicated disorders because there are a multitude of symptoms. Dr. Hirano mentioned this morning that, on average, patients with mitochondrial disease have 16 symptoms and, once again, these can be multisystemic. So, they're general symptoms that can affect any organ system, but there's a huge burden on the nervous system because, again, these are disorders of energy metabolism. The mitochondria are not making enough energy for that organ to run, and, generally speaking, the organs that require the most energy are the organs that suffer. Our nervous system requires an enormous amount of energy to run. We're talking about the brain, the nerves, and the muscle.

I also wanted to talk a little bit about the burden on families. This is a genetic disorder. There are sometimes several people in one family, either multiple siblings who are affected and sometimes also a mother is affected. So, it can be a huge burden on the family, whether the mother herself is trying to take care of her sick children, or the children are taking care of their sick mother, or a family has to handle multiple children in one family that are all disabled or affected in some way. This can again really put a huge burden on a family in terms of costs, in terms of marriage, in terms of quality of life. And sometimes families have to make really hard decisions about whether to send their child to school, or whether they can send their child out to play on the playground or have playdates. It does take a huge toll on the family.

The other burden is actually on the medical system. Our patients with mitochondrial disease, both adults and children, spend more time in the hospital on average than other people with chronic disorders and they have a longer length of stay, and we published this in a paper about two years ago coming out of our CHOP group.

In terms of management, again you have heard that there's no cure or treatment for mitochondrial disease, per se. There's no current FDA-approved medication. That does not mean that this disease isn't treatable, and we've heard this morning several examples of symptoms that are managed with specific medications. So, I want to make sure that people also get the message that the symptoms we treat the same as we would treat any other disease. Meaning, if a child has epilepsy, they're treated with anti-seizure medicines; if a child has spasticity, we treat them with medications that treat that spasticity; if they have reflux, they're treated with reflux medication. So, while there are many symptoms, those symptoms for the most part can be treated. But we're still looking for a drug that can actually treat and cure the action genetic defect and/or the lack of energy production, and in reactive oxygen that is happening in the cell.

There are very few current trials currently open for our patients. There was a review done several years ago by Patrick Chinnery and his group in England, and they found over 1,000

publications of clinical trials that failed. There were many reasons that those trials failed. Some of them contained less than five patients. But for the most part there was no unified approach to these clinical trials. It's very hard for us to develop and know what outcome measures we need to be using for some of these clinical trials. This is another huge issue that we talk about among our community, what are we going to use to follow these outcomes? How are we going to know if a drug is working or not?

There are empiric trials of supplements that some of us use, and we've heard this talked about this morning as the mito cocktail. A few years ago, through the Mitochondrial Medicine Society, we decided to survey U.S. physicians and asked them: What do you use in your mito cocktail? And we got about 36 different answers. Some of us use one, some of us use six, some of us use 12 different vitamins, some of us use none. These have never been reported to be 100 percent effective for anyone. A lot of us use them anecdotally because patients have reported benefits for some of these supplements. But, as was mentioned this morning, it may take very personalized approaches to therapy and it may depend very much so on what exactly is wrong in the mitochondria. I'm going to show a slide where it talks about treatments again, and then I will try to give you a sense of where all the targets for therapy are.

When I say it is not universally accepted, if you go to a mito clinic in Europe they're generally not prescribing supplements or recommending supplements because, again, they have not been proven to work in a randomized controlled trial.

I mentioned standards of care. This is a little bit difficult to develop because there really haven't been a lot of standards of care that have evolved from mitochondrial disease and, again, it has been difficult to do really well-run clinical trials. But there are clinical networks that have come up, and Dr. Hirano mentioned the NAMDC consortium this morning and that's one very nice network. We have also, and on that side, just established the Mitochondrial Care Network. In your bag there's a pamphlet that talks about the Mitochondrial Care Network, and again that's really our effort to make sure that doctors who are seeing mitochondrial disease patients have a venue to speak to each other, have a venue to put together care guidelines and standards of care and publish them so that our patients have something to rely on when they go to their other physicians or their emergency room.

Again, we're going to start talking about clinical features. This is a really nice paper that was published by Grainne Gorman and her group. What you see on the left in green are all of the other non-neurologic systems of mitochondrial disease, and what you see on the right are the neurological systems involved. Again, from head to toe, every organ can be involved in disease. We do see a lot of heterogeneity, again, in one family with everyone carrying the same gene mutation you can see different degrees of different organ involvement, and we see this play out all the time in many of these families. The brain certainly can be involved on many different levels, from migraines to seizures to stroke-like episodes to dementia. The spinal cord can be involved. The brain stem of the brain can be involved, and that can get very scary in children and if they get an infection they can actually have a metabolic lesion show up on their

brain stem and shut down their respiratory center and suddenly stop breathing. You have heard a little bit this morning about how unpredictable these disorders can be and how one of the burdens on families is to know, right now things are stable, but that can turn on a dime and something can come out of the blue and be a severe new symptom.

We'll also talk about peripheral nerve involvement and muscle involvement. When we talk about symptoms, the poll from this morning looking at the adults, a lot of the symptoms had to do with muscle involvement, fatigue, exercise intolerance, and weakness, and I'll be curious to see how the polling ends up this afternoon from our pediatric group.

So, one of my favorite things to do is to teach, as neurologists and adult neurologists, what we should be looking for specifically. There are many people with migraine, there are many people with epilepsy. So, what are the red flag symptoms that neurologists need to look for that are the clues that a patient can have a mitochondrial diagnosis?

Stroke again is very common in the adult population. When we talk about stroke in neurology, we're really talking about stroke that is caused by a blood clot or a bleed. When you're dealing with mitochondrial disease, one of the tip-offs is that when you look at the imaging it's not in that vascular distribution, this is not a blood vessel or a clotting problem. This is actually a brownout or blackout of the brain, and you get these lesions that are more metabolic and really demonstrating a crisis in the energy demand.

Basal ganglia lesions are another form MRI, and you'll hear about a syndrome called Leigh Syndrome. Leigh Syndrome, there's at least 90 different individual genetic causes of Leigh Syndrome, but the common features are developmental delay, commonly to have regression with illness. And then when we look on neural imaging, we see bilateral -- so both sides of the brain -- typically symmetric but not always lesions in the basal ganglia. So, the deep gray matter structures. Sometimes also involving white matter of the brain, sometimes involving the cerebellum. But when we see a scan that looks like that and then we start getting the history and put it together call, this Leigh Syndrome clinically. This was discovered by Denis Leigh, who was a British pathologist in 1951, and now we find it on MRI imaging.

The next category down is called encephalopathy hepatopathy. It's a big mouthful for something that really boils down to you have brain disease and liver disease that coexist. The scariest presentation of that is when a child with epilepsy is given divalproex acid, or what's commonly called Depakote, and they go into fulminant hepatic failure. This is almost universally fatal when it happens. There's no rescue for this. Children who have in the past received a liver transplant for their liver failure usually die in a short timeframe thereafter because it accelerates their neurologic disease.

This is what we call Alpers-Huttenlocher Syndrome, a devastating disorder caused by mutations in a gene called primary gamma. There are other disorders, other mitochondrial disorders that are also susceptible to this combination of liver failure, seizure disorder, and brain disorder, and

Depakote can also cause some issues with that. But, again, certainly this brings up for me that condition of Alpers Huttenlocher Syndrome

Epilepsy is the next category. Again, for a child neurologist 50 percent of what we see in clinic is epilepsy. So how do you know who has mitochondrial disease and, more importantly, as I just mentioned, how you know it's safe to give Depakote to? How do you know you're not going to really harm that patient? Some of these children come in with a condition called epilepsia partialis continua, which is a simple focal seizure on one side of the body but constantly twitching, and I have had patients that can twitch for months at a time. This can be very difficult to get under control. This is usually related to a new metabolic stroke in the brain either from a condition called MELAS or the condition called Alpers Huttenlocher Syndrome. But it can be from other mitochondrial disorders as well.

When people have myoclonic epilepsy or myoclonus, that can also be related to another mitochondrial disease called MERRF. We heard a little bit about MERRF this morning. Also, there are sometimes children that come in and their very first seizure is epilepsy, sometimes with fever, sometimes not. But when we see kids that come in and we really can't get their seizures under control very well, usually we have them do neural imaging and it's the labs that will suggest mitochondrial disease. It can start off very stormy.

We have heard a little bit about cognitive decline, and there are children and adults that if they get sick even with a common cold, when we talk about regression, we're talking about major regression. They can literally lose the ability to walk, to talk, and require months and months of rehabilitation to get back to normal. This is very atypical.

One of the things we stress in neurology, if you have a child that's been labeled with cerebral palsy -- which is supposed to be a static condition, usually from some type of birth trauma early on. If they undergo regression and really lose their skills during an illness we have to think differently about what their diagnosis can be.

Then there's ataxia. Ataxia is a balance disorder. People who have trouble walking but also trouble with their speech, trouble with eye movements called nystagmus, and sometimes on MRI we see cerebellar atrophy, so literally getting smaller. Sometimes this will go along with having basal ganglia lesions or a combination with epilepsy. Again, ataxia, there are many genetic forms of ataxia, many other causes. But when we see features that are together or with multi-system disease, we start thinking about mitochondrial disease.

The eye can also have a lot of manifestations from optic nerve atrophy to retinitis pigmentosa to something called chronic progressive external ophthalmoplegia, and this affects many people with many different types of mitochondrial disorders. Again, the eyes can really give us a nice clue about mitochondrial disease. Many of our patients we have go annually to an ophthalmologist to help us screen for these symptoms.

And then there's also sensorineural hearing loss, especially at a young age and especially when it's in combination with other symptoms, especially diabetes and then other neurologic symptoms. So, if we see a young adult who is short, who has a history of deafness and diabetes and is coming in with their first stroke, that's MELAS until we ruled out another condition.

I want to talk a little bit about the therapies and cures. Again, there's no proven effective therapy or cure at this time. That's one of the reasons we're here. We want to hear from the patients and parents that you're about to hear from in the next few hours. Individually, these are rare disorders. But under the umbrella, this is not uncommon. As Dr. Hirano pointed out this morning, the incidence rate is thought to be about 1 in 4,000 at this time. Again, there's a lot of heterogeneity but there's also a lot of very common symptoms and patterns, and that's what we really want to stress and talk about.

Two other things that come up besides drugs are the value of exercise and the value of nutrition. We're really trying to wrap our heads around, how are we going to study this a little bit more? Our patients know that exercise is really important. It can double the number of mitochondria you have if you do aerobic activity. If you do resistance training and you have a mitochondrial point mutation, you can literally turn over the mutation in your blood and reduce the mutant mitochondria and increase the normal mitochondria. That's what we call heteroplastic shifting. But how can we make sure our patients are exercising safely and effectively, especially when fatigue is a huge issue? This is an area that we're very interested in figuring out, and one of our colleagues is working on what he likes to call exercise in a bottle. How can we trick the body into thinking it's exercising and really set off that cascade of chemicals and hormones that can improve mitochondrial function?

There's also a lack of clarity on the optimal diet and nutrition in mitochondrial disease. Our mitochondria are trying to make energy from the food that we eat, and so one of the questions is, can we capture that in some way and really learn and treat based on optimal nutrition?

Clinical treatment trials, as I mentioned earlier, they've been limited in primary mitochondrial disease. They've been done but, unfortunately, none have proven to be efficacious enough for our patients. Some of this again is because there's not been a universal clinical trial designed, and when we're talking about individual disorders or many different symptoms, we have to be very careful about how we design these trials.

We also need to be careful what outcome measures we pick, and Dr. Hirano helped me on a project a few years ago where we, under the NINDS, participated in their project called Common Data Elements and put together a really nice list of possible outcome measures to use in mitochondrial disease knowing that we will probably need many different types of outcome measures to capture all the symptoms that we see in our patients.

Current trials that are ongoing right now do require a genetic diagnosis, and this is a question that came up in the morning session. The reason is that we want to make sure that we know who is in the trial, what genetic issues are happening, what cascade happens from there, so

that we can really determine, is there a drug that might benefit one group of patients and possibly not the other? One of the things that I think is important to also know is that not everyone right now has a genetic diagnosis. Despite the most up-to-date testing with molecular sequencing, we're still not able to capture everybody. That hopefully will catch up to us in the next few years as we go through the rest of the unknown genes, and hopefully people will arrive at a genetic diagnosis.

Some of the trials that have been tried before, I'll just mention quickly. Co-Q10 a lot of people take as part of their mito cocktail. When it was opened and offered as a clinical trial, people didn't want to risk going on a placebo when they could go down the street and buy that from their pharmacy and it was very hard to fill that trial. There's a drug called Idebenone, which is now approved in the European Commission for something specifically called Leber's Hereditary Optic Neuropathy, LHON. EPI-743, I want to mention, this is a drug formerly from ^ Exin Pharmaceuticals now called Bioelectron. And we learned something so important from the trial, which was that this was a drug developed for Leigh Syndrome. And what we learned is they do want children who showed progress in their disease -- meaning progression, a downward course -- over the previous year. And we had trouble filling that trial quickly because we learned that many children with Leigh Syndrome are stable, and that was really earth-shattering in our community to learn that what we thought was a rapidly progressive disease could be met with periods of stability.

Then there of course are some other drugs, some that are currently in the pipeline for clinical trials.

This is the last slide that I just want to mention. And again, there are just specific treatments for primary mitochondrial disease. Something I want to point out quickly in case it comes up with our session, is that right here is what we call the energy-making factory, complex 1, 2, 3, 4, 5. At the end of this is where you make ATP. Some patients do not have a known gene cause of their disease, but they know that one of these complexes is deficient. So, if you heard somebody either earlier today or will hear later this afternoon talk about their disease as complex 1-3 deficiency, that's what they're talking about.

But what this slide also points out is again the many different routes that we have for possible treatment and why we try the cocktails. In the mitochondrial DNA, you see the complexes and we know that certain complexes really benefit from B vitamins as a cofactor, for instance. Or we know that RG might be helpful for vasodilation in metabolic strokes, for example, or creatine can help muscle make more ATP.

As we learn more and more about these diseases and where the gene defect is and where the pathway gets interrupted, we hope that we can come up with a personalized therapies for people when we know either the common pathway that's involved or the gene defect that's involved.

There are many different papers that have gone over the cocktail, and right now I would say this is certainly not the only list that exists. Once again, when you survey different clinicians, they may come up with more or less the same list. But in our most recent publication by the Mitochondrial Medicine Society, this is the list that we currently recommend. And, again, anecdotal. Some patients respond, some patients don't respond. But, once again, just to highlight the need for better outcome measures. I may put a patient on a mito cocktail; they'll come back in three months, and I'll say, So, do you think your child is better? And a parent may say, I'm not sure. And I don't know, either, because I don't have good outcome measures. I can know if they've been in the hospital or not. Usually a couple other things have happened between appointments. Maybe they have a cold, maybe it's wintertime and they're not able to get out and play as much as usual. So, it can be really difficult to know if the cocktails are working or not. This is why I think we're now moving into an effort to really look at quality of life measures, patient-reported outcome measures, so that our families can follow the effects of what we're doing and only going to help us when we get into more rigorous trial design.

That is my last slide. With that, I want to thank you very much for your attention.

(Applause.)

MR. VALENTINE: Thank you, Dr. Goldstein, for that nice overview and clinical discussion of mitochondrial disease in children with neurologic manifestations.

For those who may not have been here this morning that are joining us for our afternoon session, my name is James Valentine, and I will be serving as your meeting moderator for the remainder of today's agenda. Just so you know who I am, I am a consultant that has been working with UMDF in planning this meeting for over a year now and have worked across many different disease areas, particularly in rare diseases, to help bring the patient voice to drug developers and the Food and Drug Administration. And before I was doing that as a consultant, I was actually at the FDA for six years serving as a patient liaison, helping to bring the patient voice in to FDA's internal decision-making.

So now as we transition into our patient voice session for this afternoon, where we're going to be hearing from patients and their caregivers representing children with mitochondrial disease that have neurologic manifestations, I wanted to provide just a brief overview of how that discussion will go, knowing that many of you were not here this morning to receive the benefit of this morning’s sessions.

As was presented, our discussions are going to be split into two primary topics. We're going to first focus on the symptoms that matter most to you, and then we're going to build on that discussion and cover a second topic which covers current treatment as well as your preferences for future treatments.

For each of those two discussions, we're going to hear from the patient community in a number of different ways. First, we're going to hear from panels of patients and caregivers. They're

going to set a good foundation for our discussion, and we'll then broaden it to include those of you who are in the audience. We want you to know that the panelists were selected to represent a range of experiences with mitochondrial disease, and that we hope to supplement that and further that with all of our audience participants.

After each of our panels for both of those two topics, we're going to move to polling questions, which is going to be a tool for us to aid in our discussion. You'll be able to use your phones, tablets, laptops, any web-enabled device that you have, whether in person or following us along online to answer those questions in real-time. We do ask that only patients and family members or other caregivers of children with mitochondrial disease that have neurologic manifestations or representing that perspective participate in a polling questions.

We're going to start out with demographic polling in just a couple of minutes, but for that all patients and caregivers are invited to respond. Then for our second and third sets of polling questions, which are focused on each of our two topics, we'll ask that only one person respond on behalf of each individual patient represented here today. What I mean by that is if you have been the patient and the caregiver is present, we ask that if the patient is willing for them to be the one responding to the questions. If not, if they choose not to, then have a caregiver do that. Or if there's multiple caregivers in the room, please choose to have one of you answer these questions. Of course, you can do it together, but just have one response for each individual patient.

Once we finish the polling questions, we'll broaden the discussion and have a facilitated dialogue here in the room. I will be building on the discussions that we have with the panel and inviting you all to answer questions that I have related to the topics. When we get to that point in time, to participate you'll just raise your hand. If you can just please start by saying your name and, if you know it, your mito diagnosis. That way we can keep track of it for purposes of our summary report. And last, but not least, while this is not occurring live here today, we are going to be sending out the web to all of our participants today. So those online will have a chance to share their experiences and preferences. And those in the room, we do have limited time, so if there are additional things you would like to add you can use that survey to share those additional perspectives.

As a result of all of those things, UMDF and their collaborators are going to be developing a Voice of the Patient Report, which is the official summary of today's proceedings that will be provided to the FDA as well as the broader community to help bring your voices to different decisions that are made by drug developers as well as regulators.

Before we jump into our first polling, the last thing I would like to cover is a few ground rules for our discussion. First and foremost, we encourage patients to contribute to the dialogue. When we use the term patients, we are kind of using that as shorthand to mean those that are representing the personal experience of the disease. So that includes not only patients, but also their family members and direct caregivers. Even if the patient is here today and you're a

caregiver, I want you to feel as though your voice is important, too, and encourage you to participate and share.

We have others in the room that are not patients and caregivers, including FDA officials, drug developers, as well as clinicians and researchers. They are here to listen only, so we ask that those people please not try to participate in the dialogue today. Similarly, for all of our patients and caregivers in the room, we aren't going to be posing any questions to any of those stakeholder groups.

We are going to be focusing our discussions specifically on symptoms and treatments. I know that your personal experience with mitochondrial disease will expand beyond the questions that we will be discussing. But for the purposes of today's meeting, I do ask that you keep your comments focused on the questions at hand. I know that your views expressed will be personal, and to that end it's going to be very important for each of us to respect one another in the course of sharing both common and uncommon experiences with mitochondrial disease. To help us with that and allow as many voices as possible be heard today, I do ask that you try to be concise in answering these questions so that way we can hear from as many people as possible.

So, with all of that out of the way, we're going to go ahead and jump into our first set of polling questions, which are going to be questions for, again, patients and caregivers of children with neurologic manifestations of mitochondrial disease.

On this first question, I want to make sure that everyone is able to access a polling question. So either on page 5 of your handout that you received in the packet or at the top of the slide you can see that you can from any web-enabled device either go to a website and type in PollEV.com/EnergyInAction; or, if you don't have mobile web capabilities, you can use text messaging where you can text to the number 22333, put in the message EnergyInAction, and that will put you in the system and then you can actually type in your responses and send them as text messages as we go through. But I will say the web interface is nice if you are to access that.

Let's go to our first question. If anyone is having any issues accessing the polling, please raise your hand, and someone will come by to help make sure that you can get into the system. We want to make sure that we capture everyone's responses.

Our first question -- which a number of people already answered, which is great: Which of the following best describes you? Your options are, A, parent or caregiver of a child who has a neurologic manifestation of mitochondrial disease; or, B, you have lost a child who had a neurologic manifestation of mitochondrial disease.

It looks like responses have already come in for this. It looks like, from this, that we have represented here in the room and on the web today the vast majority are parents and caregivers of children who have neurologic manifestations of mitochondrial disease. But we

also have representation from those who have lost a child who had neurologic manifestations of mitochondrial disease. It will be important to hear both of those perspectives today.

Our second question is: Where do you currently reside? Your options are, A, the U.S. Pacific, including California; B the U.S. West and Mountain region; C, the U.S. Midwest; D, the U.S. South, including Texas; E, the U.S. northeast and New England; F, Canada; G, Mexico; H, outside of North America; or, I, other. Please let us know where you currently reside.

While the final results are trickling in, it looks like the majority of individuals represented today are from the U.S. Northeast, New England. This is similar to this morning's session, and probably has something to do with the location of this meeting. We also have good representation from the U.S. South, as well as each of the other U.S. regions. It doesn't look like we have anyone from outside of the United States.

Our next question for you is: Do you live in, A, a city; B, a rural area; or, C, a suburban area?

As the final results trickle in, it looks like the majority of people, a little under three quarters, are from suburban areas; then from the cities, and a few people representing rural areas.

Our next question is: How old is the patient now? The options here are, A, 0 to 10 years old; B, 11 to 17 years old; C, 18 to 20 years old; D, 21 to 30 years old; or, E, greater than 30 years old. If you're representing someone that has passed, you don't need to respond to this question.

For purposes of polling, the question was, if you have more than one affected child, how do you answer these questions? A great question. For purposes of polling, select one of the two children -- or however many -- one of the children to respond to these questions for, and do that uniformly throughout. In the portion of the discussion, please feel free to draw from all of their experiences. If there's multiple caregivers and multiple children, you can provide them. If you have more children possible responding, please choose particular children to respond to that.

Good point. In order to collect some of this information, we'll collect it today. When the online survey goes out, it is going to include the polling questions as well as discussion questions. So you can go back in and fill out the survey for your other children.

It looks like the largest cohort we have represented today are parents of children who are 0 to 10 years old. However, we also have good representation for the 21 to 30-year-old category, but we really have representation across the board both here in the room and online.

Our final demographic question for you is: At what age was the patient diagnosed with mitochondrial disease? Here, your response options are, A, 0 to 10 years old; B, 11 to 17 years old; C, 18 to 20 years old; D, 21 to 30 years old; or, E, greater than 30 years old. What was the age that the patient was diagnosed?

It looks like about a little under three quarters of those represented today, the patients that they're representing were diagnosed between 0 to 10 years old, after that 11 to 17. Nobody

from 18 to 20 years old, but some were diagnosed in the 21 to 30-year range. And nobody over the age of 30 at their age of diagnosis.

With that, that concludes our demographic polling. We're going to turn to our first panel discussion, which is part of our first topic. I'll invite our first panel up to the stage.

During this topic, which is on the symptoms and other burdens of living with mitochondrial disease, the panel through our polling and audience discussion, we're going to explore a number of different issues. We're going to ask you to weigh in on, what are the symptoms and health effects that have the most significant impact on your life? What activities in your lives are impacted due to your mitochondrial disease and those different symptoms and burdens? We're also interested in knowing how those things vary over time -- so from day to day, week to week, or month to month -- but also, over the course and progression of the disease, how these symptoms and burdens and impacts changed over time. And lastly, during this first topic we also want to explore, what are the things that you worry most about, about your loved ones with mitochondrial disease, thinking about the future?

To kick us off on this topic we have a panel for you today. We have Danny, Ann, Annette, Stacy, and Heather who are going to be speaking to their personal experiences with mitochondrial disease.

I'll turn it over to Danny to start us off.

MR. MILLER: My name is Danny Miller. I live in Corte Madera, California, with my wife Nikki and our two sons Carson and Chase, ages seven and six. Carson and Chase have MEPAN Syndrome, an ultra-rare condition that results in impaired mitochondrial fatty acid synthesis and has rendered them unable to walk, move independently, or talk. MEPAN is a neurodegenerative condition, so their physical symptoms may worsen and they may eventually suffer severe vision loss. Every day, my wife and I and their aides and caregivers at home and school do nearly everything for Carson and Chase from the time they wake up to the time they go to bed. What I am sharing today is told through the eyes of our older son, Carson. He's the one in the gray sweater.

My body doesn't work like it should, and it's hard for my brother and me to move like other kids. I tell my brain I want to move my arms and legs, but they don't listen. I used to be able to crawl a little bit, but not anymore. At night when I'm sleeping, my body hurts because I can't roll over by myself. I can yelp for my mom or dad to wake them up and come roll me over, but they don't always hear me and I have to just lay there and hurt.

My dad gets me and my brother dressed in the morning for school because we can't open and close our hands. We have to wake up extra early because my dad has to change our diapers, put our clothes on for us and get our AFOs on while mom makes us breakfast. I'm seven but I can't feed myself, so mom feeds me and dad gets us into our wheelchairs and down the ramp next to our house and into our van to go to school. We have a special van with wheels, and lots

of special equipment for our house like standers, walkers, therapy benches and bath and potty chairs.

Chase and me get to our classrooms at school and our helpers get us out of the van and set up in class. We have a lot of helpers. My helper at school is named Jason, and he is with me every day and helps me move around the classroom in my wheelchair. I can't sit with the other kids on the floor because I will fall over if I try to sit by myself. When I was three, I used to be able to sit on my own, but I can't anymore. My hands don't work very well, either, and I can't hold a pencil so Jason has to write for me. I'm learning to use a computer that works with my eyes to help me talk, but it's really hard to use because my eyes get tired, they don't always look where they're supposed to, and the rest of my body moves even when I tell it not to. I used to be able to walk a little in my walker, but don't do that as much. My brother can't crawl and doesn't use his walker much because, like me, his legs don't listen to his brain either. The other day some kids in my class were playing tag after school and my dad pushed me in my wheelchair to chase after some of them so I could play. That was fun, but I really just wish I could do it on my own. I would be okay with just walking on my own, too, so I can go where I want to and not have to wait for a helper to push me in my wheelchair. I have to wait around for a lot of things.

My brother can move by rolling his body and he can hold things with his hands. But I can't. I have some sign language that I use to tell people what I want, and now most days my hands and fingers don't work like they're supposed to and it's hard for people to understand my signs. I can't talk, either, so it's hard for me to tell people how I'm feeling or what I need. It's hard for my brother, too. We have a lot to say, and it makes me sad.

Sometimes I see my mom and dad not smiling, and they look kind of worried. And I know they get worried on days when my body gets tight and they have to give me soft food because it's really hard for me to chew and they think I might choke on something. Mom might have to start putting our food in a blender soon so we can eat it. And she looks worried when our teachers tell her how tired we were at school. My brother Chase puts his head down and lot when he needs to take a break and rest. MEPAN makes us really tired. My mom isn't as strong as my dad, and since we might be as tall as dad someday I think she's a little scared she's going to hurt her back again when she's getting us into our chairs or putting us on the potty. At home she's always trying to do things that our therapists do, like trying to teach us to chew better or sit up by ourselves, but I don't like that. I just want her to be my mom.

I wish my brother and me could just use our hands to play with Legos, our arms to have light saber fights, and use our legs to walk, and not have to keep going to a bunch of therapies, take pills and drink vitamin drinks every day to help us sit, stand, and move like other kids do. My dad says that there are a lot of other kids whose bodies don't work so well because of things like MEPAN, and that there are people trying to find out why and help them. It's okay that everybody is different, but nobody should have different experiences because of things like MEPAN. That's not fun for anyone, especially little kids like me.

(Applause.)

MS. KORSEN: In 1995, my husband Howard and I won the genetic lottery. Hello, I'm Ann Korsen from Mt. Laurel, New Jersey. I have two beautiful daughters. Our older daughter, Dana, lives in Washington, DC. And I would like to thank you for the opportunity to talk about our younger daughter, Mara. Ironically, Mara's name in Hebrew means gift of peace. From the moment she was born, she was not given peace. When she was three months old, she was hospitalized with failure to thrive. After many tests, it was determined that, among other things, she had microcephaly, cortical blindness, epilepsy, cardiomyopathy, and a mitochondrial myopathy. Her neurologist at the time said, although testing did not prove it, he instinctively felt she had a pyruvate dehydrogenase complex deficiency. We did not receive the final diagnosis of PDCD until shortly before Mara's 21st birthday. Howard and I were told that Mara would probably not live through her first birthday. We had to have the conversation that no parent should ever have -- where to bury our baby girl. We still refuse to buy burial plots, partly from denial and in part because Howard and I believe in a good fight. Our gift has fought hard. After heart surgery -- PDA and collateral -- six bouts of pneumonia, over 100 ear infections -- I stopped counting, but Howard has not -- swine flu in 2009, and many other illnesses, hospitalizations, and trips to the ER, Mara is very much alive and now 23 years old. Her life is not without complications. She is severely developmentally delayed, nonverbal, confined to a wheelchair, has gastroesophageal reflux, and a metabolic disorder which makes it difficult for her to digest milk proteins. Mara is small in size and we struggle to keep her weight appropriate for her four-foot, seven-inch frame, which is about 70 pounds. She is happy and deeply loved by all. Mara now attends an adult day program and enjoys listening to her special jazz music. Howard and I come from a family of music lovers. We played all kinds of music for her, but she's settled into jazz, very specifically Ella Fitzgerald, Louis Armstrong, and Nelson Riddle.

Despite how well Mara is doing, we struggle with three key symptoms. These are: Managing her epilepsy, her reflux, the ability to chew and swallow, and her physical limitations and blindness. Now that Mara has matured, we sometimes struggle with managing her seizures. They appear to be cyclic and occur most frequently just prior to menstruation. I never thought I would still be sleeping with a baby monitor, but we still sleep with one eye open and one ear to the monitor. Mara is also sensitive to extreme heat and cold, either of which can bring on a life-threatening seizure or a pulmonary issue. Mara sees her neurologist regularly as a result of her seizures and mitochondrial disorder.

We are a social family, and enjoy eating and cooking and meals with friends and happy hour. This is the environment Mara was born into. She loves to sit around a table at home or in a restaurant and listen to the chit chat. Although she is nonverbal, she has always managed to add her two cents where appropriate with a razz, eye-rolling, or cooing. We were determined she would enjoy a family life. However, her mitochondrial disease had other plans; when she was approximately nine years old, her metabolic disorder manifested itself where it caused her

the inability to keep food down. As a result, her weight dropped from 55 pounds to 40. She was on the verge of being hospitalized for failure to thrive and moments away from a feeding tube when her gastroenterologist suggested we try Peptamen Junior orally. She drank it voraciously and, more importantly, held it down. It now supplies approximately 75 percent of her caloric intake per day. She is very happy and enjoys many different foods as long as we chop them up or puree them for her. With Peptamen Junior and careful preparation of her food, the possibilities of her failing to thrive from low body weight and poor nutrition or having life-threatening choking are significantly diminished. These are two of our biggest fears over her lifetime.

With regard to Mara's inability to walk and talk and care for her own physical needs and cortical blindness, our biggest problem over the years has been to make sure she is in a safe environment. Of particular concern is having a safe sleeping environment and a safe play area because Mara cannot see or sense dangers. She has occasionally fallen out of bed or hit her head. To accomplish this, we have childproofed the den, the room in which Mara now spends most of her time at home, and purchased an appropriate child hospital bed.

Mara's condition and limitations have changed our lives significantly. Family vacations or extensive trips have not been an option. Extensive care has to be taken in the environments she can go to, especially if a relative or friend we wish to visit is ill. The 2018 trip to the UMDF meeting in Nashville was the second time Howard and I have been away in almost 23 years. We do not expect another trip for an extended period of time to happen for many years to come.

(Applause.)

MS. COTTE: Hello. My name is Annett Cotte. I live in Atlanta, Georgia, with my husband Sebastian and our eight-year-old son Jagger. I am here today to share Jagger's story.

Jagger suffers from developmental delay, seizures, cardiomyopathy, scoliosis, gastroparesis, neurogenic bladder, respiratory failure, and much more, all caused by his mitochondrial myopathy, specifically Leigh's Syndrome. His early diagnosis at age one meant that his symptoms are severe and life expectancy short. We were told he wouldn't live past the age of four. He is eight years old now and still fighting.

Developmentally, Jagger is probably the age of a three-month-old. He has muscle weakness and is unable to hold his head, sit, stand, or walk. He spends the majority of his time lying in bed, is dependent on oxygen 24/7, has a GJ feeding tube, and requires daily IV infusions. However, one of the most frustrating and challenging symptoms is the fact that Jagger cannot communicate verbally, making it nearly impossible to figure out what is wrong with him when he is screaming and arching in agonizing pain.

I will never forget Jagger's first mito crash which occurred two months after his first birthday. We were at the hospital once again for feeding issues and he screamed for an entire day until

he became too exhausted to breathe. He turned blue as he continued to cry but was unable to catch his breath. I vividly remember pushing the nurse out of the way reaching for the oxygen mask attached to the wall so I could do manual ventilation. At this point, he stopped breathing completely. He was quickly intubated and remained on a ventilator for several days. We stayed in the hospital for one month until Jagger stabilized enough to go home on hospice care.

With each mito crash, pneumonia, or even a simple cold -- the last one leading to complete heart and respiratory failure and 15 days on life support -- Jagger's baseline keeps regressing. We live in constant fear that each episode could be his last. His pain is getting worse and his seizures are increasing. Outings have become rare because sitting upright in his car seat or wheelchair is exhausting and painful for him.

Jagger is and always will be the center of our universe. My husband Sebastian and I carefully coordinate our schedules so we can first and foremost meet Jagger's needs, and without nursing or help of any kind this is tricky most days. Any errand has to be carefully planned and communicated to ensure none of Jagger's competing priorities will interfere with such outing.

Jagger typically wakes up between 12:00 and 3:00, at which point he claims our king-size bed all to himself spreading his arms out left and right. If I'm lucky, he may leave me about ten inches. He flops his arms continuously for hours due to severe movement disorder, making it feel possible to sneak in my 1,000 kisses I had promised him when he opened his eyes. I use all available pillows to construct what could resemble the Great Wall of China, but Mr. Houdini manages to bypass my fortress and sinks his right fist into my left eye socket. I continue to snuggle and sneak in kisses knowing quite well I may walk away with facial bruising. But it's all worth it. Some may ask why I don't just get up. Well, it's not that simple. Due to an underlying respiratory problem, Jagger has lots of secretions and two to four hours after he awakens are spent suctioning him putting a tube down his throat, often over 200 times a day and night. His secretions not only cause him to cough a lot, but many times he gags himself and vomits, which commands the presence of either myself or my husband to be next to him at all times to ensure he doesn't choke or swallow which can cause aspiration pneumonia, something he suffers from frequently and which most times require hospitalization.

I sneak in as many kisses as possible, and on a good day he blows me bubble kisses, makes noises like a motorboat or babbles a-hah and umpa-umpas. I procrastinate a bit on his three to four mandatory breathing treatments and enema which are part of his daily routine. Once the treatments start, Jagger usually becomes severely agitated and the rest of the evening is spent sitting with him, holding him, praying he won't start screaming, and clutching his chin in an upward position to open his airway so he can breathe more easily.

We will never stop in seeking the best possible care for Jagger. He is currently enrolled in a drug trial specifically for Leigh's disease, and we moved cross-country a couple years ago to seek alternative treatments for his seizures and pain as pharmaceuticals are no longer doing their job. We really do not want to put him on sedative medicines as this will only prolong his

life but won't actually help with his quality of life. His body would be with us, but his spirit would be gone. No more smiles, no more ah-hahs and umpa-umpas. I am devastating thinking about what his future might look like. No one wants to lose their child, but also no one should have to suffer so much. As I was sitting down writing this, Jagger has just suffered his third seizure of the day. We know the future isn't bright for our sweet boy; however, as long as Jagger has the energy to fight, we fight for him and with him, the reason why I'm here today sharing his courageous journey. Thank you.

(Applause.)

MS. TAYLOR: Hello. My name is Stacy Taylor. Thank you for the opportunity to tell you about my family. My husband and I live in Baltimore, just down the road, with our four boys, Lucas, Benjamin, Marshall, and Sam. Marshall and Sam are my youngest at 11 and 10.

In 2014, Marshall and Sam were diagnosed with mitochondrial disease, specifically combined oxidative phosphorylation deficiency, type 11. Mito affects the boys in similar but different ways, with Sam being more significantly impacted. They both have a laundry list of diagnoses, including mysterious episodic vomiting, leukodystrophy, intellectual disability, global developmental delay, hearing loss, strabismus, cortical visual impairment, incontinence, epilepsy, gastroparesis, kidney disease, spasticity, and more. Concerns that might be pretty trivial in other kids can be catastrophic for them. A common cold can land either of them in the ER, and a simple school field trip is fraught with logistical concerns.

When thinking about day-to-day living, the most impactful symptoms are communication and mobility issues. Sam is nonverbal. He is able to communicate some basic wants and needs to his father and me, but I liken it how parents know what a baby wants before it can even talk. Two-way communication with others is almost nonexistent. Even communicating that he wants something to drink can be a challenge. I cannot even imagine the frustration of not being able to convey the most basic of needs, let alone the more complex needs or feelings. He currently uses a combination of gestures, sign approximations, and a few words. But the one thing that is consistent about Sam is how inconsistent he is. We may hear him say "milk" for a few weeks and not hear it again for months or years. When Sam was three, he experienced what we now think to have been a metabolic stroke episode. He had significant regression to his skills, including losing all the language he had developed up to that point. He has never gotten back to where he was before that episode.

Sam uses a wheelchair for mobility and has to be lifted for most transfers. He currently weighs almost 90 pounds and is about four feet-four inches tall. This puts him at only about a foot shorter than me, and while he will keep growing I will not necessarily get stronger. Getting him up and down the stairs, in and out of the car, in bed, or bath is literally more than I could do some days. When I wrote the first draft of this statement months ago, Sam's mobility issues were stable. Since then, the spasticity of his muscles has increased significantly. On Monday, he will be admitted to the hospital to have a pump implanted. This is his first major surgery,

and to say that I'm nervous would be an understatement. Even to say that this is his first major surgery puts them in a different category than most kids his age.

Mobility is certainly an issue with Sam, but with his wheelchair and with the ADA we can fairly easily get him to where we need to go within the community. So though Sam is more universally impacted, mobility is actually more of a day-to-day issue for Marshall. Marshall can walk but not quickly or for long distances. He wants and needs a hand held most of the time. He is unwilling to walk on unstable surfaces like sand or dirt to the point where he will get physically ill if he has to. This makes community outings, family vacations, everything, more challenging. Three years ago, the progressive spasticity of Marshall's muscles was causing his gait to deteriorate so significantly that he needed to surgery to prevent or delay the ultimate need for a wheelchair. After six weeks in the hospital and months on rehabilitation, we went from increased spasticity to generalized weakness, and to see him trying to run around with his brothers or peers and never catch them can be heartbreaking. The gap between what he wants to do and what he is able to do is increasing, and as he gets older his awareness of that gap is increasing, too. The reality is that surgery may only delay his ultimate need for a wheelchair. In fact, we're currently planning for another surgery in June to correct flat feet and collapsing ankles. If allowed to go uncorrected, Marshall will not be able to bear weight within a few years. Think for a second about having two children in wheelchairs. I keep envisioning something like a double stroller but wheelchairs, and I don't think that exists.

But none of these challenges really tells you who they are. They both have an amazing sense of humor. Sam loves when things fall, he thinks it's hysterical. I think that is also genetic, by the way. I do, too. He loves an adventure, he will go anywhere, anytime, and I hope he always has the energy to be that way. He loves to swim and loves music. The most recognizable words that he has are in his songs.

Marshall thinks magic tricks and jokes are the best, and will try to fool his daddy by telling him "look over there," so he can win the race to the house or upstairs. Marshall is more of a homebody and would prefer if I stayed home along with him. He does also love to swim, though. I imagine that weightless feeling of the water feels incredible to them both.

There are so many things I wish I could do for them. But if I had to pick only one for each, I would make mobility easier for Marshall and communication easier for Sam, or, at the very least, halt any deterioration is occurring. This would improve the quality of their lives and provide some reassurance for their futures. I'm biased, but they're both smart, silly, fun, thoughtful boys, and deserve a chance at the best life possible. Thank you.

(Applause.)

MS. THORNBURY: Hi. My name is Heather Thornbury, and I'm from Orlando, Florida. I'm honored to have the opportunity to share my daughter Arden's story with all you today.

Arden's journey started at six weeks old. Born two months premature and in the NICU, Arden began to have trouble breathing. She was struggling. We learned that her heart had grown to take up 75 percent of her chest cavity and was ultimately crushing her lungs. She was on life support within 36 hours and fighting for her life. We didn't know then but know now that this was her first mito crisis and her body was crashing. After weeks of failed interventions, Arden was listed for a heart transplant. She received her new heart at three months old. Arden, like many others, undiagnosed for years until there is a catalyst of some kind, usually an illness onset. After two years of wondering what happened to Arden's heart, we received the devastating news that she had a mitochondrial disease known as Leigh Syndrome. Prognosis being poor, Arden wasn't expected to reach five, but will soon be seven. With expected physical abilities being minimal, she has defied the odds and has far exceeded any limitation set before her.

Arden has come a long way, but life certainly isn't easy. I want nothing more than to give her the world, help her, and meet all her needs. In Arden's case that, isn't easy as she is nonverbal. She has tremendous difficulty communicating her needs and wants. There was a period of time spanning 18 months of constant screaming. If Arden's eyes were open, she was crying and in obvious discomfort. This would happen every two to three months and last anywhere from 10 to 30 days with no relief. As a parent, I felt helpless. Knowing how frustrated I felt, I could only imagine how Arden was feeling. On top of the pain she was having, everyone around her wasn't providing any relief. Trapped in her body, she was doing all she could to show us something wasn't right. It ended up being neuropathic pain. We were relieved to give her comfort but devastated that she suffered so long. Being nonverbal not only hinders communication within our family but branches out into interactions with friends and even strangers. Arden is often left out or ignored as communicating with someone who is nonverbal can be difficult for those that have not come in contact with someone who lacks the ability to speak. To live in a world not being able to share her voice, her feelings, her wants, and even her dreams is isolating and must be extremely lonely. If given the ability to speak even just a few words would be life-changing and open endless opportunities.

Arden requires around-the-clock care and lacks all independence and mobility. Having deficits physically has made a huge impact on her life. She is fed by tube every hour due to GI issues. She wears diapers that need to be changed frequently. When out in public, this task alone is exhausting as Arden is too big for any changing table. We have to either retreat back to our car or put her on the floor, which is something I try desperately to avoid. She is limited to what she can participate in and is dependent on others to help her at all times.

Arden attends school for special needs children as well as a medical daycare. So, for example, when field trips occur, we are often asked to go with Arden and her class due to the care she requires in order to keep up with her needs as support staff is limited. Although the facility provides Arden with everything she needs, giving her the experiences she deserves can be hard to accomplish. Naturally, I jump at the opportunity to spend quality time with her, making

memories while also providing her with new experiences in inclusion she would otherwise miss out on. Although field trips are few and far between, it is the fun things in life that we want Arden to experience, and we will do whatever we can to make these opportunities happen. She may not realize what she misses out on, but we do, and she deserves those moments.

Life is unpredictable, even more so when you are living with a disease that can appear and progress at any time with each time being very different than the last. A lot of that unpredictability is due to Arden's poor immune system and its inability to fight off illness. Her immune deficiencies from her disease, in addition to the required immune suppressing anti-rejection medications she has to take to keep her heart healthy, have a huge impact on her body. Three years ago, she contracted rhinovirus, better known as the common cold. Arden ended up on life support for two months while her organs started to shut down. It was a scary time. We didn't know if she was going to make it, and if she did, no one knew if she would recover and be the same infectious person that she was before the illness. Then other times she is able to fight off the cold with very little struggle. We never know which route she will take, and the uncertainty of it all makes it unbelievably stressful. Illness wreaks havoc on her fragile body resulting in frequent hospitalizations and increased oxygen support, abilities she has acquired could potentially be lost, and even the slightest cold can be catastrophic.

Time is essential when it comes to fighting mitochondrial disease. My biggest worry would have to be losing Arden. We know it's inevitable with Leigh Syndrome, but how can we accept that? And for that, that is the very reason I am here today. Thank you.

(Applause.)

MR. VALENTINE: Thank you to each of our panelists for telling each of their children's stories so eloquently. Join me in a round of applause for this panel.

(Applause.)

Now we are going to transition into our polling questions on topic one related to the symptoms and other burdens related to mitochondrial disease. So, if you can pull out your cell phones, your laptops, your tablets, we'll move through the questions to try to get a sense of the different range of experiences we have in the room here today.

The first question is: Please select the answer that best describes the patient's stage of disability. Your options are, A, minimal disability, able to run or jump; B, symptoms are present but mild, able to walk and capable of leading independent life; C, symptoms are overt and significant, require regular or periodic holding on to the wall or another person for stability and walking; D, walking requires a walker or other aid such as a service dog, can perform several activities of daily living; E, not able to walk, confined to a wheelchair, can perform some activities of daily living that do not require standing or walking; or, F, severe disability, dependency on others for assistance with all activities of daily living.

Please select the answer that best describes the patient's you care for stage of disability.

It looks like the results are in. The largest response, which is just those are represented today, their patient's stage of disability is severe disability, depends on others for all activities of daily living. From there, it seems that we have a fair representation of minimal disability, as well as those with mild disability and some with significant disability. But all different levels of disability are represented here in the room or online today.

Our next question is to select the mitochondrial disease symptoms that most impact the patient's daily quality of life. Here, we're going to ask you to select up to five of those symptoms which represent the most or those that have the greatest impact on daily quality of life. And the options are, A, muscle weakness; B, speech problems; C, chronic fatigue; D, GI problems; E, balance problems; F, sleep difficulties; G, learning disability; H, movement disorders, which is tremors or dystonia; I, delayed milestones; J, decreased vision; K, exercise intolerance; L, seizures; M, headache; or, N, some other symptom of mitochondrial disease that has the most impact on the patient's daily quality of life. Again, you're selecting up to five of these.

We'll give you a few more minutes to get in your responses. There's a lot of options to think about here. Here's one point to note is that you're seeing percentages that are not percentages of the patients that are represented today, but because multiple options are being presented it's a percentage of the total responses. So, we're not seeing any kind of percentages of individuals but percentages of responses.

As any final results are trickling in, it appears that the top symptom that has the most impact on patient's daily quality of life is, A, muscle weakness. After that, it's a pretty fair representation, fairly close between speech, chronic fatigue, GI issues, balance, sleep difficulties, learning disabilities, movement disorders, and delayed milestones. But then each of the others that are listed here also were selected as some number of your top five most impacting symptoms of mitochondrial disease. And we can see that also there's a number of individuals that listed "other" here. So, we will be very interested in audience discussion and hearing about some of those symptoms that are not on this slide.

So here, you are going to see the same response options but slightly different questions. The question here is, as mitochondrial disease progresses, development or progression of which of the following symptoms worries you the most? We're asking here about, looking to the future, which of these symptoms worries you the most. Again, select up to five.

Just a few more minutes to get your selection of your top five symptoms that worry you the most in the development and progression of mitochondrial disease for your loved one.

It looks like, here, the greatest worry is with the development or progression of muscle weakness. After that, it looks like next the two or three are seizures, chronic fatigue, then a number of others, speech problems, GI problems, balance, vision. However, again, there's no symptom listed here that is not in the top five greatest worries of those represented in the

room today. And there's quite a few people that selected "other," and once again we importantly want to hear about that as part of the audience discussion.

Our next question on the burden of disease is, what specific activities of daily life are most important to your child and they are not able to do because of their mitochondrial disease? And here, you're going to select your top three. So activities are, A, moving around independently and safely, walking and standing; B, speaking with others, being understood especially in noisy settings; C, personal hygiene, taking a shower, dressing independently; D, feeding one's self such as cutting food and handling utensils; E, going to school or work; F, writing and typing; G, reading books, seeing a computer screen or phone; H, manipulating small objects such as keys or picking up items; or, I, some other specific activity of daily life that is important to your child that they are not able to do because of their mitochondrial disease. Please select your top three, just a few moments.

Barring some last-minute responses, it looks like our top activity that is important to your child that they are not able to do is moving around independently and safely, walking or standing, followed closely by speaking with others and being understood, and after that, going to school or work. We have good representation across each of these different activities as well as with other things that are not listed on this slide.

And our final question for you to establish understanding of mitochondrial disease is, as a result of living with mitochondrial disease, which of the following social, emotional, or economic consequences are most significant to your child? Here, you can select four. The options are, A, frustration; B, social isolation; C, loss of independence; D, communication issues; E, lack of hope for the future; F, depression and/or anxiety; G, trouble building or maintaining relationships; H, modified school hours; I, loss of hobbies or activities; or, J, some other consequence of living with mitochondrial disease that has a significant social, emotional, or economic consequence on your child, again, selecting up to four.

A few more seconds here to get in your responses. It's looking like right now the result of living with mitochondrial disease that has the most significant social, emotional, or economic consequence for your child is social isolation. After that is frustration and loss of independence, and then a fair representation across the other areas with only a couple mentioning something else that wasn't listed. So, I think this is just a very good idea of the different experiences we have in this room. I think, from what we've seen, there's almost nothing that we've listed on any slide that isn't represented here.

So now we have the opportunity to expand on your responses to these polling questions, and of course the great statements we've heard from our panels. We want to hear more from you and learn from you more about the symptoms and the direct impacts that mitochondrial disease has on your children. We have a number of discussion questions that we're going to work through at least initially focused on the symptoms of the neurologic manifestations of mitochondrial disease, and how those symptoms and health effects impact daily life. That's

really what we want to understand, what does this actually look like in daily life? What are the real-life impacts?

So, I'm going to start with a kind of broad question. I want to know, what are the activities that are important to you and to your child, and where their mitochondrial disease prevents them from doing those activities either fully or at all. So, what are those important activities that are limited or totally prevented due to mitochondrial disease? And then, when you're describing what that might be, I would be very interested in which aspects of mitochondrial disease, which of the symptoms, are really driving that activity not being participated in.

All right. Yes.

SPEAKER: Hi. I'm sort of representing three people this half by honoring my niece and nephew with mito. I know their mom through Facebook and basically, when we all get together, the fun part for the next seven days. But basically, I think the main struggle for them is, that at 14 and 16, they don't have many friends because they have to be home-schooled. The friends that they do have are through the church and sort of their routine maybe through teen impact. But their teammates like so they go to games I don't know what teen impact is. But those friends of theirs, they are 18 and 22. So it's hard to relate to young teenage issues and those with chronic illness. And also they're in and out of the hospital. They just got out yesterday from being in the hospital for three or four days for the flu. It's hard to realize that, you really, like any -- it's really hard on the mitochondria because growth takes everything. Everything that changes takes energy. So, I think it's three weeks after the cold or flu, that's when the body is most vulnerable to neurological progression. And you can help me out if I'm wrong. So for Sasha, she has the flu 15 years ago and then six months later required a GI tube because of her stomach shutdown. It's sort of like with social isolation. And when I had pneumonia when I was two, I had the same thing. So, in the winter I basically go into a hole and don't really come out because -- I mean, so you don't know it's all right, you stay home, because if you get sick you will get the death lair on you. So even going to SeaWorld and Universal is fun for us all, but it's exhausting. Because even though we all have our wheelchairs, holding onto rides and holding on so you don't fall out and fall over during rides, takes energy. Schoolwork takes energy. But things that you don't associate with being demanding on energy take energy. So I think that's it.

MR. VALENTINE: Thank you for sharing well in Sasha's stories. I think there's a lot of very important things packaged in that, certainly the whole circle on social isolation being such a big part of the disease experience. Also, mentioning not only the demands of just doing activities and then how that results in the need for recovery time, but I also heard there's major illnesses, infections, that actually for this population can result in regression and neurologic syndromes. So that's an important aspect of the disease is avoiding those major illnesses, but then trying to bounce back from that regression that happens.

Thank you very much. We see a few hands, so we'll work our way around.

SPEAKER: I may be missing the elephant in the room here. But when my daughter ended up in the PICU, all of our expectations changed. And it came to us not caring about college. It was what the heck is our life is? Is she still alive? Is she still breathing? Are we going to get out of NICU? And as far as specific activities, it was to sleep more than three hours a day. And we lost her because of this disease.

But I think it comes down to, for us who are parents, we wake up every day saying, can we just keep our child alive? And it's not can we go to the grocery store. That becomes a side note. And I think when we talk about what do people miss, it's just that state of normalcy that changes as soon as you get that diagnosis.

SPEAKER: Ditto.

MR. VALENTINE: Just a reminder for everyone, if you can just say your names for our recordkeeping.

SPEAKER: Heather.

SPEAKER: I am Ellen, representing my daughter who is 15 and she has PDC. I just wanted to echo what Heather was saying. We have been here the whole day and it's been fantastic. But with the polling questions, the one thing that we kept getting on this "other" because our main focus is just making sure our kids survive, and everything else is inconsequential.

But to answer some of the other questions, for my daughter and her condition - a couple of things that have had an impact on her life. She used to walk. So, the regressive nature of the disorder. She used to walk with a walker, still assisted, but she used to love to dance and sing. She said dad and she said mom. She got sick when she was four with pneumonia and she lost all of that, and we tried to get it back and it never came back and that's the new baseline and we're great with that. Because like Heather was saying, we don't mind as long as this is our baseline. The scary part is not knowing if something else will happen and we'll have to get used to a new baseline.

She has episodes, we were talking about this morning, where she goes weeks where she wakes up at 2:00 or 3:00 in the morning and she's crying and writhing in pain and can't tell us why, whereas she used to be able to point to parts of her body and she's lost that ability now. That's changed over time and impacted our family, because somebody had to be there with her. I had to leave my job to make sure we could stay with her 24 hours a day.

MR. VALENTINE: This is very important understanding that, I guess at age 4 was when she got pneumonia and then --

SPEAKER: It started her regression.

MR. VALENTINE: Started her regression.

SPEAKER: She was diagnosed at age two. She was always delayed, but we were reaching milestones. We were working on therapies and things like that. And then with that illness came the regression, that she didn't get the skills back no matter how much we tried.

MR. VALENTINE: Help us understand what skills she lost.

SPEAKER: She lost the ability to walk. She used to walk with a walker long distance. She used to sit on the back of her walker and dance. She used to crawl over the house and throw things like children do. And now she pretty much lays in one spot in the house, and crawl maybe three or four feet.

MR. VALENTINE: And also, medication.

SPEAKER: She's no longer -- it's sad, because you can see it in her eyes she's given up on that. She used to try a lot harder, but it's hard when you try and nobody can understand you and she becomes frustrated. I have seen over the years where her frustration has turned into apathy because she knows her needs can't be met so she just gives up on it.

Listening to the adults this morning, I thank you so much because now I feel like I have a window into what she's going through that I didn't have before, because she can't tell me.

MR. VALENTINE: How long has she been living with her new normal?

SPEAKER: I would say -- I mean, normal is relative. With each illness, she goes down a little further, a little further, and she will gain some back and then some of it not. But probably a year or so.

MR. VALENTINE: Thank you very much.

We have a couple hands over in the middle, and then we'll back over here.

SPEAKER: I have a child who is 16. Making plans for her life, experiencing that regression and being aware of the regression, and having that continually changing baseline is difficult for her. That's probably been the most significant impact on her life, because she's trying to make plans and -- very respectable plans that just come at this stage of life, but daily things get taken away from her. Not of her own accord. It's the disease that decides that regardless of what we're doing. For her, emotionally it's had a huge impact knowing that tomorrow or this afternoon her plans could be foiled by the disease. And we can't always recoup the skills and abilities that she had. And every day she's working with a new body. Six months ago, she ate by mouth and now she's primarily tube fed. The tube has always been there. But when you try to socialize and go with your friends, how much is involved with that, and when you're 16 and you're still trying to maintain some normal -- it's difficult. So, I would say emotionally that's been a huge impact for her, and her ability to plan her future is also -- it speaks about emotional.

MR. VALENTINE: Sure. When you were talking about planning, you mentioned planning for care. I'm also wondering, in her difficulty with planning is that I assume there's also some component of the disease. You were talking about as well you just --

SPEAKER: The uncertainty of the disease. What's the future hold? And speaking straight to what Devin said in her speech was this is the time of life where we start to see -- we start to lose people. And so then how do you prioritize things? Going to college versus eating by mouth. And that's a goal, eating by mouth now, which trumps schoolwork, which trumps all these other things. So that's changed. Making plans, it just changes plans every day.

MR. VALENTINE: Thank you.

SPEAKER: Hi. My name is Alexandria Yates. I am actually diagnosed with mito. I was diagnosed at 18 months old. Through my whole childhood, I had heart murmurs, asthma, seizures, dehydration. As I've gotten older, though, I've fallen out of those things a little bit but I still struggle with dehydration. I actually got a port placement when I was 14 years old, and ever since then I haven't had any hospital trips. But I still struggle on a day-to-day basis on going out with friends. I'm now 21 years old, with the peer pressure of drinking and going out with them and all of that, it's a daily issue I struggle with. I mean, that's something I would like to do, but I know that I can't in the real-world deal with those kinds of things and keep up with the mito. I guess, outlook. I am followed at Children's National Medical Center. But now I am 21, I need to start seeking adult doctors which is a struggle as well. I have grown up with all these doctors, and it's a big struggle to change when you're comfortable with something.

MR. VALENTINE: When you talked about the pressures of going out with friends and things like that, is that something that you're able to find a balance of or is that something that you avoid completely?

SPEAKER: No. I've definitely been able to find balance. Like when I go out with my friends, I get a soda instead of the alcohol beverage. But even spending a full day at the beach or walking on the boardwalk or whatever they want to do, I have to pace myself and take breaks during the day and realize that I have limitations and I need to know those limitations.

MR. VALENTINE: Is that mostly driven by the dehydration, or are there others?

SPEAKER: I struggle with muscle fatigue and weakness, and it's hard sometimes -- I live a very busy life, and I need to know that I need to stop and take a break and I struggle with that. To this day I don't know my stopping point and I crash. That's an issue as well, and my mom always yells at me about it: You need to take time with yourself. And I just don't know how to do that.

MR. VALENTINE: Does that also have anything to do with maybe the point where you crash is different from day to day versus being able to predict how far you can go?

SPEAKER: Yeah. My mom has never really held me back from doing anything. She's always said: If you think you can do it, go ahead and do it. Be yourself. I've never let anything stop me, but I still don't quite know my crashing point. It's unpredictable as whether it's winter time or the sun is shining too hot, I get heat exhaustion more. I'm not as active in the winter, so my body's not as accustomed to doing the long walks and things like that.

MR. VALENTINE: That makes sense. Thank you very much for sharing.

Yes.

SPEAKER: One thing I hadn't heard too many people talk about was that kind of severely affecting my son in in Louisiana is the heat intolerance. I mean, we have to always worry about whether he can go out and if there's air conditioning. And, I mean, cold is not as much of a problem for us. We also have that problem if we travel. But just the heat and cold intolerance and just any planning regarding that completely affects him. It completely drains him and takes everything out of him for the next several days. He can't even get -- it causes him to crash if he's been outside for too long. He just does not regulate temperature at all. And as far as his symptoms, he's been up and down his entire life. We now think he probably had a stroke in utero. He was born by emergency C-section. And then he had failure to thrive. But then he reached the point where he was better. He had a lot of illnesses as a child, but he went to regular kindergarten and all of that. But then I noticed that he was losing those skills, and I kept telling the doctor something is really not right. I noticed tremors in his voice. They would say, oh, you know, you're just -- you're just being overprotective. No. And then his teacher said he's starting to fall off the monkey bars and he used to be king of the monkey bars. He would have an illness -- in fact, it was chicken pox. He had chicken pox really bad, and suddenly everything changed after that. And that was really like when most of his mito started -- thinking diagnosis and having the chicken pox. I think he might have been one of those people who could have gotten away with mild symptoms his whole life up until that point.

MR. VALENTINE: Sure. Were there other times when something other than illness that resulted in declines? You said there were a lot of ups and downs for him.

SPEAKER: Yes. Most of the time after an illness we would have a loss and have to regain and work on something. And I would notice it, and I would point it out to his doctors and they would think that I was just being overly, overly motherly. And just little things that you notice as a mom that not everybody noticed.

MR. VALENTINE: Like what?

SPEAKER: And then after he got older, they were just more frequent and more distinguished for -- like in his schoolwork, say like math was a huge thing. He was tested gifted in math when he was little and then he really lost his skills. He couldn't remember that. He couldn't remember a lot of things. He could do this on the calculator, and so that's how he got away

with things all through college. He could do anything if he had a calculator. So, he could get the calculus.

MR. VALENTINE: Thank you.

Over here.

SPEAKER: My name is Jake, and I'm here representing my mother and two brothers and myself. The three of us have mito, and my mom. I want to start by saying something I wish I told my mom more and that I wish here: Thank you for the sacrifice that you guys have made.

When we were born and we were diagnosed with mito, I always joke that we just decided to become Team Mito. It wasn't really an option, it was- this is what's happening and this is what we're going to have to do, and it's a community team effort. I remember, my mom sacrificed so, so much to make sure we were given the best opportunities to do what we could as young adults and kids growing up. So, I wanted to start by saying thank you. She's watching in San Diego. So, thank you for all the sacrifice that you did to give us that opportunity.

Growing up as a child, I can remember that I could always tell there was something different about me. I couldn't figure out what it was. I don't know what led me to that, but I could tell that when all the other kids were in gym playing football, I was struggling to run. And I always wanted to be, like, well, I'm not different. I'm probably just tired. My mom was a very good in helping me not feel different, per se, but I could tell there was something there. Eventually, the hardest part for me and my brothers as well as for my mom was that we could tell it became more cognizant that we had mito. Growing up as an adult and into adulthood knowing you have this and watching it and watching your body deteriorate with the knowledge that you are able to watch it happen is the most difficult thing. Because you're aware and watching it happen, but you can literally do nothing in your power to stop it.

I think for me, the anxiety and depression that started around 13, 14, 15 and carries on today as an adult is probably the biggest struggle, aside from having to explain to my friends when I meet them -- because meeting them is hard to begin with when you don't go out -- that, hey, I'm not canceling on you because I don't want to hang out. I'm canceling on you because I have a condition that is completely unpredictable. On some days I feel like I can run a marathon, and on other days I'm not getting out of bed. I'm very lucky that my friends who are close got onboard with that, but what I need to work on is trying to explain people when you go into work, hey, this is kind of how this is going to work, and getting the: I'm sorry, what? That's probably the most difficult experience. I look back two or three days, it's just there. But I think for me the anxiety and depression and knowing that this is there, knowing that you can't fix it, is something that weighs on you all the way from childhood all the way up until adult.

MR. VALENTINE: And has your experience been fairly stable with the symptoms of your disease? And what you're saying you're sitting there watching your body, how has that looked over time?

SPEAKER: Sure. I used to figure skate when I was eight, nine, 10, 11 years old. I was very good. I was competing against 19 and 20-year-olds. Then when I turned 14, my body was just like: We're just not going to do this anymore, because the energy it requires and the physical strength it requires from me, my body was no longer able to keep up with that output. A couple months after that, I had feeding tube placed, and that was a very big struggle because I had self-image issues over that growing up, and then when they put a feeding tube in your stomach and you have to go and face middle school and high school students who to their credit may not know it's there but you are aware it's there does not help your self-confidence.

So, I'm very lucky and I am stable at the moment. I always finish there, because with the condition you just never know. But it's definitely made an impact on my life. It's made me the person who I am today, and I don't think I would change it at all even if I could go back. I think it's such a big part of my life that I wouldn't want to be different. So just kind of living it.

MR. VALENTINE: And have your family members had similar experience in terms of their disease progression?

SPEAKER: Sure. So, my brother Clayton was the worst of us. When he was born, I wasn't born. When he was born, my mom was told he wouldn't live to see three. He's now 21 and getting ready to graduate university, so he's proven them wrong. My other brother Cole was probably the least affected of us growing up and is now most affected in adulthood. Just interesting to see that progression. He played baseball in high school and now has issues of getting out of bed. So, it's interesting to see the ways and the roller coaster ride that has provided, not just me and my brothers, but our family and close friends.

MR. VALENTINE: Thank you very much.

SPEAKER: I just want to echo some things said earlier about a recent -- my name is Laurie Martin. My son Will has Leigh syndrome genetic 9176.

Pediatric dementia I think is the thing that was given to us recently as a label or a diagnosis for our son. I haven't fully delved into what all that means, but it's interesting when I hear people talk about brain fog and losing their abilities to do math. And it's this concept of you're going to start out okay, but the dementia concept sets in. But I just thought that was interesting, and to comment and share on how we can lose these abilities physically but also there's a level of brain loss, too, and cognitive ability. Dementia.

MR. VALENTINE: Yes.

We have a comment here, and then we'll take our final comment.

SPEAKER: My name is Debbie. My daughter Katie has complex 1-3. I actually asked her the question what her top three symptoms are, and she said tiredness, brain fog, and weird temperatures. The brain fog is what made me raise my hand. I find too when my daughter was sick this last time, I was e-mailing her specialist because I was trying to figure out, is this

something mito-related, or is it something that's got to be dealt with aspecialist, or are there mito considerations?

The brain fog, she was part of a research study at Georgia Tech where they put her in an MRI machine -- they did it with my son too, who is not affected with mito -- and they peppered her with questions. And they said, as soon as you start feeling like you're getting tired, the brain fog, tell us. A minute before she said it, you could actually see changes on the MRI before she said I'm getting the brain fog. So, the question becomes then what are you actually treating? There's a lot of kids labeled as ADHD, because the symptoms are the same but the underneath of what is happening is different.

It's really hard to figure out, is it something separate or is it something mito? If that makes any sense.

MR. VALENTINE: Sure. Just to help us understand what you meaning by brain fog, what did you notice about her?

SPEAKER: For example, we schedule her classes -- her harder classes or when she says the most boring classes -- in the morning, because she has to concentrate. In the afternoon, if she has a history class she's not comprehending what's going on as much. And she's very studious so she tries, but she's so frustrated so we know to schedule those at the beginning of the day. And she does half days at schools so she needs to see if she can do that. And then we've got an alternate schedule for taking classes.

MR. VALENTINE: Sure. Thank you.

SPEAKER: I think one of the things in thinking about the specific activities, I was thinking about like kind of like what you were saying, your priorities change so much. And would I want my kids to play soccer or football, or would I want them to be able to bathe independently? And I think at this point bathing independently would be a big plus. My children who have mito are now at an age where puberty is rearing its ugly head, and even though they don't necessarily have the intellectual capacity or the ability to verbalize it they're kind of instinctively wanting more privacy and more independence, and I can't give it to them. So my 11-year-old doesn't want me to help him get in and out of the tub and bathe him, but I have to. And my 10-year-old, who is showing signs of puberty much to my chagrin, is still in diapers. And he's not there yet where he's feeling self-conscious or shy, and I don't know cognitively if he ever will be, but frankly I don't want to change an adult man's diapers, my son, my husband, or anyone. That's not part of my life plan.

So that's something that has been really hard as they're reaching this age. Like when they were two or three, you know, okay, whatever, diaper, it's part of life. But now, as they're kind of into that age where instinctively independence and privacy become more of an issue. That's becoming a huge challenge in our house, of giving them a little bit of independence but still keeping them safe and clean and being sane.

And also -- I love you. And I'm not your mom but I'm a mom, and I want to say that I'm so proud of you. And mom in San Diego, you did a great job.

(Applause.)

MR. VALENTINE: That concludes our first topic discussion on living with mitochondrial disease. We're going to take a quick 10-minute refreshment break. We'll be starting back up promptly at 3:14 on the dot so please be back. We're going to kick off topic two with another panel discussion. Thank you.

(Break taken.)

MR. VALENTINE: We're going to get started on our second session of this afternoon's discussion on the pediatric neurological manifestations of mitochondrial disease. We're now building on this morning's discussion or perhaps an earlier this afternoon discussion where we discussed symptoms and the daily impact of mitochondrial disease. Now we're going to discuss current and future approaches to treating mitochondrial disease. In this session, we're going to be having our panelists and all you in the audience answering some questions for us, helping us understand what it is that you're currently doing to help treat your condition and its symptoms. This includes not only prescription medicines and other medical procedures, but also nondrug therapies. Things like physical therapy, diet, exercise, and also even lifestyle modifications.

In addition to telling us what it is that you do to try to manage your child's mitochondrial disease, we want to hear how well that's working. You know, whether the treatments are helping with any particular aspect or symptom of the disease, as well as whether those treatments' regimen needed to change over time. We also want to hear about any significant downsize of current treatments and how that's affecting daily life. That can be anything from side effects to needing to go to the hospital to receiving treatment.

Then once we work through kind of a discussion of the current treatments, we're going to turn and look to the future and ask you, short of a cure, what specifically would you look for a treatment or the next treatment in the pipeline?

To get us started on this conversation we have another panel for you. We have Carrie, Lori, Cheryl, Gwen, and Anne, and they're going to share their personal experiences with mitochondrial disease.

So, Carrie, take it away.

MS. MULLIN: My name is Carrie Mullin. I'm a resident of Pittsgrove, New Jersey, and proud mother to two amazing boys, AJ 14 and Patrick 11. My youngest son Patrick has mitochondrial disease, and I am here to share his story.

Patrick was born in August 2007, a healthy, happy baby boy. He hit all of his early milestones and was developing normally by all accounts. But at nine months, we started noticing delays in

his motor development. We began early intervention services, and he remained behind schedule for his developmental milestones.

Patrick's doctors couldn't find a reason for his developmental delays, and as he got older new issues began to emerge. When Patrick got sick even with a mild cold he would become very lethargic. Then, in February 2012, Patrick woke up one morning unable to walk. When he crawled, his left arm and leg were dragging behind him. We headed to the ER, and as we approached Patrick started having seizures. Patrick was admitted and was treated with seizure meds, Keppra, and Phenobarbital, which only slightly reduced his seizure activity. He then required an infusion of Midazolam, requiring intubation and a central line, so Patrick was moved to the PICU. When we did not see reduction of the seizure activity, we began to discuss the root cause of the seizures. His MRI had shown increased lactate in his brain stem and his new scans showed evidence of a metabolic stroke. Since his symptoms resembled MELAS syndrome, Patrick was given an IV infusion of L-arginine. Within 12 hours of that infusion, Patrick's EEG started to improve, reducing his seizures from 10 to 15 per hour to one to two events daily and eventually none.

When Patrick finally awoke from sedation, he was different. He had lost all of his motor skills and required intensive rehab over the next two months. Since mitochondrial disease was suspected, Patrick was started on a combination of vitamins called a mito cocktail, which included L-arginine, leucovorin, calcium, ubiquinol, B-complex vitamins, vitamins C and E, levocarnitine, alpha lipoic acid, and biotin. It was a joyous day when he was finally released home, but our lives had changed forever.

Not long after Patrick returned home from the hospital, we learned he conclusively had mitochondrial disease, specifically POLG-1 mutation or Alpers Syndrome.

Since that first episode in 2012, Patrick's journey has been a roller coaster of ups and downs. He has periods of stability, but it doesn't take much for things to go downhill. His hospital stays have ranged from 48 hours up to a few months. His disease has continued to progress with an increase in neurologic symptoms, like tremors and myoclonus and new types of seizures. He also developed an adrenal insufficiency requiring him to receive daily doses of hydrocortisone and fludrocortisone, and in times of illness Patrick receives stress dose steroids.

We have had two especially scary episodes in the past few years. In 2015, Patrick had another severe metabolic stroke again with recurring seizures, but this time he had to be placed in a medically-induced coma on ketamine. At that time, his team also started him on citrulline and we saw improvement in his scans and EEG.

Then last January, Patrick again had another long hospitalization, this time due to an underlying infection. This episode put his body into metabolic crisis, but this time we utilized an infusion of IVIG as a treatment. With the IVIG infusions, we have seen a decrease in seizure activity and remarkable improvement in Patrick's mental awareness and overall health.

Over the past year, new symptoms have emerged with his entry into puberty. We've added a fourth anti-seizure medication. His insomnia has become more prevalent requiring to treat him with trazodone. Patrick is a feisty 11-and-a-half-year-old now but has the functional abilities of a toddler. Patrick is still able to eat and drink orally. He requires a tube to receive his over 30 doses of daily medications and meet his hydration needs.

His mobility is limited, requiring him to primarily use a wheelchair to get around. He is incontinent and employs diapers. He is nonverbal, but works hard to communicate with us in his own way.

Patrick requires full-time nursing and attends a specialized school program where he has multiple sessions of PT, OT and speech weekly. He sees specialists in mitochondrial medicine, complex care, neurology, endocrinology, GI, pulmonology, cardiology, ophthalmology, immunology, audiology, and PM&R.

While his life is not easy, I know that we are one of the lucky ones. He has made it to age 11, something I once thought never would be possible. My son is still alive, but many of his mito friends are not. Our ultimate hope would be a cure, but any intervention that would reduce the frequency of his hospitalizations or minimize his symptoms could really improve his quality of life. We want to give him the best, longest life possible, and you help do that.

(Applause.)

SPEAKER: Hello. My name is Lori Martin, and our family lives in Houston, Texas. We have an amazingly special almost 10-year-old son and a vivacious nonaffected daughter. Both of our kids fill our lives with joy and humor.

Our son Will was diagnosed with maternally inherited Leigh Syndrome at the age of two. Our lives were turned upside down and inside out. Even now, almost eight years later, the diagnosis is crushing. He was diagnosed with Leigh Syndrome. It is a progressive and fatal form of mitochondrial disease. Our son has large, parallel lesions on his brain that affects his spine and gross motor skills, among other issues. He has beaten the odds that doctors originally gave us, and now at the age of almost 10 his ability for gross and fine motor skills range between a toddler and a child, and his cognitive and verbal abilities are currently assessed to be around a level of a six-year-old.

Currently, our biggest concerns are as follows: Will struggles to maintain body balance. He has weekly physical therapy and occupational therapy to help strengthen his muscles and learn safe ways to move his body. Will has worn leg braces or boots since the age of 18 months old. His ataxia and gross motor skills have continued to decline. These are the most concerning issues we have right now. And he uses a wheelchair for much of his day. His immune system doesn't work the same way as other people, leaving him immuno-compromised. He is on a weekly subcutaneous infusion of Hizentra to keep him healthy, and he has been on this drug for six years. This drug also has been shown to reduce brain inflammation.

Will's GI system doesn't work well resulting in consultation. He takes a cap of a MiraLax daily and a probiotic. Will has been receiving EPI-743, a trial drug which is supposed to help increase energy production. He has been on this drug for eight years. The major changes we noticed were increase of his verbal skills, and his feet were previously pigeon-toed in and they have they turned out straight and have remained straight since, and we do believe it has helped slow the disease progression.

Will's central nervous system is also affected. He lacks the proper fight and flight responses, and has extreme anxiety over a variety of seemingly normal issues. He is on 100 milligrams of Zoloft, and he also suffers from heat intolerance. Living in Houston, that is a problem.

In general, we work to make sure Will has access to immediate care should he become sick, proactive measures such as urinalysis and quarterly labs, as well as check-ins with GI, neurology, pulmonology, cardiology, and palliative care.

Of his many issues, we focused on the symptoms we can actually fix -- his immune system. For many years, he would catch everything from a common cold to a viral illness in his cerebellum resulting in brain inflammation and brain cell death. Getting older clearly initiated disease progression for our son.

Before starting and getting the correct dose of Hizentra, he was hospitalized two to four times a year usually for a week each time. He has remained hospital free for three years up, until this past February when he was admitted for five days for dehydration from a stomach bug. Time in the hospital creates a large setback for Will's physical and emotional health. His physical ability dropped significantly to the point of needing around-the-clock care. His emotions are highly irregular, and it taxes our entire family.

If he is able to get back to his baseline before hospitalization, it takes anywhere from four to six months. Thankfully, Hizentra continues to work and we modify the dosing as he gets older and as his IG labs show the need. However, the downside of the subcutaneous infusion of Hizentra is that it takes nearly three hours to administer. So, for a large period of time every weekend, Will is unable to move. He hates needles. He hates sitting there. And every week he wishes he didn't have to do it. I know I'm lucky enough to get to hear him beg to skip this process, but every weekend it doesn't make it any easier to have to tell him, no, we have to put the needles in.

An ideal treatment for Will would give him the chance to lead a more normal, independent life instead of having an adult help him in the bathroom or with the shower or bath, or cut up his food. He could do those types of things. Just like the immune system medicine has done for his life, a treatment for ataxia would give him the chance to participate in something more fully as simple as personal hygiene, and maybe even play baseball instead of just watching. Will's body and brain do not have the time to wait for a cure, but he would benefit from a drug development for ataxia.

Thank you for your time and compassion. Our son has battled more in his short life than most adults and he, along with his mitochondrial disease friends, deserve the chance for a better quality of life, and a viable treatment for ataxia would be a good start. Thank you.

(Applause.)

MS, PORTER: Good afternoon. My name is Cheryl Porter. My husband and I have five children, four of whom are married, and six grandchildren and live in Atlanta, Georgia.

In 2009, my middle son David was 22 years old -- he is the one standing to the right of me -- and finishing up his second year of college when he began to experience vision problems and dizziness. After visits to many doctors, a neurologist requested an MRI which showed lesions on David's brain stem. Within two months of his first symptoms, David was diagnosed with Leigh Syndrome, Surf-1 mutation, and given no hope for a future.

David worsened tremendously during this time period and was confined to a wheelchair. He could no longer walk, see, or take care of his most basic needs. Our world and his had been turned upside down. At that time, the only treatment available was the mito cocktail, which is a combination of supplements and a regime -- based on a regime of Co-Q10, health protein, and B vitamins. After further testing, it was discovered that David has a cerebral folate deficiency and the drug leucovorin was added. After six months of leucovorin and the mito cocktail, David began to regain his eyesight and some mobility. He learned to walk again and to help care for his personal needs. We were told that at any time a virus or stress to his system could cause lesions to grow and cause a mito crash. Although we were very grateful for David's improvement, we always felt like we were walking on eggshells waiting for the next crash. We also had to grieve the person that we had lost. The lesions in David's brain had affected his personality to the point that he was and is no longer the same person.

While we were told that nothing could be done, I began to hear about a new drug going through phase one clinical trial developed by Edison Pharmaceuticals called EPI-743. In 2013, it was agreed that David could receive a trial drug on a compassionate use basis. We were elated. At last, a tiny degree of hope.

In March of 2013, David received his first dose of EPI-743 at Stanford Medical Center in Palo Alto, CA. His dose doubled six months later, and he continues on that same dose today. EPI-743 proposes to increase the glutathione uptake in the brain. After the first 13 weeks, our nuclear brain spect showed significantly increased uptake.

The reality of what I have seen in David is that he has improved during the past six years that he has taken EPI-743. We had to come off of Co-Q10 in order to take EPI-743. David saw a radical increase in muscle pain and terrible muscle weakness without Co-Q10. Within two to three months of being on EPI-743, he was back to baseline as far as pain and weakness. In other words, in my opinion, EPI-743 worked as well as Co-Q10 for David in these areas. However, we

feel that he has surpassed where he was on Co-Q10 and experiences even less muscle pain and weakness, and we have seen a slight increase in cognitive ability.

David still continues to take EPI-743 leucovorin, L-Carnitine, and B vitamins. He is able to exercise, which has increased his strength and stamina. He is able to endure longer periods of walking and standing, things he could hardly do at all before. Two repeated MRIs have shown complete stability of the lesions with no growth at all.

David is not able to drive due to his neurological condition and without significant changes, never will be able to. This is the number one factor that affects his life. In an ideal world, David would love to be able to drive again. We would love to see drugs approved that would decrease or heal the lesions in his brain thereby allowing him to process correctly and drive again. We are firm believers in the effectiveness of EPI-743. Recently, we took a trip and did not bring enough of the drug with us. It has to be refrigerated. I grabbed the wrong bottle. David did not take the correct dosage for four days. The resulting muscle pain and weakness after four days was severe, and the lessening of it after returning to the correct dosage was remarkable.

Thank you for paying attention to how this disease affects our reality. We always try to remember that David -- I can't say it. We always try to remember that David is doing better than any medical professional ever promised us that he would, and we can see that where there was no hope for the future there just may be.

(Applause.)

Thank you.

MS. LOPEZ-COHEN: Hi. My name is Gwen Lopez-Cohen. I live in Westport, Connecticut with my husband and our five children, and I'm here today to talk about our son Joshua. I haven't had time to update the family photo.

We welcomed our fourth son into the world on December 6, 2013, and Josh would join his three older brothers, Jacob, Gabriel, and Ben, and now has a baby sister, Hannah, who is three months old. When Joshua was not walking independently by 15 months of age, we knew he was delayed. I enrolled Joshua in physical therapy, and while he made progress he really struggled to walk. He did walk independently at 20 months but continued to fall down frequently. I took him to pediatric neurology just before his second birthday and the neurologist recommended an MRI. The MRI findings were devastating. Joshua has Leigh's disease which genetic testing confirmed is caused by a pyruvate dehydrognease deficiency.

Joshua has DLD deficiency, a single gene disorder with a G to an A base pair switch that results in his body producing a poorly functioning DLD protein. The DLD protein is needed for metabolism and Joshua's condition affects his body's ability to produce energy. As a result of his metabolic condition, Joshua has Leigh Syndrome -- central nervous system cell damage due to insufficient energy production. Joshua has bilateral damage to the basal ganglia region of his

brain that directly affects his balance and motor coordination. He suffers from low energy, global muscle weakness, and chronic ataxia or unsteady walking. We live in fear of disease progression as it is often central nervous system cell death in brain regions needed for respiration that can cause children with Leigh's to die.

Joshua is now five years old, and we have learned through an updated MRI this past September that his disease has progressed to the cerebellum. In spite of our vigilant efforts to keep Joshua healthy and his daily mitochondrial disease supplements, the cells in his brain continue to die. None of his doctors can explain when or how the disease progression occurred or how to prevent further brain damage. We're currently addressing Joshua's global weakness and poor balance with regular physical therapy and occupational therapy to continue to build his strength. We have to adjust Joshua's physical therapy routine based on his state of health and his energy level when he is sick. Modifications often include easier exercises and shortened sessions. Joshua's occupational therapist will encourage him to lie down on a beanbag chair and rest if he is fatigued. Fortunately, we have had two- to four-month intervals where Joshua remains healthy. When Joshua is sick or fatigued, he does not have the strength needed to carry out his regular routine, and it can take as long as one month for Joshua to recover his strength and stamina after a viral illness.

Joshua takes prescribed vitamins and supplements that are monitored by his mitochondrial medicine doctors. We started Joshua on supplements immediately after learning of his genetic diagnosis and noticed that his stamina and balance both improved. His gait was steadier with fewer falls. Joshua currently takes B vitamins, N-acetyl cysteine, alpha lipoic acid, and vitamin E. We have also given him trials of argenine and carnitine. Many of the compounding vitamin preparations are noxious, and when we added argenine to Joshua's supplements he started gagging and regularly vomited up his supplement. We are now close to three years into managing Joshua's condition. We remain fearful that his central nervous system is vulnerable to incremental cell death and damage that further impacts his functioning. As Joshua grows bigger, his ataxia grows more concerning since he has farther to fall and would also be at risk for further energy deficiencies on a cellular level if he is injured from falling. We do not currently have any treatment that addresses Joshua's poor balance or any treatment to protect his central nervous system from additional damage.

As Joshua's gotten older, it has become more challenging to offer peer and educational opportunities that are safe and do not present an increased exposure to illness. As a toddler, we were able to find two other kids who could make a play group with him. Now that he's approaching Kindergarten age, the risk of sending him into a class of 25 kids is a tremendous exposure to illness. We recently visited a kindergarten that he spent time with an aide, and we were moved to tears when he sat down next to a kid on the carpet and turned to him and said, "Hi, I'm Joshua. Do you like Star Wars?" We hope for Joshua to attend school and have friends, but any cold or flu poses the risk of further neurologic decline and it's a daily challenge to decide when it's worth it to take the risk.

An ideal treatment for Joshua would of course cure Joshua's DLD deficiency. We've been following the field of gene therapy and hope that this can one day be a possible treatment for Joshua. Additional possible options are enzyme replacement therapy to introduce a functional DLD protein into Joshua's system, and investigational compounds that boost mitochondrial functioning.

We are hopeful that if we can preserve Joshua's current state of health while science advances that he can grow and develop into a healthy young man. Our fear is that as Joshua continues to sustain cell death in his brain that a cure or a treatment will be too late. Joshua is a joyful five-year-old boy who fills our home with happiness, and our family has been blessed with a motivated clinical team at the Children's Hospital of Philadelphia. We are all working together to seek out both potential treatments and cures.

(Applause.)

MS. TUCCILLO: Good afternoon. My name is Anne Tuccillo, and I live in Alexandria, Virginia. Thank you for the opportunity to speak with you this afternoon. I would like to share with you some insight into the reason why I care so much. His name is Bryan.

Bryan is our 26-year-old son who was diagnosed at age four with Leigh Syndrome, specifically complex 5, the T-8993 gene mutation inherited from me. Although diagnosed at age four, we knew that something wasn't quite right with our son from very early on in his little life. Despite a grim prognosis, Bryan continues to outlive his doctors' predictions. He is my hero, and his perseverance, kind spirit, and positive attitude are, in my opinion, the most effective treatment option available to him right now. Bryan's daily challenges include developmental delays, visual impairment, cardiomyopathy, difficulty walking, muscle fatigue, low muscle tone, difficulty swallowing, and chewing his food. As our son's disease continues to progress, it is imperative that treatments and drug therapies with great potential for slowing or eliminating mitochondrial diseases need to be found.

Bryan's treatment is focused on addressing specific symptoms of the disease. For instance, seizure control, GI issues, neurologic, vision issues, and so on. Since Bryan was diagnosed, he has taken some form of a mitochondrial cocktail comprised of Co-Q10, L-carnitine, and B vitamins. Bryan also takes two over-the-counter meditations twice a day, Prilosec and Zantac, to help control his very frequent and debilitating bouts of acid reflux. To treat neuropathy in his lower limbs and feet, Bryan takes Neurontin for over 20 years which provides moderate relief from the cramping in his legs and feet. Currently, and sadly, there are no known medical interventions to address his retinopathy that has left him legally blind.

During puberty, Bryan developed a seizure disorder and was treated with Tripletal twice a day. Thankfully, Bryan experienced his last seizure over five years ago and tapered off seizure medication. Bryan continues to have low levels of essential amino acids, typical for patients with mitochondrial diseases. We mix a powdered form of L-citrulline into his morning beverage each day. As the disease continues its progression, Bryan's muscle tone in his mouth, throat,

and esophagus has decreased, leaving him at risk for choking and aspirating thin liquids. Therefore, caution must be taken around mealtimes as beverages need to be thickened to prevent aspiration and food must be cut to prevent choking. Mealtimes and going out to eat can be challenging at times.

It's difficult to determine how well the current treatments are working to address Bryan's most significant symptoms. I feel that many of the treatments serve as a Band-Aid, cobbled together to address immediate concerns, but do not make any lasting impression towards curing or slowing the progression of his disease or reversing the damage already caused. Can we attribute Bryan outliving the prognosis we received from his doctors in 1996 from this Band-Aid approach, or other more holistic approaches we have employed, such as physical activity, strength conditioning, nutrition, social engagement, and his overall positive attitude? The answer is, we're really not sure. With so few treatment options, we have no choice but to stick with the Band-Aid approach and hope that new treatment options become available.

When thinking about the approaches to treating mitochondrial disease, there are also downsides to the treatments and side effects of the medications that patients experience. The individual medications used to address the symptoms that manifest from the disease each have their own set of side effects, some are manageable, and some may not be worth sacrificing one's quality of life.

As Bryan's primary caregivers, we constantly weigh the benefits of continuing with treatments that address only the symptoms but have little impact on curing the disease. Keeping up with the medication schedules, side effects of multiple drugs, the cost of customized cocktails and supplements, therapies, and medical appointments is a full-time job and impacts our entire family.

So short of a cure, if I could envision what an ideal treatment would look like, I see two things. First, I would like to see development of a treatment or a disease-modifying drug to slow the progression of mitochondrial diseases, similar to Tecfidera that's used for patients with multiple sclerosis. Second, any potential new drugs should also seek to repair damaged mitochondria so that the organs, systems, and other bodily functions could rejuvenate with the influx of healthier and more powerful mitochondria. If such a treatment option or new drug was developed, I feel there may be potential for Bryan to see that, care for his personal needs, walk without assistance, or live independently someday. Restoring dignity for patients like my son and so many others is so important. No one wants to be showered, assisted in the restroom, and fed by their parents. It is a humiliating experience for a 26-year-old man or anyone to endure. Implementing small steps to improve Bryan's quality of life could sustain him until a cure is found.

Thank you for the opportunity to provide my input into this very important process.

(Applause.)

MR. VALENTINE: Let's give a joint round of applause to this amazing group.

(Applause.)

All right, everyone. We have made it to our final set of polling questions for the day. So, for all of you representing patients, pediatric patients with neurological manifestations of mitochondrial disease, pull out your phone, your tablets, your laptops. We're going to ask you some questions about your current approaches to treatment as well as your thoughts about future treatments.

Our first question for you, jump right in, is: What prescription medications does the patient take now to treat symptoms of mitochondrial disease? Select all that apply. Just so you know, we will be asking you similar questions related to vitamins and minerals, other dietary supplements, as well as other types of quote/unquote treatments, things like lifestyle modifications, assistive devices, and the like. This question really focuses on prescription medications, whether that be a prescription drug or a vitamin that you receive via prescription.

The options here are, A, pain medications; B, heart medications; C, antidepressants and anxiety meds; D, muscle relaxants; E, IVIG; F, diabetes medications; G, experimental medications as a part of a clinical trial; H, other prescription medications not listed on the slide; or, I, no prescription medications. Again, please select all that apply.

While the results trickle in, clearly there's a lot of things that are not on this slide that we're going to be discussing when we get to our audience discussion, as our panel just previously. Those things we did list, since we did need to narrow it down, we have a range of experience with pain medications and antidepressants and antianxiety medications, as well as muscle relaxants. Also, some experience with heart makes and IVIG. And then some experience, not much, with experimental medications as part of a clinical trial and diabetes medications. Nobody who is a patient is not taking any prescription medications.

Our next question is on vitamins and supplements. Here, select all of the vitamins and supplements that a patient takes now to treat symptoms of mitochondrial disease. The options are, A, Co-Q10; B carnitine; C, riboflavin; D, creatine; E, vitamin E; F, alpha lipoic acid; G, vitamin B, ketamine, or niacin; H, idebenone; I, other supplements or vitamins not listed on this slide; or, J, the patient does not currently take any vitamins or supplements to help with their mitochondrial disease. Please select all that apply to you.

We're going to be just a few more moments to get in the responses. Again, there are a lot of supplements and vitamins that are not listed. As reported, of those that are, the greatest experience is with Co-Q10 riboflavin, followed by carnitine and vitamin B. How are these experienced across the board? There may be one or two people that are participating that are not taking their -- a patient that is not taking vitamins or supplements.

Our third category of approaches to treatment: What are you currently doing to help manage mitochondrial disease or mitochondrial disease symptoms? Different strategies and other

types of ways to try to get at mitochondrial disease symptoms. Select all that apply. A, physical therapy, including aqua or hippotherapy; B, modifications or accommodations at home or school; C, occupational therapy; D, use of adaptive devices; E, speech therapy; F, choice of diet; G, stretching; H, exercises including cardio or strength training; I, mental health services; J, no strategies, outside of prescription drugs or vitamins and supplements; and, K, other. So some other strategies that are beyond prescription drugs and vitamins and supplements that are not listed on this slide. Again, select all that apply.

All right. While final results are trickling in, it looks like that strategy which is most represented in the room today and with us on the webcast are modifications and accommodations at school and home. Second tier behind that is use of adaptive devices, physical therapy, and choice of diet. However, there's a fair amount of experience in each of the other strategies, including others not named. So please do not be shy when we turn this over to the audience to let us know what those strategies are. Finally, there is nobody represented today that is not doing any kind of strategy that is listed here.

All right. Our next question is, in general, how much do the selection of medications, therapies, lifestyle changes -- all the things we just asked you about. How much do they, together, improve the patient's quality of life? Your options are, A, there's no benefit; B, they help somewhat; C, they help a lot; D, they provide a significant benefit; or, E, you're not sure how much these things are improving the patient's quality of life.

Okay. The final results are coming in. It looks like overwhelmingly those represented today view them as helping somewhat. Nobody reported that they provide no benefit. There's some amount of you just, under a fifth, that are reporting that they help a lot. Under 10 percent are saying there's significant benefit. And then there's some of you that are not sure how much these are helping improve the quality of life.

Now shifting gears from thinking about your current treatments to thinking about future treatments. Please answer which outcome is most important for a possible drug treatment. Your options are, A, slowing or stopping progression of the disease, even if that means there's no gain in function, but symptoms won't get worse; B, a gain in function, such as energy, strength, mobility, dexterity, and cardiac function, or speech; C, prolonging life; or, D, some other outcome a possible drug treatment could provide that you view as most important.

Waiting for someone to break the tie. There we go. All right. All right. We're going to say there's a virtual tie between the first two responses here, which are, the outcome you view as most important from a possible drug treatment either slowing or stopping progression, and then very close equally gain in function. However, some of you did say that prolonging life would be the most important possible drug treatment. And nobody had some other outcome that was most important to them.

Going to the next round, we're again talking about future treatment options. Please select the ability or symptom you would rank as most important for a possible drug treatment today.

Here you are going to pick your top three abilities or symptoms. So, A, reduced muscle weakness; B, improved speech; C, reduced chronic fatigue; D, reduced GI problems; E, improved balance; F, reduced sleep difficulties; G, reduced learning disability; H, improved movement in disorders like tremors and dystonia; I, improved meeting of milestones; J, improved vision; K, reduction in exercise intolerance; L, reduction in seizures; M, reduction in headache; or, N, some other ability or symptom that you would rank as most important for possible drug treatment. Again, please select your top three.

Just a few more moments. Possible drug treatment options that are most important to you, we're asking you to select your top three. As it stands, it looks like the greatest response is you would like to see reduction in muscle weakness, followed fairly closely by reduction in chronic fatigue and improvement in speech. Then, again, across the board we're seeing those represented here today saying that the top three most important things, they would like to see each of these things. Those that are kind of at the bottom of the list are reduced learning disability, reduction in headaches. And then of course there are some saying other things, which of course we want to hear more about during the discussion.

And our final question for the day -- I recognize that's a little small, so I'll try not to do that for everyone. Which of the following factors would influence your decision to have your child take a new medication or just get a clinical trial or research study for a new medication? Select all that apply. So here, we're talking not just about now the benefits of a product but some of the tradeoffs. So what tradeoffs would be important to you. So, A, would you consider significant risks of serious side effects such as cardiac and kidney issues; B, common side effects of the treatment like nausea and headaches; C, would you consider the way that treatment is administered, whether it's oral, IV, or subcutaneous; D, length of treatment, requires hospitalization or frequent doctors' visits; E, the burden of administration, whether there's the need for anesthesia, radiation exposure, or surgery; F, whether there's required a changing of your current treatment or management plan, such as needing to stop a medication, supplement, or exercises; G, the cost and/or travel required; H, none of these factors would influence your decision to use the medicine; or, I, some other factor not listed that would influence your decision. And please select all that apply.

While final responses are trickling in, it looks like that factor supported by, A, most represented today as being the thing as factor that would influence the decision to take a new medication or participate in a trial, and that is significant risks of serious side effects of things like cardiac risks and kidney issues. After that, there's a pretty good spread. Perhaps number two on the list being the burden on the administration, things like anesthesia, radiation, surgery. But pretty much everything else across the board is also a top, fairly high-rated factor that people would consider. No one said that none of these things they would consider. It looks like a few people said there were other things possibly that they would consider.

So, with that, that concludes our polling.

Now to our final audience discussion for the day and of the afternoon building on these questions that we just asked and you reported to us, the different types of treatment approaches that you're using for you and your children. You told us about what those things are, and for the most part there's reporting that there's some value that these treatments are providing. But we would like to dig in a little deeper and understand, of the things that you're using, when thinking about particular top burdens for you and for your child, what are the things that are really working the best to help with those key pain points, and what things maybe have you tried that aren't working so well? So, kind of a player's choice, if you want to talk about things that are working well or if you want to talk about things that aren't working well. But what we want to hear are those treatment experiences that are important to you. We'll start right here.

SPEAKER: So, in thinking about what you're currently doing, and I think this was one of the polling questions where people said "other." I think one of those other categories may be the avoidance of certain things. As opposed to actively doing physical therapy or occupational therapy, we're avoiding certain activities with our children, including having them in a reduced school day or home schooling so they're not exposed to certain germs that kids are frequently exposed to in school, or not participating in certain social activities with peers or with family members, even avoiding like sports activities sometimes. It's not really so much an active thing that we're doing, but more of an avoidance of things that we're doing.

MR. VALENTINE: Sure. And I think that's certainly consistent with what others have said. In your experience, Stacy, the avoidance to help with which aspects of mitochondrial disease?

SPEAKER: I think it's the management of the energy limitations, which is kind of a byproduct of the overall muscle weakness, the unpredictability of the disease, all of those things. But I think somebody talked earlier about making plans, and you never know exactly what the day is going to bring; are you going to wake up and feel good and be able to do what you planned, or are you going to wake up and not feel good and you have to cancel your plans? So, I think it's really conservation of the energy.

MR. VALENTINE: How would you rate how effective avoidance of that is helping?

SPEAKER: I don't know. It's hard to rate a negative. It seems like it's pretty effective, because there were times where we have made our children and us kind of push through because of some sense of overriding obligation that we have to participate in a certain event. We definitely see the impact that it has on their energy levels for, really, days afterwards. So, I think avoiding some of those situations does help.

MR. VALENTINE: Are there any thoughts on treatments?

SPEAKER: I'm Annette. My husband's watching and son Jagger. In terms of the treatments of symptoms, I thank you for voicing sort of the symptoms and struggles that they're going through because it helps me understand my son. But in terms of treating someone with the

symptoms and conditions, it's hard when you look at your son screaming in pain trying to figure out what exactly is wrong him. Is his stomach hurting, are his muscles cramping? Does he have a migraine? All these different things that come to your head. We started exploring several different things. One of the things we did at the very beginning was massage therapy. Unfortunately, all these things that we think are outside the box and cost us. We have to pay for them out of pocket. Nobody pays for this. Insurance doesn't cover it. Again, it's not medically necessary. So that really helped a lot. We had done that for several years. Unfortunately, we lost her to Delta Airlines. She became a flight attendant. And so, we're no longer able to provide massage therapies for our son, but I could tell a difference when he was receiving it twice a week. She would grease him up head to toe. She was an adult massage therapist but started going into pediatric massage therapy. I always thanked her for returning my greasy monkey. After that session, he was so relaxed and I could tell the difference.

The other thing we tried is acupuncture for his pain and seizures. That was sort of mixed. Sometimes he did great afterwards, sometimes he did not do well whatsoever, and when we moved to Colorado we kind of just stopped doing that.

And another thing we're doing right now is he doesn't get physical therapy because we cannot take him somewhere. It's just too difficult to take him out, and we have nobody that services our area. So, either my husband and I provide the therapy or he doesn't get any. But we have a chiropractor who is more of a sport chiropractor -- not a traditional chiropractor. She does acupressure and relief. Anyway, she started treating my husband for his shoulder injuries from when he slept with Jagger for the first five years always holding him and cuddling him, always the same side and the same shoulder. His fingers started to become numb, so she started treating him. And then she treated me for my back issues. Ultimately, she was telling us, well, you need to make a lifestyle change. We both sort of laughed at her. Yeah, that's great. She volunteered to come to our house, and she comes once a week -- She was just at my house ten minutes ago -- to give him some kind of, not really adjusting him, but sort of finding spots, tension, muscle tension, knots or things sort of massages and relaxing him. You can tell, sometimes he really responds to that and sometimes he doesn't. It’s kind of trial and error. Like we started thinking outside the box, and we also give him homeopathic medicine. It’s a mix of everything.

MR. VALENTINE: So, either the massage or sports chiropractor kind of work, when those were successful, how would you describe what success looked like? What did that look like for Jagger?

SPEAKER: Him being calm. Him either just not whining or crying or screaming. Just him being kind of happy, engaged with us, looking at us, taking in what we're sort of -- I play music to him. And sort of just being with us and knowing we're there, versus him just screaming. Screaming, and then ultimately just sleeping.

MR. VALENTINE: Thank you.

SPEAKER: My name is Heather, and my daughter Arden has Leigh Syndrome. I think on a broader scale -- so, for question three, what are the most significant downsides to your current treatments? I think it goes with one of the questions that was in the polling, how effective they are? And a majority of those who answered were saying it helped somewhat. There's that unknown. Nothing is for sure with this disease as far as treatment, as many have explained from all types of aspects of parents, researchers, doctors, that we hear good things but there's no definitive. So, I would say that's a downside, because there's always pros and cons to everything. Is it even working? I don't know. They say it could, so we do it.

And then another downside to that also in how it affects us is that cost financially is a huge burden on our family. Our insurance personally doesn't cover the mito cocktails, so we pay everything out of pocket. We try to get creative and figure out ways to -- equipment, adaptive equipment and therapies. Like Annette said, we sometimes take it in as parents and learn from the times maybe it is covered or from others and try it ourselves; or we have to pay out of pocket if we want to give our children the world. And a lot of it is qualities. For instance, wheelchairs or even a stroller, insurance only covers one every so many years and then after a year of having it, it doesn't work well for us anymore but then our hands are tied. We have to fund-raise or have somebody donate it, which doesn't always work the best, but, hey, it's what we've got.

I would say, in a broader scheme and as a caregiver the burden of cost and what we're doing, now is it even working?

MR. VALENTINE: On that point, kind of the uncertainty of whether any individual treatment or any combination of treatments is actually working, it sounds like what I heard today that it seems like people don't withdraw therapy in case it is working. It's hard to tell. But have there been downsides of treatments of any nature that have led you to stop the therapy?

SPEAKER: Right. Yeah. It’s like if it doesn't work for Arden, if she definitely doesn't like it or there's a negative side effect, we'll stop it. But the ones that potentially there may be a benefit or, sure, is this just her or is this what's working? We will go with it, and then we still throw out the funds because we're desperate. We want something that does work. And it instills that hope. Whether it's false or not, we don't know but, hey, it makes us feel better that we're at least doing something, trying something.

MR. VALENTINE: Liz.

SPEAKER: Hi. Brain fog. Busy day. So first in reference to -- I mentioned the woman at the Food and Drug Administration. And I said that, hypothetically, even if there was a treatment that would make me sort of whatever normal is. But if it would require general anesthesia administered like every month, I wouldn't do it. I wouldn't do it because I'm intolerant to anesthesia, and I've been unresponsive for eight hours, after surgery. So with regard to the questions, I take Co-Q10, however if I take more than two in the morning and one at night I get a headache. This of course is like, well, if that didn't happen, I would take the whole bottle.

The same for Gatorade. That too gives me a headache. That probably could be treated with Advil. But I don't want to take too much Advil and add more problems. And then, insomnia. So globally my symptoms, like anesthesia meds, procedures, etc. But then for the insomnia, that's sort like a tripping point because -- and I'm sure I'm not the only one who thinks this. How can I possibly be awake? It's mito, I should be asleep. And insomnia and mito should not be possible, by the way. But the trials that make me feel like I'm hung over even though I can't drink. I don't really know if that is the appropriate analogy. And, oh, I also have a baclofen pump. It's worth the surgery, by the way. It took me about a year to find like the ideal dosage for that, because if you do too much, or you do too little you don't get symptom relief.

In regards to finding a cure. So, Sasha. Wow. She was nine at the time and her first crush was six. And he passed away unexpected. He was in the hospital had a procedure, and they never restarted his GI tube formula which he depended on. His blood pH became undetectable and there was no brain activity, and he died. Sasha totally completely lost it because she had no time to grieve. So, like when our friends and family, when they progress you have time to grieve and process loss. But she didn't have any time to grieve or say good-bye. So, when I was at their house one night, she poked me and said: Auntie Liz, I had a bad dream. Will you read with me? Of course. What kind of auntie would I be if I didn't? I asked what was your bad dream about? Auntie Liz, I'm afraid you're going to die. And that it felt like a knife in my heart. And I said, honey, we're all going to die. Just make the most of what we have, like live day to day, like be good to your brother, be good to your parents, grandparents. And then I said: Sasha, honey, I'll do whatever I can to find a cure mitochondrial treatments because you can't cure without treatment first. then she said: Auntie Liz, it's okay to sleep? I said: Sasha, just remember the good times. Remember sledding, Disney, and universal and let's focus on that. Don't dwell on mito don't dwell on the bad stuff. So -- yeah.

MR. VALENTINE: Thank you.

SPEAKER: I forgot my last sentence.

MR. VALENTINE: That's okay. Thank you for sharing all of that, comments on the panel. I want to say what we're approaching the end of our time for this session, and so I do want to make sure, kind of building off where Liz was taking us, that we talk about short of a cure, what specifically would be meaningful to you from an ideal next treatment? We want to definitely have a cure for mitochondrial disease. We're all in that boat together. But as we're thinking about what we can do to get us there incrementally, I would love to know, what is it that you specifically want from treatment short of that cure? Yes.

SPEAKER: So, one of the things I felt was missing from the list of the medications was seizure medications. I think a lot of us "other," meaning that as well as other things we do for our children for medication, because it often manifests neurologically in seizures or metabolic stroke or those kind of things. I do want to see a little about that. As I list all of the medications that Patrick is on, he is on four specifically for anti-seizure because he has different iterations of

what seizures look like for him. There're different kinds. They come in different stages, and one treats one one way one treats another one another way.

So, from a downside perspective, it's the balance. How much do you medicate without making him too sedated? So, can I go up on the phenylbarbitol? Yeah. I don't want a zombie of a kid laying in bed. That becomes really important in terms of the downside. Naturally there is a sedation quality to epileptic drugs, but that affects his daily life, his ability to participate in activities, his ability to even laugh and enjoy activities, to -- you know, those types of things. I think that -- and to answer your last question, since I have the microphone-I'll answer it.. You know, I think that for me in particular we heard a little bit about lesions on the brain and that leads to metabolic stroke, one of the things that happens in metabolic crisis is this happens, and it's the healing of it. So, it's like these episodes happen, and we can see some reversal. So, some of the things Patrick has had have helped in some of the skin to look better. That's still there. It's like a permanent mark on their brain. So, for me, it's a treatment. Because I was just saying yesterday, I see the potential. This is my child. This IVI and some of the medicines, I see it. He's trying to communicate with me. He hasn't had words since he was four years old. Four. He is 11. He's trying. He's tried every kind of communication device out there.

But you just need to unlock the box. The box is creeping open, and that's what I'm looking for and I think it's in the brain. It's getting what he needs, that energy, something that's going to get the energy of the brain, to empower it, to do what it's supposed to do, what it does in our bodies and our brains.

So that's what I'm looking for. Whether that's a therapy, whatever that is. Whatever that is, a drug, I don't know. But something that could do that, that would unlock a lot of doors for a lot of our kids. But also improve our quality of life, which is I think that's what we saw. At least stop the progression. We would love him to improvement. That's why you see bother of those boxes checked. But also on the flip-side, we want to get quality of life back to them.

MR. VALENTINE: Other thoughts on ideal treatment?

SPEAKER: As far as treatment, I don't know how to articulate this, I am not good at this. Maybe just streamline trials of approved drugs that already exist for use. To kind of piggyback on what Heather was saying, there's medications that I believe are out there that I know are out there that are cost prohibitive because it is off-label use for mitochondrial disease. Specifically, there's a medication acetylbuterate that is approved for a different kind of disorder, and just by happenstance they noticed that it improved the function of the PVC in these patients who do not have mitochondrial disease.

But if we were as a family to say that would be great, that would be maybe life-changing for her. We looked into lactic acidosis, we looked into it and it would be about $1 million a year out of pocket, whereas that is not the case if it were approved. So, I believe there's medication that exists that can help our kids or that we could just -- you know. And just try. All we want is the chance to kind of try to help treat our kids.

MR. VALENTINE: This may not be the case, but is part of that request also to generate information about whether these things that have not been studied mitochondrial disease are going to get some new information about whether they do have an impact?

SPEAKER: Absolutely. That's the endgame, is to trial it and see and to get as many people involved as possible to get this approved to get that treatment.

MR. VALENTINE: All right. We have a couple hands. Right here.

SPEAKER: I want to start with number 3 and kind of build to number 4 actually. So, the downside of current treatment, I feel it's touching the tip of the iceberg. It's really not day-to-day or week-by-week. It's like hour-by-hour. Is what we're giving him going to be enough to last through the night? Is he going to be comfortable to last the day without having some sort of episode? And so, without the treatments, what happened is do you exhaust what you currently give and then resort to other things like opioids for his pain management if everything else is working? Which goes into the downward spiral of opioids cause mobility issues in my son Jagger. Then the next two or three days after we would give him morphine for any kind of pain episodes, he then would not tolerate any of the other 13 medicines, which then makes him go into withdrawal syndrome for the next three to two to three days, he has sweats, he doesn't sleep for two days. It's awful. It's a vicious cycle.

So short of a cure, I think for him -- and, again, this is just guesstimating sort of what he -- some of the issues are for him the muscle weakness, which causes the breathing issues and also problems with the stomach. Something that addresses the muscle and the fatigue to sort of keep him comfortable. Because whatever we have right now is not working. Like, it's really just managing hour by hour. This is not a life I would like for him. I don't expect him to start speaking and things like that. At least from my perspective, that's not my goal. My goal is just for him to have a quality of life.

MR. VALENTINE: Thank you.

Right here. I think, given time, this is going to be our last comment.

SPEAKER: The quality of life, like she said, is a big thing for us. I think we can handle being in a wheelchair, we can handle the ventilator, we can handle the trach, we can handle him not being able to eat. But him being able to have enough of the brain power, to have good conversations, to be able to go out in public, to be able to be in a crowd and not have a seizure would be such a big thing for us. We can handle everything else. Everything else is, you know, we just deal with that. But him being able to have quality of life, to participate in like more than he is able to at this point. You know, that's just a big goal.

MR. VALENTINE: Thank you very much.

That brings us to the end of our second topic and our second session for the day. Thank you to our panelists.

On our first panel of the afternoon, Annette described her son Jagger's journey as courageous, and that really stood out to me when you said that. At the end of the morning session, Phil said he saw hope as the common thread from throughout the morning. But what I would say is what I heard throughout the day is courage. And it's courage by each of you that made the sacrifice to be here today. Each of you, from everything I've heard today, personify courage each and every day. I would add that each of you are not only courageous in everything that you do on every other day except for today, but in particular because of what you brought to the table today. For those of us, like me who are on the outside of the mitochondrial disease community, you are courageous in pulling back the curtain and showing us what it means to live with mitochondrial disease. And all of you from the morning in the adult session and this afternoon in the pediatric session, I just want to thank you for letting me be a part of your community for today and for doing what you have done, which I know will be so, so important. Thank you.

(Applause.)

Now, I have the honor and privilege of introducing our closing speaker for the afternoon session, Dr. Larissa Lapteva. Dr. Lapteva is the Associate Director in the Division of Clinical Evaluation, Pharmacology and Toxicology within the Office of Tissues and Advanced Therapies in the Center for Biologics Evaluation and Research, which is all to say she is in the part of FDA that regulates cell and gene therapies. Dr. Lapteva is a board-certified rheumatologist experienced in clinical research with novel drugs and biological products. Prior to her work at FDA, she served as clinical investigator in trials conducted at NIH. Since joining FDA in 2006, Dr. Lapteva has provided scientific and regulatory advice for clinical development programs including programs for products developed for the treatment of rare diseases. Please join me in welcoming Dr. Lapteva.

(Applause.)

DR. LAPTEVA: Good afternoon. Thank you for inviting me to share a few words upon conclusion of the afternoon session. I have been here all day intently listening and watching, and holding my breath every time when the polling results were coming out to see your responses to the polling questions to better understand what it feels like to someone with mitochondrial disorder.

On behalf of my colleagues, I would like to extend our appreciation to the organizers of this meeting, the United Mitochondrial Disease Foundation, MitoAction, and Muscular Dystrophy Association, for this really invaluable opportunity to hear directly from patients who have mitochondrial disorders, from adults with mitochondrial myopathies, and from parents of children as well as some already grownup few children who have neurological manifestations as well as others, as we've heard today other, manifestations of this very heterogeneous group of diseases.

I speak here today on behalf of the Center for Biologics Evaluation and Research, as James said. This is the part of the Food and Drug Administration that oversees development of biological products and among them cell and gene therapies. It is not really coincidental, I think, that we often, maybe sometimes some of us, think about treatments of mitochondrial diseases in terms of potential cell-based or gene-based treatments. As many of you know, and possibly because you have had to learn this upon receiving the diagnosis, mitochondria are the second place of the cell -- by second, I mean second after the nucleus -- that contains the genetic material, also we call it DNA. This means that mitochondria not only work as part of the cellular machinery to perform the metabolic functions, but that they also store the genetic information that is necessary for the correct cellular metabolism.

Mitochondria are present in every cell, and they play a critical role in many vital cellular functions including, something that I know you know, we call oxidative phosphorylation, or cellular breathing and energy metabolism. Because of the importance of the mitochondrial function, the nature under the dual genomic control where information is both stored in and read from the genes contained in the mitochondrial DNA, as well as the genes contained in the nuclear DNA, any disturbance in the system controlling the mitochondrial functioning, whether it is a mutation or a deletion in the mitochondrial DNA or in the nuclear DNA, or a defect in what is called intergenomic signaling between the nuclear DNA and mitochondrial DNA. Any defect in the systems can potentially lead to the failure to maintain the correct mitochondrial functioning and to generate sufficient energy for cells and tissues.

I didn't give you this technical scientific information for no reason. I wanted to recap some of the symptoms and signs and experiences that you have talked about today, and really say that there are three important clinical implications that's come out of this molecular origins.

First, because mitochondria are present in every cell, the mitochondrial diseases often affect multiple tissues and organs, and you know this. Second, the cells and tissues that are most energy dependent such as muscular tissue and neuronal tissue, and organs that are most sensitive to the insufficient energy metabolism such as heart, brain, and eye, are frequently affected in these types of conditions.

Third, given the multitude of the genes that control the mitochondrial function, the spectrum of mitochondrial diseases is wide and it has been called to be very heterogeneous. And, most importantly, some people commented on this today, it is still evolving.

As new mutations continue to be discovered and new clinical presentations continue to be described and refined -- some people mentioned today clinical diagnosis versus genetic diagnosis. Some folks still have clinical diagnosis because the genes perhaps haven't been discovered yet, and today's meeting is really one example of how critically important it is to listen to the descriptions of the experiences of people who live with mitochondrial disorder.

We've heard this afternoon from two panels of parents of children who have experienced neurological manifestations, but as I said earlier there are many other systemic manifestations of mitochondrial disorders.

About 15 percent of people, according to polling the results, said that they lost a child with mitochondrial disease. Most pronounced issues that were talked about today were issues with communication and mobility. People talked about neurological manifestations, including stroke-like presentations and seizures and dystonia and ataxia and twitching, and of course muscle weakness and muscle fatigue and, frankly, muscle pain, cognitive decline, brain fog, and other manifestations including gastroparesis and diabetes and neurogenic bladder. I heard that many families of children, very young children, had to learn very early what it means to have a mito crisis or a mito crash. Since I was here both morning and afternoon, I had an opportunity to hear from both adults and children, and I tried to draw some parallels between the symptoms that are experienced, and of course it is the extreme and debilitating and really draining fatigue that all people who have the disorders have commented on across the spectrum of mitochondrial diseases.

I would like to mention a couple of folks who, in their own words, described what they feel, and one of the kids and his father told us about it. He said: My body doesn't work like it should. In parallel, one of the adults said: You really want your body to be able to do what you want it to do at the time when you want it to do it. And that really is very telling for, what are the experiences of people who have mitochondrial diseases?

We heard about this different kind of planning. For me, it was really eye-opening. It's not the planning of schedules. It's the planning for one activity, to be able to perform it at the expense of other activities that you would not do in order to save the energy to really try to do something else. So, one target activity which you would want to do.

The polling results said that, really, social isolation and the loss of independence were two most important aspects for both adults and kids who have mitochondrial diseases.

In terms of treatments, what I heard was -- and I'm going to use a doctor's term here. The term that we polypharmacy. Polypharmacy really is when there are too many symptoms and too many treatments, and they kind of work, maybe kind of not. So, we've heard about the available treatments that include mito cocktail, and that's -- as many of you are using it, it's really something that is individually, perhaps combined for a number of people with vitamins and supplements. But besides that, it's the heart medications and the muscle relaxants and the anti-depressants and diabetes medications. And people really said that the results there in terms of effectiveness were very, very variable, which is not surprising. And then translated into what again the number of people mentioned in their responses were more than half of the participants said that their medications work somewhat or help somewhat.

I will quote another participant from today's meeting, when they said my worst day is every day. You know, when they said that, I really thought that we need treatments. Regardless of

the outcome of how they measure it, we want people to say that my next day would be better than their previous day. Or, if not better, at least stable or predictable, where you could potentially try to decrease the progression of the disease, prevent it from going downhill or stop it altogether.

All of these conversations today and really hearing these experiences were truly very, very important for us. For us, I mean for those who work in product development, medical product development. These descriptions of symptoms and signs and explanations of treatment preferences really help us design better studies and find new treatments and eventually help develop these treatments that would stop these devastating symptoms and save lives.

I think it is also quite remarkable that the mitochondrial community is very strong in your patient advocacy efforts. These efforts go well beyond just communication and support given to patients and families. These efforts extend to educating clinicians and healthcare professionals about the mitochondrial disorders. They also include work towards history data, which can be quite challenging in this group of diseases.

I was very impressed to learn that the mitochondrial disorders community also works towards helping development and creation of treatment guidelines for the diagnosis and treatment of mitochondrial disorders, and that help creating stakeholder collaborations to help finding new treatments for different types of mitochondrial diseases.

I recently came across an article, and that article was a systematic review of actual histories studies in mitochondrial diseases. Some of you may be familiar with it. In the article, the authors found 37 history studies that encompassed 29 disease entities, or disease subtypes, in mito disorders.

So, from the perspective of drug development, we always encourage those to look at the available natural history data and to try to leverage these data in product development. This published summary of 37 studies and 29 disease supplements was I think really very telling of what someone may find when they go and look at different clinical gene mutation manifestations of mitochondrial disorders. But also, in my mind, it is I think one perfect setting of where multinational collaboration, really creation of a shared network for information exchange and data collection for different disease subgroups, can be truly beneficial for the development of new treatments -- not just one treatment but multiple treatments -- where descriptive clinical and laboratory information, as well as information related to prognostic factors can be collected systematically. And when these data are readily available, the different subtypes of diseases, they can really be used as comparative benchmarks in product development and really speed up development of new treatments.

Some people mentioned today, more than once, parents of children who have mitochondrial diseases. They said that their doctors predicted they would live an X number of years, and many times their kids actually lived well beyond the predictions that were given. If you were to accept a doctor's mistake, it is this kind of mistake that you would really want to wish for;

because understanding or better understanding the prognostic considerations and the prognosis of different treatments and the different subtypes of mitochondrial diseases is really important, I think, and we don't have a lot of information about that.

I also would like to emphasize the role of patients and patient advocates as equal partners in product development. The perspectives we see from those who have experienced the disease are truly, truly invaluable in forming developments and design, and making good quality, safe and effective products, whether drug products or gene therapy products or medical devices, patients are the best advocates for their disease because they understand its context and they understand the activity-changing and life-changing impacts of disease. Patients would be in a good position to advise on the choice of clinical outcome assessments, the assessments that we use as measures of disease improvement and clinical trials. And patients can tell -- and they often do, and we witnessed it today -- as to where the risk tolerance would be and where the tradeoffs and what the tradeoffs would be for specific treatments. And patients and their families often provide critical input about the benefits and risk assessments of nutrients, as well as the other treatments that they have experienced before.

In the past several years, FDA has started and continued to implement some new initiatives that incorporate patient voice in the development of drugs, biologics, and medical devices. Today's meeting is called, as you all know, "Externally-Led Patient-Focused Drug Development Meeting. But I'm sure many of you know that this initiative grew out of the FDA initiative which called is internal -- so all of this is relative, external, internal. But that was the initiative that ran under the reauthorization of the Prescription Drug User Fee in 2012. We have patient development meetings conducted on MDA campus internally, so to speak, and we have had 24 such meetings and they were so informative and so helpful that people started conducting similar meetings and communications, as James has helped conduct. These meetings are now ran by the patient advocacy organizations in similar form that they were conducted at FDA.

In 2017, FDA formed the patient affairs staff in the Office of Commissioner to coordinate patient initiatives. In 2018, FDA and the National Organization of Rare Disorders signed a memorandum of understanding to enhance collaborative activities and incorporating patient experience information into the regulatory decision-making, and to better inform the FDA review staff about what is important to patients.

Under this memorandum of understanding, we now conduct listening sessions, where FDA reviewers can hear directly from patients and their parents and caregivers, patients with specific conditions. This is really very helpful to us in making assessments of the respective studies when they come in and see these applications, and it's helpful to understand what is important, again, in terms of disease burden and risk programs and the tradeoffs and impacts on the quality of life.

We also are developing a series of documents on the methodological approaches to and representative input from patients, the input that can be used in drug development and

regulatory decision-making. In the Center for Biologics -- and I think the same can be true for the Center of Drugs -- we include a special section on patient input in the review of marketing applications that are sent to us.

When we see programs for diseases or mitochondrial disorders, we usually encourage product developers to engage patients in the development of new treatments, and not after the fact but at the time of the study design, the time when you're thinking about developing specific product. Today, I would like to use this opportunity to really encourage your advocacy community to continue educating product developers about what is meaningful -- meaningful to you -- in the reduction of the disease burden, so that the future trials of mitochondrial disorders can incorporate those clinical endpoints or measures that are tangible and important to you and meaningful to you and your loved ones.

This kind of dialogue is really extremely helpful, not only to FDA and to the industry, but also to the participants of academia who are here today and probably joined our webcast, because the perspectives shared today can really help a number of stakeholders identify areas of unmet needs with mitochondrial disorders -- which we heard today are many -- and find and develop new tools that can help assessing the new normal medical treatments.

As healthcare professionals and researchers and regulators and industry partners, we all learn from you, the patients, every day, and it is your active participation that helps us design better studies and find new treatments and develop new approaches to how we can combat these very serious and devastating diseases.

I would like to once again thank the organizers of the meeting today, the United Mitochondrial Disease Foundation, and their partners and many caring individuals who were helping to put this meeting together an d who do a lot of other efforts in patient advocacy for mitochondrial diseases, and I would like to thank all of you who participated here today and those who are listening online. It is your stories and your experiences that help move progress forward.

Thank you.

(Applause.)

DR. YESKE: Thank you, Dr. Lapteva, for preparing very thorough, comprehensive, insightful comments to wrap up this afternoon session. It is a perfect segue for our final portion. If you can bear with me, we will try to get this wrapped up in 10, 15 minutes. It's been a long day. I really appreciate that a lot of the adult patients in the morning have returned and sat through the afternoon session. And, vice versa, that many of the pediatric patients or caregivers of pediatric patients took the time to listen to the adult perspective in the morning. I think it's reflective of a community that's inclusive and curious and key to support each other, and these are great attributes of the mitochondrial disease community for sure.

So, to kind of wrap up what Dr. Lapteva shared with us and Dr. Kempf earlier, of course both clinicians, James suggested that we ask Dr. Hirano and Dr. Goldstein to share a couple thoughts

from a clinician perspective on what they took away from today. And, of course, when you ask doctors to write something, it's like a prescription for Co-Q10. So, I'll do my best to interpret this and distill it down.

From Dr. Hirano, who unfortunately had to leave a little early to catch a flight, for him it was really telling that most adults with mitochondrial disease have high myopathy. I think he knew it coming in, but it just affirmed through the comments, the polling, and the discussion that came out of it. Most importantly for him from a patient experience perspective, there are good days and bad days that are unpredictable. So, it's that unpredictability of the disease I think, to a clinician hearing it from a patient's perspective, really stuck with him. And, lastly, adults with mitochondrial myopathy hope for therapies that will improve function. This gets back to that key question: What's most important to you, slowing the progression or regaining function? And I think this morning it was really skewed towards the gain in function, whereas this afternoon with the pediatric population we saw a little bit of a split vote there on the ballot. So those were his key takeaways.

For Dr. Goldstein, who is extremely thorough, her takeaways were really about the fear of progression, the fear of death. I think that really left a mark with Dr. Goldstein. The comments around socialization, which I think is again a thread that we heard over and over again in various formats. The fear. It keeps coming back to fear, and anxiety around an infection that could quickly lead to some kind of a mito crash that leads to days and weeks and potentially months of recovering from that. I think doctors really spend a lot of time concerned about this, as well, and addressing those things as quickly as possible.

From the teen perspective, sort of transition from pediatric patients to adulthood, it was really clear that we need to give some thought as a community to that transition, and the challenge of clinical care in a pediatric setting, Children's Hospitals, and as the patients age they begin to move into a healthcare system that perhaps isn't nearly as familiar with the disease and with them as individual cases. So that's a real takeaway, and certainly I think for us as an advocacy group there's great fodder for where we can continue to apply our mission.

Then lastly, from Dr. Goldstein, the number of specialists that are needed. It speaks to the complexity of the care. I don't think anybody is surprised by that. But that perhaps most importantly in this afternoon's session, that need for neuroprotective agents. That, if forced to distill it down to what's most important for you, it's maintaining that cognitive ability; so that if you have a child or someone in your life that is present and they the life that all of us would hope for.

I thank Drs. Hirano and Goldstein for those comments and for your assistance today. Thank you very much, we appreciate that.

Before I briefly summarize the next steps -- because I think it's really important that we all leave here understanding that this was not a one-day event, that we did it, we check a box, pat each other on the back, and thank the people that were here with us and online with us all day; but,

really, this is part of a process that continues of gathering patient perspective. It's incumbent on the patient advocacy groups that are involved here to continue to look for ways to more deeply involve patients in all of our mission delivery. There's lots to do. But we do want to take a moment just to thank the people that made this meeting possible.

Of course, our collaborators once more, MitoAction and the Muscular Dystrophy Association, thank you for all of that collaboration, organizing, bringing the meeting together, being a part of it, and also being a part of its success. Thank you very much.

(Applause.)

Financially, our platinum sponsors are really the ones that gave us the ability to put on the scope of meeting that we held here today. Of course, we want to thank Stealth Biotherapeutics, Bio Electron, and Edith L. Trees Charitable Trust for their support.

(Applause.)

Many other groups and organizations contributed financially, and really their time and effort, many in-kind donations to this as well. We see them listed on display as well. We would like to take a moment to thank them, too.

(Applause.)

In terms of the next steps -- actually, let me just pause for a second there, because I don't want to get into next steps and forget maybe two more things about today's meeting. One is we should take a moment to thank the FDA once more for accepting our letter of intent to do this, for their deep engagement in the meeting by providing speakers, but also, the number of individuals both here in the room and online who participated. Thank you very much. We really appreciate it.

(Applause.)

DR. YESKE: Of course, the person that should not be forgotten sitting at the front here for his great efforts -- and, again, not just today. It's been over the last year that we've worked very closely with James Valentine to pull this meeting off. But your efforts today I think demonstrated to everybody your abilities in this field. Thank you very much.

(Applause.)

DR. YESKE: Okay. Enough of that. So, the next steps. As a tease here already, I have really two calls to action coming out of this, because again this is not the end stage here today. The first related to this meeting is, we did poll during the morning sessions and afternoon sessions; we gathered some data there, but we had to restrict the number of responses, we had to restrict the number of questions, and obviously in that setting AND that context you can't really give free text responses. So, we felt it really important to run a post-meeting survey -- you see the link here displayed -- that all of you that are either patients affected by mitochondrial disease

or caregivers of one of those two populations that we covered today, mitochondrial myopathies in adults and neurological manifestations in children, please go take this survey. A couple questions came up during the day. If there are multiple people affected in your family, take it multiple times, absolutely, but we just ask restrict it to one response one time for each person that you're trying to represent in that survey.

That survey will be open for 30 days. Please don't wait for 30 days but get started right away, while you're thinking about it now, that there's every opportunity to list different priorities and, importantly, help us understand the many of those responses that fell in that "other" category; because now little boxes in there, texts, fire away. Give us all the detail we need to understand what was most important to you. So that's really important, and I do hope that you'll take advantage of that survey. That will help us in putting together the Voice of the Patient Report, which I will speak to in a second.

If you have any questions -- I noted this because I didn't want to forget it -- please, reach out to UMDF if you have any questions, but I think it would be self-explanatory.

So, the report itself. Please know that everything presented today has been captured in detail down to every umm, ah, our transcriptionist over there if you've been watching her, she's between very faithful in capturing everything. We'll pull that together. Use that as fodder then for putting together the Voice of the Patient Report there's a summary of this meeting. That will be shared with the FDA to ensure that how it was captured is consistent with how they perceived the meeting and the outcomes of it. Our intent is to have that report ready to share with everybody by the June UMDS symposium back here in this area in Alexandria, Virginia, June 27 through 29, if I'm not mistaken, this year. So that report will be publicly available. We'll encourage all of our collaborators to make it publicly available. We want as many people as possible to use that as a reference, not the least of which is FDA itself. As new drug applications begin to arrive and while they're considering sponsor efficacy data, safety data, they have the opportunity to also bring that patient perspective data to the table. So, the report will be quite a big activity over the next several months, but we are looking forward to pulling it together and getting that out to all of you as soon as possible.

My last call to action is to continue to understand the patient perspective, we need to know where you are, who you are, and we have a registry to do that called the Mitochondrial Disease Community Registry. You can find out all the information about that on the UMDF website, UMDF.org/registry. The idea there is that by having you sign up and having you identified, having you characterized from the patient perspective, we have the opportunity to continue to conduct studies from the patient perspective. And these will be critically important going forward as complementary data to clinical data that will be generated inside a clinical trial itself. So, please, if you come out of the meeting and complete the survey and join the registry, for sure, we will regard this as a huge success of the day.

Finally, I would like to just introduce the chairman of the UMDF trustees, Brent Fields, who is going to provide a couple comments from his perspective on the day and wrap things up for us. From me, personally, I thank all of you very much for your participation today and I look forward to interacting with all of you going forward.

(Applause.)

MR. FIELDS: Let me just first say, if you're still on the room or watching online, you deserve some gold medallion of endurance. Congratulations. Talk about energy. It's been a very long, powerful, but I'm sure incredibly draining day, and you're to be congratulated for whatever role you play.

And, wow, what an unprecedented monumental day of impact for all of us in this space of mitochondrial disease. I've been hanging out in this space in one way or another for about a decade, and so I've been to a few days on the Hill and fund-raising events and symposiums. I'll tell you, at this moment in time this by far stands out as one of the most powerful -- maybe the most powerful -- experience I've had that will live with me for a long time.

I think about today the vision that comes to mind -- and just humor me if you think I'm overshooting a little bit. But I think of the NASA moonshot of the early '60s, when those famous explorers on Apollo put a flag on the moon and talked about a giant leap for mankind. I feel like, in just as meaningful a way today, we collectively put a stake in the ground today and said: You know this thing, this mitochondrial disease, it's real, it looks like us, it feels like this. And I think it will forever change the way it is looked at and dealt with because of what you said today and what you've done and what you shared.

For the patient community to come together and make your voices heard and make these perspectives inescapably clear is a powerful, powerful thing, and I hope you feel that power today.

I want to just offer a closing comment about what this meeting means, and I will use my own perspective that you probably needn't know why that even matters.

Formerly, I served as the chair of the Board of Trustees for the United Mitochondrial Disease Foundation. I've been on that board for a while. I am honored serving as the Energy For Life team captain at our local walk in Central Texas for the last six years, and my wife and I have given and raised a little over $100,000 for the cure. And I'm a donor, I'm an advocate, but most importantly I am dad to a 10-year-old girl named Chloe.

So, I want to tell you from the perspective of a dad what this day means to me. And I have to mention my partner Suzette, who is the real rock in the Fields family. I get to be behind the podium, but she is the person who really makes our world work. I think of her, because I'm here today because she is at home managing the care of our daughter. So, I think of all the other patients and family members who, for whatever reasons, couldn't be here but you helped make their story known. And because of our amazing panelists, we all felt heard and seen and

understood today in a powerful way. You told our story for us. I think it's a powerful story that will inform and influence things beyond your wildest dreams.

I can only imagine what you felt up here on this stage as you verbally uttered things that most of us are afraid to admit in our deepest, darkest corners of our heart, to utter those words about your life and the life of your kids. I remember sitting a room like this, listening to our panelists practice, and I am such an emotional wimp I literally had to leave the room. I just couldn't handle it. For you to stand here and try to tell such an important story in five minutes and share it for the world and utter words that are really, really hard to hear come from your lips, you honor us, and we're inspired by you.

I want to acknowledge what it took to get here. I think every person that has approached this mic has said it in different ways, but the miles you traveled, the care of your loved ones that you had to ensure to someone else, the time and effort to try to articulate such complex and painful experiences in five minutes or less. The authenticity and vulnerability that you allowed us to experience. I heard someone say, one of the panelists I was talking to earlier and she said: You know, I'm not a professional speaker and this is not my strength. And I said: I think that's the very reason it's so powerful, because there was nothing about what you shared that was off the cuff or nonchalant.

So, I want to play caregiver a little bit, and suggest that all of you have spent a lot of energy in the last year, months, weeks, and today. So, practice some good self-care tonight and in the days to come. Get the kinds of things that you need from each other, because we are a village and we get through this together. Right?

Then I guess just final words, this day will forever live in my memory as one of the most special moments I've ever shared in this arena. But it's bigger than today. It has global impact that will go beyond today and this week, this month, this year. As evidence of that, I want to remind you that there will be a recording of this day made available on the UMDF website. So, look for that soon, and please share that for those who couldn't even participate live-streaming today.

Several of the panelists mentioned, there is no normal day in the life of a family dealing with mitochondrial disease. And we always have great intentions and hopes and plans that usually get turned upside down in the blink of an eye. So, think of those people who would be empowered to hear what was shared today and make sure they know about that recording.

I know I'll see a lot of you in June. But, again, on behalf of everybody, thank you for who you are, for what you deal with and manage and survive, and for letting us really be a part of that in intimate ways today.

With that I bid you goodwill, and we'll adjourn. Thank you.

(Applause.)

(Conclusion at 5:10 p.m.)