UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

FDA CBER Patient Listening Meeting #1: Patient and Care Partner Perspectives on Safety Considerations for Approved Gene Therapy Treatments for Rare Diseases

September 20, 2024

Contents

Welcome

MS. LORRIE MCNEILL: Hello, everyone. Thank you for joining us for our public patient listening meeting. Today's Patient Listening Meeting is hosted by the Center for Biologics Evaluation and Research, or CBER, at the U.S. Food and Drug Administration (FDA). My name is Lorrie McNeill, and I'm the Director of the Office of Communication, Outreach, and Development at CBER. I will be the meeting facilitator for the event.

I'm very pleased to welcome you all here today as we hear from patients, caregivers, and advocates on their understanding and expectations regarding safety considerations for approved gene therapy treatments for rare diseases. We appreciate all of you joining us for today's event so that we can hear your perspectives.

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 for today on the following topics:

- Session 1: Patient and caregiver safety considerations in decision making about gene therapy
- Session 2: Partnering with patients and caregivers on long-term studies after receiving a gene therapy

Each session will begin with a brief presentation from FDA. Then we will move into the listening portion for each session, where we will hear from patients and caregivers who have kindly volunteered to share their perspectives on today's topics. At the end of each session, we will have a few minutes for our FDA staff to ask our speakers follow-up questions.

Please note that 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 we ask may bring up difficult emotions. We very much appreciate your willingness to share your perspectives during today's event.

There are just a few housekeeping items that I'd like to share. Today's event is being recorded, and the recording and event materials will be posted on the FDA website in a few weeks, including a transcript. Closed captioning for this event is available directly in Zoom. We ask that you please only use the chat box to report technical difficulties. For our confirmed speakers, your mic and camera access will be available during your assigned session. Those presenting during Session 1 will receive their microphone and camera access shortly after Dr. Marks's opening remarks.

Throughout the afternoon, we expect that the presentations will likely generate additional ideas and comments. Should this happen, we encourage you to submit your feedback to the docket, which is available on www.regulations.gov and will remain open until November 19. The docket number is FDA-2024-N-3208. The presentations and docket comments will be used to develop a meeting summary.

And with that, I'll pass things over to Dr. Marks for opening comments.

Opening Remarks

DR. PETER MARKS: Welcome and thank you so much for joining this patient listening meeting.

During the meeting, we hope to provide some information in a few sessions on what we're doing at the Agency to help facilitate the development and approval of gene therapies for rare diseases. But most importantly, we're looking forward to hearing your perspectives on the safety considerations for approved gene therapies and long-term follow-up.

Our Center has a deep and abiding commitment to advancing the field of genetic medicine in order to bring its benefits to the largest number of people, in this country and globally. To achieve that goal, we're collaborating with many different partners.

Within FDA, we're working hand in hand with the Center for Drug Evaluation and Research, or CDER, to establish the FDA Rare Disease Hub, which will serve as a one-stop point of entry into the Agency for rare disease issues and for the rare disease community. It will also serve as a guiding force to align and coordinate the actions across our centers.

Outside of FDA, we're collaborating with partners at the National Center for the Advancement of Translational Sciences (NCATS) at the National Institutes of Health (NIH) and with the Bespoke Gene Therapy Consortium (BGTC) to try to advance the manufacturing and clinical study of gene therapies. We're also collaborating at a global level to try to bring these potentially transformative treatments to the greatest number of people in medical need. For example, to help more individuals get timely access to gene therapy, we're collaborating with our European colleagues to resolve differences in technical requirements in order to be able to collaboratively review gene therapy applications, potentially speeding multinational access. And to help prepare countries underserved by medical advances like gene therapy, we're working with the World Health Organization (WHO) to help educate the regulatory authorities in these regions and assist them in developing the necessary legal frameworks for the use of cell and gene therapies.

So I hope this gives you a flavor. It just describes some of the things we're doing; it's not all-inclusive. You'll hear more from others later. But it hopefully gives you an idea of what we're doing in this space.

But I'll now return to our primary purpose today, which is to hear from you and to better understand your issues or concerns regarding safety and long-term follow-up of gene therapy products. What you tell us is of the greatest importance as we move forward. And we'll be listening closely. With the knowledge that we gain, we'll work to address our strategy to best address concerns that are brought up.

So thank you again for taking the time to participate today. I very much look forward to listening to the meeting.

MS. MCNEILL: Thank you, Dr. Marks.

Polling Questions

MS. MCNEILL: 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 caregivers participating in and attending the meeting today. This will be the first of three polling sessions that we will have during the meeting. These questions are only intended for patients and their care partners. If you are not a patient or care partner, please refrain from answering today's polling questions.

Please note: During this meeting, we'll be using the terms *caregiver* and *care partner* interchangeably to mean someone who is involved in the care of the person with the 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.

- Question 1: Geographically, where do you live?
    - Pacific time zone
    - Mountain time zone
    - Central time zone
    - Eastern time zone
    - Outside of the United States

- Question 2: How would you describe your level of knowledge of gene therapies?
    - "I am an expert"
    - "I know a great deal"
    - "I know some"
    - "I know very little"
    - "I have no knowledge of this topic"

- Question 3: What does gene therapy mean to you as a patient or care partner? Please

select the one option you can relate to the most:

- "A potential treatment to slow progression of disease"
- "A potential treatment to reverse physical and mental impacts of the disease"
- "A potential treatment for my disease prior to developing symptoms"
- "A potential treatment to cure the disease at any stage"
- "A potential treatment to reduce the burden of symptoms on its own or with other treatment"
- "It is worrisome, and I would need to understand much more about it"

- Question 4: How do you prefer to receive information about the risks of gene therapy? Please select as many as apply:
  - "From my health care provider"
  - "Communication from a study where you or your loved one is a participant (for example, from the registry or study newsletter, study doctor, or research coordinator)"
  - "Product manufacturer of a gene therapy you or your loved one have used or intend to use"
  - "The FDA website"
  - "Scientific literature"
  - "Social media and/or online forums"
  - "Other patients"
  - "Patient advocacy organizations"
  - "Other"

- Question 5: We would like to know about the patients and care partners joining today's event. Please select the response that best describes you:
  - "A patient who has received gene therapy"
  - "A patient considering an available gene therapy"
  - "A care partner for someone who has received a gene therapy"
  - "A care partner for someone considering a gene therapy"
  - "I am not considering a gene therapy for myself or my loved one's disease at this time"
  - "I haven't received a gene therapy, but I would consider it if one were available for my or my loved one's disease or condition"

- Question 6: How would you describe you or your loved one's genetic disease?
  - "It is fatal or disabling in childhood"
  - "It developed suddenly and is fatal or quickly disabling"
  - "It worsens in severity slowly over a period of decades"
  - "It is not disabling or fatal but significantly impacts daily life"

Thank you.

We will now move into the public comment portion of today's meeting. But first, I want 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 for everyone.

Speakers, we greatly appreciate your interest in speaking at today's meeting. We will introduce each speaker so that you may begin your presentation. When it is your turn to speak, you will be asked to unmute yourself. Once your presentation is completed, 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 that you have been promoted to a panelist. Please proceed so that you can get your microphone access. For those who submitted slides, your slide presentations have been added to this master slide deck. When speaking, please let us know when to advance the slides. Please state your name and your affiliation at the beginning of your presentation.

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 have 4 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.

Lastly, each session will end with an opportunity for FDA to ask clarifying questions. I'd like to take a moment to introduce the subject matter experts from CBER who are serving on today's panel.

From the Office of Therapeutic Products (OTP), I'd like to introduce:

- Dr. Shelby Elenburg, the Clinical Team Lead in the Office of Clinical Evaluation, Division of Clinical Evaluation General Medicine in the General Medicine Branch 1
- Dr. Avanti Golikeri, Medical Officer, Office of Clinical Evaluation, Division of Clinical Evaluation General Medicine, also in the General Medicine Branch 1
- Dr. Megha Kaushal, Branch Chief, Office of Clinical Evaluation, Division of Clinical Evaluation Hematology, Benign Hematology Branch

And from the Office of Biostatistics and Pharmacovigilance, I'd like to introduce:

- Dr. Richard Forshee, Deputy Director

- Dr. Larissa Lapteva, Associate Director
- Dr. Adamma Mba-Jonas, Branch Chief, Division of Pharmacovigilance, Pharmacovigilance Branch 1
- Dr. Xinyi Ng, Visiting Scientist, Benefit-Risk Assessment Branch, Division of Analytics and Benefit-Risk Assessment

Thank you to our panelists for your time today.

I will now turn it over to Dr. Anne Rowzee from the Office of Therapeutic Products, who will be the moderator for Session 1.

Session 1: Patient and Caregiver Safety Considerations in Decision Making About Gene Therapy

DR. ANNE ROWZEE: Hello, everyone. My name is Anne Rowzee. I'm an Associate Director for Policy in FDA's Office of Therapeutic Products, or OTP. And like Lorrie said, I'll be the moderator for Session 1.

As you know, our Session 1 topic is on patient and care partner safety considerations and decision making about gene therapy. We'd like to start off Session 1 today with a brief presentation by my colleague Dr. Shelby Elenburg, who will provide information on OTP's commitment to the development of gene therapies for rare diseases.

DR. SHELBY ELENBURG: Thank you, Anne.

Good morning and thank you all for joining for this very important topic. My name is Shelby Elenburg, and I am Clinical Team Lead in the Division of Clinical Evaluation General Medicine, Office of Clinical Evaluation, Office of Therapeutic Products, or OTP, in CBER. I'll be giving the OTP presentation for the morning session on perspectives on safety considerations for approved gene therapies for rare diseases. I will speak a bit about gene therapies, how we at FDA examine the balance between benefits and risks when evaluating gene therapies for approval, and how crucial the perspectives of you as patients and caregivers are in our evaluation of gene therapies for rare diseases.

I have no conflicts of interest and nothing to disclose. My comments represent my own judgment and do not bind or obligate FDA.

At FDA, we have a mission to advance public health, and part of that mission is speeding innovation to make safe and effective medical products available to patients. In CBER and the OTP, we have a special commitment to rare and serious diseases with unmet medical need.

You will hear from many speakers today who are patients themselves or represent patients

from a variety of rare disease communities. When we think about rare diseases or disorders in a general sense, we know that many are serious conditions and many do not have any approved treatments available, which creates an unmet medical need. Many rare disorders are heterogeneous, meaning that two individuals with the same disorder may be very different in terms of disease severity, types of symptoms, age or time that symptoms of disease first began, and the speed at which the disease progresses over time. Often, rare disorders first present with signs or symptoms early in life; it is estimated that approximately half of rare disease patients are children.

Gene therapies hold great promise for addressing unmet needs in rare diseases. Approximately 80 percent of rare diseases have a genetic basis and thus may be suitable targets for gene therapy as a treatment option. To date, FDA has approved 20 gene therapy products, most of which are for rare disorders. Currently, the OTP oversees more than 2,600 investigational products, approximately half of which are gene therapies. And here is where you come in: Collaboration with patients and caregivers is critical to our evaluation of gene therapy products and helping to get safe and effective therapies to the patients who need them.

Patient engagement is incredibly important to the work that we do. You help us understand the impact of the disease and its management, including helping us understand what symptoms and impact on daily living and functioning are most important to you. You also help us understand perspectives on current and potential future treatments, which is an important aspect of today's session. Not only does patient engagement help us understand what expectations you may have for benefits from gene therapy, but also what risks you think are reasonable in light of the potential benefits in addressing unmet medical needs. We also hope to understand more about your perspectives on tolerance for uncertainties regarding risk of gene therapy and the potential burdens of long-term follow-up after receiving a gene therapy.

So what is gene therapy, exactly? In the technical sense, a gene therapy is a product that either seeks to change the expression of a gene in the human body or use genes to change properties of cells to achieve a certain therapeutic use. An example of the latter is CAR T gene therapies, which are modified T cells from the immune system. We have some CAR T gene therapies approved for various types of cancer, for example.

Gene therapy products that change the expression of a gene in the human body can take several forms. Genetically modified stem cells, or cells in the body that can become a lot of different types of cells, often use vectors that integrate a gene into those cells so that they continue to express those genes over time. Genome editing uses technology that directly modifies the gene instead of trying to replace it. And genetically modified microorganisms typically use viruses as vectors for the gene replacement therapy. It is important to note that these viruses are used as vectors for direct delivery of the gene to the body and do not make you sick like a cold or flu virus might.

All of these types of gene therapies have different potential risks to consider when making a decision about receiving an approved gene therapy, many of which we have learned about from currently approved gene therapies.

Here we see the 20 gene therapies approved in the United States by FDA. You'll notice these are relatively new. The first gene therapy was approved in 2017: Kymriah, a CAR T or T cell product for childhood lymphoblastic B cell leukemia. That was also the year of approval for the first directly administered viral vector gene therapy for a non-oncology rare disease due to a specific gene mutation: Luxturna, for retinal dystrophy. In 2019, Zolgensma was the first approved systemically administered viral vector gene therapy, for spinal muscular atrophy.

I like this graphic, because it helps to show how rapidly gene therapy is evolving. The products in blue are modified T cell therapies, most of which are CAR T gene therapies for various types of cancer, which you can see represent the majority of earlier gene therapy approvals. However, since 2022, we've had numerous gene therapy approvals for genetically modified stem cells, shown in green—the first being Zynteglo for beta thalassemia, in 2022—and directly administered viral vector gene therapies, shown in purple.

Of note, the first approved genome editing product—using CRISPR technology—was Casgevy, approved in 2023 for the treatment of sickle cell disease, and later expanded to the treatment of beta thalassemia in 2024. Of the 20 approved gene therapies, more than half have been approved in the last two years. We hope this list of approved therapies will continue to grow rapidly.

Gene therapies are new and exciting therapies that hold a lot of promise for rare diseases and conditions; some have already had a large impact on patients' daily lives. However, the newness of these therapies and their use primarily for rare diseases in small populations also contribute to a great amount of uncertainty regarding the risks involved in receiving a gene therapy.

As mentioned, because these diseases are rare, a gene therapy may be approved after only a very small number of patients have received it in clinical studies, which leads to a lot of uncertainty about the potential risks of gene therapy.

Questions you may ask related to identified risks or potential side effects include what the risks or side effects are, and whether enough patients been treated to know all the risks; when side effects might occur, such as shortly after a gene therapy or many years later; how severe a particular side effect might be or how it might affect you; how long a side effect might last, whether it will go away or be permanent, and if it can be treated; how common particular side effects are in patients who receive the gene therapy; why some people have side effects and others don't; and whether there are certain factors that may place some people at increased risk of certain side effects compared with other people.

We hope to hear from some of you today about how you considered or would consider receiving a gene therapy in light of these uncertainties.

Although there is a great deal of uncertainty, there are some risks or safety concerns we know are possible with gene therapies. This slide includes some of the identified potential safety concerns for gene therapy products, but it is important to note that this is a general list. It does not apply broadly to all gene therapies or to all patients who receive gene therapies. For example, cancer or malignancy has primarily been identified as a rare but potential risk primarily of integrating stem cell gene therapies that happens years after gene therapy treatment.

In an example I will discuss in more detail shortly, cancer has been observed following one gene therapy treatment, Skysona, in 9 percent of clinical study patients. And in those patients, it was diagnosed between 14 months and 7 1/2 years after gene therapy. It is important to note that cancer has not been observed with every approved integrating stem cell gene therapy, but it has been identified following a few gene therapy treatments. It is not clear if this is because there are differences in individual products, differences in risk factors for developing cancer based on a specific disease, differences in risks based on other medications given around the same time as gene therapy, or other yet unknown factors.

Additionally, because cancer may take several years to develop, it is possible more cases may be identified as patients are followed longer after receiving gene therapies. Cancer is one of the main long-term risks of gene therapy that led to the recommendation for long-term follow-up after gene therapy, as will be discussed in more detail later this afternoon.

Liver toxicity, on the other hand, is a relatively common side effect following administration of certain viral vector gene therapies. Using Zolgensma as an example, in one study, 96 percent of patients experienced elevated liver enzymes. Elevated liver enzymes are the typical presentation, and it commonly happens in the weeks following some viral vector gene therapies. Because patients don't usually have symptoms associated with elevated liver enzymes, frequent laboratory monitoring is important. Liver toxicity can often be managed or even prevented with medications. But without proper evaluation and management, it can lead to liver failure.

Another common adverse effect after gene therapy is infection. It is most often a short-term risk in the days to weeks after gene therapy, and the risk may be increased by several factors, including medications given around the same time as gene therapy, procedures to administer the gene therapy, or simply being in a hospital to get the gene therapy and around people who may be sick. It is also important to note that many rare diseases include an increased risk of infection at baseline. Infection can be an important long-term risk, though, in the months to years after gene therapy. One example is that CAR T gene therapies that work against blood cancers by reducing B cells may also have an increased infection risk over time, because those B cells also help protect against infection. That B

cell effect can last in some cases for several years.

And lastly, I want to highlight immune responses. The body may view a viral vector gene therapy, for example, the same way it does a virus that makes you sick. Immune responses can also happen with other gene therapies. Often this is a short-term risk in the hours to weeks after receiving the gene therapy. Examples may include inflammation that can present with flu-like symptoms, allergic reactions, increases in immune cells without any particular symptoms, and immune cells attacking the gene therapy at the site of administration or in other body sites that could lead to other effects, like blood clots or kidney injury. But most are mild and easily managed or prevented with medications, though they do need to be closely monitored to ensure that they are caught early and managed appropriately.

One potential long-term immune response is the development of antibodies to the gene therapy or the protein or enzyme product of the gene therapy. This can commonly happen with certain viral vector gene therapies. The impact of these antibodies is unclear but could potentially decrease effectiveness of the gene therapy over time or may affect one's ability to receive another dose of gene therapy or another therapy in the future, if the antibodies might prevent those therapies from working.

When considering gene therapy approvals for rare diseases, FDA evaluates the balance between benefits and risks of the gene therapy based on evidence from clinical studies. The first thing we look for is substantial evidence of effectiveness. This typically is evaluated by looking at the clinical meaningfulness of gene therapy effects such as a life-changing impact including on activities of daily living and addressing an unmet medical need. Patient input is critical here for understanding the disease and its manifestations, as well as what effects of a gene therapy represent meaningful improvement.

The next thing we look for is evidence of safety or acceptable safety of the dose range for the population with the disease or condition. Patient input is really important here for understanding what risks of gene therapy are considered acceptable in the context of specific diseases, other available treatments, and expected benefits of the gene therapy. Approval of a gene therapy is supported if available data demonstrate that the gene therapy's benefits outweigh its risks.

I'd like to go through an example of a gene therapy approval and the benefit-risk assessment that incorporated patient and caregiver input in the approval decision. Skysona is an integrating stem cell gene therapy that was approved in September 2022 for slowing progression of neurologic dysfunction in boys with cerebral adrenal leukodystrophy, or CALD. In terms of substantial evidence of effectiveness to support approval, when assessed 24 months following initial symptom onset, boys with CALD who received Skysona had slower progression of neurologic dysfunction to major functional disability (MFD) or death, compared with similar untreated patients. Patients and caregivers helped identify the clinical meaningfulness of slower progression of neurologic dysfunction to

functional disabilities, such as wheelchair dependence or cortical blindness.

When evaluating safety, the major risk identified following Skysona at the time of approval was hematologic malignancy, or blood cancer, diagnosed in 3 percent or 4 percent of patients treated with Skysona in clinical studies. A public advisory committee meeting held prior to approval allowed for discussion of the balance between benefits and risks of the gene therapy and included patient perspectives that helped us to understand the patient community's willingness to accept the risk of cancer in light of the potential benefits of the gene therapy.

Following approval, after additional cases of malignancy were identified (for a total of six patients, or 9 percent, treated in clinical studies as of April this year), the product label was updated to provide additional details on the new cases of malignancy and additional information to help guide patients and caregivers in the discussion of benefits and risks of the gene therapy with their health care providers and informed decision making about receiving the gene therapy.

As more and more gene therapies are approved, we are learning more about the benefits, but also more about the risks. As patients and caregivers, your input is critical to enhancing our understanding of when potential benefits outweigh potential risks for gene therapies for rare diseases and enhance our ability to achieve balance between benefit and risk of treatment options as part of our regulatory assessment.

Thank you so much for joining us today. We are very excited to have you all here and very much look forward to learning from you and hearing about your different experiences and perspectives as we all navigate the rapidly evolving and incredibly complex topic of safety of gene therapies for rare diseases.

Thank you for your time. I will now turn it back over to Anne.

DR. ROWZEE: Thank you so much, Shelby.

Polling Questions

DR. ROWZEE: We're now going to start a second round of polling. Please note, again, that these questions are intended for patients and their care partners. During this time, we're also going to be giving our first set of speakers camera and microphone access. I'm going to read through the questions and the possible responses.

- Question 1: What information about risks, or uncertainties about risks, of gene therapy products did you consider or would you consider when determining whether to receive the gene therapy? Here we'd like you to select all that may apply:
    - "Risks of the gene therapy that were identified from treatment of previous patients"

- "Risks that have been identified with other gene therapies, either those for other diseases or a different gene therapy for the same disease or condition"
- "Risks that were considered possible as observed in animals but not observed thus far in humans who have received the gene therapy"
- "Unknown risks of the gene therapy that may not have been identified yet"
- "Risks of the disease or condition getting worse while waiting for an alternative therapy"
- "I don't know"
- "I did not or would not consider"
- "I would receive a gene therapy regardless of the risks"
- "Other"

- Question 2: Imagine there was another option to treat the disease or condition, beyond managing the symptoms, available now or in the near future. What do you think is most important to consider in making the decision to move forward with gene therapy versus the other option? Here we'd like you to select up to three responses:
  - "Which aspects of the disease each therapy is intended to treat"
  - "Effectiveness and duration of expected benefit of each therapy"
  - "Whether the therapy is required to be taken alongside other medications"
  - "The route of administration (for example, intravenous—or IV—or injection into the brain)"
  - "Short-term (meaning days to weeks) safety risks of each therapy"
  - "Long-term (meaning months to years) safety risks of each therapy"
  - "Which therapy has studied patients who have a similar stage or type of disease as myself, my child, my family member, my care partner"
  - "The ability to receive other currently available or future treatments for the disease if the gene therapy doesn't provide the expected benefit"
  - "Personal beliefs or values about the treatment options"
  - "My or my child's medical provider or disease expert's opinion"
  - "Other"

- Question 3: What information about gene therapy risks were or would be most important to you when determining whether to receive the gene therapy? Again, please select up to three responses here:
  - "The number of patients who have already received the gene therapy in clinical trials and/or for commercial use"
  - "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 a particular side effect occurs"
- "Other considerations"

Thank you very much for your responses to those questions.

Speaker Presentations, Part I

DR. ROWZEE: We're now going to hear from public speakers who have volunteered to share their perspectives and responses related to these main three questions:

- What risks or uncertainties did you or would you consider when determining whether to receive an approved gene therapy?
- What do you believe patients and care partners making decisions on behalf of patients should know about gene therapy?
- In a scenario where more than one treatment option is available to treat a disease or condition, what information would you want to know?

I think we have 19 speakers for this session. Everyone should be teed up now, and each speaker will have 4 minutes. I'd like to remind our speakers to please start by stating your name and your affiliation at the beginning of your presentation.

Again, to ensure transparency at this listening meeting, we encourage you to advise the audience of any financial relationship that you may have with a firm, group, company, or product at the start of your presentation. If you do not have any disclosures, you can simply make a statement to that effect.

Our first speaker is Steve Bedsole.

MR. STEVE BEDSOLE: I'm Steve Bedsole. Thank you for inviting me to participate.

I don't have any disclosures. My history is with hereditary amyloidosis. It's a mouthful to say. I've been on messenger RNA (mRNA) gene silencer therapy since 2018. So my experience really is dealing with mRNA gene silencing and trying to compare that with new gene editing therapies that are under consideration now.

So I'll start with the first question. For me, the risk and uncertainties include understanding how the gene therapy works, whether it's mRNA delivery therapy or if it's actually modifying the DNA itself. In the case of mRNA therapies, the drugs don't make permanent alterations to your DNA. And should you develop adverse reactions in the near term or even years into the treatment, the treatment can be stopped without further harm. And ideally, there'll be other treatment options that the patient can switch to should that

happen. And it does frequently happen.

I personally developed allergic reaction symptoms to the first silencer that I was on after being on it for 2 years. But I was fortunate to be able to switch to a second approved drug that was another silencer. I stayed on that for a few months, until a third one was approved by FDA. And each one of those changes improved how I felt while I was taking the treatment, by lessening the side effects and the ease of administration. So I was fortunate that I had options.

Well, in the case of actual DNA modification, nobody really knows what the long-term ramifications are of changing your DNA. And those modifications, in my way of thinking, are permanent. There's no going back to changing the therapy. So in the risk-reward consideration, for me, it would have to show us a substantial reason for taking such a risk.

In the case of currently approved mRNA gene silencers versus the gene editing drugs for treating hereditary amyloidosis, the published data is showing that there's not a significant amyloid knockdown rate between them. And the gene editing studies have been conducted on a much smaller pool of patients. So early in my treatment, the thought of gene editing being a cure was the golden orb. We thought that's what we were shooting for. We thought that would be the cure. Now that we're seeing the study data, I'm not sure that there's a significant difference. And I wouldn't be willing to take the risk of permanent DNA modification for that slight difference in the results that they may get.

So Question 2: "What do you believe patients and caregivers making decisions on behalf of patients should know about gene therapy?" Well, with mRNA, we've got a little over 10 years' data of long-term effects. We know the effects of the disease without the treatment, so the risks versus rewards seem prudent. Who knows what the next 10 years are going to be? We may be trading short-term physical disabilities for long-term mental disabilities. We just don't know what the next 10 years are going to bring.

But one thing we do know is there's no cure. So the important thing is starting treatment as soon as diagnosis can be made, because with the silencing treatments that we have available, all they do is slow down the progression of the disease. So the day you start treatment is really the best day physically for the rest of your life.

So if you wait until you're an invalid to start the treatment, is it really worth preserving your life as an invalid? I know, in my mother's case, she decided it wasn't, and she chose hospice care instead. For me, I was able to get on treatment early, and I've maintained a good quality of life. So when you start treatment and which treatment you take are important.

In the third question, if there's more than one treatment option available, the things I would consider is: How is the drug administered, and what's the frequency of administration? What's the effectiveness? In our case, what's the amyloid knockdown rate? What side effects and adverse effects have been reported, and what are the percentages of

those instances? What was the size of the study group, and what did the study compare the treatment with? How easy will it be for me to switch to another treatment should my body not respond well to this one? And probably one of the more important questions for most people is: Will my insurance pay for it? If not all of it, how much is it going to financially set me back compared with other treatment options and their effectiveness? And that's all.

DR. ROWZEE: Thank you so much for sharing your perspective today. We really appreciate hearing from you.

Also, I just want to take a quick second to note: You'll see the list of speakers for Session 1 up on the screen, so you can get an idea of where you are in our lineup. We have folks listed in alphabetical order here. My understanding is that our next speaker has not joined yet. So we're going to skip to the next speaker on the list, Gabi Conecker.

MS. GABI CONECKER: Thank you so much. I really appreciate the opportunity to speak today, and I appreciate FDA holding this session.

I am Gabi Conecker. I am the Executive Director and Co-founder of Decoding Developmental Epilepsies. And I am also mom to my son, Elliott, who is 11 years old and lives with SCN8A-DEE and lives with many profound disabilities.

Through our organization, I'm the executive director and co-founder of a number of projects, including the International SCN8A Alliance, as well as a program that works to educate and empower caregivers of loved ones who have developmental and epileptic encephalopathies called DEE-P Connections. So I speak as both a caregiver and a community leader. And I have no disclosures or conflicts to report.

This really comes down to the fact that we know that caregivers are really hungry for change, but in order to have clear consent and clear information around gene therapies, we need to have a balancing act between hope and honesty about the risks.

Many caregivers have lost hope for current treatments that exist. We've been through all of them, and they are maybe a Band-Aid for the seizures, but don't really deal with the plethora of other non-seizure challenges that we deal with. So there's this sense that a lack of options is currently available to us. And the sense I get from talking with a lot of families in the community is that they really feel that genetic therapies are the answer.

So there's a need to balance that with real honesty and truth about what the risks and uncertainties are. I think there are a lot of families that really feel like this, that don't necessarily understand this "one and done" idea for some of these gene therapies and how that may impact their ability to access future gene therapies or treatments.

This is all very new, and I think it is critical that we have intensive education in advance about both known and unknown risks to fully understand the protocols, around what's expected of families, what administration looks like, what the risks are, and how long they should expect the potential benefits and effectiveness to last. In other words, a lot of the

questions we're getting at.

I'm speaking as a caregiver of a child who's very profoundly impacted by this genetic disorder, SCN8A. In our work through the SCN8A Alliance, we recently did a community poll, answered by nearly a quarter of those in the world known to have the disorder, a pretty significant portion of the population. And you can see here that 75 percent of the community is really banking on and excited about gene therapy. So there's this excitement and this drive to see something more. But it's often seen as the last hope that remains for many of our kids who are really, really struggling, if their condition is catastrophic or they're deteriorating. And we need to make sure that they fully understand the risks.

We also have done this through the Inchstone Project, a project of the DEE-P Connections that I mentioned. We did a recent survey across DEEs, or developmental and epileptic encephalopathy families. And you can see that the kinds of things that they are interested in seeing outcomes in and the expectations are higher for gene therapy, right?

For me personally, if I were to do a clinical trial on just a drug, I would say what I really want to see is increased awareness and engagement. But if I'm talking about a gene therapy, I'm going to expect more from that with the kind of risk that's involved there. So we need to also make sure that there's adequacy and sensitivity with regard to clinical outcome assessments that look at the clinically meaningful aspects of what's important to our families. And here you can see some of the things that came up. Expressive communication reigns supreme in that sense.

Essentially, I think that the developmental and epileptic encephalopathy community is really supportive of gene therapy and other potentially transformative therapies. But we need to ensure that these communities have a meaningful seat at the table early and often to discuss these trials, including equity and access down the line, which is something that Steve brought up.

Thank you so much. I appreciate the time today.

DR. ROWZEE: Gabi, thank you so much for sharing perspective from the SCN8A community and your family's perspective.

Up next, we have Stephanie Cozine from the National Mucopolysaccharidoses (MPS) Society.

MS. STEPHANIE COZINE: Hello, I'm Stephanie Cozine, and I'm an MPS parent advocate. I do not have any disclosures.

I've been a part of the MPS community now for 9 years, since my son's MPS I (Hurler syndrome) diagnosis, in 2016. MPS I is a lysosomal storage disorder currently with no cure. Based on the natural progression of this disease, you can expect a life span of 5 to 10 years, significant neurocognitive disability, significant orthopedic and organ system manifestations, and a significant deterioration of quality of life.

I've been able to speak at length with numerous families as they determine which treatment options to choose, including gene therapy. MPS I does have multiple treatment options to choose from. So I'd like to guide you through some of the decision-making considerations with regards to all current treatment options, both FDA-approved and clinical trials.

I listed specific considerations when comparing various FDA-approved therapies known as the standard of care and clinical trial options. I've highlighted where some of the unique considerations are for clinical trials, specifically with gene therapy, right now for MPS. You're going to look at short-term risk. So this would include "What risks are there with the procedure itself? What complications can happen? Do we know the likelihood of treatment failure or complications in that 90-day window short-term?"

But if you look at long-term risk, what effects can the treatment have in the years and decades to come? One of the treatment standards right now is a bone marrow transplant. So some of the complications you consider are the potential for cancer and organ damage, or failure over time and then the loss of reproductive abilities. And then you would compare morbidity and mortality rates of existing treatment options.

Again, you want to consider the limitations of each of your options. Does the treatment not address a specific manifestation of the disease? With MPS I specifically, we want to look at treatment of the neurocognitive effects on the brain, as well as the other systemic effects in bone, heart, lungs, etc. Some treatment options do address both; some only address one. And then when you only address one, you have to consider an adjuvant therapy.

And one of the things that many families consider are the logistics of your treatment options. Is this a onetime treatment? Is this a weekly treatment? Is this a treatment that requires a significant inpatient stay with significant follow-up within the first year? Are there additional protocols that are a part of this? Are there weekly infusions, immunosuppression, or isolation protocols that can come either with bone marrow transplant or port placement for access? And then does this also include missed school days, especially when you're looking at the pediatric population?

Something else to consider is accessibility. Do patients need to move or travel for the treatment? Where are the treatment centers located? Are there going to be lifestyle changes or quality-of-life changes due to this? And then the cost of the treatment itself: If the patient has health insurance, is it currently covered? Are the specialists covered as well? Other financial impacts would be missed workdays and extended leaves of absence. Other considerations for families are cultural or religious beliefs, which some treatment options conflict with.

Looking at data that's available, what type of outcomes have been reported, and how robust are the findings? Is there data from all treatment options available to compare with natural history data? Are there peer-reviewed comparative analyses between treatment options? If it's a clinical trial, how will long-term follow-up data be recorded, and will my family have access to this information, and how?

Specifically, some of the things with clinical trials that families take into consideration are: "What are the risks that my child will not receive treatment for an extended period of time if there is a placebo arm in the trial?" "What does this mean for irreparable damage, specifically to the brain?" "Is there a treatment arm that uses the current standard of care, and what are those risks compared with the risk of the gene therapy?" "Is this looking at allogenic versus autologous stem cell transplants and the risk associated with those, and then just the randomization into those groups?"

Families will look at the risk versus benefit weighing their short- and long-term risk with the potential benefits of improved quality of life. Each family is going to look at this differently in terms of what they value most in their outcomes. And these are just some of the considerations during the decision-making process.

DR. ROWZEE: Stephanie, I'm sorry to cut you off, but we are at time. I'd invite you to add your comments to our docket, please. We want to hear everything you have to say, but we need to save time for everyone. Thank you so much for your comments today.

Our next speaker is Alicia DeVinney from the National Multiple Sclerosis (MS) Society.

MS. ALICIA DEVINNEY: Hi, thank you for inviting me to be here. I really appreciate that you are highlighting the patient perspective, and that it's in the forefront of ongoing advancements in health care. So I will keep this short.

One of the things that has come up often in a lot of patient groups, obviously, is the benefit versus the risk. And when you think about efficacy, for instance, a lot of patients wonder, "Is this something that is lasting? Or is it something that wanes over time?"

And there are also questions that have come up around variability in different patient populations. For instance, in clinical trials, how reflective are those patients of different people? And from a long-term safety perspective, a lot of patients were concerned about the cancer risks, organ damage, and the potential for allergic reactions or immune system reactions.

There were also some interesting questions around "What are the burdens of long-term follow-up? What does that look like? And from a testing perspective, what does that look like for patients?"

That's all that I have. Thank you very much.

DR. ROWZEE: Wonderful. Thank you so much, Alicia, for sharing your perspective today.

Next up is Rolf Hill.

MR. ROLF HILL: Good afternoon and thank you for holding this listening session. My name is Rolf Hill, and I have no conflicts and nothing to disclose.

I live in Annapolis, Maryland, and I have three daughters. My oldest and youngest daughters, Sam and Rebecca, have a genetic illness called Friedreich's ataxia (FA). This May, Sam will graduate from the University of Southern California, and Rebecca will graduate from high school. Every day, my daughters live with this progressive illness that makes each day a little bit worse than the day before. They face unique challenges in everything that they do.

The FA community is very hopeful about the prospect of gene therapy to treat FA. Because FA is a progressively degenerative illness, time is an extremely important factor for our family, superseded only by safety. When considering FDA's first question about the risks and uncertainties a family would consider when determining whether to receive approved gene therapy, my first consideration is whether taking an approved gene therapy treatment would preclude my daughters from taking any other gene therapy or non-gene therapy treatment in the future. We know in the FA community that it's unlikely for a single gene therapy product to treat all of the symptoms of FA. So understanding how an approved therapy would impact our ability to receive other therapies in the future is very important to us.

And this raises another uncertainty and risk related to the durability of the treatment. My daughters need these therapies now, as their disease is progressing. When considering a potential gene therapy, we may be willing to tolerate some uncertainty in regard to durability if there are mechanisms in place to continue to collect postapproval data and share that data back with the FA community.

We also believe it's critical for there to be governmental supportive research efforts to overcome the challenges that currently limit some of these therapies to a single administration, and to evaluate gene therapies in combination with other therapies.

Another concern is that because gene therapy may potentially be delivered via a viral vector, we would want to know the risks of my daughters being potentially immune to the virus. And because I have two affected daughters, would they need to receive gene therapy at the same time to avoid one of them building an immunity to the virus because of her exposure to her sister's treatment?

My daughters' illness is a result of their bodies producing a very limited amount of a protein called frataxin. Gene therapy would be treating the disease at its root cause. We're willing to receive approved therapies with some uncertainties and risks when there is a prospect of benefit. Having data from preclinical studies and clinical trials that show that frataxin is increasing is meaningful and important to us. And that data showing an increase in frataxin may come before data showing a clinical benefit. This evidence of increased frataxin may be enough for us to choose to receive a gene therapy even prior to seeing clinical benefit.

This leads me to FDA's next question about what patients and care partners should know about gene therapy. I think it's critical for the maximum amount of data, including pretrial

studies, trial results, and postapproval data, to be made available. In order to make an informed decision, we would want to know the reasons if and why patients withdrew from a trial or screened out, as well as information on any adverse effects during and after the trial. We would want to know the types and frequency of efficacy assessments performed to evaluate the benefits and the outcome.

Thank you very much for your time.

DR. ROWZEE: Thank you, Rolf, for sharing your insights and the story from your daughters and their perspectives as well.

Our next speaker is Veronica Hood from the Dravet Syndrome Foundation.

DR. VERONICA HOOD: Hi, my name is Veronica Hood, and I'm the Scientific Director for the Dravet Syndrome Foundation. And while I'll be speaking today on behalf of the Dravet community, I do also have personal lived experience and insight into these topics as a caregiver to my own son, who passed away from a progressive neurological disorder. I do not have any financial relationships to disclose today.

Dravet syndrome is a rare catastrophic developmental epilepsy. It includes difficult-to-control seizures that begin in the first year of life, and the disease progresses with accumulating impacts on developmental domains. The majority of cases of Dravet syndrome are attributed to loss of function mutations in one copy of *SCN1A*, a gene that encodes a sodium channel that's important for regulating brain activity.

While there are no FDA-approved gene therapies yet for Dravet syndrome, many are in development, and two therapies are now being evaluated in clinical studies. As such, we've had many formal and informal conversations through various mechanisms with the community about this topic. And while a lot of our current insights relate more to the trial phase of gene therapy development, these learnings can also be extrapolated to reflect on postapproval topics.

You can see in this graphic on the slide a variety of symptoms that caregivers desire to be addressed by genetic or other disease-modifying therapies. And while there is some consensus on which symptoms rise to the top of that list, you can also see there's variability reflecting the individual priorities of patient families and the heterogeneity of this disorder. As such, more so than with the traditional medications our community is familiar with, very clear data on which symptoms are addressed and to what extent they're addressed is going to be critical to families facing the decision of whether to try a novel genetic therapy or choosing between multiple approved therapies.

As part of our externally led patient-focused drug development meeting, we polled the community on its willingness to try genetic-based therapies, using scenarios that involved different delivery routes, permanency, and the extent to which the therapies might address symptoms. While this graph is pretty complicated, what was striking to me was that across

all of these contexts, 98 percent of caregivers were interested in gene therapy on at least one of these levels. And a majority would still consider even the most invasive and permanent options as long as they have confidence in the symptoms it would address. Again, this reflects that the community needs to have very clear data, including clear indications of the extent to which symptoms improve, to make these complicated decisions about gene therapy products.

Lastly, I want to reflect on some recent comments collected from caregivers whose loved ones are participating in the current trials for genetic-based therapies, and how these insights might also help predict the needs that will arise post-approval. We find that caregivers chose to participate in gene therapy trials because of the extremely high unmet needs that are not being addressed by current top line therapies. This level of need can lead to desperation. What more could you desire as a parent than to improve the life of your child? And it is reasonable that the risk-benefit assessment is shifted for severe and debilitating diseases. But as such, it really does become critical that caregivers or patients fully understand the breadth of potential risks, as well as the impact on symptoms, so that they can carefully weigh that decision. This is again underlined when you look at comments about top concerns entering these trials, including worries of making symptoms worse or causing undesirable side effects.

We also asked families about what may have prevented their participation. And while some were willing to do anything, a common theme was difficulty in traveling to sites. I know this will continue to be an issue along with other challenges related to access, meaning that some families won't be able to make decisions based on this cost-benefit scenario but rather on whether they can access the therapy.

I'll wrap up with that, as I'm out of time, but thank you so much for your time and for hearing the patient perspective on these important topics. My final slide has my contact information if you have further questions. Thank you.

DR. ROWZEE: Thank you, Veronica, so much for sharing the perspective from the Dravet syndrome community and from your family as well.

Next up, we have Katie Jackson. She's from Help 4 HD International.

MS. KATIE JACKSON: My name is Katie Jackson, CEO of Help 4 HD and a Huntington's disease (HD) family member. I don't have any financial disclosures or conflicts.

My husband passed away from HD 5 years ago, and I walked his journey with him to the end of his life. Now I fight for my three children, who have a 50 percent chance of inheriting an HD. Today, I speak to you not only as a parent fighting for her children's lives but also as someone deeply involved in the HD community. We are publishing a white paper on a risk-versus-benefit survey in which over 250 HD and JHD, or juvenile onset Huntington's disease, patients have participated. I'll be discussing insights from that

survey.

With 19 years of advocacy, relationships with thousands affected by HD and JHD, curating clinical data from over 500 patient accounts, hosting nationwide events attended by thousands over the past decade, I've conducted hundreds of interviews. I hope to provide a comprehensive perspective on the questions posed today, not just from my experience but reflecting the HD community as a whole.

When discussing the risks that the HD community is willing to take, you may find that our risk tolerance is higher. Living with a terminal illness that takes away quality of life makes you more willing to accept risks. Having a generational disease with children facing the same fate, your risk tolerance intensifies further. Regarding unknown risk, it depends on the nature. For risks that are manageable with medication—like fatigue, dry mouth, headaches, slight sedation—we have a higher risk tolerance. However, severe life-changing risks—such as heart complications, unmanageable pain, unmanageable headaches, or life-threatening reactions—are generally unaccepted, according to our white paper and community feedback.

We understand that entering clinical trials or starting a new therapy may involve unidentified long-term risks. When facing a terminal illness with diminishing quality of life, you are willing to accept potential future risks. We have already faced death as our fate, so we are prepared to confront uncertainties that may arise years later, because the known outcome of HD and JHD is death and suffering.

If we had more time—especially in a progressive disease, where early intervention is crucial—we might wait to learn more about long-term risks before opting into a gene therapy. But time isn't a luxury we have. Waiting may mean that our loved ones may become too advanced in the disease to qualify for future trials or therapies. If there's an option now that can slow the progression of the disease and preserve quality of life, we are willing to take it rather than wait for a possible better therapy that may never come.

What should patients and care partners know about gene therapies? Is it a single treatment or multiple? How is it administered? Would it have an off-target effect on other genes? How long will it last? Is it a cure or treatment? What are all the known side effects, and are they manageable? How effective is the therapy? What are the side effects of administration? Is there evidence of disease improvement post-therapy? Will it improve quality of life? Can it reverse damage caused by the disease? And do risks differ from early and late-stage patients?

In scenarios where multiple treatment options are available, we may want to know comparative effectiveness of the treatments, side effects of each option, which treatment works better at specific disease stages, duration and longevity of each treatment, methods of administration, and treatment schedules.

Hosting education events across the nation has taught me that people come seeking hope.

When one has a terminal diagnosis and limited treatment options, the search for hope is desperate. It is no surprise that HD has a suicide rate three times higher than that of the general public. However, the hopelessness has lessened as gene therapy trials have emerged in the HD community.

I conclude by emphasizing that the HD community is willing to take risks. Many fight not only for themselves but for their children and future generations facing HD. When confronted with a fate of prolonged loss, grief, and loss of quality of life, accumulating in death, we are prepared to take risks.

Thank you.

DR. ROWZEE: Katie, thank you so much for sharing your insights and sharing your family's journey with us today.

Next up, we have Michelle Lorenz.

MS. MICHELLE LORENZ: Thank you. My name is Michelle Lorenz, and I have no conflicts of interest.

Today, my presentation is specifically focused on the safety and efficacy in terminal heterogeneous rare diseases. When you have a 100 percent chance of dying, and when there are no disease-modifying treatments, what constitutes an unacceptable safety risk may be quite different. Many patients are willing to accept unknowns about efficacy and durability and time, just as the prior speakers discussed, as any chance of survival is better than no chance of survival. And this is important: What constitutes a clinically meaningful change may appear quite minute to others when you understand that we use subjective clinical outcome assessments.

So to that end, I want to discuss a few things that impact both amyotrophic lateral sclerosis (ALS), where I'm a patient advocate, and amyloidosis, the disease that killed my mom.

My mom had amyloidosis. She died 7 months after she was diagnosed, but nearly 10 years after she first became symptomatic. We think it's unacceptable to approve a drug for a symptomatic population but then require carriers to wait another decade until they manifest symptoms to get access to that therapy. In ALS, researchers believe that up to 50 percent of motor neurons are damaged or dead before they manifest functional symptoms. In protein-misfolding diseases like amyloidosis, we don't yet know the extent of damage to the organs that suffer irreversible damage from the amyloid protein before they're symptomatic.

So we're asking FDA for four things. We want to know if the gene therapy was tested in a presymptomatic population. Today, most gene therapies aren't. Second, we want to encourage FDA to require drug sponsors to concurrently test the presymptomatic population in their safety and efficacy trials. Third, we need long-term data about this presymptomatic population that knows with 100 percent certainty that they're going to die.

So when you approve a drug, please mandate a postmarket patient registry that continues to collect the data. And fourth, specifically include on the label that gene therapy is also approved for a presymptomatic population, as we know that those benefits may be clinically meaningful to them.

I just want to give an example from amyloidosis. We know there's significant heterogeneity in this disease. As you can see, with the hereditary form of amyloidosis, there are over 150 different variants. Similarly, in ALS, there's over 180 variants of one gene, *SOD1*.

We know that when we talk about risks with heterogeneity, we want to talk about what variants were tested in the trial population. Do those variants share phenotypic similarity? Do different subtypes respond the same? So, in my mom's disease, amyloidosis, does the cardiomyopathy subtype respond similarly to the neuropathy subtype?

In ALS, my friend just buried her 29- and 30-year-old sons, both of whom had SOD1 ALS. One had bulbar onset, but he could still walk when he died. The other had lower-limb onset, but he could still eat and swallow. Their 60-year-old father still doesn't have any symptoms. Thus, we need FDA to encourage drug sponsors to report data about the differing responses to the therapy within these subtypes. We need data about the polygenic risk factors. So in ALS, for example, is there also an *SETX* mutation that may predispose people to earlier onset? Or is the *cAMP 1* gene present as well that speeds up progression?

Now I want to talk about diversity. As you can see on this particular slide, we know that we have problems with diversity. The U.S. population is about 19 percent Hispanic, but in ALS and amyloidosis trials that I recently looked at, the population is only 6 percent. And you can see in the Genome-Wide Association Studies (GWAS), the population is only 5 percent. And so, what we know is if there's missing data in the GWAS, we're missing people who have these diseases. And so, we want to encourage the Office of Minority Health, or OMH, to get involved and help us.

We know that Black Americans are 12 percent of our population, but only 3.5 percent of our trial population. And you can see here that ATTR amyloidosis has a variant that specifically affects Black Americans. About 4 percent of Black Americans carry this variant. That's 1.6 million carriers. And yet there's incomplete penetrance. This speaks to what we discussed earlier about understanding that and reporting on that.

This is my last slide with other treatment options. I just want to keep in mind that with rare diseases, many members of our community are not close to centers of excellence or research hubs. So we need the materials you see on this slide to be available to us, our family members, and treating physicians in the local community. If FDA could establish hyperlinks and at-a-glance documents that make it easy for the unexperienced person, that would help a lot.

Thank you for the time.

DR. ROWZEE: Michelle, thank you so much for your insights and your comments today. If we didn't get to everything, I encourage you to please go to the docket and submit the remainder of your comments there.

Next up, we have Miranda McManus from the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS).

MS. MIRANDA MCMANUS: Hi, everyone. I'm Miranda McManus. I am the parent of a 19-year-old son with neurofibromatosis (NF) type 1. I'd like to thank FDA for holding these meetings. I'm on faculty in the biology department at the College of Charleston, but I'm here presenting on behalf of REiNS.

So I don't really have time to get into what NF and schwannomatosis are, but this is a group of rare monogenic progressive genetic syndromes that cause a predisposition for both malignant and benign tumors. There's a really wide range of manifestations. There's an equally diverse spectrum of pathogenic variants. And for a lot of reasons, it's an attractive target for gene therapy. REiNS, the organization, is tasked with developing standardized response criteria or endpoints for clinical trials. And so, in preparation for gene therapy trials, we established a working group in 2022.

The state of gene therapy, NF, and schwannomatosis involves no human trials yet. We have multiple animal and cell models but have no idea what's going to bubble to the top first. So we don't know what clinical features will be targeted, which types of gene or cell therapy, even which specific conditions or which patients will be the next candidates.

So in preparing, education's a really important component. I don't have time to get into that, but we've been doing a lot of education within our community. But what we've really focused on is trying to understand patient preferences and concerns.

In the gene therapy group, we've designed a patient preference study and decided to use a discrete choice experiment, or DCE, which is used commonly in marketing research. I mean, it's a formal process to examine tradeoffs between perceived risks and benefits. And you start by defining a set of attributes that are most important to patients. We used a really rigorous process to get there. The study is opening soon. We plan to publish the results next year.

So these are the attributes that we came up with, and you can see the different levels on the righthand side. Again, I don't have much time to cover this, but you can see that this is broken down into perceived benefits and perceived risks. And then the whole idea of the DCE is to pair these up against one another. For benefits in our population, it was important to understand the chance of presenting a new tumor disease manifestation, as well as the impact on current health. So those were separated out. And then you can see some of the things we've seen already today. The risk of getting serious side effects, the ability to conduct the usual treatments, invasiveness, and known evidence for safety side effects were important as well.

This is an example DCE question. Our questionnaire presented to each patient or caregiver 12 questions, but we have 24 total. There's a lot of demographic information and disease information that is incorporated into this as well.

Basically, individuals who take the survey are going to be choosing whether they would have more interest in taking gene therapy A or gene therapy B. And through this process, we should be able to elucidate which things are more important to patients—what those tradeoffs are. And we plan to hopefully be able to do some sub-analysis for this as well. Our work is funded by the Gilbert Family Foundation.

These are the people that I have to thank. And since I didn't have much time to get into what REiNS is, this QR code will take you to the REiNS website, and hopefully, we'll be publishing results to the study this year. Thanks.

DR. ROWZEE: Thank you so much, Miranda.

Up next, we have Paul Melmeyer, from the Muscular Dystrophy Association (MDA).

MR. PAUL MELMEYER: Thanks, Anne. Good morning or afternoon, everybody. Thank you for the opportunity to speak today on the experiences of those in the Duchenne muscular dystrophy, or DMD, and spinal muscular atrophy, or SMA, communities with FDA-approved gene therapies. I am Paul Melmeyer, Executive Vice President of Public Policy and Advocacy at the Muscular Dystrophy Association, or MDA. And I do not have any financial relationships to disclose.

We serve the neuromuscular disease community through a variety of programs, including supporting families through the journey of obtaining gene therapies. We have collected the perspectives of many in our community through forums, surveys, and our MDA gene therapy support network.

Many in both the SMA and Duchenne communities have successfully obtained FDA-approved gene therapies in the last 5 years. And they've relayed their perspectives on what risks and uncertainties they considered when determining whether to pursue a gene therapy. We've heard routinely the reminder that time is muscle, and those decisions often have to be made rapidly due to the severe and rapid progression of SMA, or the limited time window in which boys with Duchenne are or were eligible.

The #1 concern we hear from our community is about durability: How long will the effectiveness last? Parents can be frustrated that data on the effectiveness of these gene therapies is available only for a handful of years post-administration. Parents are often unclear as to what signs they should be looking for in their treated child that show the gene therapy is working, or signs that the gene therapy may be losing its effectiveness.

The progression of untreated Duchenne and SMA is relatively clear; the progression of treated Duchenne and SMA with the gene therapy is not. Moreover, the relative long-term benefits can be different for different individuals. Plus, everyone will be starting from a

personally unique stage of progression, making the assessment even more challenging.

The second-biggest consideration we hear is whether the risks and benefits of taking today's gene therapy outweigh the risks and benefits of waiting for a different or perhaps better therapeutic option in the future. As one parent put it, "If we do something now, are we shooting ourselves in the foot later?" But parents are also keenly aware that these conditions are irreversible. If they wait, are they doing irreversible damage to their child? This leads parents to try to rapidly become experts on redosing efforts, nonviral delivery mechanisms, baseline editing, and more in order to understand what might be coming.

Members of our community who have already gone through this journey would emphasize to parents approaching this decision that today's gene therapies are not cures. They can stop or slow progression, but efficacy varies from person to person. There are no guarantees about the benefits that your child will get from it. At this point, there is limited long-term data; ensuring that parents understand this is a complex, multistep process with significant monitoring; it can be long and complicated.

Insurance denials and appeals come with the territory and should be expected. In fact, we've heard from several parents that the insurance coverage process was actually the worst part of the entire process due to the ambiguity, the waiting, the paperwork, the blood draws, the testing, and having to decide whether additional treatment should be administered while waiting months for insurance to approve the gene therapy access.

Finally, both Duchenne and SMA have other treatment options. The onetime dosing of the gene therapies is certainly appealing to parents evaluating their options, as is the easier route of administration compared with, for example, spinal taps and other therapies. Cost and insurance coverage are also considered across the different options, as are the proximity of treatment centers.

In conclusion, parents of children with Duchenne and SMA face complex choices as they decide whether FDA-approved gene therapies are right for their children. For some, choosing gene therapy was an easy and obvious choice; but for others, not so much due to the many reasons stated today.

Thank you again for the opportunity to speak on the experiences of the Duchenne and SMA communities with FDA-approved therapies.

DR. ROWZEE: Thank you, Paul. And thank you to all of our speakers for Session 1 so far who shared their perspectives.

We're now going to take a 30-minute break, then will continue Session 1 at 1:00 p.m. Eastern time. As a reminder, we're requesting all of our Session 1 speakers to return after the break, as our FDA panelists may have some follow-up questions for you.

Thank you, everyone.

Speaker Presentations, Part II

DR. ROWZEE: Welcome back from break, everyone. Thank you again to our speakers from Session 1 who've already provided their perspectives.

I'd like to invite our next speakers, Kimberly Nye and Tanya Brown.

MS. KIMBERLY NYE: Thank you to FDA and CBER for giving up the opportunity to speak today. My name is Kim Nye, and I am the founder and Executive Director of TESS Research Foundation for SLC13A5 Epilepsy. I am also the mother of two children with this disease. I am joined today by Dr. Tanya Brown, our Scientific Director, who will speak in just a moment. We will be talking about the parent and patient perspective on gene therapy safety considerations for SLC13A5 epilepsy, which is also known as citrate transporter disorder. We have no disclosures or conflicts of interest.

Before we can talk about the risks and benefits of a gene therapy, we want to share what this disease looks like and why treatments like gene therapies are so necessary. This is a severe disorder that affects global development and requires 24/7 care for affected individuals. What makes this disease particularly immutable to gene therapy is that it is a monogenic disorder caused by loss of function changes to the *SLC14A5* gene.

The discussion today is about approved therapies. As with so many rare genetic neurological disorders, we currently have one gene therapy in preclinical development. Our community is hearing about approved treatments in the news, and they are asking a lot of questions about gene therapy risks and uncertainties, timelines, and options.

Now I will hand it over to Dr. Brown.

DR. TANYA BROWN: Thanks, Kim. As we think about gene therapies and their potential to treat the underlying cause of a disorder and improve quality of life more globally, we decided to survey our affected community to determine which symptoms were the most important to address. Survey results show that this disease involves more than just seizures; improving the movement disorder and communication is also incredibly important to families. Caregivers ask about how gene therapies will impact each of these symptoms. Additionally, from our natural history study, we know that our patients are on an average of three to five anti-seizure medications, along with medications addressing additional symptoms. Parents hope that a gene therapy has the potential to reduce the number of daily medications their child is currently on.

As the Scientific Director, I'm frequently asked questions about gene therapy. And as I answer these, my goal is to set realistic expectations, so that caregivers are prepared to make informed choices about any potential approved gene therapies. The common questions are: "Is my child too old to get a gene therapy?" "Will a gene therapy address all of my child symptoms?" "Will my child be able to walk and talk?" "How long will it take for this to work?" "When will this be available?" "How much will it cost?" "Is gene

therapy safe?"

Some additional questions I field are about access. "Will there be a placebo in a clinical trial?" "Will my child receive a treatment if they received a placebo during a trial?" "Who will have access to these approved treatments?" This is particularly relevant for rare diseases with dispersed populations.

It's important to clarify that the science is moving quickly, and we don't have all the answers to these questions yet, because they are still actively under investigation and even change as more drugs are approved.

As that happens, our families ask about and want to understand the clinical trial and approval process. They ask, "What information does a gene therapy clinical trial provide, and what doesn't it provide?" Our community wants to know about the long-term impacts of gene therapies, and we need to acknowledge that because these are new treatments, there's limited long-term data. Our community also needs to understand how receiving a gene therapy may affect access to future treatments, including next-generation gene therapies.

In conclusion, we need improved education and guidance about gene therapy drug development. We also need continued education about the long-term impacts of gene therapy treatments. This information would help our community make informed decisions regarding approved gene therapy treatments.

Thank you.

DR. ROWZEE: Thank you both so much for sharing your perspectives today.

Next up, we have Joan Powell, a myelodysplastic syndrome (MDS) patient and advocate.

MS. JOAN POWELL: My name is Joan Durnell-Powell. I'm an MDS patient. I've been diagnosed since 2014. A lot of you are probably not familiar with the disease. It's a rare blood cancer. There's no cure; there's only treatment. It's a rare form of anemia. Today I'm a patient looking toward the fact that a possible gene therapy program could be established for me. These are some of the questions that they asked me to touch on today.

The most important thing when I started my research: What is gene therapy? I understand what it is now, but I possibly could be a candidate in the future, because not only do I have this rare blood disease but my disease could also—I hate to say it—become leukemia. These are the different types of gene therapies that people have been involved in over the years.

My biggest concern is: What are the risk factors? All have to do with immune systems. I have a compromised immune system, and they talk about the virus that might be involved in and possibly other areas in gene therapy.

Then there's the cost: I'm on a low fixed income, and any dollars or cents that would go

toward this type of treatment would be very costly for me. Will my insurance pay for it? That's a big question.

For those who have the CAR T cell, FDA has approved helping them with the payment. It can cost between $1 million and $2 million if you are able to get this type of treatment.

Once again, there are potential risks. The process might be complicated, and there might be long-term effects.

There should be a registry where a patient like me can go and get some additional information on patients who have had this type of treatment with MDS and can answer any questions or concerns that I might have.

As I said, my next step now is to go into a registry. I haven't found one yet for MDS, but I'm praying that I do. Once again, I have a rare disease, and a lot of rare diseases are now being given the opportunity to have gene therapy.

Long-term effects—that's the big thing. Anyone who has a chronic disease, they want to know what the future holds. So that's some information that you would need to find out, as a patient, whether or not there would be any long-term effects from having this type of treatment.

My purpose here today is basically just to ask, as a patient: Would it be a good thing for me to continue my investigation into whether or not gene therapy should be a part of my future treatment? Has it been a success in reference to other treatments? With MDS, I'm not sure.

These are some of the references that I went to for my presentation, and my presentation will end with this: My theme in life is to get busy living. So my next thing will be to get busy looking into gene therapy for patients with MDS, and I thank you.

DR. ROWZEE: Thank you, Ms. Powell, for your insights and for sharing your perspectives today with us.

Our next speaker is Priya Stephen.

DR. PRIYA STEPHEN: Hi, my name is Dr. Priya Stephen. I'm with Wiskott-Aldrich Foundation. I have no conflicts to disclose.

I would like to share through my story the process that families go through when making a decision to opt for gene therapy when another treatment exists. Many families in our Wiskott community face the same decision, and we all have versions of the same story. So hopefully this will help.

My son, J, was born 14 years ago with Wiskott-Aldrich syndrome. It's a hereditary disease that causes low platelets and immune deficiency. When he was born, his platelets from Day 1 were low enough to cause a life-threatening bleed. By age 3 months, he ended up in the

ICU with a severe lung infection. We learned he had Wiskott-Aldrich and that his life was in imminent danger without a cure.

The standard cure is a bone marrow transplant, but he didn't have a match in our family or through the bone marrow registry. We spent the next few months interviewing leading experts in transplants, but this path felt too risky for him without a good match.

We learned that there were investigational trials in a few centers—this was in 2010—looking at a new method: gene therapy. There were no trials in the United States. At first, this seemed like a last resort, but I emailed and Skyped with the doctors who were running trials in Italy, Germany, France, and the United Kingdom. We met a doctor who was going to start a trial in Boston, but he told us that we had no time to wait while he waited for approval.

Finally, we talked to doctors in Milan, Italy. Their trial involved using a lentivirus vector, which had a good track record in other trials. They were using a gentler chemotherapy regimen, which was important, because we worried about fertility for our child if we gave him high-dose chemo. We also worried about the toxicity of high-dose chemo. They had already performed gene therapy on two patients who were doing well so far. Our child would be the third. The third! That sounded really scary. But we realized that, although this was the third patient they had with Wiskott-Aldrich, they had prior experience doing gene therapy for other diseases. They had more gene therapy than most centers in the world at that time.

Now, I'm a pediatrician. I'd heard the stories of the first patients who got gene therapy. I knew there were a lot of risks, but I also knew that the gold standard of care—the bone marrow transplant—was going to be really risky for my child without a perfect match. And we knew at that time that if we somehow had a poor outcome from gene therapy, we could always revisit the idea of bone marrow transplant if we had to.

We decided to enroll in the Italian trial. We moved to Italy for the next 5 months. We were lucky enough to have the flexibility to do so; I know for many families, that has been a major barrier. In June 2011, J had his gene therapy procedure, and his body was given the ability to produce a protein that he had been missing. It was a complicated, difficult hospital course. He lost all his hair after the chemo. He felt awful.

When we flew home, we ended up in the ICU at Children's Hospital again for another 3 weeks. But in the next few months at home, we saw his immune system start to work again. He was no longer at risk for severe bleeding and immune compromise.

My son lives a normal life now. He wrestles. He snowboards with no restrictions. We have to return to Milan for regular visits, because they monitor closely for complications, make sure the immune system remains corrected, and check that he has no sign of malignancy, like leukemia and lymphoma. I will always have that kernel of fear in my mind that we'll find some long-term complication. But there's been no sign of any of that, and it's been 13

years.

When I talk to families who have received the standard of care—a bone marrow transplant—I realize that J's life has been incredibly uncomplicated in comparison. He has no need for immune suppression, he has no graft-versus-host disease, and he's on no gene therapy -related medications.

I want to make sure that other families, including those with mild Wiskott-Aldrich, have the same opportunity to make an informed decision in their child's care. Medicine's not just about survival rates anymore; it's about survival with a great quality of life. Families deserve to have access to newer therapies that can offer this—even families who don't have the means to travel overseas.

Thanks for your time; thanks for listening.

DR. ROWZEE: Dr. Stephen, thank you for your comments and for sharing J's story and your family's journey.

Next up is Joshua Thayer from the Jain Foundation.

MR. JOSHUA THAYER: Thank you, everyone. This is Josh Thayer. I live with limb-girdle muscular dystrophy type R2, which is also referred to as LGMD type 2B and as Miyoshi myopathy. It's really one disease that's linked to the absence of the dysferlin protein, and it's broadly referred to as dysferlinopathy. I work for the Jain Foundation as their general counsel. The foundation is focused on finding treatments for people with dysferlinopathy. I have no conflicts or other disclosures to make.

I've provided a brief overview here of my journey with this disease. My pattern and rate of progression has been fairly typical for someone with this disease, though I should point out that it varies quite a lot by patient. I should also point out that dysferlinopathy is only one of a number of distinct genetic disorders that falls within the overall umbrella name: limb-girdle muscular dystrophy, or LGMD. So you'll find that heterogeneity is great not only within each subtype but of course across all subtypes as well.

So I hope to put my perspectives in some context here, and I hope that this slide shows that I'm generally willing to take risks and to endure discomfort when I believe that doing so will truly advance the science and drug development. I can only speak for myself. Here are some examples of things that I've done since my initial diagnosis. But the sense I get speaking to other patients with an LGMD—and with dysferlinopathy in particular—is that they have a similar willingness to do these things, particularly when electing or being given an opportunity to participate in a clinical study. Now, that risk profile might shift a bit with respect to approved therapies.

I do have concerns. I should point out that there's currently no approved therapy for any subtype of the LGMDs; they're horrible muscle-wasting diseases. In the context of this presentation, I'm focusing really on adeno-associated virus (AAV)-delivered gene therapies

because they tend to be the ones that are currently closest to approval, or at least in active later-stage preclinical development and clinical development.

So my first concern would be with toxicity. The AAVs are considered save vectors, but the sheer viral load required to show functional improvement in many of these diseases has caused serious adverse events in at least some clinical trial participants.

The second biggest concern for me would be a lack of clinically meaningful benefit, or a short duration of lasting benefit. After all, when you assume greater risks, you hope for a real reward.

And then related to the concern with efficacy and duration is an immune reaction that would render redosing—or even dosing with a new AAV-delivered therapeutic—not possible.

And finally, as I'm running out of time, these therapies aren't practically available unless they're covered by insurance, as Joan Durnell-Powell very clearly pointed out in her presentation. And that's obviously a concern for all of us.

I'll have to end here, I guess. Thank you.

DR. ROWZEE: Mr. Thayer, thank you so much for your comments. And again, if you have more slides or more information, we encourage you to go to the docket please and place your comments there. Thank you.

Next up is Cristina Vargas, who's representing the Juju and Friends CLN2 Warrior Foundation.

MS. CRISTINA VARGAS: Everybody, thank you for your time today. My name's Cristina Vargas. I do not have any affiliations or disclosures with any other organizations.

Today, I'll be discussing safety considerations from a patient's perspective on gene therapy and treatments. As a parent of a child with CLN2 Batten's disease, I understand firsthand the complexities and challenges of navigating the world of gene therapy. The stakes are incredibly high, and making safety considerations is paramount in every decision.

Understanding CLN2 Batten's disease: It's a rare neurodegenerative disorder with devastating impacts on children and families. There is a very high emotional toll. I collaborate with it as well, and you have constant worry about your child's progression, the quality of life, what to expect. Advocacy is essential to ensure that our voices are heard.

And safety considerations for our patients and caregivers: We need to have comprehensive information and be able to understand that families must be able to receive clear details about gene therapy; know what their options are; know the risks, the benefits, and also the importance of understanding any potential side effects and long-term outcomes. I would need to have an informed consent; caregivers need to be fully informed and involved in the consent process as well.

Transparency is key. All of our questions must be answered respectfully and thoroughly. We need an interdisciplinary approach. A collaboration among medical professionals, researchers, advocacy groups can definitely improve the understanding and implementation of gene therapy. We need long-term monitoring as well, after gene therapy is conducted, establishing a robust follow-up protocol to be able to monitor the side effect and efficacy of gene therapy. Creating a feedback loop between families and also health care providers is important.

One last thing: the emotional and psychological support that's involved. We need to be able to ensure availability of all mental health resources. For families that are navigating the treatment options, we need to be able to create support networks for sharing experiences and challenges with others in similar situations.

And a call to action: Change is necessary. As a devoted advocate, my battle does not just end with my child; it extends to all children facing the challenges of Batten's disease, and any other rare disease condition. We must demand greater accountability from pharmaceutical companies and health care systems. We need policies that prioritize patient safety and also have an informed decision-making process. We need to have increased funding for research into better treatments and potential cures as well.

Together, we can create a safer and more informed environment for patients and caregivers considering gene therapy. It's time for our collective voices to lead the change needed for our children's future.

Thank you for your attention. Let's make a difference for our children in the rare disease community.

DR. ROWZEE: Thank you, Ms. Vargas, for contributing your comments and perspectives today.

Next up, we have Jennifer Weiland Payne.

MS. JENNIFER WEILAND PAYNE: Hi, good afternoon. I'm Jennifer, adult patient with phenylketonuria, or PKU. I have no affiliations other than independent advocate, and I have no financial disclosures.

My goal today is to help FDA not only have a deeper, culturally embedded understanding that values the science of patient engagement in approved gene therapy considerations. I also want to help FDA responsibly act with what is reasonable, realistic, equitable, and impactful.

PKU fits the scenario where a rare disease treatment option is available, but availability does not mean accessibility. I am talking about medical food or food as medicine, which has never been integrated into the health care system as a vehicle for wellness and for which viability was literally shattered by the Nation's formula crises. Access is my #1 fear with gene therapies, because such barriers pose a threat to health to debunk the

unacceptable state of the art of gene therapy for PKU. Data on poor adherence to dietary therapy translates today to detrimental outcomes. Today 85 percent to 95 percent of adolescents and PKU adults having blood Phe levels exceeding the thresholds of toxicity.

PKU is a hidden disease that threatens the brain, and it is an invisible disability for which the long-term health consequences of dietary therapy are uncertain—even on kidney and bone health for my age and generation. As a PKU adult, I have been misperceived to have supernatural powers in overcoming natural history and stigma of living with this rare genetic disease as a solved disease. The pace in accelerating new and novel therapies, or even a cure, cannot come at a more critical time, with my having limited to no options, evidenced by a diet's long history of simply not achieving optimal health change as once assumed and posing global challenge to our community.

Although patients would risk and sacrifice for an approved gene therapy as a spectrum, there are shared experiences and interest when a potential cure is in scope. In the book *The Child Who Never Grew*, Pulitzer- and Nobel Prize–winning author Pearl Buck described feeling as if she were bleeding inwardly and desperately upon hearing that there was no hope for her daughter with PKU. This doctor's truth communicated to Buck is an unduly forced, still permeating culture and played out today with gene research for PKU, abandoned until recent years.

While stakeholders may not agree on what's important, patients do what they need to do, because they're the experts. As an adult with PKU, I identify with bleeding inwardly and desperately for hope, for the promises of a cure. I have no uncertainty about long-term benefits, effectiveness, or safety for gene therapies, because I trust FDA to do its job. But I expect equity to be built into the core of relevant frameworks, so that everyone has the opportunity to attain their best health, with no differentiation of rare diseases.

The final verdict that there is no hope for PKU—or disqualifying PKU, a hidden brain disease, as not serious—is misguided. It is a disease in and of itself and is downright dangerous.

Patients cannot be proactive partners in streamlining processes that support research and approval for gene therapies unless gene science is communicated with them in plain language. This slide shows that interconnectedness, communication among stakeholders, and safety considerations cannot occur in a silo. The patient values interest in order for gene therapies to meet their needs. Availability takes many factors and FDA approval. Uptake in the market takes acceptance. Awareness and education spans everyone, from the prescribers to the purveyors to all FDA partners—especially FDA—when it comes to clarifying public misunderstandings, regardless of product type.

This slide does not even touch on the influence on historic sociocultural health system—economic or political factors, which I would call holes or leaky gaps. But it shows that patients are the interface of it all.

Patient data without context or culture is missed opportunity. I do not want to see PKU left behind again. To close the leaky gaps—information access, best practices prescribed—, FDA needs to understand that communication is relational, not transactional.

Thank you.

DR. ROWZEE: Ms. Weiland Payne, thank you so much for your comments.

Next up, we have Shandra Trantham from the Friedreich's Ataxia Research Alliance.

MS. SHANDRA TRANTHAM: Hi. My name is Shandra Trantham, and I'm from Florida. I am a patient ambassador for the Friedreich's Ataxia Research Alliance, and I have no disclosures.

I was diagnosed 15 years ago with a degenerative neuromuscular disease called Friedreich's ataxia, or FA. So far, FA has robbed me of my ability to walk independently, speak clearly, and enjoy many of the things I used to do. In the future, FA may have a chance to damage my heart, take away my vision and hearing, and end my life early. On behalf of the FA community, I want to emphasize that we support the progress of research and drug development.

Gene therapy could treat FA and its root cause, and we urgently need access to it. We would rather have access earlier to a gene therapy that was approved based on a less supported surrogate endpoint than have to wait for additional evidence of clinical efficacy. Some of us will die waiting.

Certainly, this means that we won't know exactly how well an approved therapy is going to work. And we accept that, provided that clinical efficacy studies are started as early as possible and continue post-approval. We understand that these studies may take years to show results, and we believe that interim findings should be shared transparently with patients in an accessible language, as many people mentioned earlier.

For multisystemic diseases like FA, gene therapy design faces challenges that create uncertainties for approved products. With current limitations, it may not be possible to get a gene therapy that targets the heart and later get one that targets the nervous system.

Neurological symptoms impact our quality of life and ability to interact with the world, while cardiac symptoms impact our lifespan, making it crucial to treat both. We stress how important it is that every effort is pursued to address the challenges brought on by the immune response to AAV vectors to allow for redosing or additional gene therapies as new symptoms arise over time.

We need and want multiple treatment options; however, we need to understand how such treatments will work in combination. For example, in FA, extensive research has shown that there is an upper limit to the safe expression of the deficient protein, frataxin. If a protein replacement therapy and a gene therapy were both available in the future, it may

not be safe to take both. Or maybe it would help more. We don't know, and we ask that FDA encourages or even incentivizes studies early that address the safety and efficacy of multiple or combination therapies.

Finally, I want to encourage the pharma companies listening today to provide extensive training on gene therapy to the clinicians and facilities administering their product. I'm doing my Ph.D. on gene therapy, so I've gained an intimate understanding of the potential risks, uncertainties, and benefits. And I believe that the decision to receive gene therapy is complex. Patients should have access to clinicians they can trust to understand all of the variables and help individuals make informed decisions for their specific situations.

Thank you.

DR. ROWZEE: Shandra, thank you so much for your comments.

We have two speakers that we did not see on our chat today. Rama Boddanapalli and Michelle Stevens, if either of you are on the call today and would like to speak, please reach out to our support team via the chat or please put your comments in the docket.

Thank you.

Now, I think we've wrapped up all of our Session 1 public speakers. Thank you all so much again for your comments and your perspectives.

FDA Panelist Questions

DR. ROWZEE: I'm now going to open it up to my CBER colleagues to ask any clarifying or follow-up questions they may have. And I invite you all to come off mute and turn your cameras on when you're ready. Thank you.

I think our first question might come from Dr. Avanti Golikeri.

DR. AVANTI GOLIKERI: Hi, this is Dr. Avanti Golikeri. I'm a medical officer in CBER. I want to express our gratitude to all of the presenters today for sharing their perspectives. I think it was really insightful.

My first question today is to two specific speakers, Ms. Conecker and Ms. Vargas, who I think addressed this topic a little bit in their presentation.

When we are reviewing various gene therapy products through development, we often hear from patients and caregivers about what benefits are meaningful. But as it relates to risk, how would you like to see patients and caregivers having a seat at the table early and often to discuss whether the risks are tolerable in the context of the potential benefits?

Thank you.

MS. VARGAS: Just being able to have clear communication, as I mentioned in my presentation. Communication is key and being collaborative, working together between the patient, health care providers, and also organizations, such as the FDA. It will give us a chance to be able to have a paramount amount of communication, where there's nothing left to the cracks. And being able to observe studies after the trials are conducted too—that's how we know what needs to be fixed and what needs to be focused on.

Thank you for asking me a follow-up question.

DR. GOLIKERI: Thank you so much. Yes, I'll also give some time for Ms. Conecker, if she is still here.

MS. CONECKER: Thank you so much for that question.

I think that I'll kind of echo what Cristina said: The key is really active participation from the earliest stage possible as there are therapies in development, so that clinical outcome assessments are appropriate and meaningful for the community. Also, I think, really finding ways to bring in the patient voice throughout that process. I think companies are getting better at that, but really prioritizing that that meaningful change is integrated, and patient perspective about risks, benefits, and the toll of a trial are thought through early, so that people are not taken by surprise or won't enroll in your trial because you haven't really thought about what works best for them.

DR. GOLIKERI: Thank you for sharing your perspective. I can open it up and see if there are any others who may want to respond on this before I move to the next question.

Okay, I'll turn it over to Dr. Kaushal.

DR. MEGHA KAUSHAL: Hi, thank you again for sharing all your perspectives today. I'm Megha Kaushal. I'm the Branch Chief for the Benign Hematology Branch in OTP.

This is for Mr. Hill, Ms. Nye, or Ms. Brown. You all mentioned having animal studies or preclinical studies and postapproval studies to continue to collect data. So when you're evaluating the risks of gene therapy, what other different sources of information do you find most useful for decision making related to treatment options? And are there certain types of information you wish were more publicly available, or easier to access?

MS. NYE: So I guess the question is about preclinical models and what is helpful before and after gene therapy. I think that for patients, we're talking about approved therapies, but this process really starts so much earlier. So I think, on the preclinical side, really making sure that the toxicology includes patients, that the study design is patient-centric, and that we harmonize some of these protocols. I think right now, often, companies have their own immunosuppression protocols. But really making sure that those are harmonized would really help patients, because they could look across multiple disorders, not just about their specific rare disorder, in terms of making some of these decisions. It would also streamline the process for FDA.

DR. BROWN: And just to piggyback on some of that, I think some of the questions that we get from our affected community are about other rare diseases that have an approved gene therapy. "I'm reading about this in the news. Why doesn't this apply to our rare disease?" I think that improved education about what differences there are and what similarities there are between different approved treatments is key. And also, I think, from the drug development process, about what data we can publish and make publicly available that can be utilized for the development of multiple gene therapies. Are there platform mechanisms? What data can we use for general biodistribution for say, any specific AAV9 capsid? Is there publicly available data that we could use in sort of a platform mechanism?

MR. HILL: Thank you for the question. I can only answer it from a hypothetical going forward. There's only been one gene therapy clinical trial in FA, and it was a cardiac trial for which my daughters didn't qualify. But going forward, seeing the data from preclinical studies and understanding the safety implications, the transparency of what was studied, the duration of the study, what was assessed—those are the things we would want to see as a patient. And of course, some of that would be interpreted through our care team.

DR. KAUSHAL: Great. Is there any consideration where you have access to all these types of information, if you're getting it from your health care provider or other avenues where this would be more publicly available for you all?

MR. HILL: In other trials, it's been made available to us through the announcement of the clinical trial. So that's where we would look first.

DR. BROWN: I think a place that we commonly look, as a scientist, is in the peer-reviewed literature. And so, I think, as the patient advocacy group, it's our role to look through the published literature and also go through public resources—such as what's published through FDA—and make that accessible to our affected community. Just published resources that are used in the scientific community—looking on PubMed and looking for peer-reviewed publications.

And I think this also goes back to the trusted source that requires regular communication. Oftentimes, our patient community trusts the patient advocacy group, because we are regularly communicating. So in addition to more patient communication with FDA and other agencies, I think it's also important to educate and communicate regularly with the patient advocacy organizations that already have this trust and rapport and that can make some of the data accessible to our affected community.

DR. KAUSHAL: Great. Thank you. I'll hand it over to Dr. Elenburg.

DR. ELENBURG: Thank you. I'm Shelby Elenburg. I am Clinical Team Lead in General Medicine Branch 1.

I have a question for Dr. Priya Stephen: As a doctor and a mother, how did you balance the known risks of transplants with an unmatched donor and the unknown long-term risks of

gene therapy when making your decision about treatment?

DR. STEPHEN: It was hard. I think I was really lucky to have physicians on my side who were open to thinking outside the box. For me, when you go into mom mode, you kind of go back and forth between your thoughts, but the fear kind of takes over. And so, our immunologist at Children's Hospital (CHOP) was really open to the idea of looking at all the possibilities. And for us, it was about information gathering. It was about talking to a lot of different people in different centers. And when none of them could reassure me, that's when I started to look at the risks and benefits of gene therapy.

For me, it came down to looking at the data of people who had already gotten gene therapy, but also looking at the toxicity. I was really worried about chemotoxicity, about fertility, and about long-term outcomes. And so, I think, having that available access for parents to look at, I feel like I only had that access because I was lucky enough to have had contact with the right doctors. At that time, people weren't talking about gene therapy very much. One of my doctors was like, "Oh, it's kind of a Hail Mary. I don't know if you want to do that." So I did really rely on having the right people kind of batting for us and putting us in touch with people.

For me, it was taking a chance, but it was really about knowing that with a mismatch, I had a pretty not-great chance of a good outcome. So, he was not going to make it without doing something. So that made it okay to try and take the risk, I guess, if that answers your question.

DR. ELENBURG: Yeah, it does. Thank you so much. I think that's some really helpful perspective for us to understand, especially in a young child and in something that is expected to be progressive fairly quickly. Understanding the different available options is really important.

A quick follow-up question: I know you said that you had connection to the right people, and so you were kind of lucky in that sense. Do you think that that is better now? Or how would you recommend that people seek out that type of information now, as more therapies have been approved and there's more information out there?

DR. STEPHEN: I think it's a little bit better now, but I think it depends on who you talk to, right? There was a gene therapy trial that didn't go well before the trial that we were in, so I think that people are still talking about that. You have to talk to the right people. I think that for people who are connected to our foundation, they get that.

Someone mentioned earlier that the patient advocacy foundations are helpful sources of information, because if you're at a big academic center, you're going to get the information. But what we see in the foundation is that for people who are at smaller centers and not at a Wiskott center of excellence or who were just diagnosed it's hard for them to get that information. They really rely on their Facebook connections and things like that, which is hard. It would be great to see a collation of an information page, with data right

there in patient-friendly format for people to see. That way they could really see their options without being dependent on hooking up with an expert in the field right away who's open to something other than BMT, because I don't think they get buy-in from everybody across the immunology community still.

And I think part of it is also about looking at survival rates versus quality-of-life rates. I think you look at numbers and you say, "Oh, well. Bone marrow transplant has gotten better, and survival rates are similar. So why should I go to this investigational therapy? And I have to go out of the country for it, so why would I do that?"

But it's having more data out there on quality of life and actual morbidity data versus just mortality data. I think that's important too.

DR. ELENBURG: Thank you so much for that perspective. It's been very helpful.

MR. BEDSOLE: While we're talking about choices, one of the areas that we had difficulty with as the different trials progressed: You've got different pharmaceutical companies that are each running their own trials. Well, they all want to report the most favorable results they can. So it makes it very difficult for patients and even for our doctors to try and sort through and determine which is the better choice for the patient once the trials have been completed and the drugs have been approved.

And as more and more therapies are becoming available, and as I listened to all this, the amyloidosis community went through the same situation that so many of these other disease communities are having now: We didn't have any kind of treatment therapies available to us, and now we suddenly have three different gene silencers, and now there's more studies on doing gene editing that would potentially be a cure. So it kind of puts us a little bit ahead of where everybody else is. The struggle was trying to figure out, "Well, now that you've got choices, which choice is the right choice for me? How do I compare the efficacy and the risk to determine which drug is more appropriate for my situation?" And if there's some way that FDA could help with how the trials are structured, it would make the reporting easier and easier to compare.

I don't know if that's ever going to be a solution that could ever happen. But if there's some way that you could help with that, it would be a great improvement for all of us.

DR. ELENBURG: Thank you for that feedback. All of these things are very helpful for us to understand from the perspectives of patients and caregivers.

I would like to pass it back to Dr. Golikeri for another question, if we still have time.

DR. GOLIKERI: Yeah, thank you. This question is for Mr. Melmeyer.

For diseases such as DMD and SMA that have approved gene therapies available, do you mind sharing some insight on how the patient communities are getting information about risks that are identified after approval? Or maybe preferences on how they would want to

receive this information, if there are new or potentially worsening safety findings after gene therapy has been approved?

MR. MELMEYER: Yeah, that's a very good question. I'd be happy to answer that.

I would say most folks within the DMD and SMA communities are very close with their clinicians, especially the clinicians who they've gone through the gene therapy journey with. And as we know, it's oftentimes a journey. It's several months. It's many visits. And so there are very close relationships between members of those communities and the clinicians and their care teams.

From my perspective of getting to know both communities, I think that they'd be saying that their clinicians, their physicians, and their teams at the multidisciplinary care centers is where they'd want to be having these conversations. They want to be closest with the individuals in the care centers and their care settings to better understand the evolving risk profile of a gene therapy. I think, from there, that they would also go to the patient advocacy organizations—such as ourselves, Parent Project Muscular Dystrophy, CureDuchenne, Cure SMA, and the many different DMD- and SMA-related patient advocacy organizations. Within our team, we have a set of individuals who are specifically there to answer questions about gene therapy, both for individuals who are considering gene therapy for their child as well as individuals who have gone through that journey and want to learn more about what could be coming next.

And then I'd say that the third area is that individuals really want to connect with fellow parents. We hear a lot about the feelings of isolation within our community, of people wanting to talk with other parents who have had to go through these decisions and had to go through the journey of obtaining a gene therapy, and how validating it is to get to know other parents and children who have gone through this. So I'd say those are the three places that our community would be looking for that information.

DR. GOLIKERI: Perfect. It's really helpful to hear how this information reaches the patients and their care partners. Thank you.

I'm not sure if we have a couple minutes for a last question, so I'll turn it over to Dr. Kaushal.

DR. KAUSHAL: All right. This is for Ms. Trantham.

If you're online, as a patient and a researcher developing gene replacement therapy for a different disease, how would you describe your work has impacted your perspective about risks of gene therapy for yourself? And what are the considerations for receiving a gene therapy in the future?

MS. TRANTHAM: Well, I think that my personal case is based on how my individual presentation of the disease is. So a lot of people—or everyone, really, with Friedreich's ataxia—have a different presentation. Some people have the life-threatening cardiac

symptoms. I don't have those yet. So I feel privileged that my symptoms could wait for something that may be neurological in focus that is not available right now, whereas other people would need whatever they can to make sure that they stay alive.

Having that in my perspective doing research, I've really learned how much we don't know about it. I know that sounds silly, but I think my understanding before starting my Ph.D. is a lot different than it is today. I realized how big the uncertainties are, how much we don't know about what we could expect benefit-wise from it. And I think that has made me more cautious in wanting to do a gene therapy treatment.

But again, that's a privileged answer, because I don't have the life-threatening symptoms yet. Whereas other people may need to get the treatment right away, and they don't have the privilege to wait for something different or better.

DR. KAUSHAL: Thank you for sharing that perspective. Yeah, that's what we hear a lot—the durability of a product and then the unknowns of when we finally get the data on these long-term effects. So thank you for sharing that.

I'll pass it back to Dr. Elenburg.

DR. ELENBURG: I'll ask one more question. This is for Ms. Lorenz.

We like your idea about access to information and hyperlinks, or easy-to-access information for patients. If documents related to rare diseases and gene therapies were able to be put on the FDA website, for example, what types of information regarding risks would you like to see available for patients?

MS. LORENZ: Thank you. What I find as an advocate in the patient community is that there's really no place to have one consolidated picture. And unless you are really connected as one of the leaders in the patient community, when you're first diagnosed, you are so overwhelmed—especially when it's a terminal diagnosis and a rapidly terminal diagnosis. So the thing that I find is, I end up giving people kind of a one-pager that says, "Here's some of the first steps. Now, let's talk about the next things you would want to know after you look at these." It kind of helps them have a checklist.

And then the other thing in the two diseases that I'm active in—I know what has really helped a lot is having access to the AdComm, or advisory committee, testimony of the physicians of FDA and then the patients. That's really hard to find. Those of us who have participated in AdComms know where to find it, but it's really hard for people who haven't, who are new to the disease, to find those things. They don't even know what an AdComm is. They don't realize people have testified. I think if FDA could have a resource on "Here's what you should know when you have a rare disease," and then, in each disease, kind of have a summary and then the backup documentation for the people who want to dig deeper into the data.

Some people don't know how to use clinicaltrials.gov, right? There's so much that is so

overwhelming when you have a rapidly terminal disease that we need a one-stop shopping method that can take us to the resources as we need more.

DR. ELENBURG: Thank you so much for that perspective. I agree sometimes it's hard to find that information. And also, not every gene therapy that gets approved gets an advisory committee meeting, or even some of these safety signals don't always go to an AdComm. So thank you for that perspective.

MS. LORENZ: And I just encourage that from the patient community. AdComms help us probably more than anything, because it's patient-to-patient, and it makes sense to us. And so, while I understand you guys don't like to necessarily do them for all diseases, it really does make a big difference for the patient community.

MS. WEILAND PAYNE: If I could just weigh in on this real quickly, because I know you want to wrap it up. I think the question, as far as the information, kind of invokes having a centralized source. There's a lot of expertise on rare diseases throughout FDA, and this might be something to raise at the meeting for the Rare Hub for accessible, understandable information on gene therapies at the patients' level of understanding.

I know when it comes to firms and industries or drug development, there's a lot of guidance documents as far as enforcement compliance, as well as webinars. Maybe have a patient webinar series as an information campaign to really communicate the gene science at the patients' level and keep it in the centralized hub where patients can go.

Thank you.

DR. ROWZEE: Excellent. Thank you all so much.

I'm glad that I took moderator privilege there and let that question be asked and heard from some folks, because those are areas that are near and dear to my heart. So thank you to our OTP panelists for your questions. Thank you so much to our public speakers for such a rich and thoughtful discussion.

Again, I encourage folks, if you heard some questions in this panel that you didn't get a chance to respond: Please, we're happy to see your comments in the docket as well. I know we didn't have enough time today but really would like to continue the conversation and learn more from our audience.

So we're going to take a quick 5-minute break. I think we're going to begin the next section at 2:10 p.m. Eastern time. For those speakers in Session 2, you should be able to access your microphone and camera shortly after the break. When we come back from break, you'll see CBER's Patient Engagement Program Manager, Karen Jackler. She's going to take over as moderator for Session 2.

So, while I still have the mic, I'm just going to take another quick moment to thank everyone who is taking part in this meeting today, either by listening in, participating in

our polling questions, or sharing your perspective. We truly appreciate you taking the time to participate in this important conversation. Thanks so much. We'll see you in 5 minutes to begin Session 2.

Take care, everyone.

Session 2: Partnering with Patients and Caregivers on Long-term Studies After Receiving a Gene Therapy

MS. KAREN JACKLER: Welcome back. I am Karen Jackler, Patient Engagement Program Manager at CBER and your moderator for Session 2. We will now move to the second topic of the meeting, partnering with patients and caregivers on long-term studies after receiving a gene therapy.

For our confirmed Session 2 speakers, 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'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. Please proceed so that you can get your mic access.

Before we begin the speaker presentations, Dr. Larissa Lapteva, Associate Director for Clinical Science in the Office of Biostatistics and Pharmacovigilance, will provide a presentation to lead us into the listening part of the second session, after which we will have polling questions. I'll pass it off to Dr. Lapteva to talk about collecting long-term data after FDA approves gene therapy.

DR. LARISSA LAPTEVA: Thank you, Karen. Good afternoon, and welcome, everyone, to the second part of our meeting, which we plan to be about partnering with patients and caregivers on long-term studies after receiving gene therapy treatments.

As you have heard this morning, gene therapies approved by FDA are approved for all of these conditions that you see here on the slide. And out of the many technologies that are used to design gene therapies, the approved products reflect two reasonably well-developed technologies. One of them is genetic modification or editing of autologous cells, meaning patients' own cells. The other of the approved treatments is the use of adeno-associated viral vectors that cannot replicate or multiply like real viruses but can be used to deliver the needed target genes.

As many of you recognize, the field of gene therapy is still emerging and growing. Collectively, FDA-approved gene therapies have been on the market in the United States for less than 10 years. So there is still a lot to learn about these products, particularly because they are expected to persist in the body and produce long-lasting benefits.

The other side of the coin, of course, is that serious side effects may appear years after

treatment administration. Patients and families who have used viral vector-based products that are administered into the bloodstream probably understand, as we've heard this morning, that the first gene therapy administration may impact one's ability to favorably respond to subsequent gene therapies.

There are multiple product design technologies that can be used, and it is not surprising that one genetic target may be influenced by more than one gene correction technologies. That is why a good understanding of the long-term clinical effects of different gene therapy products, with different technological designs, can substantively improve treatment choices for patients. But the reality of premarketing development programs for gene therapies with rare diseases is that these programs have small sample sizes. At the same time, the frequent use of regulatory tools, such as accelerated approval and expedited development, enables earlier marketing of novel gene therapy products.

Where investigational programs are small and of limited duration but the expected effects of gene therapies are long-lasting, collection of accurate and reliable long-term data in populations of product users after product approval becomes truly critical to understanding the duration of treatment response, the long-term effectiveness, and the safety of these therapies. All stakeholders have to approach such data collection responsibly and value every participant's health and time, as well as their efforts and commitment to improve their own health and the health of others. And so, today, we will listen to patients' and care partners' perspectives on long-term data collection. But before we proceed, I would like to outline for you some of the sources of data that can be used after gene therapy approval.

First of all, for approved products, data can be collected over the course of medical practice. This includes data routinely collected through electronic health records (EHRs), medical claims, and billing databases. Sources of long-term data collection also include registries, which may be set up to enroll patients with a specific disease or related diseases, or patients treated with a specific product or class of similar gene therapy products. I have no doubt that many of you in the audience are familiar with registries powered by patients with data entered by patients and caregivers and with input obtained from digital health technologies.

These data sources that I've just described are usually called real-world data. And when they're analyzed to evaluate effectiveness or safety of a treatment, the respective analysis produces real-world evidence. Long-term data with gene therapies can also be collected in predesigned studies, observational or randomized. These sources produce clinical study data and the respective evidence. Research and analysis can be done with data from all of these sources, whether designed or simply collected over the course of clinical practice. Let me now briefly discuss these sources.

I'll start with the data from electronic health records or billing and claims databases, for example, of large health insurers like Kaiser or Aetna or others. As you can see on the slide, data collected this way would reflect the diagnosis made at a certain point in time.

Then the related administered treatment, and in this example, it is a gene therapy and an adverse event if and when it occurred and was recorded in the respective database. Examining these data permits measurement of outcomes of interest, meaning adverse effects, in terms of their rates of occurrence. The advantages of using these observational data include standardized collection of the needed information and availability of the denominator of patients receiving a target product.

However, these types of data are not intended for evaluation of treatment efficacy or safety. And safety signal evaluation through these sources is often expensive. It may not be and often is not timely. The available data are limited in capturing important patient and disease characteristics and may be short in patient follow-up, all of which may result in missing unexpected adverse effects. Sometimes the diagnostic codes may be inaccurate, and there may be difficulties with treatment verification. And so, these disadvantages may result in systematic errors, which may significantly limit accuracy and reliability of the analysis results. That's why we often turn to registries and clinical studies for reliable, relevant, and accurate data collection.

Registry is an organized system that collects prespecified clinical and other data in a standardized format for a predefined population of patients. Registries may take different forms and have different owners or governing bodies, including product manufacturers, academic centers, medical professional societies, patient advocacy organizations, and research collaboration entities proficient in data collection. One good example of postapproval data collection with CAR T therapies is the Center for International Blood and Marrow Transplant Research (CIBMTR) database, which is a research collaboration between the Medical College of Wisconsin and the National Marrow Donor Program. Another example is the American Society of Hematology Research Collaborative Data Hub, which collects data from patients with blood disorders.

Many other long-term data collections are now being created, and in the interest of time, I won't be able to name them all. But I just want to say that FDA is aware of the many efforts that different organizations put into creation of reliable and well-functioning registries. We commend these efforts, which, at the end of the day, we hope, will improve and increase knowledge about gene therapies.

In registries, patient-level data can be collected through direct data entry or through the connection of other sources into the registries. Those sources may include claims databases, EHRs, patient-generated data, or medical device outputs. Successful registries are fit for use, meaning that they're either designed or structured in a way that answers a specific investigational question (and usually more than one) and includes relevant and reliable data that are accurate, complete, and traceable. A well-functioning registry would capture data nationwide or with a broad, multiregional inclusion. It would also have an infrastructure with periodic and sufficiently frequent data analyses, to enable faster signal detection and, more importantly, faster communication of findings.

Last December, FDA published a guidance document discussing different types and settings of registries (and I cited it here at the bottom of the slide). And my colleagues in CBER have recently developed a platform to be used by patients and researchers in postmarketing studies. The description of this platform is in the publication that is also referenced here—at the bottom of the slide—and I invite you to take a look at it later.

This brings me back to the navigation slide, where I would note that regardless of what data sources are used in evaluation of the long-term effects of gene therapies—whether they're primary data collections from predesigned studies or registries or secondary data uses of medical information—all of these investigations conducted after approval can be done, for example, by independent research groups to answer their research questions, or by product manufacturers who conduct these studies to better understand their products' effects and improve their use by consumers.

Many of you probably know that upon gene therapy approval, FDA may require the respective product manufacturer to conduct either a safety study (if there is a serious safety risk that needs to be investigated) or for the manufacturer to conduct a study evaluating efficacy of gene therapy, in case an accelerated approval was granted. Typically, study requirements are in strict study completion milestones and timelines to report the results to FDA. Besides postmarketing requirements, a manufacturer may make a commitment to FDA to conduct certain studies. They will be called postmarketing commitments, or the manufacturer may conduct studies voluntarily. Results and progress of postmarketing commitments and voluntary studies alike would be reported to FDA, usually in annual reports to the agency.

Now, when we looked at various data sources and the regulatory framework for the long-term investigations, let me walk you through some of the challenges that we see with these data collections. You probably can appreciate that this is not an easy endeavor to design, maintain, and conduct to get meaningful, reliable results from a long-term study or registry. And there are many challenges to this.

Postmarketing surveillance, when it's done alone—that is, done through EHRs and claims databases—has limited utility. Science evolves with time. Standards of medical care change. Medical policies and payment models evolve. And the study or registry infrastructure, once established, may fall apart, for a variety of reasons. Ownership or stakeholder organizational partnership relations may change. Expanded horizons may increase. Key personnel may change employment. And there may be dissipation of interest to evaluate long-term safety signals on the part of product manufacturers, for various business reasons.

And so, to overcome many of these problems, long-term registries and studies are built with flexibility components in them to enable adjustments to any potential, and especially predictable, changes that may happen along the way. In any long-term data collections, there are often difficulties with patient recruitment and increased attrition of participants as

time goes on, which may understandably happen for various reasons. And we hear a lot about patients' loss to follow up in these settings.

But we also hear that people with rare diseases who received gene therapies are more willing to participate in postmarketing studies, because they understand that their diseases are lifetime disorders. And if a cure or significant reduction in disease burden is expected, people living with rare disease understand the importance of looking after their health and the health of their loved ones in the long term.

So it is clear that long-term evaluation of the effects of gene therapies becomes truly critical for understanding the benefits these therapies offer and the adverse outcomes they may induce. That is why building effective registries and designing long-term studies with high yield for product information and low burden for patients and care partners is truly a great opportunity to improve the overall care of patients receiving gene therapies and to enable people to make more informed choices about their treatments.

And so, today's listening session combines patients' and care partners' perspectives on the barriers and incentives of participation in long-term data collections. We would like to hear your perspectives on the design, governance, and operations of long-term registries and studies on approaches to communications and the best ways to partner with patient communities on long-term data collections for gene therapies.

Let me thank all of the speakers who volunteered to present their views today. I and my colleagues at the FDA look forward to hearing diverse and informative opinions from you. And with that, I give the microphone back to Karen to start the polling questions.

Thank you.

Polling Questions

MS. JACKLER: Thank you, Dr. Lapteva. I also appreciate everybody who's gathered here to share their opinions. We are going to start some brief polling questions. This is our third and final round of polling. And we have three questions for you.

- Question 1: What would motivate you to consider participating in a long-term registry or study after receiving a gene therapy product? Select up to five responses most important to you:
    - "To help researchers learn more about gene therapies"
    - "To help future generations of my family and others with the same disease who may need a gene therapy"
    - "To get medical care for my disease that is better than what I could get on my own or with my health care providers outside of the study"
    - "To have earlier access to evolving knowledge of side effects of the gene therapy"

- "To have earlier access to the evolving knowledge of long-term benefits of gene therapy"
- "To be treated sooner for any side effects of the gene therapy"
- "To be able to access another treatment option for my disease sooner if the initial benefit of the gene therapy dissipates over time, or if I develop a side effect"
- "Other"

- Question 2: What concerns do you have about participation in a long-term registry or study after receiving a gene therapy product? Select up to five responses most important to you:
  - "Taking time and energy away from work, school, or family, such as parenting responsibilities"
  - "Taking time and energy away from caring for a loved one with a rare disease"
  - "Difficulty with handling digital technologies that may be necessary for registry or study participation"
  - "The need to complete too many forms, documents, or surveys that may be required for long-term data collection"
  - "Difficulty with transportation to and from the research site"
  - "Dealing with uncertainty, knowing that a serious side effect may be found in the future and significantly affect my health"
  - "Duplicating registry or study visits with my health care provider's appointments"
  - "Expenses associated with registry or study participation"
  - "I do not have any major concerns and would be willing to participate in a long-term registry or study to better understand the effects of gene therapy that I or my loved one received or intend to receive"
  - "Other"

- Question 3: What would you be willing to provide input on for a registry or long-term study? Select up to three responses most important to you:
  - "Design of a registry or study to support relevant and reliable long-term data collection"
  - "Oversight of processes to ensure good study conduct, resource planning, data recording, and staff training"
  - "Operations, including decisions on data collection, visit frequency, and reporting of adverse events"
  - "Control of data access and secure data sharing with other stakeholders"
  - "Decision making regarding what information is communicated to the study participants and when"
  - "I'm not interested in any of these aspects and only willing to participate in a long-term registry or study to have the effects of gene therapy on my disease

evaluated regularly"
- "Other"

I'll allow about 10 more seconds, and then we'll look at the results. Thank you all for participating in the polling. That was our last set of polling questions, and we appreciate your interacting with us that way. It really helps us to understand more about the people in the audience today.

Speaker Presentations, Part I

MS. JACKLER: Now we're moving into the speaker presentations, and I just want to remind you of the questions that we asked participants to consider. The following presentations will offer their responses to three main questions:

- What knowledge or factors might positively or negatively impact a patient's decision to participate in a gene therapy registry or other long-term study that captures gene therapy outcomes over a long period?
- What is important to patients and their care partners about how a potential registry or other long-term study that includes gene therapy outcomes would be designed, operated, and managed?
- What information about gene therapy outcomes in the long term is important to be communicated to patients?

We have 17 speakers for this session, and each speaker will have 4 minutes. I'd like to remind our speakers to stay on the line after you speak and for the duration of your session in case FDA panelists have questions for you at the end of the session.

Our first speaker is Laurie Adami.

MS. LAURIE ADAMI: My name is Laurie Adami, and I am a blood cancer survivor and a CAR T patient who received CAR T in 2018 in a clinical trial. I'm a very active patient advocate helping patients navigate cancer. I have no conflicts of interest.

My first point about long-term studies and follow-up is that until CAR T is available as a first line of therapy for blood cancer patients, any long-term studies will be muddied because of all the treatments patients underwent before they received CAR T. Currently, CAR T is approved as second or third line, depending upon what your diagnosis is. To date, about 35,000 blood cancer patients have received CAR T. And most of these patients went into CAR T having had multiple failed treatment lines.

I had had six treatments before CAR T, from 2006 until 2018, and I am still dealing with difficult long-term side effects from my first six therapies. I am now 6 years out from CAR T and considered cured, but my cancer is still considered incurable. After I had CAR T, it

seems to have changed the trajectory.

We know there are lots of secondary cancers from radiation, chemo, and autologous and allogeneic stem cell transplants. Also, I want to comment on the black box. I understand why the black box was put onto CAR T, but I also don't see that there's a clear line connecting CAR T to the few secondary cancers that were reported on these 35,000-odd patients who were diagnosed with secondary cancer post-CAR T. Again, all these patients had lots of treatments beforehand.

I also found it interesting today that the list FDA presented up front highlighting the risks of CAR T is identical to the side effect lists of many standard-of-care treatments, including chemo and allogeneic and autologous stem cell transplants. And the secondary cancers' mortality and morbidity that are associated with these old-line therapies to date are much higher than CAR T. So I'd like to see any long-term follow-up studies take into account the number of lines of treatment that the patient had prior to their getting CAR T.

I live in a big city, so I was always treated at a large academic center. My follow-up has been easy. That won't be the case for patients who have traveled to an academic center from a community oncologist to receive CAR T. I think it's important that long-term studies should be conducted by the patient's local oncologist, as many patients cannot get time off work and may not have insurance plans that will cover these types of visits for the 15 years that are required following on treatment.

I also want to comment about the fact that many blood cancer patients receiving CAR T are older patients who may have limited tech skills. So there should be an option to have the follow-up conducted by the local oncologist collecting the data over the phone, or at a follow-up visit in person. For tech-savvy patients, this isn't an issue; the portal will be fine. Of course, labs will have to be drawn at the oncology practice. And again, I'd like to encourage that to happen at the local setting, to make it easier for more patients to participate.

I also want to comment on the question "How are these practices going to be resourced to do this added work?" Having been in three clinical trials between 2006 and 2018, I know the side effect info only went one way: from me to my doctor to the pharma company that was conducting the clinical trials. The only info I ever got on follow-up was by digging and finding academic papers that were published after these three clinical trials.

How will pharma work to share the data to a central repository, given this is not something that's in the wheelhouse to date? And how will the info be viewed by patients and members of the public considering cell and gene therapy? These are all important considerations.

MS. JACKLER: Ms. Adami, we have to move on to the next person. I'm so sorry to interrupt you. But please remember we have a docket. If there's anything you didn't get to say, that's a great place to put it. Thank you.

Our next speaker will be Kathryn Bryant-Knudsen.

MS. KATHRYN BRYANT-KNUDSEN: Hi. My name is Kat Bryant-Knudsen. Thank you so much for inviting me to speak today. I represent the Speak Foundation, a patient-led advocacy organization for limb-girdle muscular dystrophy, or LGMD. My disclosures are that we don't have any commercial treatments for LGMD. Speak Foundation does receive grants and sponsorships from industry for our conferences and events from time to time. Quickly, I just want to review the questions that our community was asked to discuss, and I want everybody to have those in case they weren't shared.

One thing I want to share is that I'm speaking on behalf of our patient community. My job is to make sure their voice is highlighted. One of the things that our patients are super concerned about is that they don't want their decision to ever be taken away from them, because we understand there are uncertainties with gene therapy, and we are willing to accept those risks. We don't want unnecessary burdens to be created while we wait for bureaucratic systems to be put in place.

For us, time is muscle. Since we do not have any approved treatments for LGMD in the gene therapy area nor do we have any approved treatments anywhere yet it's super critical for us to make sure that we don't lag behind and wait on systems to be put in place. We are super supportive of some of the initiatives that have been mentioned today, and I also have some others that our community wants to express.

We also understand, from our LGMD Scientific Workshop that was held earlier this year, that each LGMD subtype is caused by a mutation in a single gene that leads to the absence or dysfunction of a specific protein needed for proper muscle function. The LGMDs are an optimal candidate for AAV gene therapy.

We also want to make sure that risks are communicated to patients after commercially approved products are available on the market. Gene therapy is a new treatment, and our patients know that knowledge in this field is developing overtime. As soon as a serious adverse event occurs, patients want to be notified. We'd like that to be in some kind of online system, if possible. Again, we don't want it to be a large bureaucracy to industry, to FDA, or to medical institutions.

But one thing we should all note: It's important to understand that in Rare Disease World, we don't have commercials on TV that tell us about side effects from treatments and medications. So we're going to rely on this information from doctors, industry, and patient advocacy. We want to communicate the effectiveness of long-term efficacy as well.

When possible for long-term follow-up, we need to recruit and actively look for remote participation. Going out of town for these clinics is very difficult on our patients. We would like—because we've heard that with other rare diseases, a company has special circumstances where it ceases a program—for there to be a long-term follow-up plan in place for medical monitoring. We also feel like information dissemination expertise with

gene therapy requires a commitment from everyone. And we'd like to see things in place to help with that medical monitoring, and to help patients understand things for the future.

Innovative considerations for private-public partnerships, one-stop websites, and informed consent could be handled off site, with advisors or third parties to help. We've heard patients say that patient advocacy organizations should be involved in helping to explain some of those risks. And when possible, please reduce the burden for travel in the future; let's try to do this more locally.

Thank you so much for helping. I am so glad to be here today. Thank you.

MS. JACKLER: Thank you, Ms. Bryant-Knudsen. I appreciate that.

Our next speaker will be Barbara Ballard.

MS. BARBARA BALLARD: I would like to thank the agency for this opportunity to speak today. My name is Barb Ballard. I am currently the director of SCID Angels for Life Foundation, where I advocate for patients with severe combined immune deficiency, usually referred to as SCID. I have no conflicts of interest. My only disclosure is that, at one time, I was a consultant to the Cellular, Tissue and Gene Therapies Advisory Committee.

I am the mother of a patient with X-linked SCID. My son passed away in 2019, at the age of 25. At the time of his passing, his bone marrow transplant was failing, and we had already collected stem cells from him to use for gene therapy. This was his only remaining option, and we knew it would be a rescue attempt. He passed away before we could begin the process necessary to receive his corrected cells.

Untreated, SCID is considered fatal by the time the patient is 2 years old. Gene therapy has held the greatest promise for a full immune system recovery. Gene therapy for SCID involves transferring a normal gene into a patient's hematopoietic stem cells, which have been removed from the bloodstream using apheresis. The cells are then reintroduced back by an IV into the body after niches have been created in the bone marrow, typically with chemotherapy. This approach aims to offer the advantages of allogenic transplantation without the risks of graft rejection.

The history of X-SCID gene therapy in particular has had its ups and downs. While studies performed more than 20 years ago showed the feasibility of the therapy, successfully correcting the T-cell defects, there was an occurrence of vector-related leukemia in a handful of patients. Since then, new vectors and isolators have been tested and incorporated into the latest trials to enhance the outcome and reduce the potential for side effects.

ADA-SCID and Artemis-SCID have seen extremely successful clinical trials for gene therapy without the occurrence of vector-related leukemia. This history of adverse events is the exact reason that long-term studies and registries are necessary post-gene therapy. Long-term studies should not only include incidences of adverse events but also quality of

life for patients post-therapy.

This is critical information needed to evaluate the true efficacy of gene therapy. While patients and their families want to know immediately about any adverse events caused by therapy, what they really care about is how the patient's life is after the treatment. Patients and families who understand that the information regarding their own experience with a therapy can help other families gain an understanding of the process are more likely to consent to participate.

Additionally, knowing whether or not relevant patient advocacy groups recommend participation in a study helps patients and families decide whether or not to participate. If long-term follow-up requires additional follow-up appointments with the medical team than would otherwise be required, the patient and their caregivers need to be made aware in advance of the cost they will be expected to bear in terms of time and travel.

The patient's privacy and anonymity should of course be protected. Physicians and researchers need to explain to the families involved exactly how that privacy is ensured, in detail but in plain language. Plain language summaries should include all the information on how the registry will be used, operated, and managed, as the average person without a medical background rarely has the experience to know what to question on their own. When families feel they are presented with consent forms that they cannot fully understand, they quickly feel threatened and become defensive. Plain language summaries of all consents should be a requirement across all institutions.

Thank you for your time today.

MS. JACKLER: Thank you, Ms. Ballard.

Our next speaker is Rupjani Bhattacharya.

MS. RUPJANI BHATTACHARYA: Thank you so much. Good afternoon, everyone. I would like to thank CBER for providing me this opportunity to share my testimony today. My name is Rupjani Bhattacharya, and I am a Duchenne mom and Duchenne advocate.

My son, Anuran, has Duchenne muscular dystrophy and is about to begin college. One of the significant barriers he faces in participating in long-term follow-up studies is the scheduling conflicts and the time required to travel to study sites. Many of these studies involve multiple daylong visits, which can disrupt his busy academic routine.

To alleviate this burden, I believe that reducing the frequency of in-person visits and incorporating more frequent remote follow-ups would be beneficial. Additionally, utilizing primary doctors' offices and local labs for blood work could enhance flexibility.

Another challenge we may have is the potential for new gene mutations or the development of evolving adverse events. To address this, I suggest offering incentives such as reimbursement of costs associated with any long-term known or unknown side effects of

gene therapy and providing rapid access to information about the long-term safety and benefits of gene therapy. Furthermore, involving patients in developing success criteria or long-term outcome measures could be valuable.

I believe that a gene therapy registry managed by a public-private company would be a valuable tool. This registry should be global in nature, cloud-based, AI-powered, and allow for access by all stakeholders. To maintain the integrity and security of the registry data, different levels of access should be granted to various groups of stakeholders.

Regarding the reporting of unexpected adverse events, I would prefer a study app with features such as interoperability and direct communication with study staff. Regular communication between the registry and participants about safety risks and long-term effectiveness is also essential. The severity of a safety signal or risk should determine the speed of communication. For mild to moderate concerns, waiting for validation from the product manufacturer may be appropriate. However, in cases of severe safety concerns, a more immediate communication is necessary.

Thank you.

MS. JACKLER: Thank you so much.

Our next speaker is Rachel DeConti.

MS. RACHEL DECONTI: Good afternoon. First, I would like to thank you all at CBER for this opportunity today. I'm the Executive Director of the LGMD2D Foundation, but I'm here to share my family's story and what is important to us. I have no financial disclosures to share.

My name is Rachel DeConti. I'm the mom of two incredible boys, the oldest of which is living with limb-girdle muscular dystrophy type 2D/R3. I'm a mom who's willing to take any considerate risk for my son's future, a mom who, just 2 days ago, was at the U.S. Capitol for an LGMD Day on the Hill with my family and many others in the LGMD community, creating awareness and advocating for what we are here to talk about today: treatments, including gene therapy, that need to be approved for LGMD patients, because their lives depend on it.

My 8-year-old son, Jacob, is amazing. He's kind, funny, sweet, smart, and adventurous. He loves to learn and is a great student. Our world forever changed when Jacob was diagnosed with LGMD type 2D/R3, just after his fifth birthday. Jacob had suffered a case of rhabdomyolysis during summer break. We had no idea what was to come, or that there are no treatments approved or even available to help stop or slow the progression of this disease.

We are currently supporting research in every way possible to help advance studies for treatment approved. Jacob is in two available natural history studies for LGMD2D. Last year, we traveled to multiple states for these studies, which involved getting his blood

taken, multiple hours of MRIs, cardio appointments, bone density scans, and physical therapy assessments. That is a lot for anyone, let alone a young child. He has done everything these medical teams have asked of him in the hope of receiving a gene therapy treatment soon—and we will continue to do so.

I'm here today to talk about what we would be willing to do for gene therapy treatment, now and in the long term. To start, we would be willing to travel anywhere worldwide to participate in an effective long-term study.

LGMD is not a mild disease, and LGMD2D is in a group of the most severe subtypes that impact the heart and respiratory function. This is why there are several factors that we would consider in determining if Jacob were to participate in a gene therapy registry or long-term study.

First, there are several incentives that we feel he would benefit from in a gene therapy treatment. As mentioned, there are currently no treatment options available to help stabilize or halt this disease—and that is despite the first gene therapy treatment being an LGMD2D patient over 25 years ago. Having this option, especially at a young age, is incentive alone for us to participate.

Each time we visit a clinical site for one of Jacob's study visits, we are fearful that we will hear the terrifying news that his assessment scores, including NSAD, have declined due to continued progression. Every day that passes, his muscle is wasting. He is getting older and potentially getting weaker. He is at a prime age right now to receive a treatment. We know his age and current condition is optimal. This is a huge benefit for us to consider participating in a long-term treatment. Gene therapy will impact patients in different ways. For Jacob and so many others, stopping progression of this disease could totally change the trajectory of his life.

Continuing from considerations, I'd like to share some areas that are important to my family, and how we think long-term study outcomes should be designed, operated, and managed. It would be important for us to understand patient history knowledge in a clinical site where Jacob receives his treatment, post-gene therapy. For follow-ups in the years after the treatment, we'd like to know when that takes place.

It's important for us to be there to understand that gene therapy is documented, both currently and in the future, having the doctor state that Jacob receives the therapy, any outcomes and actions, findings, etc.

Communications: As a caregiver and mother, I would want to continue to be connected and updated on periodic reports about safety risks and long-term effectiveness for specific gene therapy, both long-term and in the future. Although all patients may act differently, it is important for us to be alerted on these types of updates.

MS. JACKLER: Thank you so much. If there's something you didn't get to say or fully

say, please do put it in the docket. We really want to hear. But we do have to make time for everybody.

MS. DECONTI: Okay. I'll post my full statement in the docket. Thank you.

MS. JACKLER: Thank you.

Our next speaker is Eric Camino.

DR. ERIC CAMINO: Hi. My name is Eric Camino, and I'm the Vice President of Research and Clinical Innovation at Parent Project Muscular Dystrophy, which focuses on Duchenne and Becker muscular dystrophy. I have no conflicts to disclose.

I want to highlight the importance of making long-term study results more accessible and actionable, for patients and clinicians alike, and the need to leverage technology to play a transformative role in achieving this goal. Collecting long-term data on gene therapies is essential. But it's equally important that we make every effort to increase the amount and quality of that data. Long-term data collection, analysis, and sharing is not just nice to have; it's also a vital piece of the puzzle in understanding how treatments work overtime, and how patients' needs evolve.

A key factor in successful data collection is meeting patients where they are. We need to use technology and build infrastructure in ways that drive active surveillance data inputs seamlessly into their daily lives. The more convenient and user-friendly we make it, the more likely patients are to be able to participate consistently. This means using decentralization strategies, such as mobile platforms, local labs, and other tools that make data collection as simple and unobtrusive as possible.

But collecting data is only part of the equation. Data sharing is imperative for building trust. Patients, families, and clinicians need to receive data back in a way that is both timely and digestible, especially for those with varying levels of health literacy. It's not enough to gather data. We must understand how that data is used by regulators and sponsors and share it with the community in a manner that is understandable and useful to average patients as they consider what impact new findings have on their personal benefit risk considerations for a given gene therapy.

Another critical point is that participating in long-term follow-up and observational studies should not prevent patients from accessing additional approved therapies. We need to ensure that pursuit of data and knowledge does not come at the expense of patients receiving the best care available to them at any given moment. Furthermore, we recognize the need to understand how developing therapies impact patients who have received gene therapy and believe efforts should be made by both sponsors and regulators to facilitate data collection of current and future investigational products with patients who have received approved gene therapies.

We also believe strongly that data collected in long-term studies should not be siloed

within individual companies or institutions. Stakeholders—including pharmaceutical companies, research institutions, and clinicians—need to work collaboratively with patient advocacy organizations to ensure that data is made promptly available to all stakeholders. Advocacy groups like Parent Project Muscular Dystrophy are essential to provide mechanisms to analyze and data. By fostering collaboration between these groups, we can use the data effectively to improve long-term care.

One area where this collaboration is especially important is in assessing the safety and efficacy of patients being on multiple treatments at once. Sponsors must be willing to leverage existing infrastructure to analyze these interactions, ensuring that patients can safely access multiple therapies without compromising their health.

We also need timely updates on new safety events related to gene therapy products, as well as long-term efficacy data. It is crucial that patient advocacy groups work hand in hand with sponsors and regulatory bodies to determine the best way to disseminate this information to patients, promoting transparency and trust in the process. When data are shared, they must be easily digestible for patients of varying health literacy. We must ensure that the information is clear, accessible, and actionable for everyone, regardless of their medical background.

To conclude, easing the burden of participation in long-term studies, data sharing, and collaboration between stakeholders are all key to advancing and improving care for patients. By making participation easier and sharing data effectively, we can empower patients and their families along with their care providers to make informed decisions about their health.

Thank you for the opportunity to speak today.

MS. JACKLER: Thank you, Eric.

Up next, we have George Eastwood.

MR. GEORGE EASTWOOD: Hi, everyone. I'm George Eastwood, Executive Director and Board Chair at the Emily Whitehead Foundation.

Thanks so much for convening this meeting on a very relevant topic for those in the CAR T space. As we are aware of, the FDA currently requires 15 years of long-term follow-up for those receiving CAR T therapy and lifelong monitoring for reporting of secondary malignancies.

As we pointed to in the intro to this session, the current process for collecting data can be challenging for all parties involved. Timing is great here, as we conducted a survey of 96 CAR T patients and caregivers with a goal of getting a better understanding of the patient's view of long-term follow-up. I'd love to share highlights and share that we collaborated with Catalyst Healthcare Consulting on this.

Our goal was to get a strong representation across a number of patients who have received CAR T, both clinically and commercially. We found an even split between clinical trials and commercial, as well as a range of times since they've received their CAR T therapy. Of respondents who were more than a year post-treatment, we found that most of them still go to their original treatment center for a lot of their follow-up visits.

I'd love to present some of the insights that we've seen from this survey in the next couple of minutes. First off, how patients are engaging with their long-term follow-up: If we look to the left, we find that 23 percent of patients have missed a follow-up appointment. And if we look to the right, we find an alarmingly high number—20 percent—of patients have stopped participating in follow-up visits, with the majority of those happening post-5 years of treatment, and a majority of those as well living 2 hours or more away from the treatment center.

In digging into the data a bit further, we find a perspective look around the intent to follow up with the 15 years. We found that 38 percent of patients don't see themselves doing the full 15 years of follow-up, and nearly half of the patients 2 years or less out are likely to finish all 15 years. In the initial trials, only 17 percent did not intend to follow through with the full 15 years of follow-up.

We also looked at the barriers to long-term follow-up participation, with the two key factors being distance to the site and cost (travel and lost wages)—two factors that we've talked about a bit already in this session. With distance being a major barrier, we've seen that 31 percent of respondents to this survey are more than 6 hours from their original treatment center, 73 percent live an hour or more away, and 70 percent need to travel by car.

When we look at the awareness and education side, we see a clear opportunity to improve the education upon administration of these therapies, both clinically and commercially. Forty-four percent of patients reported that they did not receive the information that they would need to attend follow-up for 15 years, and that data could include those not recalling at the time of treatment. At the same time, 61 percent of patients reported that they didn't receive information that they could attend follow-up away from their original treatment center. And only 27 percent were given a reason as to why this 15-year follow-up commitment exists.

In looking at this, we see an overwhelming number looking to use—and comfortable using—EHRs and allowing CAR T manufacturers to access those. The same 80 percent are looking to be able to complete appointments through telehealth, and 77 percent are comfortable entering their own data. We see a little bit lower numbers when we look at those who are comfortable using AI tools to monitor their EHRs.

MS. JACKLER: Mr. Eastwood, is this the last slide? After this slide, we'll have to move on. Thank you.

MR. EASTWOOD: So in conclusion, the Emily Whitehead Foundation believes the patient is at the heart of long-term follow-up. Our survey indicates that patients are very open to leveraging tools like EHRs, mobile apps, and telehealth to make this more patient-friendly. And we'd love to revisit when and how patients are educated around these expectations. We're really excited that FDA has demonstrated an openness to accepting new ideas to address these challenges with the patient in mind. And we'd love to establish a multistakeholder collaboration as an efficient way to explore these approaches, and we'd be happy to help.

Thanks for the time today.

MS. JACKLER: Thank you very, very much.

Our next speaker is Lauren Gibbs.

MS. LAUREN GIBBS: My name is Lauren Gibbs. I do not have any conflicts of interest, and I have spinal muscular atrophy type 3.

The SMA community is very fortunate to already have an approved gene therapy, Zolgensma. Zolgensma has truly changed the landscape of what SMA looks like today, with some children with type 1 SMA being able to walk and jump. However, since Zolgensma is only approved for children with SMA under the age of 2 years old, there is still a lot of data to be gathered and analyzed as these patients grow and develop.

Today I would like to discuss what might incentivize me and other patients with SMA or other conditions to participate in a gene therapy registry or long-term study. With two approved treatment options available for SMA in addition to Zolgensma, there is now the option for combination therapy: Zolgensma and another SMA treatment.

In a study published last year, 24 out of 81 children given Zolgensma had also been treated with other SMA drugs. This shows that each child's journey with gene therapy is unique, and outcomes can vary in the SMA population. Therefore, at what point is it best to turn to a different treatment option when gene therapy is no longer helping with the progression of the disease?

In a long-term study, especially if gene therapy is not the only treatment available, I believe patients and families would be very interested in findings along the lines of the example I just outlined. Frequent updates regarding the long-term benefits and safety profile of gene therapy, including delayed adverse events, would be another critically important aspect of a long-term study that would incentivize me and other patients, I believe, to participate in an observational study of this kind.

Regarding the benefits and safety profile of Zolgensma specifically, Novartis has been able to share long-term data demonstrating the continued efficacy and durability of Zolgensma, as well as noting adverse events reported in patients participating in the observational studies. For the SMA community, I believe that the frequent updates and information

coming out of the long-term studies has been very insightful for families with children who have received Zolgensma, families who are deciding on the gene therapy route for treatment, and patients who are not eligible for Zolgensma at this time but still want to know the benefits and risk of gene therapy if there is a time in which it is made available for older patients with SMA.

Lastly, the ability to connect with other patients and families who have received gene therapy would also incentivize me to participate in a long-term study. In rare-disease communities, patients and families are very eager to connect and share experiences. And I believe a forum designed to bring together patients and their families who have received the same gene therapy would be very beneficial as part of a long-term study, if this is just over social media, a website, or virtual meetings. For example, as patients with SMA who have received gene therapy age and grow into adulthood, I and probably other patients and families would be interested in a discussion on pregnancy, for example, after receiving gene therapy, as this is now a very likely situation for many patients with SMA who have received Zolgensma.

Thank you for your time today.

MS. JACKLER: Thank you, Lauren.

Up next, we have Radek Kaczmarek.

MR. RADEK KACZMAREK: Thank you. Hello, everyone. Thank you for the opportunity to speak today.

My name is Radek Kaczmarek. I have severe hemophilia A. I've been working as a volunteer with multiple national and international patient organizations for many years. I'm also a scientist. I study immune responses to protein replacement therapies and gene therapies for hemophilia A and B at the Indiana University School of Medicine. And I have received research funding or have been a consultant for several companies developing therapies for hemophilia, including gene therapies.

Severe hemophilia A and B are bleeding disorders resulting from deficiencies of blood clotting proteins called factor VIII and factor IX, respectively. If left untreated, hemophilia leads to disability. It's a debilitating disease. It can happen in early childhood with recurring bleeding episodes, primarily in joints. And sometimes fatal bleeds may occur, such as intracranial hemorrhages.

Because both hemophilia A and B are monogenic diseases with well-defined biomarkers, they have been very good candidates for gene therapy ever since the advent of the technology. And now, three adeno-associated viral vector gene therapies are approved: two for hemophilia B and one for hemophilia A.

There is a wide array of standard treatments for hemophilia that are generally safe and efficacious, but they are also associated with a significant treatment burden. Also, they

don't completely prevent bleeding episodes, so they don't prevent all joint damage. So the need for innovation and unmet need in the community persisted, despite all those available modalities.

The approved gene therapies and other AAV gene therapies under development have shown good efficacy and safety in phase III clinical studies but also several limitations, such as wide variability in outcomes, unpredictability of efficacy, limited eligibility due to high prevalence of preexisting anti-AAV antibodies, and mild liver toxicity that is poorly understood. In hemophilia A, additionally, these liver toxicities seem to be more common and more multifactorial than in hemophilia B. Also, there has been wider variability in hemophilia A, and the transgene expression has been slowly declining from year to year in most individuals, with a growing number of individuals going back on the standard treatment.

So these are some of the problems that we know. There are several uncertainties and unknowns, and long-term follow-up, ideally using a global registry, will be necessary to better understand both. It may help us understand some of the problems that we know already, such as liver toxicities and the need for immunosuppression.

The latest data show that we may not have struck the right balance yet between rescuing transgene expression and using immunosuppression unnecessarily for too long. On the other hand, long-term follow-up will be essential to understand the unknown risks, such as the risk of malignancy, which remains theoretical for AAV vectors for the time being. But they do integrate in the genome despite the longstanding misconception that they are non-integrating vectors, and that warrants vigilance.

So this and other potential rare adverse events will only be able to be captured using a robust, prospective, longitudinal global registry. The World Federation of Hemophilia has established such a registry in collaboration with key stakeholders, including scientists, readers, and patients. And it has been endorsed by regulators of a global standard that will hopefully help evaluate the known and unknown risks and the total benefit-to-risk ratio.

The hemophilia community has a very difficult safety legacy. Therefore, it is particularly vigilant and feels strongly about safety, especially when it comes to new and novel therapies. So the need for long-term follow-up in uncertainties are well appreciated in the community.

Thank you.

MS. JACKLER: Thank you, Radek.

Our next speaker is Sheryl Marrazzo.

MS. SHERYL MARRAZZO: Hello. My name is Sheryl Marrazzo.

I am the mom of a 21-year-old son and a 10-year-old grandson living with Duchenne

muscular dystrophy. I'm also a genetic carrier, as is my daughter. My family and I founded and run the 4 Jake's Sake Charitable Foundation, which helps families living with Duchenne make their homes and lives more accessible.

I'm also a community engagement coordinator with CureDuchenne, where I have the privilege and honor of interacting with and supporting thousands of families globally through family events, social media, and CureDuchenne's one-on-one counseling program with our science and physical therapy team. I do not have anything to disclose.

I'm here to offer my perspective as a parent and a grandparent, and from my many interactions with families. Making decisions as a parent is difficult, and parents rely on data to make informed decisions that could change the course of their child's life.

Parents are making decisions now with long-term data. So a long-term study or registry would be really important for these families, because they're trying to make these decisions and they need this data, and we really need to have it for them.

It's amazing that our families finally have these treatment decisions to make. But it also comes with anxiety and sleepless nights, when you're trying to make a decision on your child's behalf medically and wondering: Why is this so stressful? Because we don't have these complete data sets.

Parents are relying on word of mouth, social media, to help make these really tough decisions. I've personally met with parents who are agonizing over whether or not they're making the right decision, and they wept during some of our discussions. Imagine if they had data that would be able to help them come to a decision that they feel good about.

Here are some things that I think are really important for families and caregivers, whether they decide to join in a long-term study or a registry. A lot of folks have talked about travel and things like that, but the commitment of time is really huge. My son's a senior in college, and there's no way that he wants to miss class to be part of a registry. So it does need to be convenient. It needs to be realistic, and it needs to be doable.

Also, is there any unanticipated cost? Because that should never be a financial burden to families. Will it be accessible to everyone? Could they incorporate wearables? Will it be bilingual? Is there a potential to incorporate videos into data collection? Seeing videos can be really compelling. And while scientific data is super important, so is the ability to see and share real-life improvements.

With proper measures to ensure that data is captured and shared securely, can patients work with their health care providers locally and work together to ensure that there is ongoing communication and frequent updates, and that the data collection is there for the long-term follow-up? Also, how will we get this data? This data is super important for those making the decision, but also for those who have received the treatment.

We say that time is muscle, and for us in the Duchenne world, time is not on our side. We

need to make decisions that are meaningful, so we need data that comes out often and is accessible. We also need to see data that's relative to mutation, age, and ambulation, so that we can better understand the impact on our child. We all need access to this.

We also would love to see whether there's anything trending with this long-term study or registry, so that we can really stay up to date on how gene therapy is acting with our children. And also, in our future, we see combination therapies.

So our Duchenne community is made up of courageous and strong individuals, and they're committed to supporting each other and paving the way for those who come after them. It is our ultimate goal to make sure that everyone has treatment. But an opportunity to be able to share data like this would make a family like mine really want to be involved and feel so much less helpless.

I really appreciate your time. Thank you so much.

MS. JACKLER: Thank you, Sheryl. We appreciate your time too.

Our next speaker is M. Carrie Miceli.

DR. M. CARRIE MICELI: Thank you. Thanks for the discussion and for including me.

My name is Carrie Miceli. I'm a Professor of Microbiology, Immunology, and Molecular Genetics and Co-Director of the Center for Duchenne Muscular Dystrophy at UCLA, where my research laboratory focuses on Duchenne muscular dystrophy, in close collaboration with Dr. Stan Nelson's lab in the Department of Human Genetics. Dr. Nelson serves as a Co-Director for the center with me. I have expertise in the immune response, dystrophin replacement, and rescue therapies. I have also served as a paid consultant regarding potential and actual immune responses to systemic gene therapy for all four leading companies with products in the trial or approved in the DMD gene therapy space.

My lab research program is focused on characterizing changes in muscle remodeling and immunity in DMD muscle tissue and blood cells in response to systemic AAV gene therapy at single-cell resolution. Our studies apply cutting-edge technologies, generally available only at academic centers, to generate data that, when correlated with clinical response, promises to reveal cell and molecular mechanisms of gene therapy efficacy, draggable barriers to success, and better prediction of who might suffer adverse events. Access to patient tissue and data dramatically accelerates research and discovery.

For these studies, we developed a relatively less invasive needle biopsy technique. Compatible with serial biopsy, it enables patient follow-up by needle muscle biopsy over multiple years post-dosing. Some of the subjects we biopsied are already 5 years post-gene therapy, and we hope to continue to follow them. Such studies require patient willingness to participate in extended follow-up studies. The information gleaned from the dose in these trials will be most impactful with the cooperation of the dosing companies in sharing clinical trial and postmarketing data and remnant blood and muscle biopsy material, when

available.

We find that patient follow-up is most efficient when patients can go to their local site, or when the travel is necessary, expenses—including caregiver costs—are covered. We also find that patients are more interested in participating if data generated from samples collected with consent can be directly returned to patients and families, shared with professionals, and published in a timely manner. While we make clear that the studies are research and not clinical, the ongoing discussion establishes an appropriate and respectful partnership with patients' families.

I'm also the mother of a 23-year-old man, Dylan Miceli-Nelson, who is living with DMD and who received systemic AAV dystrophin replacement gene therapy 3 years ago. At the time, he was among the two oldest, most progressed, and heaviest young men dosed with the highest amounts of viral construct to date, in a cohort predicted to potentially have the greatest risk. As a 20-year-old at the time of dosing, Dylan made the decision entirely himself. But he turned to us as his parents to help guide his decisions.

Given that both Dr. Nelson and I are extremely well educated in the potential risks and benefits, we sought to give Dylan the information needed to support his decision, which is the same information we give others. First, we said, this is a serious endeavor with life-changing possibility and real remaining risk not to be taken lightly. It's irreversible and likely precludes the use of other AAV gene therapy treatments. There's been variability in response, with some benefiting more than others; in rare cases, adverse events can be significant if not life-threatening.

The available data indicates that most are dosed safely, and the therapy appears to have efficacy in slowing disease progression, though it likely, at some point, will diminish. It seems most reasonable to expect some level of efficacy even in more advanced patients, albeit perhaps not as much as in a less advanced cohort.

Patients should expect to be followed for the rest of their lives, both for patient safety and management and for better understanding of efficacy and requirements, from barriers to redosing, if that ever becomes possible. Don't wait for a therapy that's not yet been developed. DMD drug discovery takes longer than we imagine. And the likelihood of something not currently available or in the trial pipeline appearing soon as an option is low. And though current therapies are not perfect, they are effective and can be life-changing.

Our son was eager to participate. And given our knowledge, we strongly encouraged his participation. He seems to have benefited, with 3 years of stability since he was dosed, and has not suffered adverse events to date. This is in keeping with DMD's publications on family risks. I will certainly put the entire statement into the docket.

MS. JACKLER: Thank you.

Our next speaker is Debra Miller.

MS. MILLER: Hi. Thank you for having me. My name is Debra Miller, and I'm the CEO and founder of CureDuchenne and the mother of a 27-year-old with Duchenne muscular dystrophy. I have no conflicts.

CureDuchenne is a leading advocacy organization and funder of research for individuals with Duchenne muscular dystrophy. We also support clinics around the country and around the world. As the leader of CureDuchenne for 22 years, I'm in the position of interacting with thousands of families facing this disease, and with pharmaceutical and biotech companies in all stages of development, as well as health care providers.

CureDuchenne's science and medical team spend countless hours counseling families on the therapeutic landscape and available options for their individual family member. We never advise, but we consider it our role to make sure that the families are well-informed. Therefore, the data that comes out of these registries is crucially important in considering all the options to make the right decisions. Because of the rapidly evolving landscape treatments, in particular for Duchenne, these decisions are even more complex.

We recognize that long-term studies and registries provide critical risk-benefit data to all stakeholders beyond that captured in clinical trials. I'd like to point out the components and features that we think must be part of any successful registry or long-term study.

First, there needs to be clear communication as to how the data will be used in important and impactful ways. The burden of participation must be low and easy and not involve any cost to the participant. Because families are making decisions now, the data that is gathered should be disseminated in real time or as soon as possible, instead of annual corporate updates. It should go to all key stakeholders, including health care providers, patients, payers, and advocacy organizations.

This is critical as time options, treatment options, and care options change and evolve. Combination therapies, for example, are expected to be the new standard of care over time. The ability to understand long-term data as it relates to efficacy, longevity of the therapeutic response, and safety risk for all different age groups is important, including cardiac data.

We must be able to identify new or unexpected safety signals following long-term treatment. And we need to understand various immune suppression protocols that are being used by different companies. We must be able to capture information that might not be captured in primary or secondary endpoints (for example, stamina, endurance, energy, mood. All of this is critical for patients and families to make informed decisions.

For a disease like Duchenne, a registry that is owned and managed by a third party is a viable solution (for example, a patient organization that has an established registry and database supported by key opinion leaders, or KOLs). A database that includes all treated

Duchenne patients is going to give one the power to look for even small signals in the data.

CureDuchenne Link is an example of an agnostic data collection repository that is flexible and adaptable to the future needs of the community, which includes biospecimens and electronic health records. Like CureDuchenne Link, any registry should be flexible, so it can adapt to new changes over time (for example, standard measurements, new technologies, new or more meaningful clinical endpoints).

It should have the ability to track through life transitions, from pediatric care to adult care. And it should accommodate relocation, health care provider changes, and life changes while reflecting changes in the treatment landscape and the combination therapies. And of course, it must be accessible to everyone touched by the disease. That means it would include multilingual access and adaptive technology, have no economic barriers, and be available worldwide.

Thank you very much.

MS. JACKLER: Thank you very much. And thank you to all our speakers thus far for sharing your perspectives.

We will now take a 5-minute break and continue our first session at 3:35.

As a reminder, we ask all of our Session 2 speakers to return after the break, as our FDA panelists may have some follow-up questions for you.

Thank you, and we'll see you at 3:35.

Speaker Presentations, Part II

MS. JACKLER: Welcome back from the break, everybody. We are going to continue our speaker presentations, and the next person up is David Rubin.

MR. RUBIN: My name is David Rubin. I want to thank FDA and all the speakers so far for an amazing group of people. It's just really been fantastic hearing all of these thoughts. I am a patient with FSHD, a rare genetic form of muscular dystrophy. It's actually one of the more common muscular dystrophies, but a rare disease.

I'm a volunteer leader with FSHD Society. I've spent considerable time speaking with those who suffer from FSHD, including about their experiences with gene therapy clinical trials and non–gene therapy clinical trials. I also participated in numerous discussions and some focus groups regarding clinical trials.

To date, there are no FDA-approved treatments for FSHD. It is a genetic disorder. Therefore, given that it's a genetic disorder, and there's a possibility that I have passed this on to my three children (who have not yet shown symptoms) or my grandchildren, it's

important, I think, to understand, as I've heard from some others of you, that the decision to participate in a registry, a clinical trial, or any kind of long-term study is as much an emotional decision as it is a decision around the logic of all the things we've discussed today regarding the need to know the possible symptoms or consequences of participating. The fact that I may have passed this on to my children or my grandchildren will dwarf any concern or much concern for my own health and well-being regarding these studies, obviously within reason.

While I was working (I'm now retired), I would have been more concerned with things like lots of time and travel and the cost associated with that travel. I've heard a number of people talk about that, and I think there needs to be a concerted effort around having as many sites as possible throughout the country, and those sites being able to support people.

Regarding a registry, FSHD Society recently created one that I am participating in. I find it fantastic and an amazing amount of information. Its online measurements are self-generated, you can upload medical records—things like that. And I think one of the main considerations is now how do we make sure that people are using this and interacting with it. Then it becomes effectively a living document to gather information to educate the community and the medical profession.

I realize I didn't say I have no financial conflicts or affiliations; sorry I didn't say that earlier.

You know, the issue of providing people and the medical profession with that information, I think, is really critically important. I would not have been diagnosed properly for many more years had not a physical therapist noticed some symptoms. My general practitioner told me he never would have diagnosed this disease. He never would have seen it. So, luckily, I had somebody with the foresight to see that and to get me registered.

So I do think there's an important consideration to making sure that people are aware—or that a registry can be used to help educate the medical community and communicate the furthest—of medical risks. Medical risks need to be really communicated.

Thank you for your time. I'll upload whatever I have in dockets.

MS. JACKLER: Thank you very much. I appreciate that.

Up next, we have Ben Shaberman.

MR. BEN SHABERMAN: Thank you, CBER, for giving me the opportunity to talk about long-term follow-ups for gene therapy studies and treatments. I'm Ben Shaberman, VP of Science Communications for the Foundation Fighting Blindness. Our organization is a leading funder of research for treatments and cures for rare inherited retinal diseases, as well as dry age-related macular degeneration.

In addition to driving research, we provide no-cost genetic testing, as most of our diseases

are monogenic. We have a robust, large registry of patients regardless of whether they've been in clinical trials or not. And we do have a lot of longer-term natural history studies, which I'm glad we've been able to enroll pretty well.

I have no conflicts. We have many corporate partners. The foundation has many corporate partners, which are listed here.

So, excitingly, in our space, we do have an FDA-approved gene therapy. It's called Luxturna, or voretigene neparvovec. It was approved in 2017 for people with a specific form of Leber congenital amaurosis mutations, in a gene called *RPE65*. It's been one of the greatest breakthroughs in our space. It's enabled kids and young adults who were born with significant severe vision loss to put away their canes, see the faces of loved ones, and, in many cases, see fireworks and even stars in the sky.

So it's been a very successful gene therapy, and it's opened up the door to many other gene therapy development projects. Fortunately, we've had a pretty robust post-authorization safety study, which my organization and I weren't a part of, but it was presented at a foundation event in May earlier this year—87 patients, 169 eyes. We learned that most adverse events during the gene therapy administration were mild, transient, and treatable. About 27 percent of the eyes in these studies had some chorioretinal atrophy, but patients overall had much-improved vision, even if they had some atrophy.

I'd say that in a follow-up study like this or in clinical trials, patients are most concerned about cost, time, and travel in the gene therapy space in our world. One of the concerns is that once you get a gene therapy, you're potentially not eligible for other treatments and the surgery, because it's a retinal surgery. Patients are concerned that there could be damage and loss of their existing vision.

So, as a result of Luxturna, we have many more gene therapies for inherited retinal diseases and AMD emerging in clinical trials. Many are in phase III. And while there are some issues with inflammation, overall, these treatments are showing some meaningful efficacy. We're excited about the potential of gene therapy to save and restore vision for people with inherited retinal diseases.

Thank you.

MS. JACKLER: Thank you very much.

Our next speaker is Adrienne Shapiro.

MS. ADRIENNE SHAPIRO: I want to say to all of the mothers and fathers that I have heard speak on this call that 9 years ago, we in the sickle cell community could never believe that we would be in a place that we are. After almost 100 years of knowing what our disease was all about. We suddenly had three disease-modifying treatments and two curative therapies.

The other thing I want to say—other than carrying the mother heart, the father heart, and the parent heart of having someone in your life with a genetic disease—is that 90 percent of what you've already said is exactly what our community is saying about the importance of this registry, the importance of the design, the approach, collaboration.

So I'm just going to take a couple of minutes to tell you what I've been hearing from the people whom I've been working with who are now about to have gene therapy. And it does differ by age. As parents, we go hard. We want all the information. We want everybody to benefit. And when our kids are young, we have the ability to make those decisions. Our younger adults—again, we hear time, convenience, ease. Some of them want the registry to be sort of like a—it's kind of funny—a video game. And who knows what the future is going to be?

But everybody wants good design. We want transparency. They want to have input and communication, working, of course, with what's already in place and seeing how we can pull it all together. But some of the more interesting things that I haven't heard is many people say, "Yes, I want to do this, but I want to make sure that the data that we are gathering has a single home." How that feeds into that isn't important, but we would love to have a single home—a place such as FDA, which owns it—because we don't want it to run out of money. We don't want it to be insecure. We want it to be there in continuum.

The second thing they've said is, "I won't mind if I know who this data is going to and I can find out what's happening." So someone pulls the data, gets data, and my data is a part of that, and they've done something interesting and found something. I want to know about that. I don't want it to be a black box where I put my data in, and no more do I hear from it.

The last thing is the concern for safety. And when I say safety, that is, again, is it going to be safe? Cybersecurity is such a big thing, having data stolen. And I think those are the three things that are unique that I can add. Again, our communities are all in sync. We want this. We see the value of it: good design, access, collaboration, and communication.

Thank you for letting me speak.

MS. JACKLER: Thank you.

Up next, we have Donovan Decker.

MR. DONAVON DECKER: Thank you. I'm Donovan Decker, and my disclosure is that I'm a co-founder of ANGLE Therapeutics who's working on gene therapy not using AAV. I was involved in the first gene therapy safety trial for muscular dystrophy, 25 years ago, and Dr. Jerry Mandel made sure I knew I wasn't going to be helped. And I couldn't be retreated because of using the AAV.

The patient and caregiver need to understand the immune system implications down the road. If the patient does not receive a large enough dose, you don't have another option to

be re-dosed. I still had a titer over 14 years later, when I was retested. I would like to see FDA require patients to be tested yearly, to keep track of the trends. Right now, using AAV, you only get one chance. Being treated with gene therapy doesn't guarantee you'll be made stronger for a muscle disease. Patients and their caregivers need to understand that being treated doesn't mean you'll be helped. To me, this is one of the most important things patients and caregivers need to be aware of before enrolling in a gene therapy trial.

Also, the patient and caregivers need to understand that a trial is research in what can involve risk, known and unknown. Travel's one of the biggest issues in deciding to be in a trial. This is because of time away from work, expense, travel, and the wear and tear on the patient's body. Flying for some patients will be a deal-breaker, and it's not feasible. Twenty-five years ago, when I was in a gene therapy trial, flying was easy. Now it's extremely hard. There are very few places doing gene therapy trials. Patients need more options so travel distance doesn't keep them from being involved in a trial. Enough of it is how many muscle biopsies you have to have.

There need to be more options for different delivery systems. As of right now, most of gene therapy or all gene therapy trials for muscular dystrophy use AAV. There are some companies like mine looking for other types of systems, like nonviral or other viral systems. This could resolve the issue of the redosing due to the immune response.

One of the last things I will mention when doing a gene therapy trial: If you're working with a company or a university, they own the data. Which means that no one else can access it. The patient does not own the data. The other thing I'd like to mention about the SMA and the Duchenne approvals that FDA has: That all started with the gene therapy that I started with Dr. Mandel. Also, the limb girdle community has basically built the foundation for all the muscular dystrophy gene therapy being done. I think it's a shame that there are no treatments for limb-girdle muscular dystrophy.

The other thing is that the registries need to be pretty much standard. There'll be different ones for different types of diseases. But patients need to be treated fairly across all patient disease or diseases.

Thank you for allowing me to speak today.

MS. JACKLER: Thank you, Donavon.

Before we wrap up the speaker session, I just want to see if Daniel Ajayi or Natacha Bolaños might be on the line. They were scheduled to speak, and I want to make sure they don't miss their opportunity, if they happen to be here.

All right. I want to thank you all of the Session 2 speakers for sharing your perspectives. And now I will open it up to FDA panel to ask any clarifying follow-up questions.

FDA Panelist Questions

DR. RICHARD FORSHEE: My name is Rich Forshee. I'm the Deputy Director of the Office of Biostatistics and Pharmacovigilance.

First, I want to thank all of the speakers today. You have provided so much thoughtful information for our consideration, and we really appreciate your participation.

I'm going to start the questions on a theme that I heard several of the speakers talk about: the importance of getting information from these registries back to patients. That's something I completely agree with—that the patients need to know how their data are being used.

One thing that we find challenging in doing some of our postmarket safety surveillance is that oftentimes, there can be a lot of uncertainty around a signal, especially if you're talking about a rare disease. And I wonder if some of the people who talked about the importance of communicating back to the patients in our registry could say a little bit about how you would like to have information that involves a possible but highly uncertain potential risk communicated to you. If you have any thoughts on that, I'd be very interested in hearing those.

Thank you.

DR. CAMINO: I'm happy to start with a comment. I think with this, what we've seen in other instances where data has been transmitted back to our patient community is acknowledging that uncertainty is key when sharing that data. And I think the community can handle that.

And so, as long as it is presented in a way where we are explaining what this may mean and that it is uncertain, I think that's helpful for at least opening that conversation, then allowing those patients and family members to talk with their clinician to make those kinds of benefit risk assessments. So even if we don't have the complete picture at that time, I think it's still okay to engage, but just acknowledge that we don't have the answer.

MR. SHABERMAN: Thank you for that. Do any of the other speakers want to comment on this topic of uncertainty and communication?

MS. SHAPIRO: This is Adrienne. I want to say that I absolutely agree that people want to know. And I think we underestimate many times what is going to scare people off , just behavior-wise, right? And you will have those naysayers. But if you are clear on not knowing, there are going to be those of us in the community who want to know, right? As with anything new. And so we're going to be the ones who jump on it as long as you're honest with us.

Also, please use the trusted sources in the communities. You have an army of people waiting, with bated breath, to get good opportunities and good information out. So I think

listening sessions and things like that—I mean, I think FDA has a playbook, and they're doing a good job.

DR. FORSHEE: Thank you for that, Ms. Shapiro.

And yes, we recognize the importance of partnering with trusted people who we can speak together with to get information out. So I appreciate that comment.

I think I'm going to pass it on to the next panelist for the next question.

MS. JACKLER: Hi, Rich, I'm taking moderator's prerogative here. I don't know if you saw there were a few hands up as well.

DR. FORSHEE: Okay, very good.

MS. JACKLER: I think, Dr. Miceli, you were next.

DR. MICELI: Yes, I was just going to say that I'd like to see more transparency in how many patients have been dosed in a particular cohort along the way. Even if we don't know everything about potentially adverse events, if we at least know that the trial hasn't been stopped and that a certain number of people have, in fact, been dosed. I think that's been more difficult than it should be to obtain that information.

DR. FORSHEE: Thank you for that.

MS. JACKLER: And Dr. Adami, if you have anything to add, and then we'll move to the next question.

MS. ADAMI: Oh, now I'm a doctor. Thank you for the promotion. [laughter]

I was going to just say that, given how much trust nonprofits have with the patient population, it seems as though this data needs to also go through these nonprofits so that it can then be integrated into their educational documents. I think most patients are going to rely on their doctors directly if they're considering getting a gene therapy. But as far as educating the patient's population—people who maybe aren't ready for this kind of therapy yet—I think it's really important to somehow wrap the nonprofits into this type of database.

DR. FORSHEE: Thank you very much for that suggestion. Karen, I think back to you.

MS. JACKLER: No, actually, if there's another question from the group, we have some time. I saw those raised hands and just want to make sure they had an opportunity. So please proceed.

DR. ADAMMA MBA-JONAS: Hi, I am Adamma Mba-Jonas, and I'm Chief of Pharmacovigilance Branch 1 in the Division of Pharmacovigilance. I just want to reiterate our immense gratitude for all the speakers today. It's been really powerful to hear about patient experiences with gene therapies, and as participants in these long-term follow-up

studies.

I actually wanted to ask a question of Ms. Adami. You mentioned that the current black box warning in some of the product labels for some of these therapies might need reconsideration. And product labeling is a really important way we communicate risks to patients. So we're acutely interested in optimizing that labeling.

I'm wondering if you'd be able to speak a little bit more about your concerns and any suggestions you might have about improvements, what you'd like to see would be appreciated.

MS. ADAMI: Sure. You know, one thing I want to say is this kind of news gets covered by all the major media. So, you say, CAR T has a black box, 20 patients out of 35,000 had this T cell malignancy. All those big new negative news stories get communicated everywhere on social media, *The Wall Street Journal*, *The New York Times*, *The L.A Times*—you know, every one of them. And it's very scary to patients. I understand why you do it.

I know there's a black box for Botox, and that doesn't stop people from getting Botox. But in this case, the other thing that happens is community oncologists who may not be as familiar with CAR T as they are with chemo and stem cell transplants are very cautionary when they say something like this to their patients. Even though allogeneic stem cell transplant has a black box, nobody knows that. But everybody knows this current news. And I wish it weren't presented in such of a vacuum.

I understand why it has to happen, but I also know the patients that have gotten CAR T, like me, with seven lines of therapy in total. We are so heavily treated. You know, a lot of patients have radiation to manage their disease at various points, because it's pressing on an organ. We know the number of secondary cancers that come from radiation.

So who knows how many of the 35,000 patients actually are going to get this secondary diagnosis that has nothing to do with CAR T? And my own oncologists and researchers I've spoken to—they say there's no clear cause and effect of this, because the data is too dirty. So my concern is, it frightens patients who then post all over social media.

I've talked to patients who were treated by community oncologists where the community oncologist said, "I'm not going to give you CAR T, because it could cause a secondary cancer, or it could kill you. I'm not doing it." So instead, "What am I going to do? I'm going to give you an allotransplant." Well, hello, 30 percent of allotransplants die in the hospital. And that was a possibility for me when I was finally able to get CAR T in trial. The only thing left for me was allotransplant, which, you know, with an unrelated donor, also has graft-versus-host-disease, or GVHD.

So my concern about the way FDA positions this stuff is that it's just presented as fact. This is going to cause secondary cancers. How about contrasting it with what other treatments patients might get that will also lead to secondary cancers? So, I understand

FDA doing this 100 percent, but I don't believe the cause and effect is clear to be able to do this. And I can tell you how many patients I've talked to—they now can't get it because of this black box. Does that make sense?

DR. MBA-JONAS: Yes, understood.

MS. ADAMI: I'm sorry; I'm very passionate about this.

DR. MBA-JONAS: No, I appreciate your perspective.

MS. ADAMI: You know, six lines of therapy that did nothing but buy me time. I get this thing, and I'm like, "Oh, when I hear this, it just makes me crazy. Where are the good stories?" Like me, like Emily Whitehead, you know, where's the good stuff? So that's all I'll say. I'll shut up now.

DR. MBA-JONAS: Thank you.

DR. XINYI NG: Hi, I'm Xinyi, a scientist from the Division of Analytics and Benefit-Risk Assessment. I also want to express my appreciation to all the speakers for taking the time and effort to share your experiences and thoughts with us about long-term studies.

And I have a question for both Ms. Lauren Gibbs and Ms. Kathryn Bryant-Knudsen. I think both of you mentioned the importance of receiving periodic updates on information about the risk of therapy. So I was wondering if you can speak more about that. For example, how frequently would you want to receive these information updates, and what format would you want to receive them in? And for whom do you want to receive them from? For example, is it a physician, the patient at work, a specific group, a product manufacturer, or someone else?

Thank you.

MS. GIBBS: I think I would like to receive the information probably from my physician. And Cure SMA is a very well-known patient advocacy in the SMA community.

Sorry, if you can, repeat the other part of your question.

DR. NG: How frequently would you want to receive such periodic updates, and in what format?

MS. GIBBS: I think as frequently as possible, even if not all of the information is well known. But if you receive data that you think would be important for patients to hear about, I think that would be the best possible outcome. So as frequently as possible.

DR. NG: Thank you for sharing that. Does anyone else have anything to add?

MS. BALLARD: Yes, what I would say, similar to what she said: As soon as possible. I think coming from your own physician is the best option if that's available still. Sometimes physicians have left; people have changed. But even if it's from the manufacturer. I mean,

think about when your car has a recall: You get a notice in the mail. You want to hear these things.

I don't think everybody has their own preferred way of getting information. It's just the fact they need the information. The method isn't as important as the message.

DR. NG: Thank you.

I guess if there's nothing else, I'll pass it to Dr. Lapteva.

DR. LAPTEVA: Thank you. And as other panelists, I'm very appreciative of the comments and presentations made by our patient speakers today. Thank you. It was very important for us to hear different opinions.

I have a question for Mr. Camino, Mr. Eastwood, and Mr. Kaczmarek. Thank you very much for sharing your experiences from the community and, Mr. Eastwood, for sharing the results of the questionnaire about corrective therapies and, Mr. Kaczmarek, for sharing your experience with neuro-configuration and hemophilia. I hope the results of the questionnaire will be submitted to the dockets.

DR. FORSHEE: Larissa, I'm sorry to interrupt, but we can't hear you well.

MS. JACKLER: While Larissa is sorting out the technology side of this, I did notice that Sheryl Marrazzo, you had your hand up earlier, and I didn't get a chance to flag that for the people. Would you like to go ahead?

MS. MARRAZZO: Thank you.

Someone mentioned labeling. One of the things that comes up often with our families is, they're getting different information about pre- and post-treatment, how to handle if they quarantine—things like that. I'd love to see the label be a little bit more specific, so that all families are receiving the same amount of information. That was what I wanted to say back then.

MS. JACKLER: Thank you.

Just checking to see if Larissa might be with us. So, Rich or Xinyi, were there any other questions you have? Or maybe you sort of got the gist of what Larissa might've been trying to ask.

DR. FORSHEE: I'm not sure exactly what Dr. Lapteva's question was going to be. So we'll see if she can get back to us at another time. I'd like to actually move on. I believe it was Ms. Ballard who talked about plain language summaries for the people who are involved in these long-term summaries. And I wonder if she has any examples where she thinks she's seen good communication in a way that the vast majority of people can

understand. Ms. Ballard, if you're still here, could you just expand a little bit on your plain language comment?

MS. BALLARD: Yes. I haven't seen it in the context being used in consent so much as I've seen it in medical journal articles. One of the bio-pharmacists we work with frequently, KIC, has done a couple of articles where they have taken information about their product and had plain language summaries devised for families to be able to read and understand what the medical journal article is presenting so that, basically, the person who knows nothing about medicine, nothing about science, can understand what this drug can do for their child or for their family member.

And plain language summaries are becoming more and more common in journal articles, and they're very helpful. Families really do understand them much better within the full article.

DR. FORSHEE: Thank you for that. Do any of the other speakers today have any comments about good or bad examples of communication that they'd like to mention?

DR. CAMINO: I just want to make an additional comment on the plain language summaries, because we have seen some good examples in the Duchenne space. Pfizer's done that for a number of their previous trials. And I think this is something that we would like to see done more often. I know it's becoming a requirement with the European Medicines Agency, or EMA, for some of the trials in Europe.

But to a point that I think Debra raised in her comment: They need to be not just more frequent than just at the time of publication that we maybe have some of these interactions, not when families are going onto investor calls to try and tease out information that they're seeing from sponsors but to make those type of communications more frequent. And again, at a level that really enables any family to understand the data that's being presented.

DR. FORSHEE: Thank you for that perspective.

MS. JACKLER: Hi Rich, it's Karen. I just want to make sure that the panelists asked all their questions.

DR. FORSHEE: I believe we have. Do any of the other panelists have any last questions?

MS. JACKLER: Thank you. Thank you all. Thank you, panelists. Thank you, speakers.

We've now concluded Session 2, our second and final session. And so, Lorrie McNeill, I'm going to pass it back to you.

Thank you.

Closing Remarks

MS. MCNEILL: Thanks very much, Karen. And thank you all for attending today's listening session, with a special thank you to our public speakers. Your time and participation today are helping to advance 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. And as you've heard throughout the sessions, if you have additional comments to share, please add those to the docket, which will be open for public comment until November 19, 2024. To access the docket, go to regulations.gov and type *FDA-2024-N-3208* in the search bar.

Also, in the coming months following this meeting, FDA will issue a report summarizing the views expressed in the comments from the docket. This report will be published on the FDA website.

Also, we'll be hosting another listening session with patients and care partners soon. Please stay tuned for more information on that.

You can find additional information about this meeting series on patient and care partner listening sessions on our meeting webpage, which we'll include in a link in the chat.

Thank you again for joining and have a nice afternoon.