ALSTRÖM SYNDROME INTERNATIONAL

Voice of the Patient Report

Externally-Led Patient Focused Drug Development Meeting

September 22, 2022

In memory of
Katelyn Denbow
November 11th 1997 – January 7th 2023

ASI would like to thank its grassroots community, what we call The Alström Family, for its support. As always, we also acknowledge the support of all stakeholders, especially the unremitting efforts of those impacted specifically by Alström Syndrome and the dedicated commitment of the many clinicians and fierce researchers who have facilitated our arrival at such a juncture as this opportunity to be heard collectively. We especially wish to thank Dr. Clair Francomano; Dr. Alex Levin; Dr. Chase Palmer; Dr. Anne Nordstrom, who has dedicated herself for many, many years in so many ways to the mission which she helped develop in the very beginning of our voyage; and the patients and parents who testified so effectively and powerfully. Finally, we wish to acknowledge with deepest appreciation our mentor at the FDA, William Lewallen, and our tireless and talented science writer and author of this report, Dr. Carol Berkower.

- Robin Marshall, Executive Director, ASI

VOICE OF THE PATIENT – THE ALSTRÖM SYNDROME JOURNEY
ASI Externally-Led Patient-Focused Drug Development Meeting
September 22, 2022

Introduction and Key Meeting Insights

Introduction

Alström Syndrome International (ASI) hosted the Alström Syndrome (AS) Externally-Led Patient Focused Drug Development (EL-PFDD) meeting on September 22, 2022. The purpose of this meeting was to enable people living with AS to paint a clear picture of how this disease impacts their daily lives and communicate their expectations and priorities for the development of new treatments to officials at the US Food and Drug Administration (FDA) and other stakeholders. The symptoms, burdens, current approaches to treatment, and unmet treatment needs associated with AS were addressed from the perspectives of patients and caregivers. The meeting was held in hybrid format, enabling both in-person discussion for those able to attend and participation online by members of the AS community scattered around the world.

This EL-PFDD meeting was modeled after the work of the FDA's Patient Focused Drug Development (PFDD) initiative. PFDD is "a systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation."[1] This Voice of the Patient report provides a high-level summary of the perspectives generously shared at the meeting by individuals living with AS and caregivers. The report also includes selected comments that were submitted through an online portal as well as data captured by ASI's survey, "Patient and Caregiver Perspectives on AS Burden, Treatment, and Drug Development," which was held concurrently with the EL-PFDD meeting process and extended for an additional two months.

The information in this report may be used to guide therapeutic development and inform the FDA's benefit-risk evaluations when assessing therapies to address AS. The hope is that this information will catalyze better treatments, and ultimately a cure, for those affected by AS.

ASI has provided this report to the FDA, government agencies, regulatory authorities, medical products developers, academics, and clinicians, and it is publicly available for the many stakeholders in the DS community. Note that AS affects every system in the body, and every affected individual's journey is unique. While the information presented at the September 22, 2022 EL-PFDD meeting reflects a wide range of AS experiences, not all symptoms and impacts could be captured in this report.

Key Messages on the Burden of Disease

The first half of the meeting focused on the burden of disease in AS. Testimonies from patients and parents portrayed a devastating, life-limiting syndrome that charts a wildly unpredictable course, displaying dramatic variation from one patient to another. Parents of young children

[1] See https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development (accessed November 15, 2022)

described the all-consuming nature of AS, which requires constant vigilance and upends every aspect of their lives. Adult AS patients recounted their efforts to live as normally as possible and how these efforts were undercut by the sudden onset of organ failure or severe infection, leading to life-threatening crises and further reducing their capacity to live independently.

1. **Alström Syndrome affects nearly every organ of the body.** Vision loss starts early and usually leads to blindness by the mid-teens. Congestive heart failure may occur in infants and teenagers. In early childhood through early adulthood, individuals with AS experience some combination of hearing loss; developmental delays; uncontrolled weight gain; kidney, heart, and liver disease; diabetes; thyroid complications; pancreatitis; and other endocrine, metabolic, skeletal, and skin disorders. In early adulthood (if not sooner), severe organ damage may require transplantation of the kidney, liver, or heart. AS does not typically affect cognition.

2. **AS is a progressive disease, with its own timeline. Early diagnosis and regular monitoring are essential for early treatment that can slow the progression to serious organ damage.** When adult maladies, such as liver cirrhosis, occur in teenagers, they are often misdiagnosed by practitioners unfamiliar with AS. Heart failure may present as difficulty breathing, leading to pulmonary interventions. Liver disease may present as esophageal bleeding. Small changes in blood biomarkers may conceal rapidly progressing kidney disease. Fibrosis in AS is a rapid process, and organs may undergo irreparable damage during a standard "wait-and-see" monitoring regimen. Over time, untreated disease in one organ can exacerbate damage to others, complicating efforts at treatment even after the underlying cause has been discovered.

3. **AS significantly decreases both life expectancy and quality of life.** Multiple diagnoses acting at the same time can increase the complexity of treatment, disease severity, morbidity, and mortality. Any of a wide array of phenotypes may be life-threatening at any given time.

4. **The course of disease varies among individuals.** The course of AS is unpredictable, even for affected siblings carrying identical disease-causing mutations. Heart failure can occur in infancy, the teenage years, both, or neither. Parents compare living with AS to riding a roller coaster, careening from one crisis to another.

5. **Individuals with AS use a vast array of devices and treatments to manage the disease on a daily basis. Many are dependent on organ transplants or other lifesaving surgeries.** The range of assistive devices includes home oxygen, heart monitors, pacemakers, glucose sensors, and inhalers; white canes, Braillers, and guide dogs; hearing aids or cochlear implants; and wheelchairs. Patients take multiple medications, some exceeding 20 pills a day. Lifesaving interventions include dialysis; open heart surgery to implant a pump or pacemaker; and heart, liver, or kidney transplant.

6. **AS places an incalculable burden on the patient and the family.** Parents describe AS as a monster that takes over families, causing profound sadness and unrelenting fear, where just

as one life-threatening situation is stabilized, another rears its head. The day-to-day management of disease impedes educations and careers and leads to social isolation, boredom, and physical and emotional exhaustion for both patients and caregivers. Treatment for AS also imposes a significant burden, with frequent (and sometimes very long) hospitalizations, doctor's visits, and time away from home and school further impacting the quality of life of both patients and caregivers.

Key Messages on the Burden of Treatment and Access to Clinical Trials

The second half of the meeting focused on issues of treatment and drug development. Misdiagnoses led to treatments that were ineffective, while organ damage progressed undetected, sometimes for years. Participants emphasized the need to treat the patient as a whole person rather than a collection of diseased organs. Parents and patients expressed a strong willingness, in some cases desperation, to participate in clinical trials focused on developing new treatments for AS.

1. **Effective treatment for AS requires collaboration and communication among health-care professionals**. Current treatments for AS address individual symptoms rather than the underlying cause of disease. Given the complex interplay among affected systems in AS, as well as the atypical presentation and timelines of many disease phenotypes, optimal treatment requires continual communication among a team of specialists.

2. **Conscientious management and treatment can appreciably decrease morbidity and mortality.** Both medical and surgical interventions carry serious risks for AS patients. Treatment protocols should be tailored to the disorder in order to avoid unintended consequences. Polypharmacy must be managed to avoid causing potentially harmful drug interactions or exacerbating other symptoms of AS, such as liver disease or obesity. Short of a cure that targets the genetic defect, drug development is key to improving both quality of life and life expectancy.

3. **Parents and patients are eager to participate in clinical trials.** The currently available treatments for AS fall far short of patients' needs. Given the unrelenting course of disease and the limitations of existing treatments, parents are willing to accept the risks inherent to clinical research in exchange for the hope of better treatments, if not for their own children, then for others. Patients expressed their willingness to participate in clinical trials, knowing that the knowledge gained might not benefit them directly.

4. **Clinical trials should employ endpoints that are appropriate for AS patients.** The tremendous variability in disease manifestation and severity, combined with the small number of patients available for research, makes it difficult to evaluate efficacy of new treatments using current FDA standards. New endpoints may be necessary for the evaluation of treatments targeted to AS. New treatments should not adversely impact patients' quality of life.

Meeting Summary

The Alström Syndrome International (ASI) Externally-Led Patient Focused Drug Development (EL-PFDD) meeting was held in hybrid format, with both in-person and remote participants, in Towson, Maryland on September 22, 2022. This meeting represented an important opportunity for patients and family caregivers to share their perspectives on the challenges and unmet treatment needs of those living with AS. In his welcoming remarks, Robin Marshall, executive director of ASI, noted that this meeting was a long time coming and thanked the FDA for its support. The meeting agenda is provided in **Appendix 1**.

Sheila Farrell, MD, FDA Division of Rare Diseases and Medical Genetics, provided an overview of the EL-PFDD. Farrell noted that the FDA plays an advisory role throughout the drug development cycle to ensure that questions of safety and effectiveness are adequately addressed during clinical trials. Of particular relevance to this meeting, she noted, was the FDA's imperative that outcome measures are clinically meaningful to patients. PFDD is a systematic approach to help ensure that patients' experiences, perspectives, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation.

Dr. Farrell emphasized the importance of this meeting for the development of drugs for Alström Syndrome. "A cure is the goal for everything, but what is it that's important to Alström patients, that they would want to change, short of a cure?" she asked. Patients are the experts on what symptoms and burdens matter most, and only patients know the risks they would be willing to accept for a given level of effectiveness. This makes patient input crucial for guiding development of new treatments. "The information that you provide today can help investigators and sponsors design better clinical trials by focusing on demonstrating that the drug has an effect on an outcome measure that patients report is clinically meaningful to them," said Dr. Farrell. This report will be immortalized on the FDA website[2] and will be used for evaluation of future drug applications for treating AS.

This Voice of the Patient meeting will focus on *people*, said Mr. Marshall, rather than medical issues, "because what we're really concerned with today is the lived experience of Alström Syndrome, how life itself is impacted by the day-to-day demands of dealing with something as complicated as Alström Syndrome and, most importantly, what do we do about it?" In addition to AS patients, who bear the greatest burden of disease, stakeholders include parents, caregivers, researchers, clinicians, pharmacists, and many others. Mr. Marshall dedicated this meeting to the memory of his wife, Jan Marshall, "the mother of all things Alström," who "lived her life feeling and thinking and addressing those issues…trying to relieve in some way the burden of this disease, the challenges you all face…and brought us pretty far down the road."

[2] See https://www.fda.gov/industry/prescription-drug-user-fee-amendments/condition-specific-meeting-reports-and-other-information-related-patients-experience (accessed November 17, 2022)

Clair A. Francomano, MD, ASI scientific advisory board chair, gave a brief history of Alström Syndrome and provided an overview of the genetics of the disorder and the myriad cellular pathways associated with the affected protein, ALMS1. Chase A. Palmer, PharmD, ASI president, reviewed the natural history of AS, noting that every organ in the body is affected, damage is progressive and at times life-threatening, and drug development is key to improving life expectancy and quality.

Anne D. Nordstrom, MBA, PhD, conducted real-time online polling of all meeting attendees using questions from ASI's survey, "Patient and Caregiver Perspectives on AS Burden, Treatment, and Drug Development." Survey questions probed the relative contributions of the various AS symptoms to disease burden, strategies that individuals use to manage disease, the effectiveness of these strategies, and priorities for developing new treatments. To include as many voices as possible, an online survey and comment submission portal remained open for two months after the meeting. Eighteen individuals participated in polling during the meeting, and an additional 19 responded to the survey before it was closed. Caregivers responding for a patient were instructed to adopt the perspective of the individual with AS; caregivers with multiple charges were instructed to choose one individual and respond consistently for them. Selected online comments submitted during the meeting are included in the body of this report**.** Demographics of the respondents are provided with survey questions, answers, and all comments submitted via the post-meeting survey in **Appendix 2**.

The Alström Syndrome EL-PFDD meeting was structured around three key topics, each of which was addressed with a question-and-answer session as well as prerecorded videos. The morning session included Topic 1: *Quality of Life/Burden of Disease* and Topic 2: *Quality of Life/Overcoming the Odds and the Quest for Independence*. In moderated discussions, panels of young adults with AS described the difficulties of waging a lifelong battle against an unpredictable and severe disease while trying to pursue their interests and maintain some independence. In two prerecorded videos, parents of young children with AS narrated their experiences, including early misdiagnosis followed by the devastating diagnosis of AS, open-heart surgery, vision and hearing loss, autism, and developmental delays. They described heroic efforts to obtain adequate treatment, uprooting families and straining relationships, trying to create a normal life for their other children while maintaining a near-constant vigil to address the overwhelming needs of their affected child. In a third video, one mother narrated the story of her three sons with AS, the oldest of whom recently had open-heart surgery at age 16.

In the afternoon, six prerecorded videos addressed AS from the patient's perspective. In testimonies that some had composed, transcribed into Braille, and videotaped on their own, adults described the challenge of trying to live as normal a life as possible. Participants recounted their struggles to pursue a college education or employment in the face of debilitating heart, liver, and kidney disease, in addition to blindness and hearing loss. Individuals recounted their journeys in and out of hospitals, receiving (or failing to qualify for) organ transplants, as well as the hours spent each day managing the disease. The afternoon session also addressed Topic 3: *It's Complicated – Issues of Diagnosis, Burden of Treatment, Access to Clinical Trials*, which engaged all participants in a discussion of the gaps in treatment

and the risks patients would consider taking to test new therapeutic options. Discussion questions are provided in **Appendix 3**. Dr. Francomano and Alex V. Levin, MD, facilitated the discussions.

Appendix 4 provides brief bios of AS patients represented at the in-person meeting. This report, the meeting transcript, and a recording of the meeting can be found on the ASI web site.[3]

The in-person meeting was attended by eight individuals with AS, 12-15 parents, one spouse, and one sibling. Two FDA representatives were in attendance, as well as seven members of the ASI board, including researchers and clinicians. An estimated 150 individuals attended virtually. These included patients, parents, healthcare providers, and a variety of stakeholders from academia, industry, and non-profit groups.

Background on Alström Syndrome

What is Alström Syndrome?

Alström Syndrome (AS) is a rare genetic disorder that affects nearly every organ in the body.[4] AS is characterized by progressive vision loss, hearing impairment, cardiovascular disease, childhood obesity, extreme insulin resistance, non-alcoholic fatty liver disease (NAFLD), chronic kidney disease, gastrointestinal and urologic disorders, and endocrine and metabolic dysfunction. Progressive damage to kidneys, liver, heart, and lungs causes scarring, or fibrosis, which in many patients can lead to organ failure and necessitate a lifesaving transplant. The multiple signs and symptoms of AS, as well as their age of onset and severity, vary among individuals, even between siblings bearing identical genetic alterations. The nature of AS – unpredictable, incurable, clinically wide-ranging and severe – has led affected families to describe it as a monster or to compare their lives to an unending roller coaster ride from one medical crisis to the next.

What causes Alström Syndrome?[5]

Alström Syndrome (AS) is a genetic disorder caused by pathogenic variants of the *ALMS1* gene.[6] Transmission of AS is autosomal recessive, so individuals who carry one healthy copy of *ALMS1* and one pathogenic *ALMS1* variant are not affected. However, children who receive two copies of the altered gene (one from each unaffected parent) are affected. The estimated incidence of

[3] https://www.alstrom.org
[4] Marshall, J. D. (2013). *The Alström Syndrome Handbook*. Mount Desert, ME: Alström Syndrome International.
[5] Most of this content was taken from the September 22, 2022 presentation by Clair A. Francomano, MD, ASI scientific advisory board chair
[6] Hearn, T., Renforth, G. L., Spalluto, C., Hanley, N. A., Piper, K., Brickwood, S., . . . Wilson, D. I. (2002). Mutation of ALMS1, a large gene with a tandem repeat encoding 47 amino acids, causes Alström syndrome. *Nat Genet, 31*(1), 79-83. doi:10.1038/ng874

AS is one in a million live births, with roughly 1,200 cases identified to date, of which 200-300 are in the United States.[7,8,9]

ALMS1 is a large gene, covering 224 kilobases of DNA on chromosome 2, comprising 23 exons that encode the ALMS1 protein.[6] Of the more than 268 pathogenic variants of *ALMS1* that have been identified to date, nearly all (96%) bear frameshift or nonsense mutations that are expected to produce a truncated, nonfunctional ALMS1 protein.[6,10,11] *ALMS1* gene variants that produce residual amounts of protein are associated with less severe disease than those that cause a complete absence of protein expression.[11]10 There are regional differences in the frequency of mutations found along the length of the *ALMS1* gene. For example, exons 8, 10, and 16 are hotspots for mutation, and the majority of disease-causing variants are mutated in one of these regions.[10] There are also regional differences in the severity of disease associated with mutations. Variants of *ALMS1* that are mutated in exons 1-7, near the beginning of the protein coding region, cause relatively mild disease, whereas those mutated closer to the middle of the gene are associated with more severe disease.[12] Individuals carrying mutations only in exon 8 were reported to have delayed and milder renal complications.[13]

The ALMS1 protein is found in many cell types throughout the body and appears to be important for multiple processes, though its precise function is unknown. In cells with cilia, hairlike projections that are important for moving molecules within and between cells, ALMS1 can be found localized to the base of the cilia. ALMS1 is also found in centrosomes, which play a role in cell division.[14,15] The absence of ALMS1 protein has been shown to impair the function

[7] Paisey, R. B., Steeds, R., Barrett, T., Williams, D., Geberhiwot, T., & Gunay-Aygun, M. (2019). Alström Syndrome. In M. P. Adam, D. B. Everman, G. M. Mirzaa, & e. al. (Eds.), *GeneReviews [Internet]*. Seattle (WA): University of Washington, Seattle.

[8] Tahani, N., Maffei, P., Dollfus, H., Paisey, R., Valverde, D., Milan, G., . . . Geberhiwot, T. (2020). Consensus clinical management guidelines for Alström syndrome. *Orphanet J Rare Dis, 15*(1), 253. doi:10.1186/s13023-020-01468-8

[9] Robin Marshall, *pers. comm*

[10] Marshall, J. D., Muller, J., Collin, G. B., Milan, G., Kingsmore, S. F., Dinwiddie, D., . . . Naggert, J. K. (2015). Alstrom Syndrome: Mutation Spectrum of ALMS1. *Hum Mutat, 36*(7), 660-668. doi:10.1002/humu.22796

[11] Chen, J. H., Geberhiwot, T., Barrett, T. G., Paisey, R., & Semple, R. K. (2017). Refining genotype-phenotype correlation in Alström syndrome through study of primary human fibroblasts. *Mol Genet Genomic Med, 5*(4), 390-404. doi:10.1002/mgg3.296

[12] Dassie, F., Lorusso, R., Benavides-Varela, S., Milan, G., Favaretto, F., Callus, E., . . . Maffei, P. (2021). Neurocognitive assessment and DNA sequencing expand the phenotype and genotype spectrum of Alström syndrome. *American Journal of Medical Genetics. Part A, 185*(3), 732-742. doi:10.1002/ajmg.a.62029

[13] Marshall, J. D., Hinman, E. G., Collin, G. B, Beck, S., Cerqueira, R., Maffei, P., and Naggert, J. K. (2007) Spectrum of ALMS1 variants and evaluation of genotype-phenotype correlations in Alström syndrome. *Hum Mutation*. 28(11), 1114-23. doi: 10.1002/humu.20577

[14] Hearn, T., Spalluto, C., Phillips, V. J., Renforth, G. L., Copin, N., Hanley, N. A., & Wilson, D. I. (2005). Subcellular localization of ALMS1 supports involvement of centrosome and basal body dysfunction in the pathogenesis of obesity, insulin resistance, and type 2 diabetes. *Diabetes, 54*(5), 1581-1587. doi:10.2337/diabetes.54.5.1581

[15] Collin, G. B., Marshall, J. D., King, B. L., Milan, G., Maffei, P., Jagger, D. J., & Naggert, J. K. (2012). The Alström syndrome protein, ALMS1, interacts with alpha-actinin and components of the endosome recycling pathway. *PLoS One, 7*(5), e37925. doi:10.1371/journal.pone.0037925

and formation of cilia.[16,17] However, the precise function of ALMS1 protein is unknown; indeed, the protein is likely to be produced as multiple isoforms with diverse functions.

BOX 1. A Brief Timeline of Alström Syndrome [18]

1959 - AS was first reported by Carl-Henry Alström, who described three cousins with similar symptoms.[19]
1973 - AS was identified in three sisters whose parents were unaffected, suggesting an autosomal recessive pattern of inheritance.[20]
1997 - AS was linked to the short arm of chromosome 2 (region 2p).[21]
1998 - The AS gene was further narrowed down to region 2p12-13.[22]
2002 - The AS gene, *ALMS1,* was identified and characterized.[6]
2005 - A mouse model of AS was developed.[23]
2020 - The first consensus clinical management guidelines for AS were published.[8]**Error! Bookmark not defined.**

Other roles of the ALMS1 protein include organization of actin (important for muscle); trafficking of proteins within cells; and cell cycle regulation.[15,17,18] Consistent with its multiple roles and its presence in tissues throughout the body, disruption of the ALMS1 protein can lead to many adverse outcomes, as is seen in AS. Due to the localization of ALMS1 to cilia, AS is referred to as a ciliopathy, and it shares some clinical features with other ciliopathies, such as Bardet-Biedl, Meckel-Gruber, and Joubert Syndromes.[24]

Researchers have begun to decipher the role of ALMS1 in the regulation of blood sugar, which is important because many individuals with AS develop severe insulin resistance, culminating in Type 2 diabetes.[8] ALMS1 is required for trafficking of the insulin receptor to the plasma

[16] Jagger, D., Collin, G., Kelly, J., Towers, E., Nevill, G., Longo-Guess, C., . . . Forge, A. (2011). Alström Syndrome protein ALMS1 localizes to basal bodies of cochlear hair cells and regulates cilium-dependent planar cell polarity. *Hum Mol Genet, 20*(3), 466-481. doi:10.1093/hmg/ddq493
[17] Hearn, T. (2019). ALMS1 and Alström syndrome: a recessive form of metabolic, neurosensory and cardiac deficits. *J Mol Med (Berl), 97*(1), 1-17. doi:10.1007/s00109-018-1714-x
[18] From the September 22, 2022 presentation by Clair A. Francomano, MD, ASI scientific advisory board chair
[19] Alström, C. H., Hallgren, B., Nilsson, L. B., & Asander, H. (1959). Retinal degeneration combined with obesity, diabetes mellitus and neurogenous deafness: a specific syndrome (not hitherto described) distinct from the Laurence-Moon-Bardet-Biedl syndrome: a clinical, endocrinological and genetic examination based on a large pedigree. *Acta psychiatrica et neurologica Scandinavica. Supplementum*, 1-35.
[20] Goldstein, J. I., & Fialkow, P. J. (1973). The Alström Syndrome: Report of three cases with further delineation of the clinical, pathophysiological, and genetic aspects of the disease. *Medicine, 52*(1), 53-71.
[21] Collin, G. B., Marshall, J. D., Cardon, L. R., & Nishina, P. M. (1997). Homozygosity mapping at Alström syndrome to chromosome 2p. *Human Molecular Genetics, 6*(2), 213–219. doi:10.1093/hmg/6.2.213
[22] Macari, F., Lautier, C., Girardet, A., Dadoun, F., Darmon, P., Dutour, A., . . . Grigorescu, F. (1998). Refinement of genetic localization of the Alström syndrome on chromosome 2p12-13 by linkage analysis in a North African family. *Human Genetics, 103*(6), 658-661.
[23] Collin, G. B., Cyr, E., Bronson, R., Marshall, J. D., Gifford, E. J., Hicks, W., . . . Naggert, J. K. (2005). Alms1-disrupted mice recapitulate human Alström syndrome. *Hum Mol Genet, 14*(16), 2323-2333. doi:10.1093/hmg/ddi235
[24] Grochowsky, A., & Gunay-Aygun, M. (2019). Clinical characteristics of individual organ system disease in non-motile ciliopathies. *Translational science of rare diseases, 4*(1-2), 1-23. doi:10.3233/TRD-190033

membrane of fat cells and for regulation of pancreatic beta cells, which produce insulin.[25] A recent study found that ALMS1 constitutes part of a molecular switch inside fat cells that triggers these cells to absorb glucose from the bloodstream in response to insulin.[25]

What are the symptoms of Alström Syndrome?[26]

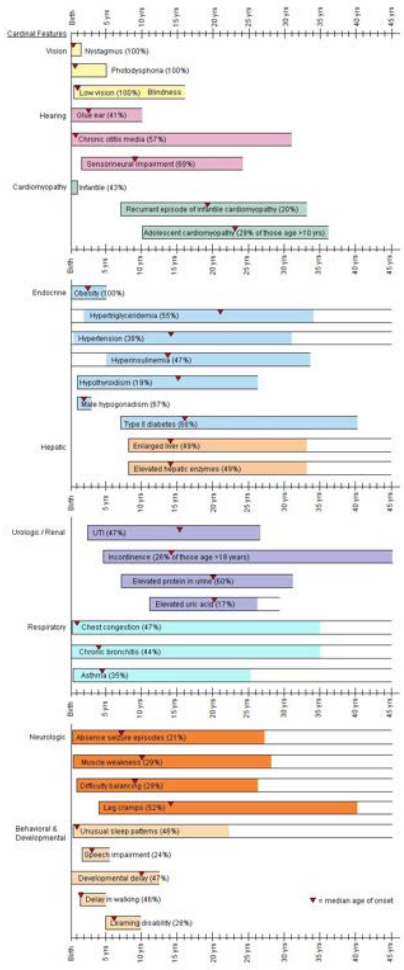
AS is a multi-system, progressive disorder that affects every cell and system in the body.[4] Clinical features of AS vary considerably among patients, even siblings carrying identical pathogenic mutations. There is also wide variation in the age of onset of the each of the signs and symptoms of disease (Figure 1). The multiple comorbid conditions that characterize AS lead to a significantly lowered lifespan as well as reduced quality of life years, with a significant fraction of patients' lives spent in doctor's appointments or hospitalized. The combination of blindness and debilitating organ damage can lead to difficulty with ambulation, leading many patients to use a wheelchair.

There is considerable variation in the constellation of clinical features and disease trajectories experienced by AS patients (Figure 1). For many individuals, the first signs of disease are nystagmus (wobbly eyes) and severe light sensitivity in infancy. By age 12-16, most children are legally blind. Hearing loss becomes noticeable in the first decade. Many children with AS experience cardiomyopathy (weakened heart muscle), often as infants, and almost two-thirds of individuals develop congestive heart failure at some stage in their lives.

[25] Schreyer, E., Obringer, C., Messaddeq, N., Kieffer, B., Zimmet, P., Fleming, A., . . . Marion, V. (2022). PATAS, a First-in-Class Therapeutic Peptide Biologic, Improves Whole-Body Insulin Resistance and Associated Comorbidities In Vivo. *Diabetes, 71*(9), 2034-2047. doi:10.2337/db22-0058

[26] Most of this content was taken from the September 22, 2022 presentation by Chase A. Palmer, PharmD, ASI president

Figure 1. Features reported in Alström Syndrome patients according to the organ systems that are affected, showing the typical age range when each feature's onset can be expected.[7]



Most children with AS have very large appetites and develop serious truncal obesity, which often moderates after puberty. Almost all AS patients develop insulin resistance, and most go on to develop type II diabetes and dyslipidemia. Non-alcoholic fatty liver disease and chronic kidney disease are also common and progressive. Damage to tissues may cause thickening and scarring, called fibrosis, which impairs function. Starting in their teenage years, patients may require liver, kidney, or heart transplants to replace failed organs.

In addition to the above symptoms, recurrent inflammation of the middle ear (otitis media) is common, and AS patients have a high prevalence of respiratory tract infections as well as genitourinary symptoms. Up to 20% of patients develop seizure or other neurological manifestations. Developmental milestones can be delayed and autistic-spectrum behavioral abnormalities are common, but cognitive impairment is very rare. Individuals with AS have demonstrated impressive academic achievements despite the considerable burden of disease.

In all its manifestations, AS decreases life expectancy and quality of life and places an incalculable toll on the patient and the family. Among a large collection of disease phenotypes,

any one can be life-threatening at any given time. On top of that, multiple comorbid conditions acting simultaneously have a compounding effect. One condition exacerbates another, which can lead to organ failure, hospitalization, and death.

How is Alström Syndrome diagnosed?

The earliest and most consistent symptom of AS is visual impairment. According to the consensus clinical management guidelines for AS, a history of early visual impairment and/or cardiomyopathy/heart failure should raise the possibility of AS. Differential diagnosis proceeds by ruling out other causes of retinal dystrophy. AS is confirmed by DNA sequencing and identification of the pathogenic mutations in both copies of the *ALMS1* gene.[8] A more nuanced set of diagnostic criteria can be used when only one mutant allele is detected.[4,7]

How is Alström Syndrome currently treated and managed?

There is no single treatment for AS; each symptom is treated on its own. Severe photophobia in young children can be ameliorated with special tinted glasses, but there is no way to halt progressive vision loss, and early training in Braille and white cane skills is recommended. Hearing loss is generally well treated with bilateral hearing aids. Calorie reduction and exercise are used to treat obesity, though problems with hypothalamic function may limit their effectiveness. Diabetes is treated through diet, exercise, and drugs that increase insulin sensitivity or through insulin injection (for patients who lose the ability to produce insulin). Cardiomyopathy may be managed with medication, but progressive damage to the heart may require surgery to implant a pump or pacemaker, or a heart transplant.

A combination of diet and medication is used to manage both liver and kidney disease, with dialysis for severe kidney disease and possible transplantation of either organ. Scoliosis may be treated with bracing, though severe cases may require corrective surgery. Hypertriglyceridemia must be controlled with medicines to reduce risks to the heart and pancreas. Endoscopic ligation (“banding”) is a commonly used treatment for enlarged veins (varices) in the stomach or esophagus that result when blood is diverted through these organs due to impaired flow in the liver. Seizures are treated with anticonvulsant drugs.

The pill burden with AS is extreme. Patients can be on ten different medications, some of which are taken multiple times per day, including injectables. In addition, patients use some combination of hearing aids, canes, glucose monitors, CPAPs, and many other medical devices on a daily basis. Conscientious management and treatment can optimize longevity for individuals with AS, and proper medication regimens can appreciably decrease morbidity and mortality.

Given the multiple systems that are involved, and the complex ways in which damage to one system affects others, patients should be treated in a team setting. Several publications have described a standard of care for AS, most recently the consensus clinical management guidelines published in 2020.[4,7,8]

What research is currently being conducted to develop new therapies for Alström Syndrome?

New drug development is the key to improving both quality of life and life expectancy for individuals with AS. However, there have only been two clinical trials to date of therapies targeted to this disease. In addition, recent clinical findings using a drug that recognizes premature nonsense mutations, which lead to truncated proteins, are of interest.

Clinical trials specific to Alström Syndrome

- Twelve AS patients in Birmingham, England participated in a phase 2 clinical trial of the drug PBI-4050, which demonstrated anti-fibrotic and anti-inflammatory activity in animal models.[27] In animals, PBI-4050 was able to prevent or reverse fibrosis in the heart, kidney, lung and liver, all tissues that are impacted by AS. Ten participants went on to a phase 2/3 clinical trial of PBI-4050, which intended to recruit additional participants, but this trial was prematurely terminated due to the Covid-19 epidemic.[28]

- A phase 2 trial of the drug setmelanotide suggested that it might reduce hunger and body weight in individuals with AS and the related disorder, Bardet-Biedl Syndrome (BBS).[29] Six AS patients participated in a phase 3 study conducted in the US to evaluate the efficacy and safety of this drug.[30,31] Following completion of the study, the US FDA approved setmelanotide for use in BBS but not AS, for which the results were inconclusive.[32,33]

- Liraglutide belongs to a class of drugs called glucagon-like peptide-1 receptor agonists (GLP1RA), which were developed to treat type 2 diabetes and have shown promise for the treatment of obesity.[34] A European study is being developed to test liraglutide for treatment of AS. Polling at this meeting revealed that a substantial number of AS patients already take Ozempic (semaglutide), another GLP1RA, off-label to aid with diabetes and weight loss.

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[27] Baig, S., Veeranna, V., Bolton, S., Edwards, N., Tomlinson, J. W., Manolopoulos, K., . . . Geberhiwot, T. (2018). Treatment with PBI-4050 in patients with Alstrom syndrome: study protocol for a phase 2, single-Centre, single-arm, open-label trial. *BMC Endocr Disord, 18*(1), 88. doi:10.1186/s12902-018-0315-6

[28] ClinicialTrials.gov Identifier for Phase 2 trial: NCT02739217 For Phase 2/3: NCT03184584

[29] Haws, R., Brady, S., Davis, E., Fletty, K., Yuan, G., Gordon, G., . . . Yanovski, J. (2020). Effect of setmelanotide, a melanocortin-4 receptor agonist, on obesity in Bardet-Biedl syndrome. *Diabetes Obes Metab, 22*(11), 2133-2140. doi:10.1111/dom.14133

[30] Haws, R. M., Gordon, G., Han, J. C., Yanovski, J. A., Yuan, G., & Stewart, M. W. (2021). The efficacy and safety of setmelanotide in individuals with Bardet-Biedl syndrome or Alstrom syndrome: Phase 3 trial design. *Contemp Clin Trials Commun, 22*, 100780. doi:10.1016/j.conctc.2021.100780

[31] ClinicialTrials.gov Identifier for Phase 2 and Phase 3 studies: NCT03746522

[32] Haqq, A. M., Chung, W. K., Dollfus, H., Haws, R. M., Martos-Moreno, G., Poitou, C., . . . Argente, J. (2022). Efficacy and safety of setmelanotide, a melanocortin-4 receptor agonist, in patients with Bardet-Biedl syndrome and Alström syndrome: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial with an open-label period. *Lancet Diabetes Endocrinol*. doi:10.1016/s2213-8587(22)00277-7

[33] See https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-treatment-weight-management-patients-bardet-biedl-syndrome-aged-6-or-older (accessed November 15, 2022)

[34] Drucker, D. J. (2022). GLP-1 physiology informs the pharmacotherapy of obesity. *Mol Metab, 57*, 101351. doi:10.1016/j.molmet.2021.101351

New investigations of relevance to AS

- The drugs ataluren/PTC124 and amlexanox enable the machinery that synthesizes proteins to bypass premature stop codons, which lead to formation of a truncated protein, and restore production of full-length protein.[35,36] About 40% of pathogenic variants of the *ALMS1* gene contain nonsense mutations, which create premature stop codons and lead to production of truncated ALMS1 protein. In laboratory studies, both ataluren and amlexanox restored production of ALMS1 in cultured cells from AS patients and improved the formation and function of cilia.[37] Importantly, these translational readthrough inducing drugs (TRIDS) have been approved for use in humans - ataluran as a treatment for Duchenne Muscular Dystrophy, and amlexanox to treat asthma and mouth ulcers.

- The novel modified peptide PATAS was recently shown to ameliorate whole-body insulin resistance and improve glucose intolerance, liver steatosis, and fibrosis in rodents.[38] PATAS acts by binding to the ALMS1 protein, and it requires a functional ALMS1 in order to act. PATAS might have potential for use in AS cases where the ALMS1 protein retains partial function.

[35] Welch, E. M., Barton, E. R., Zhuo, J., Tomizawa, Y., Friesen, W. J., Trifillis, P., . . . Sweeney, H. L. (2007). PTC124 targets genetic disorders caused by nonsense mutations. *Nature, 447*(7140), 87-91. doi:10.1038/nature05756

[36] Gonzalez-Hilarion, S., Beghyn, T., Jia, J., Debreuck, N., Berte, G., Mamchaoui, K., . . . Lejeune, F. (2012). Rescue of nonsense mutations by amlexanox in human cells. *Orphanet Journal of Rare Diseases, 7*(1), 58. doi:10.1186/1750-1172-7-58

[37] Eintracht, J., Forsythe, E., May-Simera, H., & Moosajee, M. (2021). Translational readthrough of ciliopathy genes BBS2 and ALMS1 restores protein, ciliogenesis and function in patient fibroblasts. *EBioMedicine, 70*, 103515. doi:10.1016/j.ebiom.2021.103515

[38] Schreyer, E., Obringer, C., Messaddeq, N., Kieffer, B., Zimmet, P., Fleming, A., . . . Marion, V. (2022). PATAS, a First-in-Class Therapeutic Peptide Biologic, Improves Whole-Body Insulin Resistance and Associated Comorbidities In Vivo. *Diabetes, 71*(9), 2034-2047. doi:10.2337/db22-0058

BOX 2. The Many Clinical Features of AS[39]

The most commonly observed symptoms of AS are listed here.[8,40,41]

Visual Impairment and Photophobia

Visual impairment is a significant clinical feature of AS, with nystagmus (wobbling eyes) often presenting as the first sign of disease during infancy. Photophobia (a physical intolerance to light) is also common. Retinal dystrophy occurs due to a degeneration of the light-sensing cone and rod cells, leading to rapid visual decline and legal blindness, which is usually reached before age 10 but may not occur until the teenage years.

Hearing Impairment

Deafness can occur as early as one year old. By age 10, 70% of AS patients have experienced hearing loss, beginning with the high frequency ranges. Bilateral hearing aids and cochlear implants can significantly improve hearing.

Diabetes and Insulin Resistance

Insulin resistance commonly occurs between ages 1 and 4, and type 2 Diabetes Mellitus can be diagnosed as early as 5. By age 16, over 80% of patients have diabetes. Insulin resistance can be extreme, and insulin doses of over 1000 IU daily have been reported in teenagers. Diabetes commonly leads to negative downstream effects, including kidney failure.

Obesity and Hyperphagia

Obesity is a significant clinical feature of AS, with rapid weight gain occurring between infancy and 3 years of age. Insatiable hunger (hyperphagia) begins in early childhood and contributes to increased weight gain.

Hypertriglyceridemia and Cholesterol

Most AS patients have moderate or severe hypertriglyceridemia, which raises the risks of both heart disease and acute pancreatitis. This is managed with aggressive dietary changes and drug therapy. Many patients also have dyslipidemia and low HDL levels.

Heart Failure and Other Cardiologic Problems

Cardiomyopathy is one of the cardinal features of AS and can be the first noticeable symptom in babies, even before eye problems are observed. Patients may develop infantile dilated cardiomyopathy and life-threatening congestive heart failure. Heart failure may recur or present for the first time later in life. Drug treatment is paramount to managing symptoms, but Individuals with AS may require open heart surgery, with implantation of a pacemaker or pump to assist the weakened heart muscle, or a heart transplant.

[39] From the September 22, 2022 presentation by Chase A. Palmer, PharmD, ASI president

[40] Marshall, J. D., Beck, S., Maffei, P., & Naggert, J. K. (2007). Alstrom syndrome. *Eur J Hum Genet, 15*(12), 1193-1202. doi:10.1038/sj.ejhg.5201933

[41] Marshall, J. D., Maffei, P., Collin, G. B., & Naggert, J. K. (2011). Alström Syndrome: Genetics and Clinical Overview. *Current Genomics, 12*(3), 225-235.

BOX 2. The Many Clinical Features of AS (continued)

Renal Dysfunction

Kidney dysfunction is another cardinal feature of AS, typically appearing in the late teens and 20's, and dysuria is common. The combination of hypertension and diabetes further damages the renal system. This can progress to renal failure, which has been successfully treated with kidney transplantation.

Liver Dysfunction

The degree of liver involvement varies widely among AS patients. However, Non-Alcoholic Fatty Liver Disease occurs in most patients, and cirrhosis and liver failure are common. Liver disease can lead to serious problems elsewhere in the body. For example, blood may be diverted from the liver to veins in the esophagus and stomach, which can become swollen (varices) and rupture, causing life-threatening bleeding. Liver failure can also lead to changes in mental function and to severe acute pancreatitis, which may be fatal. Some AS patients have been successfully treated with liver transplants.

Respiratory and Lung Disease

Patients with AS develop frequent infections of the respiratory tract and lungs, ranging from colds to pneumonia. Chronic inflammation of the airways leads to restrictive lung disease. Pulmonary hypertension is another big problem, and this can also have downstream effects on the heart.

Endocrine Disorders

Dysfunction of the pituitary gland and hypothyroidism result in a wide range of hormone deficiencies in patients with AS, who produce low levels of growth hormone and attain a relatively short adult stature.

Gastrointestinal Issues

AS patients of all ages can experience severe heartburn, known as gastro-esophageal reflux disease (GERD), as well as nausea and vomiting.

Developmental Delays

Developmental delays are common in AS patients due to a lack of gross and fine motor skills and deficits in sight and hearing. Autism diagnoses are also common, but no cognitive impairment has been observed.

TOPIC 1: Living with Alström Syndrome: Quality of Life and the Burden of Disease

Alström Syndrome affects every system in the body. However, disease profiles vary from one individual to another

> "Nothing is ever simple. Nothing is the same with any of us. One thing could be happening with me, it could not happen at all with someone else." – Callie Marshall, age 26

Prerecorded videos highlighted the distinct nature of each patient's AS journey. Nonetheless, certain phenotypes are nearly universal, and others are common enough to be considered cardinal features of the disease. Among the 37 AS patients, ranging in age from several months to 45 years old, who were represented in responses to the survey, 100% experienced visual symptoms. Most also had hearing symptoms (72%) and obesity (81%). A majority also experienced disorders affecting cardiopulmonary (69%), liver/gastrointestinal (56%), or nervous (56%) systems, as well as structural (skeletal, dermatological, or dental) anomalies (69%), such as scoliosis, skin tags, dental anomalies, hair loss, or short stature. Diabetes affected 47%, endocrine function was disrupted in 47%, kidney disease affected 38%, and 31% had additional symptoms not listed in the poll. The percent of patients who experienced non-visual symptoms tended to increase with advancing age.

Symptoms vary among siblings with identical mutations. Jennifer Potter compared the AS journeys of her three sons: Chad (age 17), Matthew (13), and Nolan (10). Chad is the most affected brother; he "presented with almost all of the typical symptoms and then some of the more unusual ones as well. Chad is blind and has been from a very young age…he had dilated cardiomyopathy in infancy at about six months old and was recently in severe heart failure… he had absence, myoclonic, and drop seizures…He was diagnosed with Crohn's disease, so that's another unusual characteristic. He has type 2 diabetes, kidney and liver dysfunction. The kidneys were good up until recently. They were impacted by the heart failure. He suffers from high cholesterol and high triglycerides and he has some scoliosis." Chad also wears a hearing aid.

Matthew, also blind from a young age, is the least affected of the three. Matthew is overweight. "However, he doesn't have type 2 diabetes, which has always been a mystery to me as both of his brothers do...He had pretty significant scoliosis [corrected with braces]…He also has some respiratory issues and liver dysfunction." Jennifer's youngest son, Nolan, "has more of the classic Alström symptoms. He is blind…hearing impaired…type 2 diabetes…slightly overweight…some liver dysfunction."

Alström Syndrome follows its own timeline. Organ damage progresses far more rapidly than it does in the general population, causing "adult" disorders in children

> "Today is the healthiest that our son will ever be, and tomorrow he will be sicker than he was today, and this will continue each and every day." – Ed Conlon, father of Jack, age 6

Participants do not always receive timely treatment from pediatricians unaccustomed to seeing a 16-year-old girl with cirrhosis of the liver or a 16-year-old boy with heart failure, for which the only symptom may be sluggishness or labored breathing. Treating anomalous test results as might be done for an otherwise healthy patient – "we'll check again in two years" – risks delaying the detection of imminent disease until organs have been irreparably damaged.

Heart failure occurs in infants and teens, though reaching a correct diagnosis can take years

"Every time we thought our world would plateau, it would fall apart again," said Sarah Durfey, mother of 5-year-old DannieGrace. "In March of 2019, Dannie started to pass out. She went into stage three heart block. She needed a pacemaker. They explained to me that they were going to have to crack open my baby's chest to place it. I once again desperately hoped this was the fix and that our world would plateau."

Heart failure can recur in the teenage years. In February of 2021, "my husband and I started to notice some changes in Chad", said Jennifer Potter. "They were minor changes really. At first, he was cold all the time, he was tired, sleeping more than normal, and then loss of appetite." Chad's cardiac and Gi specialists sent him to the hospital, where "ultimately Chad was in severe heart failure. The dilated cardiomyopathy that he had in infancy did present again in the teenage years." Unlike Chad's earlier bout of heart failure, this one did not respond to medication, so he underwent open heart surgery to install a left ventricular assist device (LVAD), a type of heart pump. "Typically a heart pump [with external batteries carried in a bag] is not a long-term solution," said Jennifer, adding, "Chad has been approved for [heart] transplant."

Yet signs of heart failure in children with AS can be missed for years. While congestive heart failure in infancy increases the likelihood of a recurrence later in life, a first bout can occur at any stage in AS. Shortness of breath (dyspnea), fatigue, and a worsening cough are cardinal signs of CHF among AS patients, but these are frequently attributed to unrelated pulmonary issues. When she was young, Katelyn Denbow (age 24) was treated "as if it was cystic fibrosis…[her mother was]…taught to do the pounding on the back…I was also put on a nebulizer with hypertonic saline." Katelyn's mother, Gina, noted that this "helped some but didn't fix anything." As the years passed, said Katelyn, "It was harder to breathe. I would have really bad coughing spells…I'd have trouble getting my breath back."

Then, several years ago, said Gina, "when we saw the cardiologist, he said her ejection fraction is slightly off from what it was before but nothing to be too concerned about, we'll check her again in two years. I said, I think we should do that in six months. [In the meantime] COVID hit and it was two and a half years later, then we were in full-blown congestive heart failure. It's those timelines of them looking at what they normally do for their normal patients with those numbers, they don't work for our kids with Alström Syndrome."

Ed Conlon, father of 6-year-old Jack, echoed Gina's story. "We had the same exact experience, and you always have to point them to the [2020 consensus clinical] guidelines[8] and say, 'No, this is what you actually should be following. Instead, it should be more frequent.'"

"That hit home because we are dealing with doctors who tell us, 'We don't know why she's having breathing problems,' said Wesley Jarboe, whose wife, Doula, has AS. "That's one of the problems that I'm dealing with as a caregiver right now. I'm asking questions, the doctors are saying, 'We did a bronchoscopy, we did all this other stuff, we can't find anything wrong with her lungs, but she's having breathing problems.' Now I find out that congestive heart failure can mimic breathing problems. I don't like that. I want doctors to be able to give me valid information."

Children have adult disorders that pediatric practitioners may not recognize early enough to prevent irreversible organ damage

Katelyn had already been diagnosed with AS when, at around age 14, she started having esophageal varices (swollen veins in the GI tract that can occur when blood is diverted there to circumvent a damaged liver). Katelyn's varices had to be banded (tied off with rubber bands) regularly – a total of 20 or 30 hospital visits to band perhaps 150 varices. "It seemed like every time we were going in just to have them checked, they ended up banding more varices. Her liver enzymes also were elevated much more during that time, and her spleen was really enlarged, yet nobody ever said anything to us about cirrhosis of the liver or [that] what was going on with her liver may be causing the varices," said Katelyn's mother, Gina.

At 16, Katelyn went into complete liver failure, which caused her to be hospitalized for over a month with internal bleeding. She became unresponsive due to hepatic encephalopathy, which occurs when ammonia builds to dangerous levels in the blood. "After a few days, they finally figured it out and were able to drain the blood off, and she came around again. However, they still weren't looking at this as being a liver issue. They were actually ready to release us at one point in time," said Gina, but then Katelyn vomited blood, the liver involvement became clear, and she was given a TIPS procedure to put a shunt in her liver.

A transition from pediatric to adult providers may be needed to receive an accurate diagnosis and appropriate care

"When Callie [Marshall, age 26] was in the pediatric world, they weren't used to treating adult issues," said her mother, Shelly. "So I don't think they paid attention to the important things like her liver that they needed to. They treated the symptoms, and we had some great

doctors…I really wish we would have moved to the adult world years before we did, because our pediatric doctors were not used to treating these adult problems. Also, when we moved to UT Southwestern, there was much more communication amongst specialties. Our doctors talk. They message each other." Callie added, "It will be like, 'I don't want to push for this yet. I want to talk to liver first.'"

After Callie transferred from Cook Children's Hospital to UT Southwestern at age 20, she said, her medical care improved. "We had doctors that worked better together…We found out about the esophageal varices," a sign of liver disease that was not caught in the children's hospital. Callie also experienced hepatic encephalopathy, a result of severe liver disease that causes changes in mental functioning. "I would get to sometimes where I would fall and I'd have to have someone help get me back up." Callie received a liver transplant when she was 23.

Using a "typical" timeline to approve a transplant can have dire consequences

It's too early for a transplant, until it's too late. Doula Jarboe, age 45, described ongoing efforts to get a kidney transplant. "I tried to get an evaluation for a kidney transplant five years ago, when I was healthier. They said, 'Your kidneys aren't bad enough. You're not eligible for transplant even though you're healthy enough to have the surgery.' Now that my kidneys are failing, I have a lot more health complications, and so it's harder to find somebody to say, 'Oh yeah, we'll give you a kidney transplant and you'll be successful with the surgery.'" Doula emphasized doctors' need to "understand the fact that this is going to be organ deterioration and…to possibly catch these things earlier."

Blindness is the most prevalent symptom of AS, affecting 100% of patients by their early teens or twenties, but it is not necessarily the worst symptom, or even among the three worst, for all patients

> "Imagine a disease so horrible that if you told me today that the only thing that could happen to Jack is that he would go completely blind, I would actually feel so lucky**." –** Ed Conlon, father of Jack, age 6

There was considerable variation in participants' assessments of the relative burden of each physical manifestation of AS. Among ten categories of symptoms related to AS, poll respondents were asked to choose the three that had most negatively affected their lives. Each category was ranked among the worst three symptoms with the following frequency: vision (81%); cardio/pulmonary (38%); hearing (34%); obesity (34%); gastro/liver (31%); diabetes (16%); kidneys (9%); structural (skeletal, dermatological, or dental) (9%); endocrine/growth (9%); and nervous system (9%); with 16% listing "other." When asked which symptoms were most important for future treatments, respondents provided a similar (though not identical) profile of responses (Appendix 2).

Only two of seven participants in the panel discussion chose blindness as their #1 priority, underscoring the wide range and severity of damage caused by AS

Despite the universal experience of vision loss among survey participants, only 81% ranked this among the worst three symptoms of AS. Among the seven adult participants in the panel discussion, there was significant disparity regarding which symptom ranked as their #1 top priority. Two chose sight; two heart; two kidney; and one pancreas. Among others who replied online, two chose sight and one liver.

When other symptoms are relatively stable, or for young children with fewer complications, vision becomes a priority. With a successful kidney transplant behind him, Adam Kozarewicz's greatest wish is for sight. "I would love to…see my mother and all my family and all these friends here today…have a nice pickup truck and drive where I want to go and do what I want to do."

Chad Potter, who recently underwent open heart surgery, prioritized vision because "I already got a heart."

A remote participant responding for her young daughter chose vision, "because it's what's most affected right now and it affects her ability to ambulate."[42]

Damage to any organ can have devastating downstream effects, putting other organs at risk of failure

Collateral damage from kidney disease. Doula's diseased kidneys have caused collateral damage to other organs in her body, reducing her eligibility for a kidney transplant. **"**I'm at the very top of stage 5 kidney disease, and I'm looking at dialysis, trying to get into a kidney transplant program, but they don't like me because I've got so many complications. Then also when I'm anemic, that's hitting my oxygen, and I already have lung issues. I wonder how much of my lung issues are being caused by kidneys and not having oxygen in the blood cells, so it's sort of a circle." Doula used a portable oxygen tank throughout the meeting.

Three years after her liver transplant, Callie is focused on her kidneys, "because we're looking at a transplant, and I'm scared of dialysis and having to change my diet."

Everything depends on the heart. Katelyn's priority is her heart, "because all the problems with my heart made my other organs worse, and because it's a daily struggle to figure out what I can and can't have to eat or the amount of food I can have in the run of the day."

Milan Boekhoudt, age 21, who struggles with heart disease and diabetes, was recently hospitalized for an acute bout of pancreatitis that caused "indescribable pain" and a lung

[42] Translated from Spanish

infection. "For that I needed to go directly into the hospital. At that moment I could not…eat or drink because the way from my stomach to my intestines was blocked…I had a drain in my stomach and I had a drain to pee and I got water by my infusion. Then I got three different painkillers to kill the pain. For my lung infection, I got antibiotics and oxygen. My pancreatitis had to heal by itself because it was not [due to] a bacterial infection." Despite this recent crisis, Milan prioritized the heart among all organs for treatment. **"**If you don't have your heart you die on the ground," he reasoned. "When your heart is not working well, your whole system will fail. So it begins with your heart and goes further and further and further."

But damage to other organs can also be life-threatening. A father responding online for his son was most concerned about liver damage, "because one of our big fears coming up is cirrhosis, and it seems many people need transplants in order to continue living."[43]

Hannah Wedel, age 30, noted that "pancreas and diabetes go together, and…I'd love to go a day in which you don't have to prick yourself for blood sugars or take insulin."

Daily management of AS can be a full-time job, punctuated by unpredictable and life-threatening crises. Families are profoundly affected

> "She's had three blood transfusions. She's had over 15 surgical procedures, including her open-heart surgery. She's attended over 350 doctor appointments, and she now has a beautiful set of sternum wires and a seven-inch scar down her chest…She's spent most of her days fighting for her life." – Sarah Durfey, mother of DannieGrace, age 5

> "Katelyn didn't have any heart issues when she was a baby, and we were hoping since she had liver failure…that was going to be our big major event…and we recovered from it…then we got stuck with [heart failure]." – Gina Denbow, mother of Katelyn, age 24

Just as AS patients vary in array and severity of symptoms, each individual's journey through AS is marked by relatively good and bad days. Even good days, however, are dominated by the demands of managing serious disease in multiple systems.

Management of AS can be all-consuming

In a recorded interview with her mother Gina, Katelyn described her daily routine. "First thing that happens is I get weighed on the scale to check if there's any fluid on my body. After that, I do my fasting sugar. Then I have breakfast with my pills…I do my Ventolin [bronchodilator]…I wait 10 minutes and then put on the nebulizer with the hypertonic saline, about 15 minutes.

[43] Translated from Spanish

Then I do my breathing reps on my Aerobika, 3 sets of 10. Then I take two puffs of Inspiolto [bronchodilator]**."** Gina continued, **"**We take your blood pressure and...your pulse. Sometimes we check your oxygen level. All of that gets written down. That takes us close to two hours…then it's almost lunchtime."

At lunch, "we have to keep track of the amount of sodium, carbs, protein, and fluid…there's not much I can have," said Katelyn. "If we didn't have to calculate all those numbers, it'd be a lot easier." Lunch is followed by 15 to 20 minutes of exercise and an afternoon nap, during which "I have to wear a CPAP that also is hooked up to oxygen." Katelyn's sugar is tested again after supper; and once weekly, "we have to take a shot of Ozempic." "That's a lot that we have to go through every single day…just so that we can function and breathe a little bit," said Gina.

Families careen from one crisis to another

Genetic testing confirmed Dannie Grace's AS diagnosis when she was seven months old, and "life as we knew it shattered," said Sarah. "The next year was a whirlwind, one crisis after another, one diagnosis after another. Dilated cardiomyopathy, heart block, small airway disease, cone-rod dystrophy, photophobia, one pulmonary or kidney issue after another."

Serial crises lead to frequent hospitalizations. In fifth grade, "Alström really started having more of an effect on Callie daily and she was spending probably about a week every month in the hospital," said Callie's mother, Shelly. Callie was hospitalized several times for pancreatitis, abdominal migraines, unexplained abdominal pain, and diabetes, including "one time where it was over 800," said Callie. Recalling Callie's hospitalization for a diabetic coma one Christmas morning, Shelly said, "It wore us out, didn't it? Your blood sugar being so high and trying to get it down." "I was once on 1500 units of insulin a day," replied Callie.

Callie graduated from high school at Cook Children's Hospital. In her early 20's, Callie was hospitalized "every four to six weeks" to band esophageal varices that had developed due to liver disease, said Shelly. Three years after Callie's liver transplant, her kidneys are starting to fail. She takes medicine "five times [a day], and…seven or eight" doses of insulin, and "you require a lot of monitoring and a lot of help…sometimes that's hard," said Shelly. Callie, who broke both feet in the past, used a wheelchair at the meeting.

Lifesaving surgeries are followed by long rehabilitation periods

For Chad, rehabilitation following a 111-day hospital stay and open-heart surgery to implant his LVAD was "really, really hard work," said his mother, Jennifer. "Hard work for Chad and hard work for mom and dad. He was very sick, and he basically had to learn to walk and learn to eat and learn to do all those things that he had done when he was an infant. He had physical therapy, occupational therapy, recreational therapy, and speech and feeding therapy every day, six days a week, starting bright and early through the end of the day. It was very intense, but he was up for the challenge…There were definitely very tough days in therapy."

The Covid-19 pandemic added pressure to an already stressed system

The combination of DannieGrace's AS and the Covid-19 pandemic placed additional stress on every member of Sarah's family. "I can't even describe how scary that was, how isolated we felt. My older kids wanted so desperately to go to school, but we couldn't allow it. They were crushed. Sports ended. Friendships ended. My marriage of 21 years ended."

COVID precautions complicated college life for Hannah, who is blind, wears bilateral hearing aids, and was already struggling to understand a math professor with a foreign accent. "I felt like I was having to have him repeat everything he was saying, then throw on a mask that turns the volume down on everyone who speaks to you. That was a frustration that I would not like to relive."

AS takes a severe emotional toll on patients and parents

Participants reported a range of emotional stresses in coping with AS, including: frustration (73%), anxiety (61%), uncertainty (58%), fear (55%), isolation (52%), loss of independence (48%), depression (42%), exhaustion (39%), anger (39%), low self-esteem (36%), and hopelessness (27%); with 6% listing "other."

The emotional toll of AS is comparable to that of the physical symptoms. When asked to select the three most significant difficulties they face as a result of living with AS, out of a list of 6 possible responses, participants overwhelmingly cited the emotional (79%) and physical (79%) burdens of disease. Other challenges included dealing with bureaucracy (29%), obtaining social support (26%), strained family dynamics (18%), and obtaining financial resources (9%).

"How is it to live with Alström, and how does it feel?" asked Milan. "You never have a life like a healthy person and you are always busy accepting that. It feels confrontative and intense, but also like a challenge. The challenge is to live the most normal life possible."

Katelyn summed up her life with AS: "it's hard, but you make it work."

Alström Syndrome is a process of decline that can rob hope for the future

The progressive nature of AS challenges parents' hopes for their children's future. Erin Conlon considered the prospects for her 6-year-old son, Jack. "We know that we have it easy only currently dealing with the vision and hearing loss, the obesity, and the speech and developmental delays." "Jack will fight progressive vision loss, hearing loss, obesity, diabetes, fibrosis, and failure of his organs, and thus will likely need various organ transplants…[but] only if the doctors will even approve him for one due to all of the other complications of Alström Syndrome," said Ed.

Following a series of crises that culminated in open-heart surgery for DannieGrace, said Sarah, "we found out she also had diastolic dysfunction with secondary pulmonary hypertension. Not only were her lungs fibrosed, now they had extra pressure on them and her heart was working

extra hard. Our conversations changed. They started talking about quality of life. My mother's heart broke for my baby girl…the mourning for the life I want for her started again."

Adult AS patients compared the unpredictable nature of the disease to a game of whack-a-mole, magnified by the knowledge that AS shortens lives. "The life expectancy stuff scares me," said Callie. "One problem can be fixed, but then I always get another problem. I have liver fixed, but now I have kidney problems. It's very difficult to balance it."

"It never follows a normal path," said Katelyn.

Doula worried about "trying to keep up the balancing act of coordinating everything. Even as hard as you try, being cognizant of the fact that even though you do your best, it's still going to be a battle and a challenge. I think the other thing that worries me is the people who care for me, the life expectancy, and leaving them behind, especially my husband."

An online participant described a similar struggle to deal with "the dependency and the sum of [my] symptoms together, and also that every time something comes up, you need the help of more and more people."[44]

Some deal with the uncertain future by focusing on the present. "I don't really have any worries because the way we look at things, my mom and I, is that we take things one day at a time and don't really look to the future all that much. We just focus on things as they come," said Katelyn.

"It's a day-by-day thing, that's how my mother and me believe. Every day you get up and you enjoy life a certain way, and you keep on going," said Adam, age 42.

Patients with AS rely on a wide array of assistive devices and medical treatments, including extensive medication use, organ transplants, and other lifesaving surgeries

> "She has 15 serious diagnoses. She has 12 daily medications and supplements. She has 7 medical devices that she needs at home. She sees 11 specialists and does 4 types of therapies." – Sarah Durfey, mother of DannieGrace, age 5

Medical interventions and medications are critically important

> **"**Do you have any idea how many pills you're taking?"
> **"**No, I do not."
> **"**In the morning it's -"
> **"**Thirteen, maybe."
> **"**Yes, right around there, and at night?"

[44] Translated from Spanish

“I want to say maybe ten.”
“I think it's nine.”
- Gina Denbow and Katelyn, age 24

Current treatment for AS targets each affected system separately, resulting in the administration of many drugs in combination. Participants reported use of the following classes of drugs: Antibiotics/Antimicrobials (61%), GI/Stomach medications (39%), Metformin (39%), Steroids (36%), Statins (30%), Antidepressants (15%), Anti-Rejection Medications (12%), other blood pressure medications (9%), and blood thinners (6%); with 85% using additional medications not listed here. Several respondents reported use of Ozempic or other GLP-1 receptor agonists to treat their diabetes. Among all participants, 32% said their current drug regimen controlled symptoms very well, 58% moderately well, 6% poorly, and 3% not at all.

In addition to medications, individuals with AS rely on a panoply of medical interventions and assistive devices – some for help with daily living, others to save their lives. Assistive devices and interventions used by participants in the September 2022 meeting included walking canes (94%), glasses (88%), Brailler (76%), audiobooks (76%), computer apps (65%), screen readers (59%), and guide dogs (12%); hearing aids (65%); glucose monitor (41%), insulin pen (24%), and dialysis (12%); inhaler (35%); transfusion (35%), organ transplant (24%), and pacemaker (12%); and wheelchair (24%). Many respondents also noted use of a reduced calorie or special diet (71%) and an exercise program (65%).

Patients make extensive use of medical devices at home. Sarah highlighted three of the seven medical devices that DannieGrace relies on at home. “Home oxygen and heart monitor keep us out of the hospital at times…shaker vest [airway clearance system] has been a lifesaver! It has helped us have less and shorter hospital stays.”

Transplants and other surgeries have been lifesaving. At some point in the life of an individual with AS, often in the teens or twenties, he or she is likely to require major, lifesaving surgery. Among the eight adults and two children with AS represented at the in-person meeting (age range 5 to 45), there had been two open-heart surgeries, two liver surgeries (one a transplant), and two kidney transplants. Two attendees are currently seeking approval for kidney transplants.

In addition to surgeries, members of this small group had undergone hospitalizations for kidney failure, liver failure, heart failure, lung failure, severe acute pancreatitis, complications of diabetes, severe and nearly terminal lung infections, and hepatic encephalopathy, among other serious ailments.

Maintenance of a transplant requires medication forever. Adam said, “I was on dialysis for about a year and a half…Got the kidney on June 6th [2014] and, knock on wood, we're healthy, stable eight years…the FDA gave me all the right drugs for the kidney, my diabetes…I just got to take them at the right time of day, keep taking them, and go for blood tests to see what they need to change…I don't want to have a rejection of this kidney, because I'd like to have a long, nice life.”

Patients use canes, guide dogs, and phone apps to aid with vision and hearing

Individuals with AS use canes and/or guide dogs to increase mobility and independence. Doula used a guide dog to help navigate her college campus. "The summer before my junior year, I decided to get a guide dog…You have to have good mobility skills and know where you're going when you're using a guide dog because they're not a GPS system…College campuses are challenging because a lot of times you have intersecting paths, and you don't have a lot of tactile identifiers for where the paths veer off to, which way you need to go. I really enjoy the teamwork of working with a guide dog."

Phone apps provide multiple functions, from hearing assistance to monitoring metabolites. To manage her diabetes, Hannah uses a Dexcom (a small wearable device that provides continuous glucose monitoring). "I have that Bluetoothed to my phone and that's what I use for my blood sugars. Then my hearing aids are also paired into my phone so that helps me hear what's on my phone. I find these days I can't use a regular phone because I can't hear."

Adam uses the Libre 2 patch to monitor his glucose. "It works very well," he said. "It's hooked to my hearing aids and hooked to my phone so it's always with me, next to me. It tells me my diabetes readings."

Phone apps can help point you in the right direction. Hannah navigated her college campus with her guide dog, and when she was lost, used FaceTime to get back on track. "The darn Kansas wind or rain would get me turned around so stinking easily, and I would be lost on campus so I would just pull out my phone and call mom through FaceTime to get me back on course and be on my way."

However, current interventions fall short of addressing the needs of AS patients

It is not surprising that the majority of participants (79%) would say their visual symptoms are not fully addressed by current treatments or devices. But a considerable number of additional symptoms are not adequately addressed, including obesity (42%), diabetes (36%), structural (skeletal, dermatological, or dental) symptoms (33%), autism and other disorders of the nervous system (27%), kidney disease (24%), gastrointestinal/liver disease (24%), emotional disorders (24%), cardio/pulmonary disease (21%), endocrine/growth disorders (18%), and hearing loss (9%), as well as other symptoms (12%).

Adults with AS struggle to balance the need for help with the desire for independence

> "Being dependent on people for things because you're not able to do everything by yourself. It's a challenge." – Tehara Algama, age 25

Doula struggles to balance the need for other people with the desire for independence. "Yes, it's definitely a challenge. I am a very independent person. If I can do it for myself, I want to do it for myself. At the same time, you have to be willing to know where you need help and ask for help…let people know, 'Okay, this is something I can do,' and then also let people know if this is something that I need help with."

Hannah's mother stayed on her college campus to help her through an episode of enlarged bladder that required catheterization. "When you are in your early 20s, you don't really want your mom hanging around at college, but it worked out in the end since she became my driver for me and a friend."

Individuals with AS display remarkable physical and educational achievements

> "I want to let the world know that if you have a dream or something you truly believe in, you can accomplish it, and in my life, the normal way is never used." – Milan Boekhoudt, age 21

> "Our children can really accomplish anything." – Jennifer Potter, mother of Chad, Matthew, and Nolan, ages 17, 13, and 10

The numerous achievements of teenagers and adults with AS, despite their unending struggles to stay healthy, served to underscore their resiliency, tenacity, and strong cognitive skills. These included educational, artistic, athletic, relationship, and career pursuits. In nearly every instance discussed at the meeting, the greatest challenge to reaching educational or career goals was posed by symptoms relating to health issues other than blindness.

Adults and children with AS are highly capable individuals. Doula described a youth spent hiking, biking, swimming, riding horses, and skiing. "The National Federation of the Blind has three training centers in the United States. I'm very blessed and fortunate to have one of them here in Colorado, and I went through their summer programs. I was living with other young blind teens and adults, learning from other blind people how to cook, how to clean, how to travel to different places, use the bus, and we did extracurricular activities like rock climbing."

Hannah graduated from college in May with majors in mathematics, general education, and special education, and a minor in philosophy and religion.

Jennifer described the wide range of activities enjoyed by her three sons. All three are enrolled in public school, where Chad (age 17) and Nolan (10) play drums in the marching band and Matthew (13) plays saxophone. Jennifer showed photos of her sons swimming, sledding, cycling, jumping on a trampoline, and carving pumpkins. Chad, a high school junior, is "a member of the chess club. He goes to competitions. He participates in the social recreation programs as well as a Buddies Club at school." Matthew "loves to read and he loves basketball. He knows every fact about basketball…loves to be outside…he's playing baseball using a T." Nolan "is just full of life. He loves school [and] spending time with his brothers and his friends. He's very active," said Jennifer.

“We've always told our boys that you can accomplish anything that your typical sighted peers can do,” said Jennifer. “It may look a little different, but they are really and truly able to do just about anything.”

The many health complications of AS disrupt educations and careers

Educations are disrupted by surgeries, transplants, hospitalizations, and Covid-19. Doula recounted her college and postgraduate career. “I went to college, and part way through my freshman year, I ended up with pancreatitis…I was very sick, and my parents came down. They were there for me convalescing and helped me get back into doing my schoolwork. It definitely was their support that helped me not get too far behind with school and not want to drop out or quit.”

“The only health issue that put my academic career on hold was my kidney transplant,” said Hannah, adding that it “came at a perfect time…right before everything was shut down because of Covid.” Hannah skipped a semester while recovering from the transplant and did not attempt remote learning.

For Callie, who has a passion for history and was one of the top-ranked high school students in her regional history competition, the continuous onslaught of disease robs her independence and diminishes opportunities for personal growth. Callie is not currently enrolled in college. “For me, it's just such a challenge because I get from one [medical crisis] into the other, so it's really hard for me to do a lot of independent things. But what we can do, we try to. We get some things in Braille as much as we can and audio as much as we can, too, for me to be able to do some things on my own as much as possible.” Though Callie had a liver transplant three years ago, takes a high dose of insulin, and may soon need a transplant for failing kidneys that require constant monitoring and medication, when asked what she was facing right now, she replied, “boredom.”

Jobs and careers are derailed by medical emergencies and progressively worsening disease. Milan struggles with heart disease and diabetes. In the aftermath of his recent hospitalization for acute pancreatitis and a lung infection, “I have low energy and I feel sick in the morning. In the morning, it takes a long time to take my medicine because I feel broke...I lost 18 kilos of weight and my appetite is less…. I also have a job for 24 hours packing candies, but I work just 12 hours because I feel sick.”

Following Doula’s graduation from college with a BA in Political Science, “I had an internship working for the client assistance program for a vocational rehabilitation, and finally decided on a career path of mediation. I decided that I wanted to go to graduate school and study conflict resolution, which I did for a while…As I went through adulthood, my medical conditions got worse, so even though I got my training in mediation, I never have had a career in that field.”

Obtaining necessary services requires constant advocacy by parents and patients

> "As the parent or as the individual with Alström Syndrome, you are the expert. If you think something's wrong it probably is, and don't hesitate to get help." – Jennifer Potter, mother of Chad, Matthew, and Nolan

Advocacy for medical care. Jennifer drew on her experience as the mother of three Alström boys when Chad experienced heart failure, detectable only by "minor changes" and her intuition that something might be seriously wrong. "I'm glad that I reached out when I did…Be a constant steadfast advocate for your child in all situations and all things. We did not leave his side during that time that he was in the hospital, and it was really important…We've always taught him that he has to advocate for himself, but he didn't have a voice in that situation, so we were there every day advocating for him, asking the tough questions, and we were able to provide valuable information to the doctors throughout that process."

Doula considered how better education about AS might have helped her become a better advocate as a patient. "I think it's important that as a patient, you educate yourself so that you can know what you're dealing with…looking at numbers and being able to intelligently ask questions of your doctors, because they're not always going to know it all, especially with something like this where they probably don't have much experience, or you're their only patient."

"I encourage younger parents to consider moving to the adult world, even though it's scary, earlier than you probably think you need to," said Shelly, citing Callie's experience with the transition from pediatrics to a teaching hospital, whose physicians were better able to treat the type of organ damage that is characteristic of AS.

Medical advocacy extends to the political realm. Doula described her advocacy work as a member of the National Federation of the Blind. "We are working on a piece of legislation right now to get through Congress that would allow the FDA to put regulations into place that would make medical devices that use things like displays accessible. It would put in rules and guidelines for companies, like dealing with the insulin pumps that Hannah was just talking about, that they would be required to get accessibility into medical devices like that…We're hoping to try to get that legislation passed."

Parents and patients must also advocate for their education

All three of Jennifer's sons are enrolled in their local public school system. "From day one I've been very involved. I attend every meeting in person and really made the school step up and provide what the boys need to get their education in the best means possible."

Hannah transferred from a public community college, "where I had to fight for my accommodations," despite the presence of at least half a dozen visually impaired students on campus, to a private college, "where a friendly reminder of all I needed was all it took…[though]

I was the only blind student." In community college, Hannah struggled "without textbooks in electronic format" and "with online exams that were timed and open-book, since…the exam was not hard to navigate, but it always took me too long to find the answer in the book." In math classes, "it seemed like something was always the problem." Hannah would receive printed handouts in class, "and you can't transcribe in seconds, so I would be teaching myself the material in the next math class." Other difficulties included understanding teachers with foreign accents and one teacher who "seemed like he just did not want to work with me."

"If there is anything I have learned from my academic career, it is to be a great advocate for yourself, since no one else is going to do the job for you," said Hannah. "Be willing to be flexible on some things, and know what you cannot be flexible on. Above all else, do not be afraid of communicating with professors and other staff on campus…They [may] not realize that an easy fix to the solution just might help both you and your peers at the same time."

Early Braille instruction is essential. "Braille is so critically important," said Jennifer. "All three boys read Braille, and it is beautiful that they're able to do so."

"There are a lot of hoops and obstacles we have to go through to get what our children need," commented one participant online.

TOPIC 2: Issues of Diagnosis, Burden of Treatment, and Access to Clinical Trials

Misdiagnoses are agonizing for parents. The eventual diagnosis with AS is shattering

> "I was sent home feeling like an overreacting parent." – Sarah Durfey, mother of DannieGrace, age 5

> "It was like Jack was just given a death sentence. It was a sadness that was so profound. I had never felt like that before." – Erin Conlon, mother of Jack, age 6

89% of respondents noticed symptoms of AS in the first year of life. Nonetheless, many had to wait years for an accurate diagnosis, often after receiving a litany of other diagnoses in the meantime. Among the 32 participants who'd had symptoms from their first year of life, 15 were diagnosed many years later, either in late childhood or their teens or twenties.

Symptoms were downplayed or misdiagnosed by pediatricians. Sarah recounted the weeks following the birth of DannieGrace. "She entered our world blue and not crying… After her birth, DannieGrace spent seven days in the NICU and [after she] came home…her breathing never really improved. She slept all the time even while she was nursing. I'd have to shake her awake. Her primary care sent us to see a pulmonologist, at the pulmonology appointment they

couldn't get her SATs above 68, and they blamed a faulty machine. They didn't try again…I was sent home feeling like an overreacting parent." A few days later, when DannieGrace stopped breathing and Sarah rushed her to the hospital, she began to show signs of cardiomyopathy. "Over the next few months, it didn't stop. We were in-patient numerous times for IVIG infusions to try to combat what we thought was a virus attacking her eyes and heart."

Jack first presented with nystagmus (flickering eyes) at four months, and he was tested for neuroblastoma, a lethal pediatric cancer. "This was our first intro into how everything was just going to be harder for Jack and our family," said Ed. "As obesity comes with Alström syndrome, Jack was a very chubby baby and they had to prick him a ridiculous number of times before they could draw blood for testing, which just made Jack scream and cry unlike we had heard any of our kids before…After three days of agony, we were relieved to hear that Jack did not have neuroblastoma." Jack started missing milestones and showing developmental and speech delays, said Erin, but "when we asked the ophthalmologist about these things, he would just shrug his shoulders and say that Jack had nystagmus and that there wasn't much more he could do. He didn't offer any avenues for further testing or assistance."

"It was hard to watch Jack's lack of progress," said Erin. "Our parental instincts kicked in and we realized we needed to chart a different course." Despite living in Long Island and seeing "a highly renowned pediatric ophthalmologist," it was only after Ed and Erin brought Jack to St. Louis Children's Hospital that they received the appropriate evaluation, genetic testing, and diagnosis of AS.

"We actually were given seven possible diagnoses before they decided upon Alström Syndrome," said Gina, whose daughter Katelyn was diagnosed with AS at the age of four and a half years.

Confirmation of AS is devastating. Before Jack received his AS diagnosis, less than two months before his second birthday, "we thought we were…getting to the bottom of Jack's struggle so we could fix it," said Ed. Instead, Ed described his sorrow "as the reality of the devastation of Alström Syndrome began to bring us to our knees. I walked over to my son Jack, threw my arms around him, squeezed him as hard as I could, and then I just sobbed as the life I thought and hoped my son could have effectively died and this Alström Syndrome monster took over."

Systemic changes are needed to get better care for people with AS. Patients identified lack of coordination among healthcare providers as a significant obstacle

> "Finding a cure would be a dream, but there is no cure, so fixing the system would make dealing with the syndrome easier." – Katelyn Denbow, age 24

> "Each doctor tends to look at them for their organ only…Nobody wants to actually step back and take the whole picture and treat as a full person." – Sarah Durfey, mother of DannieGrace, age 5

Educate healthcare providers to improve care for AS. Doctors need to be educated in the treatment of AS, said Sarah. "Having access to more research with Alström and having more knowledge for the doctors would be very helpful. More of a pathway would increase the care…to where the doctors understand how important it is and that we can't wait six to eight months, a year, and that they have to be able to roundtable and intervene quickly instead of waiting to see what happens next, because it's an unknown beast."

Where Milan lives in the Netherlands, "my doctors don't have a lot of information about other patients…that makes it so hard to give me treatment." He advocated better sharing of information between providers in the US and elsewhere.

Sarah dreams of finding a doctor trained specifically to treat AS. "When you look at a child or a person with Alström, each doctor tends to look at them for their organ only…the heart for the cardiac, pulmonary wants to look at the lungs…If we could have an Alström's doctor that does just Alström's patients, that would be amazing."

Enhance cooperation among healthcare providers. Callie cited the siloing of medical specialties as a systemic feature that compromises the care of Alström patients. "Get the doctors to coordinate better. That was one of the problems we had when I was younger…They need to work together more, instead of just focusing on their one organ."

Some hospitals, particularly those engaged in research, seem better equipped to provide the collaborative care needed to effectively treat AS. "The best thing we have is a teaching hospital in Chicago," said Adam. "[After my] kidney transplant, I've been going every month…in the beginning, it was every couple of days for blood tests and telling me how the kidney's doing. I had three wonderful nurses who would call and tell me…a good team...they work with all the doctors."

"It depends on where you are and who you're working with," said Doula. "I am very blessed. I have a team of doctors. They're willing to communicate with each other."

Jack sees 11 specialists within one big hospital system. "We'll often take Jack out of school," said Ed. "He'll miss a lot of time. That means he's missing his services… it's just so difficult; we have not found any help or a good way to organize those appointments." Ed would like to see "something that can help coordinate the care so that someone helps us make three or four appointments together on the same day, for example, so he's just missing that one day."

Treatment for AS should be covered by insurance. "Right now, I'm trying to get a potassium binder and insurance isn't wanting to cover it," said Doula. "It's confusing to me, doctors that give me this medication and then insurance says they don't want to cover it. It just seems like there's something incorrect about that."

Increasing the pool of organ donors could reduce long waits for transplants. Adam waited five years for his kidney transplant. "It was a long five years, and I understand what Doula's going through, and everybody else in this group waiting…for a kidney. In the US, I think there needs to be more help for donations of organs."

Current medical and surgical interventions carry serious risks for AS patients

> "In true Alström fashion, she ended up with recurring pericardial effusions due to the surgery. She still deals with this today. We dealt with one lung issue or effusion after another for over a year." – Sarah Durfey, mother of DannieGrace

It is almost commonplace for individuals with AS to undergo lifesaving organ transplants or open-heart surgery. While these interventions are essential, they can create new problems. Parents and patients discussed some of the fallout from surgeries they'd experienced.

Surgical interventions can have serious unintended consequences

Following DannieGrace's surgery to implant a pacemaker, "life took a complete 180 for all of us," said Sarah. "Dannie had come out of her open-heart surgery different. She didn't talk anymore. That sweet 'mama' that I used to hear, I don't hear anymore. She didn't potty train anymore. In that moment, I realized Alström Syndrome was stealing my baby from me. Her vision started to get worse. We had to tint our car windows. We drove hours away to get tinted sunglasses that helped Alström's kids." DannieGrace's surgery also led to recurring pericardial effusions.

Adam told how a simple surgical procedure to insert two stents resulted in lymphedema and nerve damage. "My left arm, because I had a fistula put in it for dialysis, and had two stents, because I have stenosis of the aorta, it damaged the lymph glands in my arm…It's swollen right now, but I wear compression sleeves. I have a machine at home that takes the swelling down, but then in between, they found out I have nerve damage. I've gone for three rounds of needles, different times of the month, because insurance will only let you go for one every so many months. I had the last treatment on September 8th, and right now, I don't feel like it helped. I may have to go and get a stimulator put in my body…then I will have a remote control to control the pain of my four fingers in my left hand. It's a lot going on right now."

Managing interactions among the various medications is difficult

Jennifer's son Chad is challenged by "all the medication interactions" – in particular, the effect of heart medications on his kidney. "He's always had underlying kidney dysfunction, but it was never high on our priority list. Then after the heart [surgery], the kidneys took a hit. He's on tacrolimus, that impacts the kidneys. We're trying to find a medication for that. He's been on a good dosage of metformin, but then the kidney doctor was worried that maybe we should

come down on that. Just constantly playing with the different meds and how much he's taking, and trying to find the right combination so he has optimal function, but it is definitely a challenge."

Pharmacogenetic testing provided Tehara Algama, age 25, with "a score [indicating] which drug suits her body," said her father, Don. "That also will be given to a specialist. Acetaminophen affects her liver. Even for a cold or cough, we have to find alternate drugs. For cholesterol, we give her a medication called Colesevelam**,** which is not Lipitor or any other thing, so it affects other areas of her management. It's the combination of those drugs. We have a report [that] gives which medications she should go with…then when a doctor selects the medication, go to the chart and select what is appropriate to match with her genes."

Dr. Francomano encouraged pharmacogenetic testing for AS patients. "Looking at these long lists of medications that so many people are on…you have drug-drug interactions and drug-gene interactions, and they're all going on inside this one body. Having the knowledge about how that body can handle those drugs is a really useful thing."

Dietary regimens are complicated and contradictory

Doula struggles to identify an optimal diet. "When I started having any kind of medical issues, it was high triglycerides…[they] got so high that I had pancreatitis, then diabetes. I had diabetes for a number of years, then my kidneys started to fail. Every time you add something like that, they're changing your diet. Every dietician has their own special section, so you try to find a dietician who knows all of it - triglycerides, diabetes, kidney disease - which by the way, diabetes and kidney disease have opposite diets. To find somebody who can help you figure it all out is very difficult. If we could get a holistic, whole picture dietician - I've done tons and tons of research to figure out how to do my own diet, but most of the time when I'm talking to a dietician, they really struggle to say, 'This is what you should be eating.'"

Alternative treatments have helped some patients

Participants discussed their experiences with nontraditional or holistic therapies, which alleviated symptoms in some cases but had unacceptable side-effects in others.

Acupuncture can have multiple benefits. Doula mentioned several of these. "I just started acupuncture a couple of months ago. I love it. It helps with opening up my lungs…sinus issues…pain…sleep, it helps with so many different things."

Mike Kirby, who attended in-person, commented, "My daughter was able to lose weight and manage her insulin resistance with acupuncture. It also helps with sleep."

What works for one patient may not help another. Callie described her experience with alternative treatments for migraines and abdominal migraines. **"**I've tried acupuncture once…it didn't really work well…Botox actually worked well for migraines, though."

Botox had unacceptable side-effects for Adam. "I went for three rounds of Botox three different times, and I kept losing hearing. I told my mother and my father right away, 'I'm

done,' because…for four days I couldn't hear them and I had hearing aids in then too, and it was very tough." At the recommendation of his neurologist, Adam gets a monthly massage to treat "two muscle problems on the side of my head" that developed after his kidney transplant. "It takes away the stress… Just laying there for an hour and letting somebody rub your back and hands and legs and neck."

Chiropractic and physical therapy together for joints and muscles. Doula combines traditional and non-traditional approaches to her musculoskeletal issues. "I get chiropractically adjusted, which helps with my scoliosis [and] joint and muscle issues. I also have physical therapy…that and chiropractic have both helped a lot with posture, being able to move more easily, and dealing with different muscles, having more control, not having as much pain.

"When she was young, we started [DannieGrace] on elderberry," which is purported to boost immunity, said Sarah. "It was very helpful. However, after her open-heart surgery, using the elderberry… her immune system [is] geared up, and…she ends up with a heart effusion, which gets larger. We've had to stop that for the time being, because we think there's a correlation."

Patients seek improvements in disease management

> "The insurance I have, I can't always get my triglycerides drawn…Something where you can check them more often to actually see what they are, instead of having to wait six months." – Hannah Wedel, age 30

Adult patients want innovations to help control hunger and weight gain, monitor metabolites, and reduce the burden of managing symptoms

Devices for real-time monitoring of metabolites. Doula raised the possibility of monitoring organ function in real time. "I have a Dexcom [continuous glucose monitor], and it's great because you can look at what your sugar is doing. You can see how it changes. There have been times when I would go, 'Hey, that would be nice for my triglycerides. That would be nice for my kidneys.' Right now we're testing my kidneys once a month, and that seems like a long time to go and then find out, 'Oh, this is worse, or that is worse.' Better access, I guess, to being able to monitor things."

Control hunger and better manage the metabolism of salt and fat. "Stop the hunger," wrote one online participant. A later online comment read, "From a realistic, do-able standpoint, it would be great to have a drug that addresses the hunger and weight gain. Healthier weight has a trickle-down effect on so many organs and systems." A third pushed for a targeted treatment for steatosis (fatty liver).

Katelyn suggested "something that can make it easier to get sodium out of your body for heart issues and not out of the food, so that things still taste good, but you don't have to worry about it affecting your heart."

Spend less time each day treating the disease. "Right now, a lot of my treatments have been making my symptoms stable," said Katelyn. "There's so many different treatments for all the different symptoms, that it would be nice to have something that could take care of all the symptoms at once because it takes so long to do all of them in the run of a day."

Medical devices need to be more accessible for blind users

Medical devices do not support use by visually impaired individuals. "I have medical equipment I can't really use," said Doula. "I need somebody else to make it work because there's screens that are touchscreens, or they're digital, and there's no way to make them -- at this point, the company has not made a way for them to talk or to work with a Braille display. Then I have to depend on somebody else to make sure my oxygen is at the correct level or things of that nature. To me as an independent person, that's frustrating."

Hannah continues to monitor her own blood glucose levels and inject insulin manually, rather than use an automated pump. "One of the reasons I never switched over to the pump," she said, "is because of the inaccessible access to it, because you have to change it every three days, and I wasn't going to be able to do that on my own. I'm very much a person who likes my independence and doesn't like it taken away."

Not all patients have access to existing devices. An onlne participant would like to see "more availability of cochlear implants, as [we] have heard how well they work and people that are using them."[45]

Three different online participants expressed the desire for enhancements to existing cell phone technology. This would include more phone apps that connect to hearing aids and enable patients "to go for a walk," said one.

Targeted research with disease-specific evaluation methods is needed to find effective treatments for AS

"The lack of knowledge, the lack of research, the lack of funding to get that research…I think that's where we really have the hardest problem," said Sarah.

"We need more doctors to get together…more financial…and more research…everything is a money thing in this world," said Adam.

Bryce Johnston, an AS patient who participated remotely, wrote, "Ideally what is needed is to cure Alström, but from a realistic, do-able standpoint, it would be great to have a drug that addresses the hunger and weight gain. Healthier weight has a trickle-down effect on so many organs and systems. It is disappointing the FDA did not approve Rhythm to continue studying Alström."

[45] Translated from Spanish

Dr. Levin noted that the FDA rejected approval of setmelanotide for use in AS because the clinical trial was unable to demonstrate the necessary combination of efficacy and safety for this disorder; it's worth noting here that the phase 3 study included only six AS patients, so it was not highly powered. Dr. Francomano pointed out that Rhythm Pharmaceutical can still study the drug for AS, but it "now has to raise the funds and develop the resources to do another study that's going to have more power," which is a challenge for such a rare disease.

"There isn't enough research out there because of how rare the disorder is," said Katelyn. "Some of it is that we don't have all the same symptoms, that it varies from one person to the next, what your major symptom is," further complicating the ability to evaluate efficacy, noted Hannah.

Alström Syndrome requires a multidisciplinary approach to drug selection and development

Dr. Palmer recommended "taking a multidisciplinary approach to drug choice…like picking something that treats multiple indications and doesn't negatively affect something downstream that we know is going to go wrong. What's first line might not be first line in Alström Syndrome. For example, if there's a diabetic medication that also is renally protective, maybe pick that one, or pick the one that has weight loss and not weight gain as a side effect. A lot can be done in the repurposing of what we already have [and] in the development space, trying to look at things that might attack a couple of issues at once and not do more harm than good."

"We're hearing a lot about…finding commonalities in treatment," remarked Dr. Levin, "having doctors in sync with each other, as opposed to the Band-Aid approach of fix the kidney, fix the bladder, and one isn't talking to the other."

Targeted treatments need to be tested in a way that can satisfy the FDA's requirements; however, it may be necessary to establish different endpoints for AS than for other diseases

Robin Marshall considered the results of the ProMetic trial of PBI-4050, which were inconclusive. "Because we have fibrosis in every organ, it makes it very hard to test for the impact…All the data were very promising, but when it came down to it, does the heart get better because you made the liver better? Does the liver get better because you made the kidneys better? Those are things that they're looking for in scientific research, for clear endpoints, immediate cause and effect. And as with everything else about Alström Syndrome, it's not clear…The FDA has enormous power in that particular situation, and I think something like today goes a long way to break that particular pattern and that particular frame of thinking."

Drug developers also need to take the full course of disease into consideration, said Hannah. **"**When they're developing drugs, since we have to have transplants later on in life, try to develop them so they won't [interfere] with the new kidney or liver or heart." Hannah's

mother, Kim Wedel, wants to see new treatments designed to "prevent liver failures during the kidney issues and the heart failures."

"It's such a multi-organ mess sometimes that…we don't always have all the tools in the bag. You can't nail in a screw, and we really do need a screwdriver," said Dr. Palmer, mentioning "a few indications I can think of where drugs have been tested and they didn't get through clinical trials, but…this is a problem I could solve with a new drug. It really would just be as simple as that…so there really is a lot that needs to be done."

Given the complexity of AS, the only way to address all the issues is to target the genetic defect, though other approaches might offer systemic improvements

> "If you solve one problem, another will follow. It's not the answer." – Milan Boekhoudt, age 21

"My biggest issues at this moment are my pancreatitis, my lungs, my heart, and my diabetes," said Milan. When asked what treatments he would most want, Milan answered, "Stem cell transplant and gene therapy to really solve this problem…the whole problem…because there's still no solution and that's the biggest problem for all of us…It's affecting every system, every organ, every single cell. That makes it difficult. But I think you can make it simple because you know the mutation points…In some way you're halfway done, but you're not at the end."

One online participant pushed for "liquid retina for eyesight." Another wrote that research focused on identifying "a mechanism to figure out cellularly exactly what's going on…would be very helpful and would be able to help advance the treatment of the disease."[46]

Efforts at drug development should target the underlying molecular defect. Ed saw promise in the recent demonstration that translational readthrough inducing drugs restore production of ALMS1 in cultured cells from AS patients.[38] **"**Given the complexity of Alström Syndrome and all the different systems and organs that are involved," he said, "what we'd really like to see ultimately, because we know it's this protein that's the problem…something that addresses it at its root, which hopefully ripples through everything else…either a gene therapy that gets the correct sequence there, or maybe some type of drug that tricks the [ribosome] so it skips over that stop codon…and makes the right protein, instead of whatever truncated version that our kids and loved ones are getting."

Antifibrotics have potential to address multiple systems affected by AS. "We know that the process that involves the liver, the kidneys, the heart, the lungs is a product of fibrosis," said Dr. Francomano. "What about antifibrotics, drugs that stop that fibrotic process in its tracks?" "It

[46] Translated from Spanish

seems that it is the organ failure that ultimately leads to the early fatality. If we can hit that at least, and put in some kind of antifibrotic measure, hey, that's it," agreed Ed.

"We're pretty desperate" for treatments that improve the quality of life of AS patients

> "I think what you're hearing - I'm trying to speak directly to the FDA now - is we're pretty desperate. There's probably not much that would deter us from whatever it might take to give our loved ones more of a fighting chance against...this horrible disease." – Ed Conlon, father of Jack

The cure should not be worse than the disease

There was widespread agreement with Ed's statement that "we're pretty desperate," with a caveat that the cure should not affect patients' quality of life, cognition, and prospects for future treatment. Asked for their three most important considerations in deciding whether to adopt a new treatment, most chose severity of side effects (74%) and evidence that the treatment improves specific symptoms important to them (65%), with less concern regarding the number of side effects (41%), cost (35%), delivery mechanism (29%), physician's recommendation (18%), or frequency of administration (18%).

Treatment should not degrade quality of life. "Our loved ones may not have as much time as we would like," said Sarah. "The time that they have right now is important…my biggest no-go is if it were to stop her from dancing, stop her from laughing, make her tired too much. That would be something that I would probably shy away from, because her quality of life now is so important, because the quantity of life may not be as much as we would like."

"That's the only thing that would deter treatment…to suffer further by treating them and then taking away what they have," said Don.

Kim raised specific concerns about cognition. "They're learning so much about dementia and Alzheimer's. [She would decline a treatment] if it would affect our kids' brains at all, because that's what they have going for them."

"For me mainly, it's please just don't make me change my diet or be away from my puppies," said Callie.

"Certainly, if it makes their quality of life worse, or leads to some other crazy - what they can maintain their dignity, all of them have very smart, good brains. But other than that, ultimately, I think for us, we're basically desperate to find something else, a weapon to be able to fight with…You won't find a lot of resistance," said Ed.

Any new treatment should be supported by research. Sarah wants "knowledge of what, exactly, a cure would do. Is it going to cure the whole system? Are we going to see deterioration in different parts of the body? In order to find that out…you have to have funding and you have to have research. Research would be a big part of something that I would look

for in an ideal treatment for AS, what kind of research has been done, what effects, what type of things these children or adults have seen with this cure, and what exactly does it cure? Is it the genetic aspects of it? Is it just the symptoms of it? Research would be really huge."

There is great willingness to participate in clinical research

There have been few opportunities to enroll in clinical trials for AS. Only one respondent (3%) had participated in a trial, though four (11%) had tried but were ineligible, and another 43% were interested. Fourteen percent had not considered participating, 20% were unaware of any trials specifically targeted to AS, and 9% said they had considered participating in a trial but chose not to. When asked to choose the three most important factors guiding their decision to participate in a clinical trial to test a new drug, most participants cited potential side effects or interactions (84%). Additional concerns included distance to the trial site (42%), whether they would need to stop current treatments (42%), route of administration (26%), frequency of appointments (23%), the time commitment (19%), and whether they might receive a placebo (16%).

"I like to see some kind of evidence showing this works," said Wesley, prompting Dr. Levin to ask participants whether they would be willing to participate in a clinical trial, where "sometimes you don't even know if you're getting the drug, let alone does it work or not…sometimes even the side effects are unknown at phase one," or if they would take a drug that had been tested in such a small sample that a serious side effect that could harm as many as one patient in a hundred would not have been detected.

Parents are willing to take risks now to help their own children and future generations. "We love our children," said Sarah, in response to Dr. Levin's question. "There is nothing we wouldn't do…We know that we are the roadmap, and because of that I think we will take chances that other people may not take, because it isn't just our lives that we will affect. Our children, the adults with AS, they are paving the way for the young ones. They're setting the bar. And if we can make a difference in their lifetimes…giving them the research, everything they need to have a cure so that in 20 years, no parent has to go through what Shelly has gone through, no parent has to go through what I have gone through. Please take a chance on us. We are out here to help. We will make that happen."

"When you have nothing to lose then you have an easy-to-sign-up-for research program," said Don. "Because if you cannot see anything, and there's a drug that's going to…maybe give some [vision] back, I don't think there's anything to think about, unless it has a drastic effect that causes harm."

Patients are also willing to take risks for clinical research. "There's nothing more sorry than losing your own child or your own husband," said Milan. "But with our rare disease that is a reality, and I have accepted the reality that maybe I will die earlier than my own mom. But that's okay, because we're doing this to create a better future for the next generation. The biggest issue…is money…because that's the only way to make this happen."

Dr. Levin noted that "there are people who have to sign up in the beginning, people that have to be in phase one. That's when you're in the most experimental phase, it's the safety phase…Adam just said to me, 'Man, you got something to go, I'll sign up in a second to be a research subject.'"

Incorporating patient input into a benefit-risk assessment framework for Alström Syndrome

Introduction

The FDA has developed an enhanced structured approach to benefit-risk assessment in regulatory decision-making for human drugs and biologics. The Benefit-Risk Assessment Framework involves assessing five key decision factors: "Analysis of Condition," "Current Treatment Options," "Benefit," "Risk," and "Risk Management." Each decision factor represents one row in a table. When completed for a particular product, the Framework provides a succinct summary of each decision factor and explains the FDA's rationale for its regulatory decision.

Within the Framework, "Analysis of Condition" and "Current Treatment Options" summarize and assess the severity of the condition and therapies available to treat it. This assessment includes valuable information for weighing the specific benefits and risks of a particular medical product under review, providing an important context for drug regulatory decision-making.

The input provided by patients and caretakers through the Alström Syndrome Patient-Focused Drug Development meeting and survey informs our understanding of the Analysis of Condition and Current Treatment Options for this disease. This information is summarized in the table below, which represents the top two rows of a sample Framework for a drug under review.

Benefit-Risk Assessment Framework for AS

	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Alström Syndrome (AS) is an autosomal recessive disorder that impacts nearly every system in the body starting in infancy or early childhood and causes progressively worsening disease over the lifespan. In all patients, cone-rod retinal dystrophy leads to blindness by the late teenage years. Nearly all individuals with AS are also hearing impaired. Life-threatening cardiomyopathy occurs in infants, older children, teens, and adults. Patients	Due to its multifactorial nature, unpredictable course, and life-threatening complications, AS places a severe burden on patients and parents, starting in infancy or childhood and progressively worsening throughout life, as organs grow increasingly diseased, develop fibrosis, and fail. AS affects every aspect of life, overtaking families, educations, and

	experience a range of respiratory, gastrointestinal, endocrine, skeletal, and neurological disturbances. Most develop obesity and type 2 diabetes in childhood. Organs suffer progressive disease and fibrosis, leading to heart failure, liver failure, and kidney failure in adolescents and adults. Many patients develop painful pancreatitis. Developmental delays are common, though cognitive impairment is rare. Any of multiple symptoms can be life-threatening at any time. There are an estimated 200-300 individuals with AS in the United States. Roughly 1,200 AS cases have been identified worldwide, though the true numbers are likely higher. AS is extremely unpredictable. The array of symptoms varies among individuals, even siblings with identical disease-causing alleles, as do age of onset and severity.	careers. Patients and caregivers compare the disease to a roller coaster. Just as one symptom appears to be under control, another life-threatening condition erupts. Parents describe a life of constant vigilance and frequent hospitalizations. Parents of severely affected children inhabit a landscape of grief punctuated by terrifying medical emergencies. As they reach college age and beyond, patients find it increasingly difficult to pursue educations or careers and to live independently due to their overwhelming medical needs. Adults with AS master an array of assistive devices and display great resilience, but their progressively worsening medical conditions and frighteningly short lifespans frustrate these efforts.
Current Treatment Options	Current treatment for AS addresses individual symptoms. This leads to polypharmacy, which carries special risks for AS patients, in whom medication to treat heart disease (for example) may stress an already damaged kidney or liver. Aggressive dietary interventions treat obesity, diabetes, hypertriglycidemia, liver and kidney disease, but these are difficult to manage and fraught with contradictions – for example, diabetes and kidney disease have mutually exclusive diets. Treatment for AS requires frequent visits to specialists to monitor organ	Patients living with AS have great unmet needs. Existing treatments do not adequately address most symptoms. Given the multitude of impacted systems, the ideal treatment would target the underlying molecular defect via gene therapy. Stem cell transplants are needed to restore vision in patients with advanced retinal dystrophy. Patients also seek improvements in disease management, including real-time monitoring of metabolites and equipment that can be operated by the blind. They seek treatments for hunger and weight gain and for

	function and catch small indicators of disease before it progresses to organ failure, which occurs much more quickly than in the general population. Patients use a variety of assistive devices to aid with vision, hearing, and breathing. Once vision is lost, patients rely on aids for the blind. Some also use home heart monitors, oxygen, and other devices. Individuals with AS depend on lifesaving surgeries, including heart, liver, and kidney transplants to replace failed organs. Though these operations are often successful, disease in multiple systems can impact a patient's eligibility for transplant. The rarity and complexity of AS have made it difficult to evaluate treatments for this condition in controlled clinical trials.	diseases of heart, liver, kidneys, and pancreas. Antifibrotics might address a range of organs. A multidisciplinary approach should be applied to drug development and selection. Drug interactions must be considered, as well as side effects like weight gain and kidney damage. Drugs should not interfere with possible future treatments, such as transplant. Evaluation of any new therapy needs to take into account the background of progressive multi-organ disease that characterizes AS. For clinical trials, it may be necessary to establish specific endpoints that are achievable in the context of AS. Parents and patients are eager to participate in clinical research despite the risks and the knowledge that they may not benefit directly.

Appendix 1. Meeting Agenda

VOICES OF THE PEOPLE – THE ALSTRÖM SYNDROME JOURNEY

ASI Externally-Led Patient-Focused Drug Development Meeting

September 22, 2022

AGENDA

07:00 – 08:30 **Breakfast for Participants in the Duncan Room**

08:30 – 08:40 ***Welcome and Overview of the EL-PFDD*****:** Sheila Farrell, MD, US Food and Drug Administration

08:40 – 08:45 ***Welcoming Remarks***: Robin Marshall, Executive Director, Alström Syndrome International

08:45 – 08.55 ***The Genetics of Alström Syndrome*****:** Clair A. Francomano, MD, Chair, Scientific Advisory Board

08:55– 09:05 ***The Natural History of the Disease*****:** Chase A. Palmer, PharmD, Board of Directors

09:05 - 9:25 ***Overview, Demographic Polling*****:** Anne D. Nordstrom, MBA, PhD

09:25 – 09:55 **Panel 1: *Quality of Life/Burden of Disease***: Tehara Algama, Katelyn Denbow, Callie Marshall, Chad Potter

09:55 – 10:05 **BREAK IN THE HALLWAY**

10:05 – 10:35 ***The Little Warrior – Living from Crisis to Crisis*****: Prerecorded presentation about Dannie Grace Priebe's turbulent early life.** Narrated by Sarah Durfey

The Three Amigos**: Prerecorded presentation demonstrating genetic variability and different journeys even within families.** Narrated by Jennifer Potter

Jack's Tale: **Prerecorded presentation about Jack and the early years on his Alström Journey.** Narrated by Ed and Erin Conlon

10:35 – 10:50 ***Panel 2: Quality of Life: Overcoming the Odds and the Quest for Independence***: Hannah Wedel, Doula Jarboe, Adam Kozarewicz, Milan Boekhoudt

10:50 – 12:00 **Polling and Discussion with the Global Alström Community:** Conducted by Anne Nordstrom, MBA, PHD and facilitated by Clair Francomano, MD and Alex Levin, MD

12:00 – 13:00 **BUFFET LUNCHEON IN THE DUNCAN ROOM**

13:00 – 14:00 ***Coming of Age and Experiencing Setbacks*****:** Prerecorded presentation by Milan Boekhoudt

A Life of Independence and Marriage**:** Prerecorded presentation by Doula Jarboe

A Survivor and Man of the House**:** Prerecorded presentation by Adam Kozarewicz

The Rough Road to a Good Education**:** Prerecorded presentation by Hannah Wedel

Two Tales of Surviving the Burden of the Disease - Courageous Mothers and Daughters**:** Prerecorded presentations by Katelyn and Gina Denbow and Callie and Shelly Marshall

14:00 – 15:30 **Panel 3: It's Complicated - *Issues of Diagnosis, Burden of Treatment, Access to Clinical Trials*****:** The Assembled Alström Parents, Adults and Children

Polling and Discussion with the Global Alström Community: Conducted by Anne Nordstrom, MBA, PHD and facilitated by Clair Francomano, MD and Alex Levin, MD

15:30 – 15:40 ***Closing Remarks*****:** Robin Marshall, Executive Director, Alström Syndrome International

Appendix 2. Survey Questions and Results

ASI conducted a survey of patients and caregivers, "Patient and Caregiver Perspectives on AS Burden, Treatment, and Drug Development," concurrently with the EL-PFDD meeting. This survey was extended for another two months to enable maximum participation. The goal of the survey was to obtain a wider perspective on patients' experiences than could be gleaned from the in-person meeeting. The survey was developed and shared by ASI via their web site and through ASI email lists and social media. There were a total of 37 respondents to the survey queestions: 18 during the meeting and 19 afterwards. Some respondents were patients and some were caregivers who were asked to answer questions from the patient's perspective. Each response represents a unique patient.

1. Where do you live? [n=37]	**# of Responses**	**% of Responses**
East Coast time zone USA	16	43%
Midwest time zone USA	5	14%
Mountain time zone USA	2	5%
West Coast time zone+ (incl Hawaii and Alaska) USA	4	11%
Canada	2	5%
Asia (including China and Russia)	1	3%
Africa	0	0%
South America	0	0%
Europe (including Scandinavia)	7	19%

2. What is your status regarding Alström Syndrome (AS)? [n=37]	**# of Responses**	**% of Responses**
Individual living with AS	13	35%
Parent or Caregiver of a child living with AS	18	49%
Representative (friend or family member) of an adult living with AS	5	14%
Parent, caregiver, or representative of a deceased individual with AS	1	3%

3. What is the biological sex of the individual with AS? [n=22]	**# of Responses**	**% of Responses**
Female	12	55%
Male	10	45%
Prefer not to answer	0	

4. What is the current age of the individual living with AS? [n=36]	**# of Responses**	**% of Responses**
1 month to 5 years	8	22%
6-12 years	7	19%

13-18 years	4	11%
19-29 years	10	28%
30-39 years	2	6%
40-49 years	4	11%
50 years and older	0	0%
Deceased	1	3%

5. At what age did the first AS signs, symptoms, or medical events begin? [n=36]	**# of Responses**	**% of Responses**
Within the 1st year	32	89%
Early childhood	3	8%
Puberty	0	0%
Early Adulthood	1	3%

6. How long ago were you diagnosed correctly with AS, either clinically or genetically? [n=37]	**# of Responses**	**% of Responses**
a. Less than 1 year ago	6	16%
b. 1-5 years ago	11	30%
c. 6-12 years ago	6	16%
d. 13-18 years ago	7	19%
e. 19-29 years ago	5	14%
f. 30-39 years ago	2	5%
g. 40-49 years ago	0	0%
h. Not Yet Diagnosed	0	0%

7. Fill in the Blank: My friends and family would describe me as ___

Blessing, strong, resilient, warrior, amazing, pure, determined	DannieGrace Priebe
Stubborn, funny, sarcastic, lazy, intelligent, inspiring, amazing, clever, loving, interesting, strong	Katelyn Denbow
Smart, sports lover, sensitive, caring	Jennifer Potter
Positive, lazy, stubborn, cute, blingy, intelligent	Callie Marshall
Smart, sarcastic	Hannah Wedel
Difficult, friendly	Milan Boekhoudt
Intelligent, silly, caring	Elder Joseph
Adventurous	Don Algama
Kind, funny, generous, curious, determined, thorough	Debra Szumlinski
positive	Shelly Marshall
The mayor, funny, tough as nails, brave	Chad Potter
Lovable, adorable, challenging, funny, musical	Erin Conlon
Resilient, smart, funny, energetic, loving	Megan Fielder
Positive, happy, funny, smart, mature	Bryce Johnston
Crazy	Nolan Potter
Inspirational, optimistic, strong, empathic	Doula Jarboe

A positive person with many challenges	Callie Hurst
Happy	Emerson Fielder
Bright, introverted, frail	Lauren Gillem
Quiet but spunky. Creative	Rachel Mayour
Loving, curious, smart, and stubborn	Jennifer Farley
We described our children as a "Warrior"	Jack Chu
The sweetest girl. Very smart and a very good friend	Emma Atkinson
Determined, smart, kind, athletic, self-motivated, friendly	Colin Smith
Intelligent, determined, soft spoken, athletic, funny, caring	Ian Smith
Brave	Britany Bretaud
Persona sordociega con múltiples patologías	Nacho Antoranz Cañas
Talented, smart, stubborn, beautiful	Brooke Mullins
Hard to understand what Nimal is thinking, he seems to be living in his own world	Nimal Prakasam
Fun, beautiful, whiny, caring, big sister, smart, curious	Stephanie OKeeffe
A persevering person with a great sense of humor	Sergio Cazalilla
Very kind, curious, and fun. Full of life!	Julie Kroener
Intelligent determined caring talented woman	Jamie Seeger

8. Fill in the Blank: One thing everyone should know about living with AS is ___

Challenging, wonderful, pure, loved, life changing, rollercoaster, hopeless at times, educational	DannieGrace Priebe
Struggle, frightening, overwhelming, stressful, exhausting, frustrating, tiring, lonely	Katelyn Denbow
Patience	Mike Kirby
Rollercoaster ride	Jennifer Potter
Unpredictable, educational, challenging, difficult, stressful, anxiety provoking	Callie Marshall
Flexible, emotional	Hannah Wedel
Difficulty	Milan Boekhoudt
Rollercoaster	Elder Joseph
Being dependent on	Don Algama
Challenging, educational	Debra Szumlinski
Challenging, scary	Chad Potter
Conditions you, life changing, brings out best	Valentina Vignali
It's not easy, lots of doctors	Erin Conlon
Too many doctors, too many tests	Adam Kozarewicz
The challenges	Megan Fielder
Hard	Bryce Johnston
Juggling, balancing act, complicated	Doula Jarboe
My life can change at a moment's notice. There are constant doctor's appointments. As a person with no vision and cochlear implants, it is difficult to understand things, especially on the phone, as quickly as others. Because of this, people lose patience with me and treat me as an inferior person.	Callie Hurst

Complicated	Emerson Fielder
It is exhausting. There is always some new health factor to confront. It's hard to get solid answers about why things are happening in the body, much less how to treat it.	Lauren Gillem
We just want to be like everyone else	Rachel Mayour
It's so different for everyone	Jennifer Farley
On diet!	Jack Chu
It's a very emotional journey and ever-changing	Emma Atkinson
Alström does not define you as a person	Colin Smith
Don't let it hold you back	Ian Smith
Always have hope	Britany Bretaud
Vivir con miedo a no saber que pasará en el future	Nacho Antoranz Cañas
With Alström, it's easier to live than to die. People with Alström have heart of the god, even though they look out of place in this world, that's why they choose to live.	Nimal Prakasam
Terrifing, but you can overcome this	Sergio Cazalilla
There are so many unknowns and people are unfamiliar with the syndrome	Julie Kroener
It can get overwhelming with all the doctor appointments and tests	Jamie Seeger

9. Fill in the Blank: If my outlook on life could be summed on a bumper sticker it would be ___

Windshield / bug, #alstromsucks, #alstromstrong	DannieGrace Priebe
One day at a time, think positive, don't worry be happy, persevere	Katelyn Denbow
Think positive, laugh always, you laugh or you cry, walk by faith	Callie Marshall
Find the positive ❤️	Hannah Wedel
It comes ok	Milan Boekhoudt
Just keep swimming	Elder Joseph
Challenging	Don Algama
Enduring, laugh, pray, hope, strong	Debra Szumlinski
Focus on positive	Shelly Marshall
Never give up, God's got me	Chad Potter
Going to get there	Valentina Vignali
Donate your organs	Adam Kozarewicz
Every day is new	Megan Fielder
Don't tell me I can't, watch me do it	Bryce Johnston
Let's have fun	Nolan Potter
Unique, extra special	Doula Jarboe
Wait a moment, things will change	Callie Hurst
Living my best life	Emerson Fielder
Just keep reading	Lauren Gillem
Just keep going	Rachel Mayour
3 2 1 BLAST OFF!! The sky is the limit	Jennifer Farley
We are AS Winner	Jack Chu
Alström Sucks!	Emma Atkinson
Get the most out of life while you can	Colin Smith
Do your thing	Ian Smith

Empathy	Britany Bretaud
"Mierda de Alström"	Nacho Antoranz Cañas
Treat me like an equal	Nimal Prakasam
I will enjoy every moment	Julie Kroener
One day at a time	Jamie Seeger

10. Which of these symptoms of AS have you experienced? Choose all that apply. [n=32]	**# of Responses**	**% of Respondents**
Physical symptoms (such as scoliosis; kyphosis; flat feet; skin tags; hair loss; dental anomalies; short stature)	22	69%
Vision (such as photodysphoria; nystagmus; cone-rod dystrophy; cataracts; partial blindness; full blindness)	32	100%
Hearing (such as sensorineural hearing loss; conductive hearing loss; otitis media; symmetric hearing loss; asymmetric hearing loss; glue ear)	23	72%
Endocrine/Growth (such as hypothyroidism; hypogonadism; hyperandrogenism; hyperinsulinemia; advanced bone age; growth hormone deficiency)	15	47%
Diabetes (such as Type 1, Type 2, Acanthosis Nigricans (darkening, thickening of the skin), polydipsia (excessive thirst), polyuria (excessive urine), glycosuria (glucose in urine))	15	47%
Obesity (such as hyperphagia, food-seeking, uncontrolled weight gain)	26	81%
Cardio/Pulmonary (such as cardiomyopathy (dilated, restrictive); congestive heart failure; arrythmias; chronic bronchitis; lung disease (restrictive; obstructive; interstitial) hypoxia; hypertension; hyperlipidemia; atherosclerosis)	22	69%
Gastro/Liver (such as GERD; steatosis (fatty liver); non-alcoholic steatohepatitis (NASH) liver fibrosis/cirrhosis; portal hypertension; GI bleeding; ascites (fluid in peritoneal cavity); hepatic encephalopathy)	18	56%
Kidneys (such as nephropathy (kidney disfunction); end-stage renal failure (ESRD))	12	38%
Nervous System (such as such as abnormal pituitary; Autism; seizures; hypersomnia (excessive daytime sleep); hypotonia (decreased muscle tone); ataxia (impaired coordination))	18	56%
Other	10	31%

11. Of all the symptoms of AS that you have or had, choose the 3 that have most negatively affected your life. [n=32]	**# of Responses**	**% of Respondents**
Physical symptoms (such as scoliosis; kyphosis; flat feet; skin tags; hair loss; dental anomalies; short stature)	3	9%
Vision (such as photodysphoria; nystagmus; cone-rod dystrophy; cataracts; partial blindness; full blindness)	26	81%

Hearing (such as sensorineural hearing loss; conductive hearing loss; otitis media; symmetric hearing loss; asymmetric hearing loss; glue ear)	11	34%
Endocrine/Growth (such as hypothyroidism; hypogonadism; hyperandrogenism; hyperinsulinemia; advanced bone age; growth hormone deficiency)	3	9%
Diabetes (such as Type 1, Type 2, Acanthosis Nigricans (darkening, thickening of the skin), polydipsia (excessive thirst), polyuria (excessive urine), glycosuria (glucose in urine))	5	16%
Obesity (such as hyperphagia, food-seeking, uncontrolled weight gain)	11	34%
Cardio/Pulmonary (such as cardiomyopathy (dilated, restrictive); congestive heart failure; arrythmias; chronic bronchitis; lung disease (restrictive; obstructive; interstitial) hypoxia; hypertension; hyperlipidemia; atherosclerosis)	12	38%
Gastro/Liver (such as GERD; steatosis (fatty liver); non-alcoholic steatohepatitis (NASH) liver fibrosis/cirrhosis; portal hypertension; GI bleeding; ascites (fluid in peritoneal cavity); hepatic encephalopathy)	10	31%
Kidneys (such as nephropathy (kidney disfunction); end-stage renal failure (ESRD))	3	9%
Nervous System (such as such as abnormal pituitary; Autism; seizures; hypersomnia (excessive daytime sleep); hypotonia (decreased muscle tone); ataxia (impaired coordination))	3	9%
Other	5	16%

12. Which emotional stresses have you experienced while coping with AS? Choose all that apply. [n=33]	**# of Responses**	**% of Respondents**
Isolation	17	52%
Uncertainty	19	58%
Fear	18	55%
Depression	14	42%
Anger	13	39%
Low self-esteem	12	36%
Anxiety	20	61%
Hopelessness	9	27%
Exhaustion	13	39%
Frustration	24	73%
Loss of independence	16	48%
None	1	3%
Other	2	6%

13. What are your most significant difficulties as a result of living with AS? Choose top 3. [n=34]	**# of Responses**	**% of Respondents**
Dealing with Physical Symptoms	27	79%
Handling Emotional Impact (stress; anxiety; depression; guilt; hopelessness; anger; frustration; fear)	27	79%
Obtaining Social Support (to connect; promote understanding; share experiences)	9	26%
Finding Financial Resources (to deal with insurance deductibles; uncovered costs; missing work; quitting work; being unable to save)	3	9%
Dealing with Bureaucracy (such as Educational; Medical; Insurance)	10	29%
Straining of family dynamics (siblings get less attention; siblings have more responsibilities; marriages break up; caregivers don't have time for themselves)	6	18%
Other	1	3%

14. What resources or supports do you rely on most to receive help with AS? Choose top 3. [n=35]	**# of Responses**	**% of Respondents**
AS patient advocacy group	6	17%
AS multidisciplinary clinics (9/22 survey said "AS research clinics")	7	20%
AS family support group	9	26%
Peers, other affected persons	9	26%
Rare disorder group	0	0%
Symptom-specific support group	0	0%
Social services	2	6%
Family and friends	27	77%
Educational services	16	46%
Medical professionals	19	54%
Other	3	9%

15. Which procedures or assistive devices have you had or used? Choose all that apply. [n=17]	**# of Responses**	**% of Respondents**
Hearing Aids	11	65%
Cochlear Implants	0	0%
Audiobooks	13	76%
Screen Reader	10	59%
Glasses	15	88%
Walking cane	16	94%
Guide Dog	2	12%
Computer Apps	11	65%
Brailler	13	76%
Inhaler	6	35%

Glucose Monitor	7	41%
Insulin Pen	4	24%
Organ Transplant	4	24%
Pacemaker	2	12%
Transfusion	6	35%
Dialysis	2	12%
Reduced Calorie or Special Diet	12	71%
Exercise Program	11	65%
Wheelchair	4	24%
Other	8	47%

16. Overall, which three of your assistive devices or procedures have most improved your quality of life? Choose 3. [n=33]	**# of Responses**	**% of Respondents**
Hearing Aids	14	42%
Cochlear Implants	2	6%
Audiobooks	6	18%
Screen Reader	6	18%
Glasses	14	42%
Walking cane	12	36%
Guide Dog	0	0%
Computer Apps	7	21%
Brailler	7	21%
Inhaler	3	9%
Glucose Monitor	1	3%
Insulin Pen	1	3%
Organ Transplant	2	6%
Pacemaker	1	3%
Transfusion	1	3%
Dialysis	0	0%
Reduced Calorie or Special Diet	4	12%
Exercise Program	3	9%
Wheelchair	0	0%
Other	1	3%

17. Which medications have you used to treat your symptoms of AS? Choose all that you have used. [n=33]	**# of Responses**	**% of Respondents**
Statins (Atorvastatin, Crestor, Lipitor, etc.)	10	30%
Metformin	13	39%
Other Blood Pressure Medications	3	9%
Anti-Rejection Medications (Tacrolimus, Mycophenolate, etc.)	4	12%

Steroids (Prednisone, fludrocortisone, etc.)	12	36%
Antibiotics/Antimicrobial	20	61%
Antidepressants	5	15%
Blood thinners (Warfarin, Eliquis, Plavic, etc.)	2	6%
GI/Stomach Medications (Omeprazole, Famotidine, Pepcid, Zofran, etc.)	13	39%
Other	28	85%

18. In general, how well does your current pharmaceutical treatment improve or control your symptoms? [n=31]	**# of Responses**	**% of Responses**
Very well	10	32%
Moderately well	18	58%
Poorly	2	6%
Very poorly	0	0%
Not at all	1	3%

19. Which AS symptoms do you have that are NOT fully addressed by your current treatments or devices? Choose all that apply. [n=33]	**# of Responses**	**% of Respondents**
Physical symptoms (such as scoliosis; kyphosis; flat feet; skin tags; hair loss; dental anomalies; short stature)	11	33%
Vision (such as photodysphoria; nystagmus; cone-rod dystrophy; cataracts; partial blindness; full blindness)	26	79%
Hearing (such as Sensorineural hearing loss; conductive hearing loss; otitis media; symmetric hearing loss; asymmetric hearing loss; glue ear)	3	9%
Endocrine/Growth (such as hypothyroidism; hypogonadism; hyperandrogenism; hyperinsulinemia; advanced bone age; growth hormone deficiency	6	18%
Diabetes (such as Type 1, Type 2, Acanthosis Nigricans (darkening, thickening of the skin), polydipsia (excessive thirst), polyuria (excessive urine), glycosuria (glucose in urine))	12	36%
Obesity (such as hyperphagia, food-seeking, uncontrolled weight gain)	14	42%
Cardio/Pulmonary (such as cardiomyopathy (dilated, restrictive); congestive heart failure; arrythmias; chronic bronchitis; lung disease (restrictive; obstructive; interstitial) hypoxia; hypertension; hyperlipidemia; atherosclerosis)	7	21%
Gastro/Liver (such as GERD; steatosis (fatty liver); non-alcoholic steatohepatitis (NASH) liver fibrosis/cirrhosis; portal hypertension; GI bleeding; ascites (fluid in peritoneal cavity); hepatic encephalopathy)	8	24%
Kidneys (such as nephropathy (kidney disfunction); end-stage renal failure (ESRD))	8	24%

Nervous System (such as such as abnormal pituitary; Autism; seizures; hypersomnia (excessive daytime sleep); hypotonia (decreased muscle tone); ataxia (impaired coordination))	9	27%
Emotional (such as anxiety, depression, exhaustion)	8	24%
Other	4	12%

20. Which 3 AS symptoms would you choose as most important for future treatments or therapies? Choose 3. [n=35]	**# of Responses**	**% of Respondents**
Physical symptoms (such as scoliosis; kyphosis; flat feet; skin tags; hair loss; dental anomalies; short stature)	1	3%
Vision (such as photodysphoria; nystagmus; cone-rod dystrophy; cataracts; partial blindness; full blindness)	24	69%
Hearing (such as Sensorineural hearing loss; conductive hearing loss; otitis media; symmetric hearing loss; asymmetric hearing loss; glue ear)	9	26%
Endocrine/Growth (such as hypothyroidism; hypogonadism; hyperandrogenism; hyperinsulinemia; advanced bone age; growth hormone deficiency	5	14%
Diabetes (such as Type 1, Type 2, Acanthosis Nigricans (darkening, thickening of the skin), polydipsia (excessive thirst), polyuria (excessive urine), glycosuria (glucose in urine))	13	37%
Obesity (such as hyperphagia, food-seeking, uncontrolled weight gain)	11	31%
Cardio/Pulmonary (such as cardiomyopathy (dilated, restrictive); congestive heart failure; arrythmias; chronic bronchitis; lung disease (restrictive; obstructive; interstitial) hypoxia; hypertension; hyperlipidemia; atherosclerosis)	15	43%
Gastro/Liver (such as GERD; steatosis (fatty liver); non-alcoholic steatohepatitis (NASH) liver fibrosis/cirrhosis; portal hypertension; GI bleeding; ascites (fluid in peritoneal cavity); hepatic encephalopathy)	10	29%
Kidneys (such as nephropathy (kidney disfunction); end-stage renal failure (ESRD))	9	26%
Nervous System (such as such as abnormal pituitary; Autism; seizures; hypersomnia (excessive daytime sleep); hypotonia (decreased muscle tone); ataxia (impaired coordination))	4	11%
Emotional (such as anxiety, depression, exhaustion)	1	3%
Other	0	0%

21. What factors are most important when you select a new treatment or drug? Choose the top 3. [n=34]	**# of Responses**	**% of Respondents**

How the treatment is delivered (oral, injection, IV, etc.)	10	29%
How often one must take the treatment	6	18%
Number of side effects	14	41%
Severity of side effects	25	74%
Cost and/or whether covered by insurance	12	35%
Evidence that the treatment improves specific symptoms important to you	22	65%
What your physician recommends	6	18%
Other	6	18%

22. Which of the following applies to you regarding participation in a clinical trial for a drug to treat symptoms of AS? Choose one. [n=35]	**# of Responses**	**% of Responses**
I have already participated in a clinical trial	1	3%
I attempted to participate but did not meet eligibility	4	11%
I would be interested to participate in a clinical trial but have not attempted to do so	15	43%
I have not considered participating in a clinical trial	5	14%
I have considered participating in a clinical trial but I chose not to do so	3	9%
I am unaware of any clinical trials for drugs to treat specific symptoms of AS	7	20%

23. What are the most important factors related to your decision to participate in testing a drug in a clinical trial? Choose 3. [n=31]	**# of Responses**	**% of Respondents**
Whether I might get a placebo	5	16%
Whether I need to stop my current treatments	13	42%
Potential side effects or interactions from a new drug	26	84%
How the drug is taken (by mouth, injection, IV)	8	26%
Having the time to commit to participating	6	19%
Frequency of exam appointments	7	23%
Distance to the trial site	13	42%
Length of the trial	1	3%
Other	2	6%

[The questions below (except for #43) were asked in the second, post-meeting survey. They were not in the 9/22 survey; instead, many were used as prompts for the panel discussion. A handful of 9/22 participants offered online responses to these questions in the comments section during the meeting. Those comments are included below, along with all responses to these questions from the second survey.]

24. Of all the symptoms that you experience due to AS, which symptoms have the most significant impact on your life? Talk about a few of these symptoms.

My fatigue, cognitive problems when I don't know what's going on around me, incontinence, not knowing where I am in space to do mobility and vision	Callie Hurst
Poor vision	Barbara Zagraba
All of it. From being immunocompromised to seizures to all the hospital and doctor's visits.	Emerson Fielder
Fatigue, pain from gout, hearing loss	Lauren Gillem
Eye condition affects my schooling, how I interact with people, my independence from parents	Rachel Mayour
The vision impacts have delayed development and speech	Jennifer Farley
The patient cannot see that impact her daily life and studying	Jack Chu
Vision impairment has been all-consuming and is the most obvious symptom	Emma Atkinson
Low-vision. No other symptoms currently.	Colin Smith
Low vision	Ian Smith
Autism is constant surveillance. Despite her visual impairment, Britany is doing very well.	Britany Bretaud
Perder la audición y la vision.	Nacho Antoranz Cañas
Vision. Brooke only has 3 symptoms as of now but this one is the hardest for her.	Brooke Mullins
I think my son's vision and seizure issues affects him to grow, while heart issue scares parents.	Nimal Prakasam
Vision loss, hearing loss	Sergio Cazalilla
The overall progression of pulmonary, vision, and hearing. The unknowns and loss that could be a part of the process while ensuring the best quality of life for my son.	Julie Kroener
My vision. Being totally blind is a real pain in a sighted world. Hearing loss, especially in crowded situations.	Jamie Seeger

25. What worries you most about living with AS? Why?

Possibly needing an organ transplant down the road. I'm worried that I might not be able to receive a transplant in time of need, thus ending my life. I'm also concerned that my life with be cut short and I won't get to accomplish all I want to do with my life.	Callie Hurst
That my health can get worse and all the doctor appointments.	Rachel Mayour
As a parent, I worry that my son will lose independence because of the syndromes and potential to affect his senses.	Jennifer Farley
Her daily life because she cannot see well. In some situations, e.g., crossing the road, it is very dangerous. In school, she cannot read from the blackboard or book well, that is affecting how she learns.	Jack Chu
Potential shorter life span. Living in pain, not able to be independent.	Emma Atkinson

Reduced life span. Other symptoms arising in the future	Colin Smith
Dying	Ian Smith
Life expectancy and autistic disorders	Britany Bretaud
También el miedo a llegar a la fibrosis y tener que hacer un trasplante para vivir.	Nacho Antoranz Cañas
She worries about losing her vision the most and what will happen when she is older.	Brooke Mullins
Will my son (who has AS) outlive me? Can he take care of himself after myself and my wife are done with this world?	Nimal Prakasam
Cardiovascular risk	Sergio Cazalilla
The unknowns and limited treatments	Julie Kroener
My parents having to bury me, something no parent should have to face. My brother losing his battle to this monster and any of my symptoms getting worse	Jamie Seeger

26. What resources do you use to help you cope with living with AS? What resources do you need but cannot access?

I use the Alström support group on Facebook. I would like to be able to access an adult day program.	Callie Hurst
Family, therapy, doctors	Emerson Fielder
Technology: refreshable Braille device, cochlear implant. Insurance coverage	Lauren Gillem
More social interaction	Rachel Mayour
Preschool and development therapies	Jennifer Farley
We are studying in VI school, where is the only one VI school in the city, but the school is not quite helpful...And we want to change to mild intellectual disability schools, however, the bureau is not allowed or supported.	Jack Chu
Friends and family	Ian Smith
Treatment with research to cure this disease AS	Britany Bretaud
Recursos tecnológicos como ordenadores con lector de pantalla (Jaws, voice over) Linea braille. No puedo acceder a sesiones de físico o psicólogo por falta de recursos económico, ni a las clínicas multidisciplinarias ni a conferencias internacionales por el mismo motivo.	Nacho Antoranz Cañas
Alström españa, medical proffesionals	Sergio Cazalilla
School, medical and Alström international networking. I worry about future resources later in life for my son, especially financial	Julie Kroener
I use hearing aids, screen readers, a braille display, my iPhone with voiceover, a glucose monitor, implant of a pacemaker, audiobooks, my white cane. Wish websites were more accessible to screen readers, and medical devices like glucose monitors and blood pressure monitors, or more easy to use for a blind person	Jamie Seeger

27. What are you currently doing to help treat the symptoms of AS? How has this changed over time? Why?

Medications, surgeries, therapist, dietician. As new symptoms arise, meds are changed and procedures are done.	Callie Hurst
Medication and therapies	Emerson Fielder
Medication	Lauren Gillem
I am trying to work on diet and exercise because that can help make a lot of things better for my health	Rachel Mayour
Wearing glasses with color tint, eating healthy portioned meals, and exercising	Jennifer Farley
I am controlling her diet and arranging more exercise work for her to avoid insulin resistance or diabetes. See whether any symptom appearing or not that medical paper mentioned	Jack Chu
None	Ian Smith
Lock all the rooms in the house	Britany Bretaud
Seguir los tratamientos mandados por los médicos	Nacho Antoranz Cañas
Hearing aids. Nothing for vision because we haven't found anyone to really help	Brooke Mullins
We started with vision issues, TVI is trying to prepare him for the world with out vision, seizures are still under medication, there is no solution in place	Nimal Prakasam
in recent years I have started to exercise. It has been a very positive change	Sergio Cazalilla
Management medication, IEP, exposure to as many life experiences as possible.	Julie Kroener
I see 4 specialists at different parts of the year. They all run their own medical tests. This has grown over the years as more issues are found	Jamie Seeger

28. How well does your current treatment regime address your most significant symptoms of AS?

Poorly	Callie Hurst
It helps with some of it	Emerson Fielder
Nothing helps the fatigue. Can't use NSAIDs due to kidney disease. Pain from gout has been unremitting	Lauren Gillem
Not on a treatment program	Rachel Mayour
Vision is still challenging. Son does not communicate what he sees	Jennifer Farley
She doesn't have acanthosis nigricans at this moment and the insulin and glucose level are under control	Jack Chu
His sleep and his autism	Britany Bretaud
El tratamiento actual que tengo, no abordan los síntomas más significativos, porque ya soy ciego total y sordo	Nacho Antoranz Cañas
Hearing aids have helped. Struggling with vision	Brooke Mullins

Vision - he has to live with it. Seizures - under control with medical treatment. Heart - near normal. There is no scope with treatment as such	Nimal Prakasam
I take antidiabetic drugs (metformin and liraglutide) and levothyroxine. This treatment works well with minimum side effects	Sergio Cazalilla
It is currently managed	Julie Kroener
They do a good job since I am still living with this monster at the age of 44	Jamie Seeger

29. How well do your treatments address specific symptoms?

Some symptoms are managed well and others not	Callie Hurst
Pretty well	Emerson Fielder
Not on a treatment program but it is still very hard to lose weight and control my appetite	Rachel Mayour
Weight is stable and led signs of uncontrolled hunger. Speech is improving	Jennifer Farley
Under control insulin and glucose level, I am examining whether her eye or hearing loss will be delayed or not...still doing the experiment	Jack Chu
His sleep and his autism	Britany Bretaud
Mis tratamientos a nivel general funcionan bien, pero la enfermedad sigue avanzando al ser degenerative	Nacho Antoranz Cañas
It addresses heart and seizures, while vision and weight issues are not under control.	Nimal Prakasam
I take antidiabetic drugs (metformin and liraglutide) and levothyroxine. This treatment works well with minimum side effects	Sergio Cazalilla
It works, currently	Julie Kroener
Well, I wish somebody could find some new retinas. I am knocking on wood that my hearing stays stable. My diabetes is under control, and the kidneys are holding their own health wise. I will not have to deal with any more kidney stones and my pacemaker is doing great	Jamie Seeger

30. What resources or supports, including medical and pharmaceutical, are missing or could do more to help you?

i would like to be able to control incontinence, and not just use supplies. Receiving supports when services are ordered and months go by without those services.	Callie Hurst
More overall treatment and support. More coordination of treatments	Emerson Fielder
Medication for fatigue. Help for liver illness	Lauren Gillem
A weight loss drug that makes it easier to lose weight	Rachel Mayour
None right now. He is healthy at the moment	Jennifer Farley
Hope the medical team/hospital can raise more systematic clinical test that can relieve or delay the development of the symptom through diet or exercise, which can do it at home with parents	Jack Chu

A full-time facility, as Britany is not full-time at its center for the visually impaired	Britany Bretaud
Hay mucha burocracia a la hora de financiar algunos medicamentos. Debería darse prioridad a las enfermedades raras a la hora de acceder a los medicamentos huérfanos	Nacho Antoranz Cañas
We could def use help with vision	Brooke Mullins
I think better visibility of how to address vision issues on longterm	Nimal Prakasam
A more comprehensive understanding and ways to help find a cure or new treatments	Julie Kroener
Have more medical devices that are accessible to the blind	Jamie Seeger

31. What are the most significant drawbacks to your current treatments, and how do they affect your quality of life?

It takes a very long time to get scheduled services and appointments with specialists, it is very time-consuming and exhausting to try and secure services. It can be overwhelming and depressing	Callie Hurst
There are many doctor's appointments and hospital visits and therapies. It greatly affects the quality of life	Emerson Fielder
On diet is sometimes very difficult for children	Jack Chu
it's such constant surveillance with Britany that we can't go see friends	Britany Bretaud
Que tengo que estar pendiente de que no se me olvide toda la medicación son 13 pastillas diarias, más inyecciones etc. Y no puedo llevar una vida normal	Nacho Antoranz Cañas
We had to skip appointments because he gets sick often, rebooking appointments takes minimum six months	Nimal Prakasam
Number of medical appointments to specialists. As a single parent, I miss a lot of work and struggle managing everything at times. I also worry about the appointments' impact on my son	Julie Kroener

32. Which symptoms are best controlled by treatment?

Cardiac, hearing, liver	Callie Hurst
Seizures and GERD	Emerson Fielder
High blood sugar	Lauren Gillem
Insulin & glucose level	Jack Chu
His sleep	Britany Bretaud
La hiperfagia, la diabetes, los problemas gástricos, la depresión, los problemas urinarios etc.	Nacho Antoranz Cañas
Heart and seizures	Nimal Prakasam
Endocrine symptoms	Sergio Cazalilla
Currently, pulmonary. Vision and hearing are still a work in progress	Julie Kroener
Diabetes, kidney disease, cardio	Jamie Seeger

33. Which are least controlled despite treatment?

Bladder, vision, pulmonary, nervous system	Callie Hurst
Seizures and delays	Emerson Fielder
Kidney disease	Lauren Gillem
Weight	Rachel Mayour
His autism	Britany Bretaud
Colesterol, trigliceridos, hepatopatia	Nacho Antoranz Cañas
Vision and weight, autism	Nimal Prakasam
Non-alcoholic fatty liver disease	Sergio Cazalilla
Vision and hearing, they are still collecting info	Julie Kroener

34. Which symptoms are not addressed? Why not?

Neurological, waiting to see the specialist	Callie Hurst
All of them have been addressed, but so many are wait-and-see	Emerson Fielder
Fatigue. No one wants to say exactly what causes it	Lauren Gillem
Hearing loss, studying delay	Jack Chu
His autism because there are no treatments	Britany Bretaud
Poco pelo, dermatitis, manchas en la piel, acanthosis. Creo que no se aborda porque los médicos no le dan importancia	Nacho Antoranz Cañas
Vision is not addressed, not sure if there is treatment	Nimal Prakasam
Vision loss, because currently there is no treatment	Sergio Cazalilla
Vision because there's nothing on the market right now that can be done for it	Jamie Seeger

35. Short of a cure, what specific things would you look for in an ideal treatment for AS?

I would like to see all the doctors at once in a clinic and have all of them collaberate	Callie Hurst
Vision treatment would be huge. Obesity and then prolonging organ function	Emerson Fielder
Make my vision better and help me lose weight	Rachel Mayour
Something to help with the light sensitivity and lack of color vision	Jennifer Farley
On diet and exercise	Jack Chu
Targeted gene therapy for retina	Colin Smith
Treat retinopathy	Ian Smith
That Britany will speak one day, that Britany will be clean at the level of cleanliness, and that Britany will not be autistic anymore	Britany Bretaud
Retraso del avance de la enfermedad	Nacho Antoranz Cañas
Help with vision	Brooke Mullins
How to make vision available to these guys	Nimal Prakasam
Vision and hearing loss	Sergio Cazalilla
Comprehensive approach that does not require so many separate appointments. It would also be nice to have specialists who are familiar	Julie Kroener

with treating Alström so they can evaluate best line of care for kiddos with the syndrome	
Something that can slow down the fibrosis in all of our organs so we can live a more full life	Jamie Seeger

36. Without considering side effects, what is most important to you for a future therapy or treatment?

Eye transplant, a way to be a typical 32 yr old cognitively	Callie Hurst
Quality of life	Emerson Fielder
Effectiveness of the drug to help lose weight	Rachel Mayour
Translational readthrough inducing drugs (TRIDs) can restore the protein of AS by the experiment on mice. (https://www.sciencedirect.com/science/article/pii/S235239642100308X). Hope this is the therapy direction of AS.	Jack Chu
Efficacy	Colin Smith
That it lasts	Ian Smith
Autism	Britany Bretaud
Retraso del avance de fibrosis y cirrosis	Nacho Antoranz Cañas
Getting vision back	Nimal Prakasam
Vision loss	Sergio Cazalilla
Quality of life can be maintained	Julie Kroener
Will it work or do anything for you?	Jamie Seeger

37. Are there any “no-goes” or things that would deter you from a treatment plan?

If it were to damage my organs in any way	Callie Hurst
Side effects and pain levels	Emerson Fielder
Severe side effect	Jack Chu
Pain	Ian Smith
Distance and side effects	Britany Bretaud
No, cualquier adelanto por pequeño que sea me valdría	Nacho Antoranz Cañas
Nothing	Nimal Prakasam
Serious side effects	Sergio Cazalilla

38. What outcomes would be most meaningful to you?

Being able to have vision and normal cognitive ability	Callie Hurst
Better quality of life	Emerson Fielder
Having enough energy to participate in life would change so much	Lauren Gillem
Having better vision	Jennifer Farley
The root cause (cilia problem) is totally restored	Jack Chu
Improved vision	Colin Smith
Restoring vision	Ian Smith
Certainty that the results are proven that it works	Britany Bretaud
Fixing his vision	Nimal Prakasam

Stop hearing and visual loss	Sergio Cazalilla
If it can potentially increase their quality of life	Julie Kroener

39. How many medical care givers have had a role in the affected person's care? Choose all that you have worked with. [n=18]	**# of Responses**	**% of Respondents**
General Practitioner	7	39%
Cardiologist	14	78%
Pediatrician	15	83%
Otolaryngologist (ENT)	10	56%
Optometrist	5	28%
Ophthalmologist	15	83%
Urologist	6	33%
Pulmonologist	10	56%
Neurologist	8	44%
Dietician	10	56%
Endocrinologist	11	61%
Gastroenterologist	7	39%
Nephrologist	7	39%
Hepatologist	4	22%
Geneticist	14	78%
Therapist (PT, OT, Speech, Vision)	11	61%
Therapist (emotional, educational)	5	28%
Dermatologist	3	17%
Other	3	17%

40. Who are the medical care givers that make up your current medical support team? [n=18]	**# of Responses**	**% of Respondents**
General Practitioner	10	56%
Cardiologist	14	78%
Pediatrician	8	44%
Otolaryngologist (ENT)	8	44%
Optometrist	0	0%
Ophthalmologist	15	83%
Urologist	4	22%
Pulmonologist	6	33%
Neurologist	5	28%
Dietician	6	33%
Endocrinologist	14	78%
Gastroenterologist	5	28%

Nephrologist	6	33%
Hepatologist	3	17%
Geneticist	10	56%
Therapist (PT, OT, Speech, Vision)	7	39%
Therapist (emotional, educational)	4	22%
Dermatologist	3	17%
Other	3	17%

41. How well does your current medical support team help to improve your living with AS? [n=17]	**# of Responses**	**% of Responses**
Very Well	6	35%
Moderately Well	11	65%
Poorly	0	0%
Very Poorly	0	0%
Not at All	0	0%

42. What are your 3 biggest challenges with Health Care Providers? Choose top 3. [n=14]	**# of Responses**	**% of Respondents**
Narrow Focus (cannot look beyond their specialty)	8	57%
Poor Cooperation (not willing to work with other specialists)	3	21%
Poor Communication (not willing to work with caregiver)	3	21%
Refusing to Research (unable to learn about the complicated medical history)	4	29%
Slow response time (tests or treatments are not timely)	6	43%
Giving Up (HCPs won't seek any more answers or solutions)	3	21%
Other	3	21%

43. What do you feel right now --- after reflecting about your Alström Syndrome journey?

Motivated, hopeful, frustrated, scared, determined, blessed to have ASI, alstromstrong	DannieGrace Priebe
Enlightened, calm, not alone, relieved	Katelyn Denbow
Overwhelmed	Edward Conlon
Scared, overwhelmed, hopeful, grateful, thankful, blessed	Jennifer Potter
Comfortable, anxious, unsure, important	Callie Marshall
Hope, family	Milan Boekhoudt
Overwhelmed, hopeful, worried, anxious	Elder Joseph
Hope, awareness, possibilities	Don Algama
Hopeful, motivated, frustrated, impatient, determined	Debra Szumlinski
Hope	Shelly Marshall
Tired, overwhelmed, thankful	Chad Potter
We're orphan...data is needed	Valentina Vignali
Hopeful, not alone	Bryce Johnston

Tired	Nolan Potter
Chaotic, manageable, challenging	Doula Jarboe
Good	Hannah Wedel
Inspired	Jamie Seeger
We are not alone, hopeful, overwhelmed	Megan Fielder
Overall, I feel I'm in good hands and my symptoms are managed fairly well	Callie Hurst
I feel supported and lucky to have found a great group of people who care	Jennifer Farley
The supporter will try to understand or explore what AS is after we reflected our AS journey	Jack Chu
Hopeful	Colin Smith
I wish that someone would investigate why my twin brother and I are so different from other Alström people. We gave a skin biopsy years ago, but no one has looked at it	Ian Smith
We are brave	Britany Bretaud
Es una manera diferente de vivir, que es una mierda pero en la que tienes que aprender a intentar ser feliz con tu discapacidad	Nacho Antoranz Cañas
Confusing	Brooke Mullins
My son is too young to answer this question. We spend a lot of time making my son happy , which we fail more often than not	Nimal Prakasam
It has been a long journey, but I can overcome it	Sergio Cazalilla
Overwhelmed!	Julie Kroener
Grateful for ASI	Jamie Seeger

44. Do you have other comments you would like to make about your journey with Alström Syndrome?

I wish my diagnosis came when I was a child instead of when I turned 30. A lot of questions would have been answered and I would have been more prepared for the possible changes I was going to face	Callie Hurst
I found out about my son's condition at an extremely challenging time in my life. Every day since the diagnosis has been a bonus day for me. I will continue to educate myself and advocate for him	Jennifer Farley
1. Seems no clear path to cure. 2. Studying delay makes her difficult to learn in mainstream class.	Jack Chu
My twin brother and I have a mild form of Alström Syndrome. I believe a lot can be learned from me and my twin brother, but no seems to be interested in why, because of our unique mutations, we have a mild form of the syndrome	Colin Smith and Ian Smith
To be informed on the level of research on AS and to help us to finance the trip for the future conference with AS	Britany Bretaud
Que busquen cuanto antes una cura	Nacho Antoranz Cañas

I left a lot of these blank. I feel as if I can't answer these for my daughter. Her case also seems mild, so she does not have a lot of symptoms/treatment.	Brooke Mullins
Thank you for your efforts to find answers and work towards a cure!	Julie Kroener
Yes, living with Alström syndrome right now is not easy, but one can beat the monster. I currently work part time as a Braille proofreader and I am an accomplished pianist with several YouTube videos.	Jamie Seeger

Appendix 3. Discussion Questions

Morning Session

DISCUSS: Of all the symptoms that you experience due to AS, which symptoms have the most significant impact on your life? Talk about a few of these symptoms.

- What worries you most about living with AS? Why?
- What resources do you use to help you cope with living with AS? What resourcces do you need but cannot access?

DISCUSS: What are you currently doing to help treat the symptoms of AS? How has this changed over time? Why?

- How well does your current treatment regime address your most *significant* symptoms of AS?
- How well do your treatments address *specific* symptoms?
- What resources or supports, including medical and pharmaceutical, are missing or could do more to help you?

Afternoon Session

DISCUSS: What are the most significant drawbacks to your current treatments, and how do they affect your quality of life?

- Which symptoms are best controlled by treatment?
- Which are least controlled despite treatment?
- Which symptoms are not addressed? Why not?

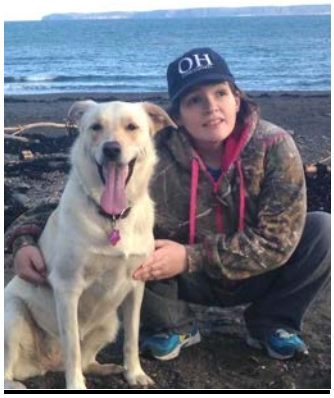
DISCUSS: Short of a cure, what specific things would you look for in an ideal treatment for AS?

- Without considering side effects, what is most important to you for a future therapy or treatment?
- Are there any “no-goes” or things that would deter you from a treatment plan?
- What outcomes would be most meaningful to you?

Appendix 4. Bios of AS Patients from Panel Discussion

Milan Boekhoudt

Milan lives in Arnhem, the Netherlands, with his mother and two younger brothers, Feran and Denan. Both Milan and Denan have AS. Milan was born in 2000, but he and Denan were not diagnosed until 2013. Milan has appeared on Dutch television and spoken at international AS conferences. Milan's favorite sport is shooting on sound, in which he was proud to win first prize in international competition in 2022. In June of 2022, Milan was very sick with acute pancreatitis, losing over 40 pounds. He had a long recovery and is still dealing with low energy.



Katelyn Denbow

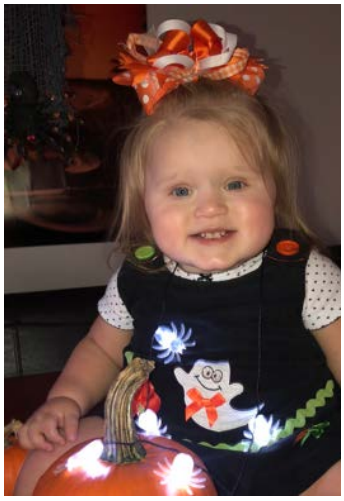
Katelyn's journey with AS was a roller coaster ride with many twists and turns. Katelyn's eyes started shaking when she was three months old, and she would scream whenever she was taken outside. She started gaining weight early and was off the charts by her first birthday. At two, Katelyn was given a "probable" diagnosis of AS by her ophthalmologist, along with six other possible diagnoses, and genetic testing confirmed AS when Katelyn was four-and-a-half. Katelyn was relatively healthy as a young child and loved school and playing with her friends. Around the age of 15, Katelyn made frequent hospital trips to band over a hundred esophageal varices, while her chronic anemia was treated with blood transfusions and iron infusions. She suffered liver failure at 18, and after spending a month in the hospital, underwent a TIPS procedure to allow blood to pass through her liver. Katelyn's breathing problems worsened during Christmas of 2021, and the following June she was diagnosed with congestive heart failure, with an ejection fraction of ~10%. With new medications added to her daily cocktail, she was doing well. Katelyn had a passion for history and learning about other cultures. She was an avid Braille reader, enjoyed audiobooks, and was a fan of cooking competitions and Bobby Flay. Katelyn loved to play with her two young nephews and spend time with family. Katelyn also loved all things Mickey Mouse and recently spent her 25th birthday in Walt Disney World. Katelyn passed away on January 7, 2023.

Doula Jarboe

When Doula Jarboe was a child, no one knew about Alström's Syndrome. She was diagnosed with progressive retinal degeneration at age two, learned Braille in kindergarten, and benefited from blind adult role models she met through the National Federation of the Blind. As a child and young adult, Doula was a downhill ski racer. She joined the roller-skating club in middle school and enjoyed choir and theater in high school. Doula was diagnosed with AS in 1994 at 17. She has a BA in political science, studied for an MA in conflict resolution, and was certified in mediation. Doula currently does advocacy work for deaf-blind people at the NFB. She has two service dogs and enjoys watching movies and listening to music. She is applying for a kidney and pancreas transplant and is experiencing lung deterioration.

Adam Kozarewicz

Adam's AS journey began with his diagnosis in 1997 at the University of Chicago. This required extensive testing, as the ALMS1 gene had not yet been identified. Adam had a sister, Erin, who passed away before their family learned about AS. After his diagnosis, Adam attended several AS conferences, through which he had the pleasure of gaining an extended new AS family; Adam met his girlfriend at one of these conferences in 2007. In 2015, Adam received a kidney transplant. Adam enjoyed audio books, rooting for the Chicago White Sox, and going on vacations with his family. For the last five years, he held down a janitorial job. Adam's next goal was to get a seeing eye dog. Adam passed away on April 7, 2023.



DannieGrace Priebe

DannieGrace entered this world like the Category 5 hurricane she was born in, chaotic and unpredictable. She had her first cardiac event when she was two months old and spent the next month in the pediatric ICU. As other issues arose, Dannie was treated by heart, lung, eye, and neurology specialists. At seven months, Dannie was diagnosed with Alström Syndrome. As time went on, more diagnoses were added, more specialists, more surgeries, and many more inpatient stays. One year after her diagnosis, Dannie had open heart surgery to implant a pacemaker. Surgery was followed by loss of skills and talking, as Dannie slowly slipped away mentally and physically. Dannie still loves to dance and play with anything that lights up and makes noise, and her family hopes to hear her talk and sing again someday. Dannie loves school and spending time with her papas and grandmas. She loves her parents, Sarah and James, and her 5 siblings. Through all her struggles with AS, Dannie still smiles.

Hannah Wedel

Hannah displayed the cardinal signs of AS - vision loss and heart disease - as an infant. In second grade, she received bilateral hearing aids. She sailed through school, excelling in math and history, until seventh grade, when she was hospitalized for pancreatitis and then heart disease. Finally, in the spring of 2006, genetic testing determined that Hannah had AS; she was the 373rd individual to be diagnosed. Hannah's heart condition and her very high tryiglycerides, diagnosed in tenth grade, interrupted her education, but she graduated from high school and enrolled in college in 2014. In 2019, Hannah received a kidney transplant from her father. Hannah graduated from McPherson College with honors in 2022, with majors in mathematics, special education, and general education, and a minor in philosophy and religion. She was recently diagnosed with glaucoma. "I do not know what other curve balls Alström Syndrome will give me next, but whatever they are, I am ready for them…all we can do for now is to look for the positives in every day and live our life to the fullest. Just because you have an…illness that takes up most of your life, does not mean that you should not work hard to reach your goals."