Voice of the Patient Report on the Externally-Led Patient-Focused Drug Development (EL-PFDD) Meeting on Angelman Syndrome

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Disclosures

The host organizations, FAST and ASF, receive funding from life sciences and other companies for activities unrelated to the Externally-Led Patient-Focused Drug Development meeting. None of the companies were involved in planning or developing the content of the meeting, the survey, this report, or related communications. Ryan Fischer and Jennifer Panagoulias are employees of FAST and have no disclosures. Amanda Moore is an employee of ASF and has no disclosures.

Faegre Drinker Consulting is a professional services division of Faegre Drinker LLP that provides regulatory, policy, and research services to patient organizations and life science companies. FAST and ASF engaged Dave Zook, Tim Franson, and Sanjyot Sangodkar to guide and document the Angelman Syndrome EL-PFDD meeting, pre-meeting survey, and related communications. This matter presented no conflicts of interest with other clients.

RTI International is a scientific research institute that provides research and technical services to the government agencies, commercial groups, and patient organizations. FAST and ASF engaged Holly Peay, Anne Wheeler, Sarah Potter, and Emily Cheves to develop, administer, and analyze the pre-meeting survey. Anne Wheeler, Sarah Potter, and Emily Cheves are all employees of RTI-International and received research support from FAST and ASF. Holly Peay is now an employee of Faegre Drinker Consulting; in her prior role at RTI International she received research support from FAST and ASF.

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Statement of Use

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Executive Summary

Angelman syndrome (AS) is a rare, genetic neurological disorder. It results from the loss of function of a gene called *UBE3A*, which provides instructions for making a protein (ubiquitin protein ligase E3A) that plays an important role in the development and function of the brain. AS leads to severe developmental delays, intellectual disability, lack of speech, movement and balance problems, and seizures, among other symptoms. AS care across the typically normal lifespan is exclusively symptomatic. As a result, people living with AS and their caregivers face years of varying and severe challenges with independence and activities of daily living. Due to the cognitive impacts of AS on patients, data on patient experiences and treatment preferences must be collected directly from caregivers.

With the goal of accelerating attention to and progress towards better treatment options, families living with the condition gathered virtually on April 7, 2025 to describe what it is like to live with this serious condition, share their experiences with available treatments, and urge therapeutic developers and regulators at the U.S. Food and Drug Administration (FDA) to intensify efforts to develop more effective therapies and improved drug development tools for AS. This virtual, **Externally-Led Patient-Focused Drug Development Meeting on Angelman Syndrome** was hosted by Foundation for Angelman Syndrome Therapeutics (FAST) and Angelman Syndrome Foundation (ASF). It was organized and conducted according to the FDA guidelines for these activities.

Key goals of the meeting were:

- To provide people with AS, through their caregivers, an opportunity to share their experiences and perspectives;
- To provide the FDA and drug developers with a better understanding of the challenges of living with AS and aspects of the condition people with AS, through their caregivers, would most like to see drug treatments address; and
- To inform FDA reviews of future AS treatments by providing insights on the treatment outcomes that matter most to people with AS through their caregivers.

The meeting was broadcast to the public from a dedicated website set up for the initiative; a full recording can be viewed at the following link: www.angelmanadvocates.org/voiceofpatient

Before the meeting, 342 caregivers of people with AS completed a detailed survey of their experiences with this serious condition. Data from the survey informed the meeting content, and meeting participants were polled with similar questions during the meeting.

A series of remarks set the stage for the meeting. The ASF President shared her perspective as the caregiver of a family member with AS and community leader. These powerful views were complemented by a description of the value of patient experience insights by the FAST Chief Operating Officer. An FDA official presented an overview of patient-focused drug development and how the Agency uses the information generated by this program for clinical trial design and product reviews. In addition, two medical experts provided background on the clinical nature of AS, its symptoms, currently available symptomatic- treatments, and potential therapies in development.

The core of the meeting was two sessions with invited AS family panelists who reflected a representative range of AS types and various demographic characteristics, as well as input from audience members consisting of families and caregivers of those with AS, that addressed:

1. The symptoms of AS and their effects on daily life; and
2. Perspectives on current and future drug treatments.

Several key themes emerged from both the pre-meeting survey and the meeting itself:

Angelman syndrome symptoms are pervasive and sustained across a typically normal lifespan. The Angelman syndrome journey involves a ceaseless pattern of chronic symptoms from birth with profound impacts on the activities of daily living. Families living with AS become experts in navigating the many aspects of this demanding reality. Examples of the varied symptoms include, but are not limited to:

1. Developmental delays;
2. Cognition and attention challenges;
3. Communication and speech impairment;
4. Behavioral issues;
5. Movement and balance problems (ataxia);
6. Sleep disturbances; and
7. Seizures.

The current health care paradigm for AS involves an array of drugs and supportive therapies aimed at mitigating symptoms as much as possible. There are no disease-modifying treatments for AS. Families pursue a wide variety of symptom management approaches as the condition manifests across the patient and the activities of daily living.

While families are deeply committed to the well-being of their loved ones living with AS, the continuous and formidable demands of managing the condition exact a heavy physical, mental, and emotional price. It is important to keep in mind the significant burden which AS places on the family and other caregivers. Although the survey and session questions were posed to the participants in their role as observers and supporters of the people with AS, their comments naturally reflected on the many, daily challenges of caring for their loved ones.

Current treatments that sometimes marginally mitigate symptoms, if at all, leave families of loved ones living with AS hoping for new therapies that can improve the ability to function and achieve some small level of independence in ADLs. Even relatively minor steps toward independence for the person living with AS would be important to these families. Meeting participants brought strong views on how they aspire to have treatments and care that can change the course of AS. Given the pervasive and unrelenting nature of the condition, these views ranged widely across the lived experience.

Introduction

On April 7, 2025, the Angelman syndrome (AS) community gathered for a virtual, externally-led patient-focused drug development (EL-PFDD) meeting to inform stakeholders about the experience of living with AS and what matters most to patients and families for treatment of the condition. The meeting followed Food and Drug Administration (FDA) guidelines for conducting an EL-PFDD meeting. There were 383 total participants, with over 227 Angelman syndrome caregivers and family members, 67 industry representatives, 41 FDA staff, and 27 researchers and healthcare providers present.

Pre-meeting survey

Before the meeting, an IRB-approved survey was distributed to gain a greater understanding of the experience of living with AS and what caregivers would value from new therapies. The survey results informed the meeting design, including panel composition and discussion questions. It was developed and conducted in collaboration with Research Triangle Institute (RTI) International with input from FAST, ASF, and Faegre Drinker Consulting and consisted of a combination of ranking, rating, and open-ended questions. Survey data was collected between October 18 and November 25, 2024.

Survey participants were caregivers of individuals diagnosed with AS and were responding as observers. The severity of AS cognitive limitations precludes those with the condition from being able to complete the survey on their own. Participants were recruited through outreach to the membership email lists and social media platforms of the meeting hosts. Table 1 and Table 2 provide a detailed breakdown of the demographics of the 342 survey participants.

Table 1. Characteristics of Individuals with AS Represented in Survey (N=342)

Characteristic	n (% of those who responded)
Age	
Child	221 (66.4)
Adult	112 (33.6)
Specific Age Unknown	9 (2.6)
Gender	
Female	167 (51.4)
Male	158 (48.6)
Race	
White Non-Hispanic	232 (68.0)
Other race/ethnicities	109 (32.0)
Age at Diagnosis (n=294)	
Before 1 year of age	41 (13.9)
1-year-old	107 (36.4)
2-years-old	75 (25.5)
3-years-old	26 (8.8)
4-years-old	9 (3.1)
5-years-old and older	36 (12.2)
Genotype	
Deletion	218 (63.7)
Mutation	56 (16.4)
Uniparental Disomy/ Imprinting Center Defect	45 (13.2)
Other/Unknown	23 (6.7)
Previous participation in a research study	237 (69.4)

Table 2. Characteristics of Caregiver Respondents (N=342)

Characteristic	n (% of those who responded)
Biological parent of individual with AS	322 (94.2)
Gender	
Female	275 (81.6)
Male	62 (18.4)
Race	
White Non-Hispanic	244 (72.0)
Other race/ethnicities	95 (28.0)
Educational Status	
Some high school	2 (0.6)
High school diploma or equivalent	39 (11.6)
Associate's degree or equivalent	39 (11.6)
Bachelor's degree or higher	256 (76.2)

The survey assessed key areas of AS burden:

1. Assess the most impactful Angelman syndrome (AS) symptom and symptom domains
    a. On person living with AS
    b. On caregiver respondents
2. Explore the most important AS symptoms to treat
3. Self-define a "minimal but important change" in priority symptoms
4. Explore willingness to enroll in an AS trial based on defined benefit/risk scenarios

Results of selected aspects of the survey are described in the sections below.

*For access to the pre-meeting survey questions please contact Ryan Fischer (ryan.fischer@cureangelman.org) and Amanda Moore (amoore@angelman.org)

Meeting format and desired outcomes

The five-hour meeting was livestreamed with interactive segments to maximize participation of all stakeholders. It was designed to provide first-hand insights to the FDA and drug developers about the daily challenges and treatment needs of those living with AS, to help ensure that what matters to people living with the disease is prioritized in the drug development and FDA review processes.

Tim Franson, M.D., a principal at Faegre Drinker Consulting, moderated the meeting.

The meeting included the following introductory presentations:

Amanda Moore, Angelman Syndrome Foundation Chief Executive Officer, opened the meeting and described the challenges faced by families living with AS, including her own, emphasizing the serious and sustained nature of the condition.

Ryan Fischer, Foundation for Angelman Syndrome Therapeutics Chief Operating Officer, also welcomed and acknowledged all participants and provided a description of the value of patient-focused drug development and patient experience data from his decades of experience in the field.

Michelle Campbell, PhD, Associate Director for Stakeholder Engagement and Clinical Outcomes with the FDA Office of Neuroscience, gave an overview of the agency's patient-focused drug development initiative and the role of the meeting results in developing new treatments for AS.

Ron Thibert, DO, MSPH, Director of the Angelman Syndrome Clinic at Mass General Brigham for Children, presented the overview of AS and its symptoms prior to the first AS family panel session, summarized in the relevant section below.

Elizabeth Berry-Kravis, MD, Professor of Pediatrics and Neurological Sciences and Director of RUSH Pediatric Neurosciences FAST Center for Translational Research at RUSH University Medical Center, presented at the mid-point of the program on the current AS treatment paradigm, community participation in clinical trials, and the immediate outlook for new therapies.

Meeting format and desired outcomes

The primary elements of the EL-PFDD meeting were sessions on:

1. The symptoms of AS and their impact on daily life; and
2. Current and future treatment approaches.

Each session included a panel of testimonials from caregivers of people affected by AS, a series of online polling questions for all participants, and a moderated discussion during which remote participants could provide comments online and by phone. All panelist statements were recorded prior to the meeting and the audience polling and discussions were livestreamed.

Overview of Angelman syndrome

Angelman syndrome is caused by a loss of function of the *UBE3A* gene on chromosome 15. This gene plays a critical role in brain development and function. Angelman syndrome occurs by a gene defect when it is on the maternal copy of the chromosome 15. In neurotypical individuals, UBE3A in neurons comes exclusively from the maternal gene and the paternal gene is silenced. In AS, there is little to no *UBE3A* in neurons when the maternal gene has a defect and the paternal gene is still naturally silenced.

There are several types of mutations that cause Angelman syndrome. The most common is a deletion of the gene which occurs in approximately 70% of people living with AS. Another 10% to 15% of AS cases result from a gene (or point) mutation. The other two primary genotypes of AS are imprinting center defects and uniparental disomy (UPD) impact (approximately 3-5% of patients, each). Cellular mosaicism is rare, impacting about 1% of cases.

The key symptoms are complex and varied. Developmental delay is pervasive and deeply impacts the ability to achieve milestones. About 70-90% of individuals have no verbal speech capability. Seizures often begin around one to three years of age and can vary in type and severity. Cognitive impairment is universal, impacting learning and memory. Almost all individuals with AS also have some form of movement disorder such as ataxia (impaired coordination and balance), tremors, or myoclonus (shaking). The majority of affected people also have profoundly disturbed sleep patterns that often lead to other complications. Many also have some degree of constipation, reflux, and some have cyclic vomiting, which can present as episodes of vomiting that can last hours or days.

In terms of behavioral characteristics, people with AS have a generally happy demeanor. They can be easily excitable with hyperactivity and short attention spans impairing learning. They can have high levels of anxiety, which typically increases with age and can manifest as frustration, combative behaviors, tantrums, etc. AS has a profound impact on activities of daily living and quality of life. Due to cognitive impact, it demands lifelong support. This, together with the effect on communication, behavior, and functional independence, significantly limits opportunities for people living with AS and their caregivers.

Topic 1: The symptoms of AS and their impact on daily life

Participants in both the meeting panel and the pre-meeting survey described the complex, seriously disruptive burdens created by AS and its symptoms. Each of the five family members who made recorded remarks gave compelling descriptions of the challenges faced by their loved one living with AS, as well as themselves as caregivers. These presentations were followed by live polling of the online audience and a moderated discussion of the topic. Polling was limited to caregivers of individuals living with AS; all questions and results are available in Appendix 3. Key observations from those various inputs are set out below in both statistical and testimonial forms.

AS Symptoms are varied, life-altering, and persist over the entire lifespan

The AS journey involves a ceaseless pattern of chronic symptoms often punctuated by episodes of more acute challenges such as seizures, intense anxiety, and GI distress. Families living with AS must become experts in navigating all aspects of this reality.

The mother of a nine-year-old son with UPD subtype of AS shared the relentless daily effects of AS:

> **Being nonverbal, [our son] struggles to communicate his needs, which becomes especially challenging during times of distress. His chronic sleep deprivation can trigger seizure activity, and he often will resort to self-injurious behaviors; biting his arms, hitting his head, sometimes headbutting the walls. He'll even lash out at myself or his dad, my husband. [Our son] never slept through the night, which means that he must be awake or one of us must be awake with him 24/7. So my husband and I do take turns caring for him try and prevent caregiver burnout."**

The mother of an eight-year-old son with mutation subtype of AS spoke to the contrast between her son's innate nature and the wide-ranging impacts of AS, pointing out:

> **Despite having an infectious laugh and enduring sweetness, I am a first-hand witness to his deep suffering that is increasing. His impulsivity, anxiety and hyperactivity are becoming more acute, while at the same time, his need for social connections and belonging are growing. Angelman syndrome is stealing from him the thing he values most; forging new bonds and participating in groups."**

Noting that her 10-year-old daughter has mutation subtype of AS, her mother observed that:

> **On her best days, her laugh is contagious. She's a light for her people, her mom and dad, big brother, her dog, her teachers, her nurses. She likes to throw things and gets a tickle from loud noises. She loves to sit outside when it's warm and she loves the ocean. On her worst days, we are monitoring her oxygen levels and her breathing. She cannot talk or play and it saddens us she cannot engage with children her age in the neighborhood. Given her dependence, it takes an inordinate amount of time and coordination to take her places. We do not have a wheelchair van, so my husband lifts her 130 pounds in and out of the vehicle. Often, one of us stays home with her while the other goes with our son, so we do not do many things together as a family of four outside."**

The father of a 20-year-old son living with deletion subtype of AS recalled the clinician views shared 17 years earlier:

> **We received the Angelman syndrome diagnosis at age three, together with a long list of won't do's. Won't talk, won't walk, won't sleep more than a few hours a day, won't be able to go up a set of stairs, ride a bike, swim, be potty-trained or get dressed."**

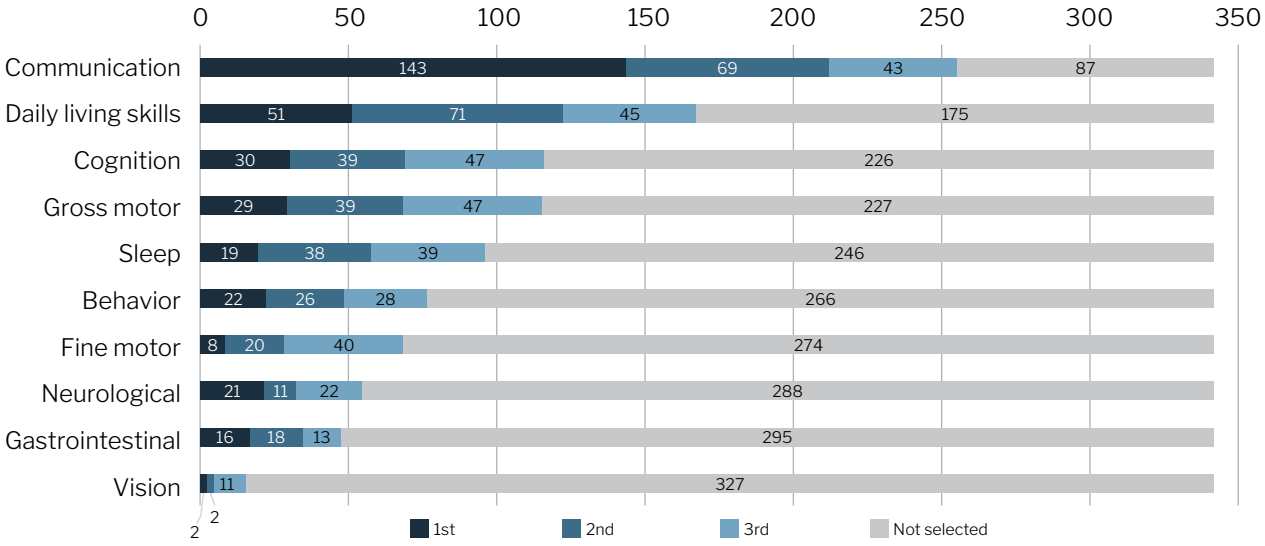
A mother of an 11-year-old son who called in to the meeting session noted:

> **Our son requires care in everything he does, helping him with dressing, toileting and getting to school. Independence is non- existent, which is unusual for an 11-year-old. As he gets older and bigger, so do these needs."**

AS Symptoms that matter most and impact on daily life

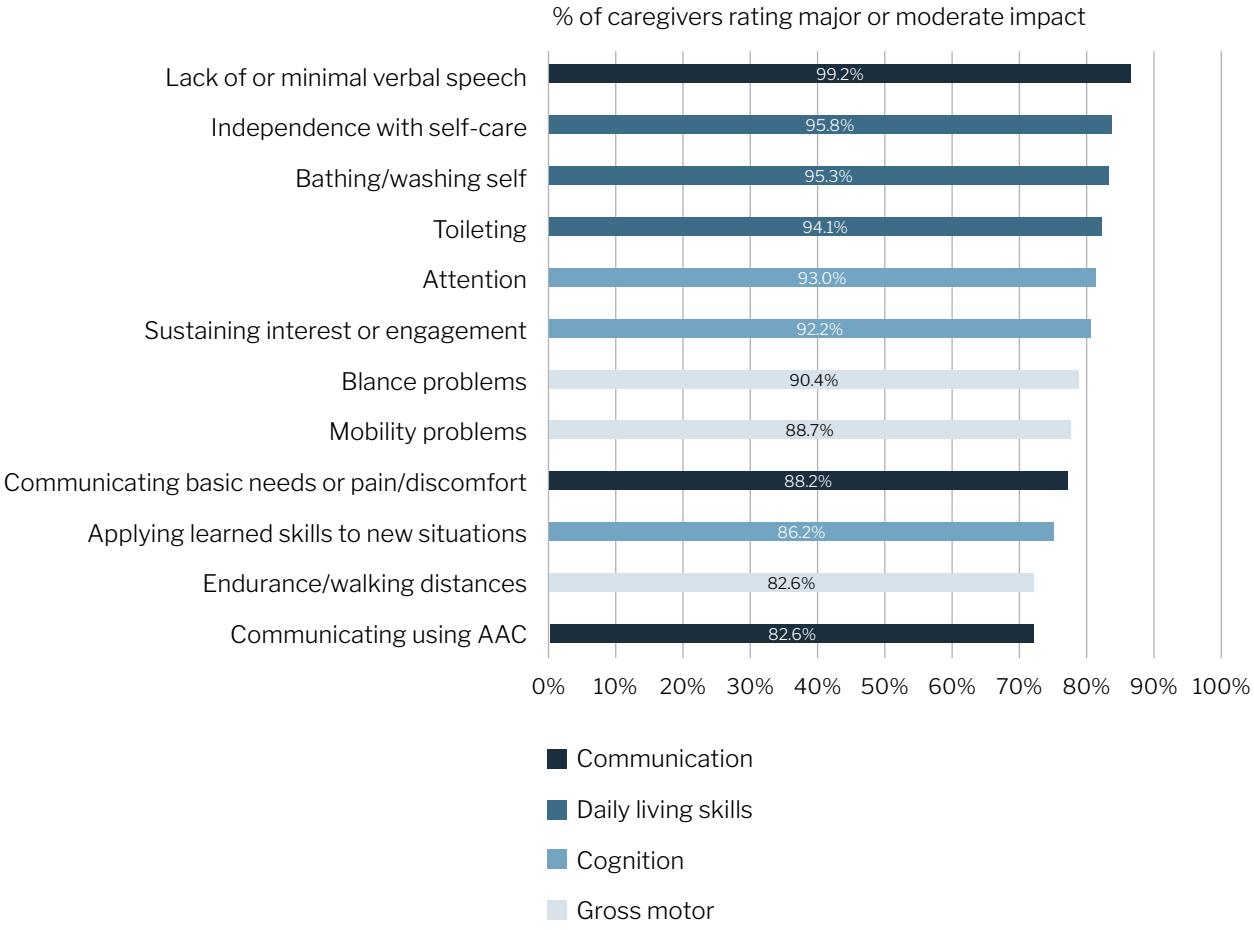
The pre-meeting survey asked respondents to indicate which symptom domains have the most significant impact on the patient's daily life. Respondents were allowed to choose up to three. Figure 1 summarizes the responses to this question.

Figure 1. Top Three Symptom Domains Having the Most Impact on Individuals with AS, According to Caregivers (n=342)

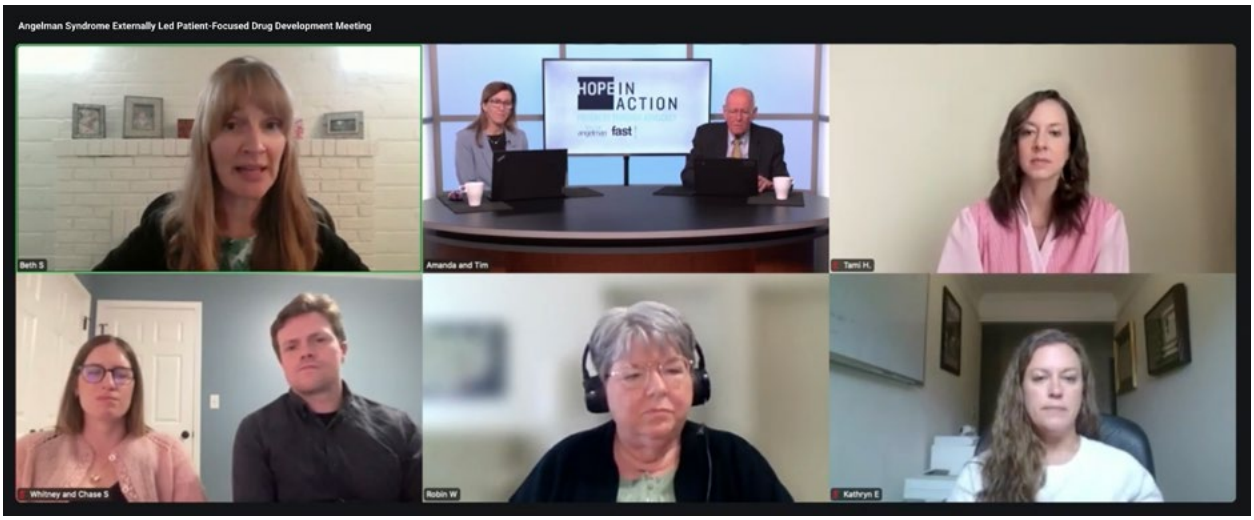


Respondents to the pre-meeting survey also were asked to rate the level of impact of specific symptom domains on the daily life of the person living with AS. Figure 2 summarizes the response to this question.

Figure 2. Symptom Domains Having the Highest Impact



Meeting participants made statements that provided critical insights into the impact of AS symptoms on those living with the condition and their families. Polling responses and discussion comments mirrored the pre-meeting survey responses, supporting the generalizability of these critical symptom groups.



Communication

Under this symptom domain, caregivers reported a range of specific impacts and challenges with not being able to communicate effectively.

On the topic of most impactful symptoms, the mother of a 24-year-old young man with deletion subtype of AS shared:

> **"When it comes to those challenges, I would say nonverbal communication is number one. I feel like the behaviors that are a result of him not being able to communicate quickly and verbally is something that, if he had five words, I would give my life for him to have five words."**

Confirming the immense difficulties and frustrations linked to an inability to communicate, the mother of a 12-year-old son with deletion subtype of AS added:

> **"The nonverbal, complex communications needs as [son] has grown have been very challenging, between wanting to express his opinions, his likes, his dislikes, and not just for us as caregivers, but everyone on his team. Whereas we might understand what he is trying to do or what he's trying to communicate, the world does not. And that's really difficult."**

Looking to his three-and-a-half-year-old son's future living with AS, a father offered:

> **I think that we are worried about…challenges with communication in the future and especially his ability to advocate for himself once we are not around…Right now, the only thing he's able to do in order to communicate are behavioral things like headbutting, or hair-pulling, or just shouting, things like that."**

Activities of Daily Living

Impacts on the activities of daily living were a constant and compelling theme among the caregivers when discussing symptoms.

Reflecting decades of living with AS, the mother of a 31-year-old daughter with UPD subtype of AS confirmed:

> **As far as what affects daily life for her, the fact that she can't live and function independently and depends on other people for her activities…she has over-identified with me and because of this…becomes so anxious when others are around me. She screams, she pushes people away. And she loves them so dearly, but the anxiety is just so severe."**

A mother called in to the meeting to comment on her son's AS impacts:

> **From the moment he wakes up to the moment he falls asleep, he needs constant supervision, full physical support in many tasks, and help navigating even basic things like transitions, meals, or getting dressed."**

Touring her family's home for the meeting participants, a mother of two children living with mutation subtype of AS, a five-year-old son and a three-year-old daughter, displayed the many assistive devices and support strategies used every day for their care and observed:

> **We've tried to manage with the resources available, but it feels like we're fighting a war on three fronts with more battles like [communication] devices and toilet training headed our way so we definitely need more help."**

The father of a nine-year-old boy with mutation subtype of AS commented:

> **I think about how different our life could be if [son] could do something that most parents take for granted, like self-feeding without a constant struggle, small to many, but enormous to us. If there were even a slight improvement in his independence, we could adjust our childcare needs, maybe keep a nanny, maybe spend more time with his twin brother or even as a family, go out to a restaurant. For us, these changes are massive. They would transform our daily routine."**

Sleep Disturbances

Both survey respondents and speakers at the meeting elevated the profound impacts of sleep disturbances for both the individual living with AS and their families.

Responding to this topic and her 12-year-old son's experience with deletion subtype of AS, his mother emphasized:

> **What [sleep disturbances] lead to can just be debilitating. Not just for the individual with Angelman syndrome that can lead to seizures, can lead to illness, can lead to behaviors, can lead to everything. But, also, the family and the family not being able to get sleep and then becoming more susceptible to illness and just how hard it is as a family unit when your child's not sleeping well."**

The mother of a nine-year-old son with UPD subtype of AS noted:

> **He never slept through the night, which means that he must be awake or one of us must be awake with him 24/7. So my husband and I take turns caring for him to try and prevent caregiver burnout."**

On the recorded tour of her family's home, the mother with two young children with mutation subtype of AS, gave a vivid sense of what this symptom means from a practical standpoint:

> **In my son's bedroom, you'll see his safe sleep bed on the right and travel tent bed on the left. The doors on the permanent bed fold up and down to close, and the travel tent bed unzips to pen. Poor sleep was likely his first sign of AS. Neither of my children can sleep through the night without prescription medications. Our daughter who sleeps on the second floor has even worse sleep and none of the medications have helped. Most nights, the kids wake us up at least once, often for hours at a time."**

Behavior

When speaking to symptoms and how they manifest across the lifespan, behavior was a topic of rising concern as the person living with AS ages.

The mother of an eight-year-old son with mutation subtype of AS described the "viscous cycle" of AS:

> **I see him already working hard with the tools we are teaching him for containing his impulses, but when he is irritable from a lack of sleep or suffering from painful constipation, which can be weekly, he lacks the energy and focus to fight impulses and his behaviors escalate. He also has considerable anxiety about any new caretaker or even new places or situations, which is also getting worse. He sometimes experiences episodes of just sheer terror in what would otherwise be a normal new situation for an eight-year-old to experience."**

Reflecting on this topic, the mother of a three-and-a-half-year-old daughter with mutation subtype of AS, described:

> **One of the things I was thinking about…is the mouthing behaviors and how impactful those can be in our lives. She puts everything in her mouth, so trying to keep her safe at home is difficult. We have an older daughter and so, of course, she's got little Barbie shoes and Legos, and our daughter with AS is constantly putting those in her mouth, which is, of course, a choking hazard. It also means when we go out in public, she gets a lot of funny looks and people saying, "Oh, don't do that," or, "That's gross. And so trying to keep her safe, both from the germs that might be on the toys, as well as small objects going in her mouth and being a choking hazard is a challenging part of every day."**

And, in terms of how the behavior impacts of AS evolve into adulthood, the mother of a 23-year-old son with UPD subtype of AS, added:

> **"As an adult, he's had the experience that I have most feared. He's big, he looks like an adult when he doesn't feel like getting shaved. And he had a caregiver in his group home who wasn't familiar with him, who panicked because of his behaviors and called the police who then came into the home, and wanted to take him to the emergency room. And we all know horror stories of police being involved when adults have had behaviors because the police, the community, don't understand that sometimes even their informed caregivers can't protect them from very scary, occasionally fatal intervention because somebody's afraid of this adult with disabilities, particularly ones who cannot speak. So, I've already experienced what has been one of my greatest fears for years."**

Overview of Angelman syndrome treatment approaches

Current treatments do not correct the primary defect of the absent or deficient UBE3A in neurons. Most significantly, they do not treat the underlying disease. The current standard of care for treatment of AS mainly includes supportive treatments for the myriad of disease-related symptoms.

Epilepsy is a common AS associated clinical problem that is treated with anti-convulsant or anti-epileptic drugs. The field also makes use of bridging and rescue medication regimens for illness and fevers when seizures tend to cluster. There is a high variability of the actual frequency of the seizures and a high variability of the treatment effectiveness. Anti-epileptic drugs can have side effects that can be limiting and affect alertness, coordination, swallowing, and GI symptoms.

Sleep issues are another common problem and are addressed with environmental modifications and behavioral and medication approaches. These strategies include safety beds, sleep training, and behavioral sleep routines. Melatonin is the first-line choice in most cases with clonidine, guanfacine, trazodone, and quetiapine also of use for these symptoms. There is a high variability of the treatment effect with these medications.

There also are a range of behavioral problems associated with Angelman syndrome such as aggression, anxiety, impulsivity, hyperactivity and inappropriate hypersocial behavior. Treatments may include alpha-agonists, buspirone, SSRIs, antipsychotics, and sometimes stimulants, if the family chooses to use these medications. Again, there is a high variability of treatment effect and such interventions almost never resolve the behavior issue.

People with AS often will have tremor or non-epileptic myoclonus, gastrointestinal issues, scoliosis, strabismus, and frequent otitis media in younger children. Many patients are taking multiple medications for these various problems based on the natural history study treatment data for this condition. Younger people tend to take less medications and, as they age, add medications to manage multiple types of problems.

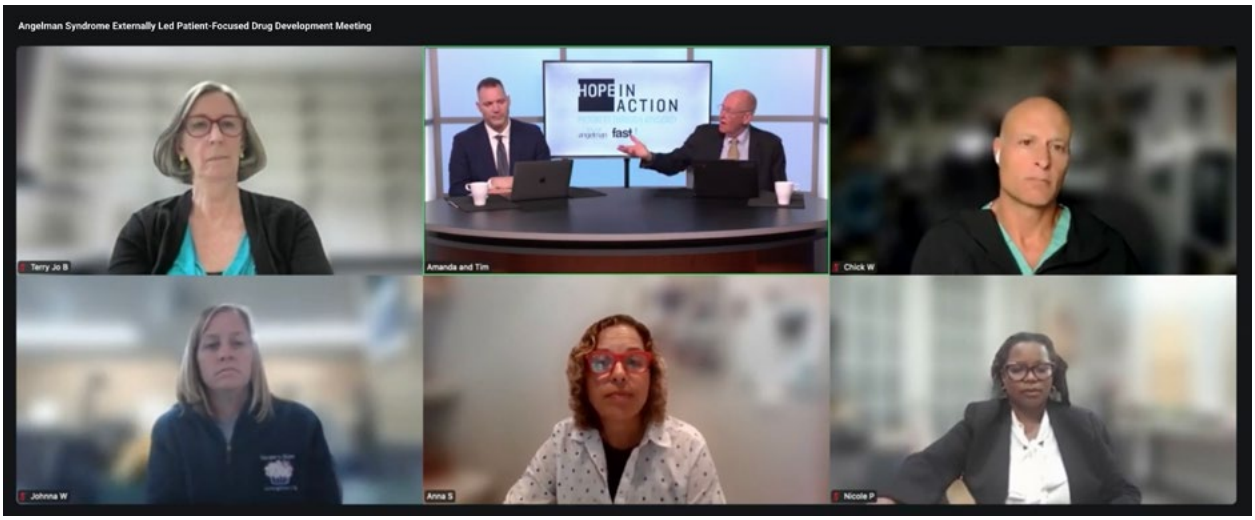
Speech delays and communication problems are the biggest challenge across all individuals living with the condition. These are treated with supportive strategies of speech therapy, alternative augmentative communication devices, sign language, and therapy intensives. Motor delays and ataxia or apraxia, which are also substantial problems, are treated with physical and occupational therapy, leg bracing, shoe inserts, gait trainers, walkers, and/or intensive therapy.

Cognitive and attention deficits in AS are addressed with special education programs, one-on-one aids at school, and intensive school supports. Children living with AS need full-time supervision and help with their activities of daily living, including toileting. When they become adults, they might need an adult placement with a one-on-one assistant full-time, which can be difficult to obtain.

Current research and clinical trials are directed at treating the underlying a disease mechanism, as opposed to being just a supportive treatment, to activate the paternal *UBE3A* gene, which is normally silenced, replace the maternal *UBE3A* gene, or to enhance synaptic plasticity or improve synaptic functioning. In upcoming years, there are several proposed clinical trials that could be initiated with additional approaches for treating Angelman syndrome, including a CRISPR-based strategy, an AAV9-based *UBE3A* gene therapy to replace the maternal gene, and a small molecule growth hormone analog that could be helpful in combination with some of the genetic strategies.

Topic 2: Views on current approaches to treatment and future treatments

In the absence of disease-modifying therapies, living with AS and its wide-ranging effects often requires an expanding array over time of symptomatic treatments with limited benefits. Families also access a diverse set of healthcare providers in their efforts to mitigate the condition. Caregivers of people with AS express a critical need for new treatments that would make even modest improvements in core symptoms such as communication, daily living skills, or cognition. As in the first topic, five AS family members provided panelist remarks on their lived experience and perspectives and were followed by a combination of polling and discussion with the live audience.



The current health care paradigm for AS involves a vast array of medical and caregiving strategies aimed at managing serious symptoms as much as possible.

As noted, there are no disease-modifying treatments for AS. Families pursue a wide variety of symptom management approaches as the condition presents in many ways.

The mother of a nine-year-old daughter with deletion subtype of AS emphasized:

> **"The anti-seizure medications have been moderately effective in reducing the frequency and severity of [daughter's] seizures. However, any progress can feel fragile. For example, even when she meets the clinical criteria for weaning off the medication, a seizure can set us back. Her ADHD medication, on the other hand, has shown little improvement in her symptoms and does not adequately address her focus or behavior challenges. The most significant downsides of [daughter's] treatments include side effects like the anti-seizure medications cause irritability and behavioral issues requiring medication changes. Her nonverbal limitations, the inability to articulate side effects or discomfort, makes managing her treatments more challenging and increases the emotional strain on our family."**

Highlighting several of the treatment approaches across the life of her 23-year-old-son with deletion subtype of AS, his mother observed:

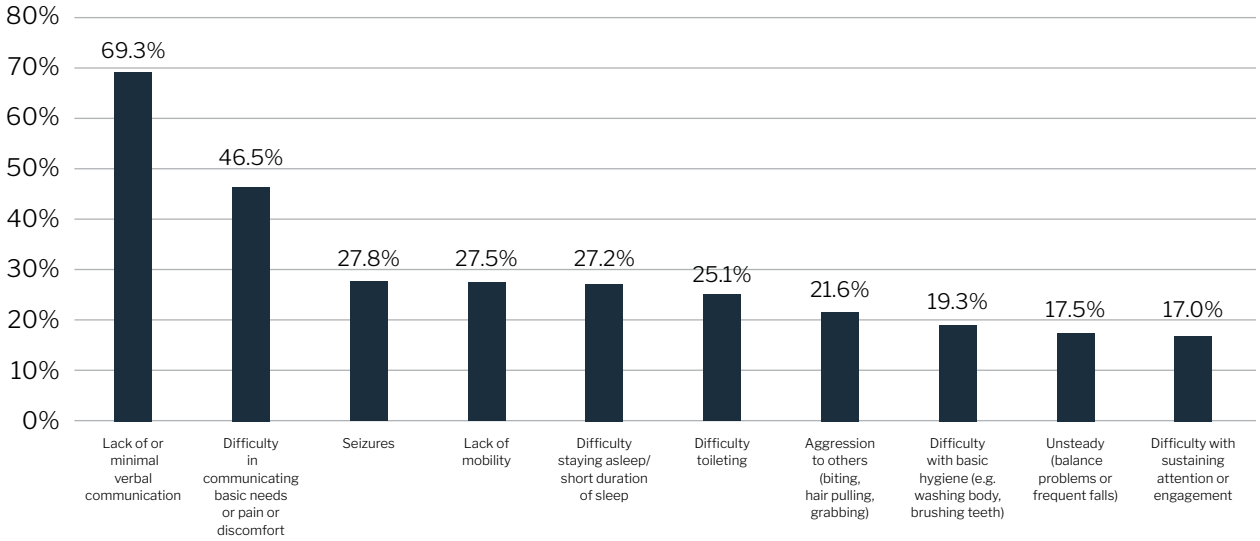
> **"For his first six years of life, he participated in intense therapy five days a week layered with horseback riding therapy, music therapy, and listening therapy to help immerse him into daily living with the sensory overload. His seizures started at the age of two and a half with the peri-seizure, which paralyzed his whole left side of his body, of which he lives with some residual impact to this day. Needless to say, he has been on a minimum of three-to-five seizure medications for the last 21 years. In addition, [children with AS] struggle with sleep as Angelman syndrome causes sleep disturbances. All of the tools and guidance experts give for new parents to manage sleep does not impact our children. While a vitamin like melatonin may help for a couple of years, after five to six years of interrupted sleep every night, prescribed medication is necessary. No parent wants to keep adding medication, but you learn quickly that with good sleep, our children have a better shot at learning and managing their seizures. In his more recent years, anxiety became a major issue, whether getting on a plane, visiting the ocean, leaving the house, or doing activities that he once loved in an early age, something flipped as the years went on and he became very anxious. Again, with the behavioral management and intervention, medication has been prescribed for him to experience the world and continue to live, learn, and laugh."**

The mother of a nearly three-year-old daughter with deletion subtype of AS shared:

> **[She] has difficulty communicating her needs despite participating in speech therapy for the last 18 months. She does not speak words, has poor fine motor control, which does not allow for the ability to sign, and has difficulty isolating her pointer finger to hit a button on her AAC device to accurately communicate. When she cannot communicate her needs, she becomes vocal and engages in maladaptive behavior such as biting, hair pulling and kicking. It has become very apparent that her deficits cannot be therapied away despite all of the hours she has spent in provider offices or at home practicing these skills. Her short life has been consumed with medical therapies and doctor's appointments, rather than being a child. And I have spent more hours being her therapist and medical provider, rather than being her mother."**

Pre-meeting survey respondents were asked what they view as the most important potential treatment benefits for AS. Results shown in Figure 3 indicate that improved communication would be the highest priority followed by relief from seizures, mobility impairments, and sleep disturbances, and other activities of daily living.

Figure 3. Treatment Priorities According to the Caregiver (n=342)



Families are deeply committed to the well-being of their loved ones living with AS and desire new treatments that can make any meaningful improvement in core symptoms and help them move toward independence. The importance of even incremental benefit in treatment management of AS is significant and cannot be overemphasized.

It is clear across the pre-meeting survey responses, the panelist comments, and the live audience discussion, that there is a very high level of unmet medical need and an intense desire for treatment innovation that can improve communication, daily living skills, cognition, or other challenges of living with AS.

The father of a nine-year-old boy with mutation subtype of AS provided these insights:

> **"[Caring for him is] a full-time job for us, one that we willingly undertake, but one that exacts a heavy emotional and financial toll. If a new treatment offered a small benefit, improvements in cognition, communication, or motor function, that would mean a huge step forward in giving him autonomy in reducing our family's stress and anxiety. The biggest risk I think would be to do nothing at all. New therapies might come with uncertainties, but the cost of waiting, of letting [son] stay trapped in a condition we already understand, feels far greater to us. Even a tiny boost in his cognitive abilities could help him to communicate better, to solve problems, and to stay safe."**

Confirming the widespread emphasis on the importance of communication and cognition impact for a new treatment, the father of a seven-year-old son living with AS noted:

> **"The promise of meaningful future treatments and the fast-paced amazing science, which backs them, causes us to reflect on what would make the most difference to our family and our son. Continuously come back to speech being the largest single thing that we would wish to cure. For [son] to have the ability to communicate what he needs, feels would be truly life-changing, and as caregivers, reducing the constant guesswork, frustration, and fatigue from trying to do the best for your child without any of your child's input."**

The mother of a 15-year-old son with AS added:

> **With all the therapies and all the medications that [son] has received over the years, we wish he could communicate better and we wish that his cognitive ability would be a little bit better. Even if we could see a little improvement in any of those areas, that would be huge for us. If we could teach [son] how to use the restroom independently, if he could self-feed, if he could sleep through the night without requiring a lot of medications, all of those would be huge for us and for [son] and for us as a family. So we could function, we could spend time with our older children as a family, so we could travel. And for [son], so his quality of life would be more in line with other teenagers, because he's just a 15-year-old boy who craves connection like everybody else."**

Similarly, the mother of a four-year-old son with AS called in to the meeting to convey:

> **Having a treatment that could help with some of these areas of growth and motor development, his skills with feeding and bathing, could actually allow us to have a relationship that is less therapist, more mom and child, which is so important. So, some of the things I'd love to see in the future really focus on giving him a wider base for those skills. Communication, obviously, is super-important, those gross motor and fine motor skills, so we can enjoy time not playing therapist."**

A father of a 10-year-old daughter living with AS added:

> **What my daughter needs to do is learn. That will help her across everything, and anything that can help her learn. Now, I said we live in [large city], it can be a dangerous place. [Daughter] doesn't routinely respond to her name. She doesn't respond to 'no' or 'stop.' And if she could do that, she could recognize those things, it could prevent her from stepping off a curb and walking into traffic. It could prevent her from putting her hand on a hot stove or grabbing a sharp knife at dinner. And this can prevent harm. It could save her life, if she was able to do this. Even these tiny little changes can completely change our life and the life of our daughter."**

These observations by meeting participants align with results from the pre-meeting survey*, in which caregivers were asked what would constitute a small but meaningful benefit.

*To review more results of the pre-meeting survey visit https://angelmanadvocates.org/voiceofpatient

Incorporating patient and observer caregiver input into a benefit-risk framework for AS

Patient experience and perspectives are important to inform the FDA benefit-risk framework for AS. The input provided by caregivers as observers of family members with AS during the EL-PFDD meeting and the pre-meeting survey are incorporated in Table 3.

Table 3. Benefit-Risk Dimensions for AS

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• AS is a rare neurogenetic disorder that leads to deficiency in UBE3A, a protein involved in brain function. • UBE3A deficiency leads to developmental delays, balance and movement issues, severe communication limitations, debilitating seizures, disrupted sleep, and various physical characteristics. • Individuals with AS have a normal life expectancy, but their development essentially plateaus at a level akin to 3–4-year-old.	• Individuals with AS have severe cognitive, communication, and physical challenges that require continuous care and preclude independent living. • People living with AS are unable to perform many activities of daily living. • The burden of daily care is demanding in terms of providing comprehensive support for basic functions. • Care intensity has a secondary negative impact on the ability of families to provide optimal support for siblings of children with AS and for themselves. • Symptomatic treatments, afford minimal relief for patients and significant unfulfilled needs persist.
Current Treatment Options	• At present, there are no approved therapies available directed at the root cause of AS (UBE3A deficiency). • Treatment of AS symptoms and signs is limited to symptomatic, supportive, and palliative care options. Such treatments are often associated with suboptimal effects as well as untoward adverse events, which present additional care management challenges. • The multi-system impact often requires numerous treatments, with little observed benefit. • Research on disease-modifying interventions is in various stages of clinical development, with some preliminary encouraging results.	• The severity of AS symptoms and limited impact of current symptomatic care underscore a significant unmet medical need. • Impact on families and/or caregivers for people living with AS is demanding at best and significantly disruptive to familial daily life. • Families/caregivers are encouraged by the hope for even smaller incremental advances in the effects of care interventions, which could move people living with AS toward independence and a more typical daily living for all involved.

Conclusion and Key Takeaways

Angelman syndrome is a serious neurogenetic condition that affects the brain and causes profound developmental and cognitive challenges across the typical lifespan. Current treatments only address symptoms and have minimal effects on how individuals with AS feel or function. The Externally-Led Patient-Focused Drug Development Meeting highlighted the need for increased awareness of the impact of AS, on both the person living with the condition and their caregivers, as well as the need for improved treatments.

Key takeaways include the following items:

- The symptoms of AS are wide-ranging and complex, with devastating impacts on an individual's activities of daily living that significantly limit his or her independence.
- Communication challenges, cognitive limitations, challenging behaviors, and sleep disturbances are among the symptoms that place the greatest strain on people living with AS and their caregivers.
- Treatment of AS is limited to symptom management through a dizzying array of medications, assistive technologies, and other interventions deployed across a normal lifespan with minimal improvements in quality of life at best.
- AS has significant physical and mental impacts on both the individuals affected and their caregivers. Caregivers must provide constant care for the entirety of their child's life.
- There is an urgent need for a disease-modifying treatment for AS. Families are eager for a treatment that could provide even small improvements in cognition, communication, and the ability of their loved ones to carry out activities of daily living.
- The need for FDA concurrence on the utility of existing outcome measures and possible biomarkers intended to measure potential effects of new disease-modifying treatments will help advance late-stage trials. Such advances could accelerate innovation to address AS unmet needs.

Appendix 1: Meeting agenda

Hope in Action: An EL-PFDD Meeting on Angelman Syndrome
April 7, 2025 | 10:00 a.m. to 3:00 p.m. ET
Meeting Agenda

10:00-10:05 a.m.	**Welcome** *Tim Franson, MD, Moderator* *Principal, Faegre Drinker Consulting*
10:05-10:15 a.m.	**Opening Remarks** *Amanda Moore* *Chief Executive Officer* *Angelman Syndrome Foundation* *Ryan Fischer* *Chief Operating Officer* *Foundation for Angelman Syndrome Therapeutics*
10:15-10:25 a.m.	**Overview of Patient-Focused Drug Development** *Michelle Campbell, PhD* *Associate Director, Stakeholder Engagement & Clinical Outcomes* *Office of Neuroscience* *Center for Drug Evaluation and Research* *Food and Drug Administration*
10:25-10:35 a.m.	**Overview of Angelman Syndrome Symptoms** *Ron Thibert, DO, MSPH* *Director, Angelman Syndrome Clinic* *Massachusetts General Hospital for Children*
10:35-10:45 a.m.	**Discussion Format Overview and Demographic Polling** *Tim Franson, Meeting Moderator*

Appendix 1: Meeting agenda

Topic 1: Symptoms of Angelman Syndrome and Impact on Daily Life	
10:45-11:10 a.m.	**Panel Remarks from Caregivers of People with Angelman Syndrome**
11:10 am.-12:30 p.m.	**Polling and Facilitated Discussion**
12:30-1:00 p.m.	**Break**
1:00-1:10 p.m.	**Overview of Angelman Syndrome Treatment Approaches** *Elizabeth Berry-Kravis MD, PhD* *Director, F.A.S.T. Center for Translational Research* *Rush University Medical Center*
10:35-10:45 a.m.	**Discussion Format Overview and Demographic Polling** *Tim Franson, Meeting Moderator*
Topic 2: Views on Current Approaches to Treatment and Future Treatments	
1:10-1:35 p.m.	**Panel Remarks from Caregivers of People with Angelman Syndrome**
1:35-2:45 p.m.	**Polling and Facilitated Discussion**
2:45-2:55 p.m.	**Pre-Meeting Survey Data Presentation** *Ryan Fischer* *Chief Operating Officer* *Foundation for Angelman Syndrome Therapeutics*
2:55-3:00 p.m.	**Closing Remarks** *Tim Franson, Moderator*

Appendix 2: Meeting discussion questions

Hope in Action: An EL-PFDD Meeting on Angelman Syndrome Discussion Questions

Topic 1: Symptoms of AS and the impact of the condition on daily life

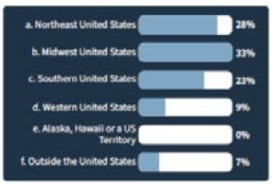
1. In terms of addressing Angelman syndrome symptoms, let's ask our audience to weigh in on what 1 – 3 symptoms are most challenging to manage and, for those with older loved ones, how those have changed over time?
2. Let's hear more insights from our families in the audience about how your loved one's symptoms impact their daily life?
3. Finally, given the various and lifelong effects of Angelman syndrome, what worries you most about your loved one's future?

Topic 2: Approaches to treating AS and priorities for future treatments

1. Let's start this part of our discussion hearing a little more about family experiences with the effectiveness of current symptom treatments and, for those with older loved ones, how they may have changed over time.
2. Assuming there is no complete cure for AS, what specific things would you look for in a new treatment in terms of changes to how your loved one feels or functions?
3. I'd like to ask our audience to share their thoughts on areas where any improvement might be meaningful to you and your loved one living with Angelman syndrome and how it could impact their daily life.

Appendix 3: Meeting polling questions and results

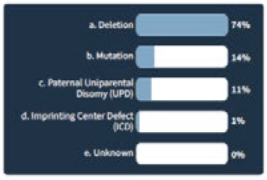
01. Where do you live?



Response options	Count	Percentage
a. Northeast United States	16	28%
b. Midwest United States	**19**	**33%**
c. Southern United States	13	23%
d. Western United States	5	9%
e. Alaska, Hawaii or a US Territory	0	0%
f. Outside the United States	4	7%

57
Responses

02. What is your loved one's AS genotype?



Response options	Count	Percentage
a. Deletion	**53**	**74%**
b. Mutation	10	14%
c. Paternal Uniparental Disomy (UPD)	8	11%
d. Imprinting Center Defect (ICD)	1	1%
e. Unknown	0	0%

72
Responses

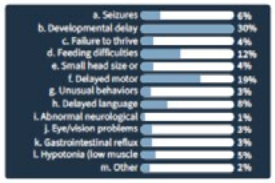
03. How old was your loved one when you or your family personally first observed signs and symptoms of AS?

Response options	Count	Percentage
a. 0-6 months	**34**	**52%**
b. 7-11 months	19	29%
c. 1-3 years	12	18%
d. 4 years or older	0	0%
e. Not sure	1	2%

66
Responses

Appendix 3: Meeting discussion questions

04. What signs and symptom(s) first led you or your physicians to consider a diagnosis of AS? Select up to THREE.



Response options	Count	Percentage
a. Seizures	12	6%
b. Developmental delay	**62**	**30%**
c. Failure to thrive	8	4%
d. Feeding difficulties	26	12%
e. Small head size or distinctive facial features	8	4%
f. Delayed motor development	39	19%
g. Unusual behaviors	6	3%
h. Delayed language development	17	8%
i. Abnormal neurological exam	2	1%
j. Eye/vision problems	7	3%
k. Gastrointestinal reflux	7	3%
l. Hypotonia (low muscle tone)	10	5%
m. Other	5	2%

209
Responses

05. About how much time elapsed between when your loved one's signs and symptoms of AS started and wher your loved one was officially diagnosed?

Response options	Count	Percentage
a. 0-6 months	27	30%
b. 7-11 months	25	28%
c. 1-2 years	**31**	**35%**
d. 3 years or more	6	7%

89
Responses

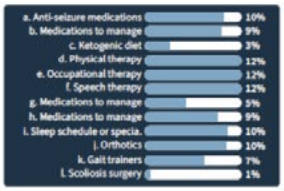
06. Which one area of AS has the greatest impact on the life of the person for whom you care?

Response options	Count	Percentage
a. Behavior	7	9%
b. Cognition	5	6%
c. Communication	**54**	**68%**
d. Daily living skills	6	8%
e. Fine motor skills	0	0%
f. Gastrointestinal	1	1%
g. Gross motor skills	4	5%
h. Neurological	1	1%
i. Sleep	2	3%
j. Vision	0	0%
k. Other	0	0%

80
Responses

Appendix 3: Meeting discussion questions

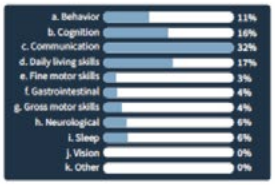
01. Has your loved one ever taken or received any of the following to manage the symptoms of AS? Select ALL that apply.



Response options	Count	Percentage
a. Anti-seizure medications	58	10%
b. Medications to manage gastrointestinal problems / constipation	56	9%
c. Ketogenic diet	18	3%
d. Physical therapy	**72**	**12%**
e. Occupational therapy	71	12%
f. Speech therapy	71	12%
g. Medications to manage behavior	30	5%
h. Medications to manage sleep issues	54	9%
i. Sleep schedule or special needs safety bed	61	10%
j. Orthotics	60	10%
k. Gait trainers	44	7%
l. Scoliosis surgery	4	1%

599
Responses

02. When thinking about the effects of a potential treatment, what would be the most meaningful area to address? Select top THREE.



Response options	Count	Percentage
a. Behavior	25	11%
b. Cognition	36	16%
c. Communication	**73**	**32%**
d. Daily living skills	39	17%
e. Fine motor skills	7	3%
f. Gastrointestinal	8	4%
g. Gross motor skills	10	4%

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Responses

HOPE IN ACTION

PROGRESS THROUGH ADVOCACY

angelman SYNDROME FOUNDATION

fast