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Externally-Led, Patient-Focused Drug Development Meeting on Down Syndrome-Associated Alzheimer's Disease (DS-AD)

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Report submitted to the US Food and Drug Administration (FDA)

Down Syndrome-Associated Alzheimer's Disease (DS-AD)
Voice of the Patient Report

This *Voice of the Patient* report was published by the National Down Syndrome Society (NDSS) as a summary of the input shared by individuals with Down Syndrome and their loved ones during an Externally-Led Patient Focused Drug Development (EL-PFDD) meeting on Down Syndrome-Associated Alzheimer's Disease (DS-AD) conducted virtually on June 2, 2026. The NDSS mission is to create a world where individuals with Down syndrome thrive.

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Executive Summary and Key DS-AD Insights

1. **Alzheimer's disease (AD) is now the leading cause of death for adults with Down syndrome over the age of 35.** Down syndrome-associated Alzheimer's disease (DS-AD) has become one of the most urgent challenges facing the Down syndrome community.
2. **Adults with Down syndrome have worked exceptionally hard to build purposeful lives and achieve recognition, inclusion, independence, and a place in their communities**. Individuals with Down syndrome occupy meaningful roles in their communities based on relationships, work, service, and advocacy.
3. **DS-AD symptoms arrive swiftly and progress at a devastating rate.** DS-AD causes a broad range of symptoms such as behavioral and mood changes, memory impairment, communication challenges, and functional decline, over a very short period of time. The average time from diagnosis to death is 5.6 years.
4. **The impacts of DS-AD are so profoundly life changing for individuals with Down syndrome and their families, that they live in fear of the future.** The devastating loss of key living skills and physical abilities leads to the eventual loss of community participation, ability to manage personal care and activities of daily living, important relationships, and the independence and autonomy built over a lifetime.
5. **The DS-AD caregiving burden is intense and increases as the disease progresses and independence continues to diminish**. The nationwide dearth of care options requires many elderly parents and siblings to care for individuals with DS-AD. Many families navigate increasingly complex needs without specialized support, as the availability and affordability of those supports is not universal.
6. **DS-AD carries a catastrophic emotional burden**. Individuals with Down syndrome and their families experience profound fear, loss, and grief about the certainty that they, or their loved one, will develop DS-AD in the future.
7. **The Down syndrome community urgently needs safe and effective treatments to prevent and slow DS-AD**. People with Down syndrome deserve the same urgency, attention, and access to effective treatments as anyone else at risk for AD.
8. **In the absence of treatments specific to the unique trajectory of DS-AD, current treatment approaches are limited to symptom management.** Most individuals living with DS-AD rely on a variety of approaches to manage their symptoms or to try to prevent symptoms from getting worse (e.g., Aricept, Namenda, antipsychotic medications, anxiety or depression medications anti-seizure medications, sleep-related medications and pain management drugs). At best, current approaches help to manage DS-AD symptoms, however families report that some of the medications used by the general population to alleviate AD symptoms tend to have no impact or actually exacerbate symptoms among their loved ones with Down syndrome. None of these approaches prevent or stop the disease.
9. **The community expressed a strong willingness to contribute to research that may improve outcomes for current and future generations of individuals and families affected by DS-AD.**

Despite this willingness, there are too few opportunities for Down syndrome families to participate in clinical research and trials. Caregivers discussed the factors influencing whether they would participate in a clinical trial, such as: the level of invasiveness of procedures, the safety profiles of investigational drugs, the study team's background in working with individuals with Down syndrome.

10. **The Down syndrome community identified other important priorities.** In addition to better DS-AD awareness, information, and resources along the entire disease spectrum, the community needs more early AD screening and diagnostics, and quick access to new or repurposed AD medications.

Introduction

Clinical Summary of Down Syndrome-Associated Alzheimer's Disease (DS-AD)

- **People with Down syndrome are living longer and healthier lives than ever before**. Life expectancy for people with Down syndrome has tripled in the last four decades because of advances in medical care, the advocacy of caregivers, and the relentless determination of self-advocates. Tragically, this newfound longevity is overshadowed by the statistical certainty of acquiring DS-AD, making DS-AD an urgent challenge facing the community.
- **Down syndrome is the leading genetic cause of Alzheimer's disease**. More than 90% of all adults with Down syndrome acquire Alzheimer's disease in their lifetime. At any given time, an estimated 20,000 - 30,000 people in the United States are living with DS-AD.
- **Individuals with Down syndrome have three copies of chromosome 21, which encodes the amyloid precursor protein (APP).** Because people with Down syndrome have an extra 21st chromosome, their brains naturally produce more APP. Processing of the APP protein causes byproducts, in particular amyloid-beta, to accumulate with time and cause changes to the brain.
- **DS-AD arrives early and progresses quickly, with an average survival after diagnosis of only 5.6 years**. Nearly all individuals with Down syndrome accumulate amyloid plaques by the age of 40; however, visible symptoms are still uncommon at this age. The average age of symptom onset is 54 years, compared to the general population whose symptoms typically onset in the mid-80s.
- **Although the disease progression is more rapid in DS-AD, the disease trajectory of DS-AD is nearly identical to all other forms of Alzheimer's disease**. Symptoms can include psychological or behavioral changes, memory impairment, executive function impairment, loss of skills, incontinence, gait impairment, seizures, and dysphagia.
- **Alzheimer's disease is now the leading cause of death for adults with Down syndrome over the age of 35.**

DS-AD EL-PFDD Meeting Summary

The Externally-Led Patient-Focused Drug Development (EL-PFDD) meeting on Down Syndrome-Associated Alzheimer's Disease (DS-AD) was held virtually on June 2, 2026. The meeting was focused on two key topics: *DS-AD Symptoms and Daily Impacts* and *Current Approaches to DS-AD Treatment*. The meeting featured recorded presentations, moderated discussion between individuals on live Zoom panels and those who dialed in by phone. Individuals living with DS-AD, family caregivers, siblings, and parents of both affected adults and younger individuals with Down syndrome also contributed through online polling and by submitting comments through the online portal. Many of those who participated in the meeting were bereaved parents or siblings of those who had passed away from DS-AD.

More than 160 individuals attended the meeting, including: 63 people with Down syndrome, their caregivers, family and friends; 34 from not-for-profit organizations; 21 FDA or NIH staff; 17 scientists and researchers; 15 healthcare industry staff; four healthcare providers; and six others including

regulatory advisors and students. According to online polling, most individuals participating in the meeting were caregivers of someone with Down syndrome. Most meeting registrants were residents of the United States. However, attendance was dynamic, so individuals from other countries may have joined as the meeting progressed. The individuals with Down syndrome who attended the meeting were split equally between males and females, and most of them did not yet have a DS-AD diagnosis. Most were under the age of 60, with almost half, 41%, of those represented under the age of 40, 31% between the ages of 41-50, and 24% between 51 and 60 years old.

The meeting video recording, meeting agenda, meeting discussion questions, meeting attendee demographics, online polling results, as well as additional written comments submitted through the online portal are available through the NDSS EL-PFDD website, https://ndss.org/el-pfdd.

The Voice of the Patient Report

This *Voice of the Patient* report is provided to the Down syndrome community and stakeholders including: the FDA, other government agencies, regulatory authorities, medical product developers, academics, clinicians, and any other interested individuals. This report is organized to highlight insights that emerged at the June 2, 2026, EL-PFDD Meeting on DS-AD. The content of this report may help inform the development of DS-AD-specific, clinically-meaningful endpoints and overall trial designs for current and future clinical trials, as well as encourage researchers and industry to investigate better identification, development, and evaluation of potential therapies, devices, or diagnostic tools for DS-AD.

The input received from the June 2, 2026, EL-PFDD Meeting on DS-AD reflects a wide range of experiences of individuals and family members living with DS-AD however not all symptoms and impacts may be captured in this report. Comments from the Down Syndrome community included in this *Voice of the Patient* report were edited slightly for clarity and readability.

Dedication: *We dedicate this report to the many individuals from our community who have already passed away from Down syndrome-associated Alzheimer's disease. We also dedicate this report to the late Lois Kelly, the VP of Research and Clinical Operations at NDSS, who was the initial driving force behind our DS-AD EL-PFDD meeting, and who is sorely missed.*

The final report is available through the NDSS EL-PFDD website, https://ndss.org/el-pfdd

Topic 1: DS-AD Symptoms and Daily Impacts

During the morning session of the EL-PFDD meeting, individuals with Down syndrome who were concerned about DS-AD, individuals living with DS-AD, and caregivers, including siblings and parents, reflected on their experience of living with DS-AD, or living with the imminent risk of DS-AD. Their stories reflected different stages of the disease journey, from families focused on prevention and early detection to those living with active symptoms, to those whose loved ones had died from Alzheimer's disease. Insights from this session are summarized and illustrated with quotes from those at risk of, or living with DS-AD, their caregivers, family members, and loved ones.

DS-AD Insight

Adults with Down syndrome have worked exceptionally hard to build purposeful lives and achieve recognition, inclusion, independence, and a place in their communities.

Individuals with Down syndrome, their parents, and siblings spoke proudly about how hard they worked to overcome the barriers to full participation in their chosen careers, volunteer work, service, advocacy, relationships, athletic accomplishments, artistic pursuits, self-determination, and independent living. Many stories were shared about individuals with Down syndrome, who are deeply cherished by their families and friends, and are serving meaningful roles in their communities today.

> *"I have a full-time job at a law firm. I raise the money for my nonprofit by giving talks and workshops all over the country and sometimes out of the country. I am an avid reader. I'm pretty good at jigsaw puzzles and gin rummy. However, it is important to me that you know that I am not the exception for people living with Down syndrome. Look all around the country and you'll find people with Down syndrome who have graduated from their high schools. Some are going on to colleges. They are actors and musicians, golfers, surfers, hockey players, Ironman triathletes, fashion models, congressional lobbyists, public speakers, hardworking employees, and open water swimmers. This sounds wonderful, doesn't it? Until you realize that this can all be wiped out by the time we're in our 50s."* - Karen, a 49 year old self-advocate with Down syndrome

> *"Suzanne was joyful, expressive, determined, deeply connected to her community. She worked for over 20 years bagging groceries, she started her own greeting card business, and she had a remarkable ability to connect with people. She rode horses for 17 years. She participated in Special Olympics and grew up into a life of increasing independence. Like so many individuals with Down syndrome, she thrived with the right expectations, inclusion, and support, but I am not here to talk about her childhood. I'm here to talk about what happens as individuals with Down syndrome age."* - Jean, parent and caregiver of a 50-year-old with DS-AD

Poll 1&2 Results DS-AD symptoms and health concerns are devastating.

Individuals with DS-AD, caregivers, and their loved ones described experiencing a wide range of DS-AD-associated symptoms including behavioral and mood changes, memory impairment, communication challenges, challenges with executive function, changes in physical functioning and mobility, seizures, dysphagia, and others. These symptoms intensify as DS-AD progresses. DS-AD symptoms are described below, with quotes from caregivers and family members.

Behavioral changes

Behavioral changes are often one of the earliest symptoms that individuals with DS-AD experience. These changes can appear as stubbornness, resistance, defiance, lack of cooperativity, and uncharacteristic impulsivity. Eventually, lack of motivation, withdrawal, and loss of spontaneity, and rigidity become more apparent.

> *"She had always been pleasant, cooperative, eager. Now, she refused to do things like take her seat on the van. By 2016, her refusal behaviors became so extreme that she could not participate in the programs she once loved. One day in a brief moment of clarity, she pounded her fists on our kitchen table and cried, 'I hate this.' She would scream, 'No,' at the top of her lungs, flail, and strike out, especially around showering."* - Jane, bereaved sibling and caregiver of a sister who passed away from DS-AD at 52 years of age

> *"In her 50s, Beth's behavior started to change. She entered her housemate's rooms without permission. She seemed to be intentionally sabotaging her chores, clogging up the sink and letting it overflow onto the floor when it was her turn to clean up the kitchen. She folded wet laundry and put it away in her dresser. She left the group home without telling anyone where she was going and walked for miles, before a benevolent stranger gave her a ride home."* - Norma, sibling and caregiver of a 61-year-old with DS-AD

Mood changes

Many described experiencing mood changes and mood swings, depression, anxiety, anger, agitation, emotional outbursts, and even aggression in some cases. Caregivers observed their loved ones feeling discouraged and frustrated as everyday tasks became more difficult.

> Mia's mood swings and behavior changes were an early symptom. *"What was very difficult for us as care partners was the mood swings that she experienced. If something was frustrating to her, she would yell at us, things that she never in her life did. Our daughter took her to her favorite restaurant and Mia became frustrated and there she is in a restaurant acting out, yelling at her sister and her sister could not calm down the situation. That was really horrible for both of them."* - Carol, bereaved parent of a daughter who passed away from DS-AD at 47 years of age

> *"The aggression and anxiety hurts so much, knowing what this disease is doing to my kind, gentle son."* - Donna, parent of a 48-year-old with moderate DS-AD

Memory impairment

Memory impairment and cognitive changes can include slower thinking, poorer memory, forgetting routine tasks or directions, losing track of location or time. As DS-AD progresses, individuals experience increased confusion and eventually, heartbreakingly, begin to forget their friends and family members, and often lose their own sense of self.

> *"She has lost a significant amount of short term memory. Best days are when I don't have to remind her of things she knows, worst are the constant reminders as she can't remember what she was just told."* - Amie, parent and caregiver of a 48-year-old daughter living with DS-AD

> *"Then she started having obvious memory glitches, like being dressed and ready for work at 4 am on a Sunday. That scared her, because she had already seen our parents and then her soulmate with Down syndrome develop AD, and she realized that it was happening to her. She became anxious and depressed, and her care needs exceeded what her group home could provide."* - Norma, sibling and caregiver of a 61-year-old with DS-AD

Communication challenges

Many with DS-AD experience difficulties with speech or word finding. Some begin to repeat themselves and lose the ability to engage in conversation. As communication abilities decline, families must guess what their loved one is thinking or feeling.

> *"Finding my words is very frustrating. Sometimes I can't even say things especially on demand. The words just get stuck. Even when I want to say a lots of things, the words just get trapped in my head."* - Kate, 45-year-old self-advocate, blogger, and friend, living with DS-AD

> *"My brother Leary was diagnosed with Alzheimer's in 2020. We noticed changes in his speech first, and then his motor skills. His personality went from friendly to hitting and then friendly again."* - Kathleen, bereaved sibling and caregiver of brother who passed away from DS-AD at 60 years of age

Challenges with executive function

Meeting participants described how their loved one experienced difficulty maintaining attention, planning, problem solving, organizing, and adapting to new situations. Decision-making falters, and it takes much longer to complete daily tasks. Handling money can be an issue.

> *"The most noticeable symptom is occasional confusion with steps in a routine task. We simply remind her what comes next. She confuses others by lashing out, yelling when no one else is nearby."* - Martha, caregiver of a 47-year-old living with DS-AD

> *"He went to work at four in the morning instead of four in the afternoon, and was found on the street, hypothermic, because it was Minnesota and it was in the middle of January, and it was the most terrifying thing."* - Sonja, bereaved sibling of a brother who passed away from DS-AD

Changes in physical functioning and mobility

Individuals living with DS-AD experience gait impairment, and loss of motor coordination and balance. Some experience stumbles, falls, and injuries. As DS-AD advances, many become immobile and wheelchair bound, requiring a lift and other specialized equipment. Some families reported that their loved one experienced muscle twitching and spasticity later.

> *"She began to lose her mobility. First, she needed a hand to walk, then a walker, then a wheelchair. She developed seizures."* - Jean, parent and caregiver of a 50-year-old with DS-AD

> *"When Matt was 49, I began getting reports of changes such as gait issues that included stumbles and falls as well as confusion and difficulty with dressing and personal hygiene."* - Jadene, parent of a 51-year-old living with DS-AD

> *"He had 47 unwitnessed falls [in one month]. It was horrible. His personality changed from a kind loving person to a frustrated grumpy one."* - Diane, bereaved parent of a son who recently passed away from DS-AD at the age of 49 years of age

Seizures

Seizures can occur as an early symptom or later in the DS-AD progression. Those living with DS-AD experience seizures 10-18 times more often than in the general population. Some described grand mal or tonic-clonic seizures, while some experienced late-onset myoclonic epilepsy in Down syndrome (LOMEDS), a specific type of adult-onset epilepsy.

> *"On a good day Liz may have some flicker of recognition or make a comment such as 'I'm ok' but on a bad day she will have a seizure and then spend the rest of the day sleeping. Two years after diagnosis, Liz developed LOMEDS [Late-Onset Myoclonic Epilepsy in Down Syndrome]. She is now bed bound, double incontinent, unable to recognise us and unable to express any needs."* - Jennie, sibling of a 59-year-old with DS-AD

> *"Now Beth has seizures and has lost the ability to speak, walk, or care for her personal needs. She doesn't recognize me, although she seems pleased to see me when she's awake."* - Norma, sibling and caregiver of a 61-year-old with DS-AD

Dysphagia or swallowing dysfunction

As DS-AD progresses, many individuals experience difficulty eating, food refusal, weight loss, choking and may even experience aspiration pneumonia which can lead to premature death. Dysphagia can interfere with the ability to administer medications.

> *"Matt enjoyed going out to eat at least once a week. That's become more challenging because of increased incidents of choking. Even coming to join me for supper has become difficult because of the unpredictability of his energy and mood."* - Jadene, parent of a 51-year-old living with DS-AD

> *"My son is 48 with AD. He is having trouble taking the medication. We believe that he is now having some trouble swallowing, so the meds are mixed with yogurt*." - Donna, parent of a 48-year-old with moderate DS-AD

Other DS-AD symptoms mentioned during the meeting and in submitted comments

During the meeting caregivers shared their experiences with other impactful symptoms and health effects including fatigue, changes in perception, sleep abnormalities, extreme discomfort and pain, vision loss, hallucinations and delusions, and incontinence. Caregivers said these symptoms became more severe as the disease reached the end stages.

> *"The symptoms have gone from irrationality and odd behaviours to being bedbound, unable to express opinion or thought, doubly incontinent and unable to recognise family."* - Jennie, sibling of a 59-year-old with DS-AD

> *"Ellen suffered greatly from Alzheimer's disease. She became severely impaired: depth perception, language, senses. Declines continued, incontinence, loss of speech and mobility, seizures. Her declines continued and then ultimately, she was at the end stage of Alzheimer's disease, which was horrible, heartbreaking."* - Jane, bereaved sibling and caregiver of a sister who passed away from DS-AD at 52 years of age

DS-AD Insight

Many with DS-AD experience a very sharp functional decline that families are not prepared for.

Some caregivers and family members had no idea that their loved one with Down syndrome was at a higher risk for AD and felt blind-sided by the diagnosis. Many described a heartbreakingly fast progression, as they watched their generally healthy loved one decline from fully functional to bedbound in only a few short years, before experiencing a premature death. Many felt that they were not provided with adequate information or support, especially at the end stages of the disease.

> Sonja's brother declined very rapidly after diagnosis. "*My mother called it 'walking off a cliff'. He just really lost so much, he lost a lot of the joy in his life. He started having seizures."* - Sonja, bereaved sibling of a brother who passed away from DS-AD

> *"None of us were really prepared for the symptoms of dementia caused by Alzheimer's that has him now slipping away from us. It has come quickly - over the past two years - the confusion, his uncertainty, the memory loss, his preference to be alone rather than socializing. None of that is our Joe."* - Carlo, sibling and caregiver of a 63-year-old living with DS-AD

> *"The last three years we've cared for him at home. He developed seizures, diverse spasticity, and then eventually severe agitation, which was very difficult. All those symptoms caused a lot of discomfort. It was a challenge that we had to navigate on our own. There just wasn't the help to manage these symptoms."* - Colleen, bereaved sibling and caregiver of a brother who recently passed away from DS-AD at 53 years of age

Poll 3 & 4 Results

The impacts of DS-AD are so profoundly life changing for individuals with Down syndrome and their families, that they live in fear of the future.

DS-AD symptoms interfere with every aspect of daily life. Families and caregivers described their loved ones no longer being able to participate in the sports and activities, employment, and volunteering that had long been important parts of their lives, and for which they worked exceptionally hard to attain. Families spoke about the devastating loss of key living skills that had taken years to learn and maintain and about how the loss of these skills and physical abilities leads to the eventual loss of independence. Most eventually lose connection to the relationships and communities that they had worked so hard to build over a lifetime.

No longer able to fully participate in activities, programs, or sports

As individuals with DS-AD lose interest and physical capabilities, participation declines. Some described how their loved ones began to refuse invitations and activities. Families worried that the further loss of hard-earned skills and abilities would result in their loved ones no longer being able to engage in all the relationships, activities, and passions that they cultivated over a lifetime. Caregivers reported how their loved one's worlds shrank as they started to get lost in places that were familiar to them and could no longer work.

> Phyllis's sister-in-law unexpectedly started to decline social events. *"It's so hard to really figure out what's going on. The fact that her first reaction was to stay at home was something that I think was very out of character for us. We haven't dealt with behaviors that were more aggressive or anything like that, but this apathy of not wanting to come to a pool party was very unusual."* - Phyllis, family member of a 58-year-old with Down syndrome
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> *"She worked at a grocery store, and she got lost in the grocery store. She had been in that store hundreds of times and all of a sudden, she didn't know how to get back to wherever she was supposed to be."* - Carol, bereaved parent of a daughter who passed away from DS-AD at 47 years of age
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> *"It is difficult not to let the fear of the future overshadow the present. Jack is physically active and enjoys playing basketball and soccer. The thought of him not being able to play the sports that he loves due to the loss of mobility as a result of Alzheimer's is heartbreaking."* - John, parent and caregiver of a 28-year-old with Down syndrome

No longer able to manage their personal care or perform activities of daily living

Families reported how their loved one living with DS-AD experience difficulties or became resistant to showering, getting dressed, brushing teeth, taking medications, and using the toilet without help. Some, after years of living independently or semi-independently, lost the ability to prepare their own food, do their laundry, or clean their own homes. Many living with DS-AD require prompting and reminders and increasing assistance with daily activities they once managed independently. Many find it frustrating to be unable to complete simple tasks that they had mastered long ago.

"*Her hygiene started going down. She was having trouble washing her hair. Things were changing. She was having trouble picking her clothes out, just different things and constantly repeating herself, not remembering things that she just told me a half hour ago*." - Laurie, parent and caregiver of a 43-year-old with DS-AD

"She needed prompts for routines that had been second nature, like taking her morning pills. One incident haunts me as a mile marker. She forgot how to dispose of a sanitary napkin in the trash can. She flushed it down the toilet. There was a flood, but more importantly, she had forgotten what to do." - Jane, bereaved sibling and caregiver of a sister who passed away from DS-AD at 52 years of age

"I used to live independently. I did all of my own meals. I cleaned my whole house by myself. My house was even cleaner than my mom's. I did that for fifteen years! My mom and my staff noticed that my condo was not so clean and also I started forgetting to do things and I even flooded my bathroom too many times. Now, I have staff and they help me remember things like brush my teeth or do my dishes or take my medicine. They also help me when they do my laundry or vacuum and things like that. I miss being independent." - Kate, 45-year-old self-advocate, blogger, and friend, living with DS-AD

"Jack is independent with his self-care and maintains his own daily schedule. It would be heartbreaking for him to lose the skills and independence that he has worked so hard to acquire." - John, parent and caregiver of a 28-year-old with Down syndrome

Loss of relationships

For those with DS-AD, interest in social engagement drops, word finding becomes more difficult, and speech becomes more challenging. Conversations become shorter and relationships harder to maintain. Eventually, those living with DS-AD no longer recognize their loved ones. Some even described how DS-AD slowly eradicates relationships with their peers.

"Since he was little, our goodbyes included a kiss and a hug that felt like a soul level connection. About a year ago, I realized he wasn't asking for that hug and kiss when I left. Of all the changes and losses I've witnessed, this one rips my heart wide open. I know where our path leads." - Jadene, parent of a 51-year-old living with DS-AD

"My daughter is now 50. She is in hospice. I visit her almost every day. After losing her father, she felt abandoned and I want her to know she is not alone. Some days she recognizes me. Some days she doesn't. She has largely lost her ability to speak. Eating is difficult. She requires a Hoyer lift to move her. So, I sit with her, and I sing to her and I show her pictures and we talk about the past." - Jean, parent and caregiver of a 50-year-old with DS-AD

"My best friend for 30 years is at the end stage. I have spent time with her over the past three years and see how Alzheimer's has affected her and her family. We were both independent, living, working, traveling, flying back and forth from Chicago to Syracuse by ourselves. And now the best we get to do is smile at each other and hug." - Christine, 49-year-old with Down syndrome, no AD symptoms yet

Loss of independence and autonomy

Eventually, individuals with DS-AD lose the ability to live independently, their agency, and control of their own lives. Some transition from independent living by having live-in staff, or by moving in with their parents or siblings, or even to a care facility when their needs increase. Eventually those with DS-AD need help with all aspects of daily life including toileting, mobility, and even eating. Many families worry about who will care for their loved one as the AD progresses. Many older caregivers worry about how their loved one will be cared for once they are no longer able to, and some expressed fears that their loved one will outlive them.

> *"[I worry] about the fact that she loves her independence. Although she lives at home, she's able to go places. That would be so devastating: to lose her independence and then to not be herself, to not be who she is. We don't want them to be able to lose that core component of who they are, and we know that that can be a part of it. And so that's a huge worry right here*." – Makini, parent and caregiver of a 35-year-old with Down syndrome, no AD symptoms yet

> After Mia moved back in with her parents, *"You could just tell it really weighed on her that she had been so independent, so accomplished, and to have to suddenly move in with your parents, that seemed like a low blow to her."* During that time, *"We were really able to see the progression of how she lost skills. It started with the not being able to participate in sports and not being able to continue with her job, but then to not be able to take care of hygiene things herself and then to not be able to walk and then to only be able to eat soft foods. She lost every skill."* - Carol, bereaved parent of a daughter who passed away from DS-AD at 47 years of age

> *"He lived completely independently on his own, and then to lose it all was, it just seemed particularly tragic. That was, I think, the hardest part for our family, is that he had accomplished so much, with the help of my parents especially, and to lose all that at the end was really hard. As time went on, he was unable to make food on his own. He'd really taken fully care of himself for years. My mom really had to take on all of that."* - Sonja, bereaved sibling of a brother who passed away from DS-AD

> *"The first care home was entirely inappropriate for her and hastened her decline in our view. We asked for, and then demanded, a move to a more suitable facility – we asked over 75 facilities if they could/would take her and all refused for a variety of reasons. We were eventually successful in getting her a place at a brand new facility which had a Young Onset Dementia unit and she remains there now."* - Jennie, sibling of a 59-year-old with DS-AD

DS-AD Insight

The DS-AD caregiving burden is intense and increases as the disease progresses and independence continues to diminish.

The DS-AD care burden has an enormous impact on all aspects of caregivers' lives; their relationships, community engagement, financial wellbeing, mental health, and employment. Families worried about how quickly symptoms may progress, and what supports and resources

would be available for them as care needs increase. Many caregivers described how they were forced quit their jobs or had to take alternative jobs to accommodate their loved one with DS-AD.

Many individuals with DS-AD are cared for by elderly parents and siblings who described the challenges of supporting adult children through Alzheimer's disease while they themselves are aging. Some caregivers experience injuries from the lifting and physical labor. Many families navigate increasingly complex needs without specialized support, as the availability and affordability of those supports is not universal. Finding appropriate living arrangements and care for a loved one with DSAD is a difficult issue that also creates major impacts on the health and well-being (both physical and mental) on those with DSAD as well as their caregivers.

> *"Her decline came at the same time my husband and I were facing our own realities of aging. Then my husband was diagnosed with advanced lung cancer. Our lives became a cycle of survival, driving two hours each way to Boston five days a week for treatment and also trying to care for Suzanne. Suzanne began to decline rapidly, emotionally, behaviorally, physically. And this happened as my husband's health declined."* - Jean, parent and caregiver of a 50-year-old with DS-AD

> *"I couldn't lift him off the floor. I tried changing his Depends but he kicked and hit me. So I cried and tried to help him all day but nothing worked. When my husband came home we were able to lift him and clean him up. Lifting was very hard and when we put him in bed he couldn't roll over by himself. Due to all of the lifting I have had two surgeries."* - Kathleen, bereaved sibling and care partner of brother who passed away from DS-AD at 60 years of age

DS-AD Insight

DS-AD causes a catastrophic emotional burden. Individuals with Down syndrome and their families experience profound fear, loss, and grief about the certainty that they, or their loved one, will develop DS-AD in the future.

The DS-AD emotional burden of DS-AD is intense. Individuals with Down syndrome, and their loved ones have the unique and horrifying perspective of starting to think about and prepare for the very real reality of Alzheimer's decades ahead. Many adults with Down syndrome have already seen their friends and colleagues experience Alzheimer's disease-related declines and in some cases death. This makes the possibility of their own future diagnosis feel deeply personal and immediate.

> *"I know all about Alzheimer's because way too many of my friends have died from Alzheimer's, and even more of my friends have it now."* - Christine, 49-year-old with Down syndrome, no AD symptoms yet

> Kate has a hard time seeing a friend is suffering from DS-AD. *"I'm afraid [for] my friend right now, she's having Alzheimer's and dementia. She's not doing good right now. She's not herself right now. I'm afraid I might be like her. And I might feel like she might die and I don't*

want that because I'm not ready. I'm not ready to die yet." - Kate, 45-year-old self-advocate, blogger, and friend, living with DS-AD

Even those whose loved one has yet to show symptoms carry a heavy emotion burden. Caregivers are vigilant, wondering whether changes in mood, behavior, memory, communication, or daily functioning might signal the beginning of decline. The tragic reality of watching an adult child lose the interests, activities, relationships, and employment that took so much hard work to achieve, is difficult. Families worry that their loved one's well-being and unique capabilities will be compromised by depression, mood changes, and being unable to do what they love. They worry about their loved one suffering as physical capabilities decline. They worry that in the future their loved one will become confused and not recognize their environments and the people around them.

"The thing that's most prominent in our minds is that every skill, every aspect of her development was hard-earned, and to have this [disease] looming and to know that there's this risk of that independence, those skills, the things that she loves so much being lost is just, it's so frightening and there's not a day that we don't worry about it. It's really hard to not have a scrutinizing lens and to sort of be sort of inspecting for changes." - Niki, sister of a 50-year-old with Down syndrome, no AD symptoms yet

"As parents, we feel she is going to slip away from us and the pain of seeing the confusion in her face." - Amie, Parent and caregiver of a 48-year-old daughter living with DS-AD

"I fear that with the high chances our son will experience AD-DS that it may happen after we are gone and with little family he knows will be gone as well. Not only would he be faced with not understanding what is happening to him, but to face it without family. As I was listening to the stories of individuals' facing symptoms very early, as odd as it sounds, I started to hope that if he does face this horrible disease, we would still be here to provide our loving assurance. What a very sad thought to have." - Becky, parent of a 20-year-old with Down syndrome

Once a parent becomes aware that their child has a genetically pre-determined form of AD, it forever changes their perspective of their child's future and their own. Parents of younger children with Down syndrome, or young adults with Down syndrome, shared that the risk of Alzheimer's disease influences planning for adulthood, employment, independent living, and long-term care decades before symptoms ever appear.

"When Jack was born, we had so many worries. Would he have any friends? Would he be able to go to school with the neighborhood kids? Would people be nice to him? Would he ever be able to live on his own? As Jack grew, those worries were replaced by new worries. But the worry that keeps us up at night is a significant probability that Jack will develop Alzheimer's disease as he ages and lose all of the skills that he's worked so hard to acquire and the personality that makes him who he is." - Lisa, parent and caregiver of a 28-year-old with Down syndrome

"Friends slightly older [than our son] are beginning to decline in their mental and physical abilities. Benjamin wants to enjoy the present." - Kristi, parent and care partner of a 32-year-old with Down syndrome

Topic 2: Current Approaches to DS-AD Treatment

During the afternoon EL-PFDD session, those living with DS-AD and their caregivers, families, and loved ones, as well as caregivers whose loved ones had died from the disease discussed current DS-AD treatment approaches, wishes for future therapies, and identified other needs of the community. Insights from the afternoon session are summarized and illustrated with quotes from those living with DS-AD, at risk of DS-AD, and their caregivers and loved ones.

Poll 5 Result

The Down syndrome community urgently needs safe and effective treatments to prevent and slow DS-AD.

The main message that emerged from the DS-AD EL-PFDD was that safe and effective medications are urgently needed to prevent AD symptoms and to slow the progression of DS-AD before substantial losses occur. Although some FDA-approved treatments are now proven to slow AD progression in the general population, data in the Down syndrome population is insufficient. Meeting participants repeatedly emphasized that people with Down syndrome are living full, engaged, and meaningful lives, and deserve the same urgency, attention, and access to effective treatments as anyone else at risk for AD.

"Do you understand that there are no [Alzheimer's disease] treatments now for those of us with Down syndrome?" - Karen, self-advocate with Down syndrome

"With the exceptionally high risk that Jack will be diagnosed with Alzheimer's as he ages, our hope is that there will be new treatments to prevent or at least slow the progression of the disease." - John, parent and caregiver of a 28-year-old with Down syndrome

"We've always been aware that our children with Down syndrome would most likely be diagnosed with Alzheimer's. We are very focused on prevention and early detection at this point, as Christine has not shown active symptoms. We have followed studies in the general population for a cure and, at the very least, a way to alleviate the devastating symptoms for our children, starting earlier in their lives before the onset of symptoms, is what we are looking for." - Diane, parent and caregiver of a 49-year-old with Down syndrome, no AD symptoms yet

Other important treatment preferences

During the meeting and in submitted comments, the Down syndrome community shared other important treatment preferences including treatments to help maintain independence by preserving cognition, thinking, and navigation skills. They need treatments to help maintain mood and preserve their loved one's personalities. They want medications with fewer side effects and medications that specifically target seizures.

Poll 6 Result

In the absence of treatments specific to the unique trajectory of DS-AD, many different medications are required to manage symptoms.

Individuals living with DS-AD described all the medications that they rely on to manage symptoms, including traditional Alzheimer's disease medications, medications for anxiety and depression, seizures, behavioral symptom management and others. Some families found it very difficult for their loved one to be on so many medications. The medications described at the EL-PFDD and in submitted comments are listed below with patient and caregiver quotes.

Traditional Alzheimer's disease medications (e.g., Aricept [donepezil], Namenda [memantine])

While some found that these medications worked to alleviate DS-AD symptoms, others noticed that efficacy diminished with time. For others, these medications did not work at all or made AD symptoms worse. Although newer anti-beta-amyloid Alzheimer's disease medications exist (Kisunla [donanemab-azbt] or Leqembi [lecanemab]) none of the meeting participants described being offered or prescribed these medications.

> *"My brother Leary was diagnosed with Alzheimer's in 2020. We started him on donepezil [Aricept], which helped with his motor skills. Other medications we tried didn't help."* - Kathleen, bereaved sibling and caregiver of brother who passed away from DS-AD at 60 years of age

> *"My daughter did not do well on the lowest dose of donepezil. It made her symptoms much worse. As soon as I took her off, she was back to more of her old self."* - Vicky, parent and caregiver of a 50-year-old with DS-AD

> *"Early on, doctors prescribed Aricept and Namenda. After a year, neither showed any benefit and were discontinued."* - Jane, bereaved sibling and caregiver of a sister who passed away from DS-AD at 52 years of age

Anxiety or depression medications (Prozac)

Many were prescribed anti-anxiety or depression medications including selective serotonin receptor inhibitors (SSRIs) such as Prozac, or benzodiazepines such as lorazepam (Ativan) or clonazepam. Most described how well these medications worked.

> *"Our primary care physician recently put him on an anti-anxiety medication, we're beginning to see where it's working. There are no side effects from the anti-anxiety medication. A couple of months ago even there were more episodes where he was maybe raising his voice, yelling at somebody, and now he's just more calm."* - Nancy, parent of three adult children with Down syndrome including a 57-year-old with DS-AD

> *"One of the very effective medications that worked was clonazepam for anxiety. She did suffer from anxiety and stress during much of her life. She actually was placed on medications at an earlier age before she had any effects of dementia. I do think that medications helped in the final stages of her dementia because she became extremely*

anxious and unwilling to go to the doctor's office, unwilling to go in a car." - Mike, bereaved parent and caregiver of a daughter who passed away from DS-AD

Anti-seizure medications

Parents and caregivers described prescribing anti-seizure medications such as divalproex sodium (Depakote) and levetiracetam (Keppra). For some, these medications didn't work very well or had side effects such as drowsiness.

> *"The first medication added was Depakote because she started exhibiting some symptoms of small seizures with mild myoclonic twitching. I can't say we noticed anything really significant after the addition of Depakote."* - Amy, parent and caregiver of a 45-year-old with DS-AD

> *"The seizure meds tend to make her very sleepy, and we have had more than a few visits where she couldn't be conscious long enough to even look in my direction. … Now when I go to visit her, it's a toss up whether she will wake up or not. Honestly, it's depressing to me to see my formerly sassy little sister, slumping in a wheelchair and no longer responsive even to the sound of Stevie Nicks."* - Norma, sibling and caregiver of a 61-year-old with DS-AD

Antipsychotic medications (e.g., Risperidone, Seroquel)

Medications to help manage behavior changes helped some individuals but made symptoms worse for others.

> *"I take some medicines. The newest one is orange (Seroquel). It helps me relax and sleep and not be so anxious. My staff thinks my mood is a lot better since I started taking the orange one."* - Kate, 45-year-old self-advocate, blogger, and friend, living with DS-AD

> *"Later, Seroquel and then risperidone were tried for agitation. They made it worse and were stopped."*- Jane, bereaved sibling and caregiver of a sister who passed away from DS-AD at 52 years of age

Investigational medications in a clinical trial

A few participants described participating in interventional clinical trials. Families and individuals with Down syndrome were disappointed when the trials were discontinued.

> *"Andrew was the first and only person with Down syndrome to enroll and participate in the HERO clinical trial. Unfortunately, because the trial was stopped in the middle, he is now left with no further follow-up and no hope for information about how the medicine may impact the trajectory of his life. I feel his contribution was underappreciated by the pharmaceutical company and the Down syndrome research community at large."* - Erin, sibling of an individual who participated in a DS-AD clinical trial

> Kristi's son participated in a study to see if Aricept would enhance memory retention in teens with Down syndrome. *"The study was terminated early due to insufficient support for the hypothesis in the early results. We discovered during the open-label portion of the study*

that Benjamin could not tolerate Aricept at the dose given.“ - Kristi, parent and caregiver of a 32-year-old with Down syndrome

Other medications mentioned during the EL-PFDD meeting and in submitted comments

In addition to medications for other conditions related to aging (estrogen, thyroid medications, statins), other medications mentioned included sleep-related medications for night terrors, investigational medications in a clinical trial, and appetite supplements. Pain relief medications were also prescribed, especially near the end of life.

Poll 7 Result

Most individuals living with DS-AD rely on many additional approaches to manage their symptoms or to try to prevent symptoms from getting worse.

Beyond medications, a wide range of symptom management and preventive strategies were described during the EL-PFDD meeting and in submitted comments. These include exercise, education and social activities, games and activities for brain health, ensuring better sleep, visual aids for prompting and reminders, dietary changes, and behavior management strategies. Families described how they employed adaptive equipment and additional staff support and made changes to living arrangements to ensure appropriate care, especially as the disease advanced. Other AD symptom management approaches that did not generate any direct comments include changes in daily routines, physical and occupational therapy exercises, and speech therapy.

Exercise, education, and social activities for prevention

Many described how they prioritized exercise and other activities to help prevent AD symptom onset. Many of these are used as preventative strategies by those not yet affected by AD.

“I have not yet been affected by Alzheimer's. I am keeping myself very busy every day to stay healthy by riding the Peloton bike, Tai Chi, play word games. I organize Zoom activities with friends, baking, scavenger hunts. And best of all, we dance every day. I volunteer many days a week at the church to keep busy too. I have a doctor who is specialist in Down syndrome to help me stay healthy.” - Christine, 49-year-old with Down syndrome, no AD symptoms yet

“I do not want to ignore the reality of what is coming. I look at ways to make sure Benjamin has the best chance of maintaining his health mentally, emotionally, and physically to keep his advantages high and perhaps delay or negate the development of DS-AD. My hope is that treatment options will expand.” – Kristi, parent and caregiver of a 32-year-old with Down syndrome

Games and activities for brain health

This can include structured games and activities, as well as unstructured play.

“We're working with a behaviorist, and she started James on puzzles, a lot of brain health games. He is resistant to a lot of other things in life right now, but not to the puzzles and the

games. Unfortunately, I wouldn't say they're improving, but he's maintaining skills, and he's enjoying them. They have given him another source of enjoyment in his days." - Nancy, parent of three adult children with Down syndrome including a 57-year-old with DS-AD

"*I asked her, 'Why do you want Barbie dolls?' And she said, 'I can practice conversations.' Of course, I immediately ran out and bought Barbie dolls, and she sits in her room and has conversations back and forth with her Barbies. And then a couple of days later, she said, 'Oh, I also want a pretend phone.' And I said, 'Why?' And she says, 'Because I need to practice those conversations.' So we bought her a pretend phone, and so now you can hear her in her bedroom having conversations about everyday activities."* - Amy, parent and caregiver of a 45-year-old with DS-AD

Ensuring better sleep

Several described how CPAP machines help ensure a better sleep for their loved ones.

"We strongly believe that keeping Susie active physically, socially, and mentally may help delay cognitive decline. She exercises daily, sees her doctor regularly, works to maintain a healthy weight, and uses a CPAP machine. We hope these efforts will make a difference." - Dee, parent of a 38-year-old with Down syndrome, no DS-AD symptoms yet

"He'd sleep a lot and he'd wake up tired, and I think the CPAP has helped him get a solid night's sleep, and helped him fall asleep deeper and quicker. Now he sleeps, he takes fewer naps throughout the day, and he has more energy it seems like." - Joe, parent of a 26-year-old with Down syndrome

Visual aids for prompting and reminders

Visual aids include calendars, task charts, schedules, and pictures.

"Visual Prompts: We use a variety of visual aids throughout Kate's apartment to help her manage her day. Visual schedules and calendars help her keep track of her activities each day and to be prepared for future activities. Task charts help her remember to complete basic tasks each day and to follow the correct procedures. The visual prompts are helpful, but I worry there will come a time that she is unable to understand even the visual prompts." - Amy, parent and caregiver of a 45-year-old with DS-AD

Behavior management strategies

Caregivers described how behavioral redirecting and emotional coping strategies helped those living with DS-AD manage outbursts, frustration, anxiety, anger, and get through the day. These strategies were provided by counselors, occupational therapists, or educational resources from NDSS.

"When the pharmaceuticals failed for her, the one thing that really made her life and her death better than they might have been, were from an occupational therapist. Her brilliant, practical approach focused on quality of life. 'Less is more'; 'don't fight with dementia'; 'no, doesn't mean no', were the mantras. She understood living with AD. She offered problem-

solving strategies to daily challenges. She explained what worked yesterday may not work today. 'Pivot, meet Ellen wherever she is.' This improved Ellen's quality of life and, yes, the quality of her death." - Jane, bereaved sibling and caregiver of a sister who passed away from DS-AD at 52 years of age

"We are fortunate to have found a wonderful counselor who sees Kate every two weeks. Her counselor understands that we aren't seeking a 'cure' or to 'fix' anything. Kate just needs an outlet to discuss her frustration, anxiety and anger. They develop 'strategies' together to help manage her emotions between sessions. She needs an outlet and someone to share her grief with who isn't 'mom' or 'staff'." - Amy, parent and caregiver of a 45-year-old with DS-AD

Dietary changes and supplements

Some families have focused on optimizing nutrition with whole foods, while others provided their loved one with dietary supplements to help manage symptoms. Some have had to be very careful about dietary and texture sensitivities. A pureed food diet may become necessary when swallowing becomes more difficult.

"He had a severe GI distress and pain and discomfort. Even though he couldn't verbally tell us he was in pain, we knew he was having pain. We knew he needed a special diet to combat these concerns. We developed a special pureed diet with whole foods to try to decrease the inflammation and try to minimize his pain." - Colleen, bereaved sibling and caregiver of a brother who recently passed away from DS-AD at 53 years of age

"It has been a pretty steady decline that we've seen in him. What we're doing right now, and it's successful, really watching his nutrition, making sure that he's eating whole grains and a lot of protein, fruits and vegetables, limiting all those foods that all of us need to stay away from." - Nancy, parent of three adult children with Down syndrome including a 57-year-old with DS-AD

Ensuring appropriate care - adaptive equipment, additional staff support, and changes in living arrangements

As DS-AD symptoms advance, families described how their loved one requires staff to assist with daily care, home modifications, and adaptive equipment such as wheelchairs and stair lifts. Disparities in the healthcare system and long-term services and supports (LTSS), especially for middle-aged adults with DS-AD, mean that many families are unable to find the essential resources that their loved one needs. As described in the section in loss of independence page 14, many have already had to move to a home or facility that offers higher care levels.

"My daughter was an independent, active, and competent young lady until two years ago when she was 38 and we first noticed symptoms of AD. This is younger than usual and because of the symptoms she has been unable to attend the day program she had attended for over 10 years. She also has Type 1 diabetes and which requires constant management. In California there are limited day facilities to care for her, so we keep her home and have little support and are exhausted. We will also be looking for long term care facilities as her AD

progresses. Providing more day programs and treatment options would provide much relief for families like ours." - Elizabeth, parent and caregiver of a 40-year-old living with DS-AD

"As people with DS age, the resources in the community such as medical care, day programs, respite help and daily services are [incapable] of helping the families." – Leone, meeting attendee

"Our son passed way January 5 of this year from Alzheimer's. He was diagnosed four years ago. He lived in the same group home with three other guys around his age for 25 years. Year three of his diagnosis we were told we had to find different housing for Reed because they no longer felt it was safe for him to be there. (He was starting to fall alot and lived in a 2nd floor bedroom. That's when the real nightmare began. I was on the phone daily calling or emailing places that were either full, private pay at $20,000 a month or the biggest reason "he's too young. They were all 55+. He went severely down hill after we finally found a plan be to take him but it was a terrible place." - Diane, bereaved parent of a son who recently passed away from DS-AD at the age of 49 years of age

As DS-AD becomes severe, care is about anticipating and addressing physical needs. Some felt that there was not a lot of guidance, support, or resources during the final stages of the disease.

"Anticipate needs and triggers for agitation: treat pain, thirst, hunger, soiled brief, position change. All physical needs [needed to be] addressed. Worked fairly well until the last six weeks. Managing end stage symptoms difficult and most do not know how to manage." - Colleen, bereaved sibling and caregiver of a brother who recently passed away from DS-AD at 53 years of age

"Alan experienced more than fifteen hospitalizations between 2020 and his passing on October 31, 2025. Alan's dementia made these hospitalizations particularly traumatic. Alan would sob for hours at a time in the emergency room awaiting admission. He was scared, and he wanted to go home. It was heartbreaking. We and other family members took turns staying with Alan for 24-hour shifts to comfort him and let him know he was not alone. As difficult as it was to lose him when he passed, we experienced some peace of mind knowing that his immense suffering due to dementia was over." – MaryLou, bereaved sibling of a brother-in-law, who lived with DS-AD for ten years after diagnosis

Poll 8 & 9 Results

At best, current medications and treatment approaches help to manage DS-AD symptoms, but none will prevent or stop the disease.

Current medication and treatment approaches have significant downsides. As described previously, medications and strategies currently being used do not prevent or treat DS-AD and many reported that that their loved ones' symptoms progressed rapidly. Many reported that traditional Alzheimer's

and seizure medications do not help at all or stop working once DS-AD progresses. Some medications will help one symptom but not another and some come with unwanted side effects. Families report that some of the medications used by the general population to alleviate symptoms tend to have no impact or actually exacerbate symptoms among their loved ones with Down syndrome. Additional important treatment downsides mentioned at the EL-PFDD are mentioned below.

Medications only treat symptoms but do not prevent or slow the progression of the underlying DS-AD pathology, and the existing symptom treatments seem to have mixed results among individuals with Down syndrome

Again, this emphasizes the strong need for a medication that prevents AD symptoms and slows the progression of DS-AD.

> "*Kate is on quite a cocktail of medications. I feel like the medications we are using are helpful in managing symptoms. For me, the downside is knowing that we are just managing a whole bunch of symptoms (anxiety, depression, thyroid dysfunction, seizures, etc.) but we're not really treating the disease itself.*" - Amy, parent and caregiver of a 45-year-old with DS-AD

> After her daughter was diagnosed with moderate AD at the age of 47, *"We were told there were limited treatment options. We tried what was available, but nothing worked."* - Jean, parent and caregiver of a 50-year-old with DS-AD

Many with Down syndrome are medically complex which can create treatment issues

Comorbid conditions including type 1 or type 2 diabetes, cardiac issues, auto-immune diseases, and mental health conditions can interfere with medications and make AD symptoms worse.

> *"Many people with Down syndrome have multiple medical issues, it's neurology, it's cardiology, it's rheumatology, that a new medication might be prescribed to deal with anxiety, but you also don't want it tipping the scale if the person has diabetes or an autoimmune issue. You've got to be really careful when there's a new medication that it's not going to tip the scale with another medical issue."* - Nancy, parent of three adult children with Down syndrome including a 57-year-old with DS-AD

Administration challenges

As their condition advances, some living with DS-AD become resistant to taking their medications. Some are unable to swallow pills, making administration difficult.

> *"She gets really tired of having to take so many pills every day and she gets to the point where she is a little resistant with her staff. They used to be able to put them in a little cup and she'd just take them as she ate breakfast or dinner, and now they have to hand them to her one at a time to make sure she takes the medication because I think she's up to nine different pills a day and she just hates being structured that way."* - Amy, parent and caregiver of a 45-year-old with DS-AD

Side effects

Many medications have side effects. One parent described how their daughter experienced a withdrawal seizure from discontinuing her medications.

> "*At times she refused to take her medications altogether and she had a withdrawal seizure, I believe, from that* [clonazepam]*. We wondered if she had hypoglycemia at the time because we were managing her diabetes fairly tightly. But no, blood sugar was normal and it was just the withdrawal of that one medication that we believed was responsible for seizure."* - Mike, bereaved parent and caregiver of a daughter who passed away from DS-AD

Other treatment downsides mentioned at the meeting

Medication management can take a great deal of time and effort, and obtaining appropriate neurology referrals and care can be more difficult for those living in rural areas.

Poll 10 Result

Many in the Down syndrome community expressed a strong willingness to participate in research to improve outcomes for current and future generations of individuals and families affected by DS-AD.

During the meeting, many with Down syndrome and their family members described how they have already participated in interventional studies, natural history studies, biomarker research, and imaging studies. Many are motivated to help others who are facing the risk of DS-AD. Many expressed a willingness to participate despite significant burdens including a heavy reliance on caregivers, long-distance travel, undergoing invasive procedures and time away from work and daily responsibilities.

> *"My family are looking for every way for me not to get Alzheimer's. I participated in the LIFE-DSR research study for three years. I hope that by being in studies, something will be found to slow or stop our memory loss that comes with Alzheimer's."* - Christine, 49-year-old with Down syndrome, no AD symptoms yet

> *"He did have to take off work and skip participating in his favorite activities to receive the uncomfortable procedures. He had to stay in the hospital overnight, and he had to go to many clinical visits, but he never gave up. He wanted to see this trial to the end, not only to help himself, but others. My brother is a wonderful, caring human who decided to participate in this study because he wanted to help others. He wanted to help children with Down syndrome who might develop Alzheimer's one day. Those are his words and we should all care as much as he does."* - Erin, sibling of an individual who participated in a DS-AD clinical trial

> *"I am involved in a blood biomarker study at UC Irvine. There are no studies where I live, so I take three days off from work and fly to Irvine to do that. I tried to get into the HERO study, but it was canceled. And now I'm trying to get into another clinical trial that is supposed to start up soon. I will use my voice and my actions as long as I can to put us on a path to*

prevent the early onset of Alzheimer's disease before it wipes us out." - Karen, self-advocate with Down syndrome

Although many families expressed interest and willingness to participate in clinical trials, there are too few opportunities to participate in clinical research.

Throughout the meeting and in the submitted patient comments, those living with Down syndrome and their families expressed disappointment about the lack of research studies being conducted to find effective treatments for DS-AD and the lack of opportunities to enroll in clinical trials.

> *"There are so many things that made his Alzheimer's journey difficult, but one that stands out in particular is that there was no treatment to ease his last years or even a drug trial to choose to participate."* - Howard, bereaved parent of a son who passed away from DS-AD at 47 years of age

> *"People with Down syndrome deserve to be fully included in Alzheimer's research, clinical trials, biomarker development, and treatment access. Historically, this population has too often been excluded from research or treated as an afterthought despite facing one of the highest known genetic risks for Alzheimer's disease."* - Carol, parent and caregiver of a 12-year-old with Down syndrome

> *"It's scary and sad that people with Down syndrome have been left out of clinical trials for so long due to their disability. I understand the need for additional safety and concern with this vulnerable population, but they, too, have the right to access potentially life changing therapeutics."* - Erin, sibling of an individual who participated in a DS-AD clinical trial

During the meeting and in submitted comments, patients and families discussed the factors that would influence clinical trial participation.

Families and caregivers generally expressed a motivation to protect their loved ones and avoid subjecting them to voluntary physical or emotional burdens. The discussion aligned with the results of a recent NDSS survey[1] to understand how clinical trial engagement can be strengthened in the Down syndrome community, the results of which are available here, https://ndss.org/ds-ad-connection, and through the NDSS EL-PFDD website, https://ndss.org/el-pfdd.

Families and people with Down syndrome need to more fully understand what a clinical trial involves. Families want to have clear information about what drugs and procedures will entail, any safety concerns as well as potential physical and emotional burdens, and logistical accommodations. While there can be extra considerations when engaging the Down syndrome community in clinical research, many have, over time, become familiar with the processes, including blood draws, and some have consented and are willing to participate in procedures such as lumbar punctures.

[1] The DS-AD Connection: Clinical Trial Awareness and Participation study employed both qualitative (in-depth interviews with 18 individuals) and quantitative (a survey with 200 respondents) methods.

"The doctors were phenomenal in helping him understand the risks versus the benefits, and they made it so easy for us to understand how the trial would go, and what we could be anticipating." - Erin, sibling of an individual who participated in a DS-AD clinical trial

"Before the trial, he was frightened and tactically defensive when it came to blood draws. While routine for others, the procedure took the assistance of three technicians to complete. However, with each study visit and the gentle reassurance of the research team, Benjamin learned how to get a blood draw with no assistance." - Kristi, parent and caregiver of a 32-year-old with Down syndrome

"Susie has completed cognitive testing, blood work, PET scans, CT scans, and even two lumbar punctures. Susie truly enjoys being part of these studies. She appreciates all the extra attention, and she especially loves to share that she makes money from participating." - Dee, parent of a 38-year-old with Down syndrome, no DS-AD symptoms yet

Clinical trials need to welcome and accommodate the needs of people with Down syndrome. Families need the clinical trial teams to be experienced and respectful, and to truly value the input and perspective of the person with Down syndrome.

Kristi described what this looks like for her. *"This means they go at Benjamin's pace, give him time, talk to him, and respect him as a person whose life is important. Benjamin can feel this. That isn't always the case in other settings when he asks to remind someone, 'Hello, I'm in the room,' when someone is talking about him but not including him."* - Kristi, parent and caregiver of a 32-year-old with Down syndrome

"We're asking for sensitivity in this community and acknowledgement that people with Down syndrome have self-determination. They are valuable contributors to research, and deserve fair and equitable treatment in study participation, study recruitment, and follow-up." - Erin, sibling of an individual who participated in a DS-AD clinical trial

Other clinical trial factors were also discussed. Patients and families would like assurance that they would receive the study drug during the trial rather than a placebo, and that they would have an opportunity to continue the medication after the trial. Families would like to have access to all the testing, monitoring, and other clinical trial-related results. They need clinical trial sites to be more accessible, either closer or have more locations.

DS-AD Insight

The Down syndrome community identified other important priorities

During the meeting, additional important Down syndrome research, care, and treatment priorities were discussed.

Better DS-AD awareness, information, and resources along the entire disease spectrum

The EL-PFDD meeting highlighted a lack of DS-AD information all along the disease spectrum. There is a pressing need for a greater recognition of people with Down syndrome living longer and a higher awareness of DS-AD risk. Several caregivers who spoke at the meeting mentioned how they had very little guidance for how to best care for their loved ones with DS-AD near the end of life. Some families did their own homework and then shared this knowledge with their physicians. Families and those with DS-AD need access to more resources including day care programs, respite services, access to equipment, and appropriate residences, especially as the disease progresses.

> *"My brother passed away this February from Alzheimer's. We didn't even know about Down syndrome's high chance of Alzheimer's until recently. If there is some way to alert parents/siblings [of individuals with Down Syndrome]of the higher chance of Alzheimer's and the implications when they are born, it would have been helpful as we were unprepared as to how fast his decline and ultimate death was."* – Elizabeth, bereaved sibling of a brother who passed at the age of 53 from DS-AD

> *"I would like to know how I can expect this to progress and how to make it more comfortable for her."* - Martha, caregiver of a 47-year-old living with DS-AD

> *"There are limited day facilities to care for her, so we keep her home and have little support and are exhausted. Providing more day programs and treatment options would provide much relief for families like ours."* - Elizabeth, parent and caregiver of a 50-year-old living with DS-AD

More DS-AD research, early AD screening, and detection

Families and loved ones of those with Down syndrome pleaded for researchers to develop DS-AD diagnostic tests and treatments. Eariler detection would permit preventative interventions before symptoms begin.

> *"The speed of decline in our loved ones needs to be researched to give hope to families."* - Lisa, bereaved sibling of an individual who passed away from DS-AD at 51 years old

> *"Research focused not only on survival, but preservation of functional abilities and quality of life."* - Carol, parent and caregiver of a 12-year-old daughter with Down syndrome

> *"A national program be implemented to offer blood test for all people with Down syndrome over the age of (25?)."* -- Howard, bereaved parent of a son who passed away from DS-AD at 47 years of age

Quick access to new or repurposed medications

Despite the grim statistics of the prevalence of DS-AD, the Down syndrome community expressed a significant amount of hope that solutions are on the horizon for their loved ones. But the distance to the horizon, and to the relief effective treatments would bring, is becoming more concerning as time passes. Due to the urgent need for a therapy to treat or prevent DS-AD, families expressed

their need for quicker access to new or repurposed medications that show the most promise and have the greatest potential to help their loved ones facing DS-AD.

> *"I hope that the FDA, CMS, biopharma sponsors, families and patient advocacy organizations (such as NDSS, Global Down Syndrome and National Down Syndrome Congress) will come together and address this major crisis for our adults with Down syndrome."* - Hampus, parent and caregiver of a 12-year-old with Down syndrome

> Howard would like, *"All individuals with Down syndrome who are diagnosed with Alzheimer's be allowed to take any Alzheimer's drug that has been approved for the general population without a secondary drug trial for this special group alone."* - Howard, bereaved parent of a son who passed away from DS-AD at 47 years of age

> *"I would be in a trial right now if they would let me! I would have to travel a very long way, but I would do it if they would let me be in a trial. I already had cortisone shots in my back so I am not afraid of a lumbar puncture. I would just hope I get the medicine and not the placebo. I would want a medicine to help me think and speak better. I want my charisma back."* - Kate, 45-year-old self-advocate, blogger, and friend, living with DS-AD

In closing:

> *"As you know, we are at a much greater risk for the early onset of Alzheimer's than the general population. It is a huge, ugly cloud that hangs over us and our families. We are about to lose a whole generation of adults with Down syndrome to this ugly disease. We cannot let this happen."* - Karen, self-advocate with Down syndrome

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Finally, and most importantly, we are grateful to members of our community whose lives have been directly impacted by DS-AD and chose to let their voices be part of our meeting and this report. Thank you to our many speakers, panelists, and callers for openly sharing your lived experiences of what it is like to live with DS-AD and the very real threat of DS-AD. As a community, we feel the magnitude of the opportunity we have to ensure that the perspective of individuals with Down syndrome and their caregivers are part of the drug development and regulatory processes. Our hope is that this meeting will encourage additional research, foster awareness of the unique aspects of DS-AD, and lead to safe and accessible treatment options for our loved ones with Down syndrome and Alzheimer's disease.