GLOBAL FOUNDATION for PEROXISOMAL DISORDERS

GFPD

VOICE OF THE PATIENT REPORT

Peroxisomal Disorders

Externally-Led Patient-Focused Drug Development Meeting

PUBLIC MEETING: **MAY 28, 2024**

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THE GLOBAL FOUNDATION FOR PEROXISOMAL DISORDERS

VOICE OF THE PATIENT REPORT: PEROXISOMAL DISORDERS

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INTRODUCTION/EXECUTIVE SUMMARY

Meeting Overview

This report focuses on the findings from the Externally-Led Patient-Focused Drug Development (EL-PFDD) meeting held on May 28, 2024. The EL-PFDD meeting for peroxisomal disorders (PD) was hosted by the Global Foundation for Peroxisomal Disorders (GFPD), in a coordinated effort with the FDA-led PFDD meetings to more systematically engage patient perspectives on their experiences and current available therapies used to treat their conditions. This meeting identified topics, symptoms, and challenges deemed most impactful by patients, families, and caregivers. The report also contains insightful survey responses and personal stories of individuals affected by a PD. Due to speech and cognition challenges in the various PD, the majority of the information collected for this effort was gathered from family caregivers (parents and legal guardians) of individuals affected by PD.

A total of 281 individuals were present for the meeting. These included individuals diagnosed with a PD, parents of diagnosed patients, siblings of people diagnosed with a PD, community advocates, and professionals in the field. **The majority of the families represented patients who were diagnosed with Zellweger spectrum disorder (ZSD),** with some families diagnosed with D-bifunctional protein (DBP) deficiency, and one family diagnosed with alpha-methylacyl-CoA racemase (AMACR) deficiency. There were some families with more than one member living with a PD and disease severity ranged from mild to severe impacts on daily life. Existing treatments were generally reported to have varying success in terms of managing symptoms, with many experiencing unmet medical needs. A total of 35 individuals diagnosed with a PD were in attendance at the meeting. Eighty-two primary caregivers (parents/step-parents/legal guardians) of both living and deceased individuals diagnosed with a PD attended the meeting. A link for the meeting recordings can be found here.

Overview of Peroxisomal Disorders

Peroxisomal disorders represent multi-organ disorders due to the involvement of Peroxisomes in essential metabolic processes across various cells. (Braverman et al., 2016; Steinberg et al., 2006). PD can be divided into 2 major categories: peroxisome biogenesis disorders (PBD), and single peroxisomal enzyme/protein deficiency disorders (SEPD).

PBD are caused by pathological variants in one or multiple of the 14 distinct PEX genes, which encode for peroxins, proteins involved in multiple peroxisomal functions (Steinberg et al., 2006; Wanders & Waterham, 2006; Waterham & Ebberink, 2012). PBDs can be separated into Zellweger spectrum disorders (ZSD) and rhizomelic chondrodysplasia punctata (RCDP). ZSD represent a heterogeneous group of diseases originally known as Zellweger syndrome (ZS), neonatal adrenoleukodystrophy (NALD), infantile Refsum disease (IRD), and Heimler syndrome (Biase et al., 2020; Klouwer et al., 2015).

Individuals with single enzyme or protein deficiency disorders (SEPD) typically have peroxisomes within their cells, however, there are generally defects in the function of individual enzymes, membrane transporters, or other proteins within the peroxisome. SEPD disorders include acyl-CoA oxidase (ACOX1 or ACOX2) deficiency, alpha-methylacyl-CoA racemase (AMACR) deficiency, D-bifunctional protein (DBP) deficiency, X-linked adrenoleukodystrophy (X-ALD), adult Refsum disease (ARD), and several others (Hacia, 2023; Wanders & Waterham, 2006). Patients with SEPD may present less severely than those with PBD, however, this varies based on the severity of each individual's disorder (Hacia, 2023; Wanders & Waterham, 2006).

Overall, the approximate incidence of PD is 1 in 5,000 newborns, with X-ALD being the most common (1 in 17,000 births), and ZSD being the next most common (1 in 50,000 births) (Waterham, 2016; Steinberg, 1993). Given that there is already an existing Voice of the Patient Report for X-ALD, the primary focus of this report will not be on X-ALD.

Clinical Features of Peroxisomal Disorders

Symptom presentation in PD can be heterogeneous across different PD as well as within the same disorder. Neurological symptoms may present as low muscle tone, mobility symptoms, intellectual disability, seizures, balance issues, brain malformation, and leukodystrophy, which refers to deterioration of white matter in the brain (Steinberg et al., 2003). Decreased muscle tone may affect motor skills and mobility, respiratory distress, and poor feeding. Sensory impairments manifest as hearing and/or vision loss (Steinberg et al., 2003). Adrenal insufficiency may also occur in patients causing increased fatigue and low blood pressure (Berendse et al., 2014). Gastrointestinal symptoms include constipation, diarrhea, as well as liver dysfunction. Other symptoms may be present, including but not limited to: renal symptoms, respiratory symptoms, dental symptoms, and skeletal abnormalities.

Diagnosis of Peroxisomal Disorders

PD can be diagnosed through biochemical testing and/or genetic testing. Diagnosis may occur either during the pregestation phase (usually during in vitro fertilization), prenatally, in the neonatal period, or after the presentation of symptoms (Braverman et al., 2016).

Biochemical testing involves the detection of elevated very long chain fatty acids (VLCFA) and related metabolites (Braverman et al., 2016; Ferdinandusse et al., 2016; Volmrich et al., 2022). After evaluation of biochemical markers in body fluids, confirmation in cultured skin fibroblasts by measuring specific peroxisomal metabolites is important to establish diagnosis (Volmrich et al., 2022).

If a PD is suspected based on family history, biochemical testing, or symptom presentation, a targeted multigene panel for PD can confirm a diagnosis (Braverman et al., 2016).

Prenatal diagnosis of PD can be carried out by biochemical or genetic testing on cultured cells (Braverman et al., 2016). Preimplantation genetic testing can also be conducted during in vitro fertilization (IVF) to examine embryos for PD before transfer.

Newborn screening for X-ALD is now on the Recommended Uniform Screening Panel (RUSP) and several screening programs worldwide, which can be used as a first step in the diagnosis of a PD (Braverman et al., 2016; Olney et al., 2023). Newborn screening for X-ALD allows for early diagnosis of elevated VLCFA (Volmrich et al., 2022). After the detection of VLCFA in newborn screening, X-ALD is either confirmed or ruled out via genetic testing. Once X-ALD is ruled out, testing for biochemical or genetic markers in body fluids to detect other PD may be performed (Braverman et al., 2016; Biase et al., 2020).

Current Treatments of Peroxisomal Disorders

Currently, no treatments exist targeting PD. Treatment protocols are relatively limited and geared toward alleviating individual symptoms across multiple organ systems. Anticonvulsants are used to manage seizure activity in epilepsy. Feeding difficulties may result in gastrostomy tube (g-tube) feeding for nutrition support (Braverman et al., 2016). Supplementation of vitamins A, D, E, and K is recommended for fat absorption issues (Braverman et al., 2016). Hydrocortisone replacement is usually prescribed for patients with adrenal insufficiency (Braverman et al., 2016). Vision problems are generally addressed by corrective lenses, or, if present, cataract surgery to preserve sight (Steinberg et al., 2003). For auditory function, patients use hearing aids and cochlear implants (Braverman et al., 2016). Physical and occupational therapy may help encourage progress and navigate motor delays. Liver dysfunction is treated with vitamin K supplementation and cholic acid (Berendese et al., 2016; Braverman et al., 2016). Fractures and decreased bone mineral density can be treated with calcium, vitamin D supplementation, and other medications to aid in bone mineralization. Docosahexaenoic acid (DHA), an omega-3 fatty acid, may be used to enhance brain and retinal activity (Braverman et al., 2016; Martinez, 1992; Paker et al., 2010).

New therapies for PD are an active area of scientific research. Current models of in vitro and whole organisms are the groundwork of clinical studies for ZSD patients (Argyriou et al., 2021; Braverman et al., 2016).

Meeting Inputs

The EL-PFDD meeting took place as a part of the GFPD Family and Scientific Meeting in Washington DC. This town hall-style meeting consisted of live polling, prepared testimonies by patients and families, and open discussion by patients and family members of patients. The meeting was moderated by one primary facilitator and three assistant facilitators who managed time, assisted with participant discussion, and moderated the online (Zoom) discussion. Audience participants were asked about peroxisomal symptoms, daily impacts of symptoms, current treatment regimens, and what they would look for in an "ideal treatment." For each topic, a panel of patients or caregivers described lived experiences related to the topic, followed by live polling of related questions, and a semi-structured, large-group facilitated discussion with patients, caregivers, and patient representatives attending in-person and virtually via Zoom webinar.

Live polling was conducted via the Poll Everywhere® application for electronic devices. At the beginning of the meeting, participants were instructed to download the application on their electronic devices. Individual and group responses were downloaded from the Poll Everywhere® platform and included in this report when applicable.

The entire meeting was audio- and video-recorded. The audio recordings were transcribed, and used as the primary source of data for this report, along with the polling data.

Participants joining the meeting via the live Zoom webinar were able to participate in the live polling and submit comments via Zoom chat throughout the discussion. The Zoom chat comments were also downloaded and used as data for the report.

In addition to the data collected at the meeting, we conducted preliminary data collection with patients and caregivers to better organize the agenda and topics discussed during the meeting. First, we conducted four online focus groups (via Zoom conference), each consisting of 10-12 caregivers (42 total) of patients with a PD. Each focus group lasted approximately two hours. Additionally, two interviews took place with individual caregivers, lasting approximately one hour. During both focus groups and interviews, a semi-structured interview guide (See Appendix) was used to ask caregivers questions about the meeting topics described above. All focus groups and interviews were audio- and video-recorded. The audio recordings were transcribed and used as a secondary source for this report.

Next, we used the themes generated from the focus groups and interviews to develop and conduct an online survey of related topics with PD patients and caregivers (See Appendix). Sixty-four patients and caregivers participated in the survey. Results of the survey were used as a secondary data source for this report.

For all data sources, caregivers of living or deceased PD patients and adult PD patients without cognitive impairment were eligible for the study. The following PD diagnoses were included in this study: Zellweger spectrum disorder (ZSD), acyl-CoA oxidase (ACOX1 or ACOX2) deficiency, D-bifunctional protein (DBP) deficiency, and methyl acyl-CoA racemase (AMACR) deficiency. Patients diagnosed with X-linked adrenoleukodystrophy (X-ALD), adult Refsum disease, and rhizomelic chondrodysplasia punctata (RCDP) were excluded from the study because of the existing treatments and distinct differences in symptom presentation compared to ZSD and the other SEPDs (Braverman et al., 1993; Kumar & De Jesus, 2023; O'Sullivan-Fortin et al., 2022).

Report Overview and Key Themes

According to our discussions with patients and family caregivers, the symptoms affecting patients with PD most in their daily lives included sensory (hearing and/or vision) loss, cognitive and intellectual disability, mobility and other physical symptoms, and leukodystrophy, or deterioration of white matter in the brain. For some patients, particularly those that were more severely affected or experienced a regression, seizures, respiratory symptoms, and gastrointestinal issues, if they were present, were reported as extremely burdensome symptoms in patients' everyday lives. **Of all of these symptoms, vision loss (often in conjunction with hearing loss) appeared to have the biggest impact.**

Many caregivers who were present at the meeting were caregivers of patients who had passed away from the effects of their PD. In general, **caregivers of deceased patients reported that their children had a more severe form of the disorder,** with the exception of caregivers whose child passed away in adulthood. These caregivers, in some cases, reported different symptoms and impacts compared to caregivers of patients who were still alive. For example, although liver disease related to PD was not reported as a symptom that has an impact on patient's daily lives, many caregivers of deceased patients stated that the **liver disease was ultimately what their child succumbed to at the end of their life or what required frequent hospitalizations for their child.**

Among the daily life impacts of PD on affected individuals, the most common was the inability to independently complete activities of daily living, such as bathing, dressing, toileting, brushing teeth, walking, and eating. These were particularly evident in patients with significant intellectual disability. For adult patients with less cognitive impairment, instrumental activities of daily living, such as shopping and transporting themselves, required the assistance of others. Other impacts of PD symptoms included considerable effects on social interactions, overall executive functioning, as well as school or work performance. In some cases, certain symptoms were reported to exacerbate other symptoms or cause physical injury. Additionally, both patients and caregivers reported a tremendous emotional toll from symptoms. In short, the impacts of PD on the daily lives of both patients and caregivers are profound and broad.

Current treatment and overall management of PD is solely symptomatic and primarily includes pharmacological treatment, supportive therapies, and assistive devices/resources. The majority of the patients and caregivers reported treating sensory loss, mobility symptoms, seizures and gastrointestinal symptoms with one or a combination of these therapies. Most patients and caregivers shared that they do not feel like the PD affecting them or their loved one is well-managed with current treatment options due to side effects, lack of effectiveness, and the burden of administration. Additionally, in most cases, individual treatment needs increased over time for PD patients. Overall, current management of PD is fragmented and treatments for individual symptoms often do not account for the overall disease impact, resulting in treatment ineffectiveness and additional side effects. However, until more effective treatments for PD are developed, patients and families continue to rely on these services as medically necessary.

Patients and caregivers described challenges in coordinating treatment of PD with medical providers, often because their doctors did not have a thorough understanding of the severity, progression, or combination of symptoms, as well as limited natural history and treatment option availability. This limited understanding of PD often resulted in ineffective treatments or even the emergence of new issues or the worsening of preexisting issues.

The most common clinical outcomes desired for future clinical trials, according to patients and caregivers, were related to improved mobility, both gross and fine motor, improvement of vision and hearing, improved gastrointestinal symptoms, reduced bleeding issues, improved intellectual ability, reduction of seizures with minimal impact on alertness, and improvement of respiratory symptoms. Desirable clinical outcomes also depended on improvment of symptoms that have the most impact.

This meeting identified the biggest impacts of the disorder, guidance for future clinical instrument development targeted for PD, clinical trial design, as well as strategies to improve accessibility to clinical trials for patients and families. Current treatments for PD are exclusively symptomatic, and there is a considerable need for better treatments that comprehensively address the broad variation of symptoms and their impacts on daily life, independent activities, and overall quality of life. This Voice of the Patient Report for Peroxisomal Disorders provides a comprehensive account of these findings and applies them to the development of a thorough benefit-risk analysis for future clinical trials.

DISEASE SYMPTOMS AND DAILY IMPACTS THAT MATTER MOST TO PATIENTS

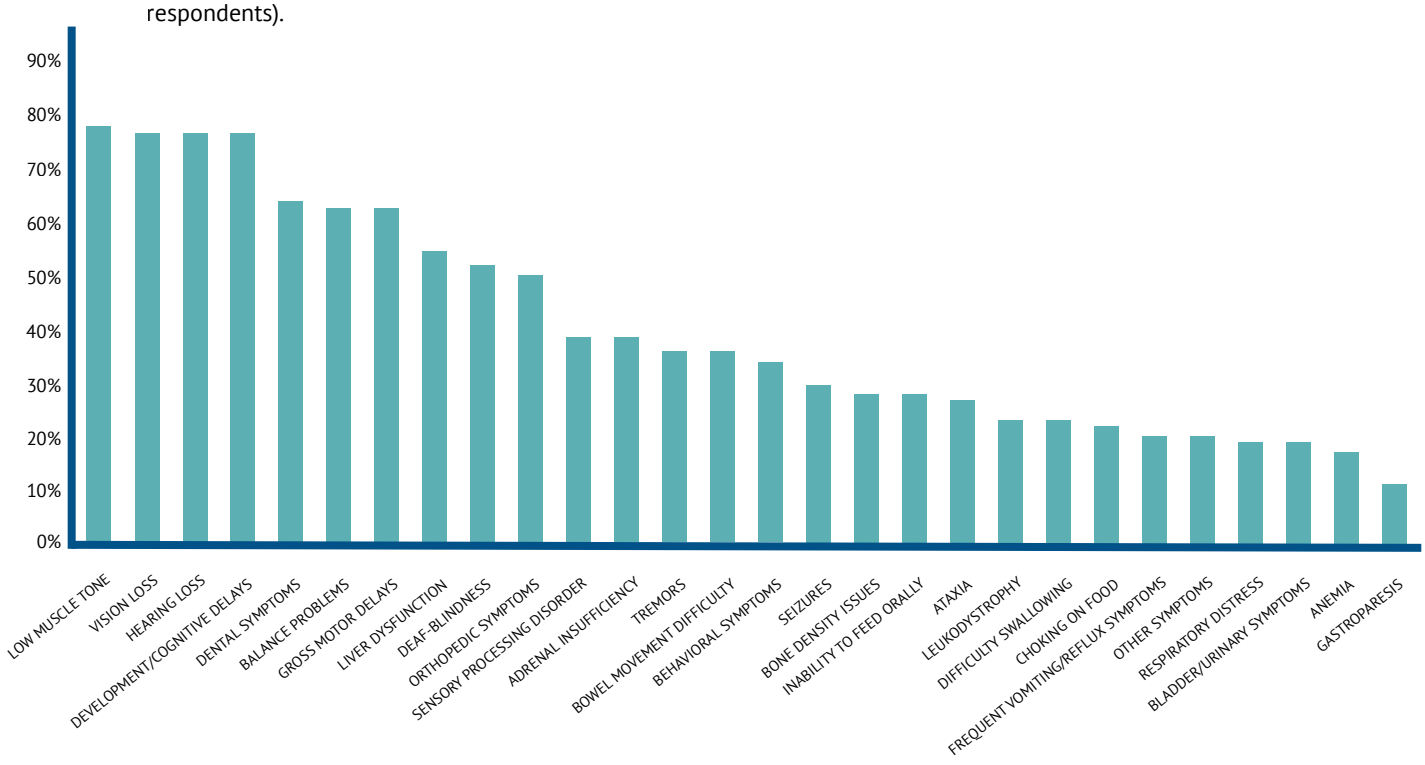
Thank you to our panelists: Angela Feist, Vicky Maag, Daniela Vargas Ramirez, Katie Sacra, Joleen Burdick, Erasmo & Melinda Torres, Andrew Betzer, Lauren Danner, Patty DelSorbo, Suzanne Collins, Jasmine Buchanan

Symptoms

According to our online survey, patients with PD experienced many symptoms from multiple organ systems, with an average of **eleven symptoms per patient**, and nine symptoms per patient being the most frequently reported number of symptoms experienced by a patient. The highest number of symptoms reported was 27 for one of the patients.

Symptoms affecting patients with PD included low muscle tone, hearing loss, vision loss, deafblindness, sensory processing disorder, developmental/cognitive delays, gross motor delays, orthopedic symptoms, balance problems, tremors, seizures, adrenal insufficiency, liver dysfunction, inability to feed orally (difficulty swallowing or choking on food), frequent vomiting, bowel movement difficulty, behavioral symptoms, bone density issues, dental symptoms, leukodystrophy, respiratory distress, and other symptoms. **The most frequently reported symptoms of patients were low muscle tone, vision loss, hearing loss, and intellectual disability (Figure 1).**

Figure 1: Frequency of Symptoms Experienced by Patients Diagnosed with Peroxisomal Disorders (n=64 respondents).



Frequency (% of total respondents, n=64) of symptoms in patients with a peroxisomal disorder, as reported by patients with a peroxisomal disorder (n=2) or patients represented by their caregivers (n=62) in the online survey.

Vision Loss and Hearing Loss

Our online survey found that vision impairment was one of the most frequently reported symptoms and one of the top ranked symptoms in having the biggest impact on the daily lives of patients with PD. Vision symptoms appeared early, and changed over time. According to one caregiver, most general vision symptoms were evident as early as six to nine months of age, with some symptoms appearing at birth. Vision symptoms included retinal degeneration and cortical visual impairment. Nystagmus (rapid and repetitive involuntary eye movements) was reported in several patients, with many patients also developing cataracts (clouding of the eye lens) over time.

> ***"His vision was CVI [cortical visual impairment] at first, but also started to develop retinal degeneration." - Anonymous polling response from caregiver***

Patients and caregivers characterized experiences living with these vision symptoms. One caregiver reported "tunnel vision" (class of peripheral vision) in their adult child with a PD and that if there was anything below their direct field of vision, they were told to be aware and proceed with caution. An adult patient with ZSD also shared their experience with vision loss:

> ***"My blind spots are kind of like Swiss cheese... So basically if a face is more than two or three feet away from me, my brain knows something is supposed to be there so it fills it in with the color of the person's skin. Or if I'm reading a book or a sign or something, it fills it in with the background color because my brain knows something is supposed to be there when it's constantly trying to adapt to what I'm looking at." - Adult patient with ZSD***

Vision loss was reported as the symptom with the greatest impact by patients and caregivers of living patients, however, this was not the case among the reports from caregivers of deceased patients. No caregivers of deceased patients reported vision loss as the most highly ranked symptom affecting their child's daily lives.

Sensorineural hearing loss was also a frequently reported symptom in PD and one of the top-ranked symptoms in having the biggest impact on the daily lives of patients with PD. Hearing loss was often bilateral and varied from moderate to profound at the time of the hearing loss diagnosis.

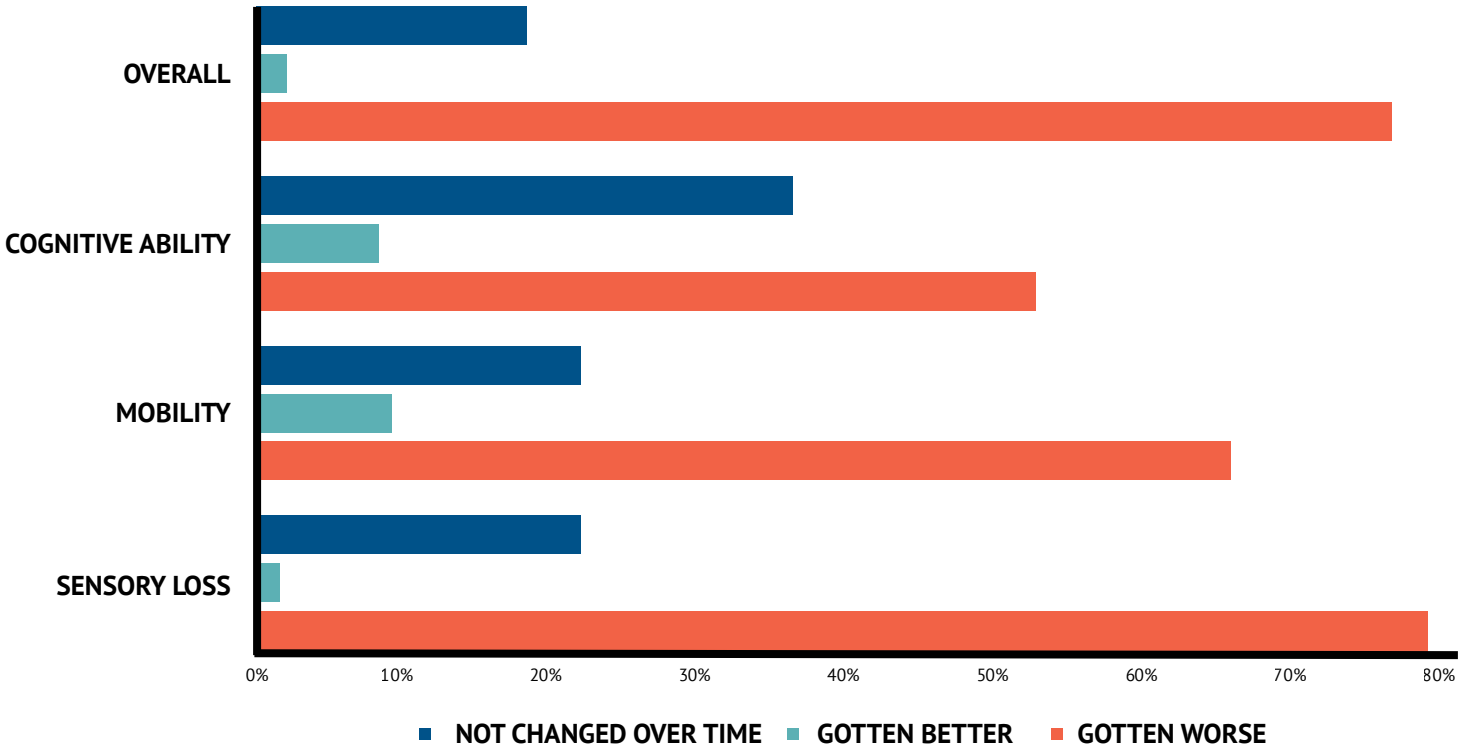
> ***"He passed a newborn hearing screen, and now has severe hearing loss which was diagnosed at maybe like 14 months or 15 months. So I think the hearing is the big one that he's lost." - Mother of child with ZSD***

Vision and hearing loss appeared to be progressive over time, with gradual and acute changes observed. For vision loss, many patients would lose complete vision over time.

Although some patients experienced primarily vision or hearing loss, most caregivers and patients reported with the loss of both, which resulted in more profound impacts than either of these symptoms alone. Furthermore, most caregivers and patients who took part in the live polling reported that both vision and hearing loss worsened over time (**Figure 2**).

> ***"After over a decade of stable vision, [my adult child] woke up one morning and told me 'It's very dark and I cannot see.'" - Mother of adult with ZSD***

Figure 2: Progression of Symptoms over Time Across Participants.



Symptom progression (gotten better, gotten worse, or not changed) over time across live polling participants. Symptoms included sensory loss, mobility, cognitive ability, and overall progression of the disease from the live polling questions during the town hall meeting. For overall symptoms (n=48), cognitive ability (n=47), mobility (n=53), and sensory loss (n=60).

Mobility

During all phases of data collection, patients and caregivers discussed orthopedic symptoms, gross and fine motor impairment, and other mobility symptoms affecting patients' daily lives. Symptom specifics included difficulty or inability with ambulation, movement-related fatigue, tremors (unrelated to the seizure disorder), hypermobile joints (increasing risk of pain, stiffness, and physical injury), spasticity (resulting in muscle stiffness and involuntary spasms), club feet (causing feet to bend inward and down), hip dysplasia (affecting hip joint stability, causing pain and limited mobility), other motor delays, and balance problems. Mobility and orthopedic symptoms were generally related to central hypotonia (low muscle tone or muscle "floppiness" caused by neurological dysfunction) or other neurological impairments, low bone density, and bone or joint malformations.

Among symptoms ranked for the biggest impact on daily lives, orthopedic symptoms, balance issues, and gross motor delays, collectively, were ranked within the top three symptoms in 27 out of 63 survey respondents.

> ***"I presented issues with my balance and my coordination as well as other symptoms such as muscular weakness, hypotonia, hypermobile elbows and knees, spasticity and callus by foot...Then I had problems with my knees because of the weakness I have and the hypermobility." - Adult patient with ZSD***

Low muscle tone was often present at birth and persisted throughout the course of a patient's life. According to our live polling, two-thirds of all participants reported that mobility symptoms worsened with time (**Figure 2**).

Intellectual Disability

Intellectual disability affects a broad range of individuals with PD according to conversations with caregivers, with the earliest impacts reported before 2 years of age and continuing on into adulthood. Caregivers described intellectual disability in their child as *"developmental delays"* in early age and later as *"cognitive delay"* as patients grew older, and these delays were often described as "severe" by multiple caregivers. Among symptoms ranked for the biggest impact on daily lives, intellectual delays or disability were ranked within the top three symptoms in 25 out of 63 online survey respondents. This ranking was primarily observed in caregivers reporting on their living children with PD as opposed to caregivers reporting on a deceased child with PD.

One caregiver shared that a school psychologist reported that the caregiver's teenage child with PD was at a *"two- to three-year-old level of cognition."* Another caregiver reported that their adult child lacked comprehension of concepts such as time due to their intellectual disability. Most live polling participants indicated that their or the child's intellectual disability had worsened over time (**Figure 2**). However, it is possible that the specific ability did not change over time, but rather the disparity between the cognitive ability of the patient with PD and that of their age-matched peers increased over time due to delayed intellectual development in patients.

Seizures

Seizure disorder was reported in 30% of PD patients, according to our online survey. According to our preliminary focus groups and during the town hall meeting, the types of seizures that were observed in PD patients included both full-body and more focused tonic seizures (sudden stiffening or tensing of muscles), clonic seizures (repetitive and uncontrolled muscle spasms), tonic-clonic seizures, and atonal seizures (also known as drop seizures, a temporary loss of muscle tone, causing limpness and increased fall injury risk). Seizures could start as early as the newborn period, but in many patients, would begin later in life. Seizure intensity ranged from mild presenting as tremors and spasms to severe epileptic seizures. In one case, seizures would precede apnea (temporary cessation of breathing) episodes.

Although seizures were not as highly rated by survey respondents and polling participants as having a large impact on patient daily lives, notably, seizures were more frequently reported by caregivers of deceased patients as opposed to caregivers of living patients in our online survey. Caregivers representing deceased patients also reported seizures as their top-ranked symptom regarding daily impact in the online survey. Considering that severe patients typically have a shorter lifespan than less severe patients, these findings suggest that seizure disorder may be more common and more impactful in more severe PD patients compared to more mildly affected patients.

"[Our child's] seizure was very small, but when I saw it, I knew right away that it was proof positive, undeniable, and right before my eyes…Once the results were read, we were told that his seizures were pretty much constant. The worst ones manifested heavily, but they were almost always there…that all he could really do is have a seizure, recover from it, and then have another one." - Father of deceased child with ZSD

Gastrointestinal Symptoms

Feeding and Other Gastrointestinal Symptoms

Low muscle tone in PD was associated with difficulty in swallowing and a subsequent choking risk. Low muscle tone also contributed to esophageal reflux (backwards flow of stomach contents to esophagus), chronic vomiting, as well as chronic constipation. Diarrhea was also reported, although less frequently, and likely related to possible fat malabsorption due to bile acid deficiency.

Although feeding symptoms were only reported by 28% of survey respondents, respondents representing deceased patients reported a greater impact of feeding issues in the daily lives of PD patients compared to respondents representing living patients.

Liver and Gastrointestinal Bleeding

Symptoms related to liver dysfunction were also reported by town hall participants. Beyond chronically elevated liver enzyme levels and liver enlargement (hepatomegaly), caregivers reported the development of ascites (fluid buildup in the abdominal cavity) and bleeding issues related to overall liver dysfunction and portal hypertension (increased pressure in the blood vessel that connects the gastrointestinal tract to the liver).

Gastrointestinal bleeding issues in PD appeared to be caused by varices (swollen blood vessels) forming from portal hypertension due to liver dysfunction. Esophageal varices were reported to be present in patients with PD by multiple caregivers.

> ***"My [child] has portal hypertension and esophageal varices, both of which caused GI bleeding issues...We've seen him throw up a large amount of blood due to a burst varyx in his esophagus." - Father of child with ZSD***

Several other caregivers stated that their child had gastrointestinal bleeding but did not report the cause of the bleeding.

Dental Symptoms

Dental symptoms in PD were briefly described by a caregiver of two adults with ZSD. These dental symptoms included significantly delayed appearance of and inadequate enamel development on adult teeth.

Respiratory Symptoms

In general, respiratory symptoms appeared to primarily affect patients who died at younger ages (<10 years). The inability to breathe without support was often attributable to low muscle tone, and several patients required the placement of a tracheostomy tube to support breathing. As a result of the tracheostomy placement, patients were often susceptible to more respiratory infections such as influenza or respiratory syncytial virus (RSV), which, due to the low muscle tone, would often progress to pneumonia.

> ***"The symptoms that had the biggest impact on [my child's] daily life and activities were his respiratory symptoms... [my child's] respiratory symptoms included a chronic respiratory illness like RSV, pneumonia, the flu, you name it." - Mother of deceased child with ZSD***

Leukodystrophy

Leukodystrophy, or white matter degeneration in the central nervous system, was often present in patients with PD and generally manifested as the progression of disease symptoms or the development of new symptoms. Leukodystrophy was reported in 23% of PD patients and was the second most frequently ranked symptom regarding daily impact among respondents representing PD patients who were deceased in our online survey. Three out of twelve respondents representing deceased individuals with PD ranked leukodystrophy as their child's most impactful symptom.

> ***"But with a leukodystrophy, with an aggressive leukodystrophy, that everything went in a matter of months, he could no longer stand up. He could no longer play, just until the loss of his smile." - Mother of deceased child with ZSD***

As shown earlier, a majority of polling participants reported that their/their loved one's symptoms or overall disease had worsened with time (82% reported worsening of sensory loss, 68% reported worsening of mobility symptoms, 54% reported worsening of cognitive ability, and 79% reported worsening of overall disease symptoms); this may have at least partially been due to leukodystrophy (**Figure 2**). Some polling participants reported symptoms and conditions not changing over time, while very few participants reported that symptoms and overall disease progression improved over time.

The conversations surrounding disease progression during the town hall meeting characterized leukodystrophy in PD as having a varying pace across patients and over time. Progression of the disease was generally described as the loss of a skill or ability to do certain activities, and these changes were often referred to as either a "gradual change," "rapid change," or a "sudden change." PD symptoms also showed varying degrees of progression.

> ***"Testing would show that [my child] had gone from a moderate [hearing] loss to a severe loss overnight." - Mother of adolescent with ZSD***

> ***"Very soon his seizures began to worsen, no longer a small tremor, but a large quake that ravaged his entire body." - Father of deceased child with ZSD***

PD Symptoms with the Greatest Impact on Patients

When participants were asked which symptoms had the most significant impact on their or their children's lives during the live polling of the town hall meeting, sensory impairment was reported to have the highest impact on patients' lives by most participants, with 27% of participants reporting deafblindness to be the most significant impact on patients' lives. Twenty-two percent reported developmental and cognitive symptoms to have the most impact, 15% reported low muscle tone, 9% reported seizures/neurological symptoms, and 8% reported GI/feeding difficulties to have the most significant impact on their daily lives (**Figure 3**).

Figure 3: Symptoms Having the Most Significant Impact on Patient's Daily Lives.

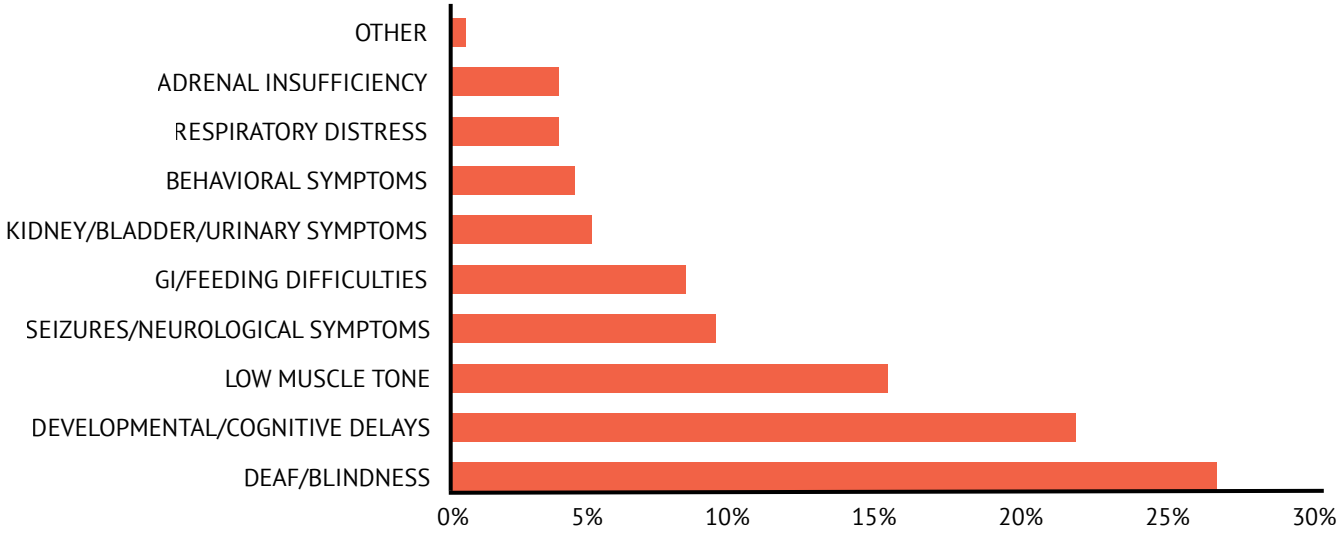
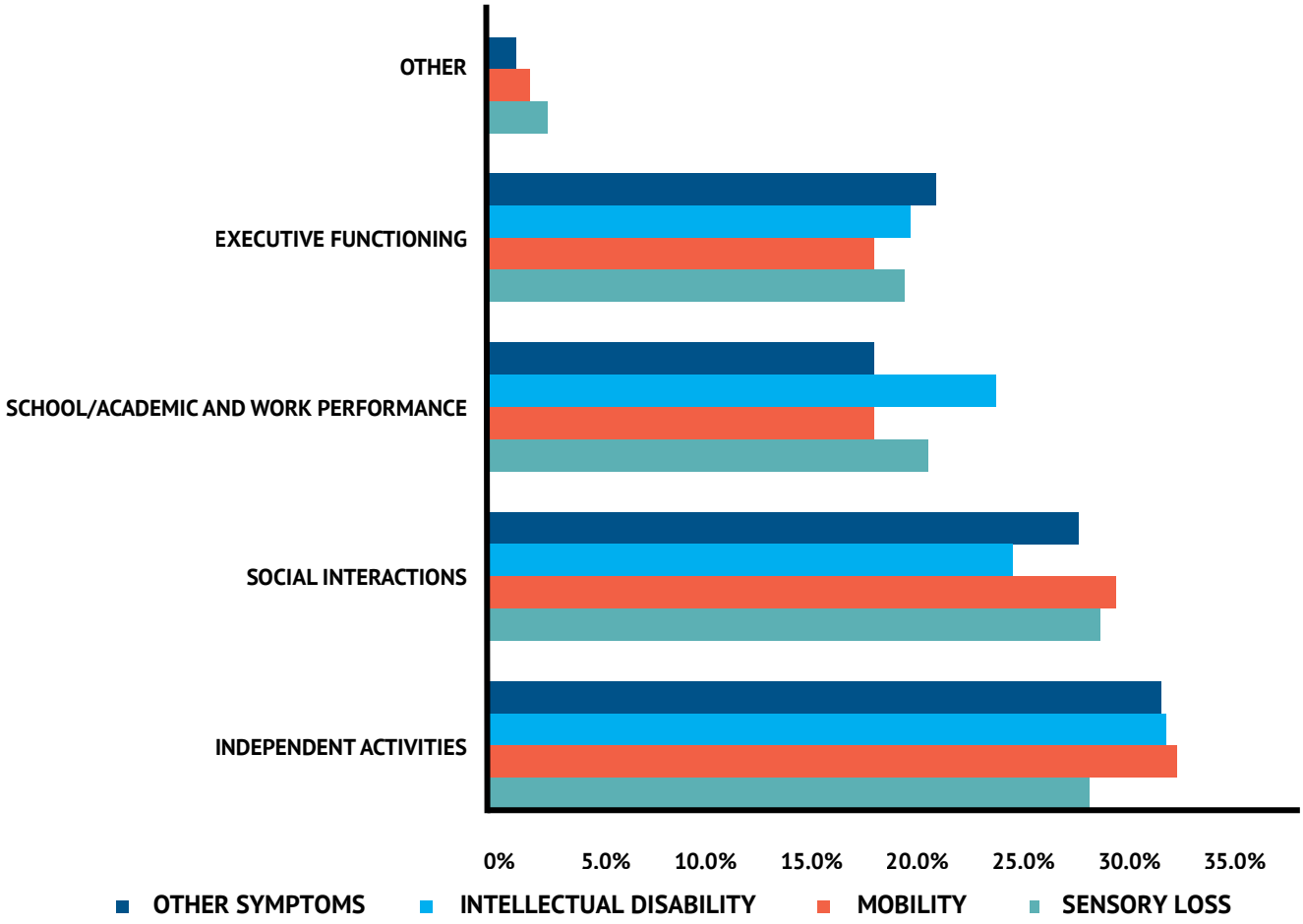


Figure displaying the symptoms with the most significant impact on patient's daily lives during live polling at the town hall meeting (n=57).

Specific Impacts of Peroxisomal Disorders

The specific impacts of PD and its symptoms that were discussed in our focus groups, surveys, and town hall discussion included daily impacts, which are outlined in **Figure 4**. There were also acute, often clinical impacts in PD that required immediate intervention, as well as various emotional impacts.

Figure 4: Daily Impacts of PD Due to Different Symptoms.



Specific activities affected by sensory loss (n=61), mobility (n=57), intellectual disability (n=47) and other symptoms (n=50), according to live polling.

Daily Impacts

Independence in Activities of Daily Living

According to our live polling and online survey, the most frequently reported impact of PD was its effect on independent activities of daily living. This included personal care, maneuverability, feeding, and other activities such as transportation. Caregivers reported a number of tasks that their patient with a PD could not do independently and was therefore reliant on their caregivers to assist, even in adolescence and adulthood.

> ***"[Our child is] 27 years old, and my day starts at 5:30. I take half an hour to myself before I start to help him to live his daily life. I help him get off the bed, help him change, wash and dress him and get him ready to take him outside to get on the bus because he can't do it by himself. He needs me to do everything, not just me, but also his mother, you know. So, we constantly... he needs us for his daily life routine."***
> ***- Father of adult patient with ZSD***

These impacts on independent activity were reported as a result of sensory loss (28% of live polling participants, n=63), mobility (32% of participants reported impacts of mobility, n=57), intellectual disability (32% of participants, n=47), as well as other symptoms (**Figure 4**).

The impact of vision and hearing impairment, mobility, and cognitive ability, both individually and collectively, was considerable on independent activities of daily living, according to the discussion from caregivers and patients. The impacts of both gross motor and fine motor symptoms were seen in recreational activities as well as activities of daily living.

As a result, individuals with PD are reliant on caregivers, other individuals, and assistive devices (including wheelchairs, strollers, walkers, canes, glasses, cochlear implants, hearing aids, orthotics, and/or service animals) to aid in their daily activities. Caregivers shared their experiences with vision and hearing loss affecting independent behavior in their children with PD. Additionally, mobility issues and sensory losses increased the physical safety risks when not monitored by a caregiver.

> ***"As a result, [my child] is completely reliant on me, my husband, and caregivers, whether in his wheelchair or when walking with assistance... We consider him dangerously mobile, and he requires constant supervision to prevent injury...And as he gets older, taller, and heavier, providing him with opportunities to be active is increasingly difficult for us as parents to physically assist with and this shrinks his world even further."***
> ***- Mother of adolescent with ZSD***

Adults with PD shared their struggles with independence due to their sensory losses and mobility issues.

> ***"Because I have to rely on external support and also, I have to rely on another human being or a walker or I don't know." - Adult patient with ZSD***

Although independent activities of daily living were impacted in adult patients with PD without intellectual disability due to sensory losses and mobility challenges, intellectual disability was described to be the primary factor in affecting a patient's independence, according to many caregivers.

> ***"Even without deafblindness, sensory issues, behavior issues, [our child's] significant intellectual challenges impact her daily living activities." - Mother of adolescent with ZSD***

Seizures also affected an individual's independent movement.

> ***"...Drop seizures, orthopedic bone abnormalities, intellectual disability and poor motor control make independent mobility nearly impossible without a significant safety risk."***
> ***- Mother of adult with ZSD***

In several cases, progression of symptoms due to leukodystrophy contributed to the loss of abilities related to activities of daily living.

"She does not walk anymore; she no longer gets up out of bed on her own."
- Anonymous polling response from caregiver

Communication Impacts

Difficulties with communication, social interactions with families and friends, and meeting new people were considerable impacts in PD, as reported by caregivers and patients. During our live polling, 29% of participants reported social interactions as the biggest impact due to sensory loss, 30% of participants reported it as the biggest impact due to mobility symptoms, 24% percent of participants reported it as the biggest impact due to intellectual disability, and 28% of participants reported it as the biggest impacts due to other symptoms in PD (**Figure 4**).

Caregivers reported that both expressive and receptive communication were impacted by PD. Sensory loss, especially hearing loss, affected verbal communication.

> ***"With no sound coming to [our child's] ears, she stopped talking, stopped laughing, and stopped communicating with us. Instead, she gave us silence." - Mother of child with ZSD***

Many participants reported that the PD had a significant impact on patients' ability to communicate their needs, feelings, or if they were experiencing pain. This presented difficulties, confusion, and frustration for caregivers when managing their child's care.

> ***"[Our child], being non-verbal, greatly delays his ability to express his wants, his needs, and emotions...He relies on facial expressions, body language, and sounds to convey meaning. Interpreting these signs can be challenging for those unfamiliar with him. It can lead to misunderstandings." - Mother of adult with ZSD***

The inability or diminished ability to communicate had also impacted social interactions with family, friends, and peers. Several caregivers reported on the role of intellectual disability in limiting interactions with others in a meaningful way.

Difficulties with mobility also resulted in increased isolation and limited interactions with peers and siblings. One adult patient discussed using a transcription application on their phone to assist with social interactions, but that also came with limitations, which exacerbated feelings of isolation.

Impact of PD on School/Work Activities

Many participants in the town hall meeting discussed how PD affects the ability to perform school and work activities. During our live polling, 20% of participants reported school/work performance as the biggest impact due to sensory loss, 18% of participants reported it as the biggest impact due to mobility symptoms, 24% of participants reported it as the biggest impact due to intellectual disability, and 18% of participants reported it as the biggest impact due to other symptoms in PD (**Figure 4)**.

Both vision loss and hearing loss affected the learning experience for individuals with PD. One caregiver of an adult patient with PD stated that their child was "*not responding*" when they were in school due to their inability to hear the teacher or their peers in the classroom. Another caregiver stated that their child could not be "*academically successful*" due to their vision loss. One caregiver reported on the impact of gastrointestinal symptoms on their child's learning experience.

> ***"When she didn't feel well...her fatigue...made learning difficult when she started school." - Mother of child with ZSD***

An adult with PD discussed how their vision loss affected their ability to commute to work, and how physical injury caused by their vision loss required them to take time off work.

> ***"I have suffered from more injuries as time goes on due to my blind spots. I have actually fallen and sprained my ankle three times in the last five years. My orthopedic said that if I fall a fourth time that's going to require surgery, which is more missed work, more PTO when I'm not actually sick." - Adult patient with ZSD***

Although many caregivers discussed adaptations and accommodations in their child's school environment to aid in their learning experience, their child's intellectual disability often reduced opportunities for active learning experiences.

Clinical Impacts

Increased Risk for Hospitalization and Medical Interventions

Beyond the everyday impacts of PD and its symptoms, PD also resulted in acute, clinical impacts that often required medical intervention and/or hospitalization. According to our focus groups and town hall discussion, hospitalizations occurred due to gastrointestinal symptoms, respiratory symptoms, acute infections, injuries due to mobility issues, and seizures. Gastrointestinal symptoms often requiring frequent hospitalizations were mainly due to bleeding issues requiring transfusions, as indicated by multiple caregivers.

> ***"She was admitted to the hospital where she received her very first blood transfusion … Instead of being a toddler playing and practicing new skills at home, she would be in the hospital or outpatient clinic for a minimum of 8 hours…Her frequency of blood transfusions were on average every two weeks, but sometimes barely making it a week."***
> ***- Mother of child with ZSD***

Respiratory symptoms requiring hospitalizations were generally attributed to acute respiratory infections, sometimes resulting in pneumonia that would prolong hospital stays. Other acute infections in PD patients also led to hospitalization.

Physical Injury

Sensory loss and mobility symptoms increased the risk of physical injury in patients of all ages.

> ***"I stumbled with a hole in the pavement, and I fell over a bollard [short pole] that hit my face…I fell a lot of times, so my knees were really, really destroyed."***
> ***- Adult patient with ZSD***

> ***"He has broken his collarbone due to one fall, but typically he receives lacerations to his head and face, requiring staples or stitches." - Mother of adolescent with ZSD***

Impact on Nutrition

The symptoms of PD also played a role in other everyday health impacts not currently classified as primary symptoms of PD. For example, one adult with PD discussed being overweight, pre-diabetic, and on hypertension medication, alluding to their vision loss decreasing their motivation to engage in physical activity. PD also impacted the nutritional status of patients in other ways. One caregiver reported that their child had trouble with growth due to gastrointestinal symptoms.

> ***"The discomfort from the bleeding on her GI tract made it difficult for her to tolerate her tube feedings, often causing her to frequently vomit after she ate and making it more difficult for her to gain weight, which was already a struggle since birth."***
> ***- Mother of child with ZSD***

Another caregiver of two adult patients with PD reported that dental symptoms limited what they were able to eat.

> ***"[My two adult children] can no longer have food that's hot or cold. Everything has to be pretty much room temperature. [My adult son is] mostly impacted where he's only eating maybe a few foods that he knows doesn't cause him discomfort and that he can chew appropriately and a lot of them have become softer, more mushier foods as he's gotten older.....And so with those limitations, you're constantly trying to balance nutrition and getting the right amount of nutrition when they're not actually chewing their food the way they used to, and can't enjoy it the same way as others." - Mother of 2 adult patients with ZSD***

Emotional/Psychological Impacts

Some of the most frequently discussed impacts included those on emotional and psychological health. Various emotions including confusion, uncertainty, loneliness, fear/anxiety, frustration, isolation, devastation, and sadness were experienced by patients with PD, as reported by patients and their caregivers.

Fear/Anxiety

Fear and anxiety were some of the most commonly discussed emotional/psychological impacts of PD among town hall participants. Two adult patients discussed anxiety associated with navigation due to sensory loss, one caregiver reported expressions of fear in their child during seizure activity, and both patients and caregivers discussed fear due to PD progression and associated deterioration of senses and mobility.

> ***"The progression, the loss of my mobility have been progressive and this uncertainty that you never know what's going to happen next. And this makes me very anxious and fearful." - Adult patient with ZSD***

Caregivers and patients also mentioned anxiety when interacting with people outside of their family, especially medical professionals.

Frustration and Isolation

Oftentimes patients expressed frustration due to their symptoms, pain related to symptoms, the inability to complete various activities of daily living, and the inability to communicate.

Impacts on Caregivers and Family Members

Considering the symptoms and impacts that affect PD patients and the associated life-long care, the focus groups, surveys, and town hall discussions revealed significant mental, physical, and emotional strain on caregivers. One caregiver reported that caring for her child has resulted in several physical injuries while taking care of her child, while other caregivers reported marital distress as a result of their caregiving responsibilities.

Various emotions described by caregivers ranged from sadness, devastation, frustration, and confusion due to the uncertainty associated with PD prognosis, as well as fear. Caregivers often felt isolated due to the increased caregiving needs of their children.

Summary of Perspectives on Symptoms and Impacts of PD

Overall, our findings show that the symptom burden of PD is considerable. Sensory impairment, mobility symptoms related to low muscle tone, and intellectual disability are the most impactful symptoms of PD. According to patients and caregivers, these symptoms affect independent activity, communication and social interactions, school and work performance, executive functioning, everyday health, and hospitalizations and medical interventions. Acute symptoms such as seizures, leukodystrophy, liver dysfunction, gastrointestinal bleeding, and respiratory symptoms were more associated with everyday health impacts and hospitalizations. These impacts also affect caregivers' daily lives, thereby diminishing the overall quality of life of all family members affected by PD.

Although there were a multitude of symptoms in PD that were reported in our discussions among caregivers and patients that affect their daily lives, it should be noted that there were several symptoms that patients experience that affect their daily lives, but were not discussed at length throughout our discussion. These include but are not limited to a richer discussion on dental symptoms, renal symptoms and cardiac symptoms. This is not to imply that these symptoms do not affect the daily lives of patients but rather to emphasize that all symptoms in PD could not be discussed at length due to time restraints on the discussions.

ADDITIONAL QUOTES

"Quite often, as soon as he was done having a seizure, his oxygen levels would tank, and he would have an apnea episode. They would literally make him lose his ability to breathe." (Father of deceased child with ZSD)

"So, with [our child], he developed portal hypertension and the esophageal varices." (Father of deceased child with ZSD)

"[Our child] loves drawing and crafting and coloring, and it's getting to be very hard for him to do those things." (Mother of child with ZSD)

"Basically, dealing with the deaf blindness, we realized that we had to be their eyes, their ears." (Father of adult with ZSD)

"So of course [my child] depends a lot on me, as to be his eyes when he goes places, making sure he steps down…I have to be that person to say, hang on, step down, look where you're going, look both ways." (Mother of child with ZSD)

"I tend to go everywhere with another human being…So in other words, because of my hearing and vision impairment combined, I have to live in a house next door to my parents." (Adult patient with ZSD)

"Being legally blind, I'm going on about nine years now. I no longer drive…Things like signs, shows, people, even cars, can completely disappear from my field of view when I least expect it." (Adult patient with ZSD)

"She isn't able to just go out the door and run, play, and explore the world." (Anonymous polling response from caregiver)

"His brother doesn't really know, he doesn't understand, the risks he's posing by aggressively playing with the kid who can't get around." (Father of child with ZSD)

"I basically depend on Google Live transcribe app to communicate with people whether it's because they're too far away or the environment is too loud or too dim or dark or I'm just tired. So, I'm just completely dependent upon using that to make sure that I can interact and that impacts my willingness to pretty much engage in social conversations with my family, my friends, and my coworkers because it's just exhausting." (Adult patient with ZSD)

"This year [my teenage child] is enjoying orchestra for her electives, but as an observer." (Mother of child with ZSD)

"We've seen him throw up a large enough amount of blood due to a burst varyx in his esophagus to require a blood transfusion." (Father of child with ZSD)

"[Our child] had lots of GI bleeds and we didn't know where they came from. He needed to receive many transfusions, plasma and he had to undergo many tests to try and find the problem. After many weeks of hospitalization, we found out that he had problems with his small intestine, and it couldn't be cauterized." (Translated from French from mother of deceased child with ZSD)

"[Our child] has sustained physical injury in the past because of these mobility symptoms, these injuries have included bruising, lacerations, sprains, and strains. One time as loss of balance was so significant it resulted in broken furniture and him nearly falling through a glass window." (Mother of child with ZSD)

"Anything that caused, at minimum a two-month hospital stay...because unfortunately these symptoms would land us into the hospital for... two months minimum...I remember 2016, we were in the hospital for at least six months out of the year." (Mother of deceased child with ZSD)

"We were shocked when the blood work came back and [our child] was in septic shock, later determined to be due to cellulitis, and his hemoglobin was less than 6 grams per deciliter." (Mother of child with ZSD)

"Following a hospitalization for a urinary tract infection, [our child] became too weak breathe on his own." (Mother of deceased child with ZSD)

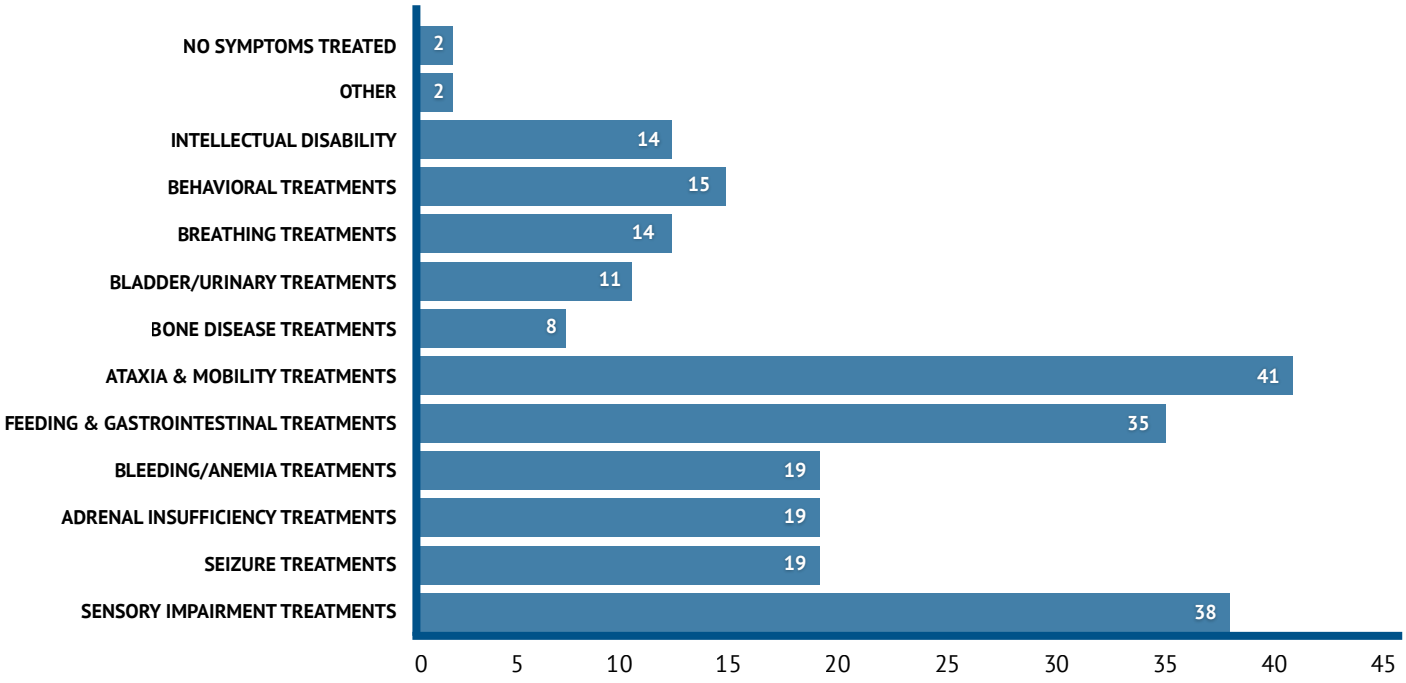
PERSPECTIVES ON CURRENT TREATMENTS FOR PEROXISOMAL DISORDERS

Thank you to our panelists: Tammy LaMaire and Sarah Heath

Overall Treatment Usage in PD

Currently, there are no approved treatments specific to addressing PD as a whole; all treatments for PD are symptom-based. When caregivers and patients were asked which symptoms were being or had been treated in PD patients in our online survey, **mobility symptoms were the most frequently treated symptom in PD patients (71.9%), followed by sensory impairment (66.7%), followed by gastrointestinal/feeding challenges (61.4%)**. Similar results were reported during the live polling. Other commonly treated symptoms included those for seizures, bleeding issues, adrenal insufficiency, and to a lesser extent, bone disease, intellectual disability, behavioral symptoms, and respiratory symptoms (**Figure 5**).

Figure 5: Treatment Usage in PD by Symptom Category.

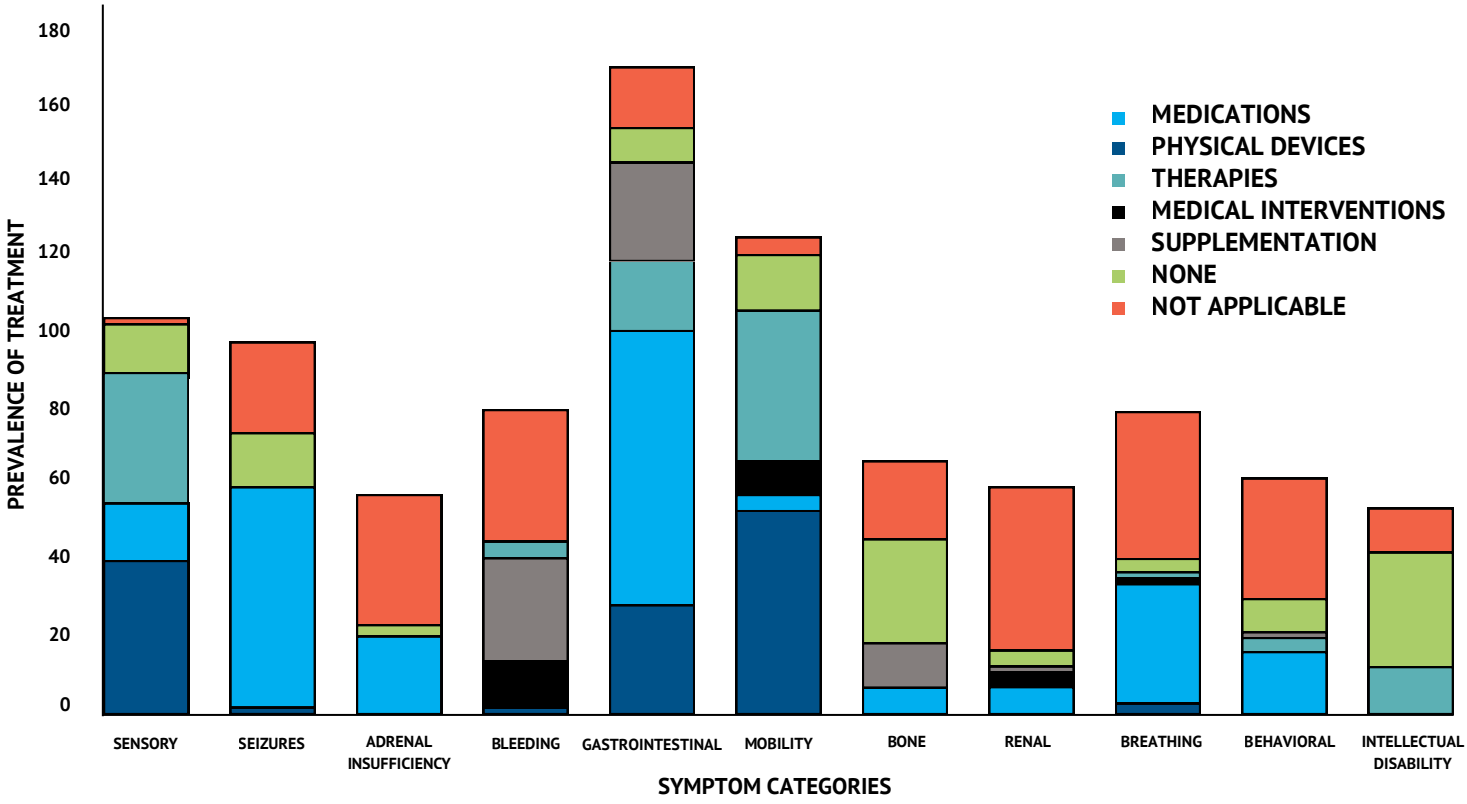


Number of respondents who reported using treatments in managing each of the listed symptoms, either for themselves or their child with PD according to our online caregiver and patient surveys (n=57).

Our online patient and caregiver survey identified the use of several categories of treatments across symptoms. This included medications (e.g. anti-epileptic drugs, reflux medications, etc.), physical devices (e.g. gastrostomy tube, walkers, etc.), therapies/accommodations (e.g. physical therapy, individualized education program, etc.), supplementation (e.g. prebiotics, iron, etc.) and medical interventions (e.g. orthopedic surgery, blood transfusions, etc.) (**Figure 6**). An average of 13 treatments total were used per each patient, the highest number of treatments for a single patient being 42 treatments. Medication usage was seen to be the most commonly reported of all treatments among the survey respondents (an average of four medications per patient), followed by physical devices, then therapies and accommodations.

Our online survey results also reported on the number and types of different treatments used, organized by symptom category. **Gastrointestinal/feeding symptoms were treated with the highest number of distinct treatment categories, with medications being the most commonly used treatment. Mobility symptoms were the next symptom category using the most distinct number of treatments, with physical devices as the most commonly used treatment.** Sensory impairment in PD, the next symptom category, mainly used physical devices as a management approach, while seizure treatment relied primarily on medications. Intellectual disability and bone density were frequently left untreated in PD (**Figure 6**).

Figure 6: Treatment Usage in PD by Symptom Category and Type.



Treatment usage in PD by symptom category and type, according to responses from online surveys (n=64 respondents). Symptom categories are indicated as bars, treatment categories are indicated as different colors.

Overall Treatment Effectiveness in PD

During our live polling, participants were asked how well-managed current treatments for PD are in the management of its symptoms **(Figure 7)**. **The majority of polling respondents indicated that PD symptoms are not being well managed (57.8%, n=26 out of 45 respondents).** Related, participants were also asked how treatment management had changed over the course of time. The vast majority of the polling participants (88.9%) reported that treatment needs increased over time **(Figure 8).**

So one of the drugs we tried with [my child] for about 6 weeks, and then we're worried about the effects of it. So then [we] did a little experiment with him and took him off the drug, and we saw no decrease in his physical ability. So we stopped giving him that drug. But then, yeah, he's on another drug to try to help with that. And we really don't know if it works or not. He still [has] ataxia symptoms. It's just hard to know whether they help or not." - Mother of child with ZSD

Figure 7: Treatment Effectiveness/Management in PD (Live polling, n=45 respondents).

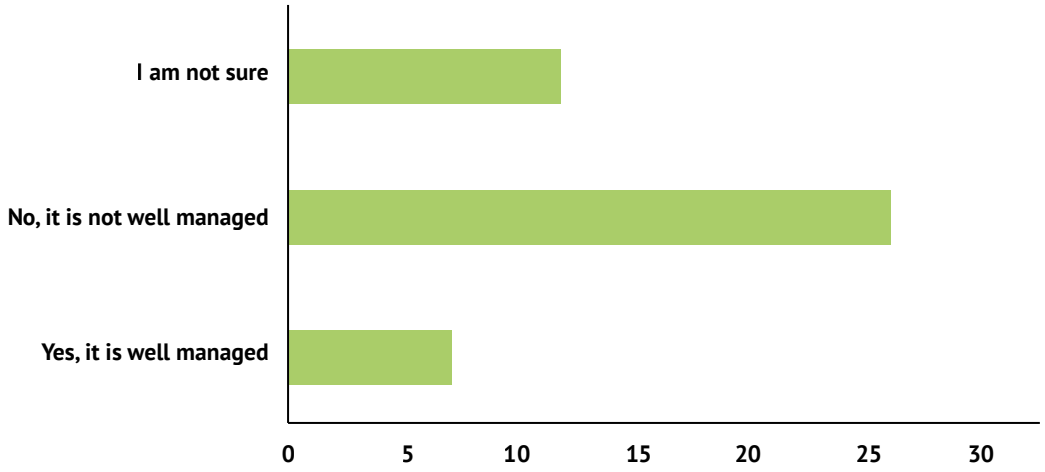
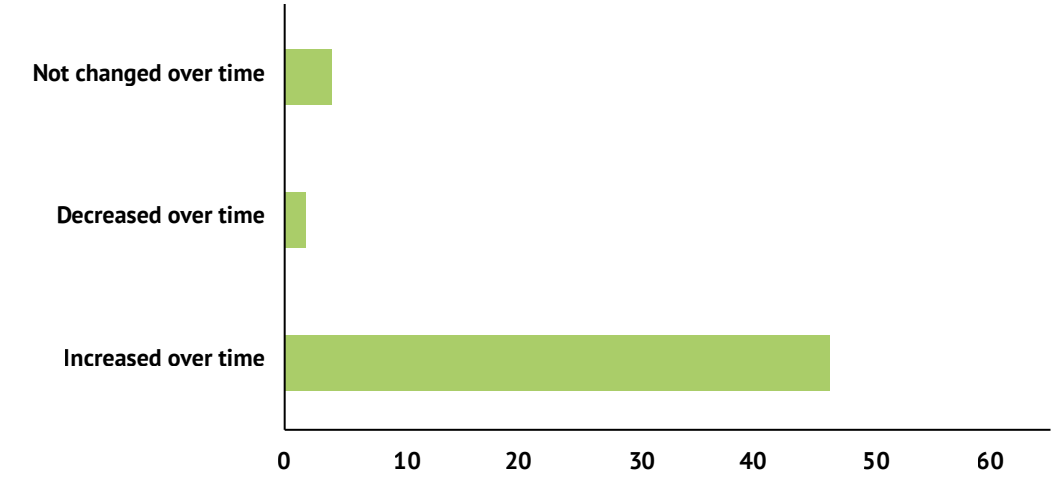


Figure showing the effectiveness of treatments/management of PD (well managed, not well managed and not sure) according to live polling respondents during the town hall meeting (n=45).

Figure 8: Change in Treatment Regimen Over Time in PD Patients (n=54 respondents).



Treatment regimen over time in PD (not changed, decreased, or increased over time) according to live polling respondents during the town hall meeting (n=54).

Treatment Effectiveness and Side Effects by Symptom Category

Sensory Impairment & Communication

A commonly treated symptom in PD was sensory impairment (vision and hearing loss), with 66.6% (n=38 out of 57 respondents) of patients using treatments **(Figure 5)**. **Treatments for vision loss in PD primarily consisted of corrective lenses, vision therapy, and some medications. Surgery to resolve cataracts was also reported by some caregivers.** Assistive physical devices such as walking canes were also reported in patients who had some ambulation.

For hearing loss, treatments were generally either hearing aids or cochlear implants. Overall, treatments have been noted to have some effectiveness in treating these symptoms although caregivers expressed inconsistent outcomes from the treatments used.

For both vision and hearing loss, participants discussed the loss of effectiveness of treatments over time, mainly due to the progression of vision and hearing loss. Additionally, some caregivers reported that the multi-system nature of PD, resulting in **sensory aversion and overstimulation, made it difficult to use certain treatment options** for sensory loss.

> ***"We do have the option of hearing aids, but this disease is a multisystem disease. So she has experienced some sensory aversions, which keeps her from wearing the aids. Even thinking into the future, considering the options of cochlear implants, would she be able to handle that with her sensory aversions?" - Mother of child with ZSD***

The dual-sensory loss resulted in significant impacts on communication, particularly verbal. To manage these challenges, patients and caregivers used several tools to aid in communication. One adult patient described being reliant on a transcription smartphone application in social situations. A caregiver stated that their adult child used a frequency modulating (FM) system for communication purposes when they were enrolled in school. One caregiver reported using multiple tools at the same time but with limited success due to additional issues with speech in their child.

A few side effects of treatments and interventions for sensory impairment were reported among patients and caregivers. Among these side effects were the **development of kidney stones due to medication for relieving retinal pressure,** retinal cyst development, and the **impact of cochlear implants on balance**. Although not discussed at length during the town hall discussion, there were some brief comments on the difficulty in obtaining magnetic resonance imaging (MRI) for patients with cochlear implants.

Mobility Symptoms

Our online survey found that 71.9% (n=41 out of 57 respondents) of patients used treatments to manage mobility symptoms, the most frequently treated symptom category **(Figure 5)**. The majority of the treatment interventions used for mobility symptoms were physical devices, such as canes, walkers, standers, and wheelchairs. These devices did often aid in standing upright, ambulation, or motion, but did not necessarily treat the underlying cause of the mobility symptoms, as shared by focus group and town hall meeting participants. It was unclear to caregivers and patients whether or not physical therapy (PT) was useful; one caregiver stated that **PT did aid in keeping mobility symptoms stable and from deteriorating**. Orthopedic surgery to increase mobility symptoms was also reported by one caregiver, although multiple surgeries were required to maintain mobility. Medications for mobility symptoms were effective in some patients and had no effect in others. Overall, mobility intervention needs appeared to increase over time as patients got older and as the PD progressed.

> ***"You know, support and things like that definitely have increased [for] his mobility as it's changed. We've had different equipment needs, different therapy needs and then different medication needs." - Mother of adult with ZSD***

Several patients and caregivers also described the unanticipated impacts of mobility interventions. One caregiver mentioned that PT and OT (occupational therapy) resulted in the patient being exhausted with little down time after these therapies.

> ***"I think, for their PT and OT and speech, the downside of that is that they have a lot less time to be at home and be kids or do whatever they do at home normally."***
> ***- Father of child with ZSD***

For low bone density, PD patients were often prescribed bisphosphonate medications to promote better bone mineralization. One caregiver discussed the effectiveness of bisphosphonate medication on bone mineral density for their child with PD, but also shared significant side effects as well. Another caregiver alluded to **bisphosphonate infusions lowering blood calcium levels in their child, requiring hospitalization.**

Intellectual Disability

There was no specific treatment meant to treat intellectual disability in PD, but rather to **manage the impacts of it in areas such as school and work performance, communication, and overall safety**. Caregivers discussed the use of individualized educational plans for patients in school, which included various accommodations, and in-school therapies. In many school settings, patients were placed in integrated, co-teaching inclusion classrooms where patients were alongside their typically developing peers during school. In many cases, there were multiple accommodations and therapies that were necessary to minimize the impact that intellectual disability (in combination with other PD symptoms) had on a patient's life.

Seizures & Neurological Symptoms

About a third of survey respondents (19 out of 57 respondents) reported that PD patients were using treatments for seizures **(Figure 5)**. **Seizure treatments primarily consisted of medications, with the use of physical devices (vagal nerve stimulator) for one patient, and ketogenic diet in combination with medications for another patient. Medications for seizures included several classes of anticonvulsants as well as various cannabinoid derivatives.** Rescue medications for acute seizure activity were usually benzodiazepines such as Ativan and Diastat. In most cases where patients were treated with medications, **multiple medications were used at one time to treat seizures.**

> ***"He ended up being on Keppra 1500 milligrams twice daily, Vimpat 200 milligrams twice daily, Primidone 25 milligrams four times daily, Gabapentin 600 milligrams daily and three milligrams of Ativan at bedtime." - Mother of deceased adult with ZSD***

One of the most commonly prescribed anticonvulsants in PD was levetiracetam (Keppra). According to one caregiver, Keppra was mostly effective in the management of their child's seizures. However, **most caregivers indicated that Keppra, as well as other seizure medications, lost effectiveness over time. This would require both increases in dose and additional medications for seizure management**. Seizure treatment increases over time were related to both the increased dose requirements related to growth and the progression of seizure symptoms over time.

> ***"[My child] had phenobarbital for seizures. And then that was not keeping it under control, so the next thing was Keppra which worked for a pretty long time, and then just even at the highest dose that was not working anymore. So then, Topamax got added to that but I feel like that really didn't do much in terms of controlling the symptoms."***
> ***- Mother of deceased child with DBPD***

In some cases, the combination of therapies was effective at managing seizure activity. However, side effects of certain treatments were reported by caregivers, even common ones like Keppra. Most commonly, **caregivers reported fatigue and sleepiness associated with seizure medications**, and sometimes adverse impacts on respiratory function.

> ***"At one point in our journey, when [our child] was being seen by a hospital neurologist, we were told, 'Do you want a sleepy baby or a baby with seizures?' What kind of choice is that? No parent should be faced with choosing one of those two options and have to be okay with it." - Father of deceased child with ZSD***

One caregiver of an adult patient described her child's experience transitioning from multiple ineffective medications to a vagal nerve stimulator, which was effective in controlling her child's seizure activity.

Feeding & Gastrointestinal Symptoms

The use of treatments for feeding and gastrointestinal symptoms was reported by 61.4% of respondents in our online survey. Among treatment usage across symptom categories, **gastrointestinal/feeding treatments and interventions comprised the largest group of distinct treatments for PD symptoms (Figure 5)**.

Most frequently, medications to treat constipation and gastroesophageal reflux were used by PD patients. Despite the frequent use of these medications, one caregiver stated that **issues with constipation were not well managed**, and another indicated that their child required multiple medications to manage constipation.

> ***"My child has to take a regimen of stuff like Miralax and Dulcolax, and mineral oil and all that for chronic constipation." - Mother of adult with ZSD***

Moreover, anti-constipation medications such as lactulose would often cause bloating, which would result in patient discomfort. Chronic vomiting related to reflux was also not well managed with available medications.

Various physical devices, and dietary supplements (probiotics, fiber supplements) were also used to increase gut motility. Dietary supplements (fat-soluble vitamins, banana flakes) were also used to manage issues related to malabsorption and subsequent diarrhea. Some medications were used to stimulate appetite.

Poor oral motor skills were treated with feeding therapy and in many cases, enteral tube placement to facilitate proper nutrition. Caregivers noted that **feeding therapy was generally ineffective and time-consuming. Often, the lack of effect of feeding therapy on oral feeding would result in more aggressive interventions such as enteral tube placement.** While enteral tube feeding allowed for a decreased risk of malnutrition and time saved from oral feeding, there were **challenges associated with tube feeding, including chronic vomiting and reflux due to a long period of adjustment to the enteral delivery of food, as well as pain, irritation and increased risk of infection due to tissue granulation and/or gastric prolapse at the site of the tube placement.**

Cholic acid replacement therapy (Cholbam) was commonly used to treat liver dysfunction in PD. The effectiveness of Cholbam was inconsistent across discussions among caregivers. **A few caregivers commented that Cholbam was managing liver symptoms adequately. Other caregivers observed no effect.**

> ***"To be honest, I cannot tell you with any certainty that the current treatment regimen for my son is working. I see no noticeable effects with Cholbam on liver function." - Mother of child with AMACR deficiency***

In one case, a caregiver stated that although the liver dysfunction in their child appeared to be well-managed with Cholbam, there were significant side effects. In particular, gastrointestinal side effects, such as stomach discomfort, vomiting, and diarrhea.

> ***"We had issues with gastrointestinal issues when she started [Cholbam] the first time about 6 or 7 years ago. Well, I took her off. And then she started back on it about 2 years ago, and her stomach issues have gotten worse... She's still on it. They cut her dose in half to see if that helps. I'm not seeing a huge improvement with the gastrointestinal issues with cutting it in half, but they want to keep her on it because her liver counts are perfect." - Mother of adolescent with ZSD***

Bleeding Issues & Anemia

Bleeding issues in PD were often a consequence of liver dysfunction and fat-soluble vitamin malabsorption. Treatment usage specific for anemia/bleeding issues was reported by 33.3% of the survey respondents **(Figure 5)**. Specific treatments included whole blood transfusions, clotting factor infusions, Vitamin K supplementation, and iron supplementation. While Vitamin K was the most frequently used treatment for PD patients with bleeding issues, **68.4% of survey respondents who reported bleeding issues in PD indicated that blood transfusions were required for their child's bleeding issues. In some cases, blood transfusions were required frequently, which resulted in hospitalization and missed school.** In one case, a caregiver described the **need for a port placement due to their child's veins becoming weak from frequent blood transfusions.**

> ***"She's needing transfusions, I mean, at one point it was every week, and then it was 2 weeks. Now we're out at a month, and this has been going on for 3 years now... So I mean, we're just managing [bleeding] with transfusions." - Mother of child with ZSD***

Dental Symptoms

Treatment for dental symptoms was not discussed at the town hall discussion, however during the focus groups, one caregiver stated that their child needed to use toothpaste and mouthwash specific to sensitive teeth. Another caregiver mentioned that their child needed multiple secondary teeth pulled out.

Adrenal Insufficiency

Although adrenal insufficiency was not discussed at length during the town hall meeting, during the focus groups, multiple caregivers stated that **adrenal insufficiency was adequately managed with available treatments.** Among the survey respondents who indicated that they or their child with PD was diagnosed with adrenal insufficiency, nearly all were treated with corticosteroid therapy once they were diagnosed. **The impact of adrenal insufficiency prior to treatment**, however, was quite severe on overall health and quality of life, according to the town hall discussion.

"I really felt like [my daughter] was kind of wearing a death mask for almost a year [due to adrenal insufficiency]. The dark sunken eyes, loss of weight, hyperpigmentation of her skin, hair was getting brittle and falling out, all of these things... that diagnosis, 100% changed her life and probably still has her here today. Honestly, she was literally on the brink of [an adrenal] crisis when it was caught." - Mother of adult with ZSD

Respiratory Symptoms

In our online survey, nearly 24% (14 out of 57) of respondents reported that PD patients use treatments for respiratory symptoms (**Figure 5**). The majority of treatments used for respiratory systems were medications, primarily meant for clearing the lungs and airways and to reduce secretions. Several patients with respiratory symptoms also required chest physical therapy and frequent suctioning for lung clearance and reduction of secretions.

Some patients required external oxygen and/or pressure support. In severe cases of airway compromise, tracheostomy placement was required to keep the airway open. Two caregivers that participated in the focus groups and town hall discussion reported needing a tracheostomy for their child with PD, which was lifesaving and necessary. However, this was associated with an increased risk of infection which would often further complicate respiratory symptoms, sometimes resulting in hospitalization due to acute respiratory infections. Additionally, oxygen and airway support had considerable impacts on overall quality of life, particularly with respect to leaving the house and being mobile.

Summary of Perspectives on Treatments for PD

Overall, as there are no specific treatments for PD, multiple treatments are required to address multiple symptoms. Moreover, among several symptom categories in PD, multiple treatments are used to address only one symptom category, and there is considerable trial and error required to determine what treatment works best for an individual patient. This is likely due to the overall ineffectiveness of most treatments currently used for PD symptoms. The next topic, "Perspectives on Clinical Trial Participation and Ideal Treatments in PD," will address ideal clinical outcomes in PD with treatment usage.

Additionally, the multi-symptom, multi-system nature of PD results in multiple obstacles in treatment management of PD, where the treatment of certain symptoms will yield side effects that exacerbate other PD symptoms, or when certain symptoms hinder the effectiveness of other treatments.

Again, discussions on treatments were limited to symptom categories that were prioritized by patients and families, and discussions on many treatments in PD were not discussed at length due to time restraints. Overall, until the development of treatments that effectively address the multi-system nature of PD, patients and families must continue to rely on these services, treatments and interventions as acceptable when compared to no intervention at all, while not fully adequate in addressing symptoms in PD.

"Even if it's a good day, they still are struggling constantly over and over again, because they're hooked up to wires and machines. And so... we still can't do the things that normal people do. {My child} likes running across the front yard. He's not able to do that anymore."
- Mother of child with ZSD

ADDITIONAL QUOTES

"And so changing from hearing aids to making the decision up to a cochlear implant, because hearing aids no longer work." (Mother of child with ZSD)

"Glasses may have worked. And then all of a sudden, they don't work anymore. So changes in that adaptive equipment and things like that." (Mother of child with ZSD)

"He uses a combination of speech, AAC [augmentative and alternative communication] and sign, but none of them are very accurate or understandable because of his apraxia of speech." (Mother of child with ZSD)

"But back to the underlying condition, we're not really addressing that. We're just giving him some tools to be a little bit more mobile." (Mother of child with ZSD)

"The physical therapy is more to make us feel better that we're doing something. I can't say it changes or decreases his falls." (Mother of child with ZSD)

"She is on Diazepam as needed, and that kind of helps her calm down with the muscle spasms and also go to sleep." (Mother of child with ZSD)

"So the most recent DEXA scan that we had showed that [with Binosto treatment] his bone density was very much in line with your typical 9 year old, which is particularly impressive because he's not weight bearing." (Mother of child with ZSD)

"And the first time that [our child took Binosto] he became very, almost comatose, like we couldn't wake him up. He was really out of it a few times and got really dehydrated. Yeah, it had a really adverse instance. So we ended up having a short hospital stay aligned with starting with that." (Mother of child with ZSD)

"Her school-based therapies and accommodations include physical therapy, occupational therapy, orientation and mobility, speech, a teacher for the hearing impaired, a teacher for the visually impaired, an intervenor, curb-to-curb bussing, an augmentative alternative communication device, her iPad, and vocational rehabilitation to prepare her for the possibility of work after high school. She receives adaptive P.E., she participates in Special Olympics, and this year [our child] is enjoying orchestra for her electives, but as an observer. All of these interventions make it possible for [our child] to have access at school and live her best life." (Mother of teenage child with ZSD)

"His treatment for seizures included Keppra, phenobarbital, Topamax and his rescue meds of Klonopin." (Mother of deceased child with ZSD)

"The Keppra does a really nice job with the seizures." (Mother of child with ZSD)

"This was his daily dosage of meds for seizures and he would still have frequent breakthrough seizures, requiring 15 to 30 milligrams of diastat which is rectal valium." (Mother of deceased adult with ZSD)

"And it was a constant race to keep up with what dosage she should be at. Is this one no longer working? Because even the slightest bit of weight gain …and [we have to] figure out how to bring it back down to the right dosage…If we had added something new, we could see that big change. But, over time, that change would no longer be so drastic and we'd have to add something else." (Mother of deceased child with ZSD)

"So they started her on like high dose Prednisolone and then moved her to Vigabatrin and then we moved to a combination of a ketogenic diet, and then 2 other medicines and this was all like in a 6-month timeframe. And now she's been, knock on wood, stable on that combination for a bit." (Mother of child with ZSD)

hen the seizures came we did try, I want to say we tried Keppra, and it made her agitated and just kind of miserable. So I went the natural route, and she's been on CBD ever since, that's worked out great." (Mother of adolescent with ZSD)

"The seizure medications helped stop the seizure at that time. And we're medicating her every 3 h or something, but it's like literally she's always just sleeping. She's never being able to even just do little baby things like very rarely do I have a picture of her with her eyes open."
(Mother of deceased child with ZSD)

ADDITIONAL QUOTES

"When [my child] was 24, he had a vagus nerve stimulator placed. This is a device that is implanted in the chest and a wire is wrapped around the vagus nerve. It sends mild electrical impulses to the brain to break up the constant electrical seizure activity. Eventually, his seizures became less intense and much less frequent. Usually 5 to 15 minutes at most. The last year of his life, he went an entire year without having a seizure." (Mother of deceased adult with ZSD)

"[Constipation is] not well managed for us right now. And there doesn't seem to be anything else out there that we've been offered yet to help with that. And I just want to touch on that because I think it's something people do deal with." (Mother of child with ZSD)

"There was a lot of trial and error with the feeds. It took like 7 months for our GI team to suggest trying continuous feeds despite him, like projectile vomiting misery like daily. So just a lot of like trial and error." (Father of deceased child with ZSD)

"Cholic acid for her has been a really well-managed thing for her liver condition."(Father of child with ZSD)

"I know [Cholbam] works with every child differently, in our case, [my child has] been on it since March. And [the liver] numbers are not perfect, but they are coming down [so] they want to keep her on it." (Mother of child with ZSD)

"His GI took him off [of Cholbam] because she didn't see much benefit for him." (Mother of child with ZSD)

"We were on Cholbam for the liver. That treatment did not work either." (Mother of child with ZSD)

"Her veins became so weak, eventually leading to surgery to have a port placed so she could have an easy access point to receive the lifesaving blood." (Mother of child with ZSD)

"A miracle for [my child] specifically, because she was down to like 75 pounds. And it was because of the undiagnosed adrenal issue and once she started her steroids, you know she's over 100 pounds now, and that's I mean it's been life-changing for her. So yes, we went from no meds and undiagnosed to some meds but way increased quality of life with those meds.... I think it just really impacted the way she was able to fight small illnesses." (Mother of 2 adult patients and one deceased patient with ZSD)

"[My child's] hydrocortisone has been great management for her adrenal insufficiency." (Father of child with ZSD)

"When [our child] got trached, I noticed that we were able to stay out more because he was able to get oxygenated." (Mother of deceased child with ZSD)

"The trach, it made them more susceptible to getting infections and colds. But [my child] wouldn't have lived as long as he had if we hadn't done those things." (Father of deceased child with ZSD)

"[Our child] was trached. He was on the ventilator. So of course, our lives changed tremendously. Just toting around that thing everywhere. It's a bit much in addition to the oxygen and everything else." (Mother of deceased child with ZSD)

"Just like managing [our child's] exhaustion in relation to the therapies." (Father of child with ZSD)

"The adrenal insufficiency, I think it was controlled [with medication]. I think it just really impacted the way she was able to fight small illnesses." (Mother of deceased child with ZSD)

"... Absolutely life-changing [referring to steroid treatment for adrenal insufficiency]." (Mother of 2 adult patients and one deceased patient with ZSD)

"I think for us I feel like their adrenal insufficiency is being well managed right now." (Mother of 2 adult patients and one deceased patient with ZSD)

PERSPECTIVES ON CLINICAL TRIAL PARTICIPATION AND IDEAL TREATMENTS IN PD

Thank you to our panelists: Kelly Dauer-Hubschmitt and Jennifer Knox

Clinical Trial Participation

When patients and caregivers were asked in our online survey if they or their children have previously participated in a clinical trial for PD, only four caregivers responded that their child had previously participated in a clinical trial for PD.

A caregiver in the town hall discussion shared the experience of their child participating in a clinical trial for cholic acid therapy for ZSD patients. This caregiver stated that **despite their child not benefiting from the therapy and ultimately succumbing to PD, they did not regret their decision to enroll their child in the clinical trial.**

> ***"Our child may not have had the chance for a long life, but what if her clinical trial participation could change the outcome for someone else? What wouldn't I be willing to do for our daughter to have that chance? I would have said yes to everything. There's not a single thing I wouldn't have done. I wouldn't have declined anything if it could have helped our child or that child, or maybe my son's children."***
> ***- Mother of deceased child with ZSD***

Forty patients and caregivers responded to an online survey question about whether or not they would enroll themselves or their child if there were a new clinical trial to study an experimental treatment for PD in our online survey. Of those responses, **52.5% (n=21) of respondents reported that they would agree to enroll themselves or their child in a new clinical trial for PD. 45% (n=18) of respondents reported that their participation would depend upon other factors, including the anticipated treatment outcomes, the mode of administration of the treatment, potential side effects, and associated risks and benefits of the treatment.** Only one caregiver reported that they would not enroll their child in a new clinical trial for PD.

We subsequently asked patients and caregivers in our online survey to rate what the most important factors were when considering enrolling themselves or their child in a clinical trials. The highest rate factor was the risk of serious side effects (average rating of importance 8.8 out of 10), followed by the specific outcome measures of the clinical trial (average rating 8.5 out of 10), followed by the potential worsening of PD symptoms (average rating 8.2 out of 10).

Multiple caregivers described their openness and readiness to participate in a new clinical trial for PD during the town hall discussion. Specifically, at least four caregivers shared that they would do whatever is required to enable their child to participate in a new trial, including undergoing invasive treatments and traveling.

> ***"I am a friend of a parent who has this disorder and there's been a handful of conversations we've had. And one area that's always stuck out is the idea of clinical trials. And I was talking to her recently, her son's currently two and she said time and time again that she would let the doctors poke and prod and take blood and skin and whatever else they need, because he's already doing so much testing and monitoring in his current state. If there is a reward, it's worth the risk. The reward would be worth putting him in that uncomfortable state temporarily, hopefully. They're willing to take that chance. They want to try anything for a better quality of life, not only for their son, but for anyone and everyone affected and that will be affected by this disorder. There needs to be more access to trials that truly treat this disorder and not just the symptoms." - Family friend of child with ZSD***

> ***"Just give us the opportunity to know what's available for us to participate in. You might get some no's, but you'll be surprised at how many of those no's turn to yes's if you also demonstrate that you have thought through what the participant is giving up, what the parents are giving up. If you make the experience easier and you care for some of those little things turning into big things, the choice to participate will be easier to make as well." - Mother of deceased child with ZSD***

Clinical Trial Design

Desirable Clinical Outcomes

When patients and caregivers were asked in our online survey to rate how important it was to improve certain impacts of PD symptoms, the highest rated impact to improve was independent activity (average rating of importance 8.4 out of 10), followed closely by communication (average rating of importance 8.3 out of 10) and walking (average rating of importance 8.2 out of 10). Many caregivers expressed how closely related these impacts were to one another.

> ***"[Our child] has very low levels of independence in her life right now. That is one real struggle for her. And if her life continues on the trajectory that it is right now, she will have fewer and fewer abilities. And so, independence and what I mean by that is her ability to stand when she wants to stand to feed herself, or communicate to us, to make decisions, any ability to socialize with others." - Mother of child with ZSD***

Improved Mobility

Improved walking and overall ambulation were commonly discussed independent activities that caregivers expressed wanting to improve in their children. At least five caregivers during the town hall discussion or in the focus groups specifically mentioned increased walking ability as a meaningful improvement. For caregivers of patients with limited to no ambulation, **walking with assistance or support would be considered a meaningful outcome. In some of these cases, even standing for a period of time would be considered meaningful.**

> ***"What would be meaningful improvement is the ability to stand, the ability to walk, even if it's assisted walking... Allowing [my child] to get back to his typical weight bearing of 4 to 6 hours a day would be very meaningful improvement. Giving him the ability to use his walker and mobilize and to be able to stand for longer periods of time. Right now, he can really only stand in a supported stander for about 15 minutes. Prior to the hip dislocation, he was able to stand for 45 minutes in a supported stander. And this not only offers functional outcomes, but clinical outcomes on his bone health if he's able to weight-bear, reducing the risk of fractures." - Mother of child with ZSD***

For caregivers of patients who had adequate walking ability, maintaining that ability over time would be considered a meaningful outcome.

> ***"If [our child] could stand and walk and we knew that she might be able to do that for years longer, those improvements would be examples of what might cause us to participate [in a clinical trial for a new treatment]." - Mother of child with ZSD***

Another outcome related to ambulation that was important to PD caregivers was the **improvement of balance and ataxia symptoms.** Two caregivers explicitly mentioned that an impact on the occurrence of falling and related injuries would be a meaningful and measurable outcome for a new treatment.

> ***"And being able to even have a treatment that would help him with his balance issues, and I would be able to measure that by having decreased falls and injuries."***
> ***- Mother of adult with ZSD***

Beyond the impact of improved walking and gross motor skills, improvement of fine motor skills and muscle tone were also desired outcomes that were expressed by caregivers when discussing clinical trials for future PD treatments, particularly in the context of independent activity. One specific activity that was mentioned by at least four caregivers in the town hall discussion was the ability to independently feed and consume food orally. For one caregiver, improved feeding was related to the ability to swallow food with improved muscle tone.

> ***"Something we always wished for [our child] was that she could eat independently... I remember she did two really good swallows, and then she got weak, and tired and kind of tapered off. So the only thing measurable I could think in that respect is just that she could have drank more, and I don't know. Maybe five good swallows."***
> ***- Mother of deceased child with ZSD***

For other caregivers, improved feeding was related to the ability to feed themselves with their hands.

> ***I would also say fine motor skill development. So, specifically abilities to be independent, like feeding herself with the utensil, being able to use her own sippy cup and things of that nature would be extremely beneficial." - Father of child with ZSD***

Improvement of fine motor skills was also related to the improved ability to engage in recreational activities. Multiple caregivers expressed their desire to simply see their child "just play more":

> ***"So I'd love for him to be able to move his hands, even just a few inches would be great. Just so he could play with toys or interact with things." - Mother of child with ZSD***

Improved Vision

Another symptom related to independent activity that caregivers wished to improve in their children with PD was vision. One caregiver stated that they would want a new treatment for PD to "fix the retinas" in their child. Another caregiver described better hand-eye coordination as a desirable outcome. Still another caregiver specifically desired the slowing of the progressive vision loss as a meaningful outcome. Similar to other outcomes like walking, vision improvement, even with support, would be considered a meaningful outcome among caregivers.

> ***"I think most impactful will be anything that would slow down the progression of vision loss to the point that, not that it has to be perfect acuity, but anything that doesn't exceed beyond the limits that glasses help would be a tremendous benefit to our family. If glasses using [a prescription strength of] seven/eight, it can still assist in vision."***
> ***- Mother of adult children with ZSD***

Improvement of vision was also related to impacts on social interactions and communication. One caregiver during the focus groups shared that improvement of vision would allow their child to better interact with her age-matched peers.

> ***"Improved lower peripheral vision, and I would see improvement by being able to chase after her friends, or like to be able to play tag and not worry about tripping over her feet, and even more specifically navigating in the snow in the winter time. She has so much trouble with it. All of her markers are gone. You can tell that she's much more cautious about what she's doing, whereas the other kids.... they're out there playing. They're running, they're jumping. And I would love for her to be able to do that."***
> ***- Mother of child with ZSD***

Another caregiver stated that improvement with vision would allow for better communication, as **most assistive devices with hearing and speech require vision to be able to use them effectively.**

Improved Hearing

Improvement of hearing was also a desired clinical outcome for caregivers of PD patients. One caregiver stated during the focus groups that **she did not require full restoration of hearing function in her child with PD for improvement to be considered meaningful. In this case, "improved hearing from severe, profound hearing loss to mild, moderate hearing loss"** was considered meaningful.

Improved Gastrointestinal Symptoms

Several families discussed the improvement of gastrointestinal symptoms as meaningful outcomes for new PD treatments. One caregiver shared that a reduction in the number of times that their child vomited in one day would be considered a meaningful improvement.

> ***"The biggest hindrance to [my child's] quality of life, I really feel, was the number of times that she vomited during the day after a meal. And just the fear and upset that that caused her. I would have loved to see [this happen only] one time a day as opposed to eight, nine, ten times a day." - Mother of deceased child with ZSD***

Among gastrointestinal symptoms to improve, the most commonly discussed among PD families were related to liver function. Two caregivers stated broadly that they would want new treatments to **slow down the progression of the liver disease.** One caregiver explicitly referred to addressing the portal hypertension and related bleeding issues caused by liver dysfunction to be a meaningful clinical outcome if there were a new treatment for PD.

"I think that anything we could do to help in terms of a treatment, to help with the progression of the liver disease, to prevent the portal hypertension and those esophageal varices would really be important, because having that chronic anemia really is debilitating." - Father of deceased child with ZSD

Related, several caregivers mentioned **reduced bleeding and a reduced need for blood transfusions** in their child with PD as a meaningful outcome. According to most caregivers that discussed bleeding and the need for blood transfusions, **a complete halting of bleeding issues was not required to be considered a meaningful change.**

"I would say something for the bleeding where we were spaced out, blood transfusions, you know? Right now we're at once a month; if we could get every other month, I'd be happy." - Mother of child with ZSD

Improvement of Cognitive and Neurological Symptoms

Cognitive ability improvement related to intellectual disability was mentioned as a desirable outcome for caregivers of children with PD. Although specific outcomes related to overall improved cognitive ability were not explicitly described, at least two caregivers related speech and communication back to cognitive ability, and one caregiver suggested that **improved speech would be considered meaningful with respect to intellectual and cognitive ability.**

"What I'd like to be able to see is something that would help her with cognition and speech. Those things are really tied together." - Mother of adolescent with ZSD

"So we have communication tools and devices, but hearing your child be able to say the words 'I love you' or more would be pretty phenomenal." - Father of child with ZSD

For PD families that experienced seizures, new treatments to adequately control seizures were important clinical outcomes to caregivers. Specifically, reduction in frequency and intensity of seizures was important, however, **it was also important that effective seizure management was achieved without significant impacts on alertness and wakefulness.** This point was raised by at least three caregivers during the town hall discussion.

"I don't want a sleepy baby or a baby with seizures. I want a golden third option, a baby with less or no seizures who is able to engage with the world around them, enjoy a better quality of life, and not have to live in a constant medicine-induced stupor."
- Father of deceased child with ZSD

"Effective seizure treatment for my family would have not only reduced the amount of seizures, but would have also done so in a manner that they did not take away his ability to interact." - Mother of deceased child with ZSD

For many caregivers, several symptoms were manageable provided that they were stable, but the progression of symptoms took a large toll on the daily lives of patients and caregivers. Therefore, in several cases, caregivers expressed that **a delay or halt of symptom progression would be considered meaningful as a measurable outcome in a clinical trial for PD.** This was generally related back to the prevention of an active leukodystrophy. Two caregivers described how slowing down this progression would be considered a meaningful change.

"Even if [the leukodystrophy] just slowed down enough that we could kind of catch things way before the progressive point that you couldn't do anything to help, whether it be seizure prevention, those types of things..." - Mother of deceased adolescent with ZSD

"Slow the progression of cerebellar atrophy." - Mother of adult with DBPD

Improvement of Respiratory Function

Three caregivers discussed wanting to improve respiratory function in their child if there was a new treatment for PD. **Explicit outcomes were primarily related to requiring less respiratory support.** In all cases where improvement of respiratory function was discussed, **minimizing the time required to be attached to bulky equipment** was considered a meaningful outcome. As with many other symptoms, a **complete restoration of respiratory function was not required and even needing some respiratory support would be considered meaningful.**

"So if there were a treatment for peroxisomal disorders, even if he couldn't come off completely of some type of mechanical intervention, maybe it just being a nighttime thing. Maybe during the day, he could be on room air, and then maybe at night on the vent, you know, something like that." - Mother of deceased child with ZSD

"I'd like to see [my child] be able to only need O2 50% of the time. I'd much rather that be during the day so we didn't have to carry huge tanks around constantly but I'll take what I can get." - Mother of child with ZSD

Other Desirable Clinical Outcomes in PD

Four caregivers in the town hall discussion mentioned that their child had experienced acute infections due to various causes (respiratory viruses, cellulitis, pressure ulcers, urinary tract infections, etc.) that had a significant impact on their daily lives and often would require hospitalization. Two caregivers shared that the reduction of the various circumstances that increased the risk for infection would be considered a meaningful clinical outcome.

"Reducing the risk of pressure ulcers that ultimately can lead to infections and hospitalizations." - Mother of child with ZSD

"Being able to avoid having to frequently do the straight cathing [catheter insertion] because I think that's what led to the frequent UTIs. So I think if we could in some way... deal with the bladder issues and the urinary retention in a way that just didn't result in just us having to cath, which leads to infections." - Father of deceased child with ZSD

One caregiver suggested that improved sleep in patients with PD may also be considered a meaningful outcome.

"So an improvement in the number of hours that a child is able to sleep through the night, I think that would be very helpful." - Mother of deceased child with ZSD

Perspectives on Placebo-Controlled Study Design

During our live polling, patients and caregivers were asked if they would enroll themselves or their children in a randomized clinical trial in which patients with PD receive a placebo instead of a drug but have the opportunity to receive the treatment at a later time. **The majority of live polling respondents (76.1%, 35 out of 46 respondents) indicated that they would participate in a randomized clinical trial in which PD patients would receive a placebo as well as treatment.** During the town hall discussion, one caregiver expressed support for clinical trial participation with PD patients, even with the possibility of receiving a placebo, noting the potential impact on the greater PD community:

"Even if you were [in] the placebo part of the study, you're still participating in something that could turn into a usable medication down the road or a usable treatment."
- Father of deceased child with ZSD

About 13% of polling respondents indicated that participation would depend on different factors, while about 10% indicated that they were unsure about participation or would not participate. During our town hall discussion, one caregiver of an adult patient expressed concerns about receiving a placebo during a clinical trial:

"I think one of the hardest things to deal with when you're trying to do a clinical trial is what I'm giving my child. What's potentially going to help her? Or is it just blank, you know, sugar pills?" - Mother of adult with ZSD

In our online survey, one caregiver mentioned that their participation in a randomized clinical trial would depend upon the impact on the quality of life of their child. During our focus groups, two caregivers described declining participation in a clinical trial not only because of the possibility of being in a placebo-controlled study, but also because of the **possibility of not being able to receive the treatment after the trial was complete, especially if benefits from the treatment were observed.**

"I didn't do one clinical trial specifically because of this, if my daughter got the actual medication, or whatever it was, they were trying it out, and it worked. Then, when the trial was done, there was nothing that said that she was still going to be able to continue it, and if she didn't continue it, was she just going to go right back to where she was before." - Mother of adult with ZSD

Perspectives on Undesirable Symptoms and Side Effects in Clinical Trial Treatment

Our online survey asked if participants would be willing to tolerate certain symptoms in order to address their or their child's most urgent symptom in a new clinical trial. Of the 27 respondents to the question, **70.3% (n=19 out of 27) indicated that they would be willing to tolerate certain symptoms if it addressed their or their child's most urgent symptoms,** 25.9% (n=7 out of 27) indicated "maybe", and one respondent stated that it would depend on certain factors, including overall impact on quality of life vs. simply life expectancy, although shortened life expectancy was stated as a concern by one caregiver during the town hall discussion. Another caregiver indicated that addressing symptoms that concerned them the most would influence the decision to participate if a clinical trial carried the risk of side effects:

> ***"[A] consideration would be the side effects. If you're going to treat [my child's] liver disease, I'm willing to put up with a lot more side effects. If you're going to try to treat her hearing loss and you're going to take away her joy or her laughter, I might be less likely to participate." - Mother of child with ZSD***

Another caregiver during the focus group stated their **concerns about treatment interactions between their child's existing medication regimen and that of the clinical trial:**

> ***"I'll be concerned about the drug-drug interactions with his routine medications and the new drugs on trial. So basically, he's on routine anticonvulsant medications. So I'll be worried if the new drugs on trial will reduce the effects of the anticonvulsants, thereby making seizures more often. So that would be one of my major concerns."***
> ***- Father of child with ZSD***

Some caregivers were concerned about overall pain and discomfort for their child if they participated in a clinical trial, and stated that they might not consider participation if pain and discomfort were possible, in addition to exacerbating symptoms. One caregiver during the focus groups shared that **for their adult daughter with DBPD, they would not consider clinical trial participation if it resulted in gastrointestinal side effects.**

Several caregivers felt that if they were **provided with adequate information on potential side effects and explicit guidance on how to mitigate or treat them,** it would help them make more informed decisions on clinical trial participation.

> ***"Regarding the potential barriers to clinical trial participation, as a parent, I would say give us information. Not just the basics, the potential side effects, but if we start to see that side effect, what are the things we can do at home to mitigate those side effects until we get a chance to go to a doctor or until a doctor calls us back."***
> ***- Mother of deceased child with ZSD***

> ***"But if we don't have a proper feedback mechanism because of that communication gap, that might be something that would cause hesitation [in clinical trial participation]. If [a new treatment is] something that can be measured and immediately stopped, that's a risk that I'm sure many of us would be willing to at least start. But if there isn't a feedback loop, and it's causing that irreversible harm and we're not going to find out until we've done excessive damage, then that's going to be a cause for concern."***
> ***- Father of adolescent with ZSD***

When caregivers and patients were subsequently asked in our online survey if they would still consider enrolling themselves or their child in a new clinical trial associated with a severe or life-threatening risk, 18 out of 39 respondents indicated that their decision would depend on the potential clinical benefits of the trial. One caregiver shared their thoughts on this point during the town hall discussion:

> ***"And I think that at least for me personally and my husband, we would be willing to take on quite a bit of risk, even if it did include something like severe or life threatening risk if we understood the benefit and if we believed the benefit outweighed that [risk] for our [child]." - Mother of child with ZSD***

When respondents were asked what specific benefits in a clinical trial would be necessary to accept a severe or life threatening risk, five respondents indicated improvement of mobility symptoms, one respondent indicated improvement of liver symptoms, and two respondents indicated treatment at the gene level, such as gene therapy, so that **multiple symptoms could be addressed.**

> ***"So for us, for a new treatment with severe life threatening risks, his ability to walk or at least walk with minimal support so that he can interact socially."***
> ***- Father of child with ZSD***

During the town hall discussion, most caregivers who were parents of children and younger patients indicated they would consider participation in a clinical trial, even if it was associated with possible life-threatening side effects. **However, adult patients and caregivers of adult patients shared that they were less inclined than caregivers of younger children to participate in a clinical trial with possible life-threatening side effects.**

> ***"For me, as a patient being 27 years old, there will not be minimal benefit if a trial has a life threatening risk because, well, I have been trying to translate it to English, we have a saying that is: 'Más vale malo conocido que bueno por conocer.' [Translation: Better the devil you know than the devil you don't]. And also I think at this point in my life, I already developed some strategies to cope and do everything I want. Well, maybe not everything, but mostly have a good quality of life. And I'm not going to risk the years I have because of a trial having a life-risking downside. So for me I think it's important to know that for young adults, maybe this question I will say no, there's no minimal benefit. But for a child, I think there is some minimal benefit. Maybe we don't have it in mind, but they have more hope of having a longer life, a better life." - Adult patient with ZSD***

> ***"I think for [my adult children], I don't know if I would participate in a clinical trial with them if there was a risk of life. At this point at [ages] 29 and 25, health-wise they're pretty stable. Now [my adolescent child who passed away at age 15], if I had the same situation with her, I think I would definitely take a clinical trial that even had a life-threatening side effect or risk involved to see a measurable difference in the slowing down of that leukodystrophy." - Mother of 2 adult patients and one deceased patient with ZSD***

Perspectives on Other Logistical Considerations for Clinical Trials

Mode of treatment administration or outcome assessment

Although most caregivers were open to various modes of treatment administration in clinical trials for PD, **several caregivers did express concern for how treatments would be administered with respect to the discomfort that it might cause their child, and whether or not the dose of the treatment was successfully being delivered to their child:**

> ***"One thing we always found when we were administering medicine was like 5 minutes after we gave it, maybe [our child] vomited and threw it up. And our concern was like, did she get enough of the dose or any of it? And hearing people talk about vomiting issues, maybe find something that these clinical trials, the administering drug, can actually make sure that it's been given to them. Just a way that we can ensure that they're getting the medicine, the correct dosage and is actually being absorbed into their body versus vomiting it up." - Father of deceased child with ZSD***

One caregiver of an adult patient with PD shared concerns not only about the treatment administration, but what measurements would need to be taken from their child.

One caregiver during the focus groups suggested that **having the option of various modes of treatment administration** may address some concerns with treatment administration and potentially increase clinical trial participation:

"I think that increasing or giving us a variety of methods to administer any treatments could definitely be a way to tailor this to help caregivers, parents, and individuals that actually have this disease. There's also individuals like my son who can't drink by mouth, and he has a feeding tube for all hydration. So just really being able to administer medications, treatments, whatever it may be in different ways. I would love to see a few options because our kids have so many different needs at different times of their life. For me, my son actually thinks that getting nose spray is kind of a part of our routine and activity. So if I could even do something like that, it would not be upsetting to him. I could also give it through the feeding tube, but anything orally through his mouth would be really upsetting for him." - Mother of adult with ZSD

Travel to Clinical Trial Site

Many caregivers shared concerns about the burden of travel to the clinical trial site as a potential barrier to participation. This included "financial burden," as described by one caregiver. Multiple caregivers during the town hall discussion described the **organizational and scheduling concerns** she had about participating in a clinical trial for PD. Two caregivers shared the burden associated with having to take time off work in order to participate in a clinical trial. One caregiver mentioned that **traveling with bulky, often life-sustaining equipment had significant effects on the burden of travel,** including cost:

"Getting to the clinical trials can be very difficult for our kids. It's hard to travel via plane, car, whatever. These kids, it's what they have to travel with. For example, wheelchair, oxygen. I know some people carry so much oxygen in their car, it should be illegal. It also raises concerns when you do travel out of state, you have to rent a car. You just can't rent the economy car. You've got to rent an SUV because you have the wheelchair."
- Father of adult with ZSD

To address these challenges, multiple caregivers suggested **multiple satellite clinic sites or opportunities for remote/telehealth sessions where certain measurements could be taken to minimize travel burden.** One caregiver stated that being given logistical information about the trial in advance could ease the organizational and financial burden of participation:

"But maybe even allowing us, me being a single mom and having two kids, giving us time in advance to prepare. So whether it's letting us know a few months in advance, this is when it's going to start. This is when this trial is going to happen so that not only are we able to prepare to be away from work, but we can make accommodations for our other children as well, too, and also try to be able to figure out those financial burdens, even if there's not resources available at that time. So letting us know ahead of time so that we're able to prepare our children, prepare ourselves and prepare the patient together as well, so that they know what's going on properly." - Mother of child with ZSD

Summary of Perspectives on Clinical Trials for PD

Overall, **families with PD are open to participating in clinical trials for PD,** regardless of the burden and even in the face of serious side effects of treatment. **Caregivers of younger patients appear to be more willing to consider participation, regardless of the burden, whereas adult patients and caregivers of adult patients are more hesitant in their willingness,** especially if there are life-threatening risks associated with treatment. Explicit, accessible and timely (long in advance of the clinical trial) information on the specific outcomes measured, the clinical trial logistics, and options for remote data collection provided by the clinical care team are important in maximizing participation in clinical trials for PD.

ADDITIONAL QUOTES

"So my first consideration would be the goal of the trial. Are you treating liver disease, which is ultimately going to kill her or are you treating her hearing loss, which is something I could manage?" (Mother of child with ZSD)

"If you were able to actually get up and walk even with assistance, we would consider an improvement." (Father of deceased child with ZSD)

"So for us, it would be a meaningful improvement in his ability to ambulate, ideally without support." (Father of child with ZSD)

"Walking is what I would like. That's [the] ultimate goal." (Father of child with ZSD)

"[Our child is] so shaky and his movements are very uncontrolled along with feeding himself and things of that nature. So that would be a great treatment for [him]." (Mother of child with ZSD)

"If he had improved vision, he would be able to be more independent. He would not need to have a guide with him at all times. That's measurable, absolutely." (Mother of adult patient with ZSD)

"And then, I would measure that with her hand eye coordination because she doesn't have much hand eye coordination. She wants to look away." (Mother of child with ZSD)

"Communication even goes with improving his vision. When you talk to speech therapists, they go to everything that's vision-based, and I gaze at devices, but [my son] can't use any of those, because he can't see that so that would be something that'd be great to improve." (Mother of child with ZSD)

"I think an ideal treatment would be something to address the liver and the progression of liver disease if somehow we could slow that down." (Mother of child with ZSD)

"Perhaps a reduction in the number of times annually that a child would need to receive a transfusion of some kind." (Mother of deceased child with ZSD)

"Then those varices, the bleeds, I mean, they also cause an extreme amount of pain. She cried for two weeks straight once, and they didn't know why. So if we could slow that down, just get rid of that pain for her and yeah, stop those bleeds." (Mother of child with ZSD)

"I'm hoping that in my lifetime, we will see medications that can better control seizures and kids with PBD, lessen their frequency and intensity." (Father of deceased child with ZSD)

"While they're on these cocktail of medications that help them relax and help decrease the amount of seizures that they have, I would really like to see some sort of development and keeping them awake, keeping them active." (Mother of deceased child with ZSD)

"Important improvements in respiratory treatment could include improvement of portable oxygen equipment and addressing muscle strength or the ability to breathe more effectively on their own." (Mother of deceased child with ZSD)

"We were approached to enroll [our child] in [a clinical trial for hydroxychloroquine], and I had to say no, because there was a 50% chance of her being off her hydroxychloroquine for 9 months." (Mother of child with ZSD)

"And because her symptoms are so stabilized, my fear of going off that for so long would cause a regression, like, maybe this is what's causing her to be stable. And I couldn't take that chance, even though the researcher in me is like this is bad. I know it's so important to be participating in this. But just as a mother I was, like, nope, I can't do it." (Mother of child with ZSD)

"I guess the factors that I would consider for [my child] is how would this trial affect his quality of life. Would it really help him or would it just cause him to just survive rather like just being a shell of a human? And I would rather have a happy, giggly baby than just a baby that's surviving and has no quality of life." (Mother of deceased child with ZSD)

"I think that a lot of people are concerned about negative side effects, even all the way to death. I actually have a concern of prolonging life [as the] outcome for some of the invasive therapies and gene therapies. Are you prolonging life without improving the quality of life?" (Mother of adult with ZSD)

ADDITIONAL QUOTES

"... anything that would maybe decrease their life expectancy. Or death, I think, would be the big one, or yeah, anything that's just gonna make things worse or progress faster rather than improve." (Mother of a child with ZSD)

"Concerns about possible side effects would be any reaction with current medications that are working for [my child]." (Mother of adolescent with ZSD)

"I think anything that would worsen his quality of life, like if he suddenly required more oxygen, or was more uncomfortable with his feeds, was spitting up more or physically just seemed more uncomfortable. I think, in general, any like increased discomfort, pain, anything that impacts this quality of life. But if his needs in other areas increased, I don't think it would be worth it." (Mother of deceased child with ZSD)

"Is it something that we could give through G tube, or is it going to be a shot that could cause some medical trauma that our kids already have? But just how it would be administered, so would a shot be off the table for [my child]." (Mother of child with ZSD)

"I think the interventions. What types of procedures that your child will have to go through? The blood work, MRIs, whatever, all that. What specific testing would be done during the trial? I think that that would be a big question for us. How much would they have to go through?" (Mother of adult with ZSD)

"... That would certainly be a concern of mine, is that there being a clinical trial that I couldn't/wouldn't be able to participate in due to locations." (Mother of 2 adult patients with ZSD, living outside of United States)

"And you also have to take into consideration the cost of gasoline, the cost of eating out, the cost of taking time off from work." (Mother of deceased child with ZSD)

"So we both work full time. So it's a lot for us to both take off at the same time for the same length of time." (Mother of child with ZSD)

"So I think it would be very important in looking at clinical trials is be able to expand those not to [just] large major hospitals, but also consider smaller rural hospitals, because if not, there's many of us that may not be able to access care and spend a lot of time in a car just for a blood draw and a doctor's appointment." (Mother of deceased child with ZSD)

"So I love the idea of remote sessions. Remote visits would be huge, but even just help financially with travel and just understanding the little things that come with that." (Mother of child with ZSD)

"I believe having some remote data collection sites for our patients, this will be very helpful to follow up visits, closer to home and doing follow up visits via websites on your Zoom platforms and everything else that you can do those without travel. It's too hard to travel." (Father of adult with ZSD)

Overall Conclusion and Summary

The multitude of symptoms in PD manifest in a variety of ways, often progressively, and can affect patients from infancy into adulthood. These symptom categories that are discussed at length in this report, including vision loss, hearing loss, mobility and motor symptoms, intellectual disability, gastrointestinal dysfunction, bleeding issues, seizure disorders, respiratory symptoms, adrenal insufficiency, and dental symptoms are by no means comprehensive and may not include all of the individual manifestations of PD. Furthermore, the majority of the patients represented are diagnosed with ZSD, which limits specific insights on other PD. Nevertheless, the impacts of the symptoms described in this report are broad with respect to day-to-day living for individuals with PD, with the primary impacts being on independent activity, communication and social interactions, academic and work performance, physical injury, increased risk of hospitalization, and nutritional status. Moreover, each of the symptom categories have multiple impacts across these classifications, with sensory loss affecting nearly every impact classification, as an example. Consequently, these symptoms together amass a cumulative impact on daily life in individuals as well as their caregivers, considerably more than any effect these individual symptoms would have alone. Finally, the symptoms in PD are progressive, often due to a leukodystrophy, which has a continually increasing impact on daily lives and general health. Taken together, the symptoms, impacts, and overall lived experiences of individuals with PD are both far-reaching and burdensome, resulting in a tremendous impact on the overall quality of life on patients and families.

Currently, there are no overall treatments specific for PD, and most existing treatments and management address only individual symptoms. Treatment for adrenal insufficiency is generally effective, but most available current treatments are, at best, inconsistently effective and have many side effects. Treatment of individual symptoms in PD also often requires the administration of multiple medications and other treatment regimens, even within symptom categories. In some cases, treatment of one symptom category may exacerbate the symptoms of another category. In other cases, treatment for a symptom is not feasible due to the reliance of treatment on other compromised symptoms, such as in the case of combined vision and hearing loss. There is an urgent need for more effective, safer, and less burdensome treatment plans and management of PD symptoms.

The development of new treatments for PD is a growing focus in scientific research. Given the multi-system, multi-symptom nature of PD, a thorough evaluation of clinical trial design will be required to ensure that new therapeutics are achieving meaningful outcomes for patients and families. Although some patients and caregivers have indicated some difficulty and inconvenience associated with the burden of travel, specific forms of treatment administration, and concerns about side effects as well as the overall clinical trial design, nearly all families participating in the meeting, preliminary focus groups and online surveys indicated that regardless of these barriers, any clinical trial for PD would be considered potentially feasible provided that the benefits of therapeutics on given outcomes would outweigh the risks, and that families were provided with thorough information regarding the trial, including possible side effects and proposed mitigation strategies, and an explicit timeline of clinical trial activities well in advance of the trial. With respect to specific patient outcomes in clinical trials, patients and caregivers shared details of what they would like to improve with respect to motor and mobility symptoms, vision and hearing loss, gastrointestinal symptoms, related bleeding issues, intellectual disability, seizures, respiratory symptoms and overall progression of symptoms related to leukodystrophy. In some cases, this related back to improvement in specific impacts, such as communication and social interactions, or improved ability to complete activities of daily living more independently. For many symptom and impact categories, **the degree of improvement that would be considered meaningful was indicated** in the discussions. In nearly all symptom and impact categories, it was evident that **new treatments offering incremental change without full restoration of function would still be considered meaningful change.**

Overall, families of individuals with PD report that various symptom categories need to be improved upon with future therapeutics, highlighting sensory loss, mobility symptoms, and gastrointestinal dysfunction. Patients and families have indicated willingness to participate in clinical trials if the treatments result in meaningful improvement of any of the outcomes identified in our meeting, focus groups, and survey responses. Moreover, families affected by PD have clearly indicated their willingness to continue to engage in the drug development process, even if their children with PD have already passed away or would not potentially benefit from treatment. The feedback provided during this meeting, the preliminary focus groups, interviews, and online survey have served as an important foundation to develop meaningful outcomes to measure in clinical trials for PD.

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APPENDICES

Appendix 1: Agenda

Appendix 2: Online Surveys
Caregiver Survey
PFDD Caregiver Survey for Report

Patient Survey
PFDD Patient Survey for Report

Appendix 3: EL-PFDD Meeting Polling and Discussion Questions
GFPD EL PFDD Meeting Polling and Discussion Questions.docx