UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

FDA CBER Patient Listening Meeting #2:

Patient and Care Partner Perspectives on Early Enrollment into Gene Therapy Clinical Trials for Rare Diseases

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Contents

Welcome

MS. LORRIE MCNEILL: Hello, everyone. Thank you all for joining us for this public patient listening meeting. Today's patient listening meeting is hosted by the Center for Biologics Evaluation and Research, or CBER for short, at the US Food and Drug Administration. I'm Lorrie McNeill, Director of the Office of Communication, Outreach, and Development and CBER, and I'll be the facilitator for today's event. I'm pleased to welcome you all here for today's listening meeting on early enrollment into gene therapy clinical trials for rare diseases.

The objective of today's meeting is to understand what patients and caregivers of patients in the pre-symptomatic or early stages of a disease take into consideration when deciding whether to enroll in a gene therapy clinical trial or potentially receive an investigational gene therapy product. We appreciate all of you joining us and sharing your thoughts and experiences to help the FDA better understand patient and caregiver perspectives on this important topic.

I'd like to start off with a brief overview of today's agenda. In just a moment, we'll hear opening remarks from CBER's Director, Dr. Peter Marks. We will then move into our sessions. We have two sessions planned today on the following topics. Session 1 is on early enrollment of children in gene therapy clinical trials, and Session 2 is on early enrollment of adults in gene therapy clinical trials. The first session will begin with a brief presentation from FDA, and then we will move into the listening portion where we will hear directly from patients and caregivers who have kindly volunteered to share their perspectives on today's topics.

At two points during the first session and at the end of the second session, we will have a few minutes for our FDA staff to ask our patient and caregiver speakers follow-up questions. Please note we have built in a few breaks throughout the day. We do ask that our patient and caregiver speakers please return after the breaks as our FDA experts may have follow-up questions for you. To our volunteer speakers, we understand that reflecting on the questions and topics covered during today's listening meeting may bring up difficult emotions. We would like to thank you again for participating in today's meeting and appreciate your willingness to share your perspectives.

There are just a few housekeeping items I'd like to share. Today's event is being recorded, and the recording and event materials will be posted on the FDA's website in a few weeks, including a transcript. Closed captioning for this event is also available directly in Zoom. If you have technical difficulties, please let us know by using the Q&A function. For our confirmed speakers, your microphone and camera access will be available during your assigned session. Those presenting during Session 1 will receive their mic and camera access shortly.

Throughout the afternoon, we expect that the presentations will likely generate additional ideas and comments, and should this happen, we encourage you to submit your feedback to the docket, which is available on www.regulations.gov. The docket number is FDA-2024-N-4605, and it will remain open until February 3. The presentation and—presentations and docket comments will be used to develop a meeting summary, which will be

posted on FDA.gov in the coming months. And with that, I'll pass it on to Dr. Peter Marks for the opening remarks.

Introduction

DR. PETER MARKS: Thanks so much, Lorrie, and thank you to everyone who's joining today. I really, really appreciate people taking the time. I also want to thank Lorrie, thank the staff at CBER, for working to set this up. So, I would just say that we're in a place now where gene therapy is increasingly becoming a reality for many different conditions. It's something that has made—taken a long time to come along over the past couple of decades, but now we're starting to see it accelerate in terms of the pace of progress.

And I think today's topic is really relevant because, as it turns out for many conditions, it does seem like administering gene therapy early on in the course of disease is an important way of doing so. In other words, in many cases, administering a gene therapy before the onset of symptoms or early after symptoms develop—prevent further decline, which can sometimes be irreversible. It's different for different diseases. In some cases, one can reverse things with a gene therapy. In other cases, one cannot.

So, the discussion today about patients' thoughts about this is really important for clinical trials because we have so many different disease states that will be looked at in clinical trials in the coming years. And I think it's important for us to understand what those of you who are potentially taking these, or those who are parents of those who might be taking these gene therapies, will expect to know what they'd expect from these trials as you're the ultimate explorers, kind of on a new frontier.

So, it's an exciting time, I believe. I think it's very helpful for us to understand your concerns, your hopes in this area. And we really look forward to listening today and learning more from you. So, thank you so much for participating and for sharing, and look forward to the session today. Thanks. And I'll turn it back over to Lorrie now.

Polling Questions

MS. MCNEILL: Thanks so much, Dr. Marks. At this time, we'll share a few introductory polling questions. These questions are intended to help us learn a little more about the patients and care partners participating in and attending the meeting today. This will be the first of three polling sessions we will have during the meeting. Please note, the questions are only intended for patients and their care partners. If you are not a patient or care partner, we ask that you please refrain from answering the polling questions.

During the meeting, we'll be using the terms "caregiver" and "care partners" interchangeably to mean someone who is involved in the care of the person with a rare disease. These individuals could be parents, spouses, other family members, or close friends who directly participate or have in the past in the care of a person with a rare

disease. Please take a moment to answer the questions that appear on your screen. You will have about a minute for each question, and we will pause briefly to collect the responses. We have participants from a diverse audience, so let's find out more about who's participating today.

Geographically, where do you live?

- Pacific time zone
- Mountain time zone
- Central time zone
- Eastern time zone
- Outside of the United States

Thank you. If we could have question two, please. Question two, what best describes the community where you live?

- Urban
- Suburban
- Rural
- Prefer not to answer

Thank you. If we could see the next question, please. Question three, what is your ethnicity?

- American Indian or Alaska Native
- Asian Pacific Islander
- Black or African American
- Hispanic or Latino
- White Caucasia
- Multiple ethnicities
- Other
- Prefer not to answer

We could have question four, please. Question four, we would like to know about the parents—excuse me, patients and care partners joining today's event. Please select the response that best describes you.

- A patient who is at risk for a rare disease
- A patient who is diagnosed with a rare disease and is pre-symptomatic
- A patient who is diagnosed with a rare disease and is in the early stages of the disease
- A patient who is diagnosed with a rare disease and is in the mid or late stages of the disease
- A care partner for someone who is at risk for a rare disease?
- A care partner for someone who is diagnosed with a rare disease and is pre-symptomatic?
- A care partner for someone who is diagnosed with a rare disease and is in the early stages of the disease?

We could have question five, please. How would you describe your or your loved one's disease?

- It is fatal or disabling
- It is not disabling or fatal but significantly impacts daily life,
- It develops quickly in a few years
- It develops slowly over a period of decades
- It has a childhood onset
- It has an adult onset
- I'm not sure
- Prefer not to answer

If we could have our final question, please. Question six, how do you receive information about gene therapy? And please select all responses that may apply.

- From my health care provider
- Communication from a study where you or your loved one is a participant. For example, the registry or study newsletter, study doctor, or research coordinator
- Product manufacturer of a gene therapy
- FDA website
- Scientific literature
- Social media and/or online forums
- Other patients
- Patient advocacy organizations?
- Other

Thank you so much for your responses.

I'd like to take a moment to introduce the FDA CBER subject matter experts who are serving on today's panel. For Session 1, Early Enrollment of Children, I'd like to introduce Dr. Najat Bouchkouj, Associate Director for Pediatrics, Office of Clinical Evaluation, Office of Therapeutic Products. Dr. John Scott, Division Director, Division of Biostatistics in the Office of Biostatistics and Pharmacovigilance. Dr. Rosa Sherafat-Kazemzadeh, Branch Chief, General Medicine Branch 2, Division of Clinical Evaluation and General Medicine, Office of Clinical Evaluation in the Office of Therapeutic Products.

And for Session 2, Early Enrollment of Adults, I'd like to introduce Dr. Vaishali Popat, Branch Chief, General Medicine Branch 3, Division of Clinical Evaluation and General Medicine, Office of Clinical Evaluation in the Office of Therapeutic Products. Dr. Anam Tariq, Medical Officer, General Medicine Branch 3, Division of Clinical Evaluation and General Medicine, Office of Clinical Evaluation in the Office of Therapeutic Products. And Dr. Osman Yogurtcu, Senior Staff Fellow, Benefit-Risk Assessment Branch, Division of Analytics and Benefit-Risk Assessment in the Office of Biostatistics and Pharmacovigilance. Thank you to our panelists for your time today.

In just a few moments, we will hear a brief presentation from FDA and then move into the public comment portion of today's meeting, but first, I'd like to give you a brief overview of the meeting process. During this event, all microphones for the general audience have been muted. Because this is a listening meeting, we will not have a Q&A portion for the audience, but we do appreciate your comments and encourage you to go to the docket if you'd like to share specific feedback on these topics. We will put the docket number in the chat.

Speakers, we are now ready to get to the heart of the meeting. The patient and care partner perspectives. We will introduce each speaker so that you can begin your presentation. When it is your turn to speak, you will be asked to unmute yourself. Once your presentation is done, you will be asked to go back on mute and allow the next speaker to present. Our first group of speakers in Session 1 should see their microphone and camera access shortly. Please note that you will see a pop-up box that will let you know when you have been promoted to a panelist. Please proceed so that you can get your mic access.

For those of you who submitted slides, your slide presentations have been added to this slide deck. When speaking, please let us know when to advance the slides. Before beginning your presentation, we ask that you please state your name and your affiliation. To ensure transparency at this listening meeting, we encourage you to advise the audience of any financial relationship that you may have with any firm, group, company, or product, at the start of your presentation. If you do not have a financial relationship as such, you can simply make a statement to that effect.

Please keep the time limit in mind when speaking. Each speaker will be given four minutes. We will give you a 30-second notice before your time is up so that you can then wrap up your presentation. If you run out of time, we encourage you to submit remaining comments to the docket. I will now turn it over to Dr. Anne Rowzee from CBER's Office of Therapeutic Products who will be the moderator for Session 1.

FDA CBER Perspectives on Early Enrollment in Gene Therapy Clinical Trials for Rare Diseases

DR. ANNE ROWZEE: Great. Thanks so much, Lorrie. Hi, everyone. My name is Anne Rowzee, as Lorrie says. I'm an Associate Director for Policy, thank you, within FDA's Office of Therapeutic Products. And as she said, I'll also be the moderator for Session 1.

As you know, our Session 1 topic is on early enrollment of children in gene therapy clinical trials for rare diseases. We'd like to start off today with a presentation by my colleagues, Dr. Vaishali Popat and Najat Bouchkouj. And I'll just take a second here to flag for our audience that this opening presentation will provide OTPs perspectives on early enrollment in gene therapy clinical trials for rare diseases for both pediatric and adult populations. So in other words, this presentation is going to lay the groundwork for both Sessions 1 and Session 2. And with that, Vaishali and Najat, over to you. Thanks.

Perspectives on Early Enrollment of Adults in Gene Therapy Clinical Trials for Rare Diseases

DR. VAISHALI POPAT: Thank you. If you can please start my video, I'll appreciate it. Okay. It looks like I'm not able to. There you go. Okay. So now I can see. Okay, great. So good morning, everyone. Thank you for joining us. We will be presenting on the Perspectives on Early Enrollment in Gene Therapy Trials for Rare Diseases.

So before we get started, I just wanted to go over the Office of Clinical Evaluation Structure so that you understand where all these evaluations from clinical perspective are happening. So within this office, we have Associate Director for Pediatrics, who is Dr. Najat, who will focus on pediatric aspect in this presentation later. And then there are three divisions. One of the divisions is the general medicine products. There's—another one is oncology and hematology products. And within these divisions, there are different branches, and these branches work on different indications.

So gene therapies hold great promise, and it has specific relevance right now to the rare disease because 80% of rare diseases have genetic basis, and there are very few therapies available for rare diseases. So FDA has approved 21 gene therapy products so far, most of which are for rare diseases, and there are many more rare diseases for which gene therapy holds great promise.

OTP currently, OTP is the Office of Therapeutic Product, so that's a super office within which we have Office of Clinical Evaluation. So this office oversees more than 2,600 active investigational products, and approximately half of these are gene therapy products. And during the development of all these products, collaboration with patients and caregivers is critical in development of gene therapy products.

So this slide is from the meeting from September where the focus was on safety and long-term studies. And I'd like to share this with you to emphasize that, number one, it was really heartwarming to see these responses, and number two, that we are closely looking at all the input that you're providing and really appreciate your contribution. So this particular question was, what would motivate you to consider participating in a long-term registry or study after receiving a gene therapy product? Select up to five items that are most important to you because at FDA, when we are considering this long-term treatment follow-up, we wonder, what is the impact on the patients? How do they view it? And what motivates them?

And if you look at the two most frequent answers here, to help researchers learn more about gene therapies and to help future generations of my family and others with the same disease who may need a gene therapy. These two are quite altruistic answers, and it was really heartwarming to see that the patients are so committed to advancing the field of gene therapy.

So, we like to really learn directly from you, the patients and the caregiver, because there are several factors that go into decision-making, and here, I have divided them into three different buckets. So the impact of disease and

its impact on treatment and management. So we like to learn from the patients, what are the most bothersome signs and symptoms? What is the burden of living with or even anticipating and managing a disease or condition? You know, that uncertainty, whether or not the child will develop severe disease can be quite unsettling. Impact on the activities of daily living and functioning, as well as what is the meaningful benefit from the patient perspective.

This is very important to us because when we are looking at the primary endpoint, which is the main question that trial is designed to answer, it's helpful to understand what is meaningful to the patients. We also like to know about your expectations of benefits, as well as tolerance for harms and risks and your preferences. What are the unmet medical needs that patients are facing on a daily basis?

And in addition to this, there are additional considerations specific for gene therapy for rare disease, which is a tolerance for uncertainty because in this space, there are very few really data-driven answers. There's a lot of uncertainties. And what is the tolerance of patients for that? And the burden of long-term follow-up after receiving the gene therapy. Questions here we may sometimes are thinking about is, do the patients feel safer if there is a long-term follow up involved, or do they think it's quite burdensome? And what is the impact of those considerations in terms of their decision to participate in the trial?

So, here is a nice schema that describes the different phases of drug development. And there are multiple opportunities for interaction with FDA during this whole process of drug development. So, if you look at the middle, the IND submission, that is where the—they are moving into humans. But before even any first in human trial is allowed to proceed, there is development from CMC perspective, as well as there are preclinical studies, and there are milestone meetings with FDA during those phases.

As the drug development process is through phase I, II, and III, there are multiple meetings. And especially at end of phase I and end of phase II meeting, but also throughout the development, we encourage the sponsors to involve patients into designing and understanding what is meaningful to the patients when they are considering the design of the trial.

So, here are the 21 gene therapies that are already approved. And as you can see, they're color coded, which is really helpful in terms of understanding the landscape out there. But we are really looking forward to many more development.

So, when it comes to our considerations, when we are looking at the rare disease gene therapy applications, we like to know what risk of gene therapy products would you consider when determining whether to receive the gene therapy. And especially focused to this session, if it is just the early phase of the disease process or even pre-symptomatic phase, what are the risks of gene therapy products that you consider?

And when the side effects might happen, do you consider whether it's shortly after gene therapy or many years later? How do you assess the response to treatment and also uncertainty about durability? What are the requirements, meaning, inpatient stay? So, for example, some parents would feel comfortable if the patient is

asked to stay in the hospital after administration of gene therapy, while other parents might consider that quite inconvenient.

When it comes to safety, of course, the FDA advises sponsor, if there are already data on safety. However, many times it's first in human trials, and some of the considerations are more based on the potential risk, not necessarily the risk that's been already shown. And so, in that phase—in that space, what do the patients think? What do they think about staying close to the site? Is it reassuring? Is it inconvenient? What information are parents using to decide for gene therapy for their child? And what is the impact of financial considerations when you decide to participate in the gene therapy trial? So, these are some of the considerations that we like to learn from you.

And when we look at the approval, when gene therapy approval applications come in for the rare disease, or even any disease, we evaluate balance between benefit and risk. And so, we look at two aspects, the substantial evidence of effectiveness, as well as evidence of safety. So, patient input is critical for understanding the disease and its manifestations, as well as what effects of a gene therapy would be meaningful improvement for the patients.

When it comes to safety, again, patient input is critical for understanding what risks are considered acceptable in context of the specific disease, other available treatments, and expected benefits of gene therapy. So, approval is supported if available data demonstrate that gene therapy's benefits outweigh its risk. So, with that, I'd like to now invite Dr. Najat to talk more about pediatric-specific issues. Thank you.

Perspectives on Early Enrollment of Children in Gene Therapy Clinical Trials for Rare Diseases

DR. NAJAT BOUCHKOUJ: Thank you, Vaishali. So, pediatrics plays a critical role in the development of therapies for rare diseases, and it is really important to recognize that the clinical manifestations for many rare diseases often appears early in life, when children are accounting for nearly half of the patients affected by such conditions. And given the vulnerability for this patient population, the regulations actually require additional safeguards when enrolling children in clinical trials.

While children can participate in clinical trials, their inclusion must be approached with caution, considering several factors. These include the available data, such as proof of concept and preclinical studies, animal studies, also the type and severity of the disease, and the availability of other existing therapies.

And the scientific approach to conduct pediatric gene therapy investigations really mirrors that for adults, where early phase trials are focused on safety, what is the optimal dose to be administered to the patients, and what are the preliminary efficacy signs, while the late phase trials place a stronger emphasis on efficacy. In addition, pediatric legislation encourages or mandates the conduct of pediatric studies for therapies developed for adult indications, in order to inform product labeling for pediatric patients.

There are several opportunities for interactions with the FDA throughout product development that can significantly advance the development of treatments for rare diseases in general, and these include the Rare Disease Endpoint Advancement, or RDEA Pilot Program. This initiative provides a platform for sponsors and investigators to work very closely with the FDA in developing novel efficacy endpoints, offering up to four non-binding meetings throughout the development process.

Another pilot program is the Support for clinical Trials Advancing Rare Disease Therapeutics, or the START Pilot Program, where selected participants in this program receive frequent advice and really enhance communication with us and all FDA staff to address specific development challenges, such as the clinical study design, what are the endpoints that are optimal for such studies, what are the product characterizations to ensure a safe and effective product.

And the Rare Disease Innovation Hub, which is—if you could just go back, yeah. The Rare Disease Innovation Hub is a cross-center FDA program, which aims to foster collaboration and advance regulatory science, helping all stakeholders navigate the complexity of rare disease product development. And additionally, the FDA really is committed to enhancing patient engagement, ensuring that your voice, the patient's voice, the care partner's voice, is really central in both product development and regulatory decision making.

So, let me now present an example of a gene therapy approval, Lenmeldy. This is the first FDA-approved gene therapy for the treatment of children with presymptomatic or early symptomatic metachromatic leukodystrophy, or MLD. MLD is a genetic lysosomal storage disorder. It is caused by an enzyme deficiency, which leads to progressive neurological decline, motor dysfunction, and cognitive impairment. And the disease has very poor genotype-phenotype correlation, where the symptoms might not be really predicted, which makes it very particularly challenging to treat. The approval was based on data from two single-arm studies and a European expanded access program. And the safety population was comprised of 41 children.

Key challenge during the review for this approval was how to assess efficacy in patients who did not yet develop the symptoms of the disease. Also, how do we evaluate the impact of the gene therapy on a very slowly progressing disease in symptomatic patients was another critical challenge. The efficacy was compared to an external and treated natural history cohort of children who were utilized as external controls. Notably, the slowing of disease progression and enhancing responsiveness and cognitive function were identified as key treatment goals by patients and caregivers for MLD.

So, on behalf of my colleagues, I would really like to extend a heartfelt thank you to all of you for joining us today. We are excited to learn from your experiences and are very eager to hear your perspective on the rapidly evolving and complex topic of early enrollment in gene therapy clinical trials for rare diseases. And here are our contact informations. And thank you for attention. Looking forward for a great meeting today, and I will turn it back to Anne.

Polling Questions

DR. ROWZEE: Great. Thank you so much, Vaishali and Najat, for that informative presentation. All right. Now, we're going to start our second round of polling. And as Lorrie noted at the start of the meeting, this meeting is divided into two sections. Session 1 is on early enrollment of children in gene therapy clinical trials, and Session 2 is on early enrollment of adults in gene therapy clinical trials.

We're now going to start session one, again, early enrollment of children in gene therapy clinical trials. But before we hear from our speakers today, we have a few polling questions for care partners of children with rare diseases, and for those who are affected by rare diseases that have a pediatric onset. So if you're joining us today as an adult with a rare disease or their care partner, please wait until Session 2 to participate in polling there. Again, please take another moment to answer the brief polling questions on your screen.

And if we could have question one for Session 1. Great. Thank you. So what are the top considerations when determining whether to enroll your child in a gene therapy clinical trial at the pre-symptomatic or early stages of the disease? And here, we're asking that you select up to three responses, and I'll read through those now.

- Age of the child
- How fast the disease progresses
- Availability and effectiveness of other treatment options
- Effectiveness and duration of expected benefit with the gene therapy
- Severity of short-term risks and side effects
- Severity of long-term risks and side effects
- Potential impact on quality of life
- Potential impact on child's development
- Requirement to participate in long-term follow-up in the clinical trial
- Ability to receive other currently available or future treatments for the disease if the gene therapy doesn't provide the expected benefit
- My child's medical provider or disease expert's opinion
- Other

And again, please select up to three responses. We'll give you a moment to finish. Okay. And if we can see the responses. Excellent.

Okay. Could we see Session 1, question two, please? Great. What information about gene therapy risks would be most important to you when determining whether to enroll your child in the gene therapy clinical trial at the pre-symptomatic or early stages of the disease? Again, here, we're asking you to select up to three responses, and I'll read the options now.

- How common the risks are expected to be
- Potential timing of risks, including short-term and long-term risks

- Severity of the risks identified from patients who have received the gene therapy
- Whether a particular risk or side effect reduces the benefit of the gene therapy
- Whether a side effect of gene therapy is permanent or has long-lasting consequences
- What treatment will be required if a particular side effect occurs
- Other

Again, please select up to three responses here. Okay. Can we see the results for question two? Okay.

Before we move on to question three, I just wanted to prompt with the following. Many factors may affect the decision to enroll in a gene therapy clinical trial at the pre-symptomatic or early stages of a disease. For example, things like other therapies, the rate of disease progression, and expected treatment benefit are some aspects that patients or caregivers may consider.

The next two questions aim to help us better understand how disease progression may impact your decision. You'll see question three is regarding diseases which progress quickly, and question four pertains to diseases which progress slowly. You may choose to answer both questions or the one that applies to you based on your best knowledge of you or your loved one's disease.

Okay. With that primer we're on question three. Great. So if the disease progresses quickly, what are the risks or uncertainties you'd be willing to accept when determining whether to enroll your child in the gene therapy trial at the pre-symptomatic or early stages of the disease? Again, here, we're asking you to select up to three responses.

- Risks associated with surgical procedures and or anesthesia to administer a gene therapy
- Risks associated with medications needed for gene therapy, such as those to mitigate immune responses
- Uncertainty of treatment benefits
- Risk of the disease or condition getting worse while waiting for an alternative therapy
- Uncertainty of long-term risks of gene therapy
- Uncertainty of eligibility to receive another gene therapy
- Unknown risks of the gene therapy that may not have been identified yet
- I don't know
- I did not or would not consider/I would receive a gene therapy regardless of the risks
- Other

Again, we're asking for you to select up to three responses here, and I'll give you a moment to finish answering. Okay, Session 1, question three results, please. Great, thank you.

Session 1, question number four, please. Great. If the disease progresses slowly over decades, what are the risks or uncertainties you would be willing to accept when determining whether to enroll your child in the gene therapy trial at the pre-symptomatic or early stages of the disease? Again, here, please select up to three responses. I'll read those now.

- The risks associated with surgical procedures to administer a gene therapy
- Risks associated with medications needed for gene therapy, such as those to mitigate immune response
- Risk of the disease or condition getting worse while waiting for an alternative therapy
- Uncertainty of long-term risks of gene therapy
- Uncertainty of treatment benefits
- Uncertainty of eligibility to receive another gene therapy
- Unknown risks of the gene therapy that may not have been identified
- I don't know
- I did not or would not consider/I would receive a gene therapy regardless of the risks
- Other

Again, please choose up to three responses here. Great responses here for Session 1, question four. Okay. Great. Thank you for your participation in our polling questions. Our first set of speakers will begin receiving camera and microphone access while I cover the next few slides.

The following speakers will share their perspectives and responses related to these two main questions. If you were to consider enrollment in a gene therapy trial for early stage or pre-symptomatic disease for your child, what would you want to know? And what would you think about regarding disease stage of progression when considering enrollment in a gene therapy trial?

And in other words, here, we're thinking, how does disease stage progression factor into this decision when considering enrolling in a gene therapy clinical trial? And how do these considerations change during the onset or progression of symptoms? Okay. Great.

Okay. We have about 30 speakers for this session and each speaker will have four minutes. Just provide a list here so folks can see where they are in the lineup. And we have about—oh, sorry, excuse me. I'd like to remind our speakers to please start by stating your name and your affiliation at the beginning of your presentation.

To ensure transparency at today's listening meeting, we encourage you to advise the audience of any financial relationship you may have with any firm, group, company, or product, at the start of your presentation. If you do not have any disclosures to state, you can simply make a statement to that effect. Our first speaker for session one is Erica Barnes. Erica, are you ready to present? So you can unmute your microphone and begin speaking.

Session 1: Speaker Presentations, Part 1

MS. ERICA BARNES: Hi, Anne, thank you so much.

MS. ROWZEE: Great. I see you. Go ahead.

MS. BARNES: Thanks. Great. Hello. My name is Erica Barnes, and I don't have any financial disclosures and I'm speaking on behalf of the Global Leukodystrophy Initiative or GLIA, Clinical Trials Network of the Patient Advocacy Group Consortia. Our consortia is composed of over 40 patient advocacy groups working in collaboration with the research community to advance clinical trial readiness for leukodystrophies. I'm also the mother of a child who passed away from metachromatic leukodystrophy. So, it's of particular value to me that we're focusing on gene therapies.

Leukodystrophies are genetic diseases that predominantly affect the white matter of the central nervous system. Scientists have identified over 50 leukodystrophies and while all of them affect white matter, disease presentation both across the leukodystrophies and within the subtypes of specific leukodystrophies is incredibly heterogeneous. So the heterogeneity of a specific leukodystrophy subtype was a main concern to my community and that they expressed that they would like to have addressed before enrolling in a gene therapy trial. Specifically, how well the sponsor understands the disease characteristics of each of the subtypes.

If a particular child is enrolled in a clinical trial and the characteristics of their subtype is not well understood, number one, there could be risk factors to that particular child that were not taken into account and increase risk for that child. And number two, the clinical trial may not have the clinical value that's relevant for the patient. So, that would reduce the value of enrolling in the clinical trial. So, part of that would be communicating clearly the clinical endpoints and showing, demonstrating, understanding of all the subtypes.

If a child has early-stage onset, have some pre-symptomatic symptoms, the next vital piece of information for a family would be what symptom management will continue while enrolled in the clinical trial and what symptom management options would the family have to forgo. For example, would a child have to discontinue seizure medications to be able to participate in the clinical trial? What sort of things might exacerbate their condition and upset the delicate balance of keeping their symptoms managed while also pursuing more effective treatments through the clinical trial?

In addition to a range of symptoms, leukodystrophies also vary in how rapid disease progression is following onset. So, very clear eligibility criteria is vital for families as they make this consequential enrollment decision. Without clear eligibility criteria, a family could inadvertently lose the window of opportunity to participate in the clinical trial due to the disease's progression.

On a more general note, my community expressed that having a clear understanding of what exactly the long-term expectations are from the start is important, especially for gene therapies whose outcomes have to be monitored over many years. Will a family be expected to come back year after year for follow up and for how many years? What resources would be available initially and long term to support their participation in the trial? Participating in a clinical trial is a massive burden on families and very few would be in proximity geographically to a clinical trial site. How will families manage a child with complex medical needs, which might increase year upon year and also be able to fulfill the expectations of the clinical trial?

Next, our community is concerned with what families would be giving up if they participate in the clinical trial. Our community feels that it's important for sponsors to be upfront in explaining the implications of participating

in the trial and what those implications would be for the families. Would participating in this particular clinical trial make a family ineligible for treatments that might be developed in the future?

Lastly, my community wanted me to speak to the issue of informed consent. Often informed consent is seen as a transactional single point in time occurrence. We want to encourage industry and sponsors to think of informed consent as a dialogue that is ongoing and not just a piece of paper that you ask a participant to sign at the start. Truly understanding—

DR. ROWZEE: Ms. Barnes, I'm sorry, I need to interject here. Our time is up. I'd like to encourage you, though, to finish—to put any comments in the docket that you didn't get to today. Really appreciate your feedback—

MS. BARNES: Okay. Thank—

DR. ROWZEE: —for you and from the leukodystrophy community. Thanks very much. Our next speaker is Ron Bartek. Ron, are you—your microphone is open. There you are. I see you. Go ahead. Please proceed. Thank you.

MR. RON BARTEK: Thank you. So, hello. My name is Ron Bartek, and I have no financial disclosures. I'm the Co-Founder and President of the Friedreich's Ataxia Research Alliance or FARA, the organization my wife, Raychel, and I co—founded in 1998, year following our son Keith's diagnosis.

We learned very quickly that FA is a rare, recessive trait, inherited genetic disorder caused by low levels of the protein named after the disease, frataxin, that is essential to life. Its function is to facilitate mitochondrial energy production, so that those born with FA have gene mutations that reduce those levels of the frataxin protein to about 10% to 15% of a full load, causing severe damage throughout the body.

That damage includes things like gradual loss of vision, hearing, speech; scoliosis requiring surgical implantation of metal rods along the spine; loss of strength and coordination in the arms and legs, so they're using wheelchairs usually by their mid-teens. A much-increased risk of diabetes, and a serious heart disease that is our leading cause of death on average in early adulthood via congestive heart failure.

So, bottom line is, as you all know, we need to treat these children as early as possible. Though the damage begins in the womb and proceeds relentlessly throughout childhood and beyond, clinical and physical manifestations of the disease, generally, do not appear until ages 5 to 15, sometimes even much later. The longer it takes to intervene with these young children, the greater the damage is done and the harder it is to stop and reverse that damage. So, I want to spend some time thanking the FDA for, first of all, inviting us all to speak to this really essential issue and your FDA leadership and concerted effort to include pediatric patients in clinical research much earlier.

We have heard Dr. Peter Marks and Dr. Nicole Verdun, for example, and others say such things as, "We no longer believe you always must begin with adults. We are learning—leaning hard in the direction of including children earlier in clinical trials, so we can begin to prevent some of their symptoms rather than trying to treat those symptoms later, when some of them might be irreversible. We are pivoting hard from trying to protect children

from clinical trials to trying to protect them with clinical trials so we can provide them with access to safe, effective treatments at the best time for them."

We've also heard you emphasize Accelerated Approval, which is so important in genetic therapies that address the underlying cause of our diseases, but might take substantial time to demonstrate clear, substantial benefit, especially in children who are early symptomatic or pre-symptomatic, when clinical endpoints developed for older patients don't work. In FA, for example, that clinical endpoint are—accepts for Accelerated Approval might likely be the increased frataxin protein levels in target tissues.

We've heard you say, too, and fully agree with you, that there will be uncertainties and some risks, especially in rare diseases with great unmet need, but that the only risk our patient families are unwilling to accept is that of doing nothing.

We've heard you. We appreciate your leadership on this critical issue. We applaud your message, and we are committed to helping socialize that message throughout the stakeholder communities, including our industry partners, patient families and organizations, clinicians, bioethicists, IRBs, so we can, together, be successful in giving access to children to safe, effective treatments at the best time for them. Thank you so much.

DR. ROWZEE: Thank you so much, Ron. Our next speaker is Geraldine Bliss. Geraldine, if you're—your mic should be open.

MS. GERALDINE BLISS: I'm ready.

DR. ROWZEE: If your ready, please begin. Great. Go ahead. Thank you.

MS. BLISS: I'm Geraldine Bliss. I don't have any financial disclosures. I'm the President and a Co-Founder of CureSHANK, a nonprofit organization, whose mission is to accelerate drug development for Phelan-McDermid syndrome. My most important role, though, is mom to Charles and Nathan.

he has autism, intellectual disability, and a severe form of epilepsy called Lennox-Gastaut syndrome. Phelan—McDermid syndrome is a neurodevelopmental disorder caused by the loss of one copy of SHANK3, a gene expressed in synapses. The result is the disruption of normal synaptic function, altering how neurons communicate with each other, and causing severe to profound intellectual disability, absent or severely delayed speech, hypotonia, and autism.

In Phelan—McDermid syndrome, like most neurodevelopmental disorders, we see that early delays alter the developmental trajectory, leading to progressively greater disparities over time. This is important to know because it underscores the great value of early intervention with gene therapy. These are my boys. You can see that in infancy, both were happy and active, meeting their developmental milestones. But around 18 months, it became apparent that Charles was not meeting communication and social milestones.

As the years passed, Charles fell further and further behind in all areas due to the cascading effects of global delays. Despite a consistent routine of speech, occupational therapy, and physical therapies, and applied behavior

analysis therapy, Charles was never able to catch up. Indeed, we observed his development tapering off at the same time, we saw his brother thriving and developing by leaps and bounds. Charles has experienced great suffering. Seizures have become a daily occurrence and have been minimally responsive to anti-epilepsy drugs.

While we do our best to enrich his life in all the ways we can, he lives quite an isolated life because of his social and communication difficulties. He has limited decision-making ability and agency over his own life. So, if I could rewind the clock and go back to when Charles was a year old or even six months old, I would, 100%, enroll him in a gene therapy trial, knowing he would have the best possible chance of independence and good health.

Because cognitive development starts at the beginning of life with experience shaping the developing architecture of the brain, and because there are critical developmental windows that make later progress more difficult, it's important to intervene as early as possible, ideally in advance, to improve outcomes in all areas of development.

Development of new skills depends on a complex interaction of existing abilities from different domains. For example, early motor skills are essential for unlocking early social communication skills, which are in turn required for the early language that fosters more advanced social communication. By targeting the underlying genetic problem at the earliest ages, we give children the best chance of having good outcomes in all these different domains.

Today, Charles is 26 years old. While there is preclinical data suggesting that gene replacement will benefit individuals in Phelan-McDermid syndrome at any age, considering the overall severity of the disease and factoring in our understanding of early brain development, the ideal timeframe for enrollment in a gene therapy trial would be as early as possible. Thank you for inviting us to share our perspectives on this extremely important topic.

DR. ROWZEE: Thank you, Geraldine, for sharing Charles and Nathan's story with us. Our next speaker is Kelly Brazzo. Kelly, if you're—your mic should be open, if you're ready to speak, please proceed.

MS. KELLY BRAZZO: Hi, yes. Good morning. My name is Kelly Brazzo, and I am the CEO of CureLGMD2i, which we founded when my daughter was diagnosed with limb-girdle muscular dystrophy at the age of two. Here are my disclosures. Today, Sammy is 17 and living with LGMD2i/R9.

This is a rare and progressive form of muscular dystrophy that causes muscle weakness, beginning from the hip and shoulder areas. Difficulty rising from the floor and climbing stairs are typically the first symptoms, eventually resulting in respiratory difficulties, heart failure, and loss of ambulation.

When Sammy was little, we kept her as active as possible, knowing that these days were numbered. Fifteen years ago, Sammy began tripping and falling and had difficulty keeping up with her peers. We were told that there were no approved therapies at that time, but she was enrolled in her first natural history study.

Currently, there are 15 years of history data at the University of Iowa, and there are 13 years of data in the Global FKRP Registry. Sammy has participated in three natural history studies. And now, there are three clinical trials, which have fast-tracked designation. Yet, to date, we have no approved treatments for this condition.

Sammy has had many challenges over the past five years. She now falls and can't get off the floor, and she's unable to climb stairs without a handrail. She can no longer stand from a regular seat, and she's had many issues with contractions.

Three years ago, Sammy had her first surgery for a bilateral Achilles tendon lengthening, followed by four weeks of serial casting. Just a year later, she had a massive spinal fusion and stayed in rehab for nearly a month to relearn how to walk.

We are constantly concerned with the cardiac and respiratory complications of this disease, and Sammy often suffers from pain and fatigue. Sammy recently said to me, "Mom, I need gene therapy." She can't afford five more years of complications and loss. She wants to get stronger and go off to college. When she was asked what a perfect day would look like, she said, "I just want to be able to go to the bathroom by myself on a regular toilet." She's not asking for much.

I also asked Sammy, what it would—what she would want to consider in order to enroll in a gene therapy trial, and she said, "I'm ready no matter what." But there are concerns as to the potential risks, such as cancer or organ damage. What invasive procedures would be required? Needle biopsies are preferred rather than open muscle biopsies. And how much time in the hospital would be required?

Could there be potential issues with fertility in the future? What type of meds are needed to combat inflammation or immune resistance? Would there be a possibility for future redosing? Is there a placebo arm or could they utilize the natural history study as a comparator? Also, if a novel approved treatment became the current standard of care, could she stay on that treatment if enrolled in a gene therapy trial?

Lastly, how long would the follow up be if a gene therapy was approved? Anything more than three to five years could be difficult due to college or work schedules. And if Sammy wouldn't qualify, would there be an opportunity to grant early access for programs with rare pediatric and orphan drug designation?

We can't help but think if Sammy have received gene therapy five years ago, the complications that she has faced could have been avoided. Although, gene therapy has potential risk, remaining untreated may be a much greater risk. Sammy can currently drive and walk short distances, but in five more years? What we do know is that time is loss of muscle and independence that could possibly never be regained.

Our LGMD EL-PFDD polling question asked patients, what worries them the most? And the top responses were becoming a burden, respiratory issues, and cardiac concerns, all things that could potentially be treated with gene therapy. On behalf of Sammy and our LGMD community, thank you for listening and helping to accelerate the future of gene therapy for rare diseases like the LGMDs. Thank you.

DR. ROWZEE: Thank you, Ms. Brazzo. And thank you for sharing Sammy's journey and the perspectives from the LGMD2i foundation and the community. Our next speaker is Laura Calhoun. Laura, if you're ready, please proceed with your comments. Thank you.

MS. LAURA CALHOUN: Hi. Good morning. My name is Laura Calhoun. I'm not here on behalf of any official organization. I have no disclosures to give. I'm here on behalf of my daughter, Meredith. She has—she's been diagnosed with a rare disease called ataxia-telangiectasia. And so, I'm here to talk about her and other children and on behalf of other children and parents with that. This is a recessive genetic disease that's caused by mutation of the ATM gene, and it affects cells in the body. Symptoms begin early in childhood and develop quickly, and it affects one in 40,000 to one in 100,000 people worldwide.

I actually sit in a position that's probably different from most. Right now, as we speak, Meredith has very little side effects. We actually found out about her diagnosis accidentally. I went and had cancer screening because of cancer in my family. They found that I'm a carrier. My husband did the same. So, we had all of our children tested. So, we found out before she had any symptoms, and I still am here to say that I would have gotten her straight into gene therapy without any symptoms and with little symptoms that she's showing right now.

This disease is diagnosed in early childhood and progresses quickly beginning around the age six. And so, this is a major factor in wanting to start treatment early because it develops—it progresses very, very quickly. So, if we can't have anything to reverse the damage, we're just fighting against time. Some of the side effects of A-T is that it's a multi-system disease. Most children are dependent on wheelchairs by the age of 10, not because of their muscles are weak, but because they can't control them. And they will lose their ability to write, and speech also become slow, slow down and slurred. And even reading becomes impossible because of eye movements.

They're also have major immune system problems for about 70% of these children. Respiratory infections become life threatening and the combination of a weakened immune system, and the ataxia can lead to pneumonia as a major cause of death. There also has a pre condition to cancer. It—they tend to develop malignancies of the blood system almost 1,000 times more frequently than the general population. And ironically, people with A-T cannot tolerate radiation. And so, certain chemotherapy drugs can't be used if they do develop cancer. Even though A-T is a multi-system disorders, most individuals are socially aware and socially skilled, and it doesn't affect their cognitive abilities.

As far as the risk, I think I would say that we were—I mean, I would be willing to take high risk tolerance. I'd want to know exactly what these risks we're talking about to really dive into that more. What safety protocols are in place and how do you watch for signs? I would not wait to enroll her with everyone else that's speaking about this.

As far as following up with clinical trials, we see doctors our entire life. This wouldn't change. I would expect that, and I would not think of that as a burden, more of a privilege that she was able to participate and help future generations.

Financial impact, I think that we will raise the money. The A-T Children's Project is doing that, and we would find a way to stay in the hospital, our family and friends staying. And honestly, I think that staying close to the site where the treatment is would make me feel better about it instead of it being a burden because then, she'd be monitored for side effects.

One of the questions was, what do you hope for, for minimum effects at the bottom level? Worst thing we get out of this, I would hope we have no negative side effects, but the gene therapy gives doctors more information to get closer to a treatment for these children. And we're—we know, we're told that are likely to outlive our children and we're not blessed with longevity with A-T. So as far as longevity safety, any additional longevity would be appreciated.

DR. ROWZEE: Ms. Calhoun, I'm sorry, I'm going to have to stop you there. Please, as I mentioned earlier, please provide your comments or any comments in the docket. We really appreciate your thoughts and feedback on this topic today. Thank you. Our next speaker is Darla Clayton. Darla, if you're on, please proceed with your comments. Great. I see you. Thank you.

MS. DARLA CLAYTON: Just looking for slides. Are they coming up? Oh, there they are. Hi, my name is Darla Clayton. I'm the Patient Affairs Director for the Alliance to Cure Cavernous Malformation. I have cavernous malformations, and I'm the mom of two affected children. I—a cavernous malformation—oh, sorry. A cavernous malformation is an abnormal blood vessel in the brain or spinal cord that resembles a mulberry. These capillary lesions can grow quite large, as large as four to five centimeters in diameter.

Cavernous malformations can become symptomatic at any age. My 21-year-old son had his first hemorrhage and brain surgery as an infant and has had many brain hemorrhages since. The lesions are leaky and blood oozing into the brain tissue can cause seizures and neurological deficits. Additionally, 25% of patients experience a more severe brain or spinal cord hemorrhage, resulting in stroke-like disabilities. Depending on the location of the lesions, these disabilities can be quite severe. For example, para and quadriplegia, ataxia, aphasia, severe vision issues, et cetera.

In the US, approximately one in 7,000 people are diagnosed with familial CCM. Familial CCM is caused by autosomal dominant loss of function mutations in the CCM1, CCM2, or CCM3 genes. Kids with a familial disease develop more lesions over time, sometimes hundreds. However, symptoms severity varies widely from person to person. Some children experience aggressive disease with multiple early childhood brain hemorrhages and intense lesion proliferation. This is more frequent with CCM3 mutation but is present with all mutations. Our family has a mutation of the CCM2 gene. Fifty percent of cases will never have a symptom or will only have mild symptoms like my daughter and me.

We're aware of two preclinical gene therapy studies for CCM. One is a gene augmentation study for CCM3 that targets brain endothelial cells, and the other is an ACE-tRNA study targeting nonsense mutations. Both are years from the clinic.

Last year, we conducted a patient survey to gauge our community's receptivity to gene therapy. Forty-five percent of adults with familial disease said they would be willing to undergo gene therapy for themselves, even if it's a 2% risk of death. But only 22% will be willing for their child to have gene therapy with the same risks. When asked if they would be willing to undergo gene therapy if it had to be repeated every 5 to 10 years, only 9% said yes for themselves. This points to a need for proof of concept in adult patients and a one-and-done treatment.

Because the effects of CCM vary so much, gene therapy decision making for asymptomatic children will be difficult since gene therapy involves risk. On the one hand, CCM patients—CCM symptoms can start in childhood, and often the first symptom is brain hemorrhage with the potential for lifelong disability or death. Gene therapy before the first hemorrhage could be transformative for a lifetime. My son's first bleed caused lifelong hemiparesis. Early gene therapy could have avoided this outcome.

On the other hand, natural history must be weighed against gene therapy risks. Fifty percent of people with familial mutations never have a serious symptom at any time in their life. We can't predict who will have a more severe course. Our families have expressed willingness to participate in gene therapy trials, but they would like adult gene therapy first as adult risk tolerance is high and the disease course is already clear. The risk tolerance of parents on behalf of their children is much lower, particularly if the children are asymptomatic. Thank you.

DR. ROWZEE: Great. Thank you so much, Ms. Clayton, for sharing your experience and-and your children's experience. Our next speaker is Courtney Coates. I see you're up. Go ahead, Courtney. Please proceed with your comments. Thank you.

MS. COURTNEY COATES: Good afternoon. Thank you. My name is Courtney Coates. I'm the Director of Outreach and Development for Hope in Focus. We do receive financial support from Spark Therapeutics, Johnson and Johnson Innovative Medicine, and Atsena Therapeutics.

We are a patient advocacy organization for Leber congenital amaurosis, which is an inherited retinal disease that causes severe vision loss in the first year of life. Unfortunately, our kids don't really have a pre-symptomatic stage as much as they do have early-stage disease from a very young age.

We are fortunate to have one approved gene therapy, Luxturna, that treats one genetic form of LCA of which there are 27 gene mutations that have been identified to cause LCA.

When I speak with our parents and caregivers on a regular basis, early enrollment in trials is key in order to save photoreceptors. Those rods and cones in the backs of our eyes that help us to see, unfortunately, deteriorate over time in these retinal degenerative diseases.

Therefore, the sooner that we can introduce gene therapy and the sooner that we can enroll children into trials, the sooner we can have meaningful benefit and potentially restoration of vision and even stabilization of this disease.

There are many within our community that have shared at previous listening sessions and previous opportunities that even to stabilize their vision or to slow the degeneration over time is significantly meaningful to their lives.

You'll find that a lot of children get used to a certain level of vision throughout their lives and to be able to just keep that and know that you may not have another serious drop off later in life would be a very meaningful benefit to them.

We also know that enrolling children early in trials will signal more efficacy. We've seen that there is a lot of safety within this gene therapy, there have been hundreds of people treated with Luxturna and we know that it can be administered safely and effectively.

Therefore, as additional gene therapies come to the market for other genetic mutations, being able to have early clinical trials with pediatrics involved can show efficacy earlier on in the trial which will help to—we all know that these therapies need to be commercialized at one point or another, and having early signs of efficacy in trials will help it be more successful in the long run.

Chatting with parents on a regular basis. Some of the things that they talk about are reducing burden on the family. A lot of them have other siblings and trying to bring a family of four or five, six kids along to the very limited centers in which rare disease trials take place is very challenging.

However, that benefit of being able to have their child maintain or slightly improve their vision is well worth the risks that are involved and the burden on the family. Some of the other points that I just wanted to hit on in the questions.

There was a question regarding exploring dosage of gene therapy and you know, I think it's really important especially within these small populations to try to reduce dose exploration as much as we can if the phase one of a trial shows that there is an effective dose, it would be great to just explore that singular dose and reduce the burden on additional people in trials that may not be dosed with what is going to be the most effective for them.

So just wanted to make that point, especially within our population. And yeah, I think that's all I have to share today. And I thank you all for your time and for pulling this together.

DR. ROWZEE: Thank you, Ms. Coates for sharing some perspectives from the LCA community. Our next speaker I see is Rachel DeConti. I believe, you're ready to go.

MS. RACHEL DECONTI: I am.

DR. ROWZEE: - - to say. Thank you. Great.

MS. DECONTI: I do have some slides. Hi, I'm Rachel DeConti. I'm the executive director of the LGMD2D Foundation and I have consulted on LGMD projects for Sarepta Therapeutics. However, I'm here today to tell you about my son Jacob as his mother and caregiver.

Jacob is currently eight years old and was diagnosed with limb-girdle muscular dystrophy type 2D/R3 at age five. His diagnosis came after a short and shocking hospitalization for rhabdomyolysis. .

I've spoken about Jacob at multiple of your important listening meetings over the past few years. But this topic specifically about enroll-early enrollment in gene therapy trials really spoke to me. That is because while we've learned of Jacob's diagnosis three years ago, he fortunately has not physically progressed much since.

He is in two LGMD natural history studies and has not shown much decline throughout his involvement in them. He can run, he plays with his friends at school, his little brother rides his bike, climbs stairs, and loves to swim.

We've been told by his clinician multiple times that he would be the perfect candidate for a gene therapy clinical trial. Yet, he does not have any available for him to participate in. Jacob does have some restrictions at school and does not play on any team sports because of his LGMD.

A few weeks ago, while on a business trip, I received a call that Jacob was asked to run a mile at school. His legs hurt him badly after and we were afraid of another case of rhabdo. We immediately requested a formal doctor's note for him in the future.

However, in his current state, if he did receive a gene therapy soon, maybe in time, he would be able to run that mile with his peers in class versus worrying about his legs hurting. Maybe he would even be able to play a few of the team sports that he's always wanted to.

LGMD is a severely progressive and life limiting disease. Yet, there are no approved treatments for Jacob to slow or stop his progression. And unlike other forms of muscular dystrophy, the entire gene that is missing fits perfectly into the viral vector. This hopefully means more effective success in the treatment.

A treatment especially now while Jacob is strong, would mean that it could slow any progression Jacob faces long enough for more treatments to become available. It could truly change his life. As treatments do become available, we don't want Jacob to be overlooked because of his strength. We would want to fully understand the impact the treatment will have on him immediately and in the years ahead.

My husband and I would want to know what invasive procedures are required for the trial, so we could consider them, prepare ourselves, and prepare him. Side effects, especially long-term, redosing considerations and what to expect in the years ahead for monitoring and follow up are all questions we would want to know.

As Jacob is getting older, he is understanding more about LGMD, especially since our LGMD day on the hill in September. Last month, when asked what he was thankful for, two things he wrote-he wrote were, my LGMD2D cure soon and traveling to places for LGMD.

He has also prayed to God and Jesus for cure to come in 2024 or 2025 if he keeps his body healthy. It is heartbreaking to see him ask for these things, especially as his mother, who can't control when they will become available for him.

So, I ask you, to please continue supporting flexible ways to get safe, effective LGMD treatments approved for patients like Jacob according to his timeline in 2025. And thank you all at the FDA for innovative and hopeful opportunities like these in the new Rare Disease Innovation Hub and the Accelerating Rare Disease Cures Program. I'm here to help the FDA and these wonderful LGMD patients get treatments they desperately need however I can. Thank you.

DR. ROWZEE: Thank you, Ms. DeConti for sharing Jacob's story and for your thoughtful remarks.

MS. DECONTI: Thank you.

DR. ROWZEE: Next move to our, our next speaker who is Ashley Dike. Ashley, if you are on, please, go ahead and proceed with your remarks. Great, I see you.

MS. ASHLEY DIKE: Okay, great. Thank you. Thank you for this opportunity to speak. I have no financial disclosures. I'm Ashley Dike, mom to four amazing boys and founder and executive director of the LCC

Foundation, a nonprofit supporting those diagnosed with leukoencephalopathy with brain calcifications and cysts or LCC.

LCC is an ultra-rare neurodegenerative condition that currently affects less than 100 people worldwide. The age of presentation of this condition is highly variable ranging from infancy to adult adulthood.

As a parent to two boys with LCC, one very symptomatic and the other asymptomatic, considering a gene therapy trial raises many crucial questions for our family. First, we would want a clear understanding of the trial's goals.

Is it focused on dose exploration, safety? And is efficacy a factor? Is it focused on halting disease progression or stabilizing symptoms? Are these outcomes realistic based on previous research? how will success be measured, through imaging, biomarkers, or improvements in quality of life and daily functioning, or all of the above?

For our symptomatic child, stabilizing symptoms or slowing progression is deeply hopeful, but we need to know if they would have to stop current medications to participate. These treatments are critical to his daily life and any risks of withdrawal must be fully explained.

For our asymptomatic child, we carefully consider the potential side effects of gene therapy especially given their current stability. Are there short or long-term risks that could impact to their health unnecessarily?

The hope would be to prevent future damage and symptoms from developing, preserving their full developmental potential. Would he be at risk for having fertility issues in the future? Additionally, would enrollment in this trial prevent participation in future potentially more advanced gene therapy trials?

Cost is another major concern. Gene therapy trials can be costly, and families may face burdens like travel, lodging, or lost income. Will there be financial support in place? If the trial doesn't achieve the desired results, will resources be available to help manage post-trial care?

Transparency is critical. We need clear upfront communication about potential delays, trial duration, and who mandates the elements of informed consent. That consent process must leave no room for uncertainty about risks, responsibilities, or expectations. Ultimately, this decision is about balancing hope with practicality.

For a symptomatic child, the opportunity to slow progression is promising, but we must also ensure their quality of life isn't compromised. For our asymptomatic child, the risks versus benefits require deep consideration to avoid jeopardizing their current well-being and enrollment into future clinical trials with potentially better outcomes.

This isn't just a medical question. It's a deeply personal and emotional one. Families like ours need clear answers and transparency to make the best decisions for our children and ensure these trials are truly centered on the needs of the patients they're designed to help. Thank you.

DR. ROWZEE: Thank you so much, Ashley for sharing your family's story and some perspectives from the LCC community. Our next speaker is Shawn Egan. I see your-your video is on, Shawn. Please proceed when you're ready.

DR. SHAWN EGAN: Good morning. My name is Shawn Egan. I have no financial disclosures and I'm the Chief Scientific Officer for the FamilieSCN2A Foundation. I'm here as the father of Harper Rose Egan. She's my reason and my inspiration.

Harper is seven years old and has SCN2A, a severe and rare genetic disorder that has forever altered the lives of her and my family. Harper was born healthy and a typical first 10 months of life filled with milestones and joy. She was our first child and life was everything we had dreamed of.

Recent PhD grads launching our careers, buying a house and watching Harper learn to sit, talk, and eat with humor and spirit that's very uniquely her. All that changed at 11 months of age. Just a few days before Christmas, when Harper developed infantile spasms, a catastrophic seizure disorder that shattered all of our expectations.

In an instant, we lost-we lost the child that we were beginning to know. Harper's seizures were absolutely relentless, often hundreds a day. She lost all motor milestones, she still can't sit, stand, or talk. Some days she can barely hold her head up. Because eating was such a struggle, we have to rely on a G-tube to meet her feeding and medical needs.

As you can see in these pictures, hospitalizations have become a regular reality of Harper. SCN2A is complex and not well understood by many medical teams that are not at major academic centers. This leads—often leads to often dangerous inappropriate interventions that are inappropriate for her particular variant and condition.

This leads to a dynamic where SCN2A families need to really weigh if the current risk of a period of acuity is high enough to warrant a hospitalization because there are inherent risks of making that decision. I bring this up because these are the kind of risk calculus that our families are currently facing every day.

The risk-benefit equation of novel therapeutics is not just a comparison of risk versus potential benefit. It's the harm and risk that are already enduring. Risk is pervasive in SCN2A. It happens daily, it is guaranteed, and it continues to compound.

Risk tolerance is unique to each family, but through our experience and conversations with our community, we've learned that the appetite for risk fluctuates over time and there are windows where it's higher. In my opinion, these windows are highest at initial presentation and diagnosis with the promise of a new therapy and during periods of acuity.

In between these windows, where rare disease families have rebase lined to learn to adapt to a new reality, the constant medical intervention, sleepless nights, and emotional strain, forces to reset and find a new equilibrium or re-manage day to day life.

The stakes feel higher, higher because we've already lost so much. And because it's harder to take risks that could make things worse after years of trying to just stabilize.

When we consider treatments for children like Harper, we understand that the window of opportunity is precious. The risk of waiting and watching the disease progress can be just as dangerous as taking a leap for new therapeutics. For our family, we know our child and we have an understanding of the risks of inaction.

When we consider evaluating clinical trials, we consider if the science makes sense. Are there class effects to consider? Are there on target effects to consider? And if there are proof of concept yet in patients? But the bar is—bar to clear is very low because the scale is already tipped so heavy in one direction.

Regarding safety risks, our family would be more concerned with near term safety risk, post dosing. Our daughter's condition is catastrophic, similar to oncology where there are risks of secondary malignancies in the future.

Our focus is on stabilizing her life right now. And if we can do that, we can manage longer term risks out of the emerge. With this in mind, longer term, follow up with a—while potentially burdensome would be valued as these longer-term risks are characterized.

One last point I wanted to bring up is that clinical trial enrollment for gene therapies or genetic medicines is not just a light switch decisions. As we all know, thoughtful consideration is required.

That's why it's critical for industry groups to engage patient communities early and often, so that the necessary goals of conversations can take place within families and that the mental infrastructure can be put in place to make informed thoughtful decisions around risk reward.

I urge you to consider these daily realities as you evaluate treatments for SCN2A and other conditions like this. Thank you so much for listening to our story and for working towards a brighter future.

DR. ROWZEE: Thank you so much, Mr. Egan for sharing Harper's story and the perspective from the DEE community. Our next speaker is Cerilyn Fernando. Cerilyn, if you're online and ready to go, please proceed.

MS. CERILYN FERNANDO: Hello. My name is Cerilyn Fernando, and I'm joined here with my husband, Mark. We do not have any financial disclosures. We have a five-year-old son who was diagnosed with alpha thalassemia major while in utero.

Essentially, it's a rare genetic blood disorder that requires regular blood transfusions. Currently, he receives these transfusions every three weeks.

Just a little background of how we got here, when I was about 22 weeks pregnant and going in for an ultrasound to find out the gender of our baby, they found some abnormalities which they then confirmed to be associated with alpha thal. At about 24 weeks, we participated in the in-utero stem cell transplant trial at UCSF. And since then, our son has had six in utero transfusions and 88 transfusions after birth.

Currently, we are exploring options for our son to cure him of thalassemia and bone marrow transplant was the first option provided to us at the time. But we want to learn more about gene therapy, not just for our son, but possibly for any future children we may wish to have.

As we know that if we did choose to expand our family, we have a 25% chance of having another child with alpha thalassemia. Both myself and my husband are silent carriers for alpha thal.

With that said, we have joined today's presentation with hopes to learn more about gene therapy as a possible option for us. We'd be interested in knowing how early one can enroll in the trial.

With the stem cell trial at UCSF, I was 24 weeks pregnant. So, I'd be curious if this is possible in gene therapy for early intervention purposes. We know that babies that are born with alpha thal typically do not make it to birth or live long after birth without early intervention. So, this is really important to us.

We'd also want to know the health side effects and changes in quality of life the patient might experience. For example, for bone marrow transplants—for transplant patients, they have to go through chemo and perhaps miss important life events such as school. So as parents with the young child, obviously, this is a very important decision for us.

And lastly, we'd be curious if gene therapy would affect those with multiple disorders or health conditions. So, for example, our son also suffers from inflammatory bowel disease. So, we'd be curious how gene therapy would affect that if at all. So, we thank you for allowing us to join and looking forward to learning more about gene therapies. Thank you.

DR. ROWZEE: Thanks, Mark and Cerilyn, for sharing your perspectives today. Our next speaker is Susan Finazzo. Susan, if you're online, please go ahead and proceed with your remarks.

MS. SUSAN FINAZZO: Hello. My name is Susan Finazzo and I've had the privilege of having two sons with Duchenne muscular dystrophy, both dosed with gene therapy. One brother showing early symptoms of the disease and the other who had not yet experiencing symptoms.

Each child had the exact same mutation and care. The only difference was the age at which they were given gene therapy.

At seven years old, the older brother had already begun experiencing many typical Duchenne symptoms. These included general clumsiness, difficulty getting off the floor, irregular running gait, and lack of overall endurance. At early four years old, his brother had not been experiencing these same symptoms of the disease.

Do the videos work? If they do, could you play them? If they don't, you can just go to the next slide. Thank you.

When deciding to enroll—sorry—when deciding to enroll in gene therapy, the most important questions I had were, what were the health risks involved? How long would it last? And what other treatments would no longer be an option post gene therapy?

Ultimately, we chose to enroll both of our children because of the one thing that Duchenne families do not have. And that is time, more time to enjoy the physical fun of being a kid, more time before they become physically dependent on others, more time to let the science catch up with more treatments and hopefully, more time on their life expectancy.

You can't see it but this was a—a jump showing our oldest that he could suddenly jump completely off the floor and clear the floor, which never before could he have done that post gene therapy—prior to gene therapy.

Immediately after dosing, we could see how much stronger each of them became. As far as the adverse side effects, both children had practically none, some nausea the next day with some food aversions for a few weeks, this amazing treatment was well worth it.

Two years later, at almost 10 years old, the older brother was still performing better than his seven-year-old self, prior to receiving gene therapy. But those results are slowly slipping. His younger brother did not show as many drastic increases in skills because he was already stronger. What he gained the most was retention.

Now, two years later at seven years old, you would not be able to pick him out on the school playground as the child with Duchenne, he clearly has a much different quality of life compared to his brother when he was seven.

It's clear to me that dosing on the earlier side is more effective in these boys. Time will only tell me how much more effective it remains. But I have clearly bought my boys more time to run and play. And this is a gift that any parent of a child with Duchenne would be desperate to give.

Here, you have the rise from the floor. I have the 10-year-old now and the seven-year-old now. And, if you look at the-the red one, that's the older son and he kind of—he increases for his time, you know, gets better for a little while, it gets lower. And then now, he's steadily rising back to being slower at rising off the floor.

And the other one, you know, he-he kind of hovers around the same. He went from 2.4, he-he moved a little and back at 2.5.

Here's the time to run, the older boy, again, he's-he, you know, he is a—slower time, he increases his time. He's doing a really good time and then now, slowly ever, so slowly creeping up. The other one again is like hovering between 3.6, 3.7 which is, you know, teeny tiny.

This is the overall North star, you could see the younger brother in blue and he is just kind of hovering 31—no, it's like 31, 29, 27, 29. He's hovering around 29 pretty much for his overall score. And the older guy is—he got a peak of 29 and it's been going down since 29, 28, 27, and I expect it to continue.

We have waited two years to get our oldest son into a gene therapy trial. It was devastating to watch so many other families miss these opportunities because their sons reached an age limit. The longer families have to wait, the higher risk of having antibodies to the AAV delivery.

We need to offer to this—to younger, younger non-symptomatic children to afford these families as much chance as we can. We are not a community who has the luxury of time. Each passing birthday is a sad reminder to each and every one of us. Thank you.

DR. ROWZEE: Susan, thank you so much for sharing the story of your boys and their experience with gene therapy for DMD. Our next speaker is Pat Furlong. Pat, if you—your mic should be open, so if you're ready, please proceed.

MS. PAT FURLONG: Yes. Thank you, Anne. Oh, thank you. My name is Pat Furlong, I have no financial relationships to disclose. I'm the president and CEO of Parent Project Muscular Dystrophy or PPMD, the leading organization in the fight to end Duchenne muscular dystrophy.

I'm honored to share perspectives on early enrollment in gene therapy clinical trials for children with rare diseases informed by our work with families navigating these complex and critical decisions.

Duchenne is a devastating condition that robs children of their ability to walk, breathe independently, and ultimately their lives. The hope of gene therapy represents a pivotal moment for our community. A chance not just to slow the disease progression, but to rewrite the future for these children entirely.

However, hope is accompanied by challenges for our community including enrolling children at a very early age in clinical trials. Families in the Duchenne community deeply value the opportunity for early intervention knowing that time is muscle and that timely effective treatment can preserve their children's function and independence.

Yet, families also need clarity about key scientific and logistical aspects of early enrollment in gene therapies. One of the most urgent questions we hear is about redosing. When gene therapy is administered to young children, their muscles grow, divide potentially diluting the effects of gene therapy over time.

Families want to know what happens if and when the therapy's efficacy diminishes? Will there be a pathway for redosing and how will it work? And beyond that, how will early enrollment in gene therapy trials affect their children's ability to access future clinical trials with therapies?

These questions highlight the need for innovative trial design that account for the evolving needs of children with Duchenne. Sequential therapy approaches, combining gene therapy with other emerging interventions must be prioritized and future clinical trials must include children who have already received gene therapy.

Early access to promising therapy should not come at the expense of future options or exclude children from continued innovations in care. To address these concerns and support families, we believe early enrollment in gene therapy trials must be guided by three principles.

One, transparent communication and education. Families need clear honest information about risks, benefits and long-term implications of gene therapy. Sponsors and regulators must provide guidance on redosing strategies, communicate the durability of therapeutic effects and how participation impacts eligibility for future trials.

Families must feel confident that they are making decisions based on comprehensive, accessible, and transparent information about the totality of issues and options and patients must have timely access to the data generated from their participation in the clinical trial.

Two, patient centered clinical trial design. Trials must adapt to the unique needs of young children and their families. This includes designing studies that evaluate sequential approaches, incorporating age, appropriate end points, and ensuring minimal logistical and financial burdens on families.

Flexible trial protocols such as home-based assessments and travel support are critical in making participation feasible and equitable.

Furthermore, patients who enroll in early gene therapy, clinical trials take the greatest risks often with uncharted long-term outcomes and deserve the greatest rewards including the prioritization of their needs in clinical trial design and post-trial access to therapies.

Three, ethical oversight and long-term commitment. Early enrollment carries an ethical responsibility to ensure that participants are not left behind after a trial concludes. This includes guarantees of long-term safety monitoring, utilizing real world data for therapeutic efficacy, transparent pathways for redosing, and inclusion in access for trials for future therapeutic innovations.

I am very thankful to share my perspectives and the perspectives of PPMD. Together, we can ensure the future of rare disease therapies is one that truly meets the needs of children and their families offering not only hope but a sustainable path forward. Thank you.

DR. ROWZEE: Thank you so much for sharing your perspectives and thank you to all of our speakers so far for your important insights into early enrollment in clinical trials.

We're now going to take a 30-minute break and we're going to continue session one at 1:15. But as a reminder, we're asking that all of our session one speakers return after the break because our FDA panelists will have some follow up questions for you. Thanks again and we'll see you back here at 1:15. Thank you.

FDA Panelist Questions

DR. ROWZEE: Apologies, everyone. Sorry for the delay there. I had some audio issues. I just need a thumbs up from someone to make sure that you can hear me, okay? Okay, great. Wonderful. Thank you. And welcome back, everyone. Thanks for bearing with me there.

Welcome back to our patient listening meeting to gather perspectives on early enrollment in gene therapy clinical trials for rare diseases. Before we move to our next set of session on speakers, I'm going to take a moment to open it up to our FDA panelists to ask any clarifying questions or any follow up questions they may have for the-our first set of session one speakers.

So, all the speakers who have provided remarks so far should still have access to their microphone so they can respond to questions from our FDA panelists. And just a reminder, our FDA panelists are Dr. Najat Bouchkouj, Dr. Rosafat-I'm sorry, Dr. Rosa Sherafat-Kazemzadeh, and Dr. John Scott.

And I think I'm going to be kicking it over to Rosa first. So Rosa, if you'd like to come on and ask your question.

DR. ROSA SHERAFAT-KAZEMZADEH: Sure. Can you hear me?

DR. ROWZEE: Mm-hmm. Yeah.

DR. SHERAFAT-KAZEMZADEH: Okay. The camera is keep coming off. So, good afternoon. I would like to all thank all the presenters for sharing your powerful stories with us. And we truly admire your strength and grit, and we are very grateful for sharing your perspective and helping us working together to bring this safe and effective gene therapies for the rare diseases to the patients.

So, my question is for Ms. Kelly Brazzo from Cure LGMD2i regarding the enrollment in long-term follow up clinical trials after gene therapy. So, you mentioned that anything, any duration of trial, after three to five years

would probably be a difficult commitment. And we at the FDA, we definitely hear you and, and we have been encouraging decentralized clinical trials.

So, my question is, would you and Sammy consider enrollment in decentralized clinical trials for a longer duration differently with that-address some of the challenges and concerns of a long duration of follow up?

MS. BRAZZO: Yes, I think that would be very, very helpful. I, especially not knowing, if my daughter is able to go to college or, anyone who is a working adult over time, I think that would be very helpful. It is difficult to travel and miss time from school and work. So that-the decentralized trials would be wonderful and much more facilitate those long-term follow-ups.

DR. SHERAFAT-KAZEMZADEH: Perfect. Thank you. So, I will pass it on to Najat for the next question.

DR. BOUCHKOUJ: Thank you, Rosa. And again, I echo your sentiment and I would like to extend really my heartfelt thank you to all of you for sharing your really experienced-your experiences on valuable perspectives with us today.

My question actually is to Rachel DiConti. Hopefully, Rachel is still with us.If not, perhaps maybe I can go to Erica Barnes. I had a question for her as well.

Kelly, maybe since your camera is on, maybe I can ask you the question and then we'll see if they can chime in a little bit later.

MS. BRAZZO: Okay.

DR. BOUCHKOUJ: But my question is, in general, in a clinical trial, one might be given a new therapy while in a natural history trial, and you would simply be monitored for the progression of your disease without any experimental intervention.

As natural history studies may play a critical role in bringing therapies to patients with rare diseases, can you please just expand or elaborate on factors on that may play a role in a decision-making to have your child participate in natural history versus an interventional clinical trial.

MS. BRAZZO: Well, I'm happy to answer that. My daughter, as I've mentioned in my report, I've-has been in three natural history studies and, when she was two and first diagnosed, that was our only option. And we were just happy to be able to participate in, contributing to science and the understanding of the disease when there really wasn't as much knowledge, 15 years ago.

And I think, I have heard people say, the effort to travel and the effort to be in these studies when there's not even a treatment available, people may not want to commit to that, but I really encourage those that especially have more newly discovered conditions that to have that understanding is critical to really potentially know if the disease-how it progresses over time.

And therefore, many of us have talked about not wanting there to be a placebo arm, that it seems unethical to have somebody participate in trials and not actually get the treatment. But if you don't have that natural history understanding, that's something you could use as a surrogate endpoint at some point as a natural history comparator.

So, I think it's really, important for patients and their families to really consider being in a natural history study. So, I'm glad that we had that opportunity over the years for Sammy.

MS. DECONTI: Yeah, and-

DR. BOUCHKOUJ: And then-oh, and I'll get back to you, Rachel. Just went-yeah, I was just going to-just follow up to that question, Kelly.

If there was an option of either enrolling in a natural history versus in a trial, a therapeutic trial, would you weigh one heavier than the other in your decision making, or what other considerations you might think about before enrolling in one versus the other?

MS. BRAZZO: I mean, in our situation, knowing the progression of this disease that is-has really affected our child-my child's life is certainly, if there were treatment available, that would be the preference.

But again, a lot of times, if there isn't a treatment available yet, if you can at least participate in the natural history study, that seems to be that the case that-potentially, that more treatments could be developed once there is an understanding of the disease, and scientists want to know that there's an understanding of how the progression of that disease is before they might be able to discover a treatment that is effective or not.

DR. BOUCHKOUJ: Thank you very much. Now we can go to you, Rachel.

MS. DECONTI: Oh, okay. And sorry, I was- I was in mute and I-

DR. BOUCHKOUJ: No problem.

MS. DECONTI: -my mute undone quickly earlier. So, apologies for the delay there. But I was going to add a piggyback on to what Kelly was saying with regards to us and our family when we were considering right now, as I had mentioned before for LGMD2D, there's no clinical trials for gene therapy or any other type of treatment available to help slow or stop this progression.

So, we see natural history studies as a way of giving back-giving back to science, the community, helping researchers understand Jacob and his progression, children with their early onset and their progression. I also consider the sites that we go to.

I know that often those are some of the best sites, the sites that we go to for Jacob's natural history study are-have the clinicians and the care team focused on LGMD, which to me is helpful in understanding, knowing that he's in the best care that he could receive while he's doing these things to help research.

So, it's super important for any patient or caregiver to consider natural history studies, like Kelly said, being able to leverage this data, Jacob will be-he's been at least in three years of one natural history study so far.

So, they have three years of data where he's had skeletal MRIs and bone density scans and physical therapy assessment-assessments. I mean, he's been in several hours of multiple times a year giving to this research, so it's critical to leverage this data and to see where he is now with data that could help once the treatment is available.

And lastly, to what Kelly said, I think if we had treatment options as more become available because I'm hopeful and confident they will, I think it would be more of a consideration potentially of a trial versus a natural history

study, depending on the patient and where they are, but with no options available as soon as one does, the patient, the caregiver is heavily going to lean on the clinical trial, the treatment option versus a natural history study.

DR. BOUCHKOUJ: Thank you. Thank you very much. And we truly appreciate it. Just your commitment to research and we definitely know how burdensome can be to just spend hours and hours in these clinical trials.

And you could see from my example that I gave in the - - approval we relied heavily on the natural history-

MS. DECONTI: Yes.

DR. BOUCHKOUJ: -to use it as a comparitor. So definitely very important in our decision making and bringing these therapies to our patients. I will turn it-

MS. DECONTI: - -

DR. BOUCHKOUJ: -yeah, sure. Thank you. I will turn it to John right now, since I think he might have a question.

DR. JOHN SCOTT: Thanks, Najat. And I do-and but first, I really would like to add my thanks to all of the presenters today for sharing your important and moving experiences. This kind of feedback is really important for FDA to help us support product development in a way that's most meaningful to patients and caregivers.

Also, I'm really struck by how many people have come today to share their experiences. It's clearly an important interaction. I have a question for Susan Finazzo and Pat Furlong about Duchenne muscular dystrophy.

So now that there's an approved gene therapy for DMD, I'm wondering about the decision-making process that a parent might have to do going forward potentially regarding enrollment in a trial for, let's say, a different new gene therapy.

So, if there were a second gene therapy being studied in a phase three trial, do you think parents would want the control arm in that trial to be the approved gene therapy? Or do you have other thoughts about that? Thanks.

[long pause]

MS. FINAZZO: Pat, are you here? Did you want to chime in first? I guess not, it's just me. Honestly-to be completely honest, I think parents are so desperate for anything, we will get anything, we will take anything we can take.

Anything that we think is a viable option, it doesn't matter, we're all just looking at the clock, watching the time tick away, every birthday is painful, every-everything. I don't think, we don't care, there just needs to be more opportunities, I don't think we-we don't care. I mean, we're literally grasping anything.

DR. SCOTT: Yeah, understood. I-the reason I ask the question is if it-if as a parent, you could simply in clinical practice, have your child treated with an approved gene therapy, what would be necessary to make somebody want to enroll their child in a phase three study for a different unapproved drug?

MS. FINAZZO: They differ though. There's like-they're already like-even when we were-we actually thought we would have a choice between gene therapy drugs because more than one company was doing it. And when we were enrolling for trials, we actually thought we were going to get into a completely different drug company and ended up with the one that we used.

And again, they all have their loopholes. They all have their-I mean, there are some that are coming down the pipeline that sound, oh, maybe it'll affect the cardio muscles more, maybe it will affect like the skeletal muscles more. And, you have to weigh it based on your family and there's room for all of them because we-there's just room for everything.

And you know what, we could use the competition. I hope like maybe this up and coming one is new. It has something better. Maybe it lasts a little longer. Maybe it doesn't require as much AAV. Maybe-I mean, they-the AAV even difference has the slightest different in between them also.

So, maybe you have higher antibiotics to one that you don't have the other. So, it really-just options. That's all that matters to us.

DR. SCOTT: Thanks. Yeah, totally understood. And I appreciate your answer. Ron Bartek has raised his hand. Ron, do you want to share something maybe related to the previous question?

MR. BARTEK: Mindless related to the previous question, John, so why don't you go ahead and finish your questions, and I'd love to make a comment about the last question from Najat.

DR. SCOTT: Unless Pat Furlong had a comment, but I actually don't see her online at the moment. So, feel free. Yeah.

MR. BARTEK: Okay. Thank you, John.

DR. SCOTT: For sure.

MR. BARTEK: Yeah, so I couldn't help but try to emphasize the comments from Kelly and Rachel in answer to Najat's very excellent question about the importance of natural history, because in our rare disease, Friedreich's ataxia, the natural history study over 20 years was absolutely essential in obtaining our first approval, first FDA approval on rare disease day of last year.

And that-that natural history study provided the comparator-the external comparator of otherwise clinical trial positive data. And it was especially important, I want to put a plug in for the FDA funded program called the Rare Disease Cures Accelerator Data Analytics Platform funded by the FDA and operated by the Critical Path Institute in coordination with NORD.

And getting-if you have natural history, obviously, several of you do, a lot of you do, I would strongly suggest or recommend and encourage you to get that-those data onto this RDCA-DAP platform, because that gives the FDA regular access to it, gives your industry partners regular access to your natural history data, and they can better design their clinical trials to make full use of it.

So, pardon the absolute commercial for plugging that, but I couldn't help myself.

DR. SCOTT: No, thanks, Ron. We appreciate it. And we really value people's participation in natural history studies. I think at this time, I'm going to pass it back to Anne to move on to the second group of presenters.

DR. ROWZEE: Thanks, John. Yes, thanks very much for FDA panelists and for our speakers for sticking around and fielding those questions. Really appreciate again your thoughts on these important topics. I'll wait till we get our slides back up.

Session 1 Speaker Presentations, Part 2

Do we have slides ready? I want to make sure our next speaker is ready to go. I think it's Yasmina.

MS. YASMINA HALIM: Yes.

DR. ROWZEE: Okay.

MS. HALIM: I'm here. Hello.

MS. HALIM: This is my daughter over here. It's a picture of her and I have something I'm going to read. This is my daughter, Lily Mansour. She was diagnosed at the age of seven and a half with a rare terminal lysomal and genetic disease called juvenile Tay-Sachs disease.

Tay-Sachs disease is a debilitating disease that is painful, and a child painfully slowly becomes trapped in their body before the disease takes over her life. Before the age of 15, she is expected to pass. When a child is diagnosed with a rare terminal disease, a parent becomes a caregiver, a researcher, and so much more.

The burden is on us as a parent to find out what treatments and trials are available for our children. A late diagnosis was disastrous for us being eligible for trials because you cannot gain what you have already lost. The time it takes to find an advocacy group that has access to the information on trials is all precious time we lose to get to where we need to be to help our children.

Our regular local doctors do not have information on trials that are readily accessible for them to give to us. If I had not found NTSAD, which is the National Tay-Sachs & Sandhoff Allied Diseases Association, I would not have had access to know where the clinical trials are and what progress has been made and what progress continues to be made. Making an informed decision is so important to me.

Lily is precious, and all I want is to give her a dignified and meaningful life and help whoever we can in the process. We have done multiple natural history studies but have yet to find a genetic trial that would help her because she has essentially aged out. If a trial was to become available for Lily, and to consider doing the gene therapy, there are many factors I would have to consider.

One being a single parent, will I be able to be there for my sick child and still care for my healthy child? Is information available on children with the same disease? Has any progress been made? Has the disease slowed or stopped regression in any way? This information is important.

Financial obligations are important factor and will I be able to keep providing for my family? How long would my child be away from her family and routine? Will her sibling be able to visit her? Who bears the burden of that cost? What will follow up care be like?

Will Lily's mental health play a role, or will she be stuck in a hospital room for weeks at a time? Will researchers and medical companies communicate with our local doctors to keep traveling at a minimum?

I believe my child has aged out of trials but if something comes available there is so much, she lost that she will never get back. Lily went from a happy bubbly child that did ballet and ran around everywhere and is no longer able to walk or talk or speak. She will continue to lose the last of her abilities that she's had.

If we do not find a gene therapy trial that can move fast enough to save my child. My child is also not alone as there are other children with this disease waiting and hoping and praying.

Clinical trials also lead to the use of medications for compassionate use. And they are also taking a lot of time to get improved-to get approved. It is imperative that we continue to facilitate faster processes of clinical trials for our children, and that the earlier and easier we make trials available to our children, the greater chances we have for finding a cure.

I would like to add a final thought that we cannot consider what we do not know. The more access we have to information, the more access our doctors have to information, the faster we can move these processes along and hopefully find cures. Thank you.

DR. ROWZEE: Yasmina, Thank you so much for sharing your perspectives and Lily's story. Our next-

MS. HALIM: Thank you.

DR. ROWZEE: -our next speaker is Eszter Hars. Eszter, your microphone should be open. Please proceed with your comments. Thank you.

MS. ESZTER HARS: My name is Eszter Hars. I'm the president and CEO of the Shwachman-Diamond Syndrome Alliance and also the mother of a child with Shwachman-Diamond Syndrome, or SDS for short.

SDS is a rare genetic disorder that affects ribosome assembly and with that the protein protection in every cell and every organ system in the body. It's particularly problematic for the bone marrow and causes a very high risk of developing leukemia or blood cancer, in particular acute myeloid leukemia, or AML.

It's estimated to hit about one in three patients by age 30, and more after. And if and when leukemia develops, it's nearly 100% fatal in our population. Our patients face frequent blood draws, infections in bone marrow biopsies and live in-the families live in constant fear of this happening. And the changes that lead to leukemia seem to occur already or start happening in early infancy or even before.

SDS is a great candidate for gene therapy because the primary organ system we want to target is the bone marrow, and the technology exists to do this right now, like for sickle cell disease, for example, it's already being done.

This is where cells from the body are taken, hematopoietic stem cells, they're fixed in a dish and then infused back into patients. And we think that in the future, in vivo gene therapy may be an option as well.

So next one, the key questions I wanted to answer today is, if you were to consider enrollment in a gene therapy trial for early stage or pre-symptomatic disease for your child, what you do-would you want to know? So, I would want to know about some safety and efficacy.

Safety because we are talking about pre-symptomatic disease, and we don't know if my child or a particular person would actually develop AML. So, we cannot justify any treatment side effects, for example, that would increase the risk of transformation or the development of cancer. And other risks would need to be very low and manageable as well, because in effect, we are treating a healthy, more or less healthy person.

Similarly, the efficacy is also important because we need to know how many of the SDS cells we need to replace or fix in order to mitigate the risk of developing cancer. Is it enough to replace half the cells or a quarter, or do we need to replace 100%?

Next question was, what would you think about regarding disease stage of progression when considering enrollment in a gene therapy trial? Again, it's similar to the previous one. We have no control of when leukemia actually hits. And once there, it's too late. So, we want to treat as early and-as early as possible.

We would want to know whether gene therapy could replace bad cells and therefore be beneficial at every stage of the disease or early-for example, on the early childhood. And we want-would want to know whether later in life, whether there is still enough good cells there to act as a substrate for gene therapy. So, there might be another disease stage question there.

And the third question was, what would be we hope for in terms of short and long-term effect? Short term effect might be difficult to measure because we really want to prevent leukemia, but we may be able to measure improved immune function, increased neutrophil count. That sort of thing.

And then, the minimum long-term effect similarly would be again, it's hard to measure a reduction in cancer risk, but we may be able to measure improved immune system performance, neutrophil count and overall improvement of bone marrow health which in turn might lead to a reduced cancer risk.

And another possible measure could be the measurement of clonal hematopoiesis. This may be something that could work as a-as an outcome measure or biomarker in the future.

So, we are working toward a future where our families and children can live without the fear of leukemia. And we're really grateful for the FDA to consider our thoughts and our needs. We are really grateful.This is just a couple of our families and children in the community. Thank you for your attention.

DR. ROWZEE: Thank you so much for sharing your important thoughts and perspectives today. Our next speaker is Heidi Leslie. Heidi, your microphone should be open. Please proceed with your comments when ready.

MS. HEIDI LESLIE: Good afternoon. I'm Heidi Leslie and I'm the director of operations with the NKH Crusaders organization, president of the Brodyn's Friends Foundation and the very proud mother to my son Brodyn, excuse me.

I also serve on the national NKH leadership board and I am. I'm so grateful for the opportunity to shine a light on the needs of our community, and I have no financial disclosures. First, allow me to briefly introduce you to NKH. Nonketotic hyperglycinemia is a rare genetic metabolic disease affecting about one in 76,000 births. Currently, there are roughly 500 known people living with the illness worldwide, and it is still classified as terminal.

Children affected are unable to break down the amino acid glycine, leading to toxic levels that disrupt the normal function of the brain, creating a plethora of devastating symptoms.

There are five types of NKH, the classic and attenuated form being the most prevalent. There is no pre-symptomatic phase in the classic presentation. It is the most severe and symptoms develop at birth or soon following.

The attenuated form, however, can present in the first months to years of life, allowing children a pre-symptomatic or early stage of the disease. And this is my experience.

Brodyn was diagnosed with attenuated NKH after a long journey. Within three days, I knew something was wrong, but the doctors assured me he was fine and just a little jaundiced. There were many other red flags in the first nine months of life, including extreme lethargy, feeding difficulties, unrecognized seizure activity, and the inability to master even the most immature milestones.

He was in the early stages of this disease, and no one knew it. It was not until 10 months old that our world completely blew up and Brodyn was no longer pre-symptomatic. He was now in the throes of the illness.

For 10 months, my son was in the early stages of this disease. And in order to consider a pre-symptomatic clinical trial, there must be an earlier and more accurate way to diagnose rare diseases. NKH, it's not unique. It-and there is no newborn screening. There is no pregnancy screening. This is such a barrier, and it must be addressed by expanding newborn screenings.

Other perceived barriers are the immediate safety of the trial and any possible long term side effects, the ease or difficulty of administration, including travel or financial burdens, clearly understanding the desired outcomes of the trial and how it could affect any future treatment opportunities. And finally, the individual child's gene mutation.

This is a huge determining factor. Having an accurate natural history that we just talked about with disease progression is critical in making decisions in to enter a trial early, which leads back to creating an environment of earlier diagnosis through newborn screening.

Recently, we surveyed our community to capture their thoughts on clinical trial willingness, the barriers that I just talked about and their risk tolerance. 500 known living cases.

And within a matter of days, 160 families responded with a resounding yes to their willingness to participate in either a gene therapy trial or an investigational gene therapy product. 97% of them are willing to take potentially significant risks to give their children a better quality of life.

Here are just some of the thoughts and feelings from some of our parents. All forms of this illness are devastating and to give our children and future children an earlier chance that a better quality of life is our dream and we're ready to make that a reality on behalf of all of our kids. Thank you for listening.

DR. ROWZEE: Thank you, Heidi. Thank you so much. And I really like how you phrase that shining a light. We're hearing from a lot of folks who are helping shine light on these important topics today. So, thanks again. Our next speaker is Estela Lugo. Estela, if you're-

MS. ESTELA LUGO: Hi.

DR. ROWZEE: -ready. Yup, okay. Please, proceed. Thank you.

MS. LUGO: Yes, I have slides. Hopefully-there they are. Thank you. Good morning. My name is Estela Lugo, and I am the program development director for the Hereditary Neuropathy Foundation. I also live with Charcot-Marie-Tooth disease type 4A or GDAP1. A rare subtype of CMT.

I have no financial disclosures to declare, and today I'm here to share the voices of our CMT community with several gene therapy approaches on the horizon for CMT. These perspectives are more important than ever.

CMT, Charcot-Marie-Tooth is a thief silently robbing the body of strength and sensation by damaging the peripheral nerves that control movement and feeling. For one in every 2,500 people, this gradual robbery takes away mobility, independence, and in severe cases, even the ability to breathe-breathe freely.

Simple daily activities like holding a pen or walking up a staircase can become impossible. For rare subtypes like ours, CMT progression can be swift and devastating, leaving families searching desperately for answers and hope.

Gene therapy could mean halting progression or even reversing it, but safety is paramount. Families need to trust that every step prioritizes their well-being. I often wonder what life would be like if my sister and I hadn't grown up fearing the loss of our independence. Gene therapy holds the promise of not just hope, but freedom for future generations.

But getting there starts with families taking a leap of faith. By enrolling in early-stage clinical trials for families, this decision comes with deeply personal questions. Is it safe? Will it work? How will it impact our lives? We need transparency to support and make these life changing decisions with confidence and hope.

Clinical trial design. The design of these trials is equally important. Families need clarity on participation, how long the trials will last, what follow up care looks like, and how often they'll need to visit a site. Tools like validated CMT skills paired with remote monitoring ensure that trials collect meaningful data while minimizing disruptions to our lives.

At HNF we're integrating FDA registered wearable devices to monitor upper and lower limb function in CMT patients. These devices provide real time data, helping researchers track efficacy while reducing the need for constant site visits.

Families need clarity when it comes to eligibility. What's up with subtypes of CMT are eligible? Will the therapy address all types of CMT or just target specific mutations? Clear inclusive criteria, ensure patients know if they qualify and can help them make informed decisions.

Families also need to know what to expect. Can gene therapy halt disease progression, restore mobility, relieve pain? These are the questions that guide our decisions. And by sharing data from similar studies, we can set realistic expectations.

Families also need to know what improvements are actually possible. Mobility, pain, what supports these outcomes. For many, it's not just about walking or gripping objects. It's about reclaiming the ability to participate in our lives.

Clinical trials also affect and impact the families. We face challenges, balancing travel, caregiving work, school schedules - - by supporting systems, such as travel and accommodations, these are essential to make trials accessible beyond what families are expecting.

And timing and benefits, Insights from our HNF's patient registry highlight the need for urgent intervention. And we see here that 57% of our patients are willing to participate in gene therapy. And this speaks to the hope and desperation for treatments that we desperately need.

CMT has shaped my life, but it doesn't shape our features. Thank you so much for this opportunity.

DR. ROWZEE: Thank you so much, Estela, for sharing your experience with CMT and some insights from the CMT community. Our next speaker is Kristin McKay. Kristin, your microphone should be open. Please proceed with your comments.

MS. KRISTIN MCKAY: Thank you. My name is Kristin McKay and I'm the President and Executive Director of Project Alive, a patient advocacy organization for Hunter Syndrome. My disclosures are that Project Alive receives event sponsorships from pharmaceutical companies like Takeda, JCR, Denali, and REGENXBIO. I have a five-year-old son and a late brother with Hunter Syndrome..

Hunter syndrome or MPS2, is a lysosomal storage disorder. The majority of our population have the neuronopathic form of the disease, meaning they suffer from the neurological impacts of Hunter syndrome, which causes progressive debilitation and very early death. Between the ages of one and four years old, children begin to show signs of developmental delay and physical symptoms leading to diagnosis.

Soon after, we see the first signs of regression. Our children lose the ability to talk, walk, eat, and smile. They die in adolescence, some not even seeing their 13th birthday. This mom says it's a feeling of running out of time to treat our boys before MPS starts affecting their body and brain. I don't want to wait until symptoms can kick in so I can look for treatment. e.

Parents and caregivers of children with Hunter syndrome understand that there are risks associated with a clinical trial. We read and learn about these studies and make the decision that is best for our families. While safety may be a risk in early phases of a trial, we know that a diagnosis of Hunter syndrome has a 100% chance of causing death.

We know all too well that time is our enemy. We know that the damage done by Hunter syndrome, every skill and ability they lose, is not reversible. Our only hope is to treat as early as possible and try to stop the disease progression.

With Hunter syndrome added to the U.S. and quickly being added to state newborn screening panels across the country, it is especially important for families to have access to early treatments. These parents have the unique opportunity to treat the disease before ever seeing symptoms. They cannot afford to wait. It is imperative that the FDA allow for infants in gene therapy trials.

Treatment as an infant is our greatest hope for preventing the devastating effects of Hunter syndrome. Another mom states, "We talk about, if only I had gotten this sooner, I truly believe he would be in a different place had he received treatment as an infant."

Parents and caregivers also understand that efficacy cannot be guaranteed in a clinical trial. But when you are told that your child has a terminal illness that has no FDA approved treatment that will extend their life, you're willing to try.

A clinical trial with potential to save your child's life gives us hope. We need hope. We need a chance. Access to early experimental treatments gives us a chance to see our kids grow up.

This is my brother, Zachary. Zach lost the ability to talk by 10 years old, the ability to walk by 14, the ability to eat by 15 and was bed bound by 17 years old. On November 21st, 2015, my brother took his last breath at the age of 19.

My son, Charlie, could have a future that looks entirely different than my brother's, thanks to the scientific advancements, but he needs access to these treatments. The risks associated with experimental treatments are far better than the certain death he faces from Hunter Syndrome.

I don't want to feel grief on every birthday that passes by for Charlie. I want to celebrate him. I want to see him grow up. These are the beautiful faces of Hunter Syndrome. Their future should not be a dream. Thank you so much.

DR. ROWZEE: Thank you so much, Kristin, for sharing your thoughts and insights on living with Hunter Syndrome. Our next speaker is Kris Pierce. Kris, your microphone should be open. Please proceed with your comments.

MS. KRIS PIERCE: Thank you. Thank you for having me today, coming in from Australia. I am the parent of a young adult with SCN2A-related disorder and also the founder of SCN2A Australia. Our organization received sponsorship from Praxis Precision Medicine and that's the only declaration that I need to give at this stage.

So, as you heard from Sean earlier which was a coincidence that he was speaking as well SCN2A disorders are rare, severe neurological conditions caused by mutations in the SCN2A gene, which is essential for brain function. These conditions often lead to early-onset epilepsy, profound development delays, and autism. And they pose serious health challenges and can be life-limiting, and it—this brings immense heartache to families but also to our community. The insights I'll share today actually come from some research that I'm currently doing under the guidance of Professor Kirsten Howard at the University of Sydney, where I serve as a chief investigator. This project has been focusing on developing a decision-making framework for high-cost gene therapies funded by—and it's funded by the Federal Health Department. This work is not yet published, but I was given permission to share today.

So, my role within this has actually been to do qualitative engagement with patients and caregivers of rare blood disorders through focus groups and consultations. I've also included feedback from a recent consultation piece we've done with the SCN2A community on clinical trials. I've just got one slide that's really there for you just to read some of the feedback that we've got and some really sort of potent quotes from participants.

So, families have consistently emphasized the need for clear and practical information around clinical trials. These are the things that they want to know before they enroll. The purpose of the trial whether it's, you know, it's a dosing efficacy and of course the safety. They want to know what the short-term and long-term risks are, and how do they compare to the potential benefits, and who's going to help them navigate that, I guess, comparison of risks. Parents also want to know how the gene therapy might affect development, both cognitive and physical. But we also heard that future reproduction outcomes were a concern largely for caregivers, and they wanted to have some surety around, yeah, reproductive—being able to have children, I guess, in the future, and yeah.

There was also a common thread that others have brought up as well, which is quality of life for the child. And we probed a little bit further on this, and we asked caregivers what it would mean to them as well if their child had a successful gene therapy, whether it was improvement in quality of life or a cure. And it was very evident that caregivers are really holding on to a lot of emotion, and we've heard that today around what it would mean to them for their child to have hope or have a chance and therefore as a parent to have real hope. And one parent actually said that if her child had a successful gene therapy, she would actually be able to exhale, and I think that's a pretty strong statement.

Families also want clarity around the information that they get. Trust was a big thing that families were looking for across the process in engaging with the industry partners for SCN2A. The disease is quite variable in how it presents. So, there would need to be sort of personalized risks assessments. I think mentioned before, severity is a big consideration for families and makes the decision different for each family. I know I'm sort of hitting time, but I just wanted to touch on also, it has been touched on before, that what we've also found in clinical trials in SCN2A is that we need to have ongoing relationships with the industry partners for transparency and trust, not only with the patient organization but also with the families. So, it's really essential that that is part of it and embedded into the trial. And I think that's my time, so thank you for having me.

DR. ROWZEE: Yes, thank you so much and thanks for joining, which I can imagine is early in the morning for you, but thanks for providing the landscape from SCN2A Australia. Just a quick reminder for folks that recording will be posted on our website and slides will be as part of that recording, so if there's something that you saw today that you didn't get a chance to fully digest, that will be available to you within the coming weeks.

And also, just a quick reminder to folks, if anything sparked an idea or a comment in your mind that you want to make today, please direct those to the docket so that we can include them when we're looking to summarize today's meeting. Our next speakers are Heather Rothrock and Chelsea Meschke. If you're available, or sorry, your microphone is open and please proceed with your comments.

MS. CHELSEA MESCHKE: Hello, good afternoon.

MS. HEATHER ROTHROCK: We have—there's our slides. So, Chelsea and I are going to tag team today a presentation both as parents. I have a five-year-old with cystinosis. Chelsea has two children, a seven and three-year-old with cystinosis. We're also on the Cystinosis Research Network board. And in terms of disclosures, our organization has occasionally received event sponsorship from Novartis, Amgen, and Recordati.

MS. MESCHKE: We're going to be talking, focusing today on nephropathic cystinosis, very quick overview with the lysosomal storage disease characterized mostly by abnormal accumulation of the cystine in cells causing widespread tissue and organ damage. Primarily, this focuses and accumulates in the kidneys, but it also can lead to multi-organ failure including lungs, brain, eyes. Through organ damage begins at birth, most of our children are typically diagnosed by their second birthday usually with symptoms beginning with polyuria, failure to thrive, unexplained vomiting, electrolyte imbalances. We usually start to see the kidneys go, and those are all going to start that process of diagnosis.

We are at about 16—600 affected in North America with about 2,000 worldwide. Like I said, it is an autosomal recessive caused by the mutation in the CTNS gene. It is—a treatment is limited. A life expectancy usually can be within less than 10 years. With rigid compliance and a successful treat—kidney transplant, we can see that life expectancy increase to adulthood sometimes in their 60s. We do have four available FDA treatments. We have two cystine-depleting therapies, as well as depleting eyedrops with a cysteamine. We do have then—and then there's the non-FDA treatments, gastronomy tube for nutrition, supplemental for electrolyte loss, growth hormone therapy, feeding therapy, dialysis for kidneys.

MS. ROTHROCK: So, this slide, we're primarily just trying to illustrate that our community is fortunate to have benefited from previous clinical trials. Again, Chelsea mentioned we have four FDA-approved therapies. Our community has also a gene therapy clinical trial underway with six patients treated and plans to enroll additional populations in the near-ish future. We've had to think about the very questions that the FDA has posed for this session today as we consider the decision to enroll our children some—at some point in the future if we're given that option. So, just wanted to highlight that this is on the table for us, and we're excited about that, but it doesn't come without its share of risks and decision-making that feels very heavy.

MS. MESCHKE: So, with our perspectives, we're talking about those pre-enrollment considerations. Obviously, we also can very much see the time, effort, and commitments that a trial will need specifically with labs, meetings with doctors, meetings with teams, meetings with the trial company, and how that's going to affect both the time and family time, things like that, how we're going to be able to do that along with our normal day-to-day process for caregiving. The clinical process, what is the preparation? We know that most clinical, especially with gene therapy, involve some sort of immunosuppressant. Is that going to cause continual issues, is there going to be adverse side effects that are going to further decline our children and their disease progress as far as kidney function, things like that, while also stopping those medications that we have to rely on every day for our children's well-being? So, stopping those medications and the decline that can take from those medications being stopped.

What are the guidelines for informed consent with the minor versus parent? We talk about a lot of our children go through a lot of medical trauma, going through multiple surgeries, going through lab work, things like that. How is this informed consent going to be when the child at seven years old is screaming, “no,” but the parents are saying we want to do this? Where are those lines drawn and how are we going to approach those things? And then the follow-up requirements, you know, if a child in this stage and in this trial goes in as a child, how are we going to ensure that they're doing a follow-up if it's the follow-up goes into adulthood and making sure that those can be addressed and just talked about us as considerations?

The disease progression consideration, again, just making sure that as we go through the trial, are these progressions going to involve our child getting way worse as we're not taking those medications that they need for their life sustainment? And then the timing of the clinical trial in relation to the disease stage, you know, specifically with cystinosis, the stem cell could hopefully, prior to the chronic kidney disease progression, mean less medication, no dialysis, hopefully avoiding kidney transplant even, or delaying that dialysis and transplant to a much later time.

DR. ROWZEE: Chelsea, I'm sorry, we've reached our time. So, if you have further comments, again, I encourage you to please put them into the docket. Your talking points and scripts would be really valuable for us to have. So, thanks very much, Chelsea and Heather, for sharing your perspectives on cystinosis. Our next speaker is Andrey Skripkin. Andrey, your microphone should be open. Please go ahead and proceed with your comments. Great, I can hear you.

MR. ANDREY SKRIPKIN: Yeah, I'm here. Hello, everyone. My name is Andrey, and I'm a father of a four-year-old daughter, Victoria. There should be slides over there. Do we have those? Yeah, yup, that's my daughter. And she's diagnosed with the OGT-XLID, a rare genetic disease. Victoria's diagnosis has been really life-altering for us, as the disease presents with significant developmental delays in both mental and physical areas, along with potential future complications like seizures. And I'm going to share my perspective as a parent on how to navigate, how we're planning to navigate the decision-making process for enrolling a child in early-stage gene therapy clinical trial.

So, as far as timing goes, we don't have a definitive answer from our research community whether it is absolutely critical and essential to do the therapy early on. But as other trials and research papers show, the earlier the better. We are not sure at this point if we will be able to treat the condition after the age of, like, currently, she's four, she's turning five, like 10, whatever. We don't know that yet. We don't have a definitive answer. But I think that the likelihood that the earlier the better is pretty high.

As far as the considerations, so basically, we are evaluating couple of things. The life without a treatment, without gene therapy, and the risks and potential benefits of gene therapy. As far as the first goes, we need to be presented as parents who are enrolling in these clinical trials with very clear evidence and data about our disease, where—what will happen with our daughter five years from now, 10 years from now, will—other complications will develop, or is it life-threatening condition? So, we need to very clearly understand what's going on. And once—if I'm presenting—presented a choice, I need to know that very well, right?

Also, another consideration, I think it's important to make that. If that is not life-threatening condition and if there are some risks associated with gene therapy, I will think twice really because I've learned how to live with this condition. It's extremely hard life, extremely, and a lot of parents will really agree to me, but I've—we kind of we somehow got used to it. Not get used to it, it's hard to get used to it, but we're living it. And we love who she is with all her minor progresses and milestones she's making.

As far as the gene therapy, when I look at the, like, the opportunity, I need to understand what are the benefits, what are the—what is the—what is the probability of the side effects and what are those side effects. People were talking a lot about cancer, blood cancer. So, if that's the case, then I need to be presented with those facts very clearly. And I would like to see what are the other studies which are happening, what do studies on cells—cell models show, what do studies on animal models show, do we have safety studies on rats or maybe even on primates?

So, all of these is very critical consideration for when we will be making this decision. So, yeah, we are currently working with our research community. We are in close touch with both labs, and we're also like exploring all of these options, and we'll be happy to partner with the FDA on that as well. Thank you.

DR. ROWZEE: Andrey, thank you so much for your comments and for sharing the work of Cure OGT and Victoria's story. Our next speaker is Cristina Vargas. Cristina, your microphone should be open, please feel free to proceed with your comments. Thank you.

MS. CRISTINA VARGAS: Okay, just give me one moment, please, because I thought that I was going to be after. Just give me one second, please.

DR. ROWZEE: Sure. I'll let folks know. We have had some shifts in our lineup today. Some folks who unfortunately couldn't make it and couldn't share their perspectives, but—so, we have a few more speakers lined up for this afternoon. Again, we'll take a brief break after our speakers have finished, and we're inviting everyone to come back because I think our FDA panelists may have some follow-up questions, maybe some clarifying questions for you. I think backstage folks—I hope I don't throw too much of a monkey wrench here, but could we perhaps promote Heidi Wallis, and then maybe we could come back to Ms. Vargas? Is that possible?

MS. HEIDI WALLIS: I'm ready.

DR. ROWZEE: Are you ready? Okay, that's—do you have slides?

MS. VARGAS: Okay.

DR. ROWZEE: Oh, sorry. Sorry, Ms. Vargas, if you wouldn't mind holding for a moment? We're going to let Ms. Wallis proceed and then we'll come directly back to you. Okay?

MS. VARGAS: Okay.

DR. ROWZEE: Great. Thank you. Ms. Wallis, did you have slides?

MS. WALLIS: I do.

DR. ROWZEE: Okay, I see you do.

MS. WALLIS: Yeah.

DR. ROWZEE: Great. Please proceed.

MS. WALLIS: Thank you.

DR. ROWZEE: Thank you.

MS. WALLIS: Okay, my name is Heidi Wallis. I'm here representing the many families and patients around the world affected by cerebral creatine deficiency syndromes, and I'm also here as the parent of two children with GAMT deficiency.

So, just briefly, there are three cerebral creatine deficiency syndromes. AGAT deficiency and GAMT deficiency are recessive enzyme disorders. Both result in decreased creatine throughout the body and are creatine synthesis disorders, so they can be managed depending on age of diagnosis with oral creatine supplementation with varying outcomes. And then the third disorder is creatine transporter deficiency or CTD. This is an X-linked transporter disorder that results in creatine not being taken into the cells throughout the body. And if you can click one time, I will be speaking primarily about GAMT deficiency and CTD today, as both of those have gene therapy research ongoing and have been for several years and we're quite hopeful about those developments.

So, symptoms of CTD and GAMT overlap with many other neurological disorders. They're not extremely distinct. They're not easy to identify. Most have an initial normal early postnatal development period with no dysmorphic features. Parents report symptoms first being observed sometime between birth and three years. So, there is sometimes a period where everything is seeming fine and then the symptoms increase over time. These are neurodegenerative disorders. And ultimately, patients develop intellectual disability, often very limited speech, seizures, movement disorders, low muscle tone, and behavioral issues. Parents also have reported that after that period where the symptoms first become noticeable, it's another on average 1.2 years until they get a diagnosis.

So, I'll first talk about the case of GAMT and the value of pre-symptomatic intervention. These two cute kiddos standing together are two of the few children in the world who have been diagnosed and treated since birth with oral creatine supplements because of their GAMT deficiency, and they're now 12 and 15. And their guanidinoacetate is never normalized, and there is concern around that and a desire for a better treatment. But we know that the early cerebral creatine replenishment is a game changer for them, and for that reason, GAMT was added to the RUSP in 2023. And you can see on this map, a lot of states are beginning to screen or planning to screen for GAMT. And on the right is a sibling who was diagnosed at five. And when creatine replenishment began, there were gains, there was gain in speech and reading and math. But the patient has never fully recovered and currently has severe epilepsy and intellectual disability.

So, this tells us a lot about other creatine deficiencies such as creatine transporter deficiency, which right now has no treatment at all, and that's one of the big motivators for our community is we do not have a treatment option for CTD. We don't really have an approved treatment for GAMT and that makes this very desirable to pursue gene therapy. A treatment such as gene therapy delivered as early as possible would make creatine available for creatine transporter deficiency patients. And we believe that would lead to the very best outcomes in CTD. I will add that our community worked with families around the world, researchers, clinicians.

And through a long research study, we developed a core outcome set of eight different outcomes that are of the most important to our community for measure in clinical trials. They include adaptive function, cognitive function, emotional dysregulation, expressive communication, fine motor function, seizures, plasma guanidinoacetate for those patients with GAMT, and then finally, MRS brain creatine.

So, that is a spectroscopy of the levels of brain creatine. And we know so much from our three disorders working together and being followed over time, the natural history and the replenishment of creatine in the case of AGAT

and GAMT deficiency that we feel firmly that creatine in the brain is the marker that should be followed for CTD. And I know that's not a popular request to follow something like that as an endpoint, but that is the goal of all the researchers and the families is to see that marker move over time. And so, thank you so much for your time.

DR. ROWZEE: Thank you so much, Ms. Wallis, for sharing that information and perspectives from the community. And I also appreciate your flexibility in going maybe just a smidge earlier than you planned on going. So, I think—next we have now Cristina Vargas. Ms. Vargas, if you're ready, please proceed with your comments.

MS. VARGAS: Hi, sorry about that. Can everybody hear me fine?

DR. ROWZEE: Yes, we can hear you.

MS. VARGAS: Okay, let me just turn my camera on as well. I do apologize if there's any background noise. Hold on one second. All right. I'm sorry, I'm just having technical difficulties. All my—okay, here we go. Hi, everybody. My name is Cristina Vargas, and thank you for having me here, and I sincerely appreciate the opportunity to be able to speak with FDA. I'm representing Juju and Friends CLN2 Warrior Foundation today. And I'd like to be able to share some insights from the patients and caregivers' perspective of—regarding the importance of early enrollment in gene therapy. And as a mother of children with two rare diseases, these issues particularly very important to me. My journey began in 2021 when my son, Juju, was diagnosed with CLN2 Batten disease, a lysosomal storage disease. It led to the founding of my organization, and this experience has inspired me to become an advocate and to also deepen my understanding of the safety and effectiveness of gene therapy.

Gene therapy offers hope by targeting the root cause of genetic disorders, including rare diseases like CLN2 Batten disease and also pulmonary atresia. However, parents often are faced with significant safety concerns considering gene therapy treatment. There's a lot of things that's incorporated with it. Gene therapy does not always promise a definitive cure, and it's essential to be able to focalize—to focus on individualized medicines that's tailored to each person's diagnosis to be able to ensure that everyone's unique needs are being met.

Early enrollment into clinical trials can also provide access to treatments that may not yet be available to the general public, which can also significantly improve the quality of life for our children. And nevertheless, it's important for families to be fully informed of the potential risk and benefits that's associated with these innovative therapies, you know, as we navigate through a challenging landscape as well.

And then, you know, receiving Juju's diagnosis was very daunting, but I quickly realized the importance of exploring clinical trials for his treatment and Serenity's condition as well. It's presented a lot of different challenges. It's only fueled my determination to find more innovative therapies for both of my children as well. And as a caregiver, I'm also—I advocate for their needs, and I understand the complexities that's involved with everything relating to clinical trials. And being able to maintain communication with healthcare professionals as well, it's very important.

The rare disease community has been a vital support network, and connecting with other families has greatly helped us navigate through this journey. And while gene therapy shows promise, it's crucial to address these concerns by ensuring that data is being collected thoroughly and analyses are being done to protect patients that's enrolled in these trials.

And in summary, participating early in gene therapy trials can provide crucial support for families with rare diseases. These trials often represent one of the few avenues available for patients who may have limited treatment options due to uniqueness of their conditions. Enrolling in these studies, it gains access to potentially groundbreaking therapies for families, and collaboration between researchers, healthcare providers, and families is important.

So, as we advocate to improve treatment options, it's vital to recognize the importance of patient voices as well in a research and process. And this way, early participation in gene therapy trials becomes a powerful tool for fostering hope and progress in the fight against all rare diseases. And I want to thank everybody for your time today.

DR. ROWZEE: Great. Thank you, Ms. Vargas. Our next speaker—

MS. VARGAS: Thank you.

DR. ROWZEE: —yes, great—is Andre Weinstock. If you're ready—

DR. ANDRE WEINSTOCK: I'm here.

DR. ROWZEE: You're ready? I can hear you and see you. Please proceed. Thank you.

DR. WEINSTOCK: So, while my slides come up, I really first want to start with thanking the FDA and the CBER for hosting this session. And so far, I've been very inspired by all the speakers and presenters who have come before me. So, I'm still waiting for my slides to come up. There we go. Really just this one slide, and I'll try to keep it within the time.

So, let me start by, again, my name is Andre Weinstock. I'm an adult Alport syndrome patient. I'm also a—trained as a research scientist in the pharmaceutical industry. And currently, I serve as research director for the Alport Syndrome Foundation. I do have a disclosure that I am a consultant for Bayer.

So, I want to start first to introduce Alport syndrome, that it is actually the most common form of monogenic kidney disease. So, it is a genetic extracellular-matrix disease of collagen stemming from three different genes, two autosomal genes and one on the sex link. So, this is actually a photo of me when I was 22 undergoing dialysis.

And instead of sticking with the script here, I really wanted to go to two overview points and then two considerations. The first is, like many of the other conditions you've heard about or seen this morning and heard the stories of, even though Alport syndrome usually doesn't express itself until teenage, young adult, or even going into 40s, in some case 50s, what we see for the current genetic therapy technologies that are out there, an

early pediatric treatment would be needed to intervene to actually cause an effect. At least that's what we believe, or the best of our understanding.

But unlike many of the other conditions that we've heard about this morning, Alport syndrome is not hyper rare. We actually believe there are at least 60,000 Alport syndrome patients in the United States. And we have, within the Alport Syndrome Foundation's roles, over 5,000 families worldwide. Most of those in the US, a good proportion also in Canada. It is a global prevalence condition. It's not associated with one particular population. So, this is actually something that is approaching the boundary of what the FDA considers a rare disease and may very well exceed it.

As genetic testing becomes more prevalent, we're seeing more and more Alport syndrome patients coming out there. So, in a sense, maybe I'm not the best poster boy for Alport syndrome because here I am as an adult and I've led a successful life, but I do hopefully represent thousands of families that are looking for cures. I, because of my genetic diagnosis, chose not to have children. However, I do have a nephew who's facing the exact same future of Alport syndrome with hearing loss and looking at kidney failure likely when he reaches age 22.

So, I'd like to summarize down to two considerations. The first staying on this slide is that while I'm extremely appreciative and most of us are appreciative of the fact that there is dialysis to allow us to live and kidney transplants, I've had two now in my life. Again, I've been extremely fortunate that I've been able to get kidney replacement therapy and live a pretty full life. But for most individuals, that's not the case. It severely degrades quality of life and severely increases the chances of mortality.

So, we're aware of members of our community who have died in their teenagers or as young adults because of the impact of Alport syndrome. So, there's a general feeling that we get from nephrology or the nephrology community that they were sort of saying, "Oh, you can always go on dialysis. You can always get a kidney transplant." But one thing I would like to sort of make clear to this audience is that we are very eager to look for therapies, genetic therapies.

This is more specific that we are aware of at least five different labs or commercial companies that are working on genetic therapies for Alport syndrome specifically. And in the past, we've used what we call the CDER pathway.

What we're hoping for guidance, especially for the thousands of families that I represent is, is it okay to just jump from a mouse study to humans? Or are there other recommendations that you may have for us or these companies that are pursuing that to find successful therapies? Thank you.

DR. ROWZEE: Thank you, Dr. Weinstock. And before we jump to break, I just want to do a quick roll call. There are four folks who we may have missed. So, I'm going to just go through their names really quickly. If you are here and are ready to provide comment, please drop us a note in the question and answer box, the Q&A box. So, that's Farhan Ali, Daiza Gordon, Raphael Ngendakumana, or Niranjan Thadaka. Those four folks, I'll give you a second just to pop into the Q&A.

And while we just give them a quick moment, again, just want to thank everybody who volunteered to speak today, sharing their perspectives on this important topic in session one, focusing in on children enrolling in pre-symptomatic phases or early stages of disease. Again, enrolling in clinical trials for gene therapy products.

I'm not seeing any communication in the Q&A window. So, those folks, if you're listening to this recording and there's still time, please submit your comments to the docket. We're going to now take a quick five-minute break. When we come back, our FDA panelists will have a few follow-up questions for our speakers.

So again, session one speakers, if you can return after the break, we'd really appreciate that. Also, flagging for session two speakers, thank you for being so patient and waiting for your chance to speak today. You're going to receive camera and mic access soon. So, I believe we'll come back in about five minutes. Thanks very much.

FDA Panelist Questions

DR. ROWZEE: Great. Welcome back. Yup. That's perfect slide timing. Welcome back, everyone. And thanks again to the speakers in session one. We hope that you've all come back so that our FDA panelists can ask some clarifying and follow-up questions. Just a quick reminder, our FDA panelists for this session are Dr. Rosa Sherafat-Kazemzadeh, Dr. Najat Bouchkouj, and Dr. John Scott. I think our first question is coming from Rosa. Rosa, if you are ready, please go ahead and get started. Great. Thanks.

DR. SHERAFAT-KAZEMZADEH: Sure. Thank you, Anne. So again, thank you very much for all the presenters for sharing your experience and perspectives with us. So, I have follow-up questions for Ms. Kristin McKay and also Ms. Cristina Vargas. I hope that they are in the audience here. So, thank you. Great.

So, you mentioned that, I mean, you emphasized the—really the need for early access to gene therapy trials for Hunter syndrome. So, my question is, in your experience, what has been the number one barrier in terms of access to early gene therapies?

MS. MCKAY: The big piece would be certainly we were just recently able to see newborn screening come to fruition for us. It was just added to the RUSP in 2022. And really this year has been the big year of seeing states actually adopt it and begin screening. So that is certainly a critical piece to it.

We need to know that our kids have this disorder to be able to have early access. And I think in general, what we see is we've been very fortunate that our gene therapy trial that's been out for Hunter syndrome was able to take infants as young as four months old, but that's certainly not the case across the board in all clinical trials for Hunter syndrome. And it's just devastating.

And currently, that clinical trial has come to a close in enrollment. And now, we have children getting diagnosed through newborn screening, which would be a blessing until you have to sit there and tell a parent, "I'm sorry, there's nothing available for your child. You have to wait until they're two or four years old, or we get something approved and, on the market, and available for your kid." That's just the most devastating conversation to have with a family already in grieving such a terrible diagnosis.

DR. SHERAFAT-KAZEMZADEH: Sure. Certainly. Thank you for your perspective. So, is Ms. Vargas with us? Yeah, okay. Just you - - unmute. Okay, perfect. So similarly, you emphasize the need for early trials for CLN2. So, if you can please share what's the number one barrier in your experience.

MS. VARGAS: The number one barrier in my experience relating to the current treatment for CLN2 or—I'm sorry, I couldn't—

DR. SHERAFAT-KAZEMZADEH: Regarding, yeah, the early access to early gene therapy trials.

MS. VARGAS: So, there's been many barriers within that factor between things being approved, safety, efficacy, a lot of - - , you know, it's been numerous times in the CLN2 community. We have hope gene therapies coming and then pharmaceutical things just doesn't work out. It's very—it's very emotionally burdening for our families. And, you know, time is of the essence when it comes to things like this. We don't have 10, five years to wait for new medicines to be developed.

So, everybody's working extensively together trying to create different ideas. And I know myself, that's what I'm doing for my son and for the community. I'm doing the best that I can. I know that rare disease community, when it comes to gene therapies, it's not something that happens overnight, but at least having more options for the families, and things like that, just a collaboration, come up with more ideas.

DR. SHERAFAT-KAZEMZADEH: Great. Thank you very much. I really appreciate your insights.

MS. VARGAS: Thank you.

DR. SHERAFAT-KAZEMZADEH: Sure. So, back to you, Najat.

DR. BOUCHKOUJ: Thank you, Rosa. My question is actually for Ms. Kris Pierce, if she is online, and it's related to quality of life.

MS. PIERCE: Yes, I'm here. Sorry.

DR. BOUCHKOUJ: Okay, great. No problem. Sure. So again, thank you for the insightful comments you made. And I just wanted to ask, earlier during the polling questions, we had asked all attendees about the key factors influencing the decision to enroll a child in a gene therapy trial. And the polling results showed that more than half of all responders identified quality of life as a crucial determination. That was also evidence in the survey results that you've conducted with your families, and you presented to us.

Now, even if a gene therapy proved successful, as you know, uncertainties remain regarding the child's quality of life after treatment. For instance, will the child experience any mild symptoms, or will they be completely free of symptoms? Could you please just elaborate on how quality of life plays a critical role in the decision-making process, when families are making the decision and weigh in on the potential risk and benefits of a therapy with uncertain outcomes?

MS. PIERCE: Well, thank you for the question. I think it does come back to, you know, what you said, the weighing it up, weighing up of the risk and benefits. But what we've found in our conversations is that families are looking for, you know, improvement. And if there is improvement in quality of life, then that will definitely sway the balance into the decision-making process. And I think we probably undervalue that, that I know we are looking for a cure and for that hope, but families would also see value in improvement and quality of life, not only for the patient but for the family. And that's come through strongly in the work that we've done.

In terms of the longer term, I mean, because it's, you know, it's not certain what that would look like. We've got families who are taking, you know, small molecules and they're telling us the fact that they can just get out, out of the house, whereas where they've been housebound has made a significant impact on the quality of their family life. And so, what we're hearing across SCN2A community is that even small increments in quality of life are actually having quite a big impact on these families that are really—that have really complex medical conditions. So, I—

DR. BOUCHKOUJ: Thank you.

MS. PIERCE: Yeah. Drawing a line, I would say that families would still be looking at it positively.

DR. BOUCHKOUJ: Thank you. And we do value quality of life. And when we reviewed, you know, clinical trials, definitely that's in our top priority when we review these trials as well. Thank you. Thank you. Then I will turn it back to John.

DR. SCOTT: Thanks, Najat. And thanks again to the speakers we just heard from. So, earlier in the first round of presentations, Rachel DeConti said something that stuck with me. She said her son shouldn't have to wait until he begins to decline for a safe, effective treatment, which I think is something anybody would understand. And then in this more recent section, we heard from Estela Lugo and others about the importance of making trials work for families' lives, you know, reducing the burden of appointments and so on.

One of the trade-offs for earlier enrollment or enrollment of children with pre-symptomatic disease or less severe disease in a clinical trial is often going to be the need for maybe significantly longer follow-up in order to understand whether the treatment is actually working. So, it's kind of an open-ended question. And maybe for Rachel, I think Estela may have dropped off. But do you think that that kind of trade-off would affect your decision-making regarding trial enrollment at all? Or do you have any thoughts for how investigators can make a much longer trial work for your families? And—or anyone else who has thoughts too would be welcome.

MS. MCKAY: I can jump in. I think the big piece for our families is we have families in all kinds of different clinical trials. And yeah, there's a lot of burden to it. But what we see is so much desperation to get any type of treatment that we're willing and able to do that. We have a—based off of the three trials that are currently taking place for Hunter syndrome, very few have people that disenroll or kind of neglect the long-term follow-up processes.

And it's something that I think a lot of families get excited about being able to see the progress. But also—and I would imagine this is very similar in all rare disease groups, is that we have a lot of camaraderie with our group and feel a sense of obligation to the future of our disease. And so, recognizing that while, yes, it can be challenging, it's serving a greater purpose. And I think that the families that I get to see that have seen a lot of benefit love to be able to show that to other families.

And we've had a lot of success with our—the pharmaceutical companies that we work with who really take time to listen to patients and make adjustments to that by working with local doctors, getting home infusions or, you know, home—local labs, having home health nurses. And that really limits the burden that people have to deal with kind of on that long-term basis.

So, I think that's important that there's a lot of—there's solution to that problem, right? And as long as we're working together, which there's been so much change in that area of pharmaceutical companies working with patient advocates and patients and to be able to solve that problem and reduce that burden.

DR. SCOTT: Thanks, Kristin. That was a great response. A couple of people raised their hands. Andre?

DR. WEINSTOCK: Yeah. I think just to add a caveat into the question, I think it's an excellent, you know, I would think that most patients compared to our very—at least the parents of patients in pediatric are very willing to, you know, be in it for the long game because in a lot of cases, what's the other choice? And I think it's something that's, you know, as long as the pharmaceutical company is likewise doing that.

One of the things that we've noticed, especially because Alport is particularly prevalent and most impactful in teenagers and young adults, is that, what do you do when you transition from being under the patient's care and the patient's obligation? And if the genetic therapy is successful enough, the patient may not be knowing, you know, why do I have to take this drug? You know, why am I doing this?

And it's something that, you know, how do you get into a 17-year-old's mind to assure them, no, this is really in your best interest, and you do want to continue doing this, even though you're busy with college or, you know, a job and raising a family yourself, something that we encounter, not specifically in the genetic therapy session yet but just with standard drugs.

DR. SCOTT: Yeah, absolutely. That's something we've heard about as well. Heidi?

MS. LESLIE: Yes, just to follow up with what Kristin had said, the long-term basis, I think, in my community shows that people are paying attention to us, right? We want some attention. And so, we're willing to take that on for sure. And I did recently find out that I believe that the Family Medical Leave Act can help to counteract some of these—some of these barriers as far as working and traveling and so forth. And so, yeah, absolutely.

And my son's 16 now, and this is our legacy, right? I've lost, you know, four other children to this illness, right? We only have 25% each pregnancy, and I got the lucky one. And so, our community, this is our legacy to help that nobody else has to hear NKH again and create a better quality of life for everybody.

DR. SCOTT: Thanks. It's really meaningful to hear everybody's commitment, not just to their own families' lives but also to the greater patient community. I think I'm turning it back over to Anne now. Thanks.

DR. ROWZEE: Great. Thanks, John and everyone. Okay. Sorry, we're doing a little bit of coordination on our end here. So, we—I just wanted, you know, again, thank our session one speakers. Thanks to everybody for sticking around and coming back and answering the questions that came from our FDA panelists. I think it really helps just continue that conversation and continue our understanding. I just—I'm going to get ready to hand over, I think, to my colleague, Karen Jackler, and we're going to transition directly into session two now.

But before I sign off for today, I just wanted to take a quick moment to express my gratitude to everyone who has taken their time to prepare and share your thoughts today. And to those folks who are coming up in session two, who've been so patient. I imagine it can be difficult to share personal stories over the virtual space.

I think I can speak for my colleagues when I say that we're honored to see the faces of your loved ones in your slides and to hear your words directly. So, thank you again from me and my colleagues. And we're looking forward to hearing more in session two. And Karen, if you're ready, I'll hand it off to you. Thanks, everyone. Take care.

Session 2: Early Enrollment of Adults

MS. KAREN JACKLER: Yes. Thanks, Anne. Great work to everybody in the first session from the patients to our moderators, to our panelists. So, I am Karen Jackler. I'm the patient engagement program manager at CBER and your moderator for session two. So, we're now going to move to the second topic of the meeting, which is early enrollment of adults into gene therapy clinical trials for rare diseases.

For our confirmed speakers, we will introduce each speaker so that you can begin your presentation. When it is your turn to speak, you'll be asked to unmute yourself. Once your presentation is done, you'll be asked to go back on mute and allow the next speaker to present. You will see a pop-up box that will let you know that you have been promoted to a panelist. And then please proceed so that you can get your mic access.

Polling Questions

So, before we get to the speakers, we're going to take another moment to answer some brief polling questions on your screen. Because the focus of session two is adults with rare diseases, we ask that only adults with rare diseases or their care partners participate in this poll. All right, I'm ready for the first polling question. Okay, wonderful.

So, the question is, what are your top considerations when determining whether to enroll yourself or your loved one as an adult in a gene therapy clinical trial at the pre-symptomatic or early stages of the disease? Is it the—you can select up to three responses.

And the responses can be:

- Age of patient
- How fast the disease progresses
- Availability of other treatment options
- Effectiveness and duration of expected benefit
- Severity of short-term risks and side effects
- Severity of long-term risks and side effects
- Availability to live independently
- Ability to participate in long-term follow-up
- Ability to receive other currently available or future treatments for the disease if the gene therapy doesn't provide the expected benefit
- My or my loved one's medical provider or disease expert's opinion
- Other

Give you guys about 10 more seconds before we show the results. All right, there we are. Thank you. Okay, let's go ahead and move to the second polling question.

Okay. For the second polling question, what information about gene therapy risks would be most important to you when determining whether to enroll yourself or your loved one as an adult in a gene therapy clinical trial at the pre-symptomatic or early stages of the disease? And we're asking you to select three responses here.

- How common the risks are expected to be
- Potential timing of risks including short-term and long-term risks
- Severity of the risks identified from patients who have received the gene therapy
- Whether a particular risk or side effect reduces the benefit of the gene therapy
- Whether a side effect of the gene therapy is permanent or has long-lasting consequences
- What treatment will be required if the particular side effect occurs
- Other

And I'll give you guys about 10 seconds. And here we have our results. Okay, thank you so much.

I think we can move on to—well, before I read—before we display the third question, I'm going to read a little bit of a preface to help you answer that question. So, many factors may affect one's decision to enroll in a gene therapy clinical trial at the pre-symptomatic or early stages of a disease, such as other available therapies, the rate of disease progression, and expected treatment benefit. The next two session—the next two questions aim to help us better understand how disease progression may impact your decision. You may choose to answer both questions or the one that applies to you based on your best knowledge of you and your loved one's disease.

So, if I could please have the third polling question? Wonderful. So, this question reads, if the disease progresses quickly, what are the risks/uncertainties you would be willing to accept when determining whether to enroll

yourself or your loved one as an adult in a gene therapy trial at the pre-symptomatic or early stages of the disease? We're asking you to select three responses.

- Risks associated with surgical procedures and/or anesthesia to administer a gene therapy
- Risks associated with medications needed for gene therapy, such as those to mitigate immune response
- Uncertainty of treatment benefit
- Risk of the disease or condition getting worse while waiting for an alternative therapy
- Uncertainty of long-term risks of gene therapy
- Uncertainty of eligibility to receive another gene therapy
- Unknown risks of the gene therapy that may not have been identified yet
- I don't know

And I'll let that stay up for another 10 seconds. All right, here are our answers. Okay, thank you so much. Let's go on to our fourth question. All right.

And this is our last polling question for this session. So, question four reads, if the disease progresses slowly over decades, what are the risks or uncertainties you would be willing to accept when determining whether to enroll yourself or your loved one as an adult in a gene therapy trial at the pre-symptomatic or early stages of the disease? And again, please select up to three responses.

So, the choices are:

- Risks associated with surgical procedures to administer a gene therapy
- Risks associated with medications needed for gene therapy
- Such as those to mitigate immune response
- Risk of the disease or condition getting worse while waiting for an alternative therapy
- Uncertainty of long-term risks of gene therapy
- Uncertainty of treatment benefits
- Uncertainty of eligibility to receive another gene therapy
- Unknown risks of the gene therapy that may not have been identified yet
- I don't know
- Would not consider/I would receive a gene therapy regardless of the risks, or
- Other

And here we have our results again. So, thank you all that participated in the polling questions. We really appreciate that, your attention and participation in that.

Session 2: Speaker Presentations

So, the following presentations will offer their responses to two main questions. If you were to consider enrollment in a gene therapy clinical trial for early-stage or pre-symptomatic disease for yourself, what would you want to know? And what do you think about regarding disease stage of progression when considering enrollment in a gene therapy trial?

So, we have 10 speakers for this session, and each speaker will have four minutes. I'd like to remind our speakers to stay online after you speak and for the duration of your session, in case FDA panelists have questions for you at the end of the session. So, our first speaker is Donna Appell. Donna, are you ready?

MS. DONNA APPELL: I am.

MS. JACKLER: All right. Go ahead, Donna.

MS. APPELL: I have slides.

MS. JACKLER: Okay.

MS. APPELL: Hello, my name is Donna Appell, and I have no financial relationships. I am the executive director of the Hermansky-Pudlak Syndrome Network, and I'm speaking about the many conversations and dreams for the future that I've had with my community.

Hermansky-Pudlak syndrome is a type of albinism with legal blindness, but what sets it apart is a platelet dysfunction bleeding disorder, fatal pulmonary fibrosis, and a Crohn's-like inflammatory bowel disease, and it can progress to kidney disease. HPS has a founder's effect in Puerto Rico, where it occurs in 1 in 1,800 in large areas of the island. HPS has 11 gene subtypes, with HPS 1, 2, and 4 100% of the time causing fatal pulmonary fibrosis. HPS 1 is by far our most common subtype. We are so prevalent in Puerto Rico that this year they kindly dedicated an ambulance to us.

HPS individuals die of pulmonary fibrosis early in their 30s and 40s without a lung transplant. This is Matt, who left his beautiful little family and our community while waiting on a list for a lung and kidney transplant. We dream of gene therapy. Early symptoms would be ideal for us because children with HPS are not lung symptomatic, so disease biomarkers might not be available to show efficacy. There would be an established diagnosis seen on CAT scan that we could follow.

Disease progression is very unreliable, so we have to start early. Some people progress slowly, and others have severe episodes that can cause rapid decline. We have no treatments, even though we have been giving specimens of blood, tissue, explant, bowel fluid for 30 years. Our only intervention is a lung transplant, which becomes like switching one chronic disease for another, needing multiple hospitalizations and therapies with a similar cost. That is, thinking about most of my community, if you're lucky enough to be able to get a lung transplant.

You see, platelet transfusions are needed frequently, and they develop antibodies and can't match for a lung in time. If gene therapy was given to early active disease, we could show maximum benefit and clinical impact. Early symptom adults would be able to report changes in health and improvements in symptoms and allow for the opportunity for us to help in dosing the children, the HPS children that we want to protect.

Gene therapy would halt, or reverse disease progression rather than just manage symptoms. It would prevent late-stage progression of comorbidities such as pulmonary arterial hypertension, kidney failure, and cardiomyopathy. It would lead to optimized treatments for HPS and other genetic disorders. .

You asked us a question and I spoke with my daughter, 37-year-old and has HPS type 1, and I asked her what she would want to know. She would like to know if it would make—if it would be safe and effective, if it would make her life easier and sustainable, and how would it be delivered and how often would I need it.

And I asked her what stage of the disease would she like the therapy. She answered, "I would like it in the early stage of my pulmonary fibrosis. If it could help my lungs, it could keep me doing what I love, singing." She also said, "I wished I could have had gene therapy before my hemorrhaging colitis got so bad." And further, she said, "I would also like gene therapy to ease the burden of caregiving on my parents and the people around me that I love."

I want to really thank the FDA for everything that you are doing for us, for listening and for giving us this opportunity to be heard today. Thank you.

MS. JACKLER: Thank you, Donna, for that presentation and for being the voice of your daughter.

Next up is Lisa Bonebrake. Lisa, are you ready**?**

MS. LISA BONEBRAKE: I am. Thank you so much.

Hi, I'm Lisa. I appreciate this opportunity to participate in the conversation. I have no financial disclosures and no slides. I live with a rare genetic kidney disease called Alport syndrome that often leads to kidney failure, hearing loss, eye conditions and other complications.

I had been misdiagnosed for more than 25 years when I started having kids, so I had no idea that I could pass down a devastating genetic kidney disease. And that's most of our community misdiagnosed more than 90 percent of the time. So, at 19, my youngest son experienced kidney failure and dialysis.

Miraculously, his older brother, who didn't inherit the disease, provided the gift of life as a living kidney donor. I should also note that I am executive director of Alport Syndrome Foundation, a U.S.-based nonprofit organization led by and dedicated to patients and families living with our rare genetic kidney disease.

My son and I both participated in a clinical trial for five years to explore an ameliorative drug to slow down the progression of our disease, but the drug didn't gain approval. But before the FDA made that decision about the drug, my son had already reached kidney failure.

My own kidney function is still in decline. With the earlier session focused on pediatrics and an overview of my disease already provided by another Alport patient, my comments are really from my perspective as an adult patient.

So based on the questions we were asked to consider in advance, before enrolling in a gene therapy trial for early stage or pre-symptomatic disease, I would want to know a few things. In layman's terms, why the scientific team that developed the drug believes it'll work in humans with my disease? What's the mechanism of action?

How will they evaluate whether I'm a good candidate or not for the therapy? For example, how will they understand whether or not there's already so much damage done in my body, even though I don't have a lot of symptoms yet, but I'm sort of beyond receiving benefit from the therapy? How will that be evaluated?

I would want to know how long the treatment will take to show signs that it's working or not. I want to know the delivery method. Is it an oral medication, a procedure, ongoing injections?

And whether this requires an all outpatient or inpatient treatment or both. I want to know what the anticipated side effects would be and which would be so troublesome that they would want to take me off the treatment. I would want to know what's going to be learned or gained from the study, when and how they're going to share how the study is going for me and for others at the end of the study.

And if the therapy given to me caused some unanticipated health problem that required some type of other medical treatment, would the study sponsor cover my healthcare needs or that fall to me to try to get coverage from my own insurance, which may be troublesome, particularly at my age. I'm almost 60. What is my risk tolerance with my rare disease?

We know that it leads to kidney failure pretty much a hundred percent of the time. So, I'm highly motivated to help find an effective treatment that will modify, repair, or cure my disease. Risk tolerance is high.

I've watched my son, and many other fellow patients deal with significant medical trauma. Even if the treatments are burdensome, I would want to participate. I don't want to spend my senior years living on dialysis or trying to find a suitable and willing living donor for someone my age.

I don't want to become a financial burden for my family or physically or emotionally. I also want my son to be able to have children without worrying that he'll have to watch them go through what he has gone through. His own life expectancy has already decreased now that he's living the kidney transplant.

Organ transplant is not a cure. As my fellow Alport patient, Andre Weinstock noted, it just isn't. These procedures are life changing, life limiting. Many people don't survive dialysis while waiting for an available organ.

The daily immunosuppressant medications required to sustain the life of the organ will eventually end the life of the donated kidney as well. And these drugs also mean living the rest of your life at major risk of infection.

So, if a potential gene therapy treatment poses a long-term cancer risk was one of the questions. So does the treatment for an organ transplant. And I'd much rather have the cure to therapy than go through dialysis and transplant.

Also just want to end with a thank you so much for being able to participate in this conversation and for the FDA helping us think ahead and get ready for genetic therapies. Thank you so much.

MS. JACKLER: Thank you, Lisa. Your timing was perfect. It was just coming on.

And thank you for sharing those perspectives. I'm sure they are shared by others as well. So, thank you for being here.

And next, Lana Escamilla is our next speaker. Lana, are you ready?

MS. LANA MARIA ESCAMILLA: I am.

MS. JACKLER: Great. Please proceed.

MS. ESCAMILLA: Oh, okay. Well, thank you for the introduction and thanks for letting me share my perspectives today.

These are my disclosures. I am a board member for Wilson's disease, and I actually was recently in a gene therapy clinical trial.

I just had the termination visit. I do not have any financial interest, but I just want to make clear that this presentation is based solely on my personal experience and personal opinions.

I was diagnosed with Wilson's disease at 22 years of age. Wilson's disease is fatal unless it's detected and treated before serious illness from copper poisoning develops. Like so many other patients with rare diseases, by the time I was officially diagnosed, I was very sick.

I was in liver failure. I was immediately put on the liver transplant list. And shortly thereafter, I lost the ability to read, write, speak coherently.

And even if I had a liver transplant, they weren't sure that I would survive that transplant.

So being diagnosed with Wilson's disease requires lifelong medications. And depending on when you're diagnosed, you might have to do some chelation. So, when I was initially diagnosed and very ill, I was fortunate because I happened to go to a hospital where they are experts with Wilson's disease. And I qualified for a clinical trial.

That clinical trial is a large part of why I'm alive today. And the study drug at that time started chelating all the copper from my system. And so, I slowly improved.

I went into the hospital in September of 2000. I left in December of 2000. And then I was able to go back to school part time.

I shortly, I graduated. And then I went to law school. And as you can see, I'm considering how sick I was, I'm pretty high functioning.

But with Wilson's disease, I have to take medication the rest of my life. I have to have a low copper diet. There's always a fear that the copper is going to build back up, and I will get sick.

And unfortunately, the drug that saved my life the first time still is not approved. So, there's the fear that if you do get sick, that there's nothing that could save you or prevent serious illness. And the current medications you take three times a day, they can cause, at least the one I'm on, causes nausea.

You have to have to get away from food, drinks. So, it's hard to comply, especially if you have a life, if you have a job. And, you know, I'm an attorney.

So sometimes I go to court, I'm in court all day long, I can't take my medication. So, there's a huge compliance issue. So, when I learned of gene therapy, I was extremely excited, as I'm sure that many people with rare diseases are, when they think of gene therapy.

So, I'm fortunate because my liver physician that I've had for over 20 years is actually an investigator for gene therapy. We discussed gene therapy, and I decided to apply for the clinical trial.

So, these are considerations that I had when I was making that decision. Or there's a few that I probably should have asked a little bit more questions about. But primarily, I want to know, you know, is gene therapy, is this trial safe? You know, what type of risks are involved?

I also want to know what type of vector is being used, and has it been used in other trials, I spent some time looking into different vectors. Knowing the potential adverse effects, you know, you want to know what those are, of course, with clinical trials, you really don't know everything.

But I also wanted to know, if I had to be on immunosuppressants, how long I had to be on those, how are those going to affect me and my body? What types of protocols are in place in the study, in case I have an adverse event from having the injection, or the gene therapy? I also want to know—

MS. JACKLER: Lana?

MS. ESCAMILLA: Yeah?

MS. JACKLER: I'm sorry, I'm sorry to interrupt, but we're at time.

MS. ESCAMILLA: Okay.

MS. JACKLER: But I just want to remind you that there is a docket, and I invite you to put whatever I had to cut, wherever I cut you off, please, you know, put those comments in the docket, and I really appreciate you taking us through those considerations, and your experience with gene therapy. Thank you.

MS. ESCAMILLA: Okay, thank you.

MS. JACKLER: All right, so our next speaker is, or speakers, rather, are Lauren Holder and Jamie Holloway. Are the two of you, is your mic open, and are you ready?

MS. LAUREN HOLDER: Yes, and we have slides.

MS. JACKLER: Okay. Tha—

MS. JAMIE HOLLOWAY: Good afternoon.

My name is Jamie Holloway, and I'm pre-symptomatic with Huntington's disease.

Looking at the Y-axis, I've ranked my willingness to enroll in clinical trials for gene therapy from zero to 100 percent. The X-axis represents which stage of HD I'm in.

I also have outlined two motivating factors, curing or delaying disease progression and scientific advancement. The pre-manifest stage is around 25 percent. This is because the disease has not caused deterioration, and we have no way to measure if a clinical trial is effective without committing to years of follow-up.

Scientific advancement is around 75 percent. This is because I strongly believe that quality of life is best preserved before neurological degeneration begins. I would be inclined to enroll in a trial if it meant that we would be closer to developing better ways of administering gene therapy in the prodromal, pre-manifest stages.

I would not enroll if I could not enroll in future clinical trials, and I would not want the adverse reactions that would result in caregiver burden. At the early manifest stage, things change. People put a lot of emphasis on quantity of life, and they see a disease that lasts for 15 to 20 years and think it is a long life.

I disagree. HD literally chips away at everything that makes me, me. So, in early manifest, I would be open to much riskier gene therapy trials. I would be open to clinical trials to explore dosage, knowing the risk would be greater.

For example, if I received a gene therapy and later developed cancer, I would view that as a merciful way to die. It is not that I do not place high value on my life. I do. It is just that HD chips away at your independence, your self-autonomy, your relationships, piece by piece until you are entombed in your body, or if you are lucky, pneumonia will set in from aspiration. With the average age of onset being between 30 and 50, while my baby watches, knowing she has a 50 percent chance of the same fate, ask yourself, which would you choose?

While this may sound bleak, I think an important takeaway is that benefit is not in the middle stages. It is in the late pre-manifest, prodromal, and early manifest stages.

In a study from 2022, 60 percent of gene-positive individuals were highly motivated to enroll in an HD clinical trial. While we all have differing views on what quality of life looks like, it is evident that we need the ability to choose, and that is what I am asking you to consider today.

MS. HOLDER: Thank you, Jamie. My name is Lauren Holder. I am a long-time patient advocate.

I am gene-positive and in the prodromal phase of HD. I want to point out that the data in this slide is IRB-approved data that was presented to the FDA during our 2022 patient listening session for the HD pre-symptomatic population. At that time, Bill Dunn, Director of Neuroscience, provided about 10 minutes of post-session remarks about the FDA's hope to treat HD patients as soon as possible.

This slide shows what Jamie and I continue to hear from others in the community. The pre-symptomatic and prodromal population of the HD community is ready and very willing to participate in clinical trials now and early on in the disease. Our sense of urgency is at an all-time high, especially with the halting of yet another clinical trial in the past couple weeks.

There is not much that would stop us from participating. For me, the only thing that would keep me from participating in future clinical trials is if I could not participate in future research, because right now I'm not looking for a cure. I'm looking for something to buy me some time until the next best thing comes along.

If that sounds desperate, it's because I am, and we are. We are running out of time. We are fighting a war with a relentless foe known as HD every single day.

Our outlook is grim right now, with several years of suffering and ultimately death being imminent. Unlike having brain cancer, we don't have a Hail Mary or any options we can try right now.

That can change with the help of the FDA, with the allowance of trial participation earlier in the disease, which all stakeholders agree is absolutely necessary in order to make a difference in people with HD, and also with other ways to accelerate the clinical trial process in HD. Some examples include more sensitive outcome measures, as the ones we currently have are not sensitive enough for early HD, biomarkers, and the use of natural control.

MS. JACKLER: I'm sorry, Lauren, I have to ask you to stop. Not because I don't want to hear more, but because we're trying to be fair to all the speakers. But, thank you both, Lauren and Jamie. The urgency came through loud and clear.

Thank you. Our next speaker is Linde Jacobs. Linde, are you ready?

MS. LINDE JACOBS: Yes, I am. Thank you. My name is Linde Jacobs. I come from a genetic family that has FTD in it. My mother there in the center passed away from the disease in 2021. She also has three siblings that are impacted by genetic FTD, as well as her mother. I have no disclosures to report.

So, a little bit more about me, my background. I'm a registered nurse. I'm a wife and a mother. Those are my two daughters in that photo.

I was a former caregiver to my mother and will be a third known generation that will be affected by a genetic mutation called MAPT, or microtubule-associated protein tau, causing FTD, or frontal temporal lobar dementia. I am a carrier for this mutation. So, at the age of 36, I am looking at about 15 years before symptoms will inevitably start impacting my brain.

So, as I said, FTD stands for frontal temporal dementia. My mutation on the MAPT gene is actually rarely used in models with FTD.

It's usually actually more commonly studied for Alzheimer's disease, as well as progressive supranuclear palsy, cortical basal degeneration, because of the involvement of the tau protein. There are current clinical trials out there for anti-tau therapies, but those that have an FTD diagnosis do not have access to these clinical trials. They're not gene editing trials, but they are even just drug trials.

That's because the FTD diagnosis does not allow them to participate in these drug trials, despite them being the mouse models in the laboratories being used to study these diseases. Testing positive for this mutation at the age of 32 basically gave me a window into a 15-year future of what was inevitably going to happen. MAPT mutations are 98% penetrant and causing changes in people's lives in their late adulthood.

Between the ages of 40 to 60 is when symptoms typically begin. And it is mainly in the personality and behavioral characteristics. Holding a professional job, loss of income, you become disinhibited, you have massive personality changes.

Similar to the HD presentation we just learned about, you lose essentially everything that makes you a unique person is lost to this disease.

So, I am one of three. Both my sisters also carry this mutation. The children to the right of that photo are all at risk. They all have a 50% chance of inheriting this gene.

While gene therapies are not really coming down the pipeline within MAPT FTD, it might not be an option for me, but I hope it is something that my kids are able to have access to, mainly with them being in this pre-symptomatic phase so that they're able to make decisions for themselves and be able to have a future free of not having to worry about what these changes will inevitably do to them.

But, as a pre-symptomatic carrier myself and with it being neurodegenerative, waiting for symptom onset is almost waiting too long. It's really making sure that you're allowing patients in the pre-symptomatic phase or within a few years of phenoconversion, the predicted phenoconversion to have access to these therapeutic trials to be able to halt the disease before it even starts to begin.

And, I see my time is running out, so thank you for the opportunity to speak.

MS. JACKLER: Thank you, Linde, for that perspective. This is very helpful, I believe, to the people who are listening. Next, we have Tammy McGuinnes.

Tammy, is your mic open? Are you ready to go?

MS. TAMMY MCGUINNESS: I'm ready to go.

MS. JACKLER: Great. Go ahead.

MS. MCGUINNESS: I'm going to take my four minutes. I'm Tammy McGuinnes.

I am a pre-symptomatic Alpha-1 patient. Five years ago, a routine CT scan revealed a pretty shocking diagnosis of bronchiectasis and mild emphysema, leading to the discovery of Alpha-1 antitrypsin deficiency. My brother also has Alpha-1 patient.

I'm lung-affected, he's liver-affected. Alpha-1 antitrypsin deficiency is a rare inherited condition that prevents the body from producing enough of a critical protein. It's a protective protein, and it's Alpha-1 antitrypsin.

Without this protein, vital organs like our lungs and liver are left vulnerable to unchecked inflammation and irreversible damage. For those of us affected, this can lead to debilitating conditions like chronic obstructive pulmonary disease, COPD, and liver disease. There's no cure, and our only option is a liver or lung transplant once the disease progresses.

I want to thank you for the opportunity to speak on behalf of the Alpha-1 Foundation and the Alpha-1 antitrypsin deficiency community. Today, I speak to you to advocate for a future where individuals with Alpha-1, both symptomatic and pre-symptomatic, have access to life-changing treatments. Enrolling pre-symptomatic individuals in clinical trials offers several advantages, including accelerating the development of new therapies and providing valuable insights into the disease progression.

The current standard of care is plasma-based augmentation therapy, a costly treatment at $100,000 to $150,000 a year, requires weekly infusions, and is often inadequate and fails to address the underlying liver complications. And note that it's hard to even qualify for infusions because they want you to be down to like a 68% breathing capacity. Gene therapy offers a promising solution, but its full potential can only be realized by including pre-symptomatic individuals in clinical trials.

As an Alpha-1 patient, I have several questions. One is what are the potential short and long-term side effects? How effective is gene therapy in preventing or slowing disease progression? How long will the effects of the gene therapy last? What kind of monitoring and follow-up will be required after treatment? And what are the potential long-term implications of gene therapy on overall health and well-being?

When considering the optimal timing for gene therapy, early intervention maximizes the potential of gene therapy by preventing disease progression, identifying biomarkers, and optimizing treatment windows. Patients have, and this is my opinion strongly, patients should have the right to weigh the potential risks and benefits of participating in clinical trials. Regulatory bodies play a crucial role in ensuring patient safety, but I believe the decision to finally enroll would be with myself and my healthcare provider.

For pre-symptomatic Alpha-1 patients, the opportunity to participate in a gene therapy clinical trial represents a powerful, proactive step. We should not be forced to wait until the disease has ravaged our organs to access

potentially life-saving treatments, and we ask the FDA to be flexible when addressing new therapies for a rare disease like Alpha-1.

There's a great need for FDA support in advancing these clinical trials, and we urgently ask the FDA to consider the accept surrogate endpoints like CT densitometry to accelerate the trial process, grant accelerated approval and priority review for gene therapies to expedite the development of treatments, and encourage adaptive trial designs to make trials more responsive and feasible for our rare patient population.

By allowing pre-symptomatic, sorry, I'm trying to read fast, the FDA can give our families a fighting chance for a future fear from the fear of irreversible disease. Alpha-1 antitrypsin is a serious altering condition by prioritizing research, advocating for policy changes, and supporting organizations like the Alpha-1 Foundation that can work to improve the lives of individuals with Alpha-1.

And thank you to the FDA for holding this session, and I want to thank you for your time and consideration. I did it.

MS. JACKLER: Thank you very much. All right, so our next speaker is Elisabeth Page. Elisabeth, are you ready?

MS. ELISABETH PAGE: Yes, I am.

MS. JACKLER: There you go.

MS. PAGE: Good afternoon. My name is Elisabeth Page. I was diagnosed with Leukoencephalopathy with calcifications and cysts, a rare and serious condition with no approved treatment.

After a long journey that started when I was just three months old, I had seizures and was put on very strong medication. And after a year, the seizures stopped. Everything seemed normal until I was about four years old and started having really bad anxiety about going to school.

During therapy, the doctor decided to do an MRI to get a baseline of my brain, and that's when they found the calcifications and cysts. That was the start of a very long journey to figure out what was wrong. No one had answers.

Later, my youngest sister started having problems in school, and they did an MRI on her, too. Unfortunately, she has the same calcifications and cysts. We spent years seeing doctors up and down the East Coast until we joined a trial at John Hopkins working with Dr. Yanick Crow in the UK. That's when they found the DNA sequence causing our condition. Since then, we've been working with Dr. Fraser and her team at Children's National. This disease has impacted my life a lot.

For example, at age 21, I decided to have my tubes tied because I didn't think I would be able to care for a child properly and worried about how pregnancy may affect my health. After having access to a treatment that could slow, stop, or even reverse this disease would be life-changing. It can let me live a normal life, not being stuck in hospitals or missing school because of seizures and hospital stays.

In my opinion, the most important factor in a decision to participate in a clinical trial is a clear explanation of known and possible risks and an honest explanation of what long-term outcomes of those risks might be. I'm keeping an open mind and want to learn all about the risk and possible benefits of any therapy. Even though I've come to terms with this disease, I'm ready to try anything that might help.

Thank you for giving me this opportunity.

MS. JACKLER: Thank you, Elizabeth. We appreciate those comments. And we hear the difficult decisions you've already had to make and then the things that you hope to be able to consider in the future. So, thank you again.

Our next speaker is Becca Reef. Becca, I'm handing it over to you.

MS. BECCA REEF: Thank you so much. Hi, everyone. My name is Becca and I serve as the scientific coordinator for the Adult Polyglucosan Body Disease Research Foundation.

Today, I have the privilege of amplifying the voice of our collective patient community. APBD is a rare adult-onset recessive neurodegenerative disease for which there are no FDA-approved treatment options. It is a condition within the spectrum of glycogen storage disease four that is characterized by pathogenic variants in the GBE1 gene.

The age at onset, symptomatic presentation, severity, and progression are variable. Symptoms include peripheral neuropathy, bladder dysfunction, decreased energy, and in some cases, cognitive decline. Individuals can begin experiencing symptoms as early as age 35.

They eventually lose the ability to walk, stand, stay continent, stay awake, perform at work, and socialize. They're robbed of nearly every aspect of their independent adult lives. Promising gene therapy approaches, small molecule drugs, and ASOs are in preclinical development, and as our community looks forward to these clinical trials, we must recognize some challenges that lie ahead that also resonate with other adult-onset conditions.

Individuals with pre-symptomatic genetic diagnosis represent a subset of our community that provides a window of opportunity into the earliest stages of disease. Advances in screening for genetic testing have resulted in increased early awareness for countless families that face the unknown, a many years-long waiting game for symptoms to manifest.

During our 2021 listening session with the FDA, several of our individuals in our community testified that they are waiting for a treatment before APBD manifests. The sacrifices that they would have to consider by participation in trials are miniscule to the sacrifices they may have to make if they become symptomatic.

So, we share many of the same key questions that others have discussed. Will participation limit access to other potentially more effective treatments in the future? Are treatment targets reflective of symptoms and treatment outcomes that patients and caregivers value most? How can we capture the nuances of this unique population in endpoint design?

How do we incentivize pharmaceutical investment when outcomes are assessed using unconventional metrics? How invasive is the treatment? What are short and longer-term side effects? How is quality of life affected?

And of course, so many questions revolving around logistics and equity, such as does participation require significant lifestyle adjustments, such as a leave of absence or relocation? What are the costs, inclusion, and exclusion criteria? How is this communicated to patients? And can patients, especially pre-symptomatic patients, participate without having to disclose the diagnosis to others, such as an employer? Can the trial be adapted to fit into daily life?

So, taking all of these questions into account, our community wants to see tangible initiatives to increase support and partnership for patients, so they feel actively informed about any risks they may be accepting.

Many pre-symptomatically diagnosed patients find themselves navigating unfamiliar and overwhelming territory. To better support these individuals, we encourage the FDA to develop or work with patient advocacy organizations, industry sponsors, or other stakeholders to develop comprehensive tools to help families navigate the complex world of clinical trial participation with confidence and clarity. This may look like a guide for those pre-symptomatically diagnosed and feeling like they're drinking out of a fire hose.

We must put the onus on us to communicate both opportunities and the preparations needed to participate in trial design or trials themselves effectively. This clear guidance is essential for patients to assess personal fit in potential trials, and through these steps we may also be able to create validated and accepted surveys that provide a glimpse into the risk-benefit conversations that the Rare Disease Patient Advocacy Organizations can build from and customize.

And I see that my time is winding down, so I've really enjoyed hearing from all of my peer-allied organizations today as well, and I think that together we have a really exciting future.

MS. JACKLER: Thank you, Becca. Thank you for representing the perspective of the APBD community and helping us understand sort of all the different types of questions that your community is trying to get answers for or would like answers for. Our next speaker is Jean Swidler.

Jean, you have the floor.

MS. JEAN SWIDLER: Thank you so much. Thank you for hosting this discussion, and I echo the thanks to all the fellow panelists for sharing so thoughtfully.

So, I'm coming from a family impacted by inherited genetic ALS and FTD. ALS is progressive and fatal paralysis leading to death within a few years. My mother, grandmother, great-grandfather, my aunt died from it.

My uncle is currently living with it, and I live with my husband and daughter, and I'm a pre-symptomatic carrier. My gene also causes FTD, which Lindy told you about very touchingly. N

So, let's just get this out of the way. Early trials in pre-symptomatic populations may be pre-symptomatic and fully functional, but the people in the trial will not be healthy, should not be considered healthy.

This is a common scenario where people are fully functional but not healthy. A woman with a cancerous lump in her breast is fully functional, but she is not healthy. Someone with high blood pressure is fully functional, but they need to get that high blood pressure taken care of.

And a person with rising creatine levels may be fully functional, but their kidneys are not healthy, and they need intervention.

Just to get it out of the way, as an advocate, I think we can accept for fully functional adults, before we take a novel gene therapy medication, safety should be somewhat established.

First, in human testing of gene therapies would appropriately be tested first in symptomatic patients in these diseases. But after some very initial safety data is established, early cohorts of those at risk with appropriate biological markers showing harm is occurring to the body would be, and that could be modified in a trial and measured, would be appropriate for testing.

This is not just about making things better for people who are getting the earlier gene therapy. This is about curing these diseases full stop.

So, unknowns that are better solved with earlier testing include, would it work better earlier? That's a pretty clear one. Is the safety profile the same earlier?

That's also something to consider. Will benefits be maintained? In a disease like ALS or some of these other diseases, you might have an efficacious drug that would still only prolong survival by a few years.

Would the benefit last for decades? You can only tell that if you're giving it to somebody who's able to live decades longer with the benefit. And finally, just to get down to brass tacks, many people don't want to pay for gene therapies when looking at quality life year assessments.

So, if you're rescuing function when somebody's already had a lot of function loss, then their quality of life here is not judged to be very much by these cruel people who look at things that way. But if you have full function, your quality life here is going to be valued more by these people who give these unfair assessments of things.

So, I think that we all need to continue pushing. And just like the last speaker said, let's all do this together. So, I look forward to being in touch with people.

And thank you so much for the FDA and for all the other speakers. Thanks.

MS. JACKLER: Thank you, Jean. That was just like all the other speakers. What you're saying is very helpful. We appreciate that. We have one more speaker, and that is Sonia Vallabh. Sonia, are you ready?

MS. SONIA VALLABH: Yes, I am.

MS. JACKLER: All right.

MS. VALLABH: Hi. Thank you. So, I'm Sonia Vallabh. I'm at the Broad Institute in Cambridge.And I'll be talking about prion disease.

So, these are photos from my wedding 15 years ago. That's my mom helping me get ready. She was 51 years old. She was healthy. But it was only a few months later that she went into sort of lightning speed neurological catastrophe.

We did not know at the time what to call this. No one knew. And we weren't able to get a diagnosis in her lifetime. But suffice to say that within a few weeks, she had gone from healthy to full-blown dementia, and then within a few more weeks, life support. I had never imagined a disease could move that fast.

So, we learned after she died from her autopsy that she had died of genetic prion disease and that I was at 50-50 risk of having inherited her mutation.

So, I got predictive genetic testing. Here's my report. So, I did inherit her mutation. So, what does this mean for me?

High penetrance, so really near certainty of developing the disease at some point in adulthood. But unlike other neurodegenerative diseases, prion disease has really rapid kinetics before and after onset. So, it does seem like people remain completely healthy, even on the molecular level, until symptom onset. And then the average patient will die in a few months, less than six months.

So, long story short, my husband and I left our old careers after we got this news and retrained in biomedicine in order to work on developing a therapy, got our PhDs, ended up here at the Broad, where we now run our own lab.

So, this is us, and, you know, we're super, super mission-focused on a therapy in our lifetime.

So, there's a lot of alphabet soup around prion disease. You hear CJD, FFI. Not all cases are genetic. 85% are sporadic, and early symptoms can be extremely various. So, there's a lot of heterogeneity.

But we're very lucky to have one molecular mechanism, one gene, one RNA, one protein. This underlies every case, and that one protein can misfold into a protein-only pathogen or a prion.

So, we are acutely focused on lowering prion protein because that is the fuel to the fire.

We have been working with prion protein-lowering therapies for a while, and here you can see the effects of early treatment. In the top plot, this is a survival curve. Early symptomatic treatment, bottom left. Advanced symptomatic treatment, when most patients are caught, symptomatic patients, bottom right.

So, I hope this says it all. In such a rapid disease, the amount that you can do after symptom onset is extremely limited.

And in the meantime, here's our own natural history data showing that pre-symptomatic carriers do not show signs of neuronal damage. They really appear healthy.

So, what would we need to do so-called primary prevention? Treat healthy people just based on their genotype, based on their DNA? I think these are the things that we need, and I think in prion disease, we have it.

Single gene, we know who's at risk. We have clear evidence that if you shut off the gene, disease could not occur.

We have clear evidence that shutting off the gene is safe. This is a non-essential gene and protein, and we can measure in spinal fluid that the amount of PRP has been reduced in the brain.

So, I want to make the case that, you know, this is a very clear-cut call for primary prevention, where the single disease-causing molecule can be reduced in the brain, and that is reasonably likely to predict clinical benefit.

And this is why this matters to me. This is me and my kids. So, I want to stay alive for them. Thank you.

MS. JACKLER: Thank you, Sonia. Thank you for taking us through the particulars of prion disease in relation to early treatment with gene therapy. And thank you to all of our session two speakers for sharing your perspective.

So, we will now take a five-minute break, and then the FDA panelists will ask their follow-up questions. Let's see. So, please be back at 3:55. As a reminder, where are we? 3:46? Let's see.

What? Yeah. So, let's actually be back at 3:50, if that's okay.

And as a reminder, we're asking our session two speakers to return after the break, as our FDA panelists may have some follow-up questions specifically for you.

So, thank you, and I will see you in five minutes.

FDA Panelist Questions

MS. JACKLER: Hello, and welcome back. So, the FDA panelists have been listening intently, and they value your input. And so, I'm now going to open this up to the FDA panel to ask any clarifying questions or follow-ups. And our first panelist who will be asking questions is Anam Tariq.

Anam, go ahead.

MS. ANAM TARIQ: Thank you, Karen. And I would like to thank all of the speakers for sharing your perspectives, and these powerful stories truly goes a long way. And we have a deep appreciation and gratitude for you coming on today and sharing with us.

My question is specifically for Ms. Lana and Jamie. However, I can open it up to others as well. For women of childbearing ages, how likely are you to enroll in this gene therapy or any type of gene therapy trial that may be offered when the information in terms of the safety is still ongoing, and we may not know how it may impact your fertility at that time or in the future?

MS. ESCAMILLA: So, I can jump in if you'd like. So, for me, I actually, my children are grown, which played a huge part in my decision to actually go with the clinical therapy. My youngest is in college, so I don't have to care for them as much as I did when they were younger.

I think that, and I actually have had a hysterectomy, so I wasn't worried about that. But children are important to me, and I think that if I was still trying to have children, I would not have gone forward with the gene therapy at this time. However, I'm fairly healthy now, and I think that it probably is, I'm guessing case by case, if it's your life and you might not be able to have children anyways, it could be different, if that makes sense.

MS. TARIQ: Great, thank you so much, Lana, for sharing that. Anybody else would like to answer this question?

MS. VALLABH: Yeah, I'll just share a perspective from my community. So, for people at risk for genetic prion disease, I think that people feel afraid that they are going to be, like, if they're women of childbearing age, I think they feel afraid that they're going to be discriminated against and excluded from trials, and really want the opportunity, like, as Lana pointed out, in this case, people are worried about not living, you know, the rest of their life. So, they are very much willing to participate, and I think it is a case-by-case basis.

For some people, you know, staying off therapy and preserving their ability to have kids might be more important, but for some people in our community, they would go for it, and they want to be able to have that choice.

DR. TARIQ: Thank you so much for sh—

MS. HOLLOWAY: I was already, actually had had a tubal and already had my children when I found out that my family had Huntington's disease, but I can say that while reproductive health does matter, and choices in family parenting are very important, some of us already have children, and we would like to be there to raise the ones that we have. There are other options as well. There's adoption, there's foster care, there's being really involved with maybe nieces and nephews, or just a lot of other ways, too, that you can nurture.

And so, I would say that that's definitely something that I would have chosen to not worry about if I had been of childbearing age and could live.

DR. TARIQ: Thank you, and I see Lauren's hand is up as well.

MS. HOLDER: Yeah, I just wanted to follow up on that because I actually have a four-year-old and a six-year-old. So, for me personally, as I want to just echo what Jamie is saying, that some of us want to be here and able to live, and if we're provided that, then the reproductive side of it is not as important, because we want to be able to have a quality of life.

DR. TARIQ: It's very understandable. Thank you so much for sharing that. I will hand over the mic now to Osman to ask his question.

DR. OSMAN YOGURTCU: Thanks, Anam. Hi, everyone. My name is Osman Yogurtcu.

I'm a senior staff fellow at the Office of Biostatistics and Pharmacovigilance, and first, I want to thank all of the speakers today. You really provided so much helpful information for our concentration. Much appreciated.

My question is, if you or a loved one have previously participated in a clinical trial for a rare disease or condition that has already progressed to a more advanced stage, we would love to hear about your experiences. And specifically, we are interested in learning from your insights and perspectives on how participating in a clinical trial at an earlier stage, for example, pre-symptomatic, might have differed from your actual experience.

Actually, your experiences and reflections could provide valuable guidance for individuals who are considering participating in clinical trials at an earlier stage of a disease, and I think Ms. Escamilla might be a good candidate, and I see Ms. Swidler. Please go ahead.

MS. SWIDLER: So, just as a leader in the community, there have been very few tries in the genetic ALS and FDD community for pre-symptomatic clinical trials. There have been a few, and people have had inclusion based on biomarkers, which are not routinely returned to people in clinical practice, and it's a hard thing for those people when the trial ends, and there's no outcome on the trial yet, and they were told that they were included based on a bad biomarker, and they're not yet symptomatic still, so these are things to really be considered when designing these things. Thank you.

DR. YOGURTCU: And Ms. Holder? You're muted.

MS. HOLDER: There we go. I actually got to participate in a clinical trial recently for a symptomatic treatment for HD. It's cognitive, focused on cognitive, and it is the only clinical trial that I could get into, even though I have a diagnosis of neurocognitive disorder related to HD, because I was told I'm too healthy to participate in clinical trials.

That's sometimes very devastating and discouraging to hear, because I'm gene positive, and I'm showing symptoms, so how am I too healthy, because my reality is death. That's where we're headed. We have nothing on the horizon other than, thankfully, a gene therapy.

So, it's discouraging to hear that, and to be able to participate in clinical trial that I did was empowering and made me feel really wonderful, even though they had to halt that trial, and they did not see benefit.

For me, it doesn't feel like a loss, because I still was able to be part of such an important thing, and it's led us to more information in a cognitive space that we didn't have before.

DR. YOGURTCU: Okay. And Ms. Appell?

MS. APPELL: I just think that the organizations and the groups that have been involved in clinical trials makes people really ready to do gene therapy trials, because we're research-ready adult cohorts, and I think a lot in gene therapy is going to need a bit of pioneering, a bunch of pioneers, personally. And I think that those that have gone into clinical trials, we've had two that have not proved successful for us. We still don't have a treatment, but we

certainly have a research-ready cohort of people that understand clinical trials, that understand risk, and we did our PFDD meeting, that we understand risk versus benefit.

It's a very trained population, and I think that that's important and can be helpful.

DR. YOGURTCU: Thank you. Ms. McGuinnes?

MS. MCGUINNESS: Yes. Hi. Thank you. I have only qualified for one clinical trial, and I did it immediately. I'm considered healthy, even though I have bronchiectasis and mild emphysema. I can still breathe well enough, so I'm not sick enough to be in a trial.

I did qualify for it. It's probably not going to go anywhere because they didn't get enough positive results, but you know, I felt also so empowered just to be able to do that, to be able to do that for my other fellow alphas because some of them have to give up infusions to be on a trial, and that decreases their breathing ability, and so coming off infusions is really dangerous.

Now, I don't qualify for infusions because I can't afford $150,000 a year, and my insurance won't pay for it because I'm not sick enough yet, but I would gladly participate in just about any trial to try to progress this looking for a treatment because this is not, you know, getting a transplant, obviously you have limited life expectancy there too, right, because the average organ is good for 10 years, and you're lucky if you get more, so I would look at, you know, a lot of options, but I was so thankful to qualify for one, and I would do more if I could qualify, but I just don't.

DR. YOGURTCU: Thank you. Ms. Bonebrake?

MS. BONEBRAKE: I would say one thing that I think is really important, so many of us here I see today are from patient organizations. Most of us have started or are involved in a high-level patient organization because it affects our own family, and we've become, you know, real experts in our own disease, not only in our own bodies, but in all the data and research and helping collect human data and all of that.

And I think one piece that is concerning to me, I participated in five years in a clinical trial, the one and only one that moved forward but did not get approved, participated for five years, and part of the issue became the study design. And I think what we really want to communicate as patients is that we want to help and are in a great position to help clinical trial, shaping clinical trials as patient organizations.

We're all involved in research. We know where the patients live. We know what their experiences are and how to shape a clinical trial that can quickly and effectively enroll patients and how they will participate, but if companies don't come to us early enough to help participate, we can't help them invest their very minimal funds for research in rare disease.

We can help them use their funds more wisely and help prepare and shape better clinical trials and the way they're designed to effectively enroll patients and help them with glitches. We can be helpful, but we need those

companies to come to us early, early in the preclinical process, so I just want to really advocate for that, not only in amelioratives but in genetic therapy as well. Thanks so much.

DR. YOGURTCU: Thank you all for all the wonderful answers, and I'll hand it over to Vaishali.

DR. POPAT: Yeah, thank you so much, and I really want to thank all the speakers here. Such a heartfelt and inspiring discussions here.

My question is for people who have already taken part into clinical trials. What role your physician or healthcare provider played in that decision making for you?

MS. HOLDER: For me, my healthcare provider, my primary care didn't really play a role in that. I went searching for research and actually fly to a site outside of my state in order to participate, so they didn't really—I mean, we're not seen.

Pre-symptomatic isn't seen at a neurologist. We're told there's no point right now if you don't have movement. That's what I was told, and I decided that wasn't good enough, and so I went and found somebody who helped.

DR. POPAT: Okay, so I'm just going to, you know, there are four people who have raised hands, so one after other, as you appear on my screen, I'm going to call the name.

So, Lisa Bonebrake?

MS. BONEBRAKE: Thank you. Yeah, no doctor brought any clinical trial to me. It really came through our patient organization sharing information with us, and then I took that information to my nephrologist and said, what do you think about this? Is the science solid?

And that made me feel confident because my nephrologist said, look, there's nothing out there for you or your son. Nothing.

And at the time, neither one of us had very, you know, we weren't very far along in our disease, but she said, look, there's nothing out there for you.

And she did say, look, this may not benefit you at all, which turned out to be the case, but it'll definitely benefit your community to get new answers and new information. And so, we both were motivated by that, but it was really on us to find a clinical trial.

DR. POPAT: Thank you. Tammy?

MS. MCGUINNESS: So, I guess I'm maybe pretty lucky. My pulmonary specialist is the one who brought it up that I should look into this trial. Now, I live in the state of Washington and my Alpha-1 specialist is in New York because there's just not a lot of people that know about Alpha-1.

And then I went to a study in California because it was easier for me to get to California than it would be for me to get to New York. But she was, the Alpha-1 specialist, the doctors are really tied into all the clinical research.

And so, they're pretty good about contacting us and telling us when we should do it. And the Alpha-1 foundation, if you join their research, they will send you a link that says, here's a new trial. You might want to consider it.

So, I think it's a pretty good tight knit group and a lot of communication.

DR. POPAT: Thank you. Donna Appell?

MS. APPELL: Our community has most trouble trying to get their clinicians to just know what Hermansky-Pudlak syndrome is. So, no one has recommended any sort of, even a standard of care gets to be difficult from any of our care providers.

So, it's only the NIH and the FDA. It's only, this is home where people actually know what it is and it's nowhere else. So just be assured that we're not finding research from anywhere but the organizations.

DR. POPAT: Thank you. And Lana Escamilla?

MS. ESCAMILLA: Thank you. So, I'm really fortunate. I've actually been part of three clinical trials.

The first one I mentioned when I was diagnosed at that point, I was probably pretty close to, I mean, I was being taken care of by a caregiver. And I know the doctors brought that to my parents and that definitely saved my life. And they were, I was actually able to stay in the hospital the entire time.

So that was great. As I progressed, the second one I did was actually about four years ago. And I asked my doctor about it.

I have the same doctor I mentioned that. I actually heard from my sister who's a physician's assistant about it, but he was an investigator and I started. And with that trial, unfortunately, they stopped it before it was completed.

And I had planned on continuing with the compassion care program. And my doctor again said, well, maybe you'll qualify for gene therapy. There's a lot going on with this.

And so, he's an amazing advocate. And I can tell you, I don't know that I would have done it without having a doctor such as him. He called me on the phone multiple times before the procedure to make sure I was comfortable.

If I had more questions, he actually stayed at the hospital the entire time when they did that. And I will say at least for Wilson's disease, I think that we're pretty fortunate. We have an association that has identified centers of excellence and the doctors at those centers are very, very good with communication, encouragement, and trying to promote more trials and better standards of care.

And I really hope that the other groups here, you know, have doctors that can start doing that for them too, because I know that as a group, we're very fortunate to have those doctors available to us.

DR. POPAT: Mm-hmm. Thank you. Now, last question I have for the group is that earlier when we were talking about children, we talked about how people feel about the control group. And if you're looking at 100%

penetrance of the disease, then it really doesn't make sense to sort of really enforce a control group in the clinical trial design, especially if you have a really good natural history data.

But when you're looking at the situation where you have either asymptomatic patient with variable penetrance, meaning, you know, we don't know for sure if this patient is going to, you know, develop the symptoms or not. And also, you know, let's say milder disease, you know, what do you guys think about control group in that situation? Because, you know, we also heard from a couple of patients here that they participated in a clinical trial, but it really did not show a difference.

And usually, you know, when you have a control group, then you can, you know, compare to the current standard of care and other factors. So just wanted to hear from you all, what do you think about control group in somewhat, you know, situation where it's not 100% that natural history shows there is certain death or certain manifestation of disease?

MS. SWIDLER: I'll just jump in.

DR. POPAT: Sure.

MS. SWIDLER: So, there in ALS and FTD genes, there can be situations with reduced penetrance, and there are signs that are already proven to be modifiable pre-symptomatically. So that's definitely where I would be thinking that would be the evidence for whether something works or doesn't work.

But as we've heard, that's not the case for everything. And if we can know that the drug works with biological measurements or with clinical outcomes, then the case for having open label makes sense. And I believe that's how this gene therapy for sickle cell was approved.

So clearly it can work. But if it's more dicey, and we're not really sure what we're seeing, then control groups can still make sense. And we need answers, most of all, and we need insurers to pay.

And so there needs to be good evidence. So, I would just say that. Thank you.

DR. POPAT: Thank you. And Sonia?

MS. VALLABH: Sure. So, the trial design that I spoke about was like fully pre-symptomatic, right? Primary prevention. And in my community, there's a lot of debate over whether placebo is ethical.

I think that in a fully pre-symptomatic trial, where you could get a biomarker readout of whether you're lowering the causal protein in six months, and ideally in that time, no one converts, but you can monitor people really closely. And if a placebo treated individual starts to show any sign of conversion, then you get them onto treatment. I think that in that scenario, I feel much more comfortable with the idea of placebo, where it's short term and we're not randomizing anyone to the death, because we're all fully pre-symptomatic.

We do have, so my mutation and others in this gene are basically fully penetrant. We do have less penetrant mutations in the prion protein gene. And in those scenarios, I think it really varies from person to person, how they perceive their risk and how much it impacts their quality of life.

If someone watched their parent die of prion disease, and they know, you know, this is only a, you know, this is a moderately penetrant variant, nevertheless, the risk is very present to them. And I think it impacts their quality of life negatively to the extent that they might choose to be part of a preventive trial. And I think they could fully contribute to that biomarker endpoint.

Their lower risk of ever converting to symptomatic disease doesn't sap the power from the trial. So that, if it was up to me, I would put in the hands of those individuals, depending on how they perceive their risk and how much it's hurting them every day.

DR. POPAT: Thank you. And I think we can end with Ms. Jamie?

MS. HOLLOWAY: If you noticed in my presentation, one of the things that I put was my desire to cure or delay the disease versus scientific advancement. I am not naive to the fact that I know that there are going to be clinical trials where I might need to get a placebo and I'm okay with that. What I want is just the opportunity to have a choice and make a movement forward.

So, I, in my personal opinion, like I don't think that that's an issue. I think for our space, it's a little bit more difficult because when we're in the pre-symptomatic stage or the early manifest stage, that's when we are most aware of who we are, how this medication is truly affecting us. Once we get into the middle stages, it's much more like our caregiver has to report those things just from the way the disease deteriorates.

So, I do believe that if we were able to have gene therapies, placebo or not earlier on, we're going to get much better data and we're going to be able to be more successful.

DR: POPAT: Thank you.

MS. JACKLER: Thank you all.

DR. POPAT: Back to Karen.

MS. JACKLER: Thank you, Vaishali. Thank you. That was amazing. We're a little bit over time.

I wish I could tell you; I had all the time to tell you how wonderful that was. And so, thank you all, not just in this session, but the session before. We had 36 experts here in all these various diseases. But thank you all so much.

And I'm going to pass this over to, back to Lorrie McNeill, who opened this fabulous meeting for us for her to wrap this up. Thank you. Thank you all very much.

Closing Remarks

MS. MCNEILL: Thanks so much, Karen. And thank you all for attending today's listening meeting. And a special thank you to all of the public speakers for taking the time to be a part of the meeting.

Your time and participation today, as you've heard from our panelists, are definitely helping to advance the development of gene therapy products for years to come.

As a reminder, a recording of today's event will be posted on FDA.gov in the coming weeks. If you have additional comments to share, and for those of you who are unable to finish your comments, we encourage you to add those to the docket, which will be open for public comment until February 3rd, 2025.

You'll see in the chat a link to regulations.gov. So, to access the docket on that website, type in FDA.2024-N-4065 in the search bar.

In the months following the meeting, we will issue a report summarizing the views expressed and the comments from the docket. This report will be published on the FDA website.

And you can find more information about this meeting on FDA.gov, which will include a link in the chat. Thank you again for joining and have a great afternoon.