U.S. FOOD & DRUG ADMINISTRATION

SUMMARY

FDA CBER Patient-Focused Drug Development Listening Meeting

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

December 4, 2024

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Introduction

On December 4, 2024, the U.S. Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research (CBER), hosted the second of two listening meetings for patients with rare diseases and their care partners.[1] This meeting aimed to understand what patients in the pre-symptomatic or early stages of disease, and their care partners, take into consideration when deciding whether to enroll in a gene therapy clinical trial and potentially receive an investigational gene therapy (GT) product.

Gene therapy aims to modify a gene or replace a faulty gene to treat a disease or medical condition. Gene therapies can work by several mechanisms, such as:[2]

1) Replacing a disease-causing gene with a healthy copy of the gene;
2) Inactivating a disease-causing gene that is not functioning properly; or
3) Introducing a new or modified gene into the body to help treat a disease.[3]

While the scientific underpinnings that made GT possible have been recognized since the mid-20th century, the first GT approvals in the United States occurred in 2017 with the chimeric antigen receptor (CAR) T-cell products tisagenlecleucel (Kymriah) and axicabtagene ciloleucel (Yescarta) and the directly administered GT voretigene neparvovec-rzyl (Luxturna). Since the first approvals in 2017, gene therapy continues to grow at a rapid pace. By the end of 2024, the FDA had approved 22 GTs, most for rare diseases[4].

The Importance of Patient Engagement

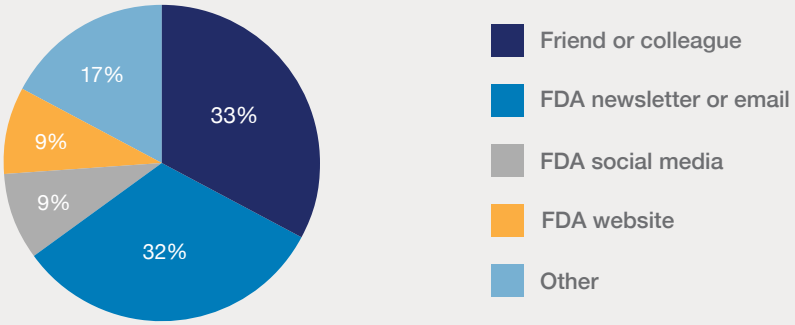
Patients are uniquely positioned to inform the understanding of the therapeutic context for drug development and evaluation. Patient engagement involves patients, care partners, and patient advocates sharing their experiences, perspectives, needs, and priorities. This input can help identify patients' priorities related to treatment benefits, risks, and burden, and determine effective methods for communicating information to health care professionals.

The FDA has established several patient engagement initiatives[5] including the FDA Patient Representative Program,[6] the Patient-Focused Drug Development (PFDD) Initiative,[7] the Patient Engagement Collaborative,[8] and Patient Listening Sessions.[9] CBER staff actively participate in and collaborate with the offices that house these programs, including attending patient listening sessions to engage directly with patient advocacy organizations.

CBER's Office of Therapeutic Products' (OTP) RegenMedEd program regularly engages with patients, caregivers, and advocates to explore opportunities to help advance development of regenerative medicine therapies like GTs.[10] CBER staff have provided feedback to the patient organizations and patient advocacy groups on natural history studies, patient preference studies, and other regulatory science

[1] https://www.fda.gov/medical-devices/home-health-and-consumer-devices/home-health-care-hub
[2] What is Gene Therapy? | FDA
[3] What is Gene Therapy? | FDA
[4] https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products
[5] FDA Patient Listening Sessions | FDA
[6] FDA Patient Representative Program
[7] The Patient-Focused Drug Development Initiative
[8] Patient Engagement Collaborative
[9] Patient Listening Sessions
[10] OTP Events, Meetings, and Workshops | FDA

Figure 1. Top Referral Sources



activities that can promote efforts related to drug development. The FDA also collaborates with a variety of national patient advocacy organizations to connect with patient-led rare disease organizations, which allows the FDA to gain a better understanding of the complexities inherent to living with a rare disease. Further, the collaborations improve the FDA's grasp of how new therapies and data collection can best be integrated into patients' lives.

Meeting Overview

CBER announced two patient listening meetings on its website on July 11, 2024, and opened registration for the December 2024 meeting on October 15, 2024. To promote and recruit participants for the meeting, CBER posted the announcement on the FDA website and shared it in the "What's New at CBER" listserv and other FDA newsletters. CBER also announced the meeting on the FDA LinkedIn and CBER X accounts. FDA staff on the CBER planning team were encouraged to promote the event on channels they use for professional communication and networking. As a result, 33% of referrals came from a friend or colleague and 32% came from FDA newsletters or emails, among other referral sources (**Figure 1**). CBER also conducted targeted outreach to sister agencies, patient advocacy groups, and organizations.[11]

The half day meeting consisted of two sessions, one each regarding the early enrollment of children and adults into gene therapy clinical trials. At the beginning of the meeting and before each session, patients and caregivers were asked to respond to a series of polling questions (**Appendix 3**), which provided demographic information and an overview of participants' views on relevant topics. During each session, patients, caregivers, patient advocates, and other stakeholders (**Appendix 2**) presented their perspectives on early enrollment of patients with rare diseases into GT clinical trials, identifying decision-making factors for enrollment and the associated risk tolerance. After each session, subject matter experts from OTP and CBER's Office of Biostatistics and Pharmacovigilance (OBPV) asked the speakers clarifying questions. The FDA's goal was to understand what factors patients and caregivers of patients in the pre-symptomatic or early stages of rare diseases consider when deciding whether to enroll in a clinical trial to potentially receive an investigational GT product.

This report summarizes the main topics and perspectives discussed during the meeting. As a supplement to the meeting discussions, stakeholders were encouraged to submit comments to the public docket (FDA-2024-N-4605),[12] which was open from December 4, 2024, to February 3, 2025. Seven comments were submitted (**Appendix 1**).

[11] National Center for Advancing Translational Science (NCATS), National Heart Lung and Blood Institute (NHLBI), National Organization for Rare Diseases (NORD), Global Genes, and National Health Council

[12] Regulations.gov

FDA Opening Remarks

Prior to the speaker sessions, FDA acknowledged OTP was overseeing more than 2,600 active investigational products (investigational new drugs), approximately half of which are GTs. For the development of these treatments, collaboration with patients and care partners is critical. Participation and attendance at collaborative events like these Patient Listening Sessions highlight the fact that patients and their care partners are committed to advancing the field of GTs. During this listening meeting, the FDA solicited input from patients and caregivers regarding factors involved in the decision-making process for whether to enroll themselves or their child in a GT clinical trial. These considerations include impact of the disease and current symptom management, risk tolerance and tolerance of uncertainties, short- or long-term side effects, requirements for clinical trial participation, long-term follow-up requirements, expectations of benefit, and financial considerations.

FDA encouraged sponsors to involve patients in study design as early as phase I trials and noted there are various opportunities for interactions with the FDA throughout product development that can enhance FDA and sponsor collaboration in expediting clinical trials and approving products for rare diseases. These include the Rare Disease Endpoint Advancement (RDEA) pilot program,[13] the Support for Clinical Trials Advancing Rare Disease Therapeutics (START) pilot program,[14] and the Rare Disease Innovation Hub.[15] FDA is committed to enhancing patient engagement and ensuring that patient and care partner voices are central in both product development and regulatory decision-making.

[13] Rare Disease Endpoint Advancement Pilot Program | FDA

[14] Support for clinical Trials Advancing Rare disease Therapeutics (START) Pilot Program | FDA

[15] FDA Rare Disease Innovation Hub | FDA

SESSION 1

Early Enrollment of Children

Session 1 speakers primarily comprised caregivers of or patient advocates for children diagnosed with rare diseases. The speakers were asked to share their perspectives on the following questions:

1. If you were to consider enrollment in a GT trial for early-stage or pre-symptomatic disease for your child, what would you want to know?
2. What would you think about regarding disease stage of progression when considering enrollment in a GT trial?

There were 24 speaker presentations followed by panelist questions. Their comments are summarized below:

- A woman whose child passed away from metachromatic leukodystrophy spoke on behalf of the Global Leukodystrophy Initiative. She emphasized the heterogenous nature of leukodystrophy and discussed how sponsors developing treatments for leukodystrophies must understand how different disease subtypes affect respective patient populations to reduce potential risks to children enrolled in clinical trials. Clear communication prior to GT clinical trial enrollment is crucial, namely regarding endpoints and study design, if symptom management discontinuation would be necessary to participate, trial eligibility criteria, and long-term expectations such as relocation requirements or potential ineligibility to participate in future clinical trials.
- The President and Cofounder of the Friedreich's Ataxia Research Alliance whose child has Friedreich's Ataxia (FA) emphasized the need to treat children with the disease as early as possible since damage begins in utero and typically results in death by early adulthood. He highlighted the importance of accelerated approval of GTs for pre-symptomatic or early symptomatic children, asserting that the rare disease community would rather accept the risks and uncertainties that come with GT clinical trials than the risk of doing nothing.
- The President and Cofounder of CureSHANK whose son has Phelan-McDermid syndrome described the early onset of her son's social and communication development delays that continued to progress despite consistent speech, occupational, and other therapies. She underscored the need for early intervention with GT to improve potential outcomes in all areas of development as there are critical cognitive developmental milestones that must be met in early childhood.
- The CEO of Cure LGMD2i Foundation whose daughter has limb girdle muscular dystrophy type 2I (LGMD2i) highlighted that although there are 15 years of natural history (NH) data, 13 years of Fukutin-Related Protein registry data, and 3 Fast Track-designated clinical trials, there are no approved therapies for the disease. The speaker expressed that her daughter is ready to enroll in a GT clinical trial but they have concerns regarding potential risks (i.e., cancer, reproductive effects, or organ damage), necessary invasive procedures, length of hospital stay, type and mechanism of placebo data gathering, potential ineligibility for other treatments, and whether early access or compassionate use for programs with Rare Pediatric/Orphan Drug Designation would be available if she were ineligible for enrollment. The speaker concluded that remaining untreated poses more of a risk than the risks associated with participation in a GT clinical trial.
- A woman who learned she was a carrier of ataxia telangiectasia through routine genetic testing stressed her desire to enroll her daughter, who was diagnosed with the disease and is pre-symptomatic, in a GT trial. Since the multi-systemic symptoms begin early in childhood and develop quickly, patients and caregivers may have a high tolerance for GT-related risks if those risks were communicated prior to enrollment. The speaker also stated that follow-up duration and financial impact would not be much of a concern if her child is able to participate early in a GT clinical trial.
- The Patient Affairs Director of the Alliance to Cure Cavernous Malformation (CCM), who was diagnosed with the disease alongside her two children, highlighted a patient survey indicating the need for proof-of-concept studies and the desire for a one-time treatment. Although some pediatric patients experience aggressive symptoms, 50% with familial mutations of CCM typically have mild or no symptoms, so GT decision-making for asymptomatic children can be difficult. The speaker asserted that the CCM community desires clinical trials for GTs to treat adult patients first, as risk tolerance may be higher for adults than for parents and caregivers of pediatric patients.
- The Director of Outreach and Development for Hope in Focus, a patient advocacy organization for Leber congenital amaurosis (LCA), whose children have LCA

acknowledged that although the community is fortunate to have a GT (Luxturna) that treats one mutation of LCA, many other disease-causing mutations of LCA have no FDA-approved treatments. She stressed that parents and caregivers desire early enrollment in clinical trials to prevent or slow early and severe deterioration of vision and increase efficacy, especially since the safety of GTs in this therapeutic area has already been established with Luxturna. Additionally, families want more locations for clinical trials to reduce the burden of travel, as well as fewer dose-exploration trials if an effective dose has already been proven efficacious.

- The Executive Director of the LGMD2D Foundation whose son has LGMD expressed her desire to see GTs developed to prevent or slow the severe progression of disease, as early intervention could lead to better long-term outcomes. She stated that considerations for enrollment include the invasive procedures required, the short- and long-term side effects, and the length of monitoring and long-term follow-up.
- The Founder of the Leukoencephalopathy with Calcifications and Cysts (LCC) Foundation and mother of four children, two of whom have LCC, stressed the importance of clear communication and transparency regarding the goals of a GT clinical trial, such as if the trial will focus on dose exploration, safety, or efficacy; if the objective will be to halt disease progression or stabilize symptoms; and how success will be measured. She added that families also want to know the potential for medication discontinuation, potential side effects of the GT, and cost of trial participation, including if there would be financial support in place to help families afford treatment.
- The Chief Scientific Officer for the FamilieSCN2A Foundation and father of a daughter with a SCN2A pathogenic gene variant indicated that the disorder is complex and not well-understood, which has made it difficult to find proper treatment. The risk-benefit equation for novel GTs for SCN2A-related disorders includes weighing the risks of continuing without treatment, which can be catastrophic, against the risks associated with receiving GT. He asserted that since treatment focus is to stabilize the patient's life, short-term safety risks are more of a concern than long-term safety risks, making it critical for sponsors to engage patient communities early and often.
- The parents of a child diagnosed with alpha thalassemia major in utero expressed their desire for early GT intervention, as most children diagnosed do not survive past infancy, and current treatment (i.e., blood transfusion) is tedious. They discussed questions families may have concerning GT trial enrollment, such as how early a patient could enroll in the trial, the potential side effects or changes in quality of life, and how/if the GT might affect those with additional disorders, such as inflammatory bowel disease.
- A mother of two sons diagnosed with Duchenne muscular dystrophy (DMD) who were both treated with GT at either the pre-symptomatic or early symptomatic stage of disease stressed the importance and impact of early intervention, noting that the son who received GT in the pre-symptomatic stage has a much better quality of life than his brother did at the same age. Prior to deciding whether to enroll in the GT clinical trial, the family's most important questions were regarding health risk/side effects, longevity of effects, and if other treatments would no longer be an option post-GT.
- The President and CEO of Parent Project Muscular Dystrophy emphasized the importance of early use of GT while asserting that families need clarity and communication about key scientific and logistical aspects of early enrollment in clinical trials, specifically if redosing will be required as the child ages and efficacy diminishes, and if trial participation would exclude the child from enrolling in future clinical trials. She underscored that early access to GT must not come at the expense of having future treatment options, and that early enrollment must be guided by three principles: transparent communication and education, patient-centered clinical trial design, and ethical oversight and long-term commitment.
- A mother of a daughter with juvenile Tay-Sachs disease who was diagnosed late in the course of disease emphasized the importance of early diagnosis and trial enrollment. She stated that local doctors should have readily accessible information regarding clinical trials for patients and caregivers. Considerations for enrollment in a GT clinical trial include inpatient versus outpatient treatment, financial obligations, length of follow-up, and communication expectations. The speaker added that while compassionate use pathways are available, gaining approval can be a lengthy process.
- The President and CEO of the Shwachman-Diamond Syndrome (SDS) Alliance and mother of a child with the disease, which leads to the development of leukemia by young adulthood, looks forward to a future where SDS is considered as a candidate for GT. She explained that since treatment would typically be administered in the pre-symptomatic stage, patients with SDS and their caregivers are primarily concerned about safety, since some side effects may not be acceptable in the context of the relative health of patient, and efficacy, as cancer

risk is hard to measure in the short-term. She believed a good measure of short-term effects could include immune function, neutrophil count, and overall improvement of bone marrow health, while long-term effects could be measured by a decrease in cancer risk.

- The Director of Operations for the Nonketotic Hyperglycinemia (NKH) Crusaders organization, President of the Brodyn's Friends Foundation, and mother of a son with NKH emphasized the need to develop earlier and more accurate methods of diagnosis, as there are currently no pregnancy or newborn screenings for many rare diseases like NKH. She noted that while a recent community survey showed that 97% of caregivers are willing to accept perceived risks of GT clinical trials, some concerns include short- and long-term side effects; ease or difficulty of product administration, including associated travel or financial burdens; the potential impact on any future opportunities for treatment; and an individual patient's gene mutation. Another determining factor in deciding to enroll early is if accurate NH data are available.
- The Program Development Director for the Hereditary Neuropathy Foundation and patient with Charcot-Marie-Tooth (CMT) disease highlighted that early enrollment in clinical trials can halt progression or reverse the course of disease, but that communication is paramount, especially regarding trial design, eligibility criteria, potential safety and efficacy, length of treatment and follow-up, and long-term expectations. She added that upper and lower limb function in patients with CMT can be measured with remote monitoring, providing real-time data to help researchers track efficacy and reduce the need for regular site visits.
- The President and Executive Director of Project Alive, a patient advocacy organization for Hunter syndrome, as well as mother to and sister of individuals with the disease, emphasized the importance of early GT intervention since progressive debilitation often leads to death in adolescence. She stated that since Hunter syndrome was recently added to state newborn screening panels across the country, it is imperative that infants with a diagnosis be allowed to participate in GT clinical trials before they become symptomatic. Caregivers have a high tolerance for risks associated with experimental treatments, since the alternative is early mortality.
- The Founder of SCN2A Australia whose young adult child has an SCN2A-related disorder discussed research that she has been conducting at the University of Sydney that focuses on developing a decision-making framework for high-cost GTs. She shared that patients and caregivers desire transparency and trust with industry partners and want clear and practical information regarding clinical trials, such as the purpose of the trial (i.e., dosing, efficacy, safety), short- and long-term risks, and potential benefits and risks. Additionally, families are most concerned with unknown effects regarding their child's cognitive and physical development, reproductive health, and quality of life.
- Two women on the Cystinosis Research Network board, both mothers to children with cystinosis, detailed how the nephropathic cystinosis community has benefited from previous clinical trials, namely four FDA-approved therapies and a GT clinical trial currently underway. The speakers noted that pre-enrollment considerations for GT clinical trials include guidelines for informed consent (e.g., minor versus parental consent); time and effort commitments (e.g., labs and other appointments); the clinical process (e.g., use of immunosuppressants, potential side effects); follow-up requirements; and disease progression considerations (e.g., inability to take prior medications).
- A father of a daughter with O-GlcNAc transferase (OGT) X-linked intellectual disability (XLID) and member of the Cure OGT organization acknowledged that although it is unknown if early treatment is necessary to see clinical improvement, there is a high likelihood that treating the condition earlier is better. Considerations for enrollment in GT clinical trials include the evaluation of quality-of-life without any treatment, specifically GT, and the potential risks and benefits of treatment. He mentioned that having clear information regarding the potential risks of GT is especially important since OGT-XLID is not considered life-threatening, therefore making risk tolerance comparatively low.
- The mother of children with guanidinoacetate methyltransferase (GAMT) deficiency, a type of cerebral creatine deficiency syndrome (CCDS), emphasized the importance of early diagnosis and pre-symptomatic intervention. She provided the example of two siblings with GAMT deficiency whose severity of symptoms are strongly correlated with early timing of diagnosis and administration of oral creatine supplements. The CCDS community has already developed a core set of efficacy outcomes for any future clinical trials related to adaptive and cognitive function, emotional dysregulation, expressive communication, fine motor function, seizures, plasma guanidinoacetate, and magnetic resonance spectroscopy brain creatine.
- The Founder of Juju and Friends CLN2 Warrior Foundation, whose children have rare diseases, stated that early enrollment in GT clinical trials offers patients

access to treatments that are not yet publicly available, which can significantly improve quality of life. Additionally, enrollment can foster collaboration among researchers, health care providers, and patients and caregivers. However, since GT may involve safety concerns and does not always offer a definitive cure, it is important for patients and caregivers to be fully informed of the potential risks and benefits associated with investigational GTs.

- The Research Director for the Alport Syndrome Foundation who lives with the disease highlighted research showing that although symptoms of the condition do not begin until adolescence or young adulthood, early pediatric intervention with a GT is needed to positively affect the course of disease and symptom development, especially since genetic testing is revealing prevalence that is higher than previously understood. The speaker stated that at least five different companies are developing a GT for Alport syndrome and asked that the patient community be provided with insights regarding clinical data and how that translates to in-human studies.

After the session 1 speaker presentations, FDA panelists (**Appendix 2**) had a chance to ask participants clarifying questions.

One panelist asked if decentralized clinical trials, where some or all follow-up can be conducted outside of a traditional clinical trial site, would help alleviate any hesitancy to enroll in trials with an extended or indefinite long-term follow-up period. Another panelist inquired if patients and caregivers would want the control arm in another trial to include treatment with the approved GT. One speaker stressed that, in a general sense, parents desire more options and opportunities and are willing to try whatever GT is approved and available.

A panelist asked what the number one barrier to early trial access has been. Speakers mentioned that access to newborn screenings is crucial, as diagnosis for children is crucial to receiving early access to GTs. Caregivers have also encountered issues with trial enrollment ending prior to obtaining a diagnosis for their child; in these cases, they have been told they must wait until a product becomes FDA approved. Additionally, the speakers spoke about the patient community's desire for more GT options and clinical trials, as some of the GTs do not end up being approved due to safety or efficacy issues.

Another panelist asked speakers to provide their perspectives on the fact that more than half of responders to a polling question had identified quality of life as a crucial deciding factor for GT (**Appendix 3**). Caregivers noted that although they would like to see GT be a cure for patients, any improvement in quality of life would be seen as positive; for example, just being able to leave the house after being housebound for years would mark an improvement in quality of life for some.

The final panelist highlighted conflicting desires concerning the need for early enrollment prior to decline versus reducing the burden of appointments and follow-up. He mentioned that one of the trade-offs for earlier clinical trial enrollment of children with pre-symptomatic or early-stage disease is often the need for longer follow-up for investigators to be able to understand whether the treatment is having a positive effect and asked if such a trade-off affects a family's decision-making. Several speakers indicated that parents and caregivers are often so desperate for any type of treatment for their child that they are willing to participate in clinical trials with any length of follow-up. The rare disease community has also been working with industry and pharmaceutical companies to try and ease the burden of follow-up in clinical trials. Some of these strategies include collaborating with local doctors, receiving home infusions, and having labs performed in the home by nurses.

Regarding long-term follow-up, another speaker stressed that new adult patients transitioning away from their parents' care need to be educated on why participating in follow-up is important for them in the long-term.

SESSION 2

Early Enrollment of Adults

Session 2 speakers primarily comprised adult patients diagnosed with rare diseases and their caregivers. The speakers were asked to provide insight regarding the following questions:

1. If you were to consider enrollment in a gene therapy trial for early-stage or pre-symptomatic disease for yourself, what would you want to know?
2. What would you think about regarding disease stage of progression when considering enrollment in a gene therapy trial?

Ten speakers (**Appendix 2**) shared their perspectives during this session, and their comments are summarized below:

- The Executive Director of the Hermansky-Pudlak Syndrome (HPS) Network and parent of an adult patient with HPS type 1 highlighted that the disease's progression is unpredictable, necessitating early intervention. Despite years of NH studies, the only treatment option currently is lung transplant, which has eligibility limitations and often results in multiple hospitalizations and expensive therapies. She stressed that GT at an early stage of disease could halt or reverse disease progression and prevent late-stage comorbidities such as kidney failure, pulmonary arterial hypertension, and cardiomyopathy. While open to trial enrollment for a GT, patients and their caregivers want to know how safety and efficacy would be established, how the GT would be delivered, and how often it would be administered.
- The Executive Director of the Alport Syndrome Foundation described her experience as a patient and the mother of a child with the genetic kidney disease. After being misdiagnosed for over 25 years, which is common for Alport syndrome, she and her son participated in a five-year clinical trial for a drug that did not gain FDA approval. She noted that despite the potential risks, many early-stage or pre-symptomatic patients would rather receive a GT than experience the life-limiting outcomes resulting from kidney transplant and dialysis. Before enrollment, however, patients want to know how investigators will evaluate whether the patient is a good candidate for the therapy, especially if kidney damage has already occurred. Other considerations include the drug's mechanism of action and delivery method, signs of efficacy, anticipated side effects, how study data would be shared with the patient, and potential financial burdens.
- A board member of the Wilson Disease Association discussed her challenges in living with Wilson disease and her experience participating in a clinical trial for a GT that has not yet been approved; she attributes her life today to participation in the trial. She noted that trial enrollment considerations include what vector is being used and if it has been studied in other trials, the safety risks involved, and the types of protocols in place if a side effect occurs.
- On behalf of Help 4 HD, a woman with pre-symptomatic Huntington's disease (HD) was joined by a long-time patient advocate with prodromal HD to highlight that many gene-positive individuals[16] are motived to enroll in a clinical trial early in the course of disease, especially since quality of life may be best preserved if GT treatment occurs before neurological degeneration begins. The speakers stated that patients may be less likely to enroll if participating in the clinical trial would preclude enrollment in future research of potentially more effective therapies, and if the GT causes long-term side effects resulting in caregiver burden. Successful early enrollment can be accelerated by more sensitive patient-reported outcome measures, biomarkers, and NH as a control.
- A registered nurse and pre-symptomatic carrier for frontotemporal dementia (FTD) whose relative passed away from the disease stated that the familial mutation of FTD that she inherited makes her ineligible to participate in ongoing clinical trials for drugs, highlighting GT as a good alternative option. She noted that waiting until symptom onset to begin treatment is not ideal due to the neurodegenerative nature of the disease. She also suggested that patients be allowed to enroll in GT clinical trials while in the pre-symptomatic phase or within a

[16] Per the 2022 "Huntington's Disease Pre-Symptomatic Population FDA Patient-Led Listening Session," 60% of gene-positive individuals are willing to enroll in a GT clinical trial. See **Huntington's Disease Youth Organization - Huntington's Disease Pre-Symptomatic Population FDA Patient-Led Listening Session Full Report**

few years of the predicted phenoconversion to potentially halt the disease before it begins.

- A woman with pre-symptomatic alpha-1 antitrypsin deficiency spoke on behalf of the Alpha-1 Foundation about the advantages of enrolling pre-symptomatic individuals in GT clinical trials, which include identifying biomarkers, preventing disease progression, optimizing treatment windows, and accelerating the development of new therapies. She stated that before enrolling, patients may question how effectively the GT prevents or slows disease progression, what the potential short- and long-term side effects are, what kind of monitoring and follow-up will occur after treatment, and how the GT's long-term implications might affect overall health. She implored the FDA to accept surrogate endpoints like computed tomography densitometry to expedite the trial process and encourage adaptive design to make trials more responsive and feasible for this rare patient population.
- A woman with LCC described her long journey to diagnosis and how her condition has negatively impacted her quality of life. She stressed that access to treatment that could slow, halt, or reverse LCC would allow patients to maintain their desired quality of life and not miss work or school due to seizures or hospital stays. Before enrolling in a GT clinical trial, patients should be transparently informed on the known and possible long-term risks of the product.
- The Scientific Coordinator for the Adult Polyglucosan Body Disease (APBD) Research Foundation noted that, per a 2021 Patient-Led Listening Session with the FDA,[17] many pre-symptomatic and early-stage patients find the potential risks associated with participating in a GT clinical trial to be minor compared to the outcomes associated with becoming symptomatic. She discussed key considerations for enrollment, which include whether participation would limit access to future and potentially more effective treatments, how invasive the treatment is and how it might affect quality of life, if pre-symptomatic patients must disclose their diagnosis to an employer or others, and if significant lifestyle adjustments such as relocation would be required. The APBD community encourages the FDA to communicate effectively and work with patient advocacy organizations, industry sponsors, and other stakeholders to develop comprehensive tools to help affected families navigate the complex world of clinical trial participation.
- A pre-symptomatic carrier of amyotrophic lateral sclerosis (ALS) and FTD, who has had multiple relatives pass away from ALS, stressed that pre-symptomatic patients enrolled in GT clinical trials may be classified as fully functional but are still in need of therapeutic intervention. Initial safety data should be established via testing in symptomatic patients before enrollment of patients with early-onset and pre-symptomatic disease whose biological markers indicate risk of severity. She noted that patients considering enrollment may question how long benefits of GT may last, especially since some efficacious drugs may only prolong survival by a few years.
- A researcher at the Broad Institute of MIT and Harvard and carrier of genetic prion disease stated that early treatment provides the most benefit since options after symptom onset are significantly limited. Based on research involving prion protein-lowering therapies, there is evidence that shutting off the single, disease-causing gene may prevent genetic prion disease from developing. The speaker stated that since pre-symptomatic carriers do not show signs of neuronal damage, primary prevention of genetic prion disease should involve treating healthy individuals based on their genotype.

Following the Session 2 speaker presentations, the FDA panel had the opportunity to ask speakers clarifying questions. One panelist asked how likely women of childbearing age are to enroll in GT clinical trials when the effects of the product on fertility are still being established. The unknown impact on reproductive health may dissuade some individuals from participating in a GT trial, but others may still be willing, especially if they would be unable or hesitant to bear children anyway. Speakers agreed that patients should maintain the choice to participate without the fear of being discriminated against simply because they're women of childbearing age. Patients also expressed that the potential for improved quality of life would benefit those who already have families by allowing them to better care for their children.

Another FDA panelist asked how earlier trial participation might have made a difference for patients whose rare disease had already progressed to a more advanced stage before trial enrollment. Speakers stated that many conditions have seen few successful clinical trials involving pre-symptomatic patients. Sometimes, a pre-symptomatic patient may be excluded from trial participation because they did not meet the inclusion criteria to participate, even though they are positive for a pathogenic gene muta-

[17] See **APBD Research Foundation Engages the FDA in Patient Listening Session - Adult Polyglucosan Body Disease Research Foundation (APBDRF)**

tion and are beginning to show symptoms. Despite these challenges, many adult patients with pre-symptomatic or early-stage rare disease are willing to participate in clinical trials to accelerate the development of an effective GT, even if the particular trial ends up being terminated due to design issues or insufficient positive results.

A third panelist asked what role health care providers play in helping patients decide to enroll in a clinical trial. A few speakers noted that many individuals turn to patient organizations versus their health care provider to gain information before deciding to enroll, as such organizations are specifically poised to dispense research information, help shape study design, and effectively enroll patients. However, patient organizations need sponsors to involve them early, such as in the preclinical stages of the trial, to be able to provide the most optimal input.

Finally, FDA panelists asked speakers to share their thoughts concerning the use of a control group in a clinical trial when prior data does not conclusively show that mortality or manifestation of the disease is the inevitable patient outcome. The speakers stated that if it's clear that the product works by surrogate biological measurements or clinical outcomes, an open-label trial may make sense; if this is not the case, having a control group may be appropriate. In a fully pre-symptomatic trial with a clear biomarker endpoint, placebo-treated patients could be monitored closely for signs of conversion, at which point they would cross over to the treatment arm. Patients considering enrollment in such trials should individually assess their risk tolerance and how much their quality of life is already being affected. Notably, speakers agreed that many pre-symptomatic patients are willing to enroll in a GT clinical trial with a placebo group to generate better data and advance GT development.

Conclusion

The December 4, 2024, virtual Patient Listening Session hosted by CBER provided patients, caregivers, and stakeholders the opportunity to share their perspectives on early enrollment of both child and adult patients with rare genetic conditions. Speakers and panelists engaged in a discussion regarding risk tolerance and other considerations when deciding whether to enroll in a GT clinical trial. Most caregivers and patients emphasized the desire for enrollment in GT clinical trials as early as possible during the pre-symptomatic or early stages of disease. Patients and caregivers implored FDA and sponsors to seek their involvement early in clinical trial design and emphasized their desire for clear communication regarding benefit-risk considerations, short- and long-term side effects, expected long-term outcomes, logistical and financial burdens of trial participation, length of follow-up, and if participation in one GT trial precludes participation in future trials.

Appendix 1: Docket Comments

As a supplement to the insight provided at the listening meeting, stakeholders were encouraged to submit comments to Docket FDA-2024-N-4605, which was open from December 4, 2024, to February 3, 2025.[18] The comments are summarized below:

- A man living with valosin-containing protein-associated multisystem proteinopathy, otherwise known as inclusion body myopathy associated with Paget's disease of bone and frontotemporal dementia, said that this community is willing and wanting to participate in a GT clinical trial as soon as possible.
- A woman with HD whose son has juvenile HD called for the FDA and pharmaceutical industry to continue working with the community to make more treatments available, especially due to the severity of disease progression and lack of current treatment options. She cited a recently published study on pre-symptomatic and early symptomatic HD, noting that such studies are critical in developing therapies that will successfully treat patients before their condition reaches late or end stages.
- A man with HD described the decision behind testing his whole family for the disease, including his personal history of positive diagnosis and his adult daughter's desire to understand risks that could affect her future children. He asked that the HD community be provided the necessary tools and treatment to combat the disease, stating that many patients are willing to take risks currently associated with treatment so that future generations can be treated without them.
- A woman who has had multiple relatives pass away from HD stated that the patient community is eager to participate in clinical trials and advance therapy development, but some patients have been denied enrollment due to exclusion criteria or other factors. She urged the importance of early enrollment and better accessibility for patients.
- A woman whose son passed away from juvenile HD highlighted his desire to participate in a clinical trial, stating that even if the drug had not improved or cured his condition, it could possibly help someone else.
- A commenter stressed that allowing patients who have an HD diagnosis to participate in clinical trials earlier is critical to provide the data needed to develop a treatment that can prevent the devastating symptoms associated with the condition.
- A Session 2 speaker who has prodromal HD and presented on behalf of Help 4 HD contributed additional comments, stating that with the recent halting of another clinical trial for a potential drug, the HD community's urgency to find a treatment is at an all-time high, even if that treatment is not curative. She stressed that with the help of the FDA, patients can be allowed to enroll in clinical trials earlier in their stage of the disease, which is necessary to accelerate successful treatment development.

[18] Regulations.gov

Appendix 2: Speakers and FDA Panelists

Speakers

Session 1:

1. Erica Barnes, *Global Leukodystrophy Initiative RDCRN Patient Advocacy Consortia*
2. Ron Bartek, *Friedrich's Ataxia Research Alliance*
3. Geraldine Bliss, *CureSHANK*
4. Kelly Brazzo, *Cure LGMD2i Foundation*
5. Laura Calhoun
6. Darla Clayton, *Alliance to Cure Cavernous Malformation*
7. Courtney Coates, *Hope in Focus*
8. Josh & Rachel DeConti, *LGMD2D Foundation*
9. Ashley Dike, *The LCC Foundation*
10. Dr. Shawn Egan, *The FamilieSCN2A Foundation Inc*
11. Mark & Cerilyn Fernando
12. Susan Finazzo, *CureDuchenne*
13. Pat Furlong, *Parent Project Muscular Dystrophy*
14. Yasmina Halim, *National Tay-Sachs & Allied Diseases Association*
15. Eszter Hars, *Shwachman-Diamond Syndrome Alliance Inc*
16. Heidi Leslie & Kristin Archibald, *NKH Crusaders*
17. Estela Lugo, *Hereditary Neuropathy Foundation*
18. Kristin McKay, *Project Alive*
19. Kris Pierce, *SCN2A Australia*
20. Heather Rothrock & Chelsea Meschke, *Cystinosis Research Network*
21. Andrey Skripkin, *Cure OGT*
22. Christina Vargas, *Juju and Friends CLN2 Warrior Foundation*
23. Heidi Wallis, *Association for Creatinine Deficiencies*
24. Dr. André Weinstock, *Alport Syndrome Foundation*

Note: Five speakers—Farhan Ali, Daiza Gordon, Niranjan Thadaka, Raphaël Ngendakumana, and Lauren Scott—were slated to speak but did not participate.

Session 2:

1. Donna Appell, *Hermansky-Pudlak Syndrome Network*
2. Lisa Bonebrake, *Alport Syndrome Foundation*
3. Lana Escamilla, *Wilson Disease Association*
4. Lauren Holder & Jamie Holloway, *Help 4 HD*
5. Linde Jacobs, *Cure MAPT FTD*
6. Tammy McGuinness, *Alpha-1 Foundation*
7. Elisabeth Page
8. Becca Reef, *Adult Polygulcosan Body Disease Research Foundation*
9. Jean Swidler, *Genetic ALS & FTD: End the Legacy*
10. Sonia Vallabh, *Broad Institute of MIT and Harvard*

FDA Panelists

Session 1:

1. Dr. Najat Bouchkouj, Associate Director for Pediatrics, Office of Clinical Evaluation, Office of Therapeutic Products
2. Dr. John Scott, Division Director, Division of Biostatistics, Office of Biostatistics and Pharmacovigilance
3. Dr. Rosa Sherafat-Kazemzadeh, Branch Chief, General Medicine Branch 2, Division of Clinical Evaluation and General Medicine, Office of Clinical Evaluation, Office of Therapeutic Products

Session 2:

1. Dr. Vaishali Popat, Branch Chief, General Medicine Branch 3, Division of Clinical Evaluation and General Medicine, Office of Clinical Evaluation, Office of Therapeutic Products
2. Dr. Anam Tariq, MHS, FASN, Medical Officer, General Medicine Branch 3, Division of Clinical Evaluation and General Medicine, Office of Clinical Evaluation, Office of Therapeutic Products
3. Dr. Osman Yogurtcu, Senior Staff Fellow, Benefit-Risk Assessment Branch, Division of Analytics and Benefit-Risk Assessment, Office of Biostatistics and Pharmacovigilance

Appendix 3: Polling Question Data

During the meeting, FDA used the meeting platform's polling to pose the following questions to attendees. Patients and caregivers were self-identified and answered on a voluntary basis. The results, presented below, were used to provide context for the speaker comments.

Demographic Questions

Question 1: Geographically, where do you live?

Question 2: What best describes the community where you live?

Question 3: What is your ethnicity?

Question 4: We would like to know about the patients and care partners joining today's event. Please select the response that best describes you.

Question 5: How would you describe your or your loved one's disease? Please select all that apply.

Question 6: How do you receive information about gene therapy? Please select all that apply.

Session 1: Early Enrollment of Children

Question 1: What are your top considerations when determining whether to enroll your child in a gene therapy clinical trial at the presymptomatic or early stages of the disease? Please select up to 3 responses.

Question 2: What information about gene therapy risks would be most important to you when determining whether to enroll your child in gene therapy clinical trial at the pre-symptomatic or early stages of the disease? Please select up to 3 responses.

Question 3: If the disease progresses quickly, what are the risks/uncertainties you would be willing to accept when determining whether to enroll your child in a gene therapy trial at the pre-symptomatic or early stages of the disease? Please select up to 3 responses.

Question 4: If the disease progresses slowly over decades, what are the risks/uncertainties you would be willing to accept when determining whether to enroll your child in a gene therapy trial at the pre-symptomatic or early stages of the disease? Please select up to 3 responses.

Session 2: Early Enrollment of Adults

Question 1: What are your top considerations when determining whether to enroll yourself or your loved one as an adult in a gene therapy clinical trial at the pre-symptomatic or early stages of the disease? Please select up to 3 responses.

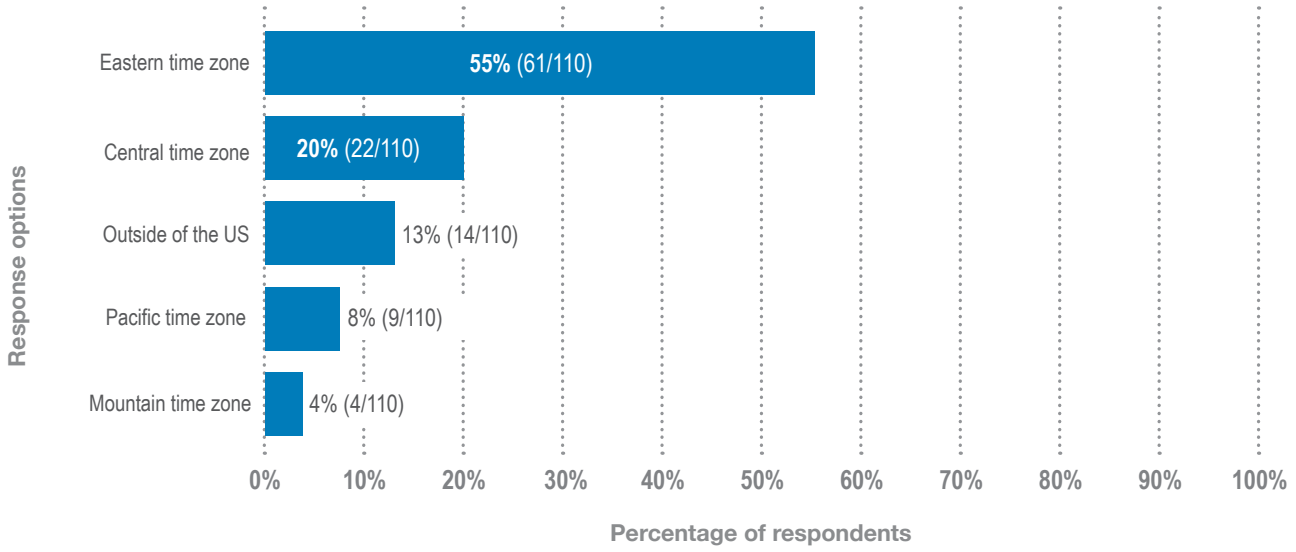
Question 2: What information about gene therapy risks would be most important to you when determining whether to enroll yourself or your loved one as an adult in a gene therapy clinical trial at the pre-symptomatic or early stages of the disease? Please select up to 3 responses.

Question 3: If the disease progresses quickly, what are the risks/uncertainties you would be willing to accept when determining whether to enroll yourself or your loved one as an adult in a gene therapy trial at the pre-symptomatic or early stages of the disease? Please select up to 3 responses.

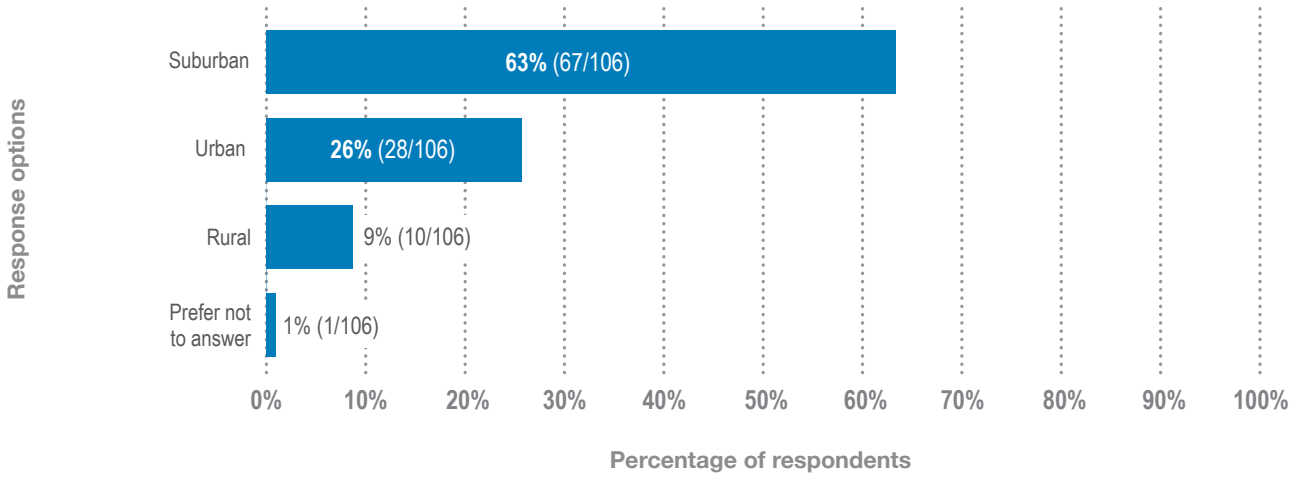
Question 4: If the disease progresses slowly over decades, what are the risks/uncertainties you would be willing to accept when determining whether to enroll yourself or your loved one as an adult in a gene therapy trial at the pre-symptomatic or early stages of the disease? Please select up to 3 responses.

Demographic Questions

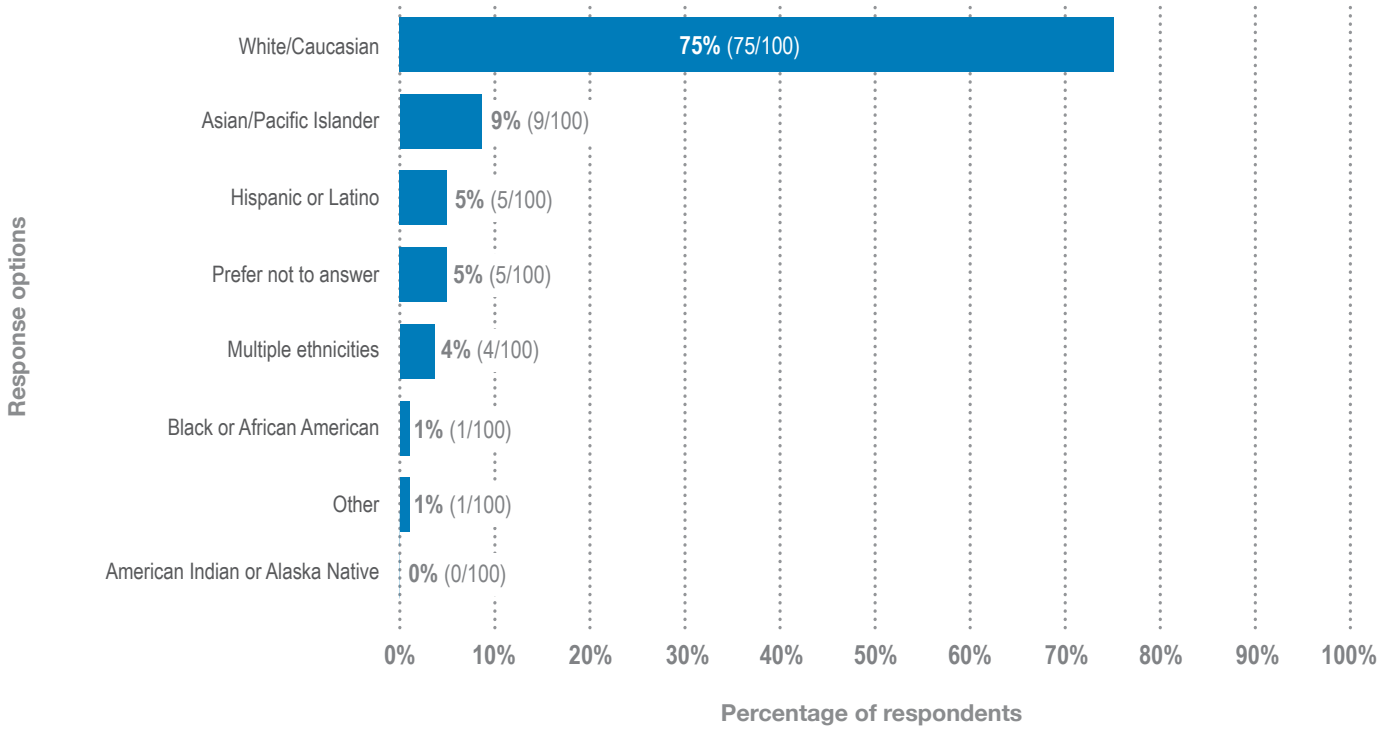
Question 1: Geographically, where do you live?



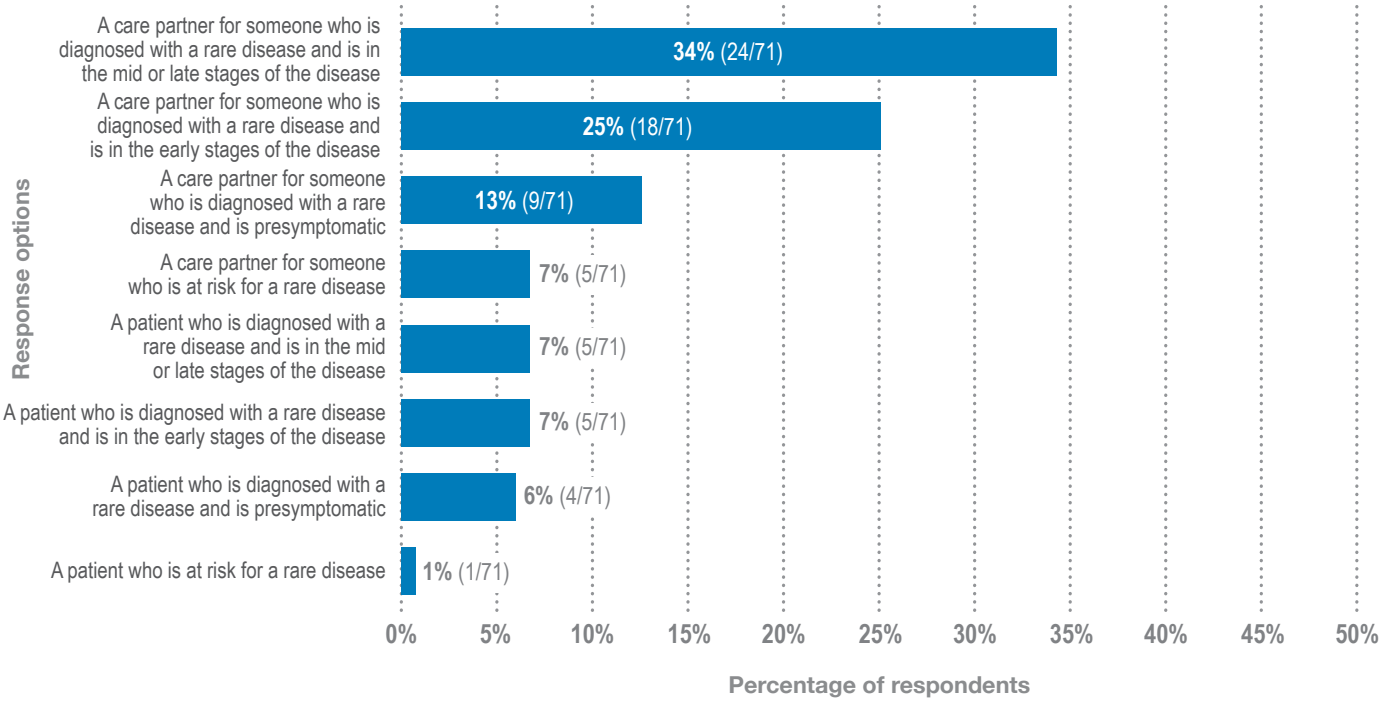
Question 2: What best describes the community where you live?



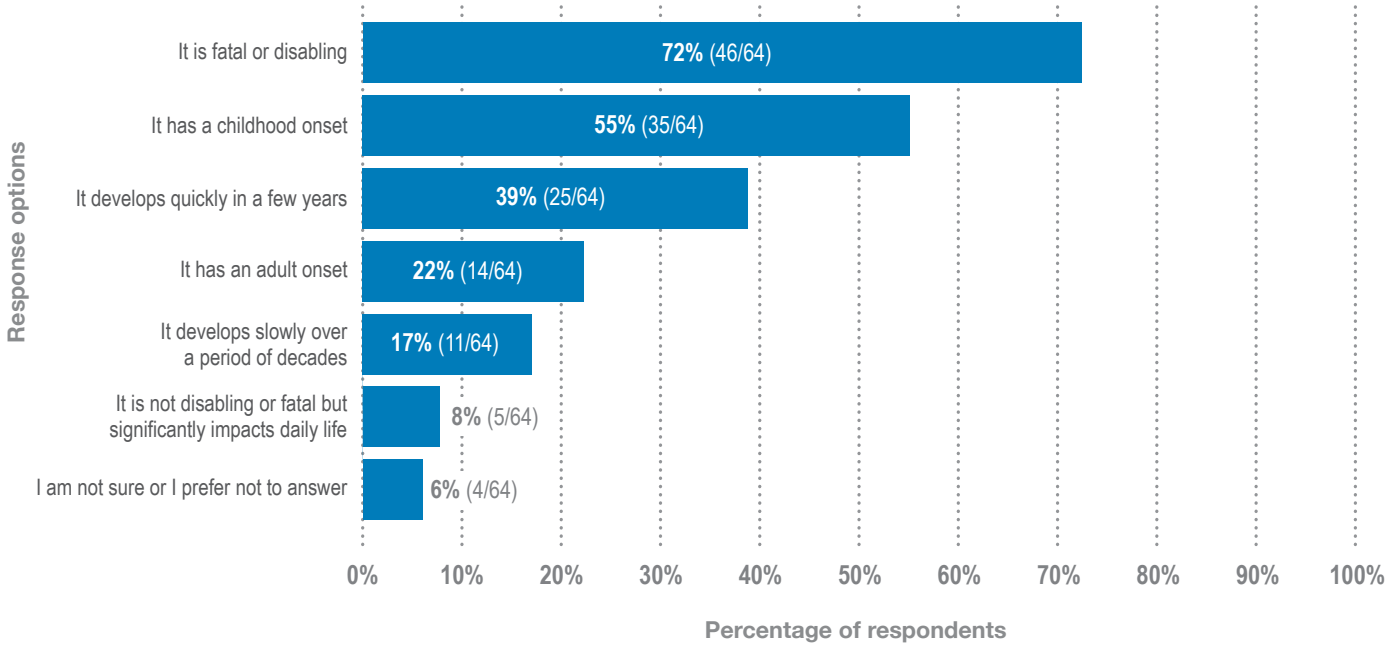
Question 3: What is your ethnicity?



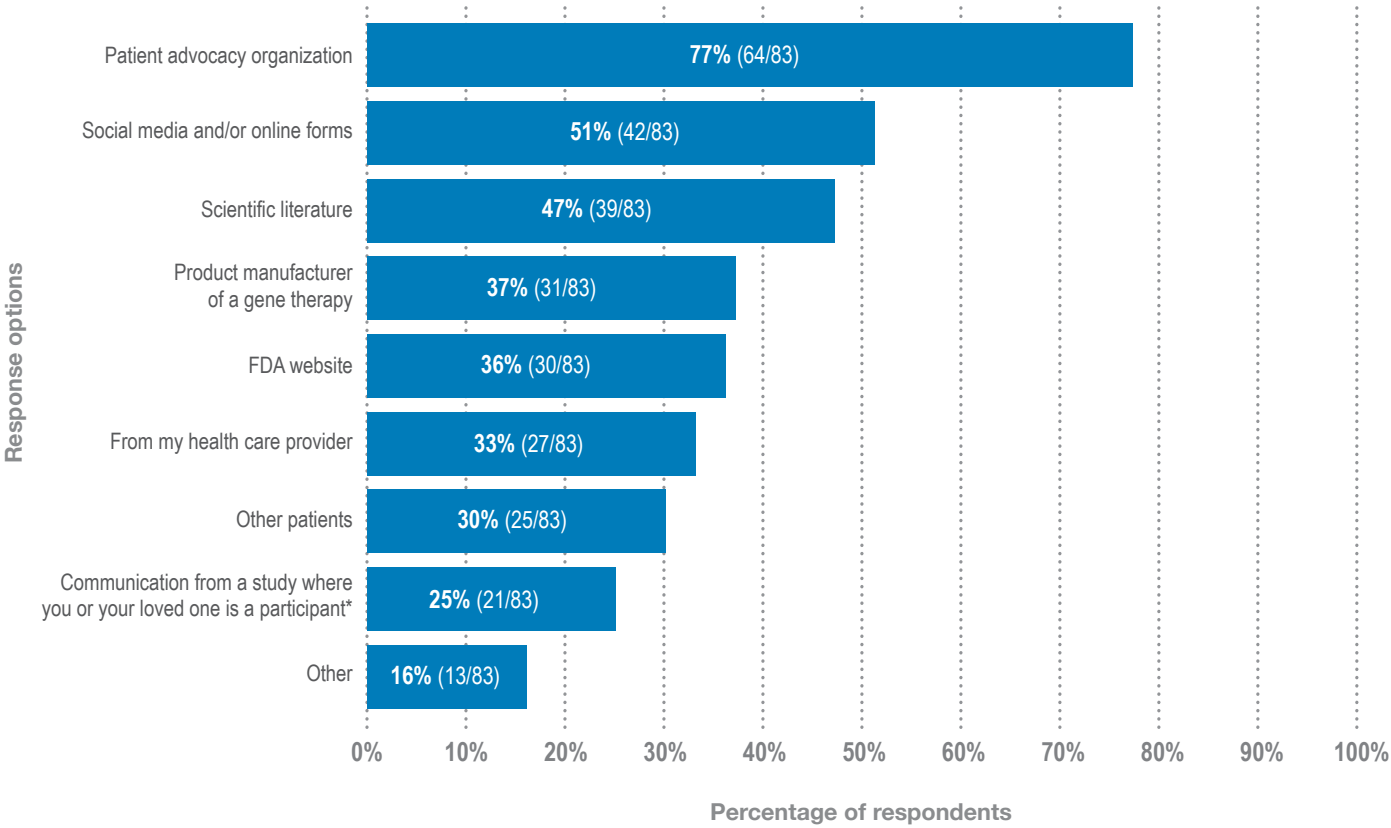
Question 4: We would like to know about the patients and care partners joining today's event. Please select the response that best describes you:



Question 5: How would you describe your or your loved one's disease? Please select all that apply.



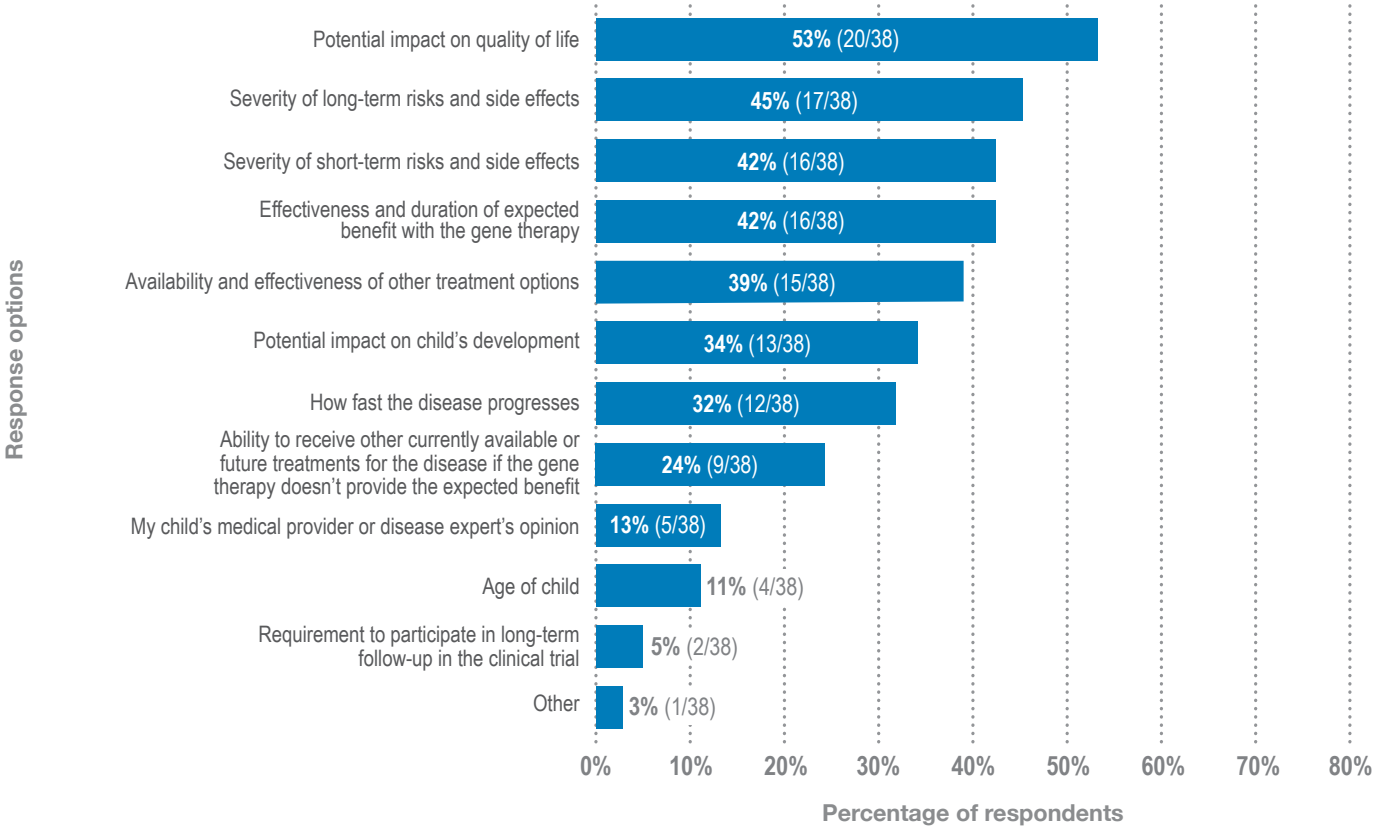
Question 6: How do you receive information about gene therapy? Please select all that apply.



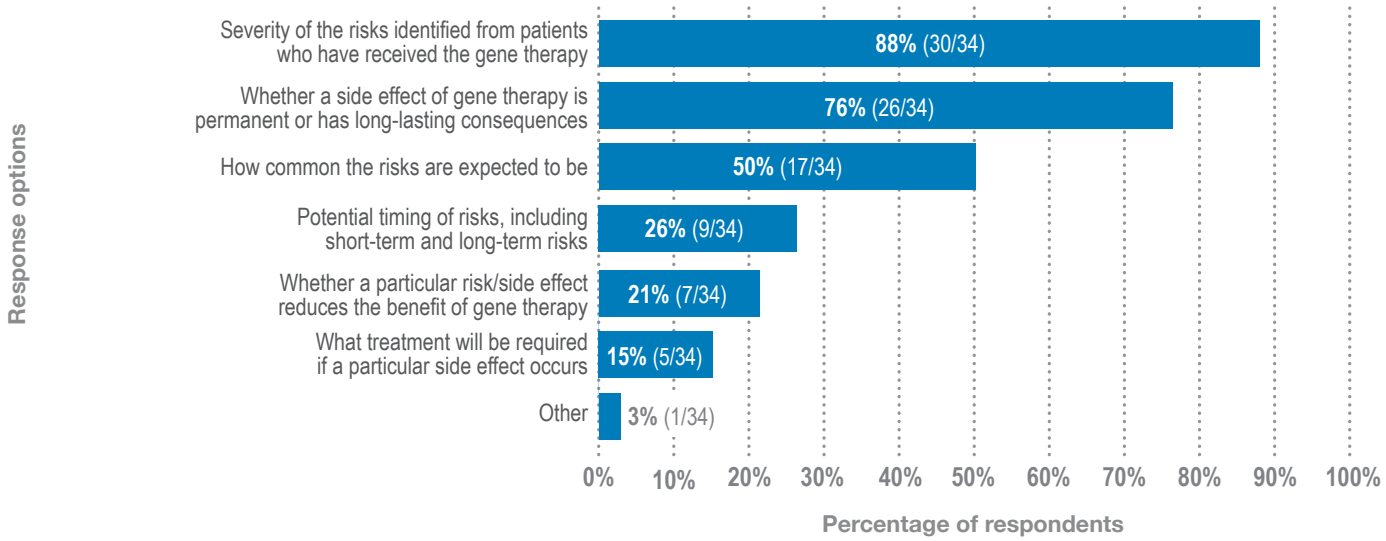
** for example, from the registry or study newsletter, study doctor, or research coordinator*

Session 1: Early Enrollment of Children

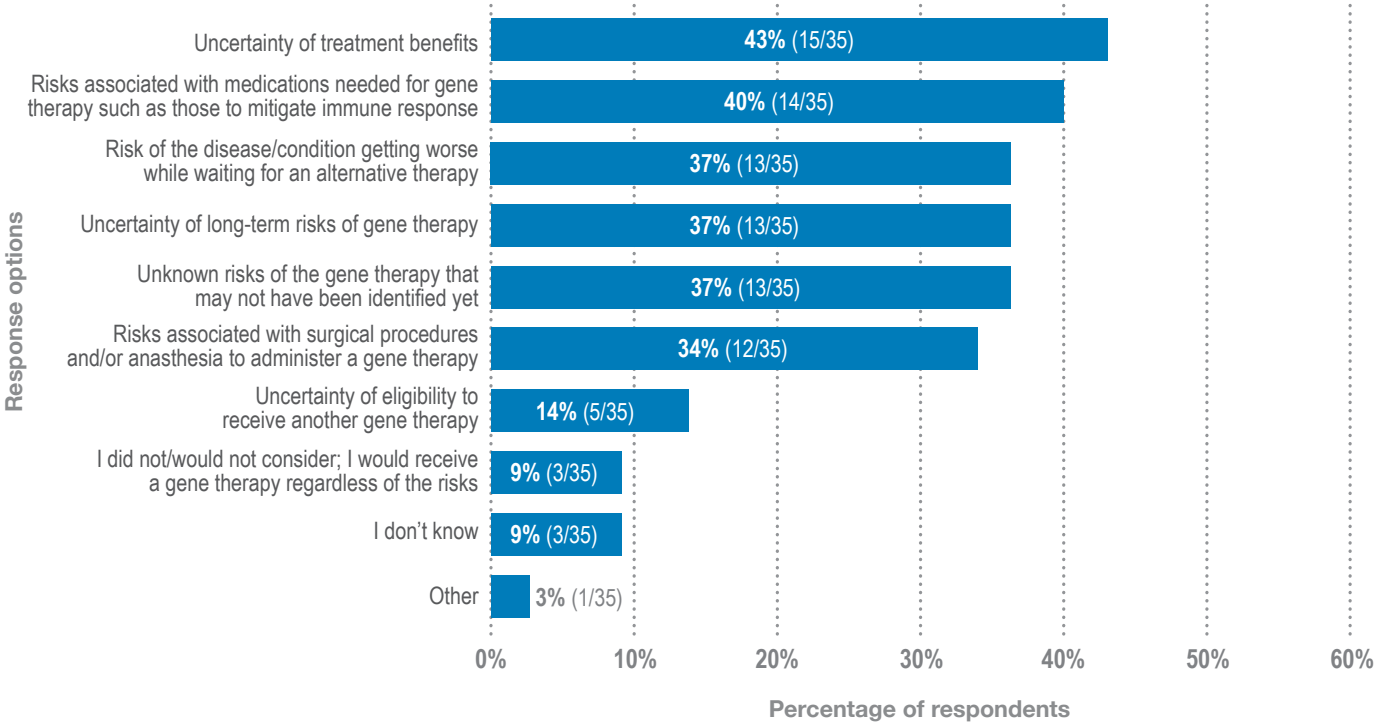
Question 1: What are your top considerations when determining whether to enroll your child in a gene therapy clinical trial at the presymptomatic or early stages of the disease? Please select up to 3 responses.



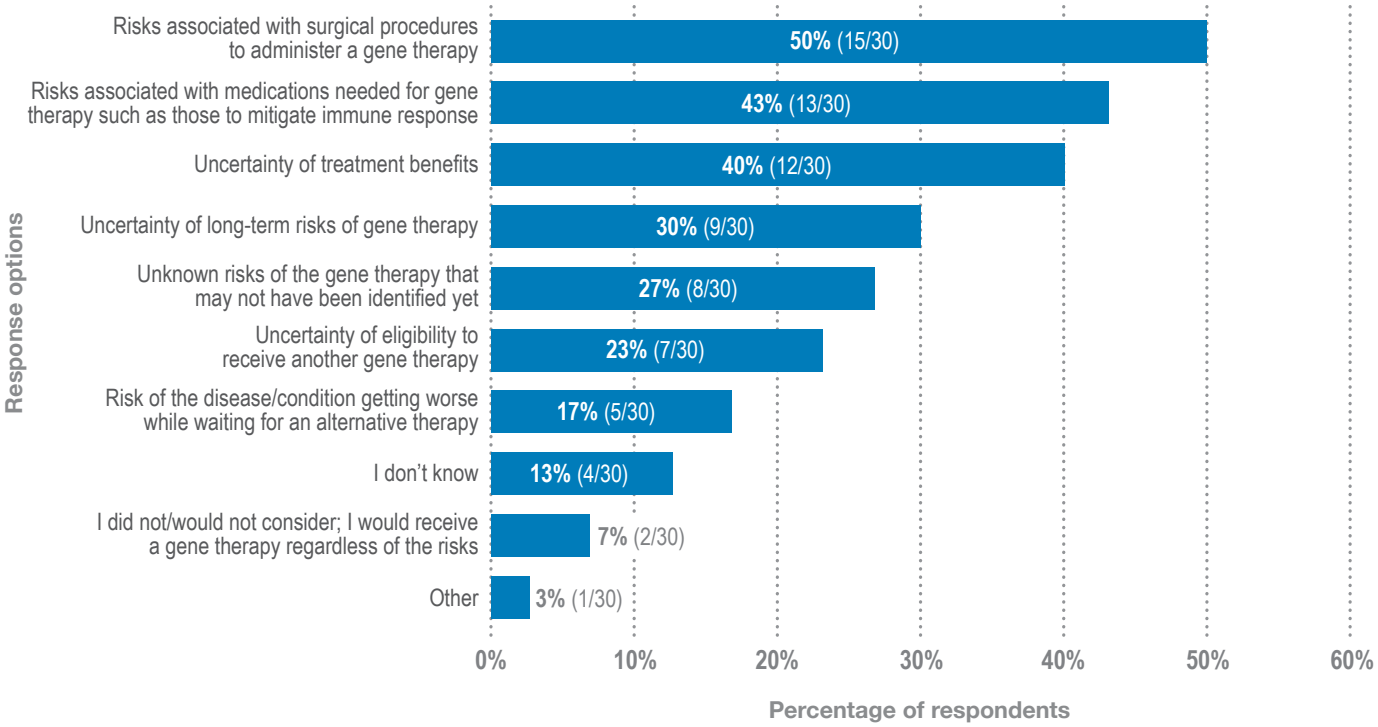
Question 2: What information about gene therapy risks would be most important to you when determining whether to enroll your child in gene therapy clinical trial at the pre-symptomatic or early stages of the disease? Please select up to 3 responses.



Question 3: If the disease progresses quickly, what are the risks/uncertainties you would be willing to accept when determining whether to enroll your child in a gene therapy trial at the pre-symptomatic or early stages of the disease? Please select up to 3 responses.

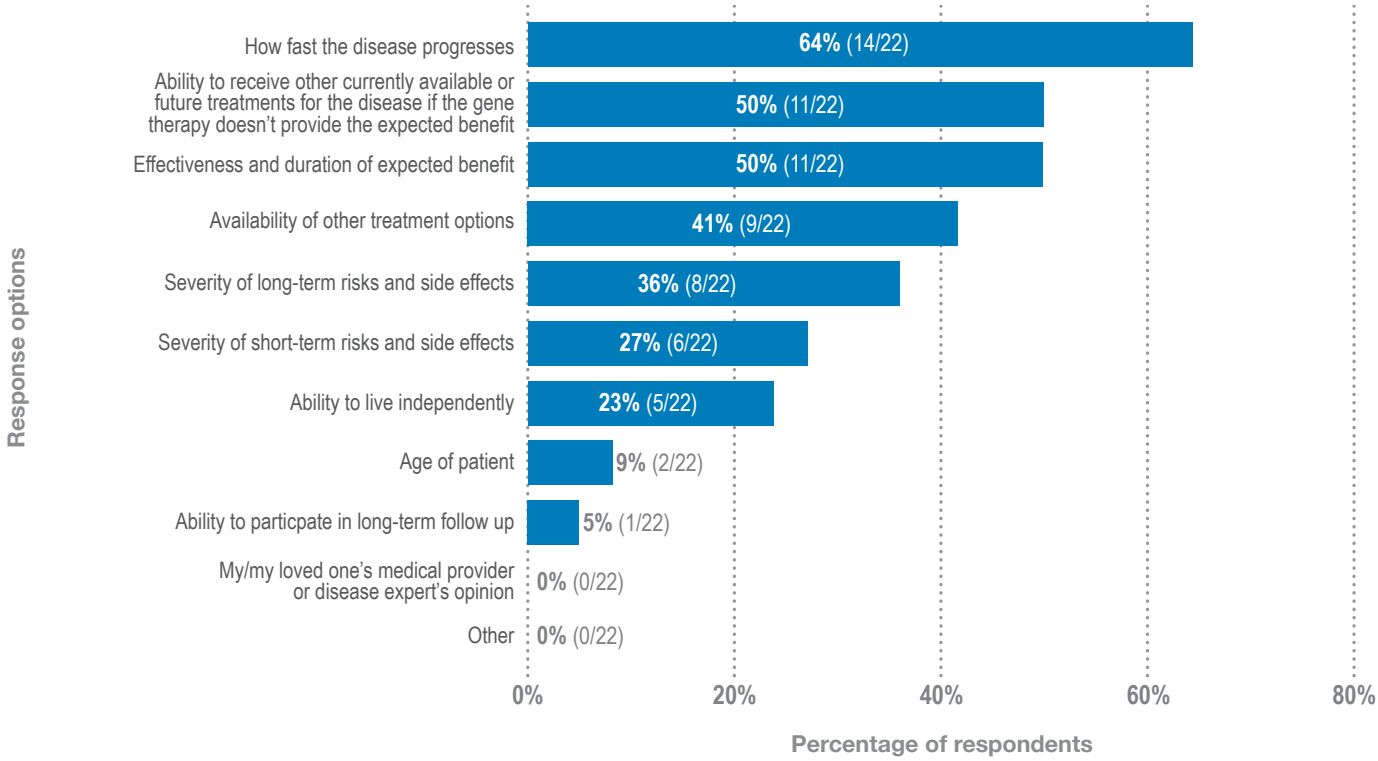


Question 4: If the disease progresses slowly over decades, what are the risks/uncertainties you would be willing to accept when determining whether to enroll your child in a gene therapy trial at the pre-symptomatic or early stages of the disease? Please select up to 3 responses.

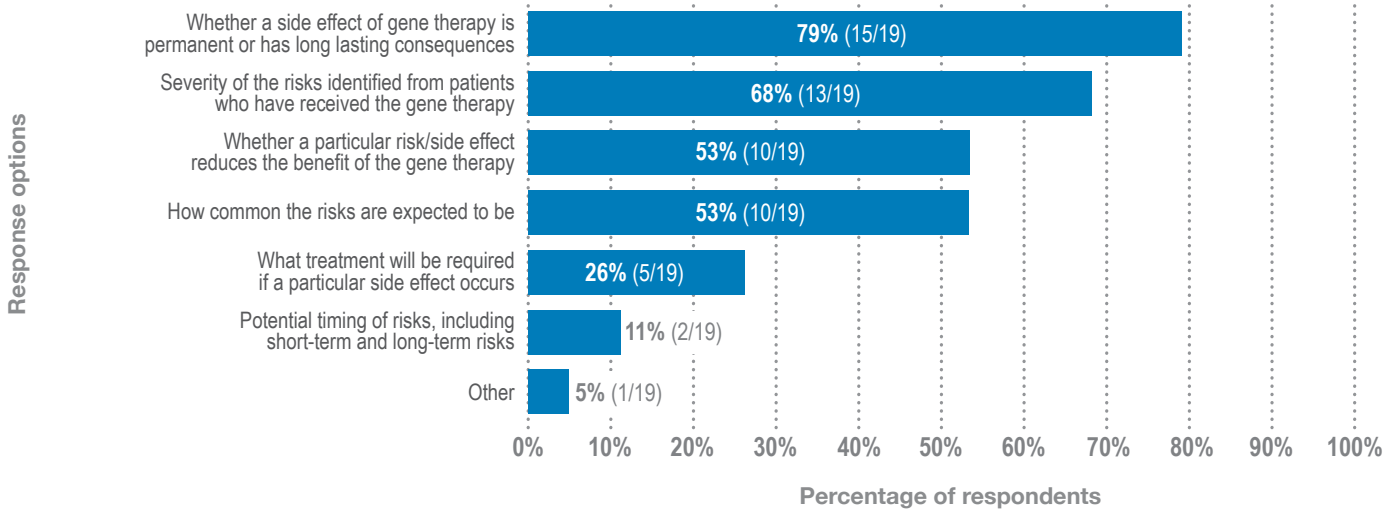


Session 2: Early Enrollment of Adults

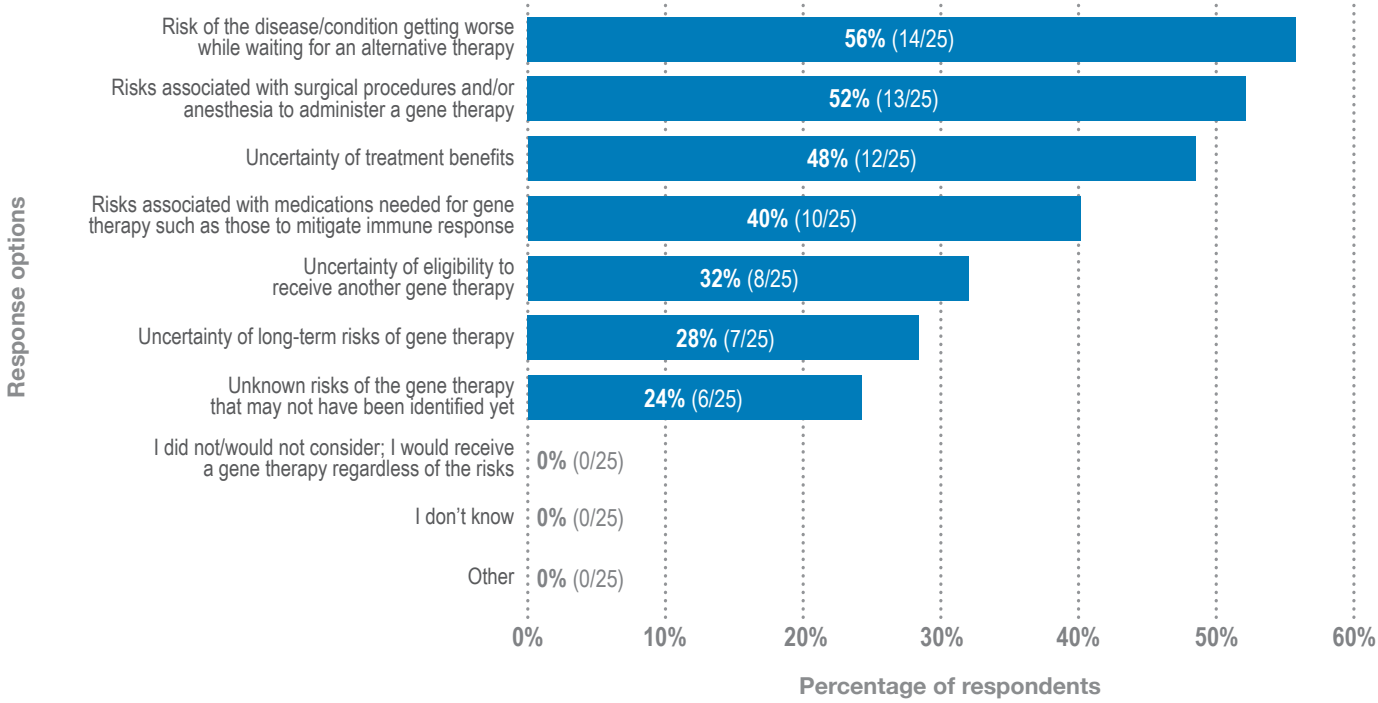
Question 1: What are your top considerations when determining whether to enroll yourself or your loved one as an adult in a gene therapy clinical trial at the pre-symptomatic or early stages of the disease? Please select up to 3 responses.



Question 2: What information about gene therapy risks would be most important to you when determining whether to enroll yourself or your loved one as an adult in a gene therapy clinical trial at the pre-symptomatic or early stages of the disease? Please select up to 3 responses.



Question 3: If the disease progresses quickly, what are the risks/uncertainties you would be willing to accept when determining whether to enroll yourself or your loved one as an adult in a gene therapy trial at the pre-symptomatic or early stages of the disease? Please select up to 3 responses.



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