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INBORN ERRORS OF METABOLISM

PATIENT-FOCUSED DRUG DEVELOPMENT

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P R O C E E D I N G S

DR. EGGERS: Good morning, everyone. I guess I don't have to tell everyone to take your seats. Usually, I have to give a pretty rowdy crowd a few minutes to get settled but you guys are ready to go, so I think we should get started with this meeting.

My name is Sarah Eggers and I'm in the Office of Strategic Programs here at FDA Center for Drug Evaluation and Research. I'm going to let my colleagues introduce themselves in a minute, but I want to welcome you here to an important meeting in inborn errors of metabolism. We have a very engaging discussion ahead and I'll explain the format of that discussion a little bit later on before we get into it.

But just a few housekeeping things and agenda items. So on the agenda, we're first going to have our FDA colleagues set the context for why we're here, why this meeting is important, a little bit of background. I'll come back and give an overview of the discussion format before we get into it.

This meeting is very different from meetings that FDA or others in regulatory agencies might conduct on this.

Then we're going to have two discussion topics today. The first discussion topic will be on the disease symptoms and daily impacts that matter most to patients followed by a discussion after a break on patients' perspective on current treatment approaches to treating inborn errors of metabolism, and this includes things such as participating in clinical trials and your experiences with treatments.

There is an open public comment session today and this gives people a chance, not just the patient and the patient representatives in the room, but anyone a chance to contribute a few comments on this topic of IEM or other things you think are important. We'll ask you to sign up at the registration table. If you haven't done so, depending on the number of people who sign up, we'll set the time for that. It will be no more than three minutes and we'll ask you to keep your comments short. We want, really, to engage in the discussion on the two

discussion topics.

And then we'll have some closing remarks by my colleague, Teresa Buracchio at the end of this meeting.

There are restrooms located around the corner behind that kiosk and keep going down the hall. There is a kiosk here for light refreshments. Please feel free to get up as you need whenever you need. And if you need anything during the meeting, my colleagues are around.

This meeting is being recorded. It's on the webcast and I want to give a special welcome to those of you who are attending on the webcast. You will also have every opportunity to participate today through the facilitated discussion, through the -- by submitting your comments. As we ask questions up here, just go ahead and respond to those through the webcast. And the meeting, as it's being recorded, a transcript of this meeting will be posted on our website some days following the meeting.

So with that, I'm going to ask my colleague, Do9na Griebel, to come and give some opening remarks.

Thank you.

DR. GRIEBEL: Good morning, everyone. Welcome to the patient-focused drug development meeting on neurologic manifestations of inborn errors of metabolism. I'm Donna Griebel. I'm the Division Director for the Division of Gastroenterology and Inborn Errors Products in the Office of New Drugs at FDA. Our division reviews drugs intended to treat inborn errors of metabolism, or I'll refer to that as IEM for short.

We're happy to see so many patients in the room today and patient advocates in the room, and we understand that you represent a wide range of IEM disorders. And I understand that there are many more patients and advocates on the -- joining us via the web, so welcome, everyone.

Today's meeting is one in a series of what we're calling FDA's patient focus development meetings. Dr. Theresa Mullin will be providing more details on this initiative in a few minutes.

The inborn errors of metabolism include a range of genetic disorders in which the body has a

metabolic deficiency that results in a buildup of harmful substances in the body. Dr. Teresa Buracchio, who is a Medical Officer in our Division and who is also a specialist in neurology, will provide a bit of background on IEM in a few minutes as well.

This is a very important meeting to us. We fully understand that inborn errors of metabolism are serious conditions and that there is an unmet medical need for patients who have these disorders. It's FDA's responsibility to ensure that the benefits of drugs outweigh the risk and, therefore, having this kind of dialogue with you is extremely valuable to us. What we hear from you today can help us understand how patients view benefits and risks for treatments for IEM.

We also know that we need better end points to measure how well these drugs are working, and that's why we want to hear from you today about the different ways that neurologic symptoms of IEM affect your daily life and/or your child's daily life. It's also important to hear what you value in a treatment and what you would like to see in future treatment for

you or for your child.

Finally, we would like to hear about the considerations that you think are important regarding clinical trial participation as well as the informed consent process.

It's important to remember that FDA is just one part of the drug development process. We don't have primary responsibility for developing drugs or for running clinical trials. Drug companies working with investigators, researchers, and the patient community are the ones who conduct the trials and who submit the application for drugs to FDA. However, at FDA, we work closely with drug companies throughout the drug development process. In our Division, we are particularly anxious to work early and often with companies who are developing drugs for rare diseases. And through these meetings, we work together to try to ensure the trial's design will be successful in defining the efficacy and the safety of the drugs in development. Our Division firmly believes that the best access for patients to an effective drug is through the availability of an approved drug.

I know there are a lot of representatives from industry, academia and others in the room or joining us via the web. Thank you, all, as well for being here and being part of this discussion. We believe this meeting will provide valuable input for you as well.

So again, welcome to everybody. I'll burn the meeting over now to Theresa Mullin who will talk about the broader efforts.

DR. MULLIN: Thanks, Donna. Good morning and so as she said, I'm Theresa Mullin. I direct the Office of Strategic Programs in the Center for Drugs, and our office has the privilege of leading this and organizing this initiative and working and supporting our medical officers and our divisions to prepare for these meetings.

So just to tell you a little bit about this. We initiated this patient-focused drug development effort as a part of a commitment that we made under the re-authorization of the Prescription Drug User Fee Act, and this is the fifth time around for this so this is a PDUFA V is what we call it. And this

initiative is intended to provide us with a more systematic way to collect information from patients, getting their perspective on serious conditions, conditions for which there may not be very many available, if any available, approved therapies. And we realized we needed a way to do this outside of the context of a particular drug because it allowed us to just get patient input without worrying about screening for conflicts of interest or anything. We'd have a much more free-flowing and rich communication, we though, from patients. We'd hear a lot more if we could just do this independent of any particular drug, and it would inform the development of a wide range of drugs perhaps for that disease.

And we knew that the patients would provide us with this unique perspective that no one else can because patients are the ones that are going to get any benefit from a drug, and they'll be experiencing whatever risks are associated with that drug. And so this patient perspective, this unique perspective gives us a better understanding of the context of the disease and the context in which we'll evaluate the

benefits versus the risks of a new drug therapy.

We thought this kind of input would help us throughout the development process even during early stages of development to weigh benefits and risks as they emerge and as the picture of evidence emerges for a new drug as well as helping us at the time of application review. And so this patient-focused drug development initiative is one in which we commit to do at least 20 different disease areas, and we see this as piloting an approach that we think we really would like to have all disease areas. We'd like to have this kind of patient input to inform every possible disease area. Within our limited resources, we're doing 20 and then some over the next -- over this five-year period, and we're learning a lot about what's effective and what works well.

Some patient groups are even approaching us to see if we can't sponsor the meeting, would they sponsor the meeting and we come and we're trying to work that out because we think this is a really important source of input for us.

And so which 20 diseases were we going to

cover in this five-year period? So we had a public -- we put out a *Federal Register* Notice with about 40 disease areas that we identified, the review divisions identified, as ones where they felt we'd really benefit from having some more input. They didn't get -- have a lot of information -- as much as they would like. We got a lot of public comments. For the first three years of the five-year period, we've picked 16 diseases. You know, this topic of neurological manifestations of inborn errors of metabolism was a kind of a cluster and one that was on our list and is on this first three years list. And here you see the diseases that we're focusing on in those first years, 2013 to '15.

And so last year we had meetings on chronic fatigue syndrome, HIV, lung cancer, and narcolepsy. And so far this year, we've had a meeting on Sickle cell disease, a meeting on fibromyalgia. Last month we had one on pulmonary arterial hypertension, and this meeting now on inborn errors of metabolism. And on the right side of the slide, you see the ones we have for the remainder of this year and then next year

and soon we'll be coming out with our process to try to identify ones that we'll try to cover in these kinds of formal meetings in 2016 and '17.

And as you note, those are -- it's a really wide range of disease areas that we had on that slide, and just to go back for a second, I mean, very wide ranging but have in common that we really would benefit from hearing more about what it's like to live with these diseases, what do patients do today to treat their disease, what kinds of therapy do they try to work with, and so we need that across that wide range.

And so we have common themes and questions that we focus on in these meetings even though the diseases that we're looking at across the whole set are quite diverse. And so with each one, we set -- start out with a fairly basic set of questions and we use a very similar set of questions each time. We have some tailoring of those questions depending on other questions that the review division may have that they would like to probe and hear from patients about this gives them a unique opportunity to get that kind

of input, so we have those kinds of questions as well.

But we start with a set of questions about what it's like to live with the disease, what are the most bothersome, most important impacts on the patient's life from a caregiver's perspective, also from a patient's -- directly from a patient's experience and their perspective if they're able to talk -- to tell us about that. And then also, what are they doing to treat their disease are the two major themes. And these are important aspects of our benefit-risk assessment. Those two questions of the degree to which this is an unmet need and the severity of this condition are two of the -- the two components that set the stage for our clinicians to make -- try to make an assessment of the context and the benefit risk and weigh the evidence of benefit and the safety information in that context.

So we further tailor the questions. For an example, we had this meeting on HIV and there is -- there was a question the review division had about cure research: How would patients who are doing fairly well on the treatments that are available today

feel about maybe going off treatment and trying a sort of a therapy that would be considered a cure; would they be willing to do that? There are potential benefits but also risks and so it was very helpful to hear their perspective on that question.

And so we've learned that patient involvement and participation is not only important, it's what makes these meetings successful or not, so we really are looking forward to hearing your perspective today. We know that it will give us very valuable insight that we don't have right now, that later today we'll have a better -- we'll be much better informed than we are right now.

And so each of these meetings produces a voice of the patient report, and we collect the information from the patient testimony that we hear in the room. We get perspectives from the docket that people submit electronically, just statements to the docket. We also will get information from people on the webcast. And those are our three major sources. We pull this together and produce a report that tries to faithfully capture what we are hearing in the

patient's words describing how it is to live with their condition and what they think about the current therapies available to them. That report not only helps to communicate to our review staff, both those who are here, those who can't make it here, and we'll be able to use that as a resource. Industry sponsors who are thinking about developing drugs in this area will also find that useful.

And we think there's a long-run impact here, too. Some of these meetings have triggered discussions about how can we try to develop measures to better capture the things, these benefits or impacts that patients are telling us about so that if we have a new therapy that might actually affect some of those things we're able to capture that information and capture that evidence more systematically and rigorously in a clinical trial, and we may not be able to do that now. So there is what we call patient-reported outcome tools that are sometimes the discussion that follows these meetings as well and how can we try to develop those.

And so with that, I'll turn it over to

Teresa Buracchio to provide you with some background.

DR. BURACCHIO: Hi. I'm Teresa Buracchio. I'm a Medical Reviewer with the Division of Gastroenterology and Inborn Errors Products, and I'm going to provide a brief overview inborn errors of metabolism or I'll just say IEM for short and talk a little bit about neurologic symptoms that are commonly seen in these diseases.

So the inborn errors of metabolism or IEM are a group of rare genetic disorders that basically cause a block in the metabolic pathway that leaves the body unable to properly break down a substance or synthesize certain substances in the body like amino acids or carbohydrates. These genetic defects typically cause deficiencies of specific enzymes that will convert one substance to another. An example would be the sugar, galactose, to be converted to glucose. These metabolic dysfunctions can lead to progressive and permanent damage. Typically, if it's upstream of the enzyme, it'll cause a buildup of a substance that can reach toxic levels in the body. Downstream of the enzyme, it may deprive the body of

essential substances that are needed to support specific functions in the body. And sometimes it alters other metabolic pathways that we haven't yet identified.

There are over 200 known inborn errors of metabolism. Individually, these diseases are quite rare but collectively, they account for a significant disease burden in our population. The IEM disorders vary widely in their symptoms and severity and disease progression, so two patients with the same disease may have a different course of the disease. Many of these diseases are fatal in infancy or childhood or even early adulthood. However, on the other end of the spectrum, some may progress quite slowly and some patients may live to adulthood or the symptoms may not even show up until adulthood and the diagnosis may not be made until that time. So that can be the case in Wilson's disease. So we do see a lot of variety in these diseases.

The diagnosis can be difficult because symptoms can be vague and non-specific initially. And in some cases in the childhood diseases, children can

develop normally for a while and then later decline, so there can be a delay in onset of symptoms that are not recognized initially. We hope that new screening technologies will increase the identification of IEM disorders before the symptoms arise, and the hope is that earlier identification will allow for earlier therapeutic interventions to improve morbidity and mortality.

So the symptoms or manifestations of IEM vary greatly depending on the underlying disorder. IEM can affect any of the major organ systems in the body, although some of the ones that we see more commonly are changes in physical appearance, involvement of the respiratory or cardiovascular system, involvement of the musculoskeletal system with ether joint contractures or muscular weakness, liver enlargement or dysfunction and very commonly, we see neurological involvement which may include cognitive symptoms, psychological, or behavioral symptoms.

The neurological symptoms are particularly common across the range of IEM disorders and are a significant burden for both patients and their

caregivers. These symptoms are important to patients and the FDA recognizes that they have a significant impact on your daily lives, and we felt that it was important to explore these symptoms further so that they can be better accounted for in drug development programs for these diseases.

So just to go into depth a little further on what are some neurologic signs and symptoms, when we talk about neurologic symptoms, we often tend to think only of the brain, but I want to remind everyone that the nervous system not only includes the brain but also includes the spinal cord and the peripheral nerves that go out throughout the body to innervate the different organs in the body.

Some of the more common symptoms that we might see in IEM diseases are seizures, vision and hearing loss. Cognitive problems are quite common, and this can range in the spectrum from poor attention and concentration to more severe cognitive decline leading to a frank dementia. There can be language delay. We're hearing from many of you that you are seeing behavior problems in your loved ones that can be

similar to those seen Asperger's or autism disorders, things like hyperactivity, impulsivity, compulsive or repetitive behaviors, or sensory processing issues. And we are interested more about those today.

And sleep problems can be problems such as apnea or insomnia. Weaknesses are pretty common as well and along with that, there may be problems with swallowing or breathing, spasticity or stiffness in the muscles can be painful. On the other spectrum of that, we can see low muscle tone and hypotonicity. Abnormal movements can occur, things like myoclonic jerks, tremors or dystonia, coordination and clumsiness both in fine motor movements and also in walking with ataxia. And invo9lvement of the peripheral nerves can lead to numbness and tingling and pain. Pain can be neuropathic pain from the nerves or it can be more, you know, diffusely localized in the body depending on the area involved.

Bowel or bladder problems can cause a significant problem for caregivers, I know. And again, walking problems or balance problems, either patients never start walking in the first place or

they do reach the point of developing those motor milestones only to decline later.

This list is not exhaustive. As I mentioned, the nerves innervate organs throughout the body, so sometimes neurologic symptoms can be vague or difficult to localize. We want to hear about the neurologic symptoms that are important to you and affect your daily lives. And feel free to tell us about any of them, no matter how small. And even if you're unsure of what you're experience even as a neurologic problem, we still want to hear.

As far as treatment options, the goal for treatment of IEM disorders is to reduce symptoms, improve quality of life and ideally, slow or halt disease progression. Current therapies are limited. They may include dietary restrictions or dietary supplementation or medical foods. Enzyme replacements are available for a select number of the diseases such as Elaprase or Naglazyme. Bone marrow transplantation may be an option early in the disease for some of the inborn errors of metabolism or organ transplantation later.

Most commonly, though, what we see are supportive therapies, things that treat the symptoms of the IEM disorders but don't necessarily alter the underlying course of the disease, medicines to treat seizures, the use of feeding tubes, ventilators. And we're also hearing from you that many of you make use of behavioral, physical or occupational therapy so we would be interested in hearing a little bit more about those as well today.

There are many challenges in developing drugs for IEM disorders. And, of course, the most obvious one is that these are rare diseases so there are a very small number of patients with the disease. PKU is one of the more common ones but, you know, we are seeing applications come in for diseases where there are less than 100 patients identified worldwide. And within these rare diseases, then there are patients with a great deal of heterogeneity or diverse presentations of the disease. As I mentioned before, two patients with the same disease may have very different symptoms.

These diseases may occur in both children

and adults which presents another special drug development challenge because children, you know, are vulnerable patients who are not able to consent for themselves. So we have to take special considerations in mind to protect children in pediatric clinical trials that we don't have to consider as thoroughly in adult patients who are able to consent for themselves.

And then most of these diseases, again, because they're rare have very poorly described natural histories or descriptions of their clinical progression over time. That makes it difficult for us to identify what endpoints we should be monitoring in clinical trials, what signs and symptoms should we be measuring, and how do we measure them.

And if it's a slowly progressive disease, do the disease symptoms progress in a time course that's amenable to a clinical trial which tend to be relatively short? Is the measurement tool that's used applicable to both children and adults? And if biologic disease markers or biomarkers exist, are they even relevant to the disease? So these are all considerations that we have to take in mind as we

review -- as, you know, the pharmaceutical industry is developing the clinical trials and as we're reviewing them.

Now in order to help identify better endpoints for clinical trials, the FDA is very interested in patient-reported outcomes. Patient-reported outcomes, or PROs, can represent direct measures of treatment benefit identifying how a patient feels or functions. An example of this might be a pain scale or a scale that measures symptoms of ADHD. For conditions like the IEM disorders that are not well understood, input from patients is especially important. Patient and caregiver input is essential to capture important and clinically relevant disease symptoms in these PROs.

And I should also mention that although these are called patient-reported outcomes, in some cases, patients cannot report for themselves if they are too young or too cognitively impaired to give us those descriptions. So in those cases, caregiver-reported outcomes may be appropriate.

I should also say that although we do want

this information and we do want these symptoms and we want to see PROs developed, all of these PROs that are developed do still need to be validated and evaluated in adequate and well-controlled randomized trials in order to be sued in more pivotal clinical trials for drug development.

So today we are here to listen to you. There are representatives here from the pharmaceutical industry, people from the FDA. Please use this opportunity to share with us the neurologic symptoms that are important to you and that impact your daily lives. And, you know, we are interested to start incorporating these into the drug development process. Thank you.

DR. EGGERS: Thank you very much to Donna and both Theresa's/Teresa's. I'm going to give a little bit of background of our discussion format but both of you have set it up very nicely, so hopefully, I don't have to spend too much time speaking. We can get right into the discussion.

Before we do that, I neglected to have my FDA colleagues introduce themselves. These are the

experts, the real experts in the drug development and review of IEM products. So I would like you to go around and just say who you are and what office you're from.

DR. FARKAS: Ron Farkas from the Division of Neurology Products.

DR. WITTEN: Rachel Witten. I'm from the Office of Cellular Tissue and Gene Therapy.

DR. BEITZ: Julie Beitz, Director, Office of Drug Evaluation III.

DR. GRIEBEL: I already introduced myself. I'm Donna Griebel from DGIEP.

DR. MULLIN: Theresa Mullin. I direct the Office of Strategic Programs in the Center for Drugs.

DR. BURACCHIO: Teresa Buracchio, Division of Gastroenterology and Inborn Errors Products.

DR. BONA: Jim Bona, the Office of Orphan Products Development.

DR. BAUER: Larry Bauer, Office of New Drugs, Rare Disease Program.

DR. EGGERS: Thank you very much, and they will be up here to help further the discussion, ask

some more follow-up questions. If you and the -- you as participants say something that really peaks their interest or they want to follow-up on that, they are free to do so.

As we've mentioned, the two topics are the neurological manifestations of IEM, that means the effects, the neurologically-related effects of IEM that matter most to your child or your, if you're the patient's, life. Here we're looking for concrete things. What particular symptoms have the most significant impact on that daily life? How do they affect the ability to do specific activities and how do they change over time?

And then we'll move into the current approaches to treating IEM. What are you doing to treat or manage your or your child's IEM; and how well are these addressing those neurological effects; and how do you know that? How do you see, what differences do you see? What are their biggest downsides? And what would you look for in ideal treatment to better serve those needs related to the neurological effects? And then we'll move into a

discussion on clinical trial participation informed consent.

For each of those two topics, we're first going to here from a panel of patient representatives typically. We do have one adult patient who will serve on the panel, but primarily your parents who are speaking on behalf of your child or children. These participants reflect a range of experiences with IEM, a range of disorders, and a range of symptoms that you wrote in about or treatment that you have experience with or thoughts you have on clinical trials.

And I just want to say thank you to everyone who submitted comments as part of the selection process for the panel participation. Those comments really are helpful to us as we plan for these meetings and understand what you might want to talk about and what's important, what effects are important to talk about.

After we hear the panel discussions which really will set up a good foundation for our facilitated discussion that follows, and this we will broaden to include all of you, patients, caretakers,

advocates, and the audience to build on the experiences we heard in the -- by the panelists. So we're going to ask questions talk show style and we invite you to raise your hand to respond. We'll ask you at least say your first name and the IEM disorder that you're talking about. That really sets a context so we know we can put -- we can have the disorder in the back.

With that said, we're not going to be focusing on specific disorders. We're not going to run through a list or anything like that. We're focusing on neurological symptoms that are -- that you experience that we can kind of draw generalizable (sic) learnings from across all the different disease areas.

I'm going to ask the panelists now, for those that are talking in Topic 1, to come on forward and make your way up to the front table. You also, here in the room and on the web, have a chance to answer polling questions and I’m going to ask the little clickers to be handed out to everyone. So if you're a patient or patient representative, please

raise your hand.

The purpose of these questions is to really aid our discussion. They're in no way a scientific survey. They're completely voluntary. You don't have to answer the question. What they do is give us a sense of who's represented, what the representation is in the room and on the web and an indication of what perspectives you might share in common and where they might be differences. Web participants, you'll see the questions in the webcast. We're asking that patients and patient representatives only please answer, and at a certain point, we're just going to ask either the patient themselves or one caretaker answer the question on behalf of that patient.

You have to -- these clickers are -- they're not too technologically challenging we hope, but you do have to push the button very deliberately, very hard in order for it to show up.

Web participants, as we mentioned, you can add comments through the webcast. Although they won't all be read or summarized today, your comments are incorporated into our summary report and we do read

them all. We'll occasionally go to the phones to give you another opportunity to contribute and there will be information on the webcast at the appropriate time.

You can also send us your comments through the public docket. This is a website that federal agencies have that we can receive comments from the public on topics that are important to us, topics that we open a docket for. We have one open for neurological manifestations of IEM. It's open until August 11th, 2014, and we really encourage you if you're here in person or on the web to expand upon what you said here or to share your fuller story through the docket. And if you know people who weren't able to make it today, encourage them to share as well. The more information we get, the more valuable it all is. Anyone is welcome to comment. It can be healthcare providers, researchers, industry, anyone.

A few ground rules to make sure this discussion is as effective as possible. We really do encourage patients, caregivers, and advocates to contribute to the dialogue. Industry, researchers and

others, we very much appreciate you being here. We ask that you be in listening mode throughout the discussion. If you'd like to contribute, there is the open public comment.

My FDA colleagues are here to listen. They might not be able to answer all of the questions that you may have. If you do have questions for us and they can't be answered today, please either send us -- there's a patient-focused email that you've been getting correspondence on. Send us an email with that or submit a larger comment, a more -- a comment you just want us -- a question you want us to think about through the docket. We will consider it then.

The discussion will focus on those symptoms and treatment and as Teresa Buracchio, it's very hard to sometimes tell if it’s a neurological symptom. We don't want you to worry about that. If it's important to you and you think it might be neurologically-related, please share it. Same with treatments -- we don't want to focus on particular treatments. This isn't here to really evaluate your experience with any specific treatments. What we're doing, again, is

looking to see what can we learn broadly about these treatment and their development that we can continue to help improve that. If you -- again, if you have other comments on other topics, please feel free to use the open public comment period, sign up for it outside on the registration table at the break. Sign up by the break so that we know -- we have that set.

Of course, the views expressed here today are personal opinions, and we truly know there is a range of your experiences, a range of severity, a range of the difficulties and the challenges you face. But everyone here today who is a patient or patient representative or an advocate is fully aware of these challenges in your own life. You experience them and you know others who do. So we feel -- please feel free to share your experiences in a comfortable setting. We're all here to listen. With that, respect for one another is paramount. That goes without saying.

And please let us know how we're doing, how the meeting went well -- how the meeting went today. We hope it went well. The evaluations will be at the

registration desk.

So with that, we will start with a few polling questions just to get our fingers warmed up and to test these things out. If you're on the web, there are polling questions as well. First one is where do you live -- and everyone with a clicker can feel free to answer this question -- within the Washington, DC area, including the suburbs, or outside of the Washington, DC area?

(Whereupon, in response to polling, the results are as follows: within DC, 17%; outside DC, 83%.)

DR. EGGERS: Okay. AS we expected, most of you live from outside of the area. We think all of you have traveled here today to be with us and to share your comments whether you just had to come around the beltway or whether you had to travel more extensively.

Have you or your loved one ever been diagnosed as having an inborn errors of metabolism?

(Whereupon, in response to polling, the results are as follows: yes, 87%; no, 13%.)

DR. EGGERS: Yes. So it looks like if I have to do some math calculations in real time, more than 25 of you here are representing patient or you're here for yourself representing them. That is great to hear. We very much value your experience.

I'm going to ask that the rest of the questions just be answered by either the person who lives with the IEM themselves or one caretaker just so that we don't over-represent any particular individuals.

What is your or your loved ones age? We understand that many of you have multiple children, so hopefully they fit in the range or think of one child, 0 to 2; 3 to 9; 10 to 17, you'll press "C"; 18 to 35, 34 to 49; 50 or greater or your loved one has passed.

(Whereupon, in response to polling, the results are as follows: 0-2, 0%; 3-9, 38%; 10-17, 17%; 18-35, 25%; 34-49, 8%; 50 or greater, 0%; deceased, 13%.)

DR. EGGERS: We do have a wide range and that's very helpful for us. Many, many -- well, actually, we have no one here in the infantile range.

On the web, can we have those numbers as well?

(Whereupon, brief pause waiting for polled responses.)

DR. FURID-HELMS: So a lot of them -- 33 percent 3 to 9; 25 percent, 10 to 17; and 23 percent, 18 to 34.

DR. EGGERS: Okay. All right. So those of you in the -- with children or anyone, you can, of course, think back to that infantile stage, the young adults -- or I'm sorry, the young infants, but we do have a very nice spread otherwise. Yes, go ahead.

AMBER MORGAN: (Off mic).

DR. EGGERS: Okay. So did anyone else have a 0 to 2 and they pushed that "a" button and it didn't work? Okay. Keep us informed of those, too. We do get sometimes where these clickers aren't the most reliable. Again, they're not used for any scientific purposes so don't worry about that, but thank you, Amber. We'll call on you.

Okay. Is you or your loved one male or females?

(Whereupon, in response to polling, the

results are as follows: male, 44 percent; female, 56 percent.)

DR. EGGERS: Okay. So we have a roughly equal split. Is it the same on the web, similar on the web?

DR. VAIDYA: Similar on the web.

DR. EGGERS: All right. With that, let's get into the discussion Topic 1. We have five people who will comments. I've put their names up here along with the disorder that they have. I will mention I am not a medical expert. That's why we look for our colleagues to help with these questions, and that includes being able to pronounce most of disease areas, so we will be sticking to the acronyms.

So we have a range of the disease areas represented. We have one person who will -- who had a family emergency over the weekend and was unable to attend, so we will dial her in by phone at the right time. And one person, a very dedicated father, took the 6 a.m. flight this morning out of Chicago. He will be joining us when he arrives. I've asked them each to prepare about three to four minutes of

comments, so they're going to go through. And we will start with Whitney. Just push the little button and the microphone will come on. And keep it very close to your mouth. We have a hard time hearing.

WHITNIE STRAUSS: Okay. Is this alright? Okay. Yeah, so I'm the mother of a 4-year-old child with CTD. My soon, Reid, has developmental and language delays, retardation, epilepsy. The disease directly Reid's brain function but it's not a progressive disease. So it's likely that Reid will live into adulthood, and it's certain he's going to have a lifetime of constant care.

While each day we deal with the obvious hurdles, like Reid's inability to speak or perform the simplest of task, it's really the secondary sensory, behavioral, and cognitive symptoms that seem to most impact Reid's daily stresses and struggles. Reid's sensory issues play an important role in his life. Strong oral aversions and intolerance of many foods limit his diet. It's a constant battle to encourage eating and a financial strain to keep stocked with his rotation of preferred foods. As a result, Reid

struggles with grow and weight gain, is frequently ill, and is extremely irritable.

As he's grown, Reid's clothing and textural intolerances have required us to shift our focus. The 4-year-old Reid is now physically able to disrobe and he does. His preference for nudity makes it very difficult to keep clothes, diapers, and shoes on him and we've really had to integrate some adaptive devices in attempts to keep him clothed in public. This battle is ongoing.

Aggressive behaviors are also part of Reid's life. Hair pulling, biting, self-injurious behaviors and throwing objects happen all the time at our house. Curtain rods are pulled out of walls, furniture is turned on end, and home decor becomes broken or obsolete. As Reid has matured, we've seen an increase in these aggressive and destructive tendencies. Unable to manipulate toys appropriately means those toys go airborne and injuries happen. Pulling glassware off counters, spilling drinks, breaking household objects, slamming doors and pulling things out of the refrigerator are his common go to tactics

for that immediate attention.

Sibling rivalries have emerged and without any speech, Reid's natural defense is to scream, bite, or pull hair. When he's upset, Reid's now biting himself. This leaves to bruising and broken skin but he just continues to use it as an outlet for his frustrations.

As the parent of a special needs child, I fear for my son's safety. Severe cognitive impairments leave Reid without any recognition of safe and unsafe and he won't hesitate to run into a busy street, walk out the front door, jump on my dining table, or walk right into a swimming pool. As his fine and gross motor development improves, we're really forced to address these safety issues head on. While he's now equipped with the ability to climb, open doors and run, he's still cognitively unaware of the dangers involved. Reid does not respond to commands such as "no," "stop" or "come," so we're always on guard. We're discovering locks on doors just aren't enough.

Despite suffering from endless effects of

his condition, it's the sensory, behavioral and cognitive issues that hold the most power. Leaving the house, whether to go to school, a restaurant, or the grocery store requires forethought and intense preparation. To do these things means that Reid must tolerate clothing, follow basic comments, and then behave in appropriate manners. Screaming and breath-holding tantrums, refusal to wear clothing and being downright uncooperative are the usual deterrents from even attempting these social activities.

These symptoms impact Reid directly but they do take a toll on the entire family. As a mother and a caretaker, I find myself forced to choose. How do you cheer on one son from the bleachers while there other is running naked toward the parking lot? While I have a strong need to support one child, I'm forced to adapt our lives to integrate the other.

I have many wishes for my son. It's so easy to wish but that just won't change Reid. There is no approved care or treatment right now. The reality of Reid's disease touches every facet of his life and ours. And sure, I would love to hear Reid say "momma"

or stop taking his seizure medicines, but if Reid would just tolerate clothing, if he would just eat something besides donuts and pepperonis, now that would be a significant improvement in his quality of life. The little wins would be the less screaming, the less throwing, biting, tantrums and more engaged and responsive behaviors. The little wins would inch Reid that much closer to a more manageable life, even if that life does require constant care.

(Pictures of Reid on slide)

DR. EGGERS: Thank you very much, Whitnie. And now we have Christine.

CHRISTINE BROWN: As the parent of two children with PKU and as the Executive Director of the National PKU Alliance, the neurological implications of PKU affect the daily lives of my children and lives of adults and families across the U.S.

(Slides with pictures of boys.)

CHRISTINE BROWN: So my two children with PKU are Connor and Kellen and in this picture, they're standing in front of the tandem mass spectrometer which is the newborn screening test. So that's the

machine that reads those results.

So as you know, many see PKU as a success story of newborn screening. We've been screening for PKU for more than 50 years in this country. We've been treating PKU for more than 50 years. However, PKU is not solved. We're not done with it. People thought that you just could put these kids on a special diet, they would be fine. However, we now know that this is not the case.

PKU is also different from many other different inborn errors in that we are not just a pediatric disorder. We estimate that there are about 5,000 adults with PKU in the United States. Some of them are doing quite well. I know adults that are doctors, dieticians, lawyers and executives. However, many are not doing so well. They find it difficult to hold down jobs, have anxiety, cannot handle social situations, and suffer from phobias.

Certainly, we are very luck in that PKU is diagnosed and treated from birth and that that treatment can mitigate the most serious consequences of the disease. Our children no longer grow up to be

mentally disabled. However, many have deficits in executive function, information processing, and suffer from depression and anxiety. For example, my son, Connor, was diagnosed with ADHD at the age of five. Research actually shows that 35 percent of all children and adults with PKU have ADHD. However, the rate in the general population is about 7 to 8 percent. Researchers don't know exactly why this happens.

We don't know much about PKU as we thought we did even 10 years ago. We just don't understand what happens when an excess phenylalanine crosses that blood-brain barrier. PKU is still not solved and many face and struggle with neurologic consequences. It's also difficult for many in our community to control their blood phe levels within the recommended range of 2 to 6 milligrams per deciliter.

For Connor, my PKU-er that also has ADHD, his symptoms of ADHD dramatically increase even when his blood phe levels are slightly elevated. For example, last year for about four months, his blood phe levels were running in about the 7 to 8 milligrams

per deciliter. This is only 1 or 2 deciliters above the recommended range. However, during this time, he could no longer focus at school. He skipped problems on tests. He had difficulty completing simple assignments and could not follow directions that were more than one step. He couldn't even fill out his sticker chart at school to reward good behavior. He went from being a bright and inquisitive model student to one that was beginning to fail second grade, and his teachers talked to us about holding him back.

Connor's struggles are not alone. Current dietary treatment for PKU is difficult to maintain. Many in our community do not have insurance coverage for medical foods. My son, Connor, is easily disorganized, forgets the task he is trying to complete, and has difficulty staying on task. My 6-year-old, Kellen, doesn't display these signs to the extent as Connor, but I do see that his brain takes longer to process information than my other older son who does not have PKU.

And here's the challenge. Here's the catch with PKU. To control your phe levels, to be on diet

with medical foods, you have to be very organized and meticulous. You have to weigh and calculate the amount of phenylalanine in every single bit of food you take. You have to record all of this in a journal. Then you have to remember to prepare your formula, use a gram scale, remember to take that formula at least three times a day and possibly take other medication. However, as you're phe levels rise, you're ability to track your treatment and the executive function skills that you need to stay on treatment decrease and so you fail.

While I feel extremely blessed that my children with PKU have a treatment, that they are not mentally impaired, that they can go to school, they can go to college, they can have a family someday, they do struggle with executive function. I only want what every parent wants for their children. I want them to have the best outcomes possible and the best opportunities available to them. I especially worry about Connor and Kellen and how they will manage PKU on their own as they grow into young man.

DR. EGGERS: Thank you so much, Christine.

Now we have Steve.

STEVE HOLLAND: Hi, everyone. In addition to being a dad of three MPS I individuals, I'm also president of National MPS Society. The mucopolysaccharidoses or MPS for short are a family of 12 individual syndromes each missing a different enzyme that fall within the broader lysosomal storage disorders.

(Slides of pictures of girls)

STEVE HOLLAND: They're all progressive, degenerative and terminal. The vast majority of the syndromes are characterized by drastic neurological manifestations including profound cognitive regression and mental retardation. Children with MPS are not typically identified at birth but start to be identified once they start missing developmental milestones. Children begin developing normally gaining skills such as speech and possibly toilet training.

However, such skills are eventually lost over time in most of the children and are replaced with extreme restless, overactive and difficult

behavior including not sleeping for days and seizures.

As the disease ravages the brain, most children start slowing down, lose the ability to walk or communicate and eventually pass away as their bodies' essential systems shut down.

Within the 12 syndromes, there can be extreme variability in the neurologic symptoms with the majority of kids having a severe clinical presentation, as I previously described, while others present with attenuated symptoms like my children. My three children have an attenuated form of MPS I called Hurler-Scheie syndrome. They were diagnosed 20 years ago. Spencer passed away 6 years ago at the age of 18 due to a medical accident. Maddie is currently 24-years-old and Laynie is 22-years-old and they both live at home with us.

Growing up, their neurologic symptoms were milder than most MPS children but included decreased memory and concentration and learning difficulties in school, especially extremely poor math skills. While they were mostly in regular classes in school, they were in special education for math and English as

their IQs dropped over time. As opposed to the extremely impaired, they understand that they have cognitive limitations that makes it difficult for them to consider normal activities such as driving a car, going to college, having close friends, getting a normal job or ever living alone. My children have benefitted physically from well over 10 years of enzyme replacement therapy allowing them to live longer, healthier lives.

However, it has not helped them neurologically. As a result, Maddie is now suffering from extreme psychiatric symptoms that were previously only seen in the most attenuated form of MPS I known as Scheie syndrome. I believe this is a problem that will continue as the Hurler-Scheie children begin to longer lives. She's developed what is being called bipolar disorder in her teenage years. It is likely a result of the GAG accumulation in a particular area of her brain. It presents itself as mania, depression and psychosis. While it was more or less controlled with medication for approximately five years, the psychosis has been back again continuously for the

past nine months. She has been hospitalized with her symptoms but normal psychiatric meds have been unable to control it.

Out of the past 24 months, she has been in a psychosis or this altered mental state for all but 7 of those months. She is extremely delusional with auditory and tactile hallucinations that constantly taunt her. The voices make her sob daily telling her bad things have happened or will happen. Her quality of life has suffered tremendously from her disease such that she cannot do anything productive including being happy or content for more than a few hours at a time or care for herself and at 22 years of age, cannot be left alone.

The neurologic impact on MPS diseases is severe and dramatic. While we currently have approved therapies that help the physical effects of some of our diseases, we have no approved therapies that treat the neurologic symptoms, and we need them, and we need them now.

DR. EGGERS: Thank you very much, Steve. And now we have Melissa who will be on the phone, and

I'm going to put a picture -- oh, operator, can we have Melissa join, please? AS I mentioned, Melissa faced a family emergency over the weekend and was not able to attend in person.

MELISSA BELINNI: Can you hear me?

DR. EGGERS: Hi, Melissa. We can hear you well.

MELISSA BELINNI: Okay, good. I just wanted to make sure.

DR. EGGERS: Can I get --

MELISSA BELINNI: Thank you very much for allowing come to call in, and I really appreciate this opportunity to speak about our Olivia and the neurological effects on our family for Gaucher's disease. She has type 2 or 3. There are three types. Type 1 is non-neurological and there is enzyme replacement therapy that works well for that. Our type 2/3 children do receive enzyme replacement therapy but that's only just to help, you know, the systemic parts of the disease process.

Many of the signs and symptoms of the neurological part such as swallowing abilities and

many neurological things -- Olivia experienced laryngeal spasms, myoclonic jerks, seizures, and spasms, increased tone which that's spasticity that Teresa touched on earlier, central apnea. These have been the most significant impact on Olivia's life.

Most or nearly all of the babies diagnosed with Gaucher's 2 or 3 have suffered from these blue episodes, but we call them laryngeal spasms. The child's larynx will clamp shut not allowing air to come in or out. As the disease progresses, so will the frequency of these spasms, and many children either succumb to the symptoms so you will not see them live past two or they undergo a tracheotomy. We would have lost Olivia had we not trached her at age one.

The myoclonic jerks or seizures and spasms increase with the disease progression as well and were best controlled by a combination of medications. Due to the metabolic nature of the disease, however, those medications will need to be frequently increased and changed often to catch up to the neurological symptoms. Many of these spasms would cause breath-

holding spells so even on a ventilator, as Olivia's disease progressed, she would still turn blue. We always had an Ambu bag ready nearby.

Increased tone is also difficult as it created pain and she was never able to sit up or crawl or roll over. So even with physical therapy, the tone was difficult to break.

As the disease progressed, my daughter was unable to do most activities that any normal infant or toddler could do. She was unable to walk, sit, talk, sit up, crawl, play with toys unassisted, etcetera. She gained a few milestones in her first five months. She was only able to scoot in a walker which happened to be backwards because her tone put her that way. And, you know, she was only able to do that until about 16 months, but it became difficult for her to hold her head up due to the multitude of anti-seizure and anti-tone and anti-anxiety medications she was on.

By 18 months, she was pretty much laying down all the time. She did have the ability to transfer a toy from one hand to the other but eventually lost that ability. She was able to reach

for toys for a while as well but in the end, you can only see just a small effort being made on her part but she couldn't quite get there. We would sit her up, play games, take her outside as you can see in the picture. We would read books to her, play with toys hand-over-hand. She did smile and laughed at silly things. She watched her favorite show. She said a couple of words, only one syllable though. As you can see, she just passed away at the age of three.

Over time, as the disease progressed, so did her neurological signs. When she was born, she only had very small movement of her eyes and eventually, she lost her ability to gaze side-to-side or up or down. I think she was able to gaze downward but that was about it. Any other effort to see required to lift up her head which eventually she -- it was really difficult for her to do that.

Her eyeballs have developed apraxia and stibismus and her spasms increased over time. (Inaudible) movements came and went depending on how much medication she was on. Myoclonic jerks increased and seizures developed, and these are very difficult

to treat.

Towards the end, she would sleep most of the time. Comfort care, palliative care became her number one as we became closer and closer to the day she left us. Towards the end, she lost the ability to urinate on her own whether or not that was neurological or just her body shutting down but it was a difficult time.

Other neurological symptoms that many of the children face, including Olivia, are the essential apnea, so she started breath-holding in her sleep and then eventually it would progress farther. So she started with her ventilator only during naps and sleep time and then eventually became 24/7. She also did require a G-tube to eat as well.

So as you can see, all of these neurological progressions are extremely difficult and extremely taxing and eventually took her life at the age of three. We were very lucky to have her until three. Many of the Gaucher's 2 children do not live past two. And thank you very much.

DR. EGGERS: Thank you so much, Melissa.

Melissa -- can she stay on the line? Yeah. Melissa will stay on the line if we, at some point, have an follow-up questions for her.

MELISSA BELINNI: Okay.

DR. EGGERS: Thank you, Melissa. And finally, we have Tracy.

TRACY VanHOUTAN: Good morning. My name is Tracy VanHoutan. I'm founder of the Noah's Hope Batten Disease Research Fund and Board Member of the Batten Disease Support and Research Association, the largest organization in the world dedicated to support a family and scientific research into a group of diseases commonly known as Batten disease.

I'd like to thank the organizers at the FDA for their thoughtfulness in putting together these meetings, and including these groups, in inborn errors of metabolism meeting.

Two of my three children have a neurodegenerative lysosomal storage disorder called late infantile neuronal steroid lipofuscinosis, more commonly known at late infantile Batten disease. Over time, due to the severe brain atrophy caused by waste

buildup in the brain, affected children suffer mental impairment, worsening seizures, progressive loss of sight and motor skills. And eventually, children with Batten disease become blind, bedridden, tube fed, unable to communicate. Presently, it is always fatal, usually between the ages of 8 and 12. My daughter Laine is currently 8 and my son Noah is 10.

To pick just a few of the symptoms is difficult because my children have experienced losing everything, and I truly mean everything. They started life as happy, normal kids. They ran and played, talked just like normal kids, read books, had many friends and playmates, and hit all of their milestones appropriately.

But all that began to change at about age 3-1/2 when the seizures and some other symptoms began. I want to speak on a few of these symptoms, first being seizures. This is the symptom that has been with us the longest amount of time. Because of the progressive nature of Batten disease, we continue to adjust the anti-seizure meds. We never decrease meds and often add new medications on top of old as my

children reached the safety limits of their old ones.

As many of you know, these anti-seizure meds have serious sedating and other side effects. Sometimes we're not sure if the children have lost abilities due to the disease or because of the many side effects of these drugs. And as many parents in the room here know, your child having a seizure exhausts their small bodies, adds damage to their brains and leaves us as parents feeling helpless and terrified.

Another symptom is loss of sight. People who have seizures often report not remembering the seizure episode, but when you're talking about the symptom of losing your sight, it's an entirely different matter. Noah and Laine were and are scared of the darkness that surrounds them. Noah had lost his ability to speak when he world went dark but Laine was still verbal as her sight gradually disappeared and she was terrified and would often cry to us asking us if she would become like Noah.

The third symptom I'm going to speak about is -- encompasses a few different things, being loss

of all motor function. It's a broad category and affects every part of our lives and the lives of our children. Ataxia was one of the early symptoms and led us as parents to restrict the last remaining freedoms our children had. Physical and occupational therapy, padded helmets and adding padding to other items in the home only did so much. Our children's frustration was apparent as they continued to lose motor function. Eventually, both Noah and Laine became totally immobile and wheelchair bound. This has affected us greatly as parents.

We had to sell our home to find one that was more accessible for the children and a growing list of equipment, the toll of continued lifting and carrying of Noah and Laine, including bathing, has taken its tolls on our bodies, on my wife and I, and we are now regulars at our local chiropractor and physical therapy clinics.

In addition to this, they lost the ability to speak. This, too, has been devastating to the children and us as parents. As our children lost the ability to tell us their wants and needs, we could

sense their constant frustration. I suppose the best way to describe these waning months of their speech, it was sort of like -- they would have a stuttered sentence that they were never able to complete. We would see Noah and Laine try so very hard to tell us something but they were never able to fully communicate with us. The countless hours of speech therapy perhaps only extended their abilities a few months. I would also say that emotionally, this took one of the largest tolls on us as parents, not being able to hear your child's precious voice is truly devastating and something we miss terribly.

They have also lost control of their bowels and bladders which necessitates our children still being diapered. Their inability to clear oral secretion requires round the clock suctioning to prevent our children from drowning on their own saliva secretions.

Noah and Laine have also lost the ability to eat. Making the decision to take oral foods from your child that they once loved, because of the choking hazard -- because the choking hazard is simply too

high, is something no parent should have to do. We would spend hours carefully feeding the children but eventually had to have a G-tube placed for safety and because Noah and Laine were losing too much weight.

As far as activities that are important to our children, I think this was pretty much covered in some of -- my first answer. Children affected by Batten disease lose everything, but here is a list of the some of the things that Noah and Laine used to like to do but cannot do any longer. Noah loved to play baseball and soccer but he can no longer see the ball, run or kick the soccer ball or even hold a bat. Noah used to have a fascination with trains. He loved to watch movies about trains. His favorite park had trains pass by every 20 minutes, and he loved playing with toy trains. All of this is now lost. Noah loved to play with his fraternal sisters, Laine and Emily. I guess the only saving grace here is that Noah never had to experience his siblings losing all of their abilities. Laine had to experience this with Noah, and Emily, Laine's unaffected twin, has had to watch both her brother and sister drift further and further

away.

Laine loved to dance on the ballet floor with her sister and classmates. We allowed her to continue doing this as long as we could but eventually, it became too great a danger for her to continue. Laine was also a natural swimmer, loved the pool, the beach, any water she could find including the kitchen sink. We actually delayed having Laine's G-tube put in against our doctor's orders because she -- we wanted her to enjoy the last few months of summer swimming at the pool as we knew it would be her last summer of swimming independently.

When talking about how the symptoms have changed over time, all of our children's symptoms have changed so incrementally, you would not really notice from day to day as abilities were lost. It's only really when looking from month to month or quarter to quarter that the losses become real and very, very noticeable. In the beginning, it was few mispronounced words or mixed up sentence structure. Now, in the end, it's silence. In the beginning, there were some mile squinting while looking at books

or watching a movie. Now darkness. And in the beginning, a few clumsy stumbles, some scraped knees and a few stitches and now stillness. In the beginning, there was some mile coughing while eating. Now just the constant hum of the suction machine and the squeaky motor of the feeding pump.

In the end, all abilities once mastered were lost and never regained. No matter how much we fought, doing everything we could, Noah and Laine are losing a tragically unwinnable battle against Batten disease.

I'm going to close now but I'd like to mention something. Decisions made by personnel at this agency matter. You do have a tough job and we realize that, but I believe my daughter, Laine, should have had the chance to potentially participate in a clinical trial testing enzyme replacement therapy for Batten disease. People in this agency decided to delay approval of the trial for some reason. The same data package was taken to multiple sites in Europe and children in Europe are now on therapy in the trial. Because of this delay here in the U.S., Laine has

progressed and would no longer be eligible if and when this trial starts here at home. We need to do better for these kids here in the United States. Thank you.

(Applause.)

DR. EGGERS: Thank you very much, Tracy. And I'm going to -- in the interest of time, we want to get to the facilitated discussion. We're a little bit over. We can make up time for that. We will have some follow-up questions for you as we go -- as we talk about the specific symptoms that are mentioned. But I would like to give a round of applause to all of the parents --

(Applause.)

DR. EGGERS: -- who we hope have spoken on behalf of the rest of you in the audience. With that, I would like to say how many people sitting out here saw something, recognized something of your own experience or perspective or that of your loved one by hearing the range of the comments provided today?

(Hands raised.)

DR. EGGERS: Anyone that said I didn't hear anything that resonated?

(No hands raised.)

DR. EGGERS: Okay. We didn't think so but again, thank you. We're going to focus as much as we can on particular effects and how they manifest themselves. And we're not going to get to all of them, but there are a few that we wanted to focus on in particular because as Dr. Buracchio mentioned, they are the hardest ones to grasp. And that is going to be the cognitive and behavioral and some of those other related symptoms. But we will focus on a number of other ones.

Before we do that, we have a polling question that will help put in context what all of you in the room think are the most important effects that affect you if you have the disease or your loved one. This type is tiny. We wanted to squeeze as much as we could into a polling question. But we want to know if you can use your clickers, and if you're on the web, go through the webcast, which of the following symptoms currently have a significant impact on your or your loved ones life as the patient. Please choose all that apply.

So those motor deficits that we heard Tracy talk about and some of the others, such as weakness, spasticity, walking problems; the balance or coordination problems, B; seizures, C; the sensory impairment such as the vision loss that we heard about or hearing loss; impaired cognition or developmental delay; behavioral problems that we heard about earlier, the hyperactivity, the aggressive behavior, the hypersensitivity; bowel or bladder problems; pain such as headaches, nerve pain or abdominal pain; or something else if not mentioned. We heard many other things even mentioned by the panelists that aren't on this list.

(Whereupon, in response to polling, the results are as follows: A. Motion, 3+%; Balance, 33%; C. Seizure 20%; D. Sensory, 30%; E. Impaired, 59%; F. Behavioral, 52%; G. Bowel, 37%; H. Pain, 44% and I. Other, 44%.)

DR. EGGERS: I think that's the number. So how do we being. So we'll try to work through as much as we can through these symptoms but it's -- you have

reiterated that you have this whole range of symptoms that are significant with the most prevalent in the group here being the impaired cognition or developmental delay. Can I ask on the web what the results are?

DR. VAIDYA: On the web, we have about a majority of folks who have said motor deficits along with impaired cognition or developmental delay, behavioral problems and bowel and bladder problems.

DR. EGGERS: Okay.

DR. VAIDYA: And there was a good -- over 50% have said others as well.

DR. EGGERS: Okay. We'll delve into this "other" category. And my -- the FDA panelists, if you can jot down if any of these are surprising to you and you want to follow-up on them in a little bit, please do so.

So let's start with the cognitive effects again and revisit some of things -- we heard Whitnie talk about them. We heard Christine talk about them. And actually, I think all the panelists talked about them -- manifesting themselves from severe cognitive

effects to more mild ones, and if it's hard to lump the cognitive and the behavioral, that's okay. Would anyone in the audience like to share your experience if you had cognitive up here that might differ from what you heard before? We have some microphones running around and there is the standing one but we can bring a mic to you. Anyone want to share? Anyone want to share even if it sounds like what was on the panel and you want to reiterate?

AUSTIN NOLL: Yes.

DR. EGGERS: Okay. We'll bring the mic to you. If you could just state your name and what the underlying disorder is.

AUSTIN NOLL: Sure. Sanfilippo MPS III A. I think it's the non-verbal, just not being able to communicate is tough because you don't know how to help them on a daily basis, so.

DR. EGGERS: The non-verbal. So you notice we didn't have non-verbal and as I was reading through, I thought well, where we would have put that. How many of you had non-verbal symptoms in as "other" that you -- okay, so if you could -- if non-verbal is

significant to you, could you raise your hands just so we can get a sense?

(Hands raised.)

DR. EGGERS: Yeah. Let's focus on this one a little bit more. Does anyone else want to follow-up on the non-verbal effects?

ROY ZEIGHAMI: My son, Reed, is six. He has Sanfilippo syndrome and he was asymptomatic until about three years old, and we put him into a natural history study, and about halfway through that, he -- we watched him lose all his speech, so going from nearly a normal child to not being able to speak in about six months. And it was a really painful process because I watched him cry every day because there was something inside of him that he wanted to get out and he -- it just couldn't happen and so a very helpless feeling as a parent to want to help your boy or your girl and see them lose everything. And what I -- at least my -- you know, what I felt was a lot of his behavioral issues were due to frustration around losing skills, and so maybe they were connected in a way because he knew he used to be able to do something

and that he couldn't anymore and that was really hard for him.

DR. EGGERS: Okay. Thank you. We heard about the progression of the language challenges as progressing slowly. Can I just ask does anyone have an experience where it happened more rapidly? In the back there.

JANA MONACO: Hi. I'm Jana Monaco and I have two children with isovaleric acidemia and my son, Stephen, is 16 and he was a late diagnosis at 3-1/2 so he was the perfectly healthy normal child who just didn't wake up one day. And he suffered severe disabilities. It was a severe brain injury and so everything that happened with him was abrupt, over a 24-hour period of time.

And he's affected in all of those categories except for behavior. He's pretty calm and happy. But I think the non-verbal is an issue because, again, he was very verbal. And when a child like that loses that ability, among other things -- he has a vision impairment as well with limited vision -- over time you work very hard to try to recover what you can.

It's been 13 years since his crisis and I've always described him as a child who his receptive language and abilities is far better than his expressive. But society doesn't quite always have that patience or tolerance and we are always two steps ahead of everyone. And so we have learned to understand a lot of his abilities and his attempts to try to communicate vocally over time but most often it's dismissed. And when you try to look for therapies and augmentive devices that try to fit that particular child, because he doesn't have the ability to use his hands, many things are not available for him. And then you basically get shoulder shrugged from the therapies, the therapists or the educational people who just say they don't have anything else to offer.

So we've had to be creative in our own ways and try to explore therapies that are not approved by FDA or the medical profession to try to tap into those abilities which are costly. But we've also pulled him out of the school system because we didn't feel that they were supporting him in the way that he needed

that was most effective for him. So that is frustrating because, you know, I think families know things that professionals don't understand but they're quick to try to dismiss it.

DR. EGGERS: I see a lot of heads nodding in the room and resonating with that. Can I ask the FDA panel, do you have any specific follow-up questions on the non-verbal or the language challenges?

(No response/no questions posed.)

DR. EGGERS: Okay. What about the other cognitive effects we heard about, impaired -- I'll say impaired executive function, the decision-making, does anyone want to follow-up on that and how you get a sense of that? So we have one right up here and then we'll go in the back.

MARY O'DONOVAN: Hi, I'm Mary, and I'm actually going to speak in regards to my sister who also has PKU. I have PKU as well. She was late diagnosed -- because she was born before newborn screening -- at 18 months of age. And she did receive treatment on and off but then she went off diet for a long period of time and had really elevated phe

levels. And when we got her back on diet -- well, during that time period, for an example, I would take her shopping and we had to get bananas. They were on her grocery list. And I kid you not, five minutes -- I timed it -- it was five minutes to pick which bananas she wanted to take home. And I event importantly said, "Well, why don't you just -- I'll just pick them." She's like, "No, I want to pick my bananas. Just give me a minute." But it was five minutes for her to pick bananas.

And then several years later after we got her levels under control and got her doing better again, we went shopping for shoes. And I said to my mom as I went out the door -- I'm like, I might be gone for a couple hours. You know, I'll see you in a couple hours. But actually, I was back in 15 minutes.

We went to Payless Shoes and there's a lot of choices there, so I was a little worried about that first of all because I'm like, she can't -- you know, how are we going to decide. She picked her shoes within 10 minutes. And I said," Okay, let's look at all the other shoes." And she's like, "Nope, I like

these." She tried them on. She's like, "Nope, these are the ones." And I'm like, "Are you sure?" You know, look at these other options." "Oh, I've looked. I'm sure. These are the ones I want." And she can make decisions now and she's so excited and so happy and so am I because I don't mind taking her shopping anymore.

But it seems like a little thing, but it is an amazing thing. It's an amazing thing to see that ability come to someone. You don't think about that taking brain snaps power to, you know, make a decision about bananas or shoes but it does. And she can tell the difference and that's what's exciting is how happy she is about her abilities to do those things.

DR. EGGERS: Thank you very much. Any other sort of cognitive -- or let's go onto the behavioral effects that you experience. Regarding the behavioral effects, let me ask a follow-up question so we can tease this out. How many of you agree with -- I forget who just said it about the behavioral effects, when you see them, you believe they may be associated with the frustrations with other challenges that your

child or you face. Okay.

(Hands raised.)

DR. KOHN: Okay. Does anyone want to talk -- so I think we can understand that. What about other behavioral effects that are not so much out of frustration but are somehow different? Okay. In the back there?

EDUARDO BALCELLS: Yes. My name is Eduardo Balcells and I have a daughter, 10. Her name is Eva. She has Leigh's disease which is a mitochondrial disorder and the mitochondria are responsible for providing energy to our body. And so Eva has significant development delay in addition to -- her behavioral issues are, that I wanted to comment on, extend from the fact that because of her limited ability to understand the situation, the environment, she has moments of anxiety. So anxiety is something that we deal with with Eva. She has -- we have learned to have routines with Eva, habits and that -- this has allowed us to give her a sense of safety and a sense of trust in her environment and in us.

The -- in addition, she has significant

motor -- loss of motor function, loss of motor tone so her -- she's non-ambulatory. And so for us, the neuromuscular manifestation of her disease is something that we deal with quite a bit on a day-to-day basis. And she's come a long way but again, a lot of that's been from supportive care, therapies, in addition, like I mentioned, the habits that she's formed to allow her to sort of live in an environment and understand what's next and sort of not get in a situation where -- a dangerous situation where safety's an issue.

But I think for her, the lack of being able to understand and the lack of her being able to also communicate gives her a sense of anxiety and that can be very difficult. So I think the psychiatric/neuropsych component is something that falls into the "others" in her situation.

DR. EGGERS: So you're all reiterating the interconnectedness, I'll say, of all of these symptoms.

Actually, Whitnie, I have a follow-up question for you because we're hearing about anxiety

but you spoke about having no fear, and I was just wondering if your son, if Reid ever does experience fear or anxiety in contrast to the times that he feels nothing?

WHITNIE STRAUSS: Right. No. He definitely has periods of anxiety, you know, especially, you know, if he were here today in a room full of a lot of people, his pants would be down and he would be running for the exit. I think -- and that's one of the reasons why we're unable to kind of take him to these social gatherings, you know, whether it be the grocery store or restaurant, loud noises and, you know, a lot of commotion, things going on around him sort of cause him to be very uncomfortable. And that progresses into some of the behavioral issues that we deal with.

DR. EGGERS: So can I get a show of hands to get these two contrasts? How many of you have your child or you where the behavior is -- falls on that aggressive -- I'm going to use inappropriate but I don't mean it any bad way, just as a sense of the word -- the behavior that falls on the spectrum that

Whitnie's talking about when you thought of behavioral problems, behavioral challenges?

(Hands raised.)

AUDIENCE MEMBER: (Off mic.)

DR. EGGERS: Oh, yeah, more like the types of behaviors that Whitnie's talking about, more that would be seen to be inappropriate in public. Okay, so a couple. Oh, maybe five or six.

Okay. How many when you thought of the behavioral problems thought more of aggression, or maybe they're all related? They're all related.

(Hands raised.)

DR. EGGERS: What about the anxiety, not so much you listed that as a behavioral problem but that's how it manifests itself?

(Hands raised.)

DR. EGGERS: Okay. All right. Any -- yes, Dr. Buracchio.

DR. BURACCHIO: I was interested in Steve's comment about the psychosis symptoms of delusions and hallucinations. And I wanted to know if there was anyone else in the audience who had experience with

those sorts of symptoms?

DR. EGGERS: We have a couple here. Would you like to comment on it?

LIDNA MUUL: My grandson, Greg, has MLD and he hears voices. And his first symptom that led to diagnosis was a psychotic breakdown in school where he heard voices telling him to hurt himself and other people.

DR. EGGERS: Does that address your question? Okay.

STEVE HOLLAND: There's -- between Tay-Sachs and MPS, they do have the same storage heparan sulfa and dermatan sulfa, so that's one reason I think it's coming from the GAGs.

DR. EGGERS: How about --

HOLLON STEVENS: Hi. My name is Hollon and my son has PKU. And I just wanted to make a comment on some of the behavioral impacts that I've seen as well and to reiterate some of Christine's comments on the difficulty of maintaining the diet. And, you know, I'm thankful for some of the aspects of PKU in that it is diagnosed at birth and we do have a

treatment for it and my son will grow up, attend college, and go to school, and, you know, I am thankful every day for that.

However, it is not cured and we do look for treatments, you know, enzyme replacement and, you know, pharmaceuticals, liver cell transplantations. We're looking for these innovative treatments and hopeful that there is a bright future for those. And in terms of what's available today, you know, it's a daily formula intake that we rely on as 80 percent of his diet in association with fruits, vegetables, medical foods and, you know, a very severely restricted, low protein diet. It involves weighting the foods as Christine mentioned, very meticulous recording of the intake, and then as levels get escalated, even when they're slightly out of range, you do see some of these behavioral impacts.

Some of those are, you know, aggression, distractibility. I've seen Drake get very frustrated easily.

One thing that's not up there is sleep disruption and I've seen some studies recently showing

the impacts of sleep on learning, and so I wonder, you know, what could be explored there. He sleep walks sometimes when his levels are elevated and has bad dreams and night tremors and that kind of thing. And also, he's had some difficulties in school with behavior when his levels have been elevated, so I just wanted to share that with people.

DR. EGGERS: Thank you very much. Yes. We'll follow-up more on the treatments and the management of all of these things in Topic 2 and we'll draw upon that as well. Peter has a question.

DR. COMO: Hi. Peter Como from FDA. Many of you folks in the audience seem to suggest a variant of a behavioral problems that is best described as obsessive or compulsive behavior, either ruminative thoughts or compulsive rituals. Is that something that you're seeing a lot in your children? And if anyone could elaborate on what those signs or symptoms, that would be helpful.

DR. EGGERS: So can we get a show of hands first for how many experience that?

(Hands raised.)

DR. EGGERS: Okay. So we'll go with you and then we'll go with you right there.

DEAN SUHR: Hi. Dean Suhr. My daughter, Lindy, who you'll meet in a little bit -- she's 33 now -- has juvenile MLD. She actually was diagnosed because of those compulsive behaviors. It was the cognitive -- the loss of the -- slow loss of cognitive skills that everybody tolerated and deferred and said, Well, that's just behavioral and this and that and so on, and lack of impulse control and so on. But when she finally, if I could say that as almost with a sigh of relief, when she had those picas and those really impulsive behaviors, we, as a society, recognized as oh, something's wrong. So, yeah, it is something that we have to deal with but at least it's something we can grab onto, too.

DR. EGGERS: Thank you very much, Dean. And then right here -- I'll bring the mic around.

JILL WOOD: Hi. I'm Jill. I'm the founder of Jonah's Just Begun-Foundation to Cure Sanfilippo Incorporated. And I wanted to give you something a little more light-hearted on the behavioral since this

is pretty heavy-duty stuff.

Sanfilippo syndrome is an MPS. It's MPS III and it covers almost all of these things. But my son's compulsion is licking. He likes to lick people and it can be funny sometimes but absolutely exasperating. We had a flight a few weeks ago and I put him in the middle so he's trapped in the middle and he can't run down the hallway and play with the window and that sort of thing. And this gentleman sitting next to me, I had the hell -- it was so awful getting my son onto the airplane. I thought we were going to get kicked off. I was like, "I'm never flying alone with him." But Jonah jumped into this guy's lap and started licking his face, licking his hands and the guy just took it. I was just so exasperated. I was like, "I love you, I love you."

DR. EGGERS: Thank you so much. Are there other -- we could go on a range of other -- oh, go ahead, yeah.

ROY ZEIGHAMI: Pica, is that how you say it I guess? My son has Sanfilippo and he's constantly chewing things and it makes him sick all the time

because he just puts everything in his mouth. And one of the things that I think is confusing to a lot of people about Sanfilippo syndrome is they see what they perceive is aggression is just impulsivity on his part. It's not actually aggression. So if he has a cup and you stand in front of him, you're likely to get the cup chucked in your face, right, and it's not because he's trying to hurt you. It's just because that's what he does with a cup that's in his hand. It's just going to get launched. And he loves his iPad. He loves to watch it. He'll look up at me. He's happy to see me and he throws it right in my face.

And so, you know, one -- I guess this isn't something -- some of the things I worry about though, these are -- how do you measure these kinds of things for a treatment. And I guess that's what you guys think about as experts, but these are really small populations and treatment effects may be very small. But I would be interested in, you know, these things that are subtle and maybe even objective. How do you measure these, right?

DR. EGGERS: I think that's why we're here today is to hear these things that we don't usually hear about in more technical settings. One here and then we'll go to --

AUSTIN NOLL: And I just want to go -- you mentioned sleep and sleep is critical. Our son, again, who has Sanfilippo will go for weeks without sleeping. And you just can't function. So you take a look at, you know, aggression and everything else, when you're in that situation, not to mention the whole rest of the family who is awake, it's something that really needs to be looked at, so.

DR. EGGERS: Can I get a show of hands who put sleep in their "other" category?

(Hands raised.)

DR. EGGERS: Okay. So the Sanfilippo, okay. Christine?

CHRISTINE BROWN: I just wanted to add that, you know, some people have asked, you know, how the FDA would measure these things. And I have to say as a parent, I don't even know how to measure them. You know, when my child decides to break out in song in

math class or, you know, I have to tell him eight times to brush his teeth in the morning, or something is happening, you know, I always wonder is that just because he's having a bad day. Is it because he has PKU? Is it because he's a boy? Is it because he's six years old and this is what happens? And it's very difficult as a parent to try to figure out how to discipline when you're not quite sure of the causes of them. And that's a constant struggle, I think, for my husband and I is to figure out, you know, what is the underlying cause of this. There's a lot of gray.

DR. EGGERS: Thank you so much.

WHITNIE STRAUSS: Well -- and I think sometimes, if I can just add, there may be multiple causes for an action. You know, let's say Reid, you know, like your son, may have a cup he's drinking from and he's going to chunk it at you. Sometimes it's because it's empty, may need some more drink, and then there's other times where he does it because that's just what he does. When he's done with a cup, he doesn't know how to put it down so he's just going to drop it. So, yeah, how do you kind of determine is it

a behavioral thing? Is it a habitual thing? It is a communication issues? There could be all of the above for one action, so.

DR. EGGERS: I think this interconnected nature, if you're going to follow-up on the docket, if you have thoughts about how you tell -- how you attribute an action that you see or behavior or an effect, how you tie them together or what else you think about when you're trying to figure out why is my child behaving in this way, if I can make sense of it.

I have not gone to the web yet so I do want to see if there are any comments that have come in so far on any of the effects that we've talked about. We'll still address others.

DR. VAIDYA: Son on the web, we have several participants and they've mentioned non-verbal as a symptom and also mentioned it actually severely affects ability to learn and socialize and it also makes it difficult to know if the patient is going through pain or any other symptoms.

On the behavioral side of things, behavioral symptoms and issues do affect the patients and due to

impaired cognition, so they don't understand the danger of running into the road or also become very anxious before going to a doctor's.

One participant also mentioned struggles with executive functions, behavioral problems causing inappropriate socialization.

And then few mentioned sleep issues as well on the web.

DR. EGGERS: Okay. So they're reiterating what they're hearing today. Ron.

DR. FARKAS: So sometimes when we're thinking about measuring behavior, it's not actually so clear if there is an unwanted behavior that goes away, are there desirable abilities that go away. And we've heard a little bit about that with some of the medications I think. But I guess just when people have been talking about how they think their child might be doing, if they could just share more about the different ways that they might separate out a good day from a bad day, from problems and then good parts of the day.

DR. EGGERS: So I think we have one comment

on there and then I think we'll ask the rest of the folks to really expand upon that in your docket comments. But we do have one comment back there.

CRISTY BALCELLS: Yes. My name is Cristy Balcells and I have a little girl, Eva, who has mitochondrial disease. I'm also the Executive Director of a national organization, MitoAction.

And in representing my daughter as well as other patients, including adults, who have mitochondrial disease who have behavioral problems and impaired cognition or developmental delay, I think that there is a stigma in those symptoms, such as depression, that it's situational. And I think that adult patients in particular often complain to us that their depression or their issues with executive functioning are blown off as being situational because they have pain or they have other physical issues which greatly impair their quality of life and so that's not really taken seriously as a symptom category. And I think that it's a real struggle then to definitively define those behavioral problems and issues that are psychological, such as depression, as

true symptoms.

Similarly, I hear from parents quite often who say that their children, who have features that are on the autism spectrum but their children has a mitochondrial disorder, that the treatment or the focus in terms of approaching those behaviors is based on as if the behavior was somehow caused by the child or the family. But in reality, it's caused by the inborn error of metabolism. It's caused by the defect in the pathway, right, and if we could approach that, maybe we could improve the behavior.

But I think that -- I appreciate the opportunity for a regulatory agency like the FDA to consider that sometimes those slippery slope symptoms really could have the greatest impact for the patient or the family.

DR. EGGERS: Thank you. I want to make sure that we hear about if there are any symptoms that have not been discussed today that you weren't able -- that were in the "other" category that are really important to your child or you if you are the patient and is having an impact -- an affect on your day-to-day

living. Anything that's not been mentioned? Roy?

ROY ZEIGHAMI: One thing I've noticed about my son is that it's hard to figure out whether he's upset because he's in pain. And just the other day, I noticed that sometimes within the span of 30 minutes, he'll go through a cycle of crying and you're trying to figure out if there's something wrong. And sometimes -- and then he'll just, two minutes later, he'll be happy. And so that seems to me it's not pain or something like that. It's -- you know, he can't describe it to me but there's just a range of emotions that doesn't even seem to make sense to somebody -- you know, to us, right and that would see related to the disease.

DR. EGGERS: Uh-huh. I see some heads nodding in agreement about the range of emotions as an effect. Are there any -- yes, Theresa?

DR. MULLIN: So, Sara, I think -- are you going to get around -- or back to Ron's question which is what does a good day look like, I mean more about, you know, kind of the flip side of things not going well but if there are things you see or you'd

associate with a good day for your child or for you if you have the disease? That would be helpful, too.

DR. EGGERS: Sure. And before we go there, I'm just going to tee up on the phone. If you are on the web, we will have time for a call or two and we're hearing -- we're primarily interested, I think, in hearing about a symptom that has not been or an effect that's not been raised today. Let me get a show of hands to follow-up on Theresa and Ron's question about how many have distinct good days versus bad days?

(Hands raised.)

DR. EGGERS: Okay. So can tell us -- someone want to tell us the difference between a good and bad day? Yes, go ahead.

RHONDA CONNOLLY: Hi. I'm Rhonda Connolly and i have two sons with PKU also and although we don't have bad days, bad days as in some of these disorders, the one thing though is that we have a treatment and because there are not such physical attributes, that my kids don't have some of the side effects. When they take their diet, they feel great. They concentrate well. They aren't anxious. They

aren't moody.

And so -- but the problems is as they get older, as my son who is now 21, you feel good all the time and you think well, I don't need to take that today or I'm too busy. I'm going to be at my friend's house. I'm not going to take that. Well, guess what? The next day he is anxious. He is moody. He can't do as well on his math and he does have issues. So part of it is that you may not have those symptoms but continue to take your diet and pills.

DR. EGGERS: Thank you. Is there any example that's not -- that's outside of a treatment -- response to treatment, that's just natural variability? Yes, did you have your hand up? Oh, did someone -- okay, first we'll go to you and then we'll go to Whitnie.

GORDON WINGATE: Hi. I'm Gordon Wingate. My daughter, Jennifer, was born with MPS III-A and she passed away with MPS III-A about five years ago. I think -- you know, in my experience, a good day was any time I had communication. I got laughter out of her. She was happy. She just spontaneously burst out

laughing and I knew something I'd done had, you know, put things right. And, you know, I think so much of the frustration, the behavioral issues come from the loss of language. In my experience, my observation, the language gave structure to the world that went away. When there's no language, there's no rules, there no reason for us behaving one way or another. I think back to the story of, you know, Helen Keller before she discovered language. And that's the kind of things, her inappropriate behavior, there's no rules. I'm just going to walk over and go out here. I'm going to walk out in the street.

But definitely, the good days were just when I had communication, eye contact, sit and stare at me for long periods of time and just interact personally. And that was powerful.

DR. EGGERS: And could you, on a -- could it vary? One day she has the communication ability and the next day she doesn't and then some days later she does so there was that variability in a week for example?

GORDON WINGATE: Yeah. And a lot of it had

to do with just spending the time to draw it out of her. I mean we had it in her I.E.P. that, you know, communication was going to be how long could she maintain eye contact because eye contact was communication and it was very directly. I could see that. So, yeah, there were good days. You know, they were spontaneous when things were just going right and, you know, she was just -- she just glows.

DR. EGGERS: Thank you very much. Would you like to quickly follow-up, Whitnie?

WHITNIE STRAUSS: Yea. I mean I think we're in a simil.ar situation where being non-verbal definitely creates issues there for Reid. However, you know, if I had to say, you know, a good day, I can deal with the lack of speech with Reid. If he's having a good day, he's patient. He'll take my hand and put it on the door knob. He'll give me his cup. I can live without speech.

It's the mornings that he wakes up and we like to call him Tas, the Tasmanian devil because in a three-minute timeframe, he's woke up, he's pulled his diaper and clothes off, he's spilled a drink off the

counter, he's pulled a bag of cereal down and it's all over the floor, and he's dancing on my dining table all within a three-minute period, and there are two other children in the house who also need care. So those days are the bad days where you just can't keep up. He's always three steps ahead of you and you're just trying your best to sort of manage the best you can. I would take Reid non-verbal. I would take him as he is if he would just be a little bit more cooperative and a little bit more even keeled. That would make a huge impact on our day and that would be a good day for me. Given everything else he's dealing with, I think that would make the biggest difference.

DR. EGGERS: Tracy.

TRACY VanHOUTAN: Just a quick little different perspective from two kids in a terminal disease, probably in the latter third of that disease. So a good day for us is no seizures and I see that was one of the lower reported outcomes here, but I don't want folks to underestimate that because I think either the medications we give our kids or the damage caused by those seizures often can lead to some of the

other symptoms that were mentioned.

But in addition to no seizures, getting a smile from our kids is a good day. Our kids being able to regulate their body temperature on their own is a good day. Having bowel and bladder movements is a good day for them. And not having sores when they come home from school or an outing because they myoclonis has caused them to bang into their wheelchairs, that's a good day, too, so just a few things from perspective of a child later on in a disease.

DR. EGGERS: And can I ask, Tracy, are all those things that you mentioned still achievable? Do you still notice those with your children? Is it -- are those rare events or are they more common even if they're variable?

TRACY VanHOUTAN: As far as seizures, I think Noah's passed them. He's older. I think he's passed the point where he's having a lot of seizures now. They're so much brain atrophy so the no seizures is more important for Laine. We get -- still get more smiles from Laine. We don't see that with Noah

anymore. The body temperature regulation is more of a problem with Noah than it is with Laine. Bowel and bladder is both of them and they both continue to -- Noah more so has more myoclonis than Laine, but she's travelling down that path as well. And secretion, saliva management is also something that they're dealing with now.

DR. EGGERS: Thanks. So we have one more comment here and then we do need to go to the phone and give folks a chance. We're a bit over our break time but I think you will appreciate being as -- we might shorten our break just a little bit and get started on Topic 2.

GINA WILLIAMS: Thank you. Gina Williams, vanishing white matter disease with an underlying mitochondrial disorder from -- is my daughter. I just wanted -- a little different perspective with weakness. We haven't talked a lot about that but a good day would be that she would be able to participate with me, help me transfer her. She's in a wheelchair predominantly. She can eat without food getting stuck. That's what we call it, right, the

swallowing issues.

The bad day would be that either it's the heat totally wipes her out. She has no energy whether it be that she sat up too long and she needs to rest, she's leaning in her wheelchair. We have to set up, hold your head up. She cannot participate in a transfer. She can't even help with the lift. I have a standing frame. She's not strong enough to participate in that and just requires extra rest. Food gets stuck is what we call it and the saliva secretions and lots of underlying -- so just a little bit of the muscle weakness and how that effects.

DR. EGGERS: Can I ask how old she is? She's how old?

GINA WILLIAMS: She's 31.

DR. EGGERS: Thirty-one?

GINA WILLIAMS: Yes.

DR. EGGERS: Okay. Can we go to the phone and see if -- operator, are there any callers on the phone?

OPERATOR: Sure. If you'd like to ask a question, you may press star one. Please make sure

you record your first and last name and make sure your line is (inaudible) before doing so. Once again, you may press star one if you'd like to ask a question or make a comment. Give us one moment, please.

DR. EGGERS: Okay. While we wait, any other questions from FDA?

(No response.)

DR. EGGERS: Any thoughts that are important about the manifestations that haven't been mentioned? Okay. in the back there?

EDUARDO BALCELLS: Again, representing Eva with mitochondrial disease. Just tying into the last comment with regard to motor strength and weakness. Eva had strokes when she was in utero. She had cerebellar strokes. She has significant ataxia. She's not ambulatory but she can crawl. She has intent to be able to grasp things and she uses an iPad and which has been a blessing. I tell you, I thank Steve Jobs every morning because it's amazing what Eva's able to do.

But in her world, using the iPad, if she has a bad day where she's weak and fatigued because of the

motor issues, it impacts her neurologic issues and she has much more dysmetria. And so she's' much less able to grasp her spoon, feed herself, gets food all over herself, is unable to enjoy the iPad which she really enjoys and engages with. So again, the motor issue ties in with the neurologic issues that she has.

Eva's blessed in the sense that she has not had progressive metabolic strokes over time, but other children with Leigh's disease do. So I think these episodic events such as strokes manifest themselves in different ways. But in Eva, it's manifested in significant ataxia. And again, tying in that motor issue with the neurologic issue is important for Eva. So when she has energy and she feels strong, her tone's better, she's able to do more and overcome her neurologic deficits.

DR. EGGERS: Okay. Thank you. We have Ross on the phone. Ross, you may speak. Operator?

OPERATOR: Mr. Bennett's line is now open.

ROSS BENNETT: Yeah. I would just say that a good day for Collin is simply one where he -- we can get him to sleep at night and where we were able to

keep him safe.

DR. VAIDYA: Okay.

DR. EGGERS: Thank you, Ross.

DR. VAIDYA: Thank you. Next caller, please, Operator.

OPERATOR: We do have a question from Eileen Linzer. Her line is now open.

EILEEN LINZER: Hi. I'm Eileen Linzer. My daughter, Quinn, passed away last August of Nemann-Pick Type A. We're a bit on the outskirts of a lot of new issues. Our Quinn was not yet 15 months old when she passed away, so its neurologic degenerative Nemann-Pick. She -- her liver actually gave out before she had a lot of those issues (inaudible). One of the -- I had selected the "other" -- I'm sorry (inaudible). It just kind of came up on the phone.

Her main issue as far as quality of life was concerned while she was here was her feeding issue. She was born and the day she was born, she started what we thought (inaudible) was extreme spitting up but, you know, it became apparent within just a month or so that it was actually more of a neurological

issue. Her swallowing issue, we used to have to hold her upright for a full hour after ever single solitary feed. I have two other boys who kind of ran circles around us while we did that. We couldn't move; otherwise, she was much more likely to vomit and she was very tiny to begin with so she couldn't afford to lose it. That was -- she did get a G-tube and it did help it but it never fully went away. So it was an issue that I know had been raised on that initial slide. It was on there, the swallowing. And perhaps because of her age, that was why it was such a big issue for us, but it was a very severe issue and it really, tremendously impacted hers and our family's quality of life.

DR. EGGERS: Thank you very much. You got a lot of -- you can't see them, but you have a lot of -- a few heads nodding in the audience resonating with what you're saying. Thank you. Do we have any more callers? Okay. So that's it for callers. How about a web summary of any comments on the web?

DR. VAIDYA: We have some folks on the web who mentioned -- one participant mentioned that in the

case of congenital disorders of glycosylation, there are several obsessive behaviors where patients have difficulty accepting any type of change. One participant mentioned that the attenuated form of mucolipidosis III show signs of short-term memory loss. And in mitochondrial disease, someone else mentioned that the autonomic dysfunction can be a major issue. And for someone with MPS Type II, the participant doesn't have congenital cognitive issues but suffers from severe migraine headaches which last five to six days every month and the pain is crippling.

DR. EGGERS: Thank you.

DR. VAIDYA: Thank you.

DR. EGGERS: There's so much we haven't -- one more -- we'll take one more question -- or a comment I mean. Sorry.

AMY MILLER: Hi. I'm Amy Miller and I'm here with my son, Danny, and my husband, Ray. Danny has Hunter syndrome and I was hoping to comment on the last question up there. What's unique in our situation is he, as a young child, had the symptoms

that many of you talked about, the extreme hyperactivity. He was the Tasmanian devil. We had our lamps screwed to the tables. We have nothing out in the house. We had locks on things.

And being a progressive degenerative disease, now we're dealing with like, is it Tracie, your children. He -- at this point, he's 17, almost 18 years old and it's unique in the fact that we dealt with those behavioral issues early on, but now we're dealing with extreme medical issues that a lot of people don't think it could possibly the same disease as it was when he was a young child. Physicians who care for him now that never cared for him as a young child can't believe that he could once run around, ride a bike, feed himself because at this point, he has not purposeful movements. He has seizures. He has autonomic instability and storming. He has a feeding tube because he was unable to swallow safely, and he is complete care 24/7.

So our complete care from a young child was keeping him safe and adapting our house to keep him safe. We had a room that was all of his own that had

toys attached to the wall so he would play with them instead of throw them to now complete care as far as monitoring him for seizures, respiratory distress, suctioning. So I just wanted to let you know that the neurological symptoms change dramatically in some of these diseases over time.

DR. EGGERS: Thank you very much. We are going to have -- oh, go ahead, Larry, yes.

MR. BAUER: Yeah. At the recent narcolepsy meeting, one of the unusual things was that a lot of the people that came to the meeting had never met other patients with narcolepsy which was kind of, I thought, an interesting thing. And I was wondering -- in this group, we have a very diverse group of diseases, and I was wondering how many of you are in touch with other families with the disease and do you find that the symptoms are similar or that there is a great deal of variability between what your children and families are experiencing?

DR. EGGERS: Let's see, so how about right here and then if someone hasn't -- in the back hasn't gone.

GINA WILLIAMS: Hi. Gina Williams again, vanishing white matter. Before, I was mitochondrial and I was in touch with those and now that I have a new diagnosis, we do -- it's not a support group because there aren't that many of us -- but it's an online and we are in touch and we share, and there are five genes that are in effect for vanishing white matter and the symptoms are very varied. My daughter is very fortunate. I'm one of the least affected.

DR. EGGERS: Thank you. In the back.

JANA MONACO: Hi. I am also the Advocacy Liaison for the Organic Acidemia Association and that combines multiple disorders that are organic acidemias. And many of us have the similar symptoms. Some of the disorders are a little more involved, involving their treatments and symptoms. Other -- especially if they were not screened at birth like my son. So there are many of us that are in the age bracket that he's in and older who have a lot of severe disabilities and all of the different issues related due to lack of screening.

However, many of the ones coming through

with newborn screening -- my daughter was screened early because of my son -- do not exhibit all of these kinds of issues. But then we work very hard to protect them and there is a fine balance. But it's -- there are many variables that affect these children and the adults that live with these disorders. So, yeah, we actually are very connected through the website, through the listserve and actually Facebook pages as well, and we have a family conference coming up this summer here in DC.

DR. EGGERS: If I could make a suggestion for the advocates in the group, we've heard a lot mainly personal stories and experiences, and I think there's an opportunity for the advocates to expand upon what Larry's asking about that variability from what we heard today and across the patient population that you work with.

We have -- okay, one more right back here.

UNIDENTIFIED MALE: My son has late infantile Batten's disease and we are in constant communication with the other families. It's a very big part of learning about the disease and how to

manage day-to-day care for our children. And it's remarkable that the story of the progression of the disease is very similar in terms of diagnosis and, you know, just the overall progression of the disease. So it's very similar and it's very important for us to be in contact with the other families.

DR. EGGERS: I'm going to have to put a time out and have us go to a break. There were so many issues we did not cover today. We didn't -- we heard a lot but we didn't get into depth in some of the issues, the motor and the other symptoms. Please feel free on the web and in here to expand upon those.

So we're going to take a break now. I'm going to suggest we come back -- try to be back at 11:15. We won't get started without -- you know, without having most of you in the room, but if we can shorten it to 10 minutes, then we can get back started at 11:15. Thank you.

(Whereupon, off the record at 11:04 a.m., and back on the record at 11:21 a.m.)

DR. EGGERS: As people work their way in -- is this mice on? Can you hear me in the back? I just

want to thank you again for the Topic 1 discussion on those effects that matter most, the neurologically-related effects that matter most and encourage to encourage you to contribute to the docket on those effects and also remind you if you want to talk about other effects that we haven't talked about -- Dr. Buracchio put up a slide recognizing that there are many effects beyond the neurological -- please feel free to comment through the docket on those if we didn't get to that, especially if you want to talk about how the effects that you talked about today stand in relationship to the other effects that you have to deal with on a day-to-day basis.

We're now going to move into our second topic which is really focused on treating and the treatment approaches. We have heard quite a bit, you know, as the panel comments from Topic 1, they worked in treatment some into their panel comments and we got some of it. So we want to build upon that now and focus more on treatment approaches recognizing, of course, that there are probably more variability in the treatment approaches as there were in the symptoms

that were discussed today, so we're going to try to work our way through this as much as -- to get as much common ground as we can. We're not focusing so much on particular treatments as much as to say what is it that you think is important about treatment.

We have five panelists to kick off our discussion, very similar to the morning, representing a range of underlying IEM disorders and a range of treatment experiences and perspectives. We're going to ask each of them to go through with three to four minutes of remarks, and we will start with Melissa, please. If you can push your -- the button on your microphone and hold it as close as possible so we can hear you well.

MELISSA HOGAN: Hello, my name is Melissa Hogan and I am the parent to a 7-year-old child named Case with Hunter syndrome or MPS II as well his 8- and 10-year-old brothers. I am the founder of Saving Case and Friends which is a Hunter syndrome research foundation and the Hunter Syndrome Research Coalition which coordinates families and foundations to find a cure for Hunter syndrome. As a context for my

perspectives on treatment, a little background on Hunter syndrome is warranted.

It involves progressive physical, cognitive, and behavioral decline with an average life span of approximately 12 to 15 years old untreated. At two years old, when Case was diagnosed, he seemed like a normal little boy with a little developmental delay and some attention issues. He laughed and sang. after diagnosis, he went on an FDA-approved enzyme replacement therapy which involved a weekly 4-hour infusion first in a hospital, then with a home nursing and eventually, I was trained to do his infusion at home which has allowed much more freedom and flexibility in our lives and less medical trauma for Case given that is a weekly 4-hour process for the rest of his life.

ERT showed positive effects that we saw because his liver and spleen reduced. He stopped falling as much while he was walking, had more energy, had more joint range of motion, was happier because I believe he was in less pain. Breathing was easier so he also began speaking more as well. It would be

great if it wasn't four hours or an IV infusion but I'll take that if I it means it works.

Although he learned with difficulty for about a year after diagnosis, he then rapidly began losing skills. He lost 18 IQ points in 8 months. Behaviorally, he became uncontrollable at times. We had a CNA in our house five days a week because of aggression towards his brothers and no sense of safety. We had gates gating off all the rooms of our house. He was strapped in a pediatric wheelchair with a six-point harness when we were in public because of lack of any sense of safety. I describe the behavioral profile of Hunter syndrome as some autism, ADHD, OCD, sensory processing, no sense of safety and aggression.

His speech began to lesson to three- to four-word sentences from nine words and he began to stutter uncontrollably. He could not understand a great deal of what was said. He could not even follow one-step directions. He would easily choke on foods.

But at 3-1/2-years-old, following the 18 point loss of cognitive points, he was able to enroll

in a clinical trial that puts the enzyme he is missing into his spinal fluid, initially, via an intrathecal PORT-A-CATH and after 18 months, via lumbar punctures. He has now been receiving lumbar punctures every four weeks for over two years with anesthesia to receive the medicine because of the failure of the initial port and delay in approval for use of the new PORT-A-CATH.

With that being said, here's how we evaluated the decision to enroll in the trial despite the potential risk of spinal and brain complications. First was the potential for the drug. Slowing the disease would be a win. Halting the disease would be a huge win. Improvement was not even contemplated. Life is most important and we'd take any shot at it. We evaluated this with our own reading of the research studies and speaking to other families and the PI.

Second in the evaluation was the risk of doing nothing. We knew the natural history. We had met other patients. To do nothing, to us, equaled death. We knew how long a drug development and clinical trials process took, and we knew this was our

only shot. That's how it is for many families and I think you would agree. The trial that the FDA is evaluating at any given time is truly the only shot many of our children have to live because these diseases are degenerative.

Only third in our evaluation was the risk of the drug or the administration method. We would have signed up for close to any risk because we know otherwise he would die a slow, difficult, and painful death.

What is most important to us about a treatment? It's potential for life, survival, a chance. Then, impacting other challenges such as the behavioral aspect, the ability for him to function in public and be safe and be independent in some ways and have language. Third after that are also the medical trauma challenges and a less invasive administration method is actually more important than the risk that it causes.

How can we tell that a drug is working? Observation is the best method. Is he safe? Can he walk? Can he be independent? What ADLs does he have?

And some thoughts I'd like to leave you with. Slowing or stability is a win. We don't need a normal child. We just want a living child.

Next, medical trauma is significant in these children who require constant interventions, tests, treatments and procedures. That has to be considered when you contemplate the measures for clinical trials and the administration method. Will they cooperate? Will the measure traumatize them unnecessarily?

Regarding measures, cognitive testing on these children is incredibly difficult, often inaccurate, traumatizing, requires often Herculean efforts by parents with planning and rewards, and probably most importantly, excludes a large portion of the patient population because there is a short window where they are above the age where they can follow directions to test but they have not yet lost all of their cognition. The original inclusion window for our trial was 15 points. When Case first tested, he was above the criteria. So to wait for a fall -- he then fell 18 points and had they not widened the criteria, he would have fallen completely through.

Treatments and trials should be designed to be tested and used across a range of genotypes, Krim (ph)status and ages. The current narrow bands of eligibility and automatic exclusions for things like shunts both make enrollment difficult and do not reflect the reality of many of our communities. For example, a large portion of our community have shunts and they are excluded in our cognitive trials.

Finally, and maybe most importantly, there should be an expectation of compassionate access passed the initial safety trial. Again, we just want our child to live and any given trial or drug may be the only shot they have.

DR. EGGERS: Thank you very much, Melissa. And we'll move to Dean.

DEAN SUHR: Good morning and thank you for inviting us and having this discussion. Hopefully, it's as beneficial to you as it is to all of us.

As you've heard, the IEMs are quite distinct. We share a lot of things in common but there are a lot of differences. The disease that I represent is metachromatic leukodrystrophy. On the

right-hand side of the screen, there is my daughter, Darcee, who passed away at age 10 after what they called a successful bone marrow transplant. She engrafted. She lived through the transplant but she had some post transplant rejection complications. That was in 1995. She was diagnosed because her our older daughter, Lindy, shown on the left there -- and that's a pretty old picture -- she is now 33 with the juvenile of metachromatic leukodrystrophy. She can no longer climb those stairs. She's in a wheelchair. We have to feed her. She wears diapers and so on and so forth.

We're blessed in that one of our two children is still alive but ironically, that's the one that didn't have a therapy. And would we go back and make the decision differently? I don't think so. We, like most parents, go into these trials and these potential therapies with our eyes wide open.

MLD is one of many rare diseases and much like rare diseases, about 50 percent of the cases of MLD are the late infantile form with an onset of 18 to 24 months and its fatal in those kids generally before

they reach the age of 8, 9, 10-years-old. So it's a very rapidly progressing disease and we are anxious to not only have our kids thrive, but to just be alive and to be able to communicate back with us.

The disease advocacy organizations are the people that know where these families are and we're quite anxious to work with the FDA and with industry. We formed the MLD Foundation and literally travel around the world meeting families, supporting families, but also in the background doing a lot of research work.

Families care about quality of life. It's not just longevity. It's quality of life. We heard this in the first session. And the therapies that are proposed or addressed need to have that component. And respectfully, I'm a big supporter of the FDA, but the FDA model of do no harm, we need to watch with the clock that says time to death. And do no harm, as Melissa pointed out, when the outcome is death, the risk-reward benefit tables turn quite a bit. And so we're anxious for safe experimental therapies. We want to make sure they're safe. But if the worst

thing that happens in a therapy is nothing, that's okay. That's a good risk for us to take because we hope and pray for the upsides.

The ideal therapy would stop progression in the short term. We're seeing a lot of enzyme replacement therapies. We have an enzyme replacement therapy in clinical trial in Europe, not here in the United States. There are issues related to getting that application here. Those are things we want to talk about.

There is a gene therapy combined with a bone marrow transplant that is in Italy right now and we're seeing wonderful results, and I hope the Vivian family has an opportunity to speak in a little bit about that. Their two children are here.

And we know there's no perfect therapy, but three and four years out, we are guardedly just blown away by the results. And we want to bring that to the U.S. and we know there are a lot of issues that need to be addressed and discussed with that.

One of the things that you asked us to talk about a bit was consent With over 50 percent of the

MLD population being, you know, 3 or 4 years old by the time you go through the diagnostic odyssey and are considering something, those kids obviously aren't old enough to give consent. So that discussion gets deferred to the juvenile and adult forms. And I think we need to be very aware with these neurological diseases that when your cognitive abilities are impaired, you aren't necessarily the best person to give consent. And so we have to allow for the caregivers and the parents and those that can take a different perspective to be involved in that consent decision.

Our third clinical trial is also only in Europe. It's another gene therapy and we're concerned that we have no clinical trials in the U.S. And just as Melissa mentioned with compassionate use, we have had numerous conversations with the folks that are making these applications, and the FDA supports compassionate use. Your rules allow that. And industry says, Well, that's a good idea but the reality is, at least with our disease, and I can't speak for others, that they aren't huge advocates of

compassionate use. And the reason is not because they don't care about the kids, they don't care about these diseases, it's because the risk is too high of an adverse event in a less controlled environment and that will mess up their clinical trial. And they have stakeholders and shareholders and all the normal corporate stuff that makes that very challenging. So it's a place where it's very, very awkward to have a three-way conversation between advocacy groups and families, the developers of a therapy, typically academia or industry, and the FDA.

And to be perfectly honest with you, as much as I -- and I'm not here to pick on anybody, to be honest -- but this meeting is of advocates and we've got some industry in the audience. When you go back later today and tomorrow and next week, you'll have closed door meetings with industry and with the FDA and we won't necessarily be at that table. And we need to have this kind of open exchange consistently amongst all three parties even if it's uncomfortable, because that's where all of this insight and perspective comes from.

Patient-reported outcomes was discussed a little bit earlier. The world is turning on its ear. PCORI is driving a lot of this but we, as advocacy groups, have been active in this for a long time. More and more data is being gathered and made available as patient-reported data. And it's not statistically valid because a nurse or somebody culled that data, but it is statistically valid because it's being reported over time by large sample sizes. So it's a different sort of validation. And I think one of the messages that we want to convey back to the FDA is that patient-reported outcomes not only are good data but it's insightful. We'll find out how many kids have, you know, green dots on their thumbs or whatever that other thing is that's not being captured because somebody in academia didn't study it 10 or 20 years ago.

And my final comment is with regard to -- actually, two comments. One is with regard to advisory panels. We're very interested as advocacy groups in being on advisory panels but in many cases, we are conflicted out because we have an educational

grant relationship with a -- maybe with industry or something and a stack of paperwork they sign and we sign to say there's no arm twisting, there's no leverage, there's no promotion. And yet we come -- we can't meet the SGE requirements for conflict of interest. And with an organization such as MLD and other rare diseases, we are the experts. We've seen hundreds of families and literally dozens of researchers at their homes, at their sites, and we're the experts and we can't participate.

And the final thing is what can we do for you? I sat with an FDA representative a number of years ago now, and they very casually just said back to me, well, we have all these regulations and we respect and we like those regulations but we are the people that can make the change. We are willing to have an act of Congress if that's what it needs to help change the world which is changing with regard to therapies. And we need to know where we can help you with that. I think PDUFA V is indicative of those sorts of things. So, thank you.

DR. EGGERS: Thank you so much, Dean. And

now we'll have Jennifer.

JENNIFER PAYNE: Hi. I just want to extend a thanks to the FDA and the CDR for having the opportunity to share my opportunity to share my patient perspectives on the current approaches to treating IEM. My specific connection is to PKU diagnosis, 1973. The provision of clinical care is through the University of Maryland and in the very early years under protocol through Maryland's newborn screening program that involved intensive home visits, blood phe drawing, and dietary monitoring with provision of medical food which is also the emphasis of my comments, but I would like to acknowledge there are some other treatments -- the open dialogue session that follows.

Medical food is the treatment that I depend upon to this day for health and survival, to perform academically, socially, and professionally, one that spared me a lifetime of institutional care and saved my children's lives. This patient-focused dialogue offers a channel of communication that I think can be very beneficial to assure that the FDA is meeting its

commitment in implementing PDUFA-V which is why we are here today, thanks to the Congressionally-mandated responsibility known as FDASIA.

I have been asked to address attributes of an ideal treatment. While the diet has its shortcomings, there have been milestones. And I think the FDA shares my concerns warranting a 21st Century approach to nutritional management of PKU that includes access to innovations. First and foremost, the attributes: Prevention: In the words of former Secretary Sebelius, preventing illnesses before they become serious and more costly to treat helps Americans of all ages stay healthier.

Key Congressional witness, Dr. Shuren of the CDRH, at November's FDASIA's hearing highlighted another key attribute, accelerated access, and reinforced the need to speed innovative new products to market without compromising safety.

And in the case of PKU, unnecessary delays and affordable access to conventional treatments, game changers within the category of medical food and emerging pharmaceuticals leads to disease progression

and devastating outcomes that are 100 percent preventable for limited, underrepresented, underserved population as the PKU adults.

In the history of biochemical genetics, there is no greater invention than treatment which takes the form of a diet that can prevent severe, devastating neurological toxicities and virtually eliminate disease manifestations. In untreated adults, there is increase in mental illness, psychological disorders like depression and phobias, anxiety, and neurological deterioration, seizures, tremors and paresis; hence, the wheelchair.

On the bottom row or bottom quarter there, there is a visual representation of the positive outcomes not possible without early and continuous treatment but the story does not end here. Children born to pregnant with untreated PKU have severe birth defects. Microcephally, congenital heart defects, developmental delay, and mental retardation. There is no cure. This would be idea.

Other attributes that I would look for in an ideal treatment -- this is something that's

personalized given the variability of the genetic mutations in the enzyme and consideration should be given to individual patient variables and their specific metabolic needs. This requires a multi-disciplinary team approach and maybe combination therapy that's afforded to all patients with PKU. Regardless of the treatment or the inborn error, the risk versus the benefits must be weighed, discussed with the metabolic team to assure patients are meeting their goals and the treatment plans optimize outcomes.

The FDA is a shepherd of resources and that includes medical food. I do not want to see PKU patients handicapped anymore by an inefficient system for which medical food fits no paradigm. The incentives under PDUFA V need to be extended to the medical foods industry, the small business innovators who hold my lifeline. Thank you.

DR. EGGERS: Thank you very much, Jennifer. And now we'll move to Roy.

ROY ZEIGHAMI: So I'm Roy Zeighami. I've told you a little bit about my son already. He's six years old and has Sanfilippo syndrome. I won't dive

into what that is. I think we've talked about it enough already. But I'll talk a little bit about what we're giving him today to try and manage his symptoms and what seems to work and what doesn't.

One of the things that showed up in animal models was that you could give Sanfilippo mice Genestein in very high doses and actually manage the underlying cause of the disease. You could reduce the substrate that was built up in the mice. And with nothing to lose, we tried Genistein on our son in a comparable dose as to what was given in the mice. And what we saw in the period that we gave him between 3 and 4 was, I mean, just extremely rapid decline. It seemed to have no effect. We took him off.

And so there was -- you know, there wasn't any assurance that this substance was helping him and that's obviously evidence that what might work in a mice doesn’t seem to necessarily work in humans. And so we were left with treatment that basically managed his symptoms. Some -- one of the symptoms is aggression and we give him risperdal to manage his aggression and we found that that made him easier to

manage in school, less aggressive and less impulsive and amitriptyline at night to help him sleep. And both of those things have been, you know, very good for him in terms of managing those particular symptoms.

Now the downside of giving him those drugs is that it makes lethargic the next day. And so, you know, as a parent, I have to sleep, right. We have to live our lives and so I sort of feel some guilt about giving him something that causes him to wake up a little sluggish in the morning but it's a choice that we make because it seems to help our family live our life.

And what I would like to see in terms of treatment is not just something that seems to treat the symptoms but something that attacks the underlying cause of the disease. I mean Sanfilippo is caused by a well-known gene defect that causes a missing enzyme that causes a well-known substrate to build up in the brain, and yet there is nothing that we can try here in the U.S. and no trials here in the U.S. to treat that.

In terms of what I'd like to see, I think

something that managed his hyperactivity would be excellent, something that helped him sleep without waking up the next morning feeling drugged, and something that managed his impulsive aggression. And I think, you know, managing and stabilizing his cognition, I mean we can him risperdal, but that's not keeping him from slipping away from me, right. And let's see, I think a homerun for me would be is if I could take my son to the grocery store and walk through the grocery store holding his hand and shopping without him ripping everything off the shelves. I mean that would be awesome, right. I'm not expecting the kid to get a medical degree someday. I just want him just to live a manageable life.

And finally, I just want to talk a little bit about consent. I think there may be a perception among the scientific and regulatory community that patients need tons of data. And what I would say is that, you know, the average run-of-the-mill parent is not going to be able to look at some animal data around longevity or whether they can swim through a maze or something like that and make a decision about

treating their son. They're going to trust what the doctors tell them, right. And so I would avoid just releasing tons of data to patients. I think it needs to be boiled down by the sponsor and by the -- you know, the industry sponsor and then the doctor that's running the trial. And that needs to be boiled down to simple language that parents can understand.

One of my concerns is that we don't necessarily want to create huge hurdles either for opportunities to try treatments. One of the things that we see in Sanfilippo, there is no newborn screening for Sanfilippo and so every kid that goes into the trial is symptomatic. By definition, they've been found -- unless they're a younger sibling of a parent that got -- or an older child that got diagnosed, they, by definition, have symptoms and that's why they were found and yet a treatment might work differently in a symptomatic patient than in a newborn. And yet I don't want to wait for animal data that says, yes, this treatment works in newborns. I mean the way every industry sponsor is going to test a drug, they're going to get an animal model, they're

going to test it on the newborns, and there is some sign of efficacy and proof of safety, that's enough for me because the option of not doing anything is certain -- it's a death sentence, right.

And, you know, we absolutely need trials in the U.S. There's an intrathecal ERT trial similar to what most have talked about and the company, the sponsor couldn't get it opened up in the U.S. and we tried everything from moving to Europe, asking for compassionate access, and there's just, you know, no opportunity, and that's a hopeless feeling as a parent.

I think we want some reasonable idea of safety but I don't think we necessarily need proof of efficacy before we try something in a phase one/two trial.

I know that this is a shocking thing, probably, for most people to hear, but, you know, my son may live 10 more years if we don't treat him, but his quality of life is rapidly decreasing. And I think if I tried something today with a reasonable belief and doing my homework that it might help him

and he died, I would know that I'd died trying and that would be something that I could live with. And I want that chance to try for my son.

And I know that -- I respect you guys so much for what you deal with because no one's ever happy with the FDA. Probably people complain if you let something go through that shouldn't and, you know, we want you to move faster. And, you know, I think our job as patient advocates is to make our perspective clear on these catastrophic diseases. We need to go to Congress. We need to give you guys air cover to let you know that you can move as fast as possible so that you guys don't have the fear of being dragged up in front of Congress. And that's our job and we're going to continue to do that.

And I think one of the brightest spots of hope for us in the Sanfilippo community, above the ERTs that are being developed, is gene therapy. And in terms of what might be very interesting to see in a consent form, you know, one of the therapies that's being developed is being done right here nationwide, and they're using an AAV9 vector. And yet they're

using that same vector for SMA, for other diseases, and maybe there's safety data from those other trials, and maybe that data can go into the consent form. And I don't know whether that safety data translates but I think that's very interesting information, and maybe -- you know, maybe that could translate to some degree, so, thank you.

DR. EGGERS: Any -- you finished --

ROY ZEIGHAMI: Yes.

DR. EGGERS: -- your -- oh, sorry. Thank you very much, Roy.

ROY ZEIGHAMI: Sure.

DR. EGGERS: And finally, we will have Andrea.

ANDREA SMITH: Hello. My name is Andrea Smith and I have a 6-year-old daughter, Katie, who was diagnosed with an inborn error of metabolism. She has a MELAS-like syndrome and was recently also diagnosed with Type B pyruvate carboxylase. Katie has low tone and transient muscle weakness. She rarely sleeps, has severe temperature dysregulation, gut dysmobility, and has seizures. When we received Katie's diagnosis, we

worked with a pediatric psychiatrist named Dr. Stanley Greenspan and moved to Bethesda. We're originally from Texas. She's also being treated at Johns Hopkins and Columbia University.

Katie has a sweet disposition and is well-behaved but she does experience extreme anxiety as she does not understand why her body receives several different messages. Dr. Greenspan taught us how to cell regulate he by carefully monitoring, on a daily basis, and working with her doing something called Floortime. It's basically a play therapy to keep her emotionally regulated, to take her to higher levels of thinking and understanding the world around her. It is very successful as we continue to do Floortime.

Since the first year of her life, she has received speech therapy, physical therapy, and occupational therapy. We spend more than the average family on food and antioxidants. Now that we have learned that her IEM takes so much work for her to convert nutrients into energy, we are constantly trying new things that she eats, things that we've noticed that work or don't work. We know that her

cells have an impact on her ATP and her mitochondria regulatory function which is why we believe all this expensive therapy has kept her alive.

Katie maintaining cellular metabolic homeostasis is a 24/7 job for me and is the most difficult because, well, you know, it affects everything she does, how she feels, her seizures, her brain disorganization, her blood pressure is all over the place, and her central nervous system.

She's also been taking a mitochondrial cocktail for over a year now and we have not seen any improvement. And I asked my neurologist slash geneticist okay, well, now what? What do we do? And he said, you know what, that's the million dollar question. I get this question from everybody and I -- and he says I don't know what to do. You just have to treat each symptom as you, you know, walk this path.

So I Googled some of her symptoms and I found a wonderful organization called MitoAction whose mission is to support those affected with an IEM or a mitochondrial disease. They don't necessarily give medical advice but they offer practical advice for

patients to manage their symptoms and family support. Also, MitoAction has helped our daughter improve her quality of life because sometimes when I don't know what to do, there are others there along the way to hold my hand.

Since there is no cure, I would want to know the modulation of her gene or mitochondria oxidative phosphorylation to match the work of her ATP hydrolysis. I don't know if that makes any sense to you but as I understand and experience what my child goes through daily is that the food she is eating is not converting enough energy or oxygen to make proper ATP. Thus, enter mitochondrial dysfunction. Then this creates the whole messed up metabolic homeostasis. Are there post transational modifications and metabolic alterations that can be adjusted? I don't know but I'm certainly looking into it in Europe.

I certainly do not want to use children as human guinea pigs. Do we continue to use experimental mice in labs? The informed consent should clearly communicate in laymen's terms how long the experiment

has existed, outcomes and statistics, and how many participants. Also, has the medicine been tested to rule out any damage to the mitochondria?

I believe a mandatory class should be taken for a certain amount of hours for parents to complete. Do not go over the paperwork the same day in the clinic, for example. Parents need time to digest the information. A second mandatory class to ensure the understand exactly what they are committing to. There should be a Q and A day especially put aside with the specialist who created the trial.

After that, parents, I believe, must have a waiting period before they sign their child up. For example, let's just say like three days. I'm sure for many parents and because of their desperation, they would do anything to help their child and my fear is they may make an emotional decision not realizing some of the side effects and risks.

In conclusion, parents of children with IEMs spend a large portion for their time trying to get their medical needs met through insurance. There should be more awareness and advocating for IEMs just

like children who have cancer or leukemia. That's all.

DR. EGGERS: Thank you very much, Andrea. And again, if we could give these parents and the individual living with the PKU a round of applause.

(Applause.)

DR. EGGERS: We thank you very much for setting up a great foundation to a discussion. We won't be able to follow-up on every point that you have made, but I think you really set the stage explaining the range of perspectives and the range of experiences that you've had. I'm going to ask again just so we get a sense of how many people, as you were listening out here, how many patients and caretakers heard your own perspectives or experiences shred?

(Hands raised.)

DR. EGGERS: Anyone who has experiences or perspectives that are widely different?

(Hands raised)

DR. EGGERS: Okay. So it sounds like there is some common ground here and we'll delve further into that.

To start, we're going to have a polling question just like we had in the first topic. This just gives us a sense of what your experiences are. And you're on the web, then you should have this polling question as well.

What therapies have you used to manage your or your loved ones condition, and please check all that apply: dietary restrictions/supplementation medical foods; enzyme replacement therapies; bone marrow or organ transplantation, that's C; other prescription medicines to help support the condition such as anticonvulsants or psychiatric medications; non-drug treatment such as dialysis, G-tubes or splinting; use of assistive technologies, a broad range of them from wheelchairs to readers, etcetera; other therapies such as behavioral, physical, speech, or occupational therapy; or something else or none of the above, then you would mark H.

(Whereupon, in response to polling, the results are as follows: A. Dietary, 68%; B. Enzymes, 28%; C. Bone, 12%; D. Other prescriptions; 64%; E. non-drug; 10%;

, use of assistive technologies, 60%;
G. Other therapies, 68%; and H. None, 8%.)
DR. EGGERS: Okay. Again, we have the wide range of experiences represented here, a little less experience collectively with enzyme replacement therapies and with bone marrow transplantation for several reasons. On the web.
DR. VAIDYA: We have a very similar distribution on the web as well.
DR. EGGERS: Okay. Thank you. Okay. We're going to touch upon some of these now in more depth and feel free to help with some follow-up questions. And we will first start with the enzyme requirement therapies. We've heard the experiences shared and we might have heard some from Topic 1.
What we're really looking for in this discussion is to get at what specific neurological effects are they addressing well and how do you know. Would anyone like to comment more on that from their experience? Yes, Steve. Hang on one second.
STEVE HOLLAND: Steve Holland, MPS I. So my children started ERT in 1998 and at the current

dosing, there's no evidence in their condition that it improves the neurologic effect of the disease. In animal studies they have to give like 20-fold in order to get any treatment from that. So absent doing it intrathecally, providing the enzyme that way, it's just not going to cross the blood-brain barrier under the current technology.

DR. EGGERS: Okay. Thank you. Anyone else want to share their experience?

DEAN SUHR: And I would say one of the other things is -- it's up here Sara -- sorry --

DR. EGGERS: Oh.

DEAN SUHR: -- that CNS versus PNS and the effectiveness of enzyme therapy in both aspects of the nervous system is something that is not consistent and something we need to learn more about.

DR. EGGERS: Okay. Any specific downsides of these treatment that you would like to highlight?

AUDIENCE MEMBER: (Off mic.)

DR. EGGERS: Just the enzyme replacement therapies at this moment?

AUDIENCE MEMBER: (Off mic.)

DR. EGGERS: Okay. We'll have Amber and then we'll go back there.

AMBER MORGAN: Hi. Amber Morgan. My daughter has MPS I. She only received enzyme therapy for about 17 weeks during the time in which she was receiving a bone marrow transplant. And the downside for us definitely was the fact that they had to access veins on a 13-month old child every single time you went in. And even when she had the port, it was easier but there are infusion issues that children can take on too much fluid and then have issues with blood pressure and other concerns. And after she had her port taken out from transplant, we were back to peripheral vein use and that was a big bummer for her.

Also, a downside would be sitting for 4 to 6 hours with a 2-year-old attached to a wire in a crib that just wants to be running around. It gets tangled up and they get wrapped around them so that's not pleasant.

DR. EGGERS: Thank you, Amber. Back there?

NADIA BODKIN: I don't have a downside to the enzyme. I have a downside to the other

treatments. I don't know if you --

DR. EGGERS: Okay. We'll probably get to those other treatments and then if we don't, we'll come back to you. What's your name?

NADIA BODKIN: My name's Nadia.

DR. EGGERS: Nadia, okay. Are there any -- go ahead, Jennifer.

JENNIFER PAYNE: I can't really comment on a downside of the enzyme replacement therapy because for PKU, we actually have one that's in Phase III clinical trials right now. So that remains to be determined. But a downside for me as far as the inclusion criteria, I've had the consent forms in my hand but one of the criterion is looking at the phenylalanine level. And Christine mentioned in the earlier session, there's a very narrow therapeutic window and they're looking at adults that are above six. I don't meet that criteria because I'm stable. So it is a concern to me as we, you know, roll out these new therapies. It's anticipated this may be something likely I'll see. In the future, how you transition adults with PKU who are in stable metabolic control to

an enzyme, it doesn't really seem that that's what they're -- right now they're just focusing on the levels. And we've seen that with Kuvane FDA approved in 2007. It's used to help stimulate residual enzyme. There's different PKU: hyper phe, classical, so you might have different functioning forms of the enzyme. This is used to boost the activity as an adjunct therapy to a diet.

The response can be different responses and I think (inaudible) can probably comment better on that. But efficacy is looking at a 30 percent drop in the phe levels and I think as far as the neuro cognitive effects, that's probably something still in study but maybe they could address. But it's an ongoing process and --

DR. EGGERS: Thank you, Jennifer. Any follow-up questions? Melissa, go ahead.

MELISSA HOGAN: I would just make two comments about downsides of ERT, the first being -- we had the workshop yesterday on immune tolerance and I think that's a very important issue to continue exploring both in intravenous ERT as well as

potentially in intrathecal ERT. Obviously, very important to me.

And the second, as I mentioned, was the medical trauma aspects of constant interventions on a weekly basis, then in clinical trials and then with additional tests that a lot of these kids are required to undergo.

DR. EGGERS: Thank you. Anything --

STEVE HOLLAND: Just one other thing. I mean not to state the obvious, but obviously the cost and the time that's involved. We're willing to accept those things so it's not a -- but you know, the second generation small molecule, taking a pill obviously would be much more preferred for all the kids on ERT.

DR. EGGERS: Thank you. We've had some discussion -- I know there is some in the audience -- I know Amber, I think -- about bone marrow or organ transplantation, and I just wanted to spend a few minutes to follow-up on if anyone wanted to share their experience. We will ask Amber to come up and just spend a few minutes on what you saw as the effects, especially the impact it had on the

neurological effects from the bone marrow transplantation.

AMBER MORGAN: When my daughter was diagnosed, she was 11 months old and the reason that we found her diagnosis was not neurological. Really, at that point, she was only six months old when I started questioning doctors as to what was going on with her. By nine months, when I finally said she's not babbling and that was a sign to me that there was something going on, then they finally started looking a little more serious at her.

And throughout transplant, she still had yet to do things like walk on her own. Rolling over was still not something that she was able to do. Sitting up on her own was quite a struggle. She learned, actually, while she was in transplant to do this motion (indicating with head up and down) with her head which was a lot of fun because then when she came down, there was a crib side that she would smack. So we had to start padding the crib for her while she went through transplant. And she wasn't speaking still yet. She learned to do the mamma, dada thing

what she was in transplant.

And so we worked a lot with all the other therapies. The physical therapy and occupational therapy and speech therapists came in every day when we were there. And by the time she got out, she was up to being able to sign six words. She still was not walking on her own but she was cruising her room for that period of time. I can't think of many other things that she gained. I mean she really seemed like she was supposed to go through transplant. She was just much stronger when she got out.

Once we got home, it was about three months that went by before she started walking on her own and speaking words and she chose a good one. Block was her first word. So, yeah, had good effects.

DR. EGGERS: Thank you very much, Amber. So we've heard very different experiences with bone marrow transplantation. Does anyone else want to share their experience with that? Right here.

BECKY VIVIAN: Hi. My name is Becky and I am here with my two children, Eli and Ella. Our story is a little bit different. My kids -- Eli, 20 months

ago, was diagnosed with metachromatic leukodrystrophy, otherwise known as MLD. We were told basically, take him home land enjoy the rest of his life, because there was no real treatments for the disease. In researching, we found out that there was indeed bone marrow transplant. But after we researched more, we found out that for MLD, just this disease specific, the mortality rate was at least 40 percent. And in the last 20 months, we met a lot of people on Facebook and through the MLD Foundation, and anyone who has had a bone marrow transplant, they are still progressing with the disease and they are still dying.

We -- by the grace of God, we got into a clinical trial in Milan, Italy and I lived there for four months with Eli last year and he got gene therapy. Ella and I --

DR. EGGERS: Eli's raising his hand.

BECKY VIVIAN: -- oh -- Ella and I just got home about four weeks ago from her gene therapy. We lived there for another four months. She was in the hospital for 64 days. For Eli, we had to pay for everything because he was accepted out of compassion.

We were going to opt to not do a transplant because of all the harmful side effects for this particular disease.

As you can see, they are doing amazing. They left Milan after four months of being there. None of them -- neither one of them were on any drugs, no immunosuppressives, obviously, because they're using their own cells that are just manipulated. And they're both doing wonderful and Eli was number 10 in the world and Ella was number 11.

And all I can say is I really hope -- I'm not here for them because they already went through treatment. I'm here for the ones that come after them and hopefully, other people get this opportunity, because when you talk about treatment, when Eli was diagnosed, unfortunately, the neurologist kept turning us down, there's nothing wrong, there's nothing wrong. So it also has to start there. I think that more people need to be more aware of these types of diseases because had he -- you know, had I waited and not trusted my gut, we would have never even gotten in that trial and then these two would be just living out

the rest of their life.

So I could just ask you, the FDA, just look at these treatments as another option because there's nothing here in the United States. And I had to leave my other two kids for eight months to live in Italy and it's obviously affected our whole family. And -- but hopefully, they can live, you know, a nice life right now, so thank you.

DR. EGGERS: Thank you very much, Becky. Any follow-up questions on what we've heard?

(No response.)

DR. EGGERS: Okay. Any comments from the web on these topics?

DR. VAIDYA: We have some comments not directly related to the -- to what we were hearing in the room, but we do have some web participants who've mentioned the issues around compassionate use of drugs and a participant mentioned concerns about applying standard clinical trial parameters to the IEM trials. Also, some other treatments have been mentioned such as IV pamidronate for mucolipidosis. And for Gaucher, there are substrate reduction therapies but the side

effects make it very difficult for the patients.

DR. EGGERS: Okay. Thank you. We've heard quite a bit about medical foods both from Jennifer's comments and from some comments earlier with regard to medical foods in PKU.

Are there any other experiences with medical foods or other dietary supplementation that you would like to share at this point? Okay. We'll go back there first because the microphone is back there and then we'll come up here.

JANA MONACO: Hi. The organic acidemias also thrive on the medical foods and the formula they -- we have a -- there is a formula devised for each particular disorder that leaves out the offending amino acid that they cannot metabolize. So for my children, their isovaleric acidemia is an ability to break down leucine. So both of my children, they consume part of their diet with natural protein. My daughter, because she does not have the same neurological defects that my son has, gets her natural protein from foods where my son gets it from a liquid pre-mixed formula all ready. But they are both

supplemented with the leucine-free formula that is vital to keeping them alive.

DR. EGGERS: Can I ask do you see effects? Can you see changes in their neurological symptoms and effects?

JANA MONACO: Oh, absolutely. My son not having the restricted diet at birth along with the amino acid supplements which is he -- they both are on Glycine and levocarnitine, Carnitor. And that helps them to rid their body of the isovaleric acid that builds up. So since he didn't have it for the first 3-1/2 years before diagnosis, there were, I guess, different times where he was almost at risk. And at 18 months, he was sick but unfortunately, when he was hospitalized, it was not discovered. No one identified the disorder so it went undetected.

But as soon as he was put on diet, he remained stable metabolically for the past 13 years and he's had a lot of hospitalizations, five surgeries in the past three years. And though he's had a lot of critical moments, he's remained metabolically stable throughout everything. And my daughter remains on the

restricted diet with the e-formula as well and the amino acid supplements and she's protected. She is 11, finishing out fifth grade.

If we don't maintain that status of maintaining that level with these foods, we can see her get a little lethargic and just not, as we say, you know -- they're off as we will say and they begin to wilt, so a huge impact.

DR. EGGERS: Okay. Thank you so much. Right up here.

CASEY CONNOLLY: My name is Casey Connolly. I'm a lifelong PKU patient. Sorry to bug you again about PKU. I know there's a lot of patients in here.

DR. EGGERS: We want to hear about PKU, of course.

CASEY CONNOLLY: So basically, PKU, growing up through your childhood, the hardest thing is, you know, being normal and being cool around other people. And growing up eating these fake processed foods that your mom has to cook for you everywhere you go, and you have to bring a fake lunch with fake cheese to school and have kids wonder what are you doing; why

are you eating that, it makes life growing up rather difficult.

And then as getting into high school, luckily enough my mom has been fully engulfed in the PKU community and I was able to get into clinical trials and be able to be a testing dummy basically for all -- for Kuvan, let's say. And I did start Kuvan since I was 14 and even since then, that's changed my life into a whole 180 because now I can eat like a straight vegetarian. And by all means, it's been one of the greatest things that I have been through in my entire life and been able to be a part of.

But now it's going through seven years of my life where I'm still on the same drug, I'm still doing the same thing. Yeah, I have to take over 30 pills (holds up a baggie of pills) a day in order to sustain just a vegetarian diet that's consisting of carbs, fruits and veggies. And in order to do that, I have to take 30 pills. Every meal I go to, I have to bring a bottle with me and to whip out the pills. So when I'm out with friends, if I go on a date, I got to bring my pills with me and I got to explain the

situation every single time. It gets tedious and it gets frustrating. And the problem with that is being a PKU patient, the number one thing that you need to do to stay healthy is take your medication. And when I have to take 30 pills a day every single meal, when I have to drink a formula twice a day every single day which consists of 500 calories per drink which sums up to 1000 calories a day, aka supplementing half my meals a day, which don't get me wrong -- it tastes disgusting, but I have to do it in order to move on. But that takes away half my meals every single day of where I want to eat, you know, a fruit salad or something delicious tasting.

And so the fact that going through this, having all these steps and processes, the volume of medication that I need to take just to become a vegetarian, which I'm not even cured yet, but it's just -- it's just temporary is making my life so tedious that I -- I'm watching my little brother go thought he same thing because he does the same -- he's 14 with PKU, but it makes him not want to take his medications. And because he resisted doing it and

which my mom has to force it upon him, he refuses even more because he's in those teen stages where you don't want to. And when he does that, then all the symptoms come, lack of focus, temper. I mean I -- when I don't take my medication in school and I have to take tests, I sit there and I just twiddle my thumb. You can't focus at all and so your temper is problems.

And now as graduating, when I'm going in the job market now and in three years, I'm going to have to start paying for this on my own -- which don't get me started on how expensive this stuff is -- it's going to be a whole new ballgame.

And so all I'm saying is just to make lives -- like Kuvan stepped my life way above where it was before. But now the next step is decrease the volume. Like I can't sit here and take four more hours of each day taking these medications, gulping down 30 pills a day and sitting here drinking this big shake of bland tasting stuff in order to survive. It sucks but I mean I will do it until the day I die because I can't go back to where it was. But just decreasing the volume, that would be the next progressive step that

we could make in making lives better.

DR. EGGERS: Thank you very much, Collin. Collin, right?

CASEY CONNOLLY: Casey.

DR. EGGERS: Casey? Sorry. Thank you, Casey.

JENNIFER PAYNE: Can I add to Casey's comments?

DR. EGGERS: Sure, Jennifer.

JENNIFER PAYNE: I think that he did a great job showing the issues with compliance, not only the diet but also the pill burden with Kuvan. As you can see, it's life-changing for him. I'm not a consumer of Kuvan. You have to be tested to respond to the medication. But he makes a good point with the medical foods. Essentially, it's medication. You have to take it religiously, like I said earlier, to perform on a day-to-day basis. And that -- you know, just the slightest change and your phe levels, you can feel the effects.

And I just want to say for me, you know, the medical food is the treatment for me. For now, I'm a

pharmacist. I need the utmost, you know, attention, focus and concentration, you know, to do my job. But the point is I -- the -- he points out some of the limitations with the diet, the high carb load. It's not perfect but, you know what, the diet got me through three pregnancies, three healthy children, and if that is not enough -- you know, that's testimony to the power of the phe-restricted diet right there.

DR. EGGERS: Thank you so much. If you're looking at the agenda, don't be nervous. We get to keep going. We have -- we only need about 15 minutes for the public comment session so we're going to keep going on this topic and stretch it out as much as we can.

If you have signed up for the public comment session, we're going to ask you to limit your remarks to three minutes and we will be pretty tight on that three minutes because we do want to make sure we have since we're going to limit it to 15 minutes so that we can have this conversation go as long as possible.

Are there any other treatments that you want to focus on before we go into a discussion on clinical

trials? Yes, Julie.

DR. BEITZ: Hi. I wanted to follow-up on a comment that Ms. Hogan made earlier and it's not necessarily about a specific treatment but to -- if I've quoted you correctly, you said there should be an expectation of expanded access pass the initial safety trial?

And if I could have you just explain a little bit more about what you mean. Do you mean that if someone's enrolled in a safety or efficacy trial and they have completed the trial through the time points for assessing safety and efficacy, that they should then allow to stay in the trial and get the treatment? Or do you mean that they can get off the trial and do something different?

MELISSA HOGAN: Thanks for the question. No. I think the extension trial, I mean, obviously, I think is a no-brainer. But I think in these very severe degenerative diseases where you have a very short timeframe in which to try to save your child, once a drug is shown to be even somewhat safe, I think it is incumbent upon industry to expect that the

community, once they see that a drug is safe and has some level of efficacy, that patients are going to want to save their children.

When my son is seven and he's learning to snorkel right now and climbing rock walls and playing computer games and his best friend is dying at the same age, that's a very difficult thing for a community to sit and accept when we see a drug that's shown safety and even at this point shown efficacy.

DR. EGGERS: I think we'll delve a little further in this in a few minutes. Any other questions on any specific treatments or treatment types?

(No response.)

DR. EGGERS: We haven't been able to talk about the very important, more supportive care treatments, the other prescription medications that you've taken, the importance of, as we're hearing, the physical, occupational, and speech therapies and behavioral therapies. So we'll encourage you to share those experiences through the docket if you have a chance to submit additional comments.

Any other comments on treatments on the web?

DR. VAIDYA: We have a web participant who mentioned his son or daughter has Sanfilippo and they're -- he treats the child with supplements but there is no evidence that these actually work. They also are on a low sodium, anti inflammatory diet regimen which has helped reduce the joint pain. That's it.

DR. EGGERS: Thank you, Pujita. Okay. We want to make sure we get to follow-up on the great comments that we heard from the panel on the informed consent in the clinical trial participation. So before we do that, we have a few polling questions just to understand the experiences and perspectives in the room and on the web.

And the first one is have you or your loved one ever participated in any type of clinical trial, study, experimental treatments for IEM?

(Whereupon, in response to polling, the results are as follows: A. Yes, 41%; B. No, 55%; C. Not sure, 5%.)

DR. EGGERS: Okay. So we have about a dozen of you in the room have not had any experience and

about 10 of you I believe had had experience. On the web?

DR. VAIDYA: About two have had experience on the web.

DR. EGGERS: Okay. Can I get a show of hands from those of you that have said no?

(Hands raised.)

Of those of you that said no, how many of you wanted to be in one and could not for some reason?

(Hands raised.)

DR. EGGERS: Okay. So there's another polling question which -- and this is a very tough one and believe me, no one's going to hold you to the responses of this. This just gives us a general sense of your thoughts toward clinical trials. Today, think about your situation today, you or your child's situation today. If you or your loved one had the opportunity to participate in a clinical trial to study an experimental treatment -- let's think of something that's either a medical treatment or a transplantation -- which of the following best describes your thoughts: Yes. Of course, it would

depend on many factors but I am generally willing to consider participating. No, I would probably not consider participating. Or maybe, I'm not really sure whether I would be generally willing to participate.

(Whereupon, in response to polling, the results are as follows: A. Yes., 100%; B. No, 0%; C. Maybe, 0%.)

DR. EGGERS: Okay. All right. You made me read through all of these really tough response choices here. You could have just stopped me and said "that's a dumb question." On the web.

DR. VAIDYA: On the web, we actually have 85 percent who've said yes; 5 percent who said no, and then 10 percent who are unsure, uncertain.

DR. EGGERS: If you're on the web, if you could provide a comment if you were one of that said generally no about why. Okay. So we now have a sense of the perspective shared in the room.

And then to follow-up this discussion, I'm going to throw one more think at you which is a scenario just to help set the stage. And when we answer the next questions, try to put yourself in this

position, that you or your child has the opportunity to consider participating in a clinical trial for an experimental enzyme replacement therapy or something similar to that, that the clinical trial is a phase one, first-in-human study involving approximately 10 patients, so it's never been studied in humans before, and for this trial, there is less animal data available to evaluate the safety than is typical for a first-in-human study of this type. Therefore, the benefits and the risks of this experimental would be highly uncertain.

So are question is what thoughts first come to your mind when you hear this scenario? What questions would you have? So I'll open it up. I'll come out here first and then we'll -- yeah, right there.

STEVE HOLLAND: Yeah. I think the key to that question is less than what is typical because our understanding is that what is typical is killing lots of large mammals when that is unnecessary. So I think -- my thoughts on that are that yes, it needs to be treated-tested in animals and I don't think any

of us are willing to do anything that's not, but it's the extent for these rare diseases of putting them through the same rigorous, you know, thresholds that for something that's affecting a lot of diseases, a lot of people when ours is affecting, you know, fewer.

DR. EGGERS: Thank you. Let's go to Roy and then we'll go to Austin.

ROY ZEIGHAMI: I think it would depend on a couple things. One, is there a reasonable treatment already available for the disease, right.

DR. EGGERS: Okay.

ROY ZEIGHAMI: I would accept more risk if there's nothing. And secondly, it would depend on where my child was in the course of the disease. If it was very early and young and there was hope that I could wait and see some data, then maybe I would sit on the sideline. But if the window is very short relative to the time of the trial, I would put him in, no doubt about it.

DR. EGGERS: Okay. Thank you. Julie, would you like to follow-up and then we'll go to Austin.

DR. BIETZ: I just wanted to clarify that

maybe one of the ways that the amount of data is less comparable to what we're used to having is not so much the number of animals but the duration of the animals' exposure. So for example, if you we would normally have a treatment in animals for six months and in this case we only had one month of treatment, how would that impact your thinking about that. So we would not have very much experience with treatment over anything longer than say a month. How would people feel about that?

DR. EGGERS: Okay. Austin, would you like to go and then we'll go to Tracy.

AUSTIN NOLL: Thanks.

DR. EGGERS: I think there's a hand up over here.

AUSTIN NOLL: Can you hear me?

DR. EGGERS: Uh-huh.

AUSTIN NOLL: To me -- so you've got two questions to ask, right? You have safety and efficacy and it's been said many times here that -- and I think everybody or most people in this room agree that safety is the primary thing you need to take a look

at. I think we're all willing to take more risk. We have to. My son's going to live three more years. So what are you going to do, you know? Sorry.

I'm not in a riskier -- I can't be in a riskier situation. Just give him a chance. Give these kids a chance.

DR. EGGERS: Thank you, Austin. There was a hand -- we'll go to Tracy first and then we'll come up here to you.

TRACY VanHOUTAN: I think I agree with the previous comments. Just, you know, give our kids a chance. To your question -- statement about the animals, in the genotype of these animals, are we seeing any improvement even in the shorter timeframe?

DR. EGGERS: Oh. This was a scenario so is that a question you would want to know about?

TRACY VanHOUTAN: Well, a scenario was given to us by the panelists. I was asking the question -- I need a little bit more information about that scenario to answer.

DR. EGGERS: Okay.

DR. BEITZ: Right. There would be -- Donna,

maybe you could answer. What I was getting at was the duration of treatment to assess safety but if -- but maybe Donna, you can talk about the efficacy.

DR. GRIEBEL: I was just going to say if we were going into phase one in children, we have to have some sign, whether it's in a -- some scientific rationale and proof that there is some hope of efficacy in the children. So in this scenario, yes, we would say that there is some evidence that there might be efficacy that would support going into the children. So the -- what Dr. Beitz was going after was going after was the duration because the duration and a treatment in these children with diseases that are lifelong diseases, the treatment would be expected to be as long as the child lived. And we learn in these animal studies what happens over time in the animals by -- they're sacrificed and we look at their tissues to see what happened to find out what might be -- we might be able to predict and what we should be looking for in the children for a toxicity. So that was the question about how you would -- how different parents might factor that information in

into a consent form about knowing what the amount is relative to what is usual in the long-term safety.

TRACY VanHOUTAN: Okay. Let me finish with this comment. A lot of our kids are dying. We aren't looking -- they're dying. They're drowning in the middle of the ocean. We aren't looking for the Queen Mary to come by and take us to the next coast. We need a lifeboat. We may not expect to be on therapy for life because in a lot of these conditions, we know there are second generation treatments coming along. Give us the lifeboat, please.

DR. EGGERS: We'll go here.

STEPHANIE BOZARTH: My name is Stephanie Bozarth and my daughter has MPS IV. And actually, it's an inborn errors of metabolism but it doesn't typically affect the brain, so we are fortunate in that sense. But her life expectancy is still pretty short so there are other parts of the inborn errors of metabolism that will affect her long-term longevity.

When it comes to this question, we do have experience with enzyme replacement therapies and we do know from what we've seen in the past, that when

you're introducing a known protein into the body, there is a less probability of toxicity. I think there does need to be safety data. But where can we learn from what we've already been doing with enzyme replacement therapies and make that a little more concise so that we can get these therapies out quicker and sooner to the children?

And like many other MPSs, time is not our friend and my daughter did, fortunately, get to get in a clinical trial at the age of five but her growth plates would probably be dead by the age of eight, which she turned eight a couple of weeks ago. So, you know, it really meant a lot to be able to get on that clinical trial as soon as possible.

So I would absolutely, knowing what the risks were and that there was some safety and efficacy and that we've been doing enzyme replacement therapies for 10 years now -- we know about them, so.

DR. EGGERS: Thank you very much. I just want to put a call out to the Operator, if you could open the phone lines for anyone to give a final though on the phone.

I have a question I would like to follow-up with which is to -- for those of you in the room, and it's probably a smaller group of you, who have a child who could because they're either old enough or they have some capacity to, could take part in the decision about whether to participate in a clinical trial, what is most important from your perspective to communicate to address how the trial and informed consent is communicated to them? Maybe some different things than you've seen in your past experience. Steve?

STEVE HOLLAND: We've been through clinical trials with our kids both as minors and as adults, so we have some -- so it's been done -- handled differently in those situations. But even as a minor and as a child, I think involving them in the process at the level they're able to understand and getting them to sign on the paper so that they buy into it at the level they can is very important as far as down the road as, you know, when you're going through some of the constraints of the trial and the effort that it takes to be in it just to get them -- they're okay in it.

But even in our case, our kids are somewhat -- are a little cognitively impaired. They still look to us as their parents to provide them that assurance and comfort, so I really thing their buy-in is more just an add-on to the parents.

DR. EGGERS: Okay. I see a lot of heads nodding. So we'll go with Christine and then did you -- sir, did you have your hand up?

CHRISTINE BROWN: My 8-year-old was all ready to sign up for a clinical trial for PKU using the enzyme replacement therapy, and I mean the clinical trial is for 18 and up. But we -- I had an opportunity a couple of years ago to meet somebody who was in the phase two trial. She laid out the shots for him. She laid out the thickness of that needle. And he said, you know what, Mom, I still want to do it. So I think that with kids, it's maybe showing them some of the things and what would be involved and how big that needle might be or, you know, what the procedure actually looks like, you know. And if he had the opportunity and if he feels that strongly about it, you know, maybe down the road, it's

something that he can participate in.

DR. EGGERS: Thank you, Christine. We're going to have to move on in the interest of time but there -- well, first of all, any pressing questions from the FDA panel? Okay, yes, go ahead, Rachel.

DR. WITTEN: Hi. My name is Rachel Whitten. I'm from Gene and Cell Therapy Deviation. And, you know, our products are different. When we give this product, you don't know how long it's present. It may, you know, die in -- it's a live vector and we don't know how long this -- the product is going to work. Maybe it's one month, maybe two years or three years.

What we started doing recently, when we receive the protocol from the sponsor, we usually try to involve patient representative. You're going to start -- we ask the patient representative start with us with pre R&D meeting. Look at the protocol. Read the consent form and go through the protocol and let us know would you enroll your child in this clinical.

But what happened -- again, we (inaudible) a lot of rare diseases but sometimes we just cannot find

patient representative who will work with us and on this point, we do need your help.

DR. EGGERS: Okay. So I will put a shout out for our colleagues in the Office of Health and Constituent Affairs who help organize the patient representative program that Rachel is talking about. And if you are interested, if you haven't made a connection yet with FDA, look up the patient representative program and reach out to one of our colleagues in that office. There is a way to do it that's explained on the website. Okay. We have one person on the phone we'd like to -- Operator?

OPERATOR: If you'd like to make a comment on the phone lines, your lines are now open.

JANE WOLFE: Yes, this is --

DR. EGGERS: Hello.

JOYCE WOLFE: Hello?

DR. EGGERS: Yes, good morning.

JOYCE WOLFE: Hello?

DR. EGGERS: Hello, we can hear you.

JOYCE WOLFE: Thank you. This is Joyce Wolfe. I am the mother of two sons with Zellweger

syndrome. They basically have liver disease, adrenal insufficiencies, deaf-blindness, myelin abnormalities and delay seizures, muscle weakness, cognitive issues, behavior and sleep problems, bowel and bladder control issues, balance and walking problems. My sons were given six months to live and there's no cure.

The clinical trials that we're involved in in the U.S. are the cholic acid for bile cid deficiency. And in Europe, the DHA, ethyl ester for the DHA deficiency. The cholic acid trial in the United States was quite easy and well managed and we had no problems with compliance. The Europe trial, we made 18 trips to Europe until the research physician passed away. And when we were unable to give the DHA ethyl ester, we saw a drop in the plasmologens and increase in liver enzyme function tests, regression in physical performance, weight loss and inability to absorb fat-soluble vitamins, increase in irritability, decrease in appetite and increase in (inaudible) seizures.

The DHA is not available in the United States but it should be since our children have

difficulty breaking down our common type glycerides from DHA. And the research that was done abroad shows remarkable benefits and improvement in liver function, myelination, vision, muscle tone and overall health.

The questions that I would put out, my children, if they wanted to be involved in a clinical trial, is they are both so anxious to be well, to have lives that are not affected by deaf-blindness and poor muscle control and deterioration in their condition, that they would do anything to -- that showed a small amount of hope for them to continue to live a profitable life.

And I really agree with the comment that was made that our children are dying, and we need the kind of help that is already out there to be brought to the United States and to use what we have in the United States as well to have it through the FDA to be available for the treatment for all other children that will come along, and to be treated as soon as possible. Thank you so much.

DR. EGGERS: Thank you. And what was your name again?

JOYCE WOLFE: Joyce Wolfe.

DR. EGGERS: Joyce. Thank you, Joyce. Well, we are to the end of our time for this discussion. Of course, it could keep going. There are so many other things to talk about. We didn't get to touch upon challenges in eligibility criteria, for example, for those of you that wanted to participate in trials and haven't been able to, or in other issues such as awareness, or other issues related to clinical trials, or the other treatments that you're taking. Again, we have the docket and we really encourage you to contribute to the docket.

With that, I'm going to turn this over to Pujita who is going to do the open public comment.

DR. VAIDYA: Hello, everyone. I'd like to thank you all for coming today. We are now moving into the open public comment session, and for those of you who are not aware, the purpose of this session is to allow an opportunity for those who have not had a chance to speak on issues that are not related to our two main discussion topics. This is an opportunity for folks who are not patients or patient

representatives to comment.

Please keep in mind that we will not be responding to your comments but they will be transcribed and be part of the public record since we would like this to be a transparent process. We encourage you to note any financial interest that you have that are related to your comment. If you do not have such interest, you may state that for the record. And if you prefer not to provide this information, you can still provide your comments.

So we have collected signups before the meeting and during the break in the interest of time. We have about six -- we have six people signed up for this session, so please be respectful for your other colleagues here and other patients and stick to the two to three limit that we have. We won't have a timer but I will be keeping track of time. So if you approach the two to three minutes, I will ask you to start wrapping up.

So I'll quickly run through the order of speakers and I apologize if I mispronounce your name. We have first, Austin Noll; second, Page Migliozzi;

Eduardo Balcells; Cristy Balcells; William Nyhan; and Jana Monaco. So could we please have Austin Noll to the mic, please?

AUSTIN NOLL: I've pulled it together. Just a quick follow-up comment and it's on the safety versus efficacy waiting. You need to think about that because efficacy is inherently extremely difficult with this patient population. You know, I can take 10 kids with Sanfilippo who are my son's age, they're all going to be different. And my son is different every day. So if you wait forever to figure out efficacy, we got a huge problem. You really need to take a look at safety and then efficacy will come as we g et things out. Thanks.

DR. VAIDYA: Thank you, Austin. Next, could we have Paige?

PAIGE MIGLIOZZII: Hi. My name's Paige Migliozzi. My son, Christopher, had MPS I Hurler syndrome.

Last night, my 8-year-old daughter cried in my arms putting herself to sleep because her brother died 10 years ago tomorrow from Hurler syndrome. So

tomorrow marks a whole decade of my life that I have been without my son.

My 7-year-old son, when he goes to school and they talk about superheroes, he comes home and says, mamma, I wish I could be a superhero so I could undead my brother and so he could come and play with me.

I want you all to know the work you do is so important. There are families out there. There are real people who need your help and need your cure. Christopher was one of the first people to undergo enzyme replacement therapy in addition to chemotherapy and transplant. And we've talked about transplants and transplants have a lot of problems. They're not to be taken lightly, and he died of post transplant complications. I only had him for 14 months but I've spent the past 10 years grieving his death.

So on behalf of me and my family, I want you to know we need you because we need hope. These kids are running against an invisible clock. We all are. So thank you for all the work that you do and remember, we need you. We need that hope for our

children. Thank you.

DR. VAIDYA: Thank you, Paige. Next, we have Eduardo.

EDUARDO BALCELLS: Thank you again for the opportunity to participate in this wonderful event. Again, my daughter has mitochondrial disease, Leigh's disease specifically. She's our youngest daughter. My background, I'm a physician so one of the things that I go through that's striking for me is that in my world of patient care, I have a list of -- my patients come in and they have a list of medications they're on, on the average of 8 to 12. In my daughter's case, she has no proven therapies, no proven treatments.

Some comments on some of the previous comments made this -- during the previous discussion. It's important for us to realize that without opening up the access to a patient's four studies that we, as parents, have to resort to unproven therapies, anecdotal treatment and that carries risk in and of itself.

So for my daughter, she's on a host of compounded pharmacy vitamins, cofactors which are

compounded. But again, that's not regulated. I don't know exactly what she's getting. We believe it's helping her so -- but we are resorting to anecdotal care. And it's striking to me that, you know, in many of the adult chronic conditions, we do a very good job with our studies and patients have choices. So there are five different types of hypertensive medications or cholesterol medications. And again, in our space, we have no therapies.

So I would ask that we -- when we look at our children and adults with these types of diseases that we maybe perhaps look at it through a different lense. and as was mentioned before, safety is key but perhaps that risk is with not a "capital R" but a "small r" because really, without anything to offer our kids, again, we're left to anecdotal care, and that's a difficult situation to be in. So, thank you.

DR. VAIDYA: Thank you, Eduardo. Next, we have Cristy.

CRISTY BALCELLS: I also wanted to thank NORD, the National Organization for Rare Diseases for having us here today because we would not have known

about this meeting had it not been for them and their support.

Again, my name is Cristy. I'm the Executive Director of MitoAction which is a national mitochondrial disease organization, and I'll speak as a mother as well as a national patient advocate in saying that the inclusion criteria and the end points which make for good published data don't really matter to us.

What matters to us is what you heard today. What matters to us is if my daughter is so shaky that I have to sit and feed her every bit of her yogurt or if she can feed herself. What matters to us is whether our kids are able to sleep through the night so that all of -- everybody in the family can have a little bit of peace. What matters to us is whether we feel like we're at the doctor every week or if we're at the doctor every couple of months. These things have huge impacts on our quality of life but they don't make good, publishable graphs, right. But they make real differences in the lives of our kids and in the lives of those that we love that have this

disease.

The second thing that I would say is that I would not have known about this meeting, and will certainly pay much more attention to the patient voice opportunities within the FDA, had it not been for NORD. But as the Director of a national organization, please, FDA, reach out to us. We're coming to you with these comments but certainly, I feel that any of us who are here today representing patient advocacy groups would jump at the chance to have our comments be heard. So please, find us. We are all using social media so it's actually pretty easy to -- for our patients to find us when they're facing that diagnosis. I believe that you could also and we really want that opportunity to share our voice. Thank you.

DR. VAIDYA: Thank you, Cristy. Next, we have William Nyhan.

DR. WILLIAM NYHAN: Yes. I'm a little different. I'm a physician, professor of pediatrics at the University of California. I've been around, I'm happy to say, long enough so that I've witnessed

the initial description of most of the diseases we're talking about here and certainly all of the ones that have been defined on an enzymatic basis and, in fact, a handful of those, we've been the people that found those defects.

I'm really delighted with what we've known to have accomplished so far but I think that there also is a future. I mean I don't think that there is going to be more in the terms of dietary restriction. I think we probably know as much as we're going to know about that. But I think there are new and different drug possibilities along the line.

Among them, I'd like to point out the development of nitisinone. That came from a biochemist in Canada who was studying this stuff that was developed as a rat poison, and he found the enzyme that it inhibited, and as soon as we knew what enzyme that was, it became apparent that this was a treatment for tyrosinemia which was killing kids and destroying their brains very largely in Canada but throughout the United States and the world. Now that's an effective treatment and we've also discovered an even more

effective treatment for alkaptonuria, a crippling disease of adults.

Finally, I would say that in terms of clinical pharmacology and the study of the mechanism of drug action, we're beginning to learn that drugs, even those already on the market, are having effects on areas of metabolism that point out that they may, in fact, be effective treatments for a particular disease. And so I'm hopeful that there is going to be more of that.

DR. VAIDYA: Thank you, William. And lastly, we have Jana Monaco.

JANA MONACO: Hi. Again, I'm the Advocacy Liaison with the Organic Acidemia Association and we, those of us who are parents with these children and young adults living with these disorders, like the other mom, I -- our anniversary was 13 years ago last week that my son was diagnosed with his disorder, isovaleric acidemia. And when you look at your child, any of us know that if you look at your child who is in a coma, on life support, who was running around playing with toys the day before or has slowly

deteriorated over time with -- for unknown reasons, you almost are willing to do anything and everything because you have nothing else to lose.

And so in the 13 years that we have been dealing with life after my son's diagnosis, I have been with families who have shared similar stories, who have lost their children, and some of us have learned. And through, for example, children like my daughter who came along a year after my son, because of what we knew, they are perfect examples of the pros and cons and what education does for rare diseases and these IEMs and what can be done.

And research prior to his diagnosis has helped many along the way and there are far less children and young adults living with the severe disabilities that my son, Steven, has and more thriving like my daughter, Caroline. And it is the effective treatment that they are on and the studies that have been done to look at that, and they've doing well.

However, for those of us with IEMs, know that the very medical foods and formulas and

supplements aren't even really recognized yet as true treatments to even get that authorization to be funded for. So families suffer, they struggle to have access to it and the funding for it, and they will compromise, unfortunately, sometimes. So we need to be able to address what's right there before our eyes and get that -- these medical foods and formulas are the elephant in the room and no one seems to be able to move them beyond stagnation and know what to do with it in healthcare reform.

And last but not least, my children are in a few different studies right now at NIH and at Children's National to study these disorders a little bit more in understanding how they affect them nutritionally and for immune sensitivities and so forth because the fact that we know that they are lifelong and we have to look beyond the early diagnosis years and how these disorders affect them throughout their life cycle.

And as far as consent, my daughter, who is 11, is part of the decision to participate in these research studies because she knows she does not want

to get sick like her brother, and he is a constant daily reminder to her of what can happen if it doesn't take place.

So thank you for your support in these conditions.

DR. VAIDYA: Thank you, Jana. Thank you, everyone, and I would like to quickly remind you to pass your clickers to the end of the rows and we'll ask some FDA folks to pick it up.

And now I would like to call Dr. Teresa Buracchio to the stand for our closing.

DR. BURACCHIO: So I would like to just start by thanking all of the patients and families who came today. I know many of you traveled long distances to come here. We are very grateful that you were willing to share your experiences and your stories with us. They're very moving and we're taking it all to heart.

So just to summarize what we heard today. In our first topic, we talked a bit broadly about the different types of neurologic symptoms that many of you are experiencing. I think one of the things that

came up is one of the most distressing symptoms was loss of language and being non-verbal. We hear that the frustration with the inability to communicate may, in fact, lead to some of behavioral problems that you're seeing and that there is great frustration on both sides with inability to express pain that the patient might be having or any distress that they might be experiencing. And of course, we understand that there is great heartbreak at no longer being able to hear your child's voice.

Other things that came up as being quite important are, of course, cognition. I think that wasn't too much of a surprise. We knew that that is a widespread problem across all of these diseases. And particularly, this discussion of executive function came up.

And then the challenges with dealing with troubling behaviors, things like impulsivity and aggression and some socially inappropriate behaviors, but just really, the main goal with those behaviors is that you want your children to be safe and not engage in unsafe behaviors and that, you know, ideally want

to be able to do the daily tasks that you need to do like go to the store.

I think one of the new things for me hearing today was some of the psychiatric symptoms, that anxiety came up several times. Also, the symptom of psychosis with delusions and hallucinations was a new one for me to hear about. And this idea of emotional regulation, that the children can go from laughing to crying pretty quickly. I saw a lot of nodding heads to that particular symptom. And sleep, insomnia or night terrors or sleep walking.

We want to encourage you to continue to tell us -- more people who didn't get to speak today or people who are on the phone, do go to that docket and enter, you know, greater -- you know, we covered a lot of these broadly and we didn't get to dig too deeply, so please go back, write it out, send it in to us. We want to hear more.

And the second -- and then I should also mention that there was a really great question that came up with we're hearing all these symptoms, so how do we measure these things. And that is a problem

that we all struggle with. You know, there are some scales that exist for some of these but they haven't really been used in these populations per se. But I think the first step into developing these scales is to know what the problems are in the first place, so we made some important first steps here today to get to that point where we can develop some scales to hopefully capture some of these symptoms.

In the second part of our discussion today, we touched on the therapies that are available and what different people's experiences have been with those therapies. I think we can all agree that the therapies are limited and there needs to be more options.

I think there is general consensus that you want the opportunities to be involved in clinical trials and that you are willing to take on some risks although those risks will vary for individuals and also depends on, you know, therapies that may be available for the disease.

But overall, I think we had a great discussion today. It was a very informative, very

productive talk.

So I'd like to just wrap up with some additional thank yous. So once again, thank you to all the families who participated and thank you to everyone else who participated either by phone or in person. I want to also thank the organizers of this -- Sara Eggers and Pujita Vaidya did a great job of organizing this -- and the support of our division leadership with Donna Griebel, Andrew Muhlberg who couldn't be here today but was very invested in this, Julie Beitz, and Amy Edgan. And also, thank you to NORD. I know that NORD provided transportation costs for some of the people who were able to come here, so thank you very much for that.

With that, I think we can end.

(Applause.)

DR. EGGERS: Thank you very much, Teresa. And she has summed it up for all of us, I think, in her thank you and in her summary.

I just have one kind of business thing which is if you haven't completed an evaluation form, we would very much appreciate your thoughts on how the

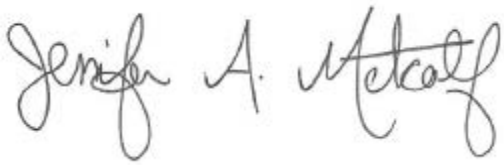
meeting went today. It's a one-page form so if you could fill it out and leave it for us.

And with that, well, thank you again for traveling here and for being here with us and sharing your experiences and perspectives. Thank you very much.

(Whereupon, at 1:02 p.m., the meeting was adjourned.)

CERTIFICATE OF NOTARY PUBLIC

I, JEN METCALF, the officer before whom the foregoing hearing was taken, do hereby certify that the testimony appearing in the foregoing hearing was taken by me in audio recording and thereafter reduced to typewriting under my supervision; that said transcription is a true record of the proceedings; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this deposition was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.



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I, LUCY T. TURNBULL, hereby certify that I am not the Court Reporter who reported the following proceeding and that I have typed the transcript of this proceeding using the Court Reporter's notes and recordings. The foregoing/attached transcript is a true, correct, and complete transcription of said proceeding.

June 24, 2014
Date

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Transcriptionist