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# THE VOICE OF THE PATIENT

## Externally Led Patient–Focused Drug Development Meeting on Alport Syndrome

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Submitted as patient experience data for consideration  
Pursuant to section 569C of the Federal Food, Drug, and Cosmetic Act to:  
Center for Drug Evaluation and Research (CDER)  
U.S. Food and Drug Administration (FDA)

This report reflects the National Kidney Foundation’s and Alport Syndrome Foundation’s accounts of the perspectives of patients and caregivers who participated in an Externally Led Patient-Focused Drug Development Meeting, an effort to support the FDA’s Patient-Focused Drug Development Initiative

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# VOICE OF THE PATIENT

## Report on the Externally Led Patient-Focused Drug Development Meeting on Alport Syndrome

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November 1, 2019. This Voice of the Patient report has not been revised or modified since November 1, 2019.

### STATEMENT OF USE

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## INTRODUCTION

On August 3, 2018, the National Kidney Foundation (NKF) and Alport Syndrome Foundation (ASF) held an Externally Led Patient-Focused Drug Development (EL-PFDD) Meeting on Alport Syndrome (AS). The broad goals of the meeting were to inform the Food and Drug Administration (FDA) and other stakeholders (e.g., drug developers) on:

- Alport syndrome patients' experiences and perspectives regarding the symptoms and burdens of AS and the impact on their daily lives
- The currently available therapies for AS, patients' experiences with these treatments, and their aspirations for new treatments
- Factors that influence patients' decisions on entering clinical trials for AS

This ELPFDD meeting was a parallel effort to FDA's PFDD initiative. The PFDD Initiative focuses especially on diseases for which treatments are inadequate or nonexistent. Recently, the Agency passed the PFDD leadership to patient advocacy groups to organize and conduct EL-PFDD meetings.

Furthermore, this report is submitted to the FDA to serve as patient experience data or related information for the Agency's consideration in the review of applications for new drugs to treat or prevent AS that are submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) or section 351(a) of the Public Health Service Act, pursuant to section 569C of the FD&C Act.

More information on this initiative can be found at:

[fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm453856.htm](https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm453856.htm)

### Overview of Alport Syndrome

Alport syndrome is a rare, inherited disorder of type IV collagen, caused by mutations in the *COL4A3*, *COL4A4*, and *COL4A5* genes. Under physiological conditions, the collagen subunits produced by each of these genes ( $\alpha$ -3,  $\alpha$ -4, and  $\alpha$ -5, respectively) come together to form a triple helix, the building block for the type IV collagen network that comprises basement membranes within the kidneys, ears, and eyes.<sup>1</sup> When there is a mutation in any one of the type IV collagen genes that either alters the structure of the gene product, or entirely eliminates one component of the triple helix, type IV collagen cannot form properly, and structures that rely on a type IV collagen matrix are dysfunctional. The renal glomerulus, the filtering unit in the kidney, is such a structure. The glomerular basement membrane (GBM), which forms the central filtration barrier, is composed largely of type IV collagen.

In AS, mutations in *COL4A3*, *COL4A4*, and *COL4A5* genes lead to a leaky GBM, which permits plasma proteins (proteinuria) and red blood cells (hematuria) to pass across the GBM. People with AS experience progressive loss of kidney function, with many progressing to end-stage renal disease (ESRD; kidney failure). Because type IV collagen in basement membranes in the cochlea of the ear is also affected, many people with AS also experience hearing loss. In addition, people with AS can have eye abnormalities, including dot and fleck retinopathy and anterior lenticonus. While in some cases these abnormalities do not interfere with vision, in others, vision is affected, and loss of vision is progressive.<sup>2</sup>

Alport syndrome is a genetically heterogeneous disease with over 1000 mutations. Recently, a new classification scheme for AS has been proposed in which X-linked, autosomal, and digenic modes of inheritance comprise the broad disease categories ([Table 1](#))<sup>3</sup>. Within each inheritance type, the nature of causative mutations can vary (e.g., nonsense, deletion, or missense). Mutations in *COL4A5*, residing on the X chromosome, give rise to X-linked AS, whereas mutations in either *COL4A3* or *COL4A4*, on chromosome 2, cause autosomal AS. Digenic AS is caused by simultaneous mutations in two of the *COL4A3*, *COL4A4*, and *COL4A5* genes.

**Table 1 | New classification system for Alport syndrome and related disorders**

Inheritance	Affected gene(s)	Genetic state	Comments	Estimated risk of ESRD
X-linked	COL4A5	Hemizygous (male subjects)	Rate of progression to ESRD and timing of extrarenal manifestations strongly influenced by genotype	100%
		Heterozygous (female subjects)	Risk factors for progression: gross hematuria, SNHL, proteinuria, GBM thickening and lamellation.	Up to 25%
Autosomal	COL4A3 or COL4A4	Recessive (homozygous or compound heterozygous)	Rate of progression to ESRD and timing of extrarenal manifestations strongly influenced by genotype	100%
		Dominant	Hematuria Includes patients previously diagnosed as TBMN/BFH Risk factors for progression: proteinuria, FSGS, GBM thickening and lamellation, SNHL, or evidence of progression in patient or family, genetic modifiers	20% or more among those with risk factors for progression, <1% in absence of risk factors
		Digenic	COL4A3, COL4A4, and COL4A5	COL4A3 and COL4A4 mutations in trans
		COL4A3 and COL4A4 mutations in cis	Clinical findings and pedigree simulate autosomal dominant transmission	Up to 20%
		Mutations in COL4A5 and in COL4A3 or COL4A4	Inheritance pattern does not simulate any Mendelian transmission	Up to 100% (affected male subjects)

*Kashtan et al; Kidney Int., 2018;93:1045-51. Permission from Elsevier though Copyright Clearance, Inc.*

The prevalence of AS in the U.S. is estimated between 30,000 – 60,000 people. About 60–70% of AS patients have the X-linked form, while about 15% and 20% have autosomal recessive and autosomal dominant forms, respectively.<sup>4</sup> The prevalence of the digenic inheritance of AS is currently unknown.

The risk of ESRD in AS is shaped by the inheritance pattern and the nature of the causative mutation. In male patients with X-linked AS caused by a nonsense or deletion mutation, the risk of ESRD is 90% by age 40, with 90% of patients having some form of hearing loss. Missense mutations are associated with older age of onset of ESRD and hearing loss.<sup>5</sup>

The risk of ESRD for both men and women with autosomal recessive AS is similar to that of males with X-linked disease. For women with X-linked AS, the risk of ESRD by age 40 is 12% and at age 60 the risk of ESRD is as high as 30%.<sup>5</sup>

Importantly, many female patients are still incorrectly categorized as “carriers,” though they may have progressive kidney disease and hearing loss.

The risk of ESRD for autosomal dominant AS reaches 50% at 70 years of age. Although this suggests slower disease progression, a subset of these patients reach ESRD by age 20.<sup>6</sup> The drivers of this phenotypic variation are unclear. Finally, the risk of ESRD for digenic inheritance varies depending on the mutation and the affected genes and ranges from 20% to 100%.<sup>3</sup>

Because microscopic hematuria is nearly always present at birth or early childhood in AS patients, the diagnosis of AS is frequently made in childhood. However, diagnosis is often delayed until other symptoms such as proteinuria and hearing loss become apparent, which may not occur until adulthood.

Diagnosis of AS is much more likely when there is a family history of AS, early hearing loss, hematuria, or kidney failure with unknown cause. Suspicion of the disease is generally heightened when hearing loss is present. Diagnosis can be confirmed by examination of kidney biopsies, where collagen expression and structural changes to the GBM can be observed by immunofluorescence and electron microscopy, respectively. In the case of X-linked AS, immunofluorescence microscopy may be employed on skin biopsies to assess the presence of the type IV collagen  $\alpha$ -5 chain. Diagnosis is increasingly confirmed by genetic testing. Knowing the genetic variant can also provide important prognostic and hereditary information.

### Treatments for Alport Syndrome

Currently there are no FDA-approved treatments for AS. A 2013 report on clinical practice recommendations for AS clarified the point in disease progression at which intervention is most meaningful.<sup>1</sup> Currently available therapies are largely nonspecific, and most often include blockers of the renin-angiotensin-aldosterone system. While these blockers lower blood pressure in AS patients, their benefits are thought to derive from the antifibrotic effects of these agents. Other nonspecific treatments used in AS are diuretics and dietary interventions. At the time of this writing, there are only two test agents for AS, in Phase 1 and 3, listed on [clinicaltrials.gov](https://clinicaltrials.gov). If approved for patients, these would represent the first therapies for AS. Given the heterogeneity of genetic defects in the type IV collagen that causes AS, and the variable clinical course of the disease, it is likely that response to drug treatments will also vary. Therefore, multiple therapeutic options will likely be necessary to achieve benefits in the broad AS population.



## Meeting Overview

This EL-PFDD Meeting on AS focused on two key topics: the patient experience of living with AS, including disease symptoms and the daily impact of the disease, and the patient perspective on the current challenges of treating AS. An additional topic on participation in clinical trials was also discussed. Discussion during the meeting provided the FDA and other stakeholders the opportunity to hear directly from patients and their caregivers about their experiences living with AS; the impact of disease symptoms on their lives; their perspectives on available treatments; the treatment goals that are most important to them; and factors that would influence their decisions to enter clinical trials for AS.

The meeting agenda and the questions that guided the discussion are included in [Appendices 1 and 2](#). To provide initial patient input on each topic, and to prepare the audience for discussions, panels for each of the two key topics were assembled before the meeting. Each panel consisted of five patients and caregivers, selected by NKF and ASF representatives. Panelists were recruited from the ASF membership and from patients suggested by the meeting Co-chairs. Criteria for selecting panelists were set to maximize representativeness by achieving clinical and demographic diversity on each panel ([Appendix 3](#)). Each panelist delivered a prepared, five-minute testimony ([Appendix 3](#)) on their experience related to their topic.

The demographic composition of the patient and caregiver attendees (in-person and remote webcast) was revealed by polling questions ([Appendix 4](#)). Following each panel, additional polling questions ([Appendix 4](#)) were posed to the participants, toward capturing their perspective on the different discussion topics. These questions were based on a pre-meeting survey of prospective attendees, input from the meeting Chairs, and literature reports. This was followed by a moderated audience discussion, in which the in-person audience was invited to share their experiences with AS and were asked follow-up and clarifying questions by the moderator. Patients' preferences concerning enrolling in clinical trials for AS treatments were also solicited through polling questions ([Appendix 4](#)) and facilitated audience discussion; panels were not employed for this topic.

Results from polling questions appear in [Appendix 5](#).

Polling was conducted via an online platform through which in-person and remote webcast attendees could respond. Only patients and caregivers were asked to participate in polling. Responses were projected instantly for audience viewing and described simultaneously by the moderator.

To expand on the perspectives gathered at the meeting, patients and caregivers were encouraged to submit comments to the NKF and ASF after the meeting. Comments were accepted until September 1, 2018. Comments from six patients and their caregivers were submitted following the meeting. Themes were identified and comments were reported under those topics ([Appendix 6](#)).

The archived webcast recording, this meeting report, and the meeting transcript are available on the NKF's and ASF's websites: [kidney.org](http://kidney.org) and [alportsyndrome.org](http://alportsyndrome.org). This meeting report is posted on the FDA's EL-PFDD website: [fda.gov/Drugs/DevelopmentApprovalProcess/ucm579132.htm](http://fda.gov/Drugs/DevelopmentApprovalProcess/ucm579132.htm)

Approximately 70 people attended the meeting, including 28 AS patients and 21 caregivers ([Appendix 5; Figure 1-A](#)). Nine representatives from FDA were present. In addition, 98 patients or caregivers attended through the live remote webcast.

Responses to the demographic polling questions revealed the diverse nature of the participants (in-person and remote webcast). The majority of respondents were from the East Coast and Midwest U.S. ([Appendix 5; Figure 1-B](#)). Representation by female and male patients and caregivers was virtually equal ([Appendix 5; Figure 1-C](#)). Thirty-three percent of participants were younger than 18, while 60% of respondents were between 18 and 59 years old ([Appendix 5; Figure 1-D](#)). Most patients received their diagnosis more than 10 years ago (59%) or between 2 to 5 years ago (20%) ([Appendix 5; Figure 1-E](#)). The most common type of AS represented by participants was X-linked AS (68%), while 18% of patients were unsure of their AS causative mutation ([Appendix 5; Figure 1-F](#)). Two percent of respondents were receiving dialysis, while 20% had received a kidney transplant ([Appendix 5; Figure 1-G](#)).

## Report Overview

This Voice of the Patient Report summarizes the perspectives shared by patients and caregivers at the EL-PFDD meeting, including responses/results ([Appendix 5](#)) to the polling questions ([Appendix 4](#)) posed during the meeting. Comments submitted to the NKF and ASF after the meeting are shown in [Appendix 6](#). The terms and language used in this report to describe AS symptoms, impacts, treatment experiences, and views on participating in clinical trials reflect those used by in-person attendees. There may be symptoms, impacts, treatments, or other aspects of the disease that are not included in the report.

This report intends to support FDA's understanding of: 1) the burden on patients and their families living with AS and its symptoms; 2) patient perspectives on the treatments currently used to manage the condition; and 3) patients' aspirations for features of ideal future treatments. This document also

provides insights into patients' preferences regarding clinical trials for AS therapies. By describing the patient experience with AS, this document highlights the serious nature of AS and the significant unmet needs of AS patients, and will enable the FDA to incorporate the patient voice when advising sponsors on their drug development programs, evaluating products for marketing approval, and assessing benefit-risk for products under review.

This patient input may also be of value to the drug development process more broadly. For example, the patient perspectives may guide pharmaceutical companies in their discovery and development processes by exposing previously unappreciated patient burdens of AS. That is, by describing unmet needs surrounding symptoms of AS, information in this report may direct research decisions toward targeting disease mechanisms that underly symptoms important to patients. Information in this report can also inform endpoints in clinical trials and help to design clinical trials to test hypotheses that are inherently meaningful to patients.

In this report, patients and caregivers are collectively referred to as "participants." When responses to polling questions are reported, the responses include those from patients and caregivers in the meeting room, and from the webinar audience. "Caregiver" refers to a family member, partner, or friend who provides direct care for the patient.

Percentages from polling questions reported in the text and as numerals in the Appendix figures are rounded-off from the original data.

We note that, while the in-person and remote webcast attendees at this meeting represented a clinically and demographically diverse group, the extent to which this group reflected the AS patient population at large is unknown, in part, due to the lack of quality epidemiology and natural history information on AS.

### Key Themes

The input from the meeting, remote webcast, and post-meeting comments emphasized the challenges of living with AS, its impact on daily and family life, and the difficulties associated with the anxiety, fatigue, and hearing loss that accompany the progression of the disease. Several key themes emerged from this meeting:

- Anxiety was a pervasive theme during the meeting. Patients and caregivers spoke of the impact of this burden on their lives.

- Parents expressed anxiety and stress over the genetic aspect of the disease affecting multiple family members across generations. They also voiced guilt about passing a devastating disease on to their children.
- Patients described their frustration with loss of energy and vitality, and the toll that fatigue had taken on their education, careers, family life, level of physical activity, and social life. This was particularly hard for the young patients, many of whom experienced ESRD during their years of peak productivity.
- Patients shared their experiences with hearing loss and how it had affected their lives, as well as the different ways they had coped with this aspect of AS. *Although hearing loss has a profound impact on patients, participants stressed that the most important goal for them is preservation of kidney function.*
- Many female patients experienced complications during pregnancy and sometimes had a family or personal history of preeclampsia, severe difficulty during childbirth, and pre-term birth.
- Other symptoms most commonly discussed were gastrointestinal issues, edema, gout, and repeated infections.
- Patients voiced frustration and anxiety about the lack of AS-specific medications, and the limitations of antihypertensive treatments. They also spoke about methods they used, such as CBD (cannabidiol oil), to treat some of the comorbidities of AS, psychotherapy, and a weighted blanket.
- Patients discussed their experiences with clinical trials for AS treatments and offered insights into how to increase participation and alleviate the family burden associated with participating in such trials.

## PERSPECTIVES FROM PATIENTS

### Topic 1: Living with Alport Syndrome: Disease Symptoms and Daily Impacts

The first discussion topic focused on the impact of AS and its symptoms on the daily lives of patients and their families. Panelists shared their personal narratives guided by discussion questions ([Appendix 2](#)). The panel consisted of five AS patients, including two patients who have affected children. The clinical and demographic representation by the panelists is shown in [Appendix 3](#). Panelists described the daily physical, emotional, and social impact of AS and its symptoms, as well as limitations the disease places on participation in daily activities ([Appendix 3](#)). Following the panel's presentations, the audience was polled to obtain their experiences living with AS. A moderated discussion followed, in which patients and caregivers in the audience reinforced the impact of AS on multiple aspects of daily and family life, the frustration with progressive loss of physical capability and vitality, and the sense of isolation that comes with having an "invisible" disease that involves hearing loss.

#### Overview of Impact of AS on Daily Life: Results from Polling Questions

Insights into the impact of AS on daily lives of patients were obtained from responses to polling questions, as described below.

Seventy percent of participants indicated that AS symptoms interfered with their daily life at least moderately ([Appendix 5; Figure 2-A](#)). When queried on eight symptoms identified in the pre-meeting survey of AS patients, the three symptoms most frequently experienced were: anxiety and/or depression (21%), being tired, exhausted or fatigued (20%), and hearing loss (15%) ([Appendix 5; Figure 2-B](#)). Of these eight symptoms, the three which most negatively affected the daily lives of respondents were: being tired, exhausted, or fatigued (29%), anxiety and/or depression (22%), and hearing loss (21%) ([Appendix 5; Figure 2-C](#)).

Participants were probed further on psychosocial burdens they face while living with AS. Respondents reported anxiety (27%), social isolation (18%), depression (17%), and hopelessness (15%) as the major psychosocial burdens they faced ([Appendix 5; Figure 2-D](#)).

When offered choices on other areas of life that might be negatively affected by AS ([Appendix 5; Figure 2-E](#)), respondents most frequently reported that others do not know what it is like to live with AS (27%). This perception was framed in the subsequent discussion as AS being a “silent disease.”

Family stress was common in the lives of 19% of respondents. Other frequently selected factors negatively affecting daily life were: not being able to participate in physical activities (18%), missing work or school (16%), and limited general daily function (16%) ([Appendix 5; Figure 2-E](#)).

### Perspectives on Most Significant Symptoms: Moderated Audience Discussion

#### Impact on Day-to-Day Life

Panelists’ testimonies ([Appendix 3](#)) and the moderated discussion on the daily impacts of symptoms exposed the effects of the above and other symptoms in greater depth and revealed insights into the relationships between symptoms and their influence on the daily lives of patients. The variability in symptoms reported by patients highlighted the heterogeneity of the severity and rates of progression seen in AS patients attending the meeting.

Symptoms of AS that were most frequently identified as having the greatest negative impact on patients’ lives were: fatigue, anxiety and/or depression, and hearing loss ([Appendix 5; Figure 2-C](#)). The audience discussion revealed that experiences of these symptoms can be intertwined, and their impacts may overlap. Patients’ experiences of specific symptoms are detailed below.

#### *Fatigue*

Fatigue was the most commonly identified symptom that negatively affected the lives of AS patients ([Appendix 5; Figure 2-C](#)). Fatigue develops gradually and was described as being associated with declining kidney function. It may be compounded by the hypotensive effects of blood pressure-lowering medications.

Several audience members described their frustration and sadness over losing their ability to engage in an active lifestyle that included sports or other physical activities, such as hiking or even household chores. Audience members also reported having to monitor their daily activities, knowing that they had a limited amount of energy to spend in a particular day. The physical limitations imposed by fatigue and exhaustion were described as particularly difficult for patients who were caring for children.

“I used to go hiking once a week with a couple of friends...We would walk up the hill, and I would be sweating, out of breath, and profusely tired, and they would look like we just went for a short walk.”

“If there's a day that I know that I have a lot to do, I don't get exercise because I know I need that physical ability to do something else. And then I feel bad because I'm not doing what my body needs to stay healthy.”

“On a day that I go and I exercise, I know that I'm pretty much not going to do much else that day.”

“I've always been a strong, dynamic woman, but I can see myself moving towards a slower pace, which is very frustrating, and not the example I want to set for my children and my grandchildren.”

“My body can't handle and recover from all the activity that I normally do. If I just don't do anything, I feel okay. But for me, not doing something and just sitting isn't something I can do well.”

“I can experience extreme fatigue, severely limiting my daily activities. There are times that I felt too tired to make dinner for my family or bring my children to their after-school activities.”

School-aged panelists described the impact that fatigue had on their education. Fatigue can prevent full-day attendance at school, interfere with participation in extracurricular activities, and hinder full social engagement.

“When I was in the fifth grade, I only went to school half days because I didn't have enough energy to go full days.”

“This past school year has definitely proven to be a challenge because the anemia wipes me out. By 5:00pm I must come home and sleep, even before I begin my homework.”

“I no longer had the desire to go swimming with my friends or [take] walks around the neighborhood with my friends.”

The interaction between fatigue and anxiety was illustrated by audience members who expressed fear that, as their disease progresses, they would be unable to provide for themselves or their families.

“The fatigue has me worried about [providing for myself]...having more and more trouble just managing my own self-care.”

### *Anxiety and/or Depression*

Anxiety and/or depression were the second most frequently cited symptoms most negatively affecting patients' lives (Appendix 5; Figure 2-C). Anxiety and/or depression can be overwhelming, especially because the uncertainty surrounding the prognosis of AS makes it difficult for patients to form expectations of disease progression. Fear of reaching ESRD was the main driver of anxiety and/or depression. Within this framework, anxiety and/or depression for the patient or family member were most often linked to uncertainty about the availability of effective, durable treatments as the disease progresses.

Anxiety and/or depression were exacerbated further by fears of reductions in future quality of life, eventual loss of physical capabilities, and likely hearing loss and its resulting sense of exclusion from social or work activities.

Examples of the impact of AS-related anxiety, depression, and stress on daily life are provided below:

“...the most significant impact of Alport syndrome on my life is emotional stress. I worry about my reduced kidney function, and my boy's progressing proteinuria, wondering when one of us might have to start dealing with the effects of kidney failure. This constant stress impacts every aspect of my life if I don't take positive steps to manage it.”

“I have anxiety [and I am] worried about what the future's going to be and how I'm going to earn a living and take care of myself...”

“[My anxiety] started to manifest in panic attacks.”

“I have trouble sleeping, heart palpitations, headaches, and it's not good for relationships or family dynamics.”

For parents who are AS patients and have children with AS, the anxiety of disease progression is two-fold; they are often left to manage their family life and the health and future of their children while facing their own challenges with fatigue, emotions, and maintaining their health.

“Aside from being terrified of my own ESRD, I'm absolutely terrified of the known fact that my son will reach ESRD.”

“It's hard for me to manage being a mom and an example, and also managing my fears and anxiety for my own progression.”



“I try to really minimize the symptoms that I manage on a daily basis and not allow my children to fear Alport syndrome because I don't want them to have it in their head that they're limited.”

“My biggest fear is that I'll go through renal failure and my son [an AS patient] will have to witness [it].”

“I felt very depressed that I could not fulfill basic responsibilities for my family.”

Several participants noted that within their family, they must work hard to ensure that AS does not become the focus of the family.

“I have to work hard every day to make sure that my kidney disease does not take over my life.”

In families with affected and unaffected children, the unaffected child can feel ignored or can feel conflicted over being a kidney donor, especially if there are multiple affected children.

“I'm also sad to see what this has done to their sister. The lack of attention, and her feeling the pressure to donate a kidney, worrying that she only has one kidney to give, but two brothers who will need it.”

### *Hearing Loss*

Slightly greater than one-fifth of participants indicated that hearing loss was a “top three” symptom that negatively affected their daily lives ([Appendix 5; Figure 2-C](#)). Moreover, they emphasized that progressive hearing loss has an isolating effect, resulting in limited participation in social situations, professional endeavors, and educational pursuits. It also reduces the pleasure of social gatherings or activities, such as watching a movie. One panelist commented that his hearing loss had begun to interfere with his performance at work.

“Oftentimes I misunderstand someone at work and make a calculated decision; only to be told I heard incorrectly. So, I must apologize and start over...I now sit quiet in meetings when I miss sentences.”

“...I spend a lot of time at sports events and sports practice, and there's just all the jokes and all the comments and things that you don't hear that you miss and everybody's laughing.”

“I even shied away from joining the Alport Syndrome Foundation, because I thought ‘I can't hear anything anyways, so what's the use of being in a big group?’”

“The technology where I work is moving more towards conference calling and all, which makes it especially difficult to hear when you don't have a face to get cues from.”

One noteworthy element of the discussion on hearing loss was that eventually, as hearing fades past the point that hearing aids can help, a sense of resignation may lead patients to stop asking questions about what was said, or to stop actively participating in social or professional situations.

“I say, ‘What did you say?’ a lot. But there comes the time where you just stop asking, [because there are] only so many times you can elbow somebody and ask them to repeat [what was said] to you.’

Finally, in addition to the social isolation caused by hearing loss, participants voiced concerns that they may lose their jobs or otherwise be limited in their career choices as a result of this component of AS.

“I've avoided telling others about my disease...It isn't that I'm ashamed of living with Alport. Rather, I fear a loss of insurance or employment...with preexisting medical conditions [and the] risk of being dropped by insurance companies, the fear is real.”

Parents expressed concern about the effects of hearing loss on the social and academic development of their children.

“I do worry about bullying and learning disability because he can't hear the teacher.”

“If he goes swimming, he can't wear his hearing aids when he's swimming and [when he] goes for sleepovers and he's sleeping in while the other kids are talking...He's not going to be able to do the normal things that kids do.”

Hearing loss was mentioned as a safety issue by a young panelist.

“It [the hearing aid] helped me hear the sounds coming from behind me, as well as in front of me, and this, of course, I need for driving.”

Adding to the impact of hearing loss is the financial burden associated with hearing aids and cochlear implants. These devices are expensive and rarely reimbursed by insurance companies.

“I delayed getting hearing aids due to the expense. But my hearing loss caused increasing difficulty for me to communicate effectively at home and at work.”

### *Social Isolation*

Distinct from the social issues that arise from hearing loss is the impact of having an “invisible disease.”

This was expressed in polling questions when 27% of respondents cited that others do not know what it is like to live with AS ([Appendix 5; Figure 2-E](#)). Participants noted that fatigue can give a negative impression to colleagues, and that the lack of visible indicators of illness can make it difficult for others to empathize. Alport syndrome patients also mentioned fatigue was a limiting factor in social engagement.

“It’s an invisible disability, so it’s very hard for people around you to understand what you’re going through.”

“My friends didn’t understand what was wrong with me, because it didn’t look like anything was wrong with me...”

“I realize now that, if you have a condition no one can see, it’s hard to get any sort of help.”

“I didn’t know anybody who had the same issues as me, so I felt isolated, like [someone in] a boat in the middle of the ocean calling for help, but no one knew it was there.”

### *Gastrointestinal Issues*

Ten percent of participants indicated that they had experienced gastrointestinal problems ([Appendix 5; Figure 2-B](#)), and 11% of participants ranked these issues as one of the three symptoms that most negatively affect their daily lives ([Appendix 5; Figure 2-C](#)). Some of these AS patients live with diffuse esophageal leiomyomatosis, enlargement of the esophagus, that can cause difficulty swallowing and breathing. In some cases, the esophagus becomes so enlarged, it eventually restricts airflow in the trachea. One panelist and one audience member shared their experiences with gastrointestinal issues.

“...imagine how it would feel to gargle water and cough at the same time...picture waking up in the middle of the night completely cut off from oxygen, and all you can physically do is that [feeling of gargling water and coughing]...The simple task of clearing my throat [was] a scary event...It was hard knowing I couldn’t do the things I loved, like softball, swimming, or anything that required breathing, without the fear of choking. My esophagus is now completely gone...surgically removed. My stomach was pulled up to take its place.”

“I have some kind of [esophageal] thickening. I have a swallowing problem...I start eating a meal and everything seems fine. And then, about the third bite...everything just stops. And I have an overwhelming pressure – pain sort of feeling low in my chest, and I just have to wait. I’ve had a couple of times where I actually regurgitate because it doesn’t go down.”

### *Family Planning and Pregnancy Complications*

Because AS is an inherited disorder, it has affected the family-planning decisions of many patients. For many who were aware of their diagnosis before beginning to have children, the prospect of having a family was wrought with anxiety over passing the disease to their children. This anxiety also stems from AS being a genetic disease that often afflicts multiple family members and multiple generations, causing families to relive this disease and anticipate similar experiences of previous relatives. For patients who already have affected children, the guilt of having passed on the disease is distressing.

“Due to the fear of raising a daughter suffering from a devastating kidney disease, I made a difficult decision to stop growing our family after two children, both boys...We still imagine how our lives would have been further enriched with the sound of a little girl's voice in our house.”

“It was absolutely devastating to think I passed this disease on to my boys and would have to relive the challenges that I watched my younger brother go through during his life.”

During the discussion, several audience members noted the significant complications they had experienced during pregnancy. The most commonly noted complications were edema, diminished kidney function (which may or may not return to normal), preeclampsia, and pre-term delivery. Many audience members commented that increased fluid retention during pregnancy and the subsequent loss of water weight following delivery were particularly dramatic. For many pregnant AS patients, preeclampsia, diminished kidney function, and the potential for preterm delivery led to very difficult pregnancies and decisions that were fraught with emotion.

“Each pregnancy caused preeclampsia symptoms and renal progression, which remained after each birth.”

“Preeclampsia caused me to retain large amounts of fluid, so that my face was almost unrecognizable...”

“I had a lot of trouble after my second and third pregnancy with recovery. My heart would just go crazy. My blood pressure was crazy. I couldn't move. I couldn't do anything.”

“Preeclampsia caused me to [be]...very weepy.”

“My kidney disease severely impacted my pregnancies. All three of my children were born preterm.”

“Each pregnancy was more challenging than the one before, so I made the difficult decision to not have more children.”

“My third pregnancy, my kidneys let us know this was going to be the last.”

### Additional Symptoms of Alport Syndrome

Other AS-associated symptoms that were discussed included: gout, recurrent infections, headaches, and vision problems. These were not as universally experienced by AS patients as the symptoms discussed above, but the impact of these symptoms was profound. Below are comments provided by panelists and audience members about their experiences with the less common comorbidities of AS.

#### *Gout*

“I live in a two-story home, so if I have a gout flare-up, I can't get anywhere. I keep crutches by my bed.”

“I keep crutches by my bed for that time when I have a big toe gout flare, because you can't put any pressure on it at all. It's excruciating.”

#### *Infections*

“I get colds that then turn into a chest infection or a more serious bacteria [I] infection...like six or seven times a year.”

“I was the manager of a business...[and I] would miss a lot of days at work. And with an invisible medical history, it seems irresponsible to other people who might not understand what I'm going through to be this manager and...taking off more time than [my] direct reports...like getting sick three times in a two-month period.”

#### *Headaches*

“We have almost daily headaches, very severe.”

“[If I exercise] I can't function for the rest of the day. I get a migraine, and I'm passed out.”

#### *Vision Loss*

“I had to give up driving because...I couldn't pass the driving test to get my license, the eye test. I have...recently been diagnosed with a thinning of the retina. I can't see, to do my work, out of my right eye. So, I'm working with one eye, and it's also thinning.”

#### *Treatment-Related Symptoms*

Overall, the most commonly noted side effect of medications used in AS was abnormally low blood pressure from ACE inhibitors or ARBs. Though these medicines are important for preservation of kidney function, many patients with naturally low-to-normal blood pressure can experience dizziness, lightheadedness, and fatigue from these agents.

## Design of Clinical Trials for Alport Syndrome Treatments

Following a presentation on the challenges of developing robust designs for clinical trials for AS treatments, audience members were polled for their experiences with participation in clinical trials and their thoughts on what features of a trial were most important to them. This was followed by a moderated audience discussion on these topics.

### Overview of Participation in and Design of Clinical Trials for Alport Syndrome Treatments: Results from Polling Questions

Sixteen percent of respondents were participating in a clinical trial for AS at the time of the meeting and 18% had participated in such a trial and would do so again. However, the majority (66%) of participants had not participated in a clinical trial because: they were unaware of the opportunity (11%), they were not eligible (41%); or for other reasons (14%). None of the participants indicated that they were not interested in participating in a clinical trial for AS ([Appendix 5; Figure 3-A](#)).

Twenty-two percent of respondents ranked potential side effects as the most important factor in a decision whether to participate in a hypothetical clinical trial for an AS treatment. Additional factors for such a decision were whether current treatments would need to stop (12%) and evidence for clinical benefits from the test agent (10%) ([Appendix 5; Figure 3-B](#)).

Polling further revealed that participants had a wide range of thresholds for the number of kidney biopsies they would undergo within one year in order to participate in a clinical trial: 31% indicated that they would enroll only if no biopsy was required; 33% indicated they would participate if only one biopsy was required; 17% would undergo up to two biopsies; and 19% would undergo up to three biopsies ([Appendix 5; Figure 3-C](#)).

### Perspectives on Design of Clinical Trials for Alport Syndrome Treatments: Moderated Audience Discussion

During the audience discussion, patients recounted their experiences with two clinical trials:

#### *CARDINAL Study.*

Panelists touched on their experiences with this study of bardoxolone methyl. Overall, patients' experiences with this study were positive.

“I can shoot hoops in my driveway and not have to worry about fainting on the cement. I can participate in [physical education class] and not have to awkwardly sit on the sidelines. The bardoxolone methyl seems to be doing a great job; my lab results are better than before.”

“Thankfully, my recent participation in a study trial for Alport syndrome [treatment] has increased my kidney function back above 50%.”

### *ATHENA Study.*

Several participants commented on their experiences with the ATHENA Study, a natural history study which tracks the progression of AS. For some patients, the experience was difficult, while for others, it was positive.

One panelist described participation as a “constant emotional rollercoaster for my entire family.”

“It was a constant worry about what my kidney function would be, and if it would be time for a kidney transplant.”

For other patients, participation in ATHENA allowed them to more closely monitor their kidney function and optimize current therapy.

“For me it was just great to have all that data, versus going to the doctor maybe every six months.”

“I'm just really hoping to gather a bunch of data, and to chart a path for my girls so that they can prepare, and they understand what might be coming for them, too.”

For one patient, the frequent monitoring in the ATHENA trial resulted in the decision to increase the dose of her ARB. This appeared to have slowed the rate of decline in her kidney function.

“As I increased [the] dose, [the trajectory of decline in my kidney function] went from straight down to straight across.”

Participants noted that the availability of genetic testing and close monitoring during a clinical trial are incentives for participation in a study. In contrast, having slowly progressing disease, the requirement of a biopsy(s) in a trial, or the availability of other therapeutic options were sometimes seen as disincentives for enrolling.

“...I participated in the ATHENA study...my genetic testing [was conducted]...and then that...confirmed [the] diagnosis. So that was super-valuable.”

“Knowing that I'm not guaranteed to reach end-stage renal disease, I don't want to risk harming myself for research.”

“I would definitely not enroll in something with biopsies. I had a...traumatic biopsy [because the nurse]...gave me the lowest possible dose of the numbing [agent] and I felt literally everything that was going on...that resulted in two years of waking nightmares, and I would not do that again.”

During the audience discussion, insights were gained regarding parents' perspectives on enrolling their children in clinical trials. Parents discussed the need for support from, and consultation with, peers, and voiced concerns about the temporary transfer of care to a trial physician.

“When you're asking pediatrics [sic] to get involved, [it is critical] to have a support system for the parent.”

“...you go to sign the paperwork and the paperwork is scary. It says all these possible things that can happen to you...I almost backed out, as a parent, but...I'll be forever grateful for that nighttime phone call [to another patient] because he had been [in] the trial for seven months and his GFR had already raised. He had no side effects. And being able to talk to somebody...to say it's okay to put this in my son's body. That was huge.”

“...just get a human being on the phone to say...I'm taking it. I feel good. I already have more positive results. No side effects.' As a parent, that's really important to be able to hear when you're signing that document that says you can be harming your child.”

“...is this doctor in the clinical trial going to be more concerned about the clinical trial than my kid? That was a huge fear because it's...not our doctor that we know. He's put us as patients first beyond anything...our experience has been very positive.”

Participants also noted that the logistical challenges inherent in travelling to a distant site for study participation can be a barrier. Participation often interferes with work or school schedules. One participant commented that, for many families, the inevitability of kidney failure is distant, and superseded by other more immediate concerns about maintaining routine family functions. Therefore, enrollment in a clinical trial did not seem feasible.

“No matter where [the study center is], the hospital time is slow and boring, and typically includes a long blood draw, EKGs, a hearing test that I'll never pass, and a lot of questions.”



“It would always be a whole day off work, as it takes two hours one way for me to get to Cleveland.”

“When you're thinking about how to design the trials, make it as friendly as possible for those who participate. For example, if they can do home visits or laboratories at home instead of having to travel, those types of things will help people engage more.”

## Topic 2: Current Challenges of Treating Alport Syndrome

The second major discussion topic focused on patients' experiences with therapies used to treat AS. Five panelists ([Appendix 3](#)) provided comments in which they shared experiences with, and perspectives on, various treatments, clinical trials, and an ideal therapy for AS ([Appendix 3](#)). Following the panel discussion, the audience was polled for their experiences and preferences regarding therapies for AS. This was followed by a moderated audience discussion.

### Overview of Current Challenges of Treating Alport Syndrome: Results from Polling Questions

Polling questions revealed patients' views and experiences with the medications and devices being used, their efficacies, patients' perspectives on decisions to take a new drug, and their ideals for future therapies for AS.

#### *Drug Treatments Taken or Devices Used*

Patients were requested to choose from a panel of potential medications they took or devices that they used ([Appendix 5; Figure 4-A](#)). Ninety percent of respondents reported using drug therapies or devices (e.g., glasses, hearing aids) for the management of their AS symptoms, while 11% of patients responded as not taking medications for AS. Twenty percent wore hearing aids and 7% wore glasses for AS-related vision problems. Eleven percent registered as not using either hearing aids or glasses. Blood pressure medication (33%), hearing aids (20%), and cholesterol-lowering drugs (16%) were the three most frequently selected items ([Appendix 5; Figure 4-A](#)).

Fourteen percent of respondents had received dialysis and 23% had received a kidney transplant. No caregiver reported a patient who died while in ESRD ([Appendix 5; Figure 4-B](#)).

#### *Effects of Treatments or Devices on Symptoms*

Only 10% of participants conveyed that their current treatment or device reduced “very well” the most significant symptoms of their disease, while 65% responded that their treatments/devices moderately

reduced such symptoms. Twenty-two percent of respondents indicated that current treatments reduced significant symptoms poorly or not at all ([Appendix 5; Figure 4-C](#)).

The symptoms most frequently cited as not being fully addressed by current treatments or devices were proteinuria (17%), anxiety and/or depression (15%), fatigue (15%), and hematuria (13%) ([Appendix 5; Figure 4-D](#)).

When asked to identify the top three factors patients consider when selecting a new drug, participants most frequently chose severity of known side effects (28%), previous evidence of reduction of symptoms similar to theirs in AS patients (25%), and cost and coverage by insurance (16%). Route and frequency of administration (7%, 4%, respectively) and the number of known side effects (6%) were less frequently cited. Interestingly, the opinion of the physician was chosen by only 11% of respondents ([Appendix 5; Figure 4-E](#)).

In terms of the impact of treatments on daily life, patients indicated being bothered more by symptoms from AS (45%) than by side effects of medications taken for the disease (7%), although 24% of patients reported being bothered equally by both. Fourteen percent of respondents were unable to detect differences between the effects of AS itself versus medication-related side effects. ([Appendix 5; Figure 4-F](#)).

In their decision to take a new drug, participants were queried on the relative importance of severity of side effects of the new drug, versus its ability to slow progression of kidney disease. Seventy-eight percent of respondents indicated they would consider taking a drug that had more severe side effects than they currently experience but that also showed clinical evidence of slowing progression of kidney disease and/or improving quality of life ([Appendix 5; Figure 4-G](#)).

When asked to rank the importance of various features in a new therapy, 74% of respondents indicated that they would most likely take a drug that showed evidence of reversing decline in kidney function without affecting hearing; while 2% would take a drug that improved hearing without affecting kidney function. Of note, evidence that the drug would improve or reduce future decline of quality of life was chosen more frequently (17%) as an incentive to take a drug than was evidence for the drug prolonging life (8%) ([Appendix 5; Figure 4-H](#)).

## Perspectives on Current Treatments: Moderated Audience Discussion

In panelists' testimonies and the moderated audience discussion that followed the polling questions, participants identified and described their current prescription treatment regimens, as well as their experiences with other treatments.

The two most commonly discussed therapies and devices were blood pressure medications (ACE inhibitors, ARBs, beta-blockers, and diuretics) and hearing aids. In addition to the medications, participants discussed treatments they take to alleviate the psychological issues related to AS and the physiological imbalances and physical symptoms of kidney failure.

## Prescription Drug Therapies and Devices

### *Medication Burden*

Overall, patients described the burden of taking numerous medications, which they noted became more difficult to manage as AS progresses.

"I've started to take, like, 20 pills a day and a potassium binder...it consumes a lot of my day and...all these different times."

"As a young adult taking many more medications, it's much more complicated. I'm compliant, as I know my kidneys depend on it. However, it's not always easy."

### *Blood Pressure-lowering Medication*

Panelists and audience members reported taking a range of blood pressure-lowering medications to prevent progression of AS. They also discussed the anxiety that comes from knowing that they are already on the maximum tolerable dose of a therapy, and that there is no "next step" or additional measure that can be taken to maintain kidney function.

"We go to the doctor, check the numbers, and there's not much else they can do."

"I was barely tolerating my medicines and they were not all that effective."

Although strong evidence supports the use of blood pressure medications for AS, the impact of these medications for individual patients sometimes varies.

"I can also look at the chronological progression of decline in my kidney function and see a linear trend, which suggests that there is no drastic intervention that [can alter] the course that AS would ultimately take in me."

“I was put on a low dose of lisinopril to at least slow down the progression of the disease. But...that didn't work too well.”

One aspect of treating AS by lowering blood pressure is that medications may eventually lose their beneficial effects. At this point, treatment options for patients are more limited, a situation that can cause significant anxiety.

“[I have] full GFR...but I'm planning for the future; the anxiety of the uncertainty of the treatments for me is very overwhelming.”

ACE inhibitors and ARBs are teratogenic and contraindicated in pregnancy. Many women with AS who want to have a family must delay treatment while they are pregnant.

“I had to wait for 10 years to start [medication], even though I knew it was beneficial, because I decided to have a family.”

#### *Treatments for Anxiety and/or Depression*

One discussant noted that psychotherapy, in particular, Eye Movement Desensitization and Reprocessing (EMDR), was helpful for processing anxiety and overcoming trauma associated with past medical experiences.

“[Psycho]therapy has helped a ton...I'm on, like, 20 pills a day. I didn't really want to add anti-anxiety or anti-depression [medications]...so I've chosen to go the therapy route, and I've chosen to think of it as a gift. It's been amazing...but EMDR was something that worked really well for me.”

“We spend so much time talking about the medical stuff, but the mental battle with AS, I think, is equally, if not as worse as, the physical side effects.”

“One of my biggest ways to relieve all the anxiety was writing, and it also helped me tell other people what I was experiencing...I felt a lot better about what I was going through because other people knew what I was going through also.”

Another audience member recommended a weighted blanket to alleviate anxiety in children who are not able to take medication. Engagement with support groups in the Alport Syndrome Foundation and communication with other AS patients and families was also reported as beneficial for coping with the illness.

## *Hearing Aids*

Twenty percent of participants indicated a reliance on hearing aids for daily function (Appendix 5; Figure 4-A). A subset of these participants voiced that, while hearing aids may be helpful, hearing loss often progresses beyond their benefits. In addition, hearing aids are expensive, costing thousands of dollars, and are not reimbursed by insurance. In these contexts, obtaining hearing aids is a significant hardship. In addition, the devices can limit physical activities, such as swimming.

“I’ve also been wearing hearing aids since the age of 10 years old. They helped, but I still have a hard time hearing.”

“I live in San Diego, where the beach and pools are main activities for me and my friends, so I’m constantly nervous that someone might jokingly push me in a pool or ocean with my hearing aids in; that’ll be disastrous.”

“Without an FM, which wirelessly allows my teacher’s voice to go directly to my hearing aids, background noise was interfering with my ability to hear the teacher...I take the bulky FM system from class to class, so each teacher can clip on the microphone.”

“I can’t carry on a conversation without putting on my devices, and that’s not easy.”

“We know so many kids who cannot afford the \$6,000 on average for good hearing aids, and it’s such an issue in our community, and so many other kids are going without...They’re seen as cosmetic by the insurance companies, rather than as a need.”

One patient who learned American Sign Language (ASL) and became part of the deaf community shared that learning to view her “hearing loss as a deaf gain” has helped her regain confidence about her hearing loss.

“Upon learning ASL and meeting other deaf and hard-of-hearing peers, however, I experienced a dramatic frame shift that makes me proud to identify as deaf.”

## **Side Effects of Medications**

Side effects were discussed in relation to blood-pressure-lowering and anti-anxiety medications.

### *Blood pressure medications*

For many patients, in particular those with normal or naturally low blood pressure, antihypertensive agents can cause fatigue, dizziness, and loss of consciousness. In some cases, the negative impact of treatments on patients’ quality of life were weighed against the potential benefits. Some patients reported the need to stop ACE inhibitors or ARBs, due to frequent hypotensive episodes and/or increasing blood levels of potassium.

“I have low blood pressure naturally, so when I took two medications to...[lower] blood pressure, mine got to be dangerously low, causing me to faint when [I] exercised. I had to give up organized sports. I changed my daily activities, my social relationships, and how I saw myself.”

“For three years I got good at anticipating the warning signs [of fainting] and would get myself to a safe place to pass out...a nephrologist recommended to take me off [antihypertensive] medications, the negative impacts on my quality of life outweighed the benefits.”

“ ... when my doctor increased the dosage of lisinopril, I experienced a severe allergic reaction that landed me in the emergency room...I took Atacand for [about] 10 years until my potassium levels were high enough that my nephrologist decided it would do more harm than good.”

“Lasix has side effects of frequent and intense need to urinate. This, plus the eight to 12 glasses of water I drink every day to stay hydrated, makes me use the restroom frequently—even at night.”

“I take so many drugs, and some side effects are dry mouth, frequent urination, and sometimes light-headedness.”

### *Anti-anxiety medications*

One parent recounted the family’s experience with a disturbing depressive effect of an anti-anxiety medicine.

“We did try an anti-anxiety medication with [our daughter]...[after] about two weeks...we noticed that her anxiety...turned into depression and she hid herself away from everyone, and then started talking about self-harm. Like life just didn't seem worth the pain that she was going through. So, we immediately took her off that. That's also a side effect of the anxiety medication...it can go the other way.”

### *Medications for pain*

One patient expressed frustration at the contraindication of taking some pain medicines as a patient with chronic kidney disease.

“When I have a migraine or a cramp, I cannot take Advil, Motrin, Aleve, or any sort of anti-inflammatory.”

## **Dialysis and Kidney Transplantation**

### *Dialysis*

Patients who are awaiting a kidney transplant or are experiencing ESRD rely on dialysis to keep them alive. Dialysis is a difficult and time-consuming treatment that has a negative impact on quality of life,

usually interrupting work, schooling, and personal interactions. For younger AS patients who are still in school, the social isolation of dialysis was noted as a special difficulty.

“Many of my treatments and appointments are [scheduled] as not to interrupt my education.”

“I basically had no social life while on dialysis. [My friends] tried to make me feel better by coming over and just hang out with me in my room at 8:00 every night, and I did feel a little better, but I was still sad.”

### *Kidney Transplantation*

For most AS patients, the outcome of a kidney transplant is positive. However, transplantation does not address hearing loss and also presents a financial, emotional, and physical burden to the patient. Furthermore, the kidney transplant patient must manage medications that prevent rejection of the donor kidney.

“The most challenging part of Alport is the mental stress of learning about this disease and realizing I am more than likely going to have a kidney transplant someday...This is a worry financially and physically.”

“I have never been a worrier or had trouble sleeping, but now I do worry constantly and have sleepless nights worrying about how I will ask someone for a kidney. I also worry about, if I am lucky enough to find a donor, how long will this kidney last and will I have to go through this again?”

### **Diet**

A central component of managing AS, especially as the disease advances, is maintaining a diet that is appropriate for the given stage of kidney disease. Such a diet would include restricting, as necessary for the individual, intake of sodium, potassium, phosphorous, protein, and saturated fats. Such diets eventually become very restrictive. Parents voiced their frustrations and concerns about managing healthy diets for their children with or at risk for AS. Others cited difficulties in limiting dietary potassium.

“...kids want to know why they can't eat Frito Taco Pie on Tuesday night like their friends...”

“There's only so much rice you can eat, or pasta.”

“I believe AS patients would also benefit if we found ways to have a less restrictive diet regarding potassium-rich fruits and vegetables.”

“When I’m nauseated or vomiting, I cannot drink a Gatorade® or an orange juice. I cannot ease my stomach with saltine crackers. The respective high potassium and sodium levels in these items are restricted from a kidney diet.”

## Other Therapies

One AS patient commented that the limited options for pain management led her to use cannabidiol [CBD] oil to manage migraines and joint pain, especially since anti-inflammatory medications are contraindicated in kidney disease. However, she was concerned that, while CBD oil is helpful, it is unregulated, and preparations vary in purity and potency.

“While CBD may not be able to slow the progression of kidney failure or cure Alport syndrome, there are tremendous potential benefits for alleviating the day-to-day symptoms that drastically affect quality of life for patients like myself.”

Alport syndrome patients who suffer from gout disclosed that taking allopurinol prevented and lessened the severity of attacks. Patients also spoke of taking potassium and phosphorus binders, ferrous sulfate for anemia, and several prescribed supplements to manage dietary deficiencies in iron, calcium, and vitamin D. One audience member noted that she improved her mental energy and clarity in the morning with dehydroepiandrosterone (DHEA) and vitamin D.

## Perspectives on an Ideal Future Treatment for Alport Syndrome

Participants also provided their perspectives on an ideal therapy for AS, including the relative importance of maintaining kidney function and preventing hearing loss. The preceding audience discussion revealed that AS patients’ day-to-day lives were significantly affected by anxiety regarding the need for dialysis and kidney transplantation. Accordingly, many participants voiced their desire to prevent further decline in quality of life and avoid dialysis and kidney transplantation.

### *Protecting Kidney Function*

Participants were most interested in a medication that would slow progression of declining kidney function, eliminating the need for dialysis or a kidney transplant. Within that framework, a range of attributes of an ideal drug were discussed. Ideally, such a treatment would be paired with physician education that would promote earlier diagnosis. Together, these would lead to earlier diagnosis and treatment so patients might not have to endure the effects of declining kidney function.

“I often wonder if the same [quality of life] would be true had I been diagnosed and treated before I was a teenager, which leads me to hope that the nephrology community continues to improve upon early testing and intervention strategies.”



In the context of an ideal drug for AS, it bears repeating that audience polling showed that, as an attribute of a future therapy, respondents overwhelmingly preferred improving kidney function over improving hearing loss, compared to improved hearing loss over improved kidney function. Improving quality of life and prolonging life were chosen less frequently ([Appendix 5; Figure 4-H](#)).

“A drug that prolongs kidney function, that actually prevents a patient from going to end-stage renal disease, is a priority.”

“Short of a cure, I think it would be ideal for a medicine to be developed that could erase the need for dialysis. I also think treatments that don't affect blood pressure would be helpful.”

“I'd like to see a targeted therapy that targets the basement membranes.”

“The ideal treatment would stop the progression of this disease, meaning my GFR will stay the same and not get any worse. The ideal medication should prevent the need for kidney transplant or dialysis.”

“...I hope that treatment for Alport syndrome includes more preventative measures or some way to regenerate the cells that we have already lost without further impeding our quality of life.”

“Something that could slow down the progression of growth of leiomyoma or stop it altogether would be awesome.”

### *Limiting Hearing Loss*

During the discussion, participants emphasized that, while preservation of kidney function is their highest priority, maintenance of hearing would be an ideal additional attribute of a new treatment. Though hearing aids are helpful, they do not restore natural hearing, and do not prevent further hearing loss. In addition, hearing aids are not financially accessible to all people affected by AS.

“Some way to prevent hearing loss, if caught early enough, would also be excellent.”

“Hearing aids help, but nothing is the same as natural hearing.”

### *Relief from Fatigue*

While the discussion of an ideal treatment was centered on preventing disease progression, participants stated that they sought relief from the fatigue that accompanies disease progression.

“If you could solve one problem for me, it would just be the fatigue. So, I have two kids; I work a full-time job. I just do not have time to take a bunch of naps.”

“Some form of treatment for fatigue so that we might be able to remain active.”

### *Long-term Safety and Side Effects*

Participants stressed that any new treatment should be safe for long-term use. The hope is that, ideally, new treatments would be used early in the disease to halt its progression. Therefore, the side effect profile should be acceptable for a life-long therapy, safe for patients as they progressed through a range of declining kidney function, including Stage 4 and ESRD.

“I think one of the challenges with Alport syndrome is you're taking a drug for a lifetime...we want people to be diagnosed early and treated early, so it has to be safe for...the long run, and it does need to be safe for women.”

“The fact that, as my renal function declines, that medication is going to be potentially nephrotoxic to me because of the potassium levels, is terrifying.”

“For me, the ideal medication should be safe and free of serious side effects.”

For some patients, the need for a treatment that does not affect blood pressure was a safety concern.

“Fainting and worrying about fainting [from low blood pressure] is no way to go through your daily life.”

### *Compatibility with Pregnancy and Managing Complications*

Patients reiterated the importance of the complications experienced by women with AS, who often suffer declining kidney function during pregnancy and are not, while pregnant, able to take ACE inhibitors or ARBs for controlling blood pressure. Furthermore, participants noted that complications during pregnancy are also not managed by current medications.

### *Compatibility with Other Medications*

Participants voiced that the ideal medication for AS would also allow patients to take everyday medications, such as birth control or antibiotics.

### *Relief from Pain*

Another feature that participants desired in an ideal medication was effective and safe management of pain.

### *Awareness/Education*

Finally, toward improving treatment of AS, participants voiced a need for heightened awareness and understanding of AS in the nephrology community, including increased early testing and improved early

intervention strategies. Patients stressed the need for a shift from the concept of females as merely “carriers,” to one in which female AS patients are recognized as having a unique disease progression.

## CONCLUSION

At this Externally Led Patient-Focused Drug Development Meeting, the FDA heard patients' and caregivers' in-depth views on challenges of living with AS, the impact of the disease on their daily lives, their perspectives on participating in clinical trials, their experiences with the available treatment options for the disease, and their hopes for future treatments.

The overall input from AS community assembled at this meeting supports the following conclusions:

- Fatigue experienced by many AS patients hinders their daily lives and participation in social, educational, work, and physical activities.
- Hearing loss can be socially isolating for patients and can present difficulties at work and in school.
- Hearing aids are expensive and are not covered by insurance, restricting their availability to many patients. Therefore, the treatment of hearing loss in AS patients represents an economic disparity in this population.
- The balance between the potential for ACE inhibitors and ARBs to slow decline in kidney function, versus the negative impact they can have on quality of life is an important clinical consideration. These medications can cause dizziness and fatigue in some patients. In addition, as kidney function continues to decline, these agents can increase potassium levels in the blood, and may no longer be useful for slowing decline of kidney function. Therefore, ACE inhibitors and ARBs cannot be considered lifetime treatments for many AS patients.
- Clinical evidence indicates that the concept of female patients as only “carriers” of AS is incorrect. Moreover, addressing preeclampsia and other severe complications of pregnancy merits attention in developing new drugs for AS.
- Following kidney transplantation, many of the immunosuppressive agents carry side effects.
- AS patients voiced the need for a treatment that would reduce or eliminate the need for dialysis and transplant.
- AS patients participating in this EL-PFDD meeting seek disease-modifying therapies that will:
  - Slow, halt, or reverse the decline in kidney function and hearing loss with this disease
  - Reduce or eliminate fatigue
  - Be safe for a lifetime

- Not have severe side effects
  - Be safe and effective when taken with other medications
  - Be safe when taken during pregnancy
  - Address complications that accompany AS in pregnancy
- Patients living with AS are willing to be active participants in clinical trials and to consider clinical trials for their children. However, they are concerned about the potential for side effects from test agents, and the rigidity of inclusion criteria (GFR, in particular; see post-meeting comments page 36).
  - When deciding to take a new drug, patients with AS are most concerned about the severity of potential side effects of a new drug and would seek evidence that the drug is effective in other AS patients.

*The FDA expressed sincere thanks and admiration for the patients' efforts to travel to the EL-PFDD meeting and for their courage and willingness to share their experiences and thoughts.*

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## APPENDICIES

Appendix 1: Meeting Agenda

Appendix 2: Meeting Discussion Questions

Appendix 3: Patient Panel Participants and Testimonies

Appendix 4: Meeting Polling Questions

Appendix 5: Results from Polling Questions

- Demographics (Figures 1A-1G)
- **Topic 1:** Living with Alport Syndrome (AS): Disease Symptoms and Daily Impacts for Alport Syndrome (Figures 2A-2E)
- Clinical Trials in Alport Syndrome (Figures 3A-3C)
- **Topic 2:** Current Challenges of Treating Alport Syndrome (Figures 4A-4H)

Appendix 6: Participant Comments Submitted After EL-PFDD Meeting

Appendix 7: Incorporating Patient Input into a Benefit-Risk Assessment Framework for Alport Syndrome

## APPENDIX 1: Meeting Agenda

8:00am – 9:00am	<b>Breakfast and Registration</b>
9:00am – 9:10am	<b>Welcoming Remarks</b> <i>David Feldman, PhD, National Kidney Foundation</i>
9:10am – 9:25am	<b>Opening Remarks</b> <i>Ellis Unger, MD, U.S. Food and Drug Administration</i>
9:25am – 9:40am	<b>Alport Syndrome: Natural History of the Disease and Treatments</b> <i>Michelle Rheault, MD, University of Minnesota (Co-chair)</i>
9:40am – 9:55am	<b>Overview of Discussion Format and Demographic Polling Questions</b> <i>James Valentine, MHS, JD (Moderator)</i>
9:55am – 10:20am	<b>Panel #1 Discussion on Topic 1:</b> <i>Living with Alport Syndrome: Disease Symptoms and Daily Impacts</i> A panel of patients and caregivers will provide comments, followed by a moderated discussion with participants in the audience. <i>James Valentine, MHS, JD (Moderator)</i>
10:20am – 11:20am	<b>Polling Questions and Facilitated Audience Discussion on Topic 1</b> <i>Living with Alport Syndrome: Disease Symptoms and Daily Impacts</i> <i>James Valentine, MHS, JD (Moderator)</i>
11:20am – 11:35am	<b>Challenges to AS Clinical Trial Design</b> <i>James Simon, MD, Cleveland Clinic (Co-chair)</i>
11:35am – 12:05pm	<b>Polling Questions and Facilitated Audience Discussion on Clinical Trials in Alport Syndrome</b> <i>James Valentine, MHS, JD (Moderator)</i>
12:05pm – 1:05pm	<b>Lunch</b>
1:05pm – 1:30pm	<b>Panel #2 Discussion on Topic 2:</b> <i>Current Challenges of Treating Alport Syndrome</i> A panel of patients and caregivers will provide comments, followed by a facilitated discussion with participants in the audience. <i>James Valentine, MHS, JD (Moderator)</i>
1:30pm – 2:30pm	<b>Polling Questions and Facilitated Audience Discussion on Topic 2</b> <i>Current Challenges of Treating Alport Syndrome</i> <i>James Valentine, MHS, JD (Moderator)</i>



2:30pm – 2:55pm

**Closing Remarks**

*Aliza Thompson, MD; U.S. Food and Drug Administration*

2:55pm – 3:00pm

**Next Steps**

*Gina Parziale, CFRE, Alport Syndrome Foundation*

## APPENDIX 2: Meeting Discussion Questions

### Topic 1 (Panel 1): Living with Alport Syndrome: Disease Symptoms and Daily Impacts

1. Of all the symptoms that you experience because of your condition, which 1–3 symptoms have the most significant impact on your life?
2. Are there specific activities that are important to you but that you cannot do at all, or as fully as you would like, because of your condition?
  - a. How do your symptoms and their negative impact affect your daily life on the best days? On the worst days?
3. How have your condition and its symptoms changed over time?
4. What worries you most about your condition?

### Design of Clinical Trials for Alport Syndrome Treatments

1. If you knew a clinical trial was planned for an AS treatment, what information would you want to know to inform your decision on enrolling in the trial?
2. In which type of clinical trial would you be more likely to enroll:
  - a. A trial that studies safety of a new drug for AS
  - b. A trial that studies how well a new drug manages the underlying cause of kidney damage in AS, but does not study symptoms or progression
  - c. A trial to study if and how well a new drug reduces symptoms of AS
  - d. A trial to study if and how well a new drug reduces progression of AS

### Topic 2 (Panel 2): Current Challenges of Treating Alport Syndrome

1. What are you currently doing to help treat your condition or its symptoms?
  - a. How has your treatment regimen changed over time and why?
2. How well does your current treatment regimen treat the most significant symptoms of your disease?
  - a. How well do your treatments address specific symptoms?
  - b. Which symptoms are not addressed well?
3. What are the most significant downsides to your current treatments, and how do they affect your daily life?
4. Assuming there is no complete cure for your condition, what specific things would you look for in an ideal treatment for your condition?

## APPENDIX 3: Patient Panel Participants and Testimonies

### Patient Panel Participants

Panelist	Age	Sex	City, State	Genetic Diagnosis	Years from Onset of First Symptoms	Years from Onset of Diagnosis	Receiving or Received Dialysis	Received Kidney Transplant
<b>Panel 1: Living with Alport Syndrome (AS): Disease Symptoms and Daily Impacts</b>								
Gabrielle	15	F	Richfield, MN	Deletions in chromosomes A5, A6	13	2	No	No
Phil	55	M	Yorba Linda, CA	X-linked	5	~17	No	No
Bryant	32	M	Cleveland, OH	X-linked	4	2	No	No
Janine	65	F	Battle Creek, MI	X-linked	56	44	No	No
Sharon	57	F	Phoenix, AZ	X-linked	55	14	No	No
<b>Panel 2: Current Challenges of Treating Alport Syndrome</b>								
Grant	15	M	San Diego, CA	X-linked	1.5	4	No	No
John	17	M	Pembroke Pines, FL	X-linked	15	11	No	No
Larry	48	M	Mt. Vernon, OH	X-linked	45	4.5	No	No
Drew	15	F	Indianapolis, IN	Autosomal recessive	10	9	Received	Yes
Jessica	28	F	Charlottesville, VA	Uncertain	25	12	No	No

## APPENDIX 3:

# Patient Panel Participants and Testimonies

### Testimonies

#### PANEL 1: Living with Alport Syndrome: Disease Symptoms and Daily Impacts

##### Gabrielle

Hello everyone. My name is Gabrielle. I am 15 years old and I live in Richfield, Minnesota. I would like to ask each of you to imagine how it would feel to gargle water and cough at the same time. Once you have this image in your mind, picture waking up in the middle of the night completely cut off from oxygen, and all you can physically do is [to feel] that. Now you know what my life has been like for the last 14 years. Due to leiomyomatosis, my esophagus got so large, it blocked my trachea, making the simple task of clearing my throat a scary event.

Like any condition, Alport syndrome has branches. And I'm that small branch at the top that no one really knows about. I have Alport syndrome with diffuse esophageal leiomyomatosis. My whole life, I've been in and out of hospitals, slowly watching my esophagus get larger, my trachea get smaller, and my breaths get shorter.

It was hard knowing I couldn't do the things I loved, like softball, swimming, or anything that required breathing without the fear of choking. I couldn't eat some of the normal foods kids loved. Not to mention, I got less sleep and a lot more stress.

My symptoms started when I was 17 months old. Since then, I've had many tests to see why my body kept changing. Every time I looked at a scan, only to see my esophagus was getting larger, my hope slowly got smaller. I actually never knew I was different until kindergarten. I mean, I looked the same and I could basically do the same things as everyone else. I realize now that if you have a condition no one can see, it's hard to get any sort of help. I didn't know anybody who had the same issues as me, so I felt isolated like a boat in the middle of the ocean calling for help, but no one knew it was there. For 13 years, I was a mystery. No one could explain to me what was happening with my body or why it was happening. Through all the fear, I was determined to live as normal as I could. I can sit here and try to explain to you all that I've went [sic] through, but I'm afraid there isn't enough time and there isn't [sic] enough words to explain the fear I have faced and the determination I've had to develop along the way.

When this all started, my choking symptoms occurred "once in a blue moon". They progressed to once or twice a week. And towards the end it could happen multiple times a day. A lot of times, I wound up turning blue as my body struggled to find oxygen. In the last year, it got so bad, I ended up having two seizures and wound up in the ICU for what felt like an eternity. I was told I had less than two years to live, or two years to fix my esophagus, or there would not be a me to fix. While in ICU the problem remained, the cause of my issue was still completely unknown. However, new issues were discovered, such as my kidneys weren't functioning 100%.

Luckily for me, the renal doctor assigned to find out what was up with my kidneys made the connection between the kidneys and the esophagus, and suggested I get a genetic test. Two weeks later I received a positive test for Alport syndrome. I can honestly tell you I was in total disbelief. I [my condition] had been misdiagnosed five times. So, I had no reason to trust yet another doctor. They assured me that this was the final answer. After that day, my life got flipped upside down. I began trying to fix the life I was given, and not the life I chose to have. I think everyone's biggest fear is death. Nobody wants to die because it's such an unknown thing. Nobody knows where we go when we leave this physical world.

And from such a young age, I've had to worry about death. I've had to worry about my body just failing me. In 2017 when they told me I had two years to live, I was scared. Those ten words brought so much more fear into my life. Before my diagnosis, my only worries were my esophagus and breathing. Now I have to think about my kidney health, my hearing, and maybe even my vision. Luckily for me, my kidney function is still very high. And knowing more about Alport, I'm still afraid. But I feel a lot more safe [sic] knowing I'm not a complete mystery. My esophagus is now completely gone, and it has been surgically removed. My stomach was pulled up to take its place.

After eight months of recovery I can eat almost normally again, and of course, with the ease of breathing. This new anatomy has left me with the need to eat more frequently and in much smaller amounts. I also have to be careful about what I eat and drink, as acid reflux has become a much bigger component in my life than before. With the new ability to breathe easier, I've been able to return to playing softball. I have also been able to act as almost a normal teenager. It has also reduced my fear of suddenly not being able to breathe. But now I worry about the possibility of not seeing you one day. I worry about the possibility of not hearing you one day. And I worry about the possibility of having to sit in a room for six hours straight, having my blood filtered through a machine, because my body can't do it itself.

My body can still fail me at any minute. But I've learned, if you focus on the worries in life, it isn't very enjoyable. So right now, I want to focus on how much I've grown. And I want to tell you how proud I am, to be born special, how proud I am to be one in a million, and how proud I am to be a born genetic mutant.

Thank you.

## Phil

Good morning. My name is Phil Seymour, I'm a configuration manager for an inflight entertainment company, and I live in Orange County, California. I've lived with Alport syndrome for over 55 years. My missense mutation of the disease has meant that for over half my life I was completely unaware of my condition. Historical misdiagnoses and lack of medical advances have contributed to my not monitoring my kidney health until I was in my 30s, when my hypertension and proteinuria became clinically obvious. A biopsy confirmed the diagnosis of X-linked Alport syndrome when I was in my latter 30s, which was later confirmed via genetic test.

When I was diagnosed with Alport syndrome, my kidney function was still well over 50%. However, it has declined steadily over the years, dropping to the 30% range in my latter 40s, and in the last year, it dropped below 30%. For years, nothing had really changed. See the doctor once a year, take my meds, cross my fingers. Thankfully, my recent participation in a study trial for Alport syndrome has increased my kidney function back above 50%.

Living with Alport has forced my hand in many important decisions in my life and in my family. In the '90s, my wife and I were building our family, one precious child at a time. Due to the fear of raising a daughter suffering from a devastating kidney disease, I made a difficult decision to stop growing our family after two children, both boys. It was not a popular decision in our house, and we still imagine how our lives would have been further enriched with the sound of a little girl's voice in our house.

We decided not to tell my two sons about Daddy's disease until there was a large complication, or when they reached adulthood. They were in college before they knew of my condition. I felt awful telling them so late, but my wife and I thought it was best, since there's no cure for Alport. What could they do except worry?

I've avoided telling others about my disease, except family members and the closest of friends. It isn't that I'm ashamed of living with Alport. Rather, I fear loss of insurance or employment. I've been unemployed before, and with pre-existing medical conditions, [the] risk of being dropped by insurance companies, the fear is real.

My life has been impacted by multiple symptoms of Alport, including hearing loss. I've recently been told I have up to a 20% loss of hearing in key frequencies. This has made me withdraw from active conversations, from enjoying entertainment, and made it more difficult to perform my job. For my entire life, I've always looked at the mouth of the speaker rather than into their eyes. It's not just a preference, rather it's a necessity. My wife and I have a standing joke that when she says something softly to me, she's saying that she loves me. And I know it's true. I've given up understanding quiet sections in movies, instead I watch the actor's expressions, and the cinematographer's angle and the musical passages to get the gist [of] the plot details, and I ask my family questions afterwards, and I've lately given that up, too.

Oftentimes I misunderstand someone at work, make a calculated decision, only to be told I heard incorrectly, so I must apologize and start over. My team has begun to text me more often now, instead of talking to me directly. I now sit quiet in meetings when I

miss sentences. And last month I had a customer indicate to a comrade that I was hard of hearing through a gesture. And I felt awful as the man repeated the question to me as my coworkers waited.

Will I still be relevant in my company in five years? How can I support my family if I can't stay employed?

Another symptom of Alport that has impacted my life is gout. There's still a stigma attached to gout. It sounds like an old and a dirty disease. I always tell others, "I hurt my toe."

I first got gout, it was 10 years ago, and I thought I had surely broken my toe, as I had never experienced such intense localized pain. For many years I didn't have any symptoms, but recently I've had flare-ups once or twice a year, which could last for multiple weeks. When that occurs, I can't walk around the office, I can't work on our yard, my wife and I can't visit museums and the gardens that we still love to visit, and I feel like a couch potato.

When thinking about the future, I worry about my health, and worry about my mortality. Last year, my kidney disease reached Stage 4, only one short step away from kidney failure. What had eluded me for so many years had seemingly arrived, and I felt helpless to reverse this downward trend. "What can I do to fix this?" "Nothing," say the doctors. "Take your blood pressure medicine, eat healthy and exercise. Hope for the best, plan for the worst."

How can I support my family if I'm on dialysis every day, or worse? Sure, we all may be able to adjust to a new norm, but how far do we need to adjust and still maintain productive lives? I recall an old saying, "Living with the plague is pretty awful, but you get used to it after a while."

Thank you for the opportunity to present my testimony.

## Bryant

My name is Bryant. I'm 32 years old, living with Alport syndrome. However, my experience might be a little different than the usual. I wasn't diagnosed with it until early in 2016, after six years of guessing and testing, trying to figure out what was going on. Being 29 at the time, I was told I might be a little bit older to just be discovering this and finding out what's the problem. The real obstacle was nobody in my family has it; it appears that I am the first to develop this. That, coupled with the condition being rare on its own, made it difficult to pin down. I really don't have many symptoms that most people do, which also contributed to the difficulty of diagnosing [it]. My hearing's normal, my vision's normal, and honestly, I felt pretty fine up until recently, I guess.

My only displayable symptoms were proteinuria and hematuria, and it wasn't that bad to where it was obvious to me that there was an issue. So again, it went unnoticed for a while. Since those have really been my only symptoms, the impact on my day-to-day activities has been minimal. I still work 60 hours a week. I go to the gym a few days a week. I play on four different soccer teams three nights a week. I go skydiving here and there; I go out regularly; I'm pretty active. The only real hindering symptom that I've come to see recently is just fatigue, being tired. And that's only been a hindrance the past few weeks. I mean, it hasn't been that bad until recently. I'm worn out; I'm tired a lot, but I don't really let it stop me from doing what I want to do. I keep, obviously, going to play [soccer] and do everything I'd like to up until recently.

In June, my GFR hit 19, and that's when I kind of started to notice I've been more tired than I have been usually. I've noticed my body just doesn't recover as well. I get through a day of work; I'm worn out and just ready to collapse and go to bed. I've been going to sleep, 6:00, 7:00, 8:00 at night, which for me is super early. I normally play soccer on Monday, Wednesday, and Saturday nights. Monday night I was playing twice, two games in a night. The second game is becoming more difficult to play. The past few weeks, I have stopped playing the second game. I mean, it's been a struggle just to make it through one, because I started to get so tired. I can feel my muscles just getting exhausted by the second half, and it's hard to continue.

By the time I get home after the game, once I sit down, I'm pretty much done for the night, and I don't want to get up and move again, because I'm so exhausted. It takes all of Tuesday to try to recover enough to go play again on Wednesday. And it's to the point I'm missing games because I can't recover the way I used to and do everything I used to. As of now, I'm going to try to drop a couple of those teams and stop playing as much, to try to allow me to recover for the ones [in which] I can still play and perform as well as I'm accustomed to. I've tried different things to try to help the recovery, missing more games, rest, different stretching techniques, more hydration, but nothing really seems to work. It's just my body can't handle and recover from all the activity that I normally do.

Even my last skydive had a particularly slow canopy that opened and gives you the least amount of impact felt, but I was so extremely sore afterwards, which typically I wouldn't have been in the past. It's [body] just not holding up to what I'm used to doing. And, as of now, that's really my only restriction or limitation. I fortunately don't have to miss



work. And if I just don't do anything, I feel okay. But for me, not doing something and just sitting isn't something I can do well. I like to be active and keep moving. I typically have done whatever I wanted to do, and to have that taken away even in just these small examples is difficult. To make it worse, there's nothing I can do about it.

There's currently no real treatment for the disease itself, other than managing the symptoms and trying to do the best you can with that, until it's time for transplant. My hope is that in the future, for things like this, there are treatment options available to treat the disease itself, to try to avoid some of these symptoms and hopefully prevent the impact that the disease can have on daily life.

Thank you.

## Janine

Hello. My name is Janine. I'm a retired dialysis nurse, and I have X-linked Alport syndrome. This disease has affected my family for more than 100 years. In 1915 my great uncle's suicide by gunshot was memorialized in an obituary that states he was also known to have suffered from Bright's disease, an old term for kidney disease. In 1959, two maternal uncles died of kidney failure. And a few years later, my mother underwent an evaluation for chronic hematuria which was misdiagnosed, never monitored. And she progressed to Stage 4 but died of other comorbidities. After I finished nursing school in 1974, I was diagnosed with Alport syndrome due to hematuria, proteinuria, and our family history.

My diagnosis was confirmed by skin biopsy, and later by genetic testing during my participation in the ATHENA Study. I have four adult children. Each pregnancy caused preeclampsia symptoms and renal progression, which remained after each birth. My second son was born by emergency C-section at 37 weeks, and was a compromised newborn who did recover, but spent his first week in a neonatal ICU. My last pregnancy included six weeks of bedrest and an induced VBAC at 37 weeks, as my renal function had declined further, and we didn't want to risk another compromised baby. Each pregnancy was more challenging than the one before, so I made the difficult decision to not have more children, as I wanted to be as healthy as possible to raise these four beauties. Plus, I didn't want to risk passing along Alport syndrome to other children.

My three sons, and three grandchildren are monitored for early signs of Alport syndrome, and so far, none are affected. My daughter has inherited Alport syndrome and has mild symptoms. We eat a low protein, mostly plant-based diet, in an effort to delay the progression of our symptoms. Counting grams of protein is a daily reminder of having this disease. I'm in CKD Stage 3 with a GFR in the 40s. My symptoms include hematuria, proteinuria, fatigue, and hearing loss. I also have dot-and-fleck retinopathy, which is associated with Alport syndrome, but does not affect my vision. My hearing loss was identified in 1997 during a routine employee screening. I delayed getting hearing aids due to the expense. But my hearing loss caused increasing difficulty for me to communicate effectively at home and at work.

I found myself avoiding social interactions rather than misunderstand what someone was saying. I would get lost in a conversation and would frequently resort to a smile and a nod, when actually, I didn't know for sure what was being said. I've worn hearing aids for three years now. They do help but work best if others are willing to understand and accommodate how they function. I had to bear the \$6,000 expense out-of-pocket. And now that I'm retired, I'm concerned about how I will cover that cost at a time when they need to be replaced. Managing my hearing loss is another continuous reminder of having Alport syndrome. I make every effort to continue with an active lifestyle that includes beekeeping, gardening, genealogy research, hand spinning, quilting, and walking, running or bicycling several miles each week.

I take lisinopril to delay my renal progression. Dosing is a daily juggling act, as I typically have a normal-to-low blood pressure which can drop so low, it affects my ability to carry out daily activities comfortably. In addition, I find that I'm frequently too fatigued to

continue with an activity I've begun. I might have to stop gardening after a few hours, be too dizzy to fix a meal, and keeping up with our little farm, or just jumping on my bike for a ride may be too much. I've always been a strong, dynamic woman, but I can see myself moving towards a slower pace, which is very frustrating, and not the example I want to set for my children and my grandchildren.

My hope for our family is to have treatment options that will delay the progression so we can avoid dialysis.

Thank you for giving me this opportunity to share my family's Alport story with you in person.

## Sharon

Hello everyone. My name is Sharon, I'm 57 years old, I live in Phoenix, Arizona, and I'm a geologist by training. I co-founded the Alport Syndrome Foundation in 2007 and have worked as a volunteer ever since. I am one of three generations, and one of seven family members affected by X-linked Alport syndrome. I have three children, two boys and a girl, and my two boys inherited the disease. It was absolutely devastating to think I passed this disease onto my boys and would have to relive the challenges that I watched my younger brother go through during his life. I was afraid that my boys would experience kidney failure by the age of 16, have to do hemodialysis during high school, and endure the extreme side effects of immunosuppression, and pass away at an early age. That was my brother's journey.

As you can imagine, the most significant impact of Alport syndrome on my life is emotional stress. I worry about my reduced kidney function, and my boys' progressing proteinuria, wondering when one of us might have to start dealing with the effects of kidney failure. This constant stress impacts every aspect of my life if I don't take positive steps to try and manage it. I have trouble sleeping, heart palpitations, headaches, and it's not good for relationships, nor family dynamics. I have to work hard on a daily basis to remain positive, and to choose to be proactive, and not live as a victim.

Physically on my best days, I have sustained energy throughout the day, allowing me to do the things I love most, such as exercising, hiking, and socializing with friends. Because of my reduced kidney function, I tire more easily than my peers, and some days don't have the energy to do the hike that I easily did the day before. I become short of breath and dizzy and need to return home. I have to work hard every day to make sure that my kidney disease does not take over my life.

On my worst days, I can experience extreme fatigue, severely limiting my daily activities. There are times that I felt too tired to make dinner for my family or bring my children to their after-school activities. I felt very depressed that I could not fulfill basic responsibilities for my family.

Other impacts to my day-to-day living include unexplained inflammation. I have high inflammatory blood markers, and experience symptoms regularly of fibromyalgia, muscle pain, swelling, and longer recovery times from exercise than others. I've had two severe episodes of knee swelling with a fever, that kept me from being able to walk, and even required me to leave a family vacation early. I went to the ER, and various doctors, and no one could ever find a cause, and it wasn't because of an injury. My symptoms have continued to worsen over the years, and I now need to take more and more medication. I take 13 pills every day, including losartan, allopurinol and Crestor. My proteinuria has been slowly increasing, along with my uric acid. Luckily my creatinine has remained stable [at] around 1.4.

My chronic kidney disease has also put me at a very high risk for cardiac disease, based on a recent CT scan of my coronary arteries, showing significant calcification. This makes me very fearful to push myself too hard, and very fearful for my future.

I'm a female with X-linked Alport syndrome, often ignored by the medical community as

a carrier of the disease, and not thought to progress to renal failure. We now know that this is not correct. In fact, my last estimated glomerular filtration rate was 41 milliliters per minute, but has varied from 39 to 64, depending on the test or calculations. This is an obvious cause of concern for me, not knowing exactly what my GFR is, and exactly where I am in my progression of my disease.

My kidney disease severely impacted my pregnancies. All three of my children were born preterm, five to eight weeks early. I experienced preeclampsia with pregnancies of my boys. One of my boys was only three pounds at birth and spent three weeks in the hospital before he could come home.

Preeclampsia caused me to retain large amounts of fluid, so that my face was almost unrecognizable, you can see in this photo. And my feet swelled from a size seven to a size nine. It made me feel extremely fatigued, lethargic, and very weepy. My blood pressure shot up to 200/100, and my organs started to shut down, so they induced my son at 32 weeks. I lost 10 pounds of fluid every night for several days after my son was born. It was an extremely traumatic experience for me and my family, but we were very lucky.

I'm an Alport patient, but I'm also a mother of two boys with the disease, and this has been very challenging. I feel the pressure to ensure that they take their medication, eat well, get to their doctor's appointments, and live a healthy lifestyle. This is hard, as my kids want to know why they can't eat Frito Taco Pie on Tuesday night like their friends and play tackle football. They don't want to hear that I'm trying to manage their sodium, potassium, phosphorus, and prevent any trauma to their kidneys. They just want to fit in with their peers. I'm also sad to see what this has done to their sister. The lack of attention, and her feeling the pressure to donate a kidney, worrying that she only has one kidney to give, but two brothers who will need it.

I am thankful that my boys are now 22 and 23 years old, and still have their kidney function. I want this to continue as long as possible, and not see their plans for graduate school or medical school get derailed by their disease. I also know that every year they remain off of dialysis or immunosuppression, allows them to lead a longer and healthier life.

Thank you very much for listening to my testimony.

## APPENDIX 3: Patient Panel Participants and Testimonies

### Testimonies

#### PANEL 2: Current Challenges of Treating Alport Syndrome

##### Grant

All right, good afternoon. My name's Grant, I'm from San Diego, California, I'm 15 years old and I just finished my freshman year of high school. Since I was diagnosed with Alport syndrome four years ago, I tried various combinations of both ACE and ARB medications, including lisinopril and Lotensin together. At higher doses, the medicines worked pretty well to slow down the spill of protein causing damage to my kidneys, but I felt very limited.

I vividly remember the first time I passed out; I had been throwing a lacrosse ball around with my brother in our backyard for about five minutes when my vision went black. I woke up on the ground with the lacrosse stick still in my hand and my brother and father leaning over me; I had no idea what had happened. I have low blood pressure naturally so when I took two medications to have the effect of also lowering blood pressure, mine got to be dangerously low, causing me to faint when I exercised or got my heart rate up too quickly.

For three years I got good anticipating the warning signs and would get myself to a safe place to pass out.

Through years of testing different combinations of medicines, I had to give up organized sports, I changed my daily activities, my social relationships and how I saw myself. I was tired all the time. In January 2018, a nephrologist recommended to take me off those medications; the negative impacts on my quality of life outweighed the benefits.

I have hearing loss caused by Alport; I've been wearing my Phonak Bolero hearing aids since July 22nd, 2014 just before I turned 12. But who's keeping track, right?

In a way, my hearing loss did me a favor, it helped me get the diagnosis that I needed so I could get treated. My hearing aids are awesome, they allow me to fully participate socially and academically. The audiologist created settings for different situations customized to me, including situations like loud restaurants, movie theaters, or going to basketball games with sounds echoing in a gym.

There are tough aspects with hearing loss: annoying things like always having to use a phone on speaker, so private conversations aren't an option. I also live in San Diego, where the beach and pools are main activities for me and my friends, so I'm constantly nervous that someone might jokingly push me in a pool or ocean with my hearing aids in; that'll be disastrous. After the first year, I also had to change my devices to the next larger size.

The first pair wasn't large enough to accommodate an FM system. Without an FM, which wirelessly allows my teacher's voice to go directly to my hearing aids, background

noise was interfering with my ability to hear the teacher. Daily, I take the bulky FM system from class to class, so each teacher can clip on the microphone.

Currently, I'm in Phase 2 of a two-year clinical trial called the CARDINAL Study. I take 30 milligrams of the study drug, bardoxolone methyl, every night in capsule form. It's designed to speed up the effectiveness of my kidneys to slow down the damage that leads to kidney fibrosis. My mom heard about the trial through [the] Alport Syndrome Foundation and contacted my nephrologist. My doctor agreed: signs were solid, and the risk is worth it. I was barely tolerating my medicines and they were not all that effective. For the past year, we frequently drove three hours to and from Los Angeles for screenings and check-ins.

My parents and doctors were confident, so that made me confident, too. Of course, I was nervous and it's weird to sign paperwork that says all sorts of bad things could happen to you in the name of science, but I knew it was better than just waiting for my kidneys to fail. I also like knowing that participating helps everybody else who has Alport syndrome.

It isn't difficult to participate in the trial; taking capsules at night, filling in a journal and tracking my weight is no big deal. Having to travel to L.A. a lot and skip a whole day of school was stressful, but now we can do our check-ins at a new site in San Diego. No matter where it is though, the hospital time is slow and boring and typically includes a long blood draw, EKGs, a hearing test that I'll never pass, and a lot of questions. Not a big deal for the upside, though. When I see really sick kids as I pass through the halls of the hospital, it reminds me that I'm lucky in many ways because I don't take blood pressure meds now; I don't pass out anymore.

I can shoot hoops in my driveway and not have to worry about fainting on the cement. I can participate in PE and not have to awkwardly sit on the sidelines. The bardoxolone methyl seems to be doing a great job; my lab results are better than before. Even if I had to undergo another biopsy, I would do it. The general downside of Alport syndrome is that I can't ever really be a carefree teenager; there are daily reminders. I can't carry on a conversation without putting on my devices and that's not easy. I also think about what Alport means for my future and the future of my own potential children; that can be heavy.

Short of a cure, I think it would be ideal for a medicine to be developed that could erase the need for dialysis. I also think treatments that don't affect blood pressure would be helpful. Fainting and worrying about fainting is no way to go through your daily life. Some way to prevent hearing loss if caught early enough would also be excellent, or treatments to improve hearing to stop it from getting worse.

Thank you for giving me this opportunity to share my story.

## John

My name is John. I'm 17 years old and beginning my senior year of high school in Chaminade-Madonna College Preparatory. I live in Pembroke Pines, Florida and I was diagnosed with Alport syndrome at the age of six, although I started showing symptoms of Alport much earlier—around the age of two. I had my first biopsy at the age of two and a half, which came back as normal. At six, I was showing signs of protein in the urine and hearing loss. I had my second biopsy as the protein levels increased and it confirmed I had Alport syndrome. I can remember the second biopsy vividly, feeling scared and being so hungry as my biopsy was delayed. Waiting in the waiting area with my parents. Of course, at the age of seven I didn't understand why my mom and the nurses would not let me eat.

I remember waking up with terrible back pain and having to remain in bed, which of course, led to my frustration. This was planned during my first week of vacation that summer, as many of my subsequent treatments and appointments are, as not to interrupt my education.

I'm the first one in my family to have Alport, with mine being the X-type. I have been fortunate because I have been on treatment since seven years old. When I was younger it was much easier, because I was only on lisinopril and vitamin D. My parents, as my caregivers, would remind me to take my meds in the morning and at night. But now, as a young adult taking many more medications, it's much more complicated. I'm compliant, as I know my kidneys depend on it; however, it's not always easy.

For example, when I travel with school, as I often do, the school mandates that the teachers hold all my medications and to distribute them as needed. One can imagine how complicated that can become because I don't look sick and most don't know that I am. I heard many questions about all of the pills; well, it's the opposite, I need to go find my meds because they are forgotten about. And because I don't look sick or act sick to others, others don't understand that I can't miss my meds. As I get older, the handing over my meds is surely a privacy issue for me.

As of right now I'm currently taking the following medications, Lasix 20 milligrams twice a day to lower my potassium levels, Lipitor 10 milligrams for my cholesterol, allopurinol 100 milligrams for high uric acid, and Atacand eight milligrams twice a day to control my blood pressure and minimize protein in my urine. And the iron pill every other day and 200 milligrams of vitamin D for a total of eight pills day. This summer I started Pylera for my low red blood [cell] count from the anemia. I'm hoping this will help with my fatigue.

My treatment regimen has changed over the past few years. When I was first diagnosed, I was stable and only on lisinopril. However, as newer symptoms of high uric acid, cholesterol, and high potassium have developed, I have to take more medications. Now I'm taking up to eight pills a day.

I've also been wearing hearing aids since the age of 10 years old. They help, but I still have a hard time hearing. They help me to hear the sounds coming from behind me as well as in front of me and this, of course, I need for driving.



Lasix has side effects of frequent and intense need to urinate. This, plus the eight to 12 glasses of water I drink every day to stay hydrated, makes me use the restroom frequently—even at night.

I am fortunate that I have been able to continue with the activities of my daily life and attend school. However, this is not always easy for me. The medications help to keep my kidneys functioning, but at this point as I progress in the disease, I take so many drugs and some side effects are dry mouth, frequent urination, and sometimes light headiness.

This past school year has definitely proven to be a challenge because the anemia wipes me out. By 5:00pm, I must come home and sleep, even before I begin my homework. Being in honors classes and AP classes, this shortens my time for my homework and other school activities that I enjoy, such as band and club meetings. This can be challenging, with the feeling of being so tired in the early afternoon. This also makes my afternoon schedule really tight because I must balance the time I'm asleep, homework, and other activities that I love to do such as playing bass or doing aikido.

I power through these symptoms, however. I know it worries my family because at times I look far worse than I feel. Or the opposite: I wear myself out and catch a cold or a virus that makes me miss a week of school.

As of right now, I just was accepted into a Stage three CARDINAL Study, and preliminary research has shown that this can improve the GFR. However, the long-term impact has not been determined yet. I hope even if I do get the placebo, it will help future generations.

For me the ideal medication should be safe and free of serious side effects. What good would an Alport treatment be if it causes liver problems, cancers, or cardiac problems? For example, when a nurse came to me about two weeks ago for my first Procrit injection, she told me and my parents, "If you feel sick, call 911." This, of course, is scary.

The ideal treatment would stop the progression of this disease, meaning my GFR will stay the same and not get any worse. The ideal medication should prevent the need for transplant or dialysis. It will also be ideal if the medication was easy to take and did not require frequent monitoring visits. Going to a doctor frequently gets in the way of my education and, in the future, of my job.

Thank you for allowing me to share my experience.

## Larry

Hello, my name is Larry. I am 48 years old. I live in Mt. Vernon, Ohio with my wife of 26 years and our two beautiful daughters, 23 and 19. Our oldest daughter is expecting our first granddaughter.

I am a patient and I have X-linked Alport syndrome. As an adult, I had physicals every two years for work, had blood drawn and had no issues other than high cholesterol. It wasn't until my family doctor retired and all the office policies changed, that I switched to my current nurse practitioner. In 2014, after my first visit with her, she informed me that I was in kidney failure and that I needed to see a nephrologist immediately. I was shocked; I had no symptoms. I truly had no idea. I work at UPS; I've been there for 29 years, which keeps me very active. I walk approximately seven to 10 miles a day on the job. I've run two half marathons and I love boating with my family.

I called Dr. Hebert's office at OSU [Ohio State University Hospital] immediately; he was my nephrologist from when I was a child and had blood and protein in my urine. He recommended that I start taking blood pressure and cholesterol meds and that I go in for a kidney biopsy. I did go ahead and have the biopsy procedure done and was diagnosed with Alport syndrome. The biopsy was not easy, it was a painful process that also caused me to have a night stay at OSU hospital due to a blood clot that formed around my kidney. At this time, Dr. Hebert recommended Dr. Simon at the Cleveland Clinic for a clinical study. I decided to try to get in the ATHENA Study because at that time I was scared for the life that I had and was willing to do whatever it took to save my kidneys and save my way of life, and if the study could help me achieve that, it will be worth it.

I was able to get into the study, and this is when I found out just how bad my kidneys were. My first blood test for my GFR was, I believe, around 30%. I was in total disbelief because I still had absolutely no symptoms. I continued in the study for approximately two years until the trial stopped. During those two years it was a constant emotional rollercoaster for my entire family. It was a constant worry about what my kidney function would be and if it would be time for a kidney transplant. It was stressful having to worry about taking time off work to get to the Cleveland Clinic. It was always – it would always be a whole day off work, as it takes two hours one way for me to get to Cleveland. And working at UPS, I do not have sick time that I get paid for; I would have to take a vacation day or a day off without pay.

I recently tried to participate in another clinical study, the CARDINAL Study. Again, I am going to put myself through this in hopes of receiving the drug that could possibly increase my kidney function by 10%. This is important to me because it would avoid the need for a transplant. I realized that I may or may not have gotten the drug but was going to disrupt my life and participate in hopes of getting lucky enough to get the drug and not the placebo. Unfortunately, my kidney function had dropped from 30% to 23% and I was not eligible for the Study. This was related to an accident I had at work earlier in the month. The emergency room doctor prescribed me NSAIDs for the pain and I took them not realizing they could have a bad effect on my kidneys. I am in hopes my function will recover.

I still feel like I do not have many symptoms of low functioning kidneys, other than that of fatigue. I do have fatigue that I noticed I didn't have three years ago. I would have to say the most challenging part of Alport is the mental stress of learning about this disease and realizing I am more than likely going to have a transplant someday. The worry—this is a worry financially and physically. My goal will be to stay at 30% function and never have to have a transplant.

I do not think that I have ever had something disrupt my life in such a negative way. I have never been a worrier or had trouble sleeping, but now I do worry constantly and have sleepless nights worrying about how I will ask someone for a kidney. I also worry about if I am lucky enough to find a donor, how long will this kidney last and will I have to go through this again?

To me, [one of the] current challenges to treating Alport syndrome is that transplant should not be a treatment. I really don't want to have a transplant; I don't want to have to put my body through this mentally or physically, or my family through this, or the person who is donating a kidney for me. It's a shame there's not more being done to create a treatment to help maintain kidney function for people like me who could possibly live the rest of their lives at 30% kidney function.

I truly hope and pray that you can find and approve a drug or treatment for people like us with this disease and for the people after us that carry this disease. I will do whatever I have to, just like my grandmother, Twyla Arnold. She bothered so many people over 92 years, searching for answers she could get to help her family fight this disease that has haunted our family for many generations.

Thank you.

## Drew

Hi, I'm Drew, I'm 15 and I just started my sophomore year at North Central High School in Indianapolis, Indiana. I was born with Alport syndrome and I first began showing symptoms when I was five years old. I had blood in my urine and kept going to the pediatrician with the urinary tract infections. The doctors were unsure why the infections kept occurring, but my mom continued to demand they search for the cause because a normal five-year-old should not be having so many UTI[s]. It was so bad that I could not even take a bubble bath without getting a UTI. At the age of six, they did a kidney biopsy on me. This led to the diagnosis of autosomal recessive Alport syndrome. I was put on a low dose of lisinopril to at least slow down the progression of the disease, but as you will see, that didn't work too well.

In elementary school I wasn't hearing my teachers well because my hearing was steadily getting worse. By the time I turned seven, I had been fitted for hearing aids. The school had to tell my parents that I wasn't hearing well because I had learned to read lips at such a young age. I didn't like wearing them, and I would try to go without them when I thought I could get by with it. On the day I got them, I cried when I passed a soda machine because it was making a noise I had never heard before. The whole world just became so loud all at once and that scared me. It was very hard to adjust to this.

After being diagnosed, I was going to Riley Children's Hospital each month to have my blood drawn so my kidney doctor could monitor creatine levels and keep an eye on my kidney function. They kept reassuring my mom that I would have nothing to worry about until my late 20s, because that is the usual age when females with Alport start to lose kidney function, if at all. My creatinine level was always around two and then in the summer after I turned 10, my creatinine levels began rising rapidly as my kidneys were failing. When I was in the fifth grade, I only went to school half days because I didn't have enough energy to go full days. I would go to school in the morning, come home, and go straight to bed and sleep. I was getting very tired all the time and I had very little energy.

I was on the local swim team and I had to quit because I no longer had the energy to go to practice every day for two hours and compete in meets. I loved swimming and this made me very sad. I no longer had the desire to go swimming with my friends or even to the park. I also no longer went on walks around the neighborhood with my friends. My friends didn't understand what was wrong with me because it didn't look like anything was wrong with me, and I was also confused because I wasn't sure what was wrong with me or what was going to happen.

When I was 11 years old, my kidneys had gotten to the point where I had to begin dialysis. My mom had them wait until the end of the school year because she wanted me to at least be able to graduate fifth grade with my friends and go on the overnight trip to the zoo with my class.

I went to Riley Children's Hospital and began peritoneal dialysis every night for eight hours. Dialysis was very painful when I started, but eventually, I got used to the strange feeling. I remember being in the hospital crying; I told my mom that I could not do this and to stop. It was the worst thing I had been through so far. I chose to do peritoneal

dialysis once a day at home so I wouldn't have to spend my days at the hospital doing hemodialysis.

The summer of 2014 was the worst summer of my life. I will never forget it. There were no family vacations, amusement parks, concerts, camp, or late nights. I was bound to my room every night at 8:00pm for dialysis. I could no longer play video games, watch movies on the big TV in the living room, play board games with my friends on the table, or even spend the night at a friend's house.

I basically had no social life while on dialysis. They tried to make me feel better by coming over and just hang[ing] out with me in my room at 8:00 every night, and I did feel a little better, but I was still sad. I didn't understand why this was happening to me and when it was going to stop. I still had to go to the doctor's every week to check my sight and numbers. I was very lucky that, in May of 2015, I acquired a new kidney. That summer, I was again admitted to Riley Hospital to receive a new kidney which meant the end of dialysis. However, I had to go through a whole new process of taking care of this new kidney, including learning about the new medication[s], the frequent doctor's visits with blood draw, and new dietary restrictions. But this was way easier to handle, versus the dialysis. Once I recovered, I had energy again.

My new kidney has been working very well for me these past three years, and every day I take four different types of pills at 8:00am and 8:00pm to make sure my body won't reject my new kidney. My 10-year-old sister, Karma, was diagnosed with Alport syndrome four years ago. She wears hearing aids, but so far, her kidneys are still doing well. She's also taking lisinopril the same as I did. I would love for her to have a medicine to take that could prevent her from going through all the things I had to deal with while—I'm so sorry—my kidneys were failing—sorry. Now that I have gone through this process, I am very grateful for Riley Hospital, all the doctors, surgeons, nurses involved, Alport Syndrome Foundation, my parents and friends, as well as my bright future to come.

Thank you.

## Jessica

Good afternoon. My name is Jessica and I have Alport syndrome. I'm 28 years old and I currently live in Charlottesville, Virginia, where I work as a barista. Treatment for Alport syndrome can only begin once one has a diagnosis. In my case, I exhibited symptoms of Alport syndrome since age three in the form of gross hematuria and proteinuria but did not receive an official diagnosis or begin treatment until I experienced a sudden, profound hearing loss at age 16. For some time, my hearing loss was mistaken for being selective but once my grades started slipping, a visit to the audiologist confirmed that I had a bilateral, moderate-to-severe neurosensory loss, and I was given hearing aids. After confirming Alport syndrome with a second renal biopsy, my nephrologist started me on a low dosage of lisinopril with the intent of slowing the progression of kidney failure by lowering the amount of protein in my urine.

Unfortunately, three months later, when my doctor increased the dosage of lisinopril, I experienced a severe allergic reaction that landed me in the emergency room. After recovering, I was prescribed Atacand which ultimately served the same function as an ACE inhibitor, though through a different channel. I took Atacand for the better part of 10 years, until my potassium levels were high enough that my nephrologist decided it would do more harm than good. I was in Stage four of chronic kidney disease and slowing the progression no longer seemed viable.

Currently, my medications mostly address the physical symptoms of kidney failure. These include sodium bicarbonate, which is ultimately intended to slow the rising creatinine as my kidneys continue to lose function. I am also taking calcitriol and vitamin D2, which respectively provide me with an active and metabolized vitamin D in order to compensate for my gross deficiency. Finally, I have a prescription for Prevacid sodium, which is intended to slow the rate of decline in kidney function by reducing serum cholesterol and proteinuria.

I cannot confidently attest to the efficacy of any of these treatments, because I have no baseline to compare them to. I do know that there were intermittent periods of four to five months where I could not afford medications without health insurance, and I felt no different without the drugs.

I can also look at the chronological progression of decline in my kidney function and see a linear trend, which suggests that there is no drastic intervention that altered the course that Alport syndrome would ultimately take in me. I often wonder if the same would be true had I been diagnosed and treated before I was a teenager, which leads me to hope that the nephrology community continues to improve upon early testing and intervention strategies.

Ultimately, the best treatment I found for accepting life with Alport syndrome was learning American Sign Language (ASL) and adopting a deaf identity. The deaf community leaves little room for the medical perspective whereby hearing loss is treated as a physical handicap that limits one's ability and needs to be fixed. I will admit that this particular ideation had [a] strong impact when I was younger and led to many problems with self-identity, including anxiety and depression. Upon learning ASL and meeting other deaf and hard-of-hearing peers, however, I experienced a dramatic frame

shift that makes me proud to identify as deaf. Moreover, I learned that my hearing loss was actually a deaf gain which enabled me to recognize that I had adapted other abilities that may not have come to fruition had I not lost my hearing.

For example, I have learned to read lips and facial expressions quite well and I have honed visual perceptive skills that place me above the 99th percentile among my peers. I've come to consider my hearing loss to be the silver lining of Alport syndrome.

End-stage renal disease, however, is no silver lining. Since my kidney function has worsened, I have experienced symptoms of extreme fatigue, frequent urination, sleep deprivation, nausea, leg cramps, high blood pressure, migraines, and anxiety. When I'm nauseated or vomiting, I cannot drink a Gatorade or an orange juice. I cannot ease my stomach with saltine crackers. The respective high potassium and sodium levels in these items are restricted from a kidney diet. When I have a migraine or a cramp, I cannot take Advil, Motrin, Aleve, or any sort of anti-inflammatory. I've been cautioned against taking too many acetaminophens, so I save those for the real pain and learn to live with the rest.

Due to lack of available pain management, I have turned to cannabis products to alleviate many of the aforementioned symptoms. Specifically, I have found a topical CBD-infused bomb that relieves the pain from leg cramps almost immediately. Similarly, when I experience a migraine due to high blood pressure, I have found that after administering a 1,500 milligram dose of a CBD tincture sublingually, I'm less inhibited by the pain, nausea, and fatigue from the migraine. However, because these supplements are not regulated, I have done so at the risk of inaccurate dosing and inconsistent quality of product. While CBD may not be able to slow the progression of kidney failure or cure Alport syndrome, there are tremendous potential benefits for alleviating the day-to-day symptoms that drastically affect quality of life for patients like myself.

In the future, I hope that treatment for Alport syndrome includes more risk-free pain management, as well as some form of treatment for fatigue so that we might be able to remain active. I believe Alport syndrome patients would also benefit if we found ways to have a less restrictive diet in regard to potassium-rich fruits and vegetables. It might be easier to manage if there were binder pills like those that exist for phosphorous.

Finally, I hope that treatment for Alport syndrome includes more preventative measures or some way to regenerate the cells that we have already lost without further impeding our quality of life.

Thank you for listening to my testimony.

## APPENDIX 4: Meeting Polling Questions

### Polling Questions Demographics

1. I am:
  - a. An individual with Alport syndrome
  - b. A caregiver of someone with Alport syndrome
  
2. Where do you live?
  - c. East Coast (Eastern time zone)
  - d. Midwest (Central time zone)
  - e. West (Mountain time zone)
  - f. West Coast (Pacific time zone)
  - g. Canada
  - h. Mexico, Caribbean Islands
  - i. Outside of North America
  
3. Do you identify as:
  - a. Male
  - b. Female
  
4. What is your age?
  - a. Younger than 18
  - b. 18–29
  - c. 30–39
  - d. 40–49
  - e. 50–59
  - f. 60–69
  - g. 70 or older
  
5. What is the length of time since your diagnosis of Alport syndrome?
  - a. Less than 1 year ago
  - b. 1 to 2 years ago
  - c. 2 to 5 years ago
  - d. 5 to 10 years ago
  - e. More than 10 years ago
  - f. I'm not sure.
  
6. Did you receive a diagnosis of:
  - a. X-linked Alport syndrome
  - b. Autosomal dominant Alport syndrome
  - c. Autosomal recessive Alport syndrome
  - d. Unknown/Unsure



7. I am:
- a. Currently on dialysis
  - b. Not currently on dialysis
  - c. A kidney transplant recipient
  - d. Not a kidney transplant recipient
  - e. A kidney transplant recipient and currently on dialysis (e.g., failed transplant)

## Polling Questions: Topic 1

### Living with Alport Syndrome: Disease Symptoms and Daily Impacts

1. How much does your AS interfere with daily life in general?
  - a. Not at all or minimally
  - b. Moderately
  - c. Significant amount
  
2. Have you experienced any of the following difficulties?  
(Select all that apply.)
  - a. Hearing loss
  - b. Anxiety and/or depression
  - c. Being tired, exhausted, or fatigued
  - d. Vision problems related to Alport syndrome
  - e. Gout
  - f. Gastrointestinal problems
  - g. Recurrent infections
  - h. Swelling (e.g., ankles, face, etc.)
  - i. Other
  - j. I do not have symptoms.
  
3. Which THREE of the following symptoms most negatively affect your daily life?
  - a. Hearing loss
  - b. Anxiety and/or depression
  - c. Being tired, exhausted, or fatigued
  - d. Vision problems related to Alport syndrome
  - e. Gout
  - f. Gastrointestinal problems
  - g. Recurrent infections
  - h. Swelling (ankles, face, etc.)
  - i. Other
  - j. I do not have symptoms.
  
4. Which have you experienced while coping with your Alport syndrome?  
(Select all that apply.)
  - a. Depression
  - b. Anxiety
  - c. Low self-esteem
  - d. Social isolation
  - e. Difficulty with relationships outside of family
  - f. Hopelessness
  - g. None of the above

5. Which of the following statements is true for you as related to living with Alport syndrome?  
(Select all that apply.)
- a. I miss work or school more than I'm comfortable with.
  - b. Family stress is common in my life.
  - c. Others don't know what it's like living with Alport syndrome.
  - d. I cannot participate in sports or other physical activities I enjoy.
  - e. My general daily function is limited by Alport syndrome.
  - f. None of the above.

## Polling Questions

### Clinical Trials for Alport Syndrome Treatments

1. What is your experience with, and perception of, clinical trials for a new kidney disease drug?
  - a. I am currently participating in a trial.
  - b. I have participated in a trial, and I would do so again.
  - c. I have participated in a trial, and I would not do so again.
  - d. I have not participated in a trial, because I didn't know about the opportunity.
  - e. I have not participated in a trial because I was not eligible.
  - f. I have not participated in a trial, although I was aware of the opportunity and eligible.
  - g. I would never enroll in a clinical trial.
  - h. Not sure.
  
2. Of the following factors related to a test drug in a clinical trial, select UP TO FIVE that you rank as most important to your decision about participating in a clinical trial:
  - a. Whether I might get placebo ("sugar pill")
  - b. Whether I need to stop my current treatment
  - c. Potential side effects from a new drug
  - d. How the drug is taken (e.g., by mouth, IV, injection in muscle)
  - e. In earlier trials, was the study drug effective for specific benefits most meaningful to me?
  - f. Knowing if I can make the commitment to participate in a clinical trial
  - g. Frequency of exam appointments
  - h. Distance to trial site
  - i. Length of trial
  - j. Whether a kidney biopsy is required
  - k. Negative things I have heard about clinical trials
  - l. Other
  
3. Would you enroll in a clinical trial if it required?
  - a. No kidney biopsy
  - b. 1 kidney biopsy within 1 year
  - c. 2 kidney biopsies within 1 year
  - d. 3 kidney biopsies within 1 year

## Polling Questions: Topic 2

### Current Challenges of Treating Alport Syndrome

1. Select the medications or devices you use for Alport syndrome:  
(Select all that apply.)
  - a. ACE, ARB, beta-blocker, “water pill” (or other drug for blood pressure)
  - b. Allopurinol (for gout or high uric acid)
  - c. Statin (or other drug for cholesterol)
  - d. Veltassa (or other drug for high potassium)
  - e. Sevelamer (or other drug for high phosphate)
  - f. Antidepressant or anti-anxiety drug
  - g. Hearing aids
  - h. Glasses (for Alport syndrome-related vision problems)
  - i. I do not take medication(s).
  - j. I do not use hearing aids or glasses.
  
2. Select all that apply. I have had ESRD, and at least part of that time:
  - a. I was on dialysis.
  - b. I received a kidney transplant.
  - c. I have not experienced ESRD.
  - d. My patient died while in ESRD.
  
3. How well does your current treatment or device reduce the most significant symptoms of your disease?
  - a. Very well
  - b. Moderately well
  - c. Poorly or not at all
  - d. I do not currently take any treatments/use hearing aids or glasses.
  
4. Which symptoms do you have that are NOT fully addressed by your current treatments or devices?  
(Select all that apply.)
  - a. Hearing loss
  - b. Anxiety and/or depression
  - c. Being tired, exhausted, or fatigued
  - d. Vision problems related to Alport syndrome
  - e. Gout
  - f. Gastrointestinal problems
  - g. Recurrent infections
  - h. Swelling (e.g., ankles, face, etc.)
  - i. Reduced kidney function (GFR)
  - j. Proteinuria (protein in urine)
  - k. Hematuria (blood in urine)
  - l. Other
  - m. I do not have symptoms.

5. Which THREE factors are the most important to you when deciding to select a new drug?
  - a. Whether drug is taken by mouth, by IV, or injection in muscle
  - b. How often you have to take the drug
  - c. Evidence in AS patients that the drug improves specific symptoms most bothersome to you
  - d. Number of side effects known for the drug
  - e. Severity of side effects known for the drug
  - f. Cost and/or whether covered by insurance
  - g. What your physician recommends
  - h. Other
  
6. In your daily life, what bothers you more:
  - a. Symptoms from Alport syndrome
  - b. Side effects from medicines you take for Alport syndrome
  - c. Both: symptoms and side effects are equal.
  - d. I can't tell the difference between effects of AS and side effects from medicines.
  - e. I do not have symptoms or side effects from medicines.
  
7. If the side effect profile of a new drug was more severe than you currently experience with your treatments, but clinical evidence indicated that the drug would significantly slow the progression of your disease and/or improve your quality of life, how likely would you be to take this drug?
  - a. I would not consider taking it.
  - b. Not sure.
  - c. I would consider taking it.
  
8. Without considering side effects of a drug, which ONE of the following would be most important to you in a future therapy?
  - a. Evidence that the drug will reverse decline in kidney function (i.e., halt progression of Alport syndrome, delay need for dialysis), but has no effect on hearing.
  - b. Evidence that the drug significantly improves hearing but has no effect on kidney function.
  - c. Evidence that the drug will improve my quality of life or prevent future reduction in quality of life.
  - d. Evidence that the drug will prolong my life.

# APPENDIX 5: Results from Polling Questions

## Demographics

Figure 1-A

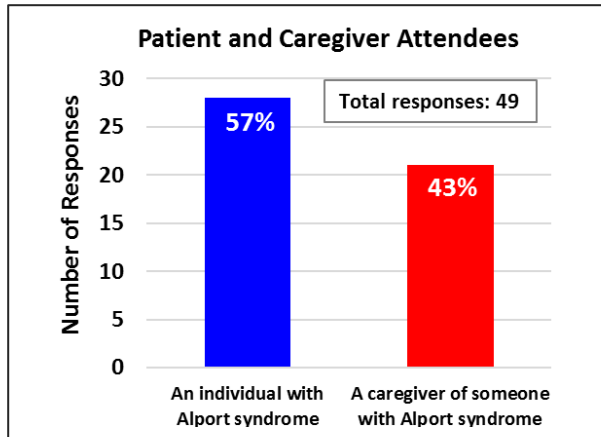


Figure 1-B

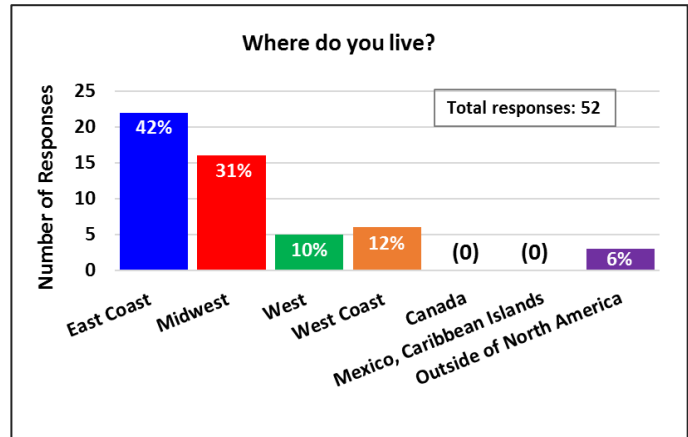


Figure 1-C

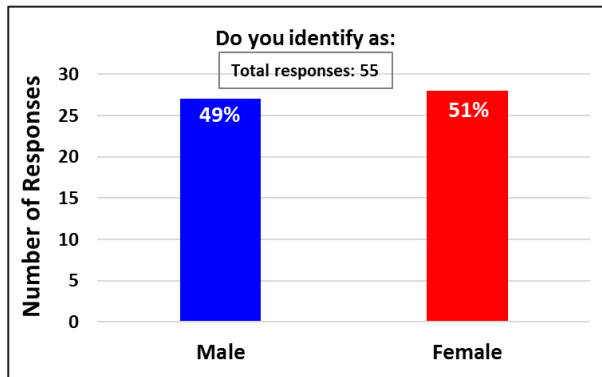


Figure 1-D

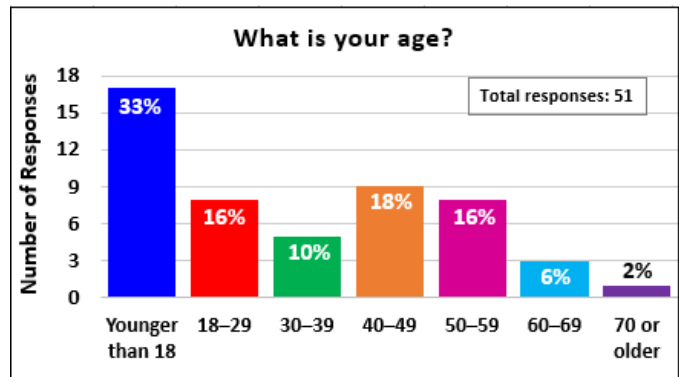


Figure 1-E

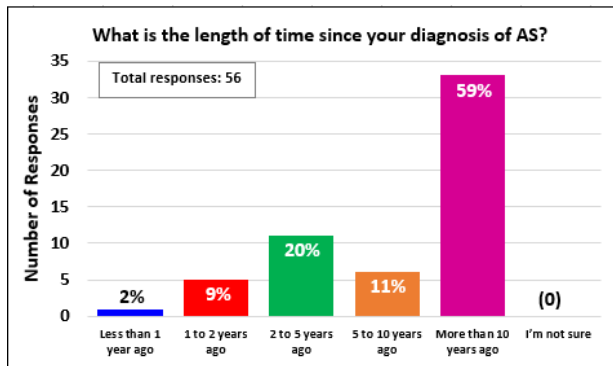


Figure 1-F

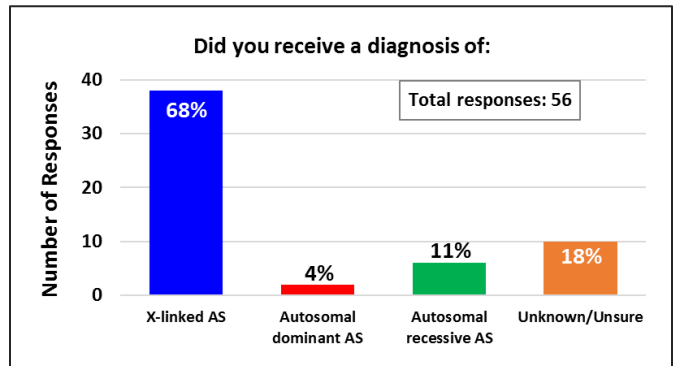
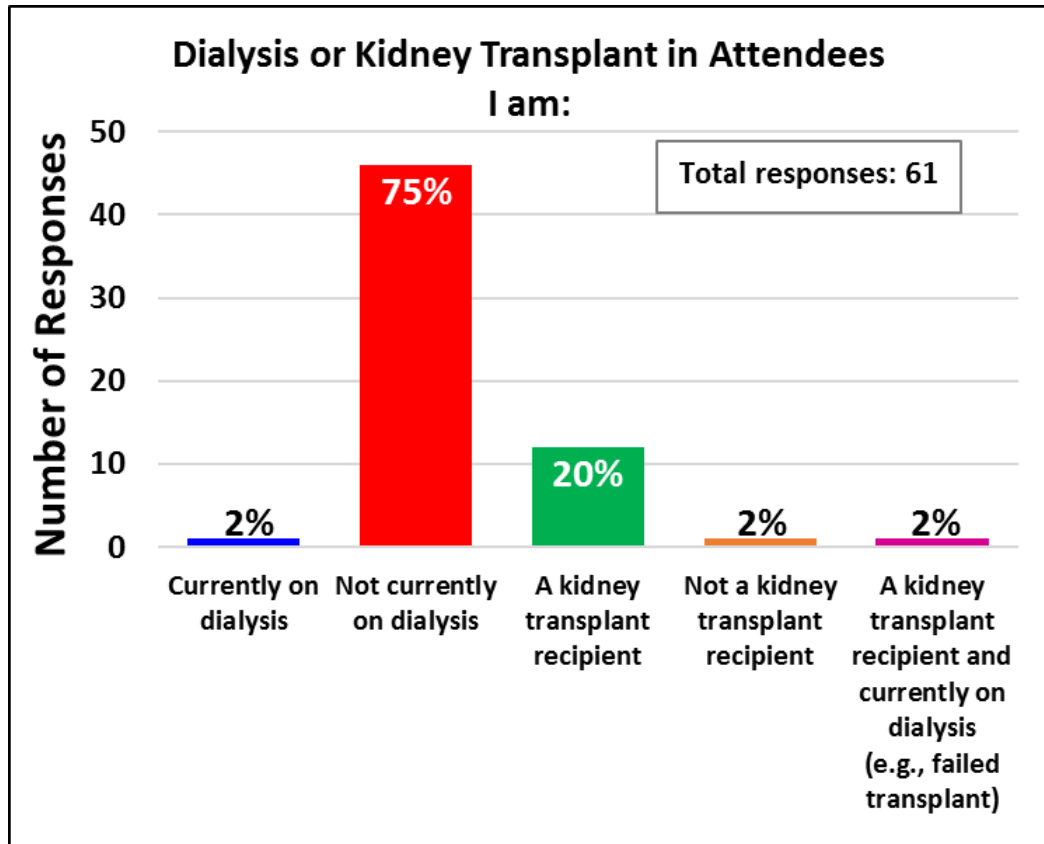


Figure 1-G





Topic 1: Living with Alport Syndrome: Disease Symptoms and Daily Impacts

Figure 2-A

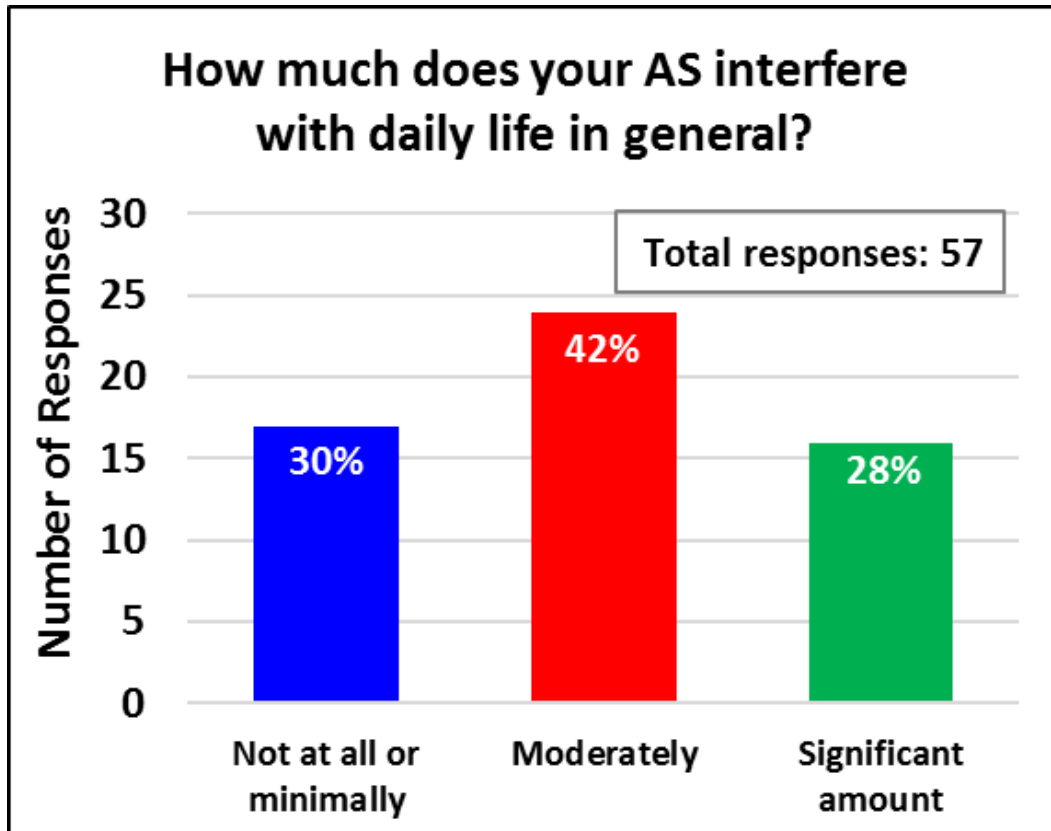


Figure 2-B

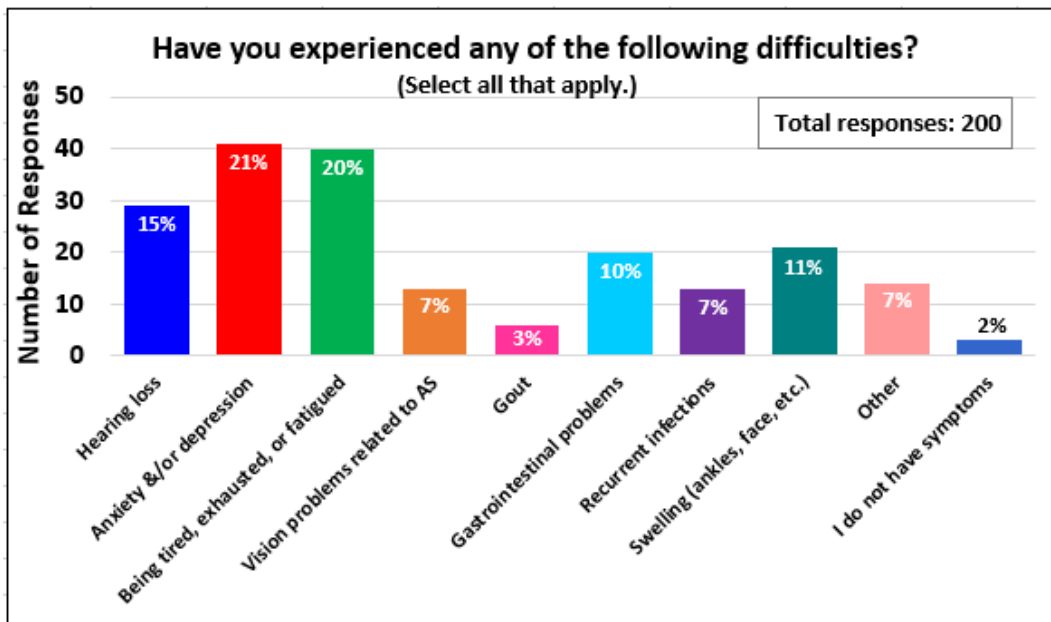


Figure 2-C

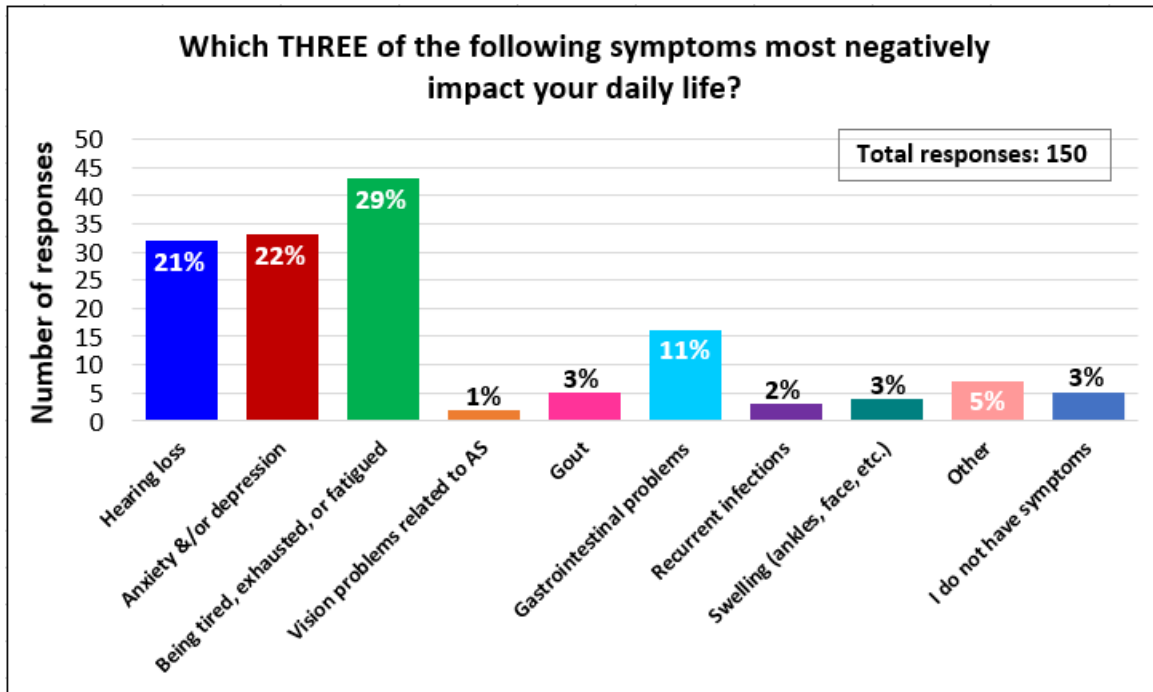


Figure 2-D

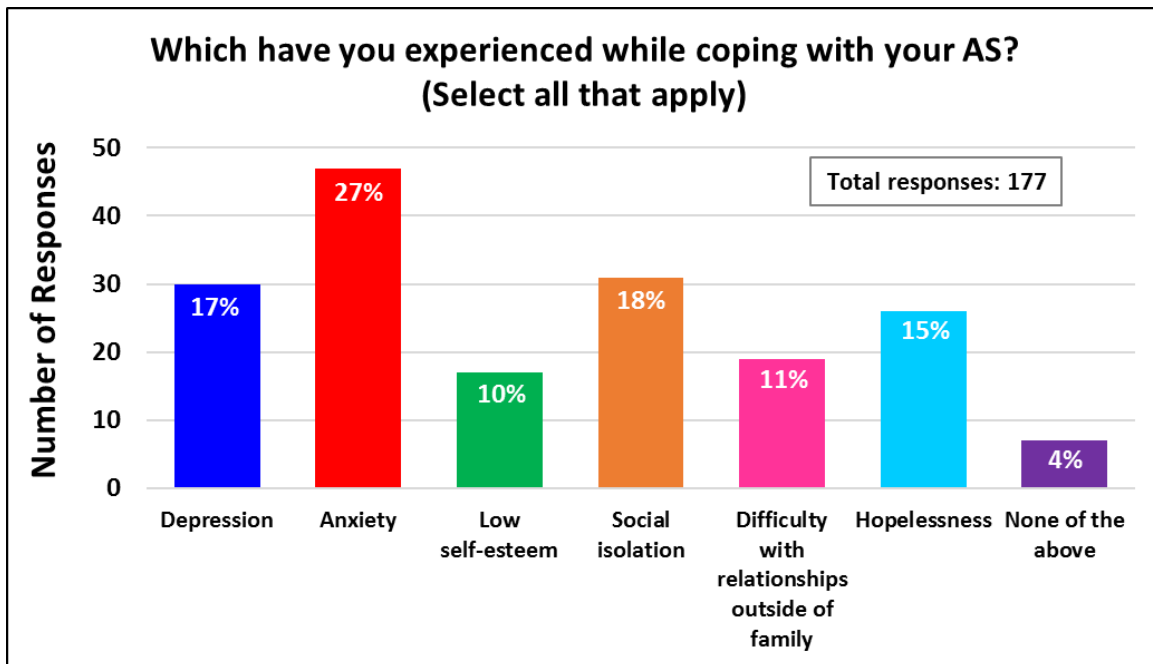
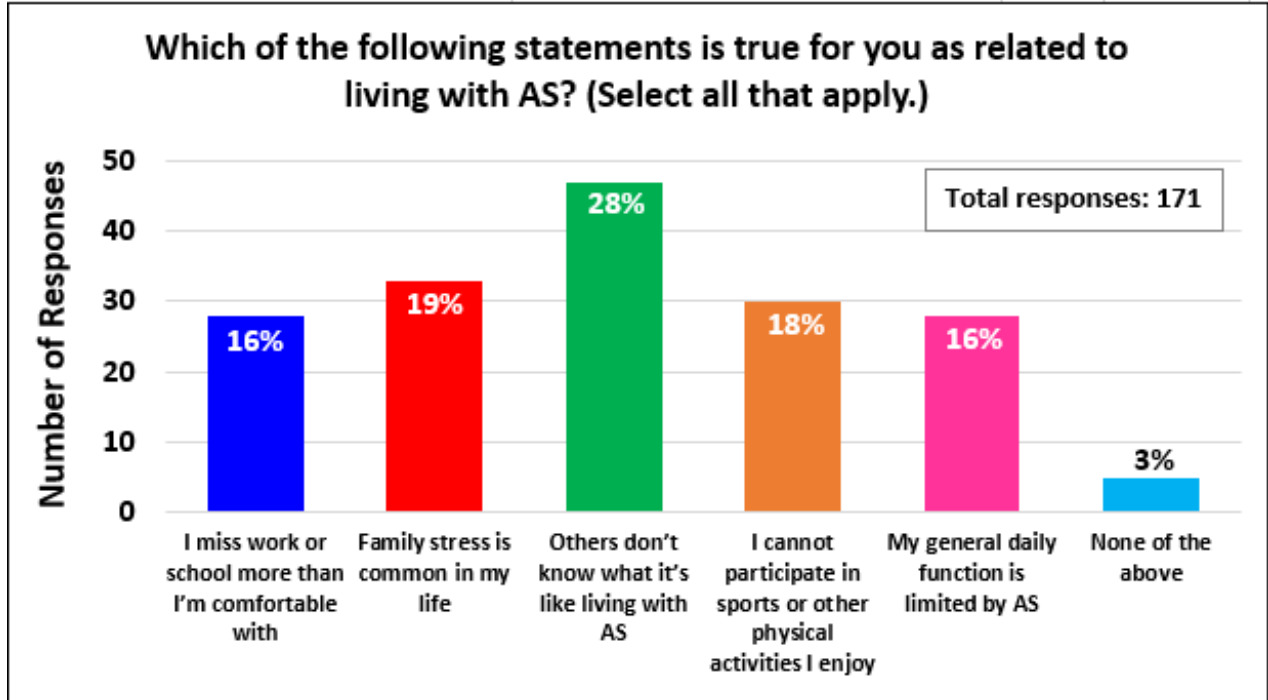


Figure 2-E



## Clinical Trials for Alport Syndrome Treatments

Figure 3-A

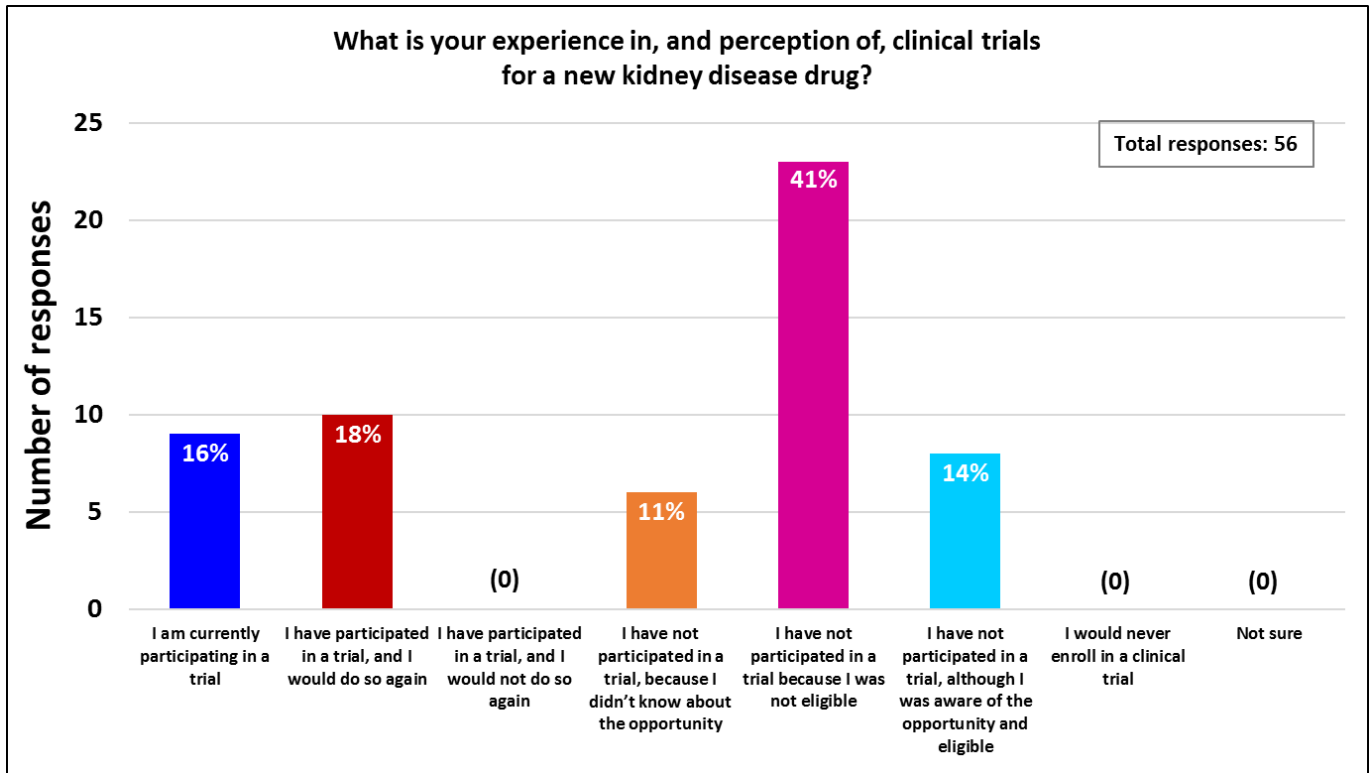


Figure 3-B

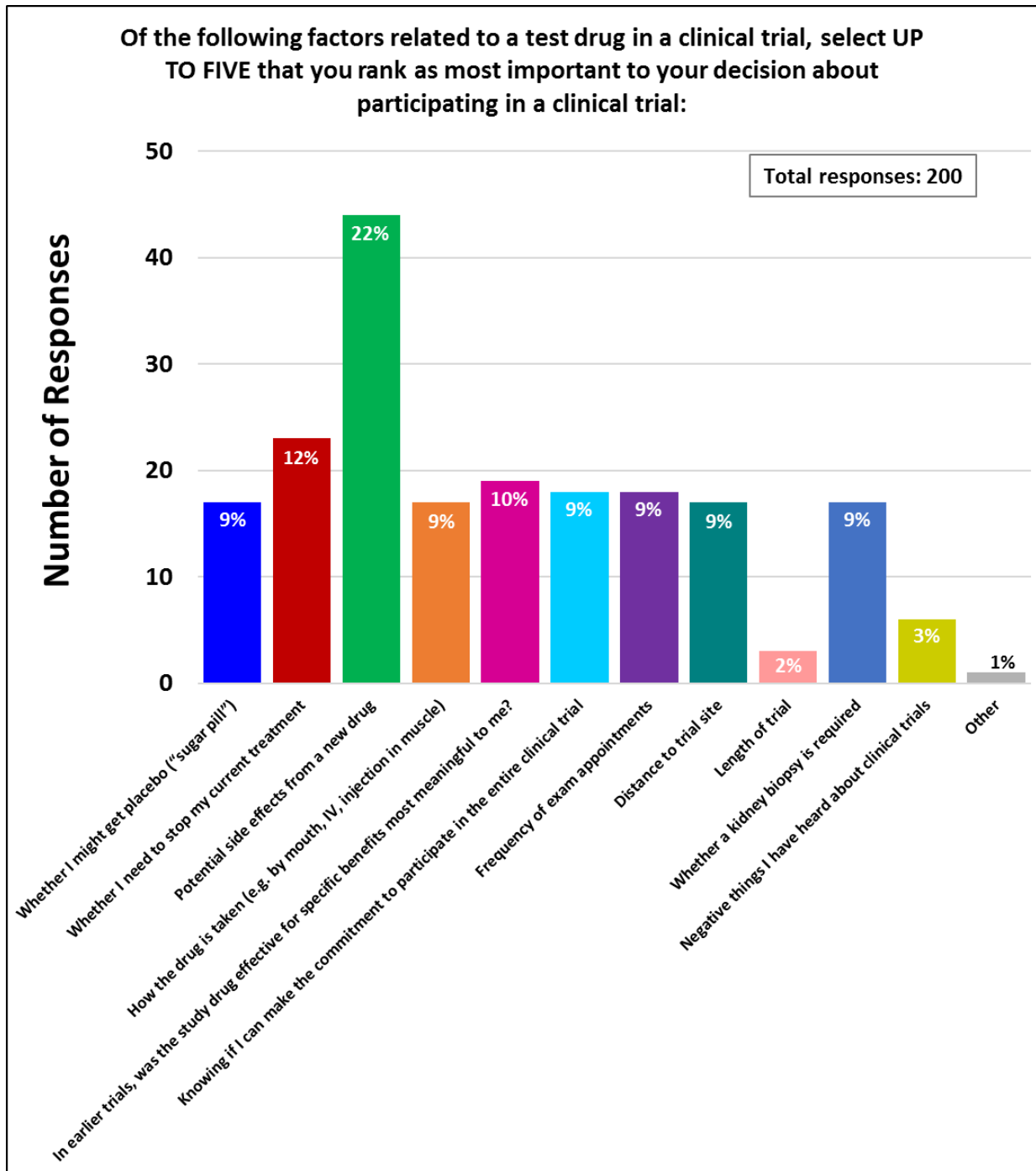
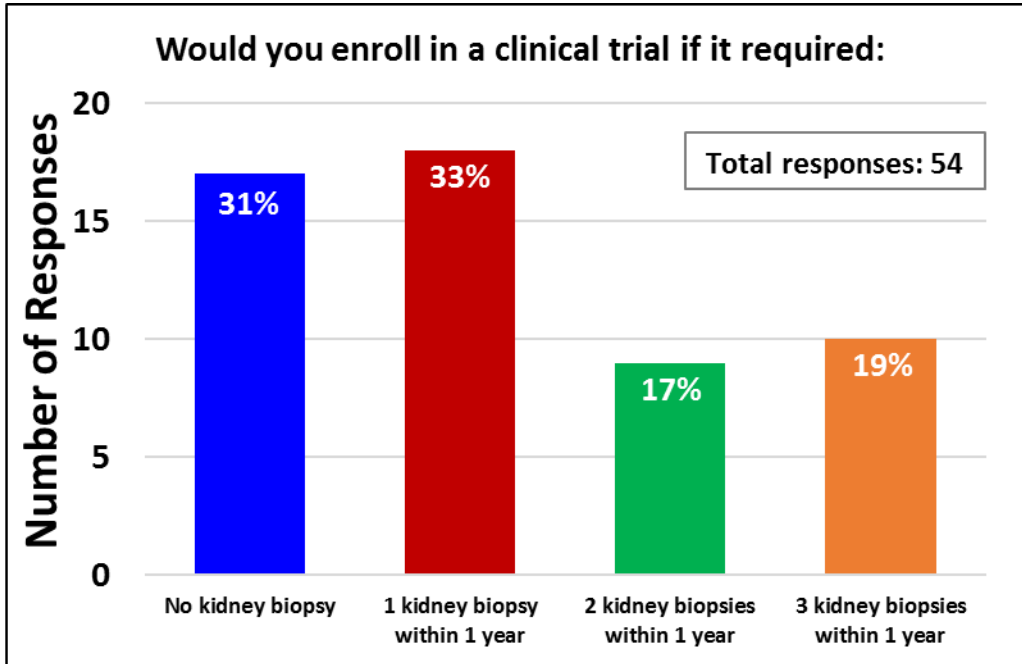


Figure 3-C



## Topic 2: Current Challenges of Treating Alport Syndrome

Figure 4-A

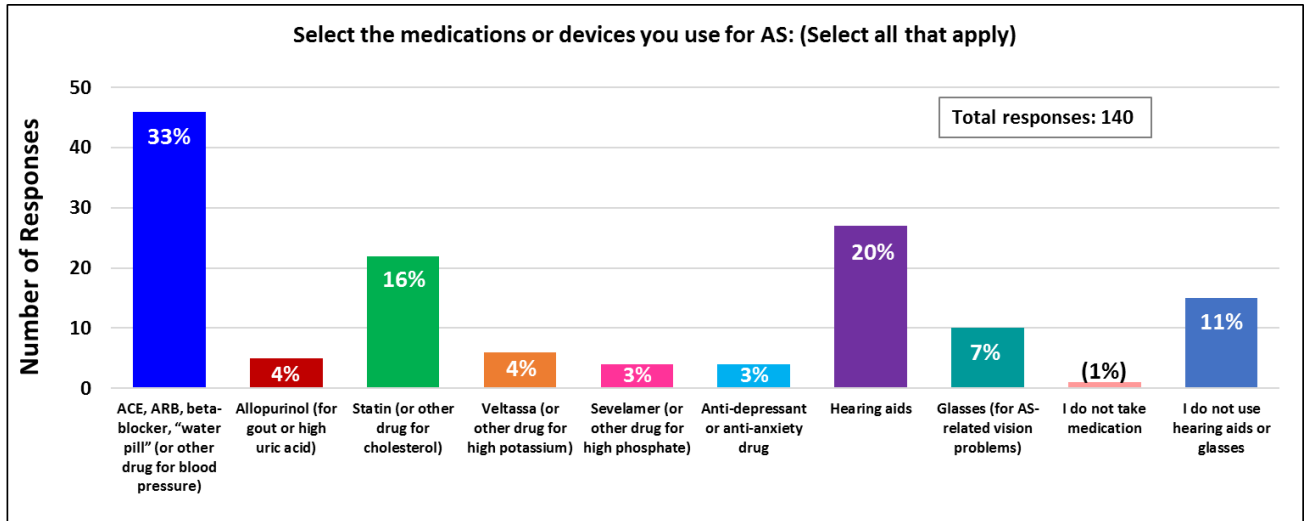


Figure 4-B

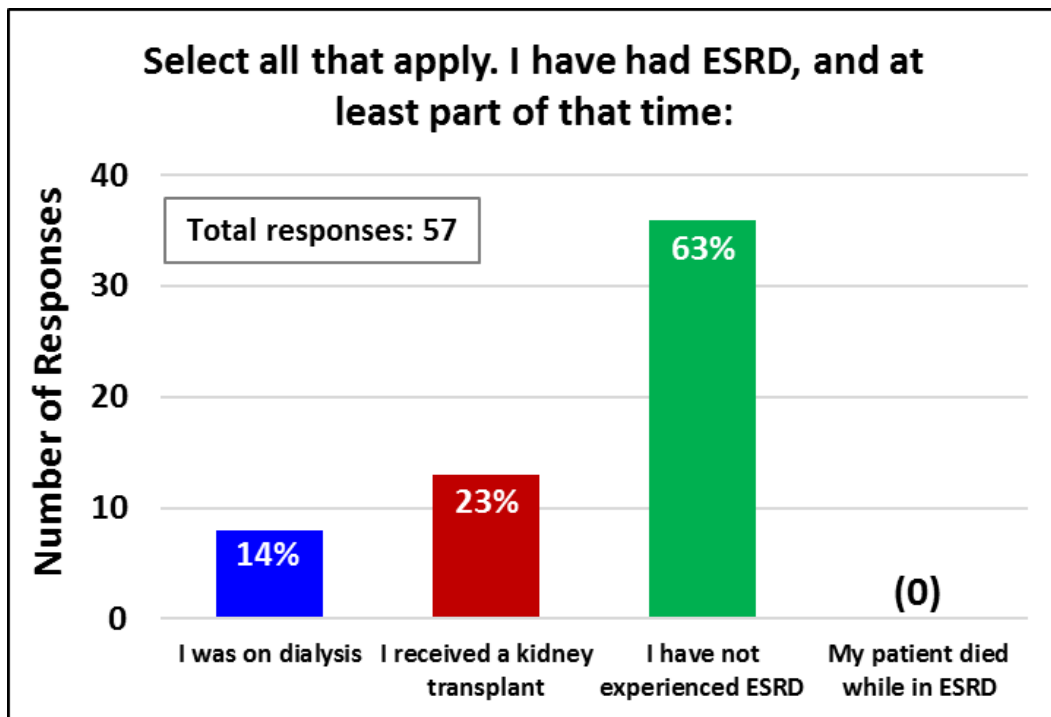


Figure 4-C

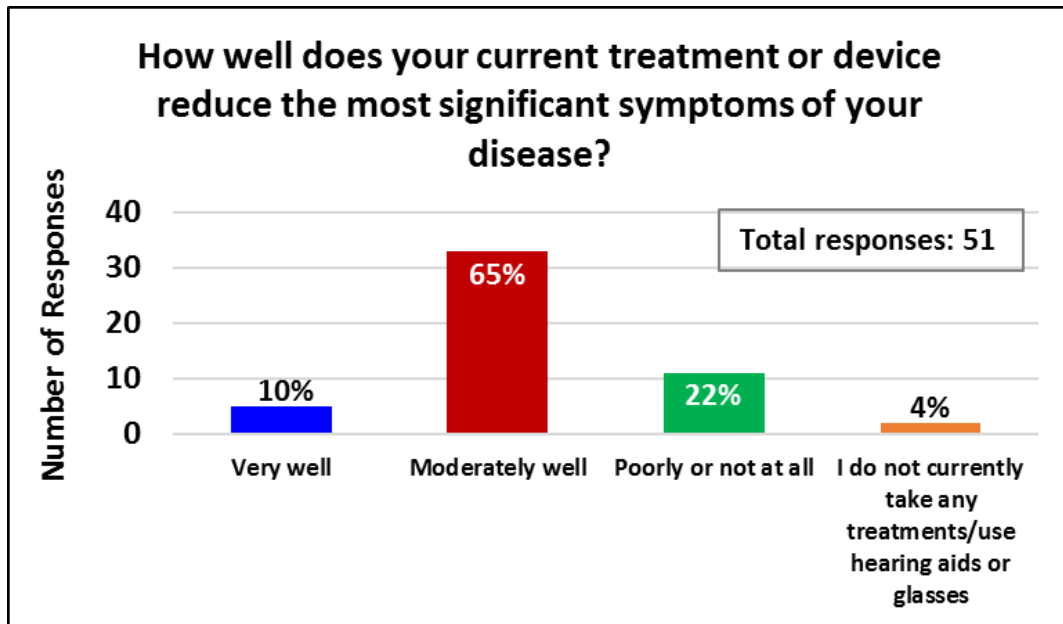


Figure 4-D

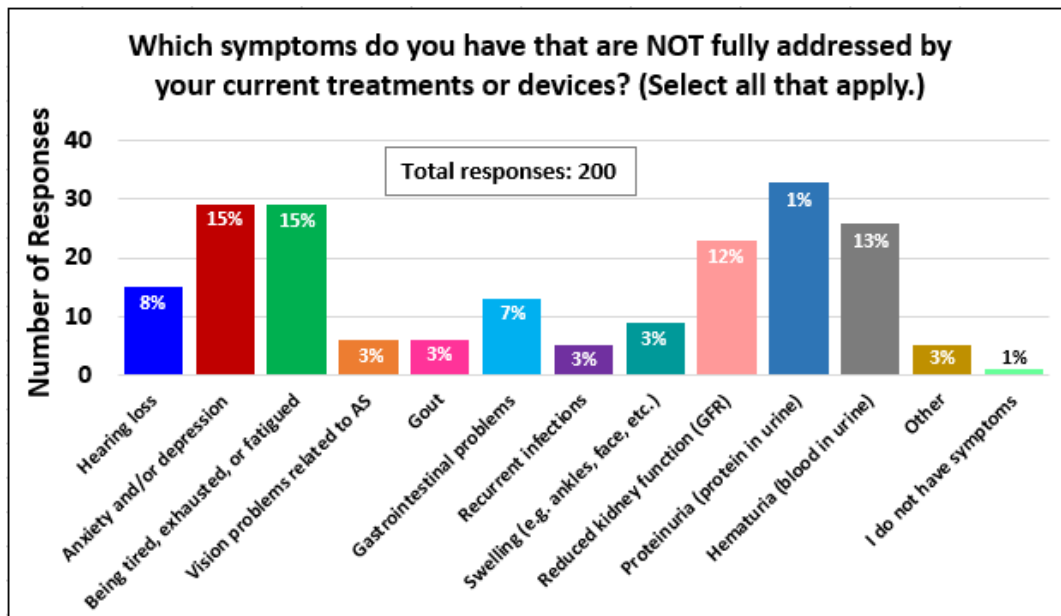




Figure 4-E

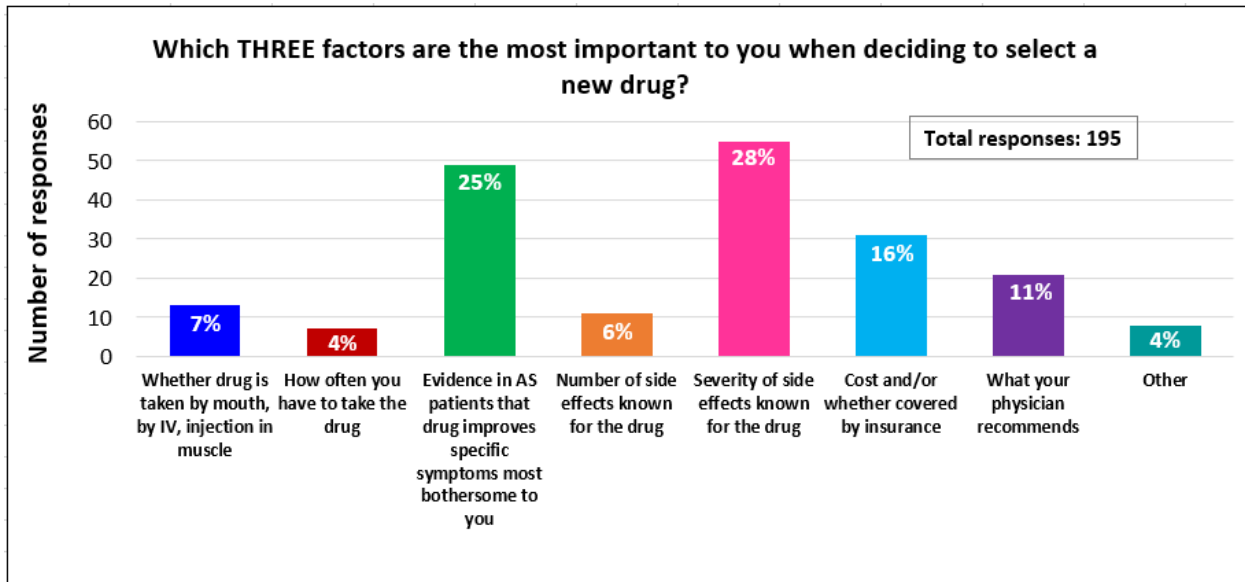


Figure 4-F

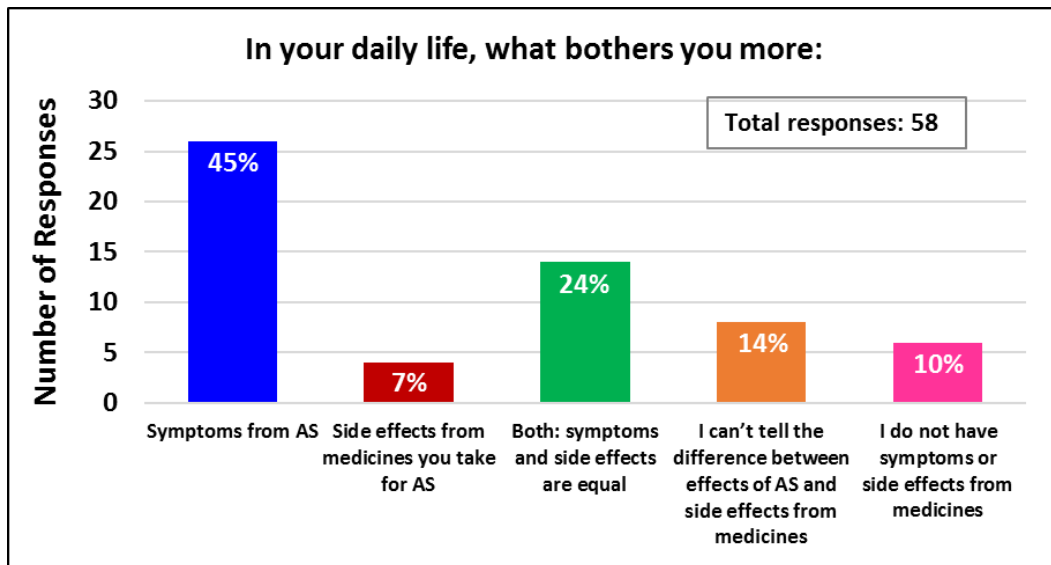


Figure 4-G

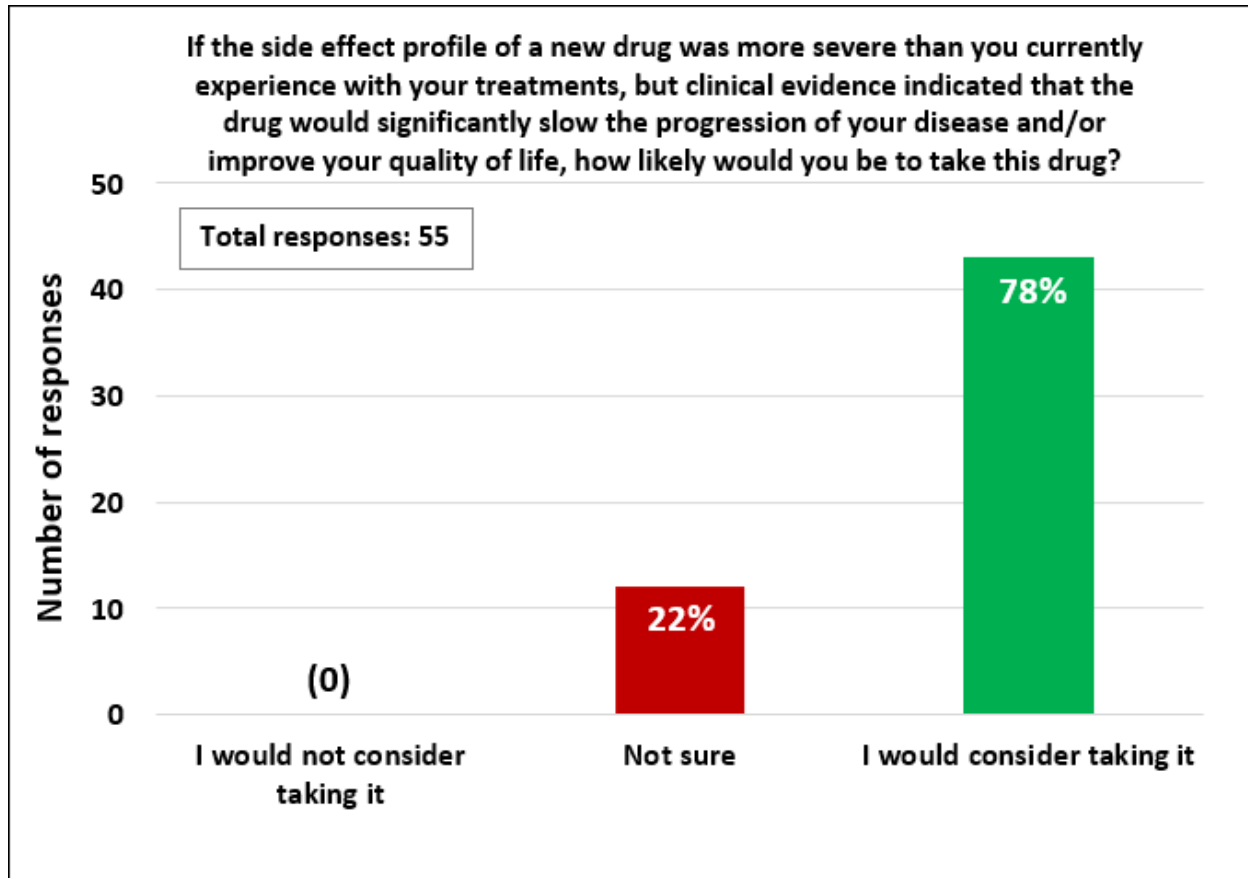
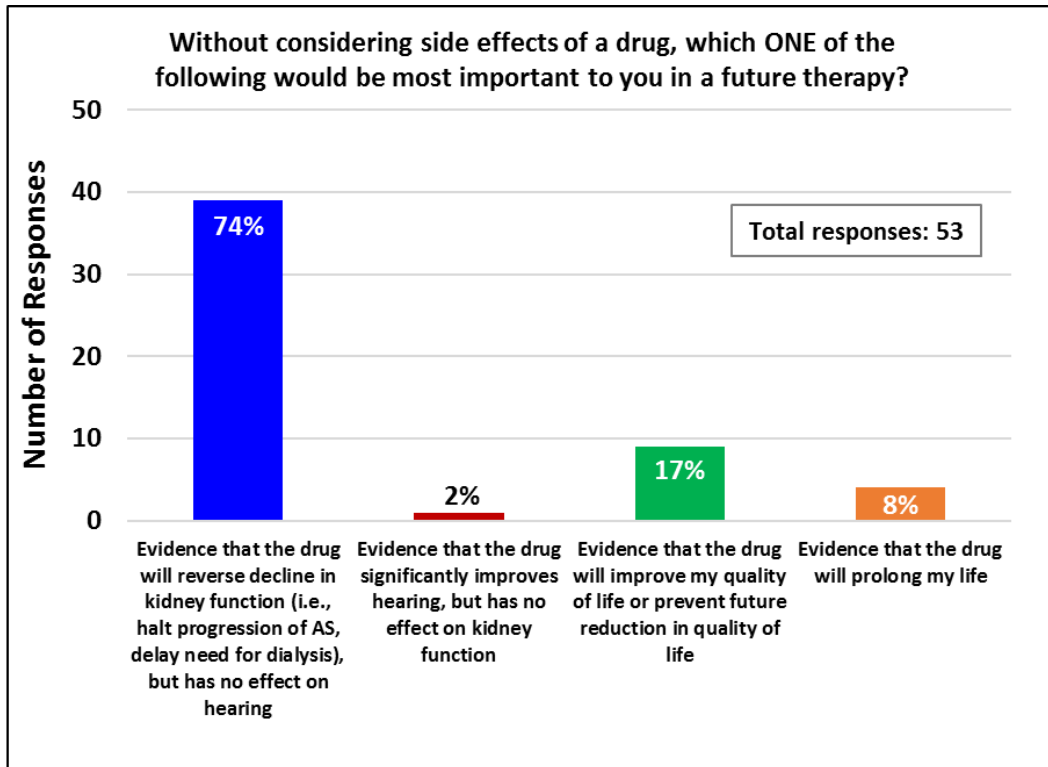


Figure 4-H



## APPENDIX 6: Participant Comments Submitted After EL-PFDD Meeting

### Comments submitted to the National Kidney Foundation and Alport Syndrome Foundation

From the date of the meeting until September 1, 2018, the NKF and ASF collected comments from patients and caregivers who attended the EL-PFDD Meeting on AS, in person or by remote webcast. Six participants submitted comments, many of which echoed the sentiments expressed at the meeting. The key topics from these comments and excerpts from them are below.

#### Treatment Options

“[Our daughter] has been on lisinopril 5mg OD [since] 2013, increased to 10mg in 2017. This April of 2018, we switched to losartan 5mg OD, as the side effect of lisinopril was taking a toll on her. The ARBs and ACE is [sic] not doing her any good; since late 2017 the hematuria and proteinuria keeps [sic] increasing, and her albumin serum [sic] keeps dropping. As of last lab...her albumin serum [was] at 2.1; her potassium number [was] still at normal range...The doctor cannot increase the dosage of the losartan, as her blood pressure is already so low...based on the [drop in] albumin serum [level]. We are looking at kidney transplant or dialysis in the next five years...We will try cyclosporine for my daughter, as it is the only choice left.”

#### Parental Concerns and Anxiety

##### *Related to treatment effects; quality of life*

“My daughter is only 13 years old...cyclosporine side effects...scares [sic] me, on how it will affect her. Since the chance of the cyclosporine improving her kidney function by 50% chance, is it worth it to put her through it? Or we just wait and hope for the next five years?”

“...my son...was finally diagnosed as Alport’s [sic]...approximately 36 years ago. [He] received one of my kidneys 17 years ago...It is still functioning well...[He] has been on...prednisone, CellCept, and cyclosporine/Rapamune...I imagine...his functioning kidney will [eventually] be poisoned by these drugs, and he will require yet another donation. Resulting from these drugs – primarily prednisone – he has osteoporosis and has also been on medication for this side effect for the past few years. He also has cataracts...”

“[My daughter] has isolated herself from her friends, due to diet restrictions...Since her [progression] in late 2017, she stopped attending parties and hanging out with friends because she feels different and tempted to eat those junk foods. The diet restriction part is a big challenge for our family...”

##### *Related to kidney health*

“Will my son not take his meds because he’s being a teenager?

Will he have to avoid certain sports because of his kidney function?

Will he be able to get the job he wants without having to think about healthcare acceptance?

Will he need a transplant?

Will there be a donor available?

What side effects from his medication will he have, pre- and post-kidney transplant?”

### *Related to hearing loss*

“Will he have learning challenges because of hearing loss?

Will he be bullied?

How many times will he lose his hearing aids?

Will we be able to afford replacements, or to buy the kind that he needs in the first place?

When he sleeps, will he be able to hear if an emergency is happening?

When he swims, he won't be able to hear his friends.

Will it affect the job he can get?”

### Living with Alport Syndrome

#### *Symptoms and burdens*

“Right now, my daughter's symptoms are swelling and, seldom, headaches. We used to run as a family, but we stopped since she easily gets dizzy because of her blood pressure...”

“Symptoms: none right now [that are] due to Alport.”

““Me: anxiety, very sensitive skin - allergic to everything, including makeup, eczema, vitiligo, seasonal allergies, hyperthyroid, goiter, trouble swallowing, lactose intolerance, acid reflux.”

“My son: anxiety, sensitive skin, eczema, seasonal allergies, allergies to bug bites – especially ticks, mild lactose intolerance, acid reflux.”

### Preferences for Clinical Trials

“Because of her age, I am reluctant to put her into clinical trials [with] unknown side effects...she is only a child, entering adolescence...she should be enjoying a normal life...our family is anxious on what is in store for her...we want our child to have a normal life.”

“My biggest concern is side effects of any new medication, short term and long term. I would do kidney biopsies, but I would not put my son through that until maybe age 16. I would do injections, but I would not put my son through that until maybe age 10. We would both do oral medication.”

“I live in Adelaide, South Australia...I have been trying to get into the Cardinal Study for about five months...My GFR is at 26 and holding...but the minimum [entry criterion for trial] is 30...I have stabilized it. (...I was in range, but nephrologist didn't know about [the trial]!)...It's hard knowing that there is a drug out there that shows such promise and works, but yet so far away for us [who are] on the lower limits of GFR and considering the alternatives. Wish FDA would consider [patients with] lower GFR that are stable and patient willing to participate.”

### Characteristics of an Ideal Treatment

“Any drug that would delay or prevent a kidney transplant. Any drug that would delay or prevent hearing loss.”

“I...[hope for]...less abrasive options for transplant recipients.”

“We hope [for]...[drugs] that...correct the cause of the damage...and...stop the fibrosis that leads...to renal failure...stem cells...modified in vitro to include the missing collagen[s] in

Alport...could be harvest[ed] and give[n] to Alport patients.”

#### Education About New Drugs

“[At the meeting, there were] so many participants that were under 18 years of age. I wish that the pharmaceutical company would collaborate more with pediatric nephrologists as well to explain how [a new drug] works and helps [sic] us to have a better [understanding] if the current clinical trial or cyclosporine is better for her.”

#### Miscellaneous

“The women who spoke of delayed diagnosis, and understandably not wanting to assume serious risk in a clinical trial when they didn’t know how serious their illness would be, was illuminating. I hope that these women start participating in a natural history study. Their natural course...will be very important for future drug development. They should also start a campaign to increase genetic testing for women who have preeclampsia.”

## APPENDIX 7: Incorporating Patient Input into a Benefit-Risk Assessment Framework for Alport Syndrome

In recent years, the FDA has developed an enhanced structured approach to benefit-risk assessment in regulatory decision making for human drugs and biologics.<sup>1</sup> The Benefit-Risk Assessment Framework involves assessing five key decision factors: *Analysis of Condition*, *Current Treatment Options*, *Benefit*, *Risk*, and *Risk Management*. When completed for a particular product, the Framework provides a succinct summary of each decision factor and explains FDA's rationale for its regulatory decision.

In the Framework table, the *Analysis of Condition* and *Current Treatment Options* rows summarize both the severity of the condition, as well as the nature and impact of the therapies available to treat the condition. The assessment provides an important context for drug regulatory decision making, providing information that can help inform the weighing of specific benefits and risks of a particular medical product under review.

The input provided by patients and patient representatives through the EL-PFDD Meeting on AS may inform the FDA's understanding of the *Analysis of Condition* and *Current Treatment Options* for this disease.

The information for *Analysis of Condition* and *Current Treatment Options* in the *sample* Framework table for AS (pp 87-88) draws from patient contributions at the EL-PFDD Meeting on AS held on August 3, 2018. This sample Framework table is an example of the type of information that may be anticipated for inclusion in a Framework completed for a drug under review for Alport syndrome.

<sup>1</sup> Commitments in the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) include further development and implementation of the Framework into the FDA's review process. Section 905 of the FDA Safety and Innovation Act also requires the FDA to implement a structured benefit-risk framework in the new drug approval process. For more information on the FDA's benefit-risk efforts, refer to: [fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm](https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm)

## Evidence and Uncertainties

Alport syndrome (AS) is a rare, genetic disease that often leads to end-stage renal disease (ESRD). The prevalence of AS in the US is estimated to be between 30,000–60,000 people.

AS is caused by a gene mutation in IV collagen, a structural protein that is necessary for normal functions of the renal glomerular basement membrane (GBM) and basement membranes in the inner ear.

The mode of genetic transmission defines three major forms of AS:

- X-linked AS: 60-70% of AS patients
- Autosomal
  - Dominant: ~20% of AS patients
  - Recessive: ~15% of AS patients
- Digenic: prevalence unknown

Dysfunction of the GBM leads to nephropathy, with hematuria and proteinuria, and in up to 90% of X-linked male patients by 40 years old, ESRD.

The defects in type IV collagen lead to hearing loss and deafness. 90% of X-linked male AS patients have some form of hearing loss by age 40.

Symptoms most frequently cited by patients as burdensome to daily life were: fatigue, anxiety and/or depression, and hearing loss. Anxiety and/or depression are driven by uncertainty of future health of the patient and/or children and siblings.

Females with AS often experience difficult pregnancies, including preeclampsia. The commonly held concept that females are merely carriers of the disease and are not severely affected is incorrect.

## Conclusions and Reasons

The genetic component of AS can lead to the inheritance of AS by multiple family members, across generations, conferring enormous stress on a family.

The three major symptoms of AS have harsh impacts on daily life.

- Fatigue and anxiety and/or depression restrict or prevent normal daily activities.
- Hearing loss is socially isolating; it affects social interactions and can interfere with performance at work or in school.

As patients approach ESRD, physical and emotional symptoms are exacerbated and dialysis and/or kidney transplantation are necessary.



## Evidence and Uncertainties

No curative or disease-modifying treatments are available for AS. Current therapies are non-specific; they most often include antihypertensive medications (ACE inhibitors, ARBs), statins to lower cholesterol, and medications to address edema, gout, and the non-specific symptoms of kidney failure.

To manage extra-renal effects of AS, patients use hearing aids and glasses for hearing loss and visual disturbances, respectively. Cannabis products are sometimes used for pain.

Kidney transplantation has a positive outcome in most cases but does not affect hearing loss. AS patients in ESRD who are awaiting a kidney transplant, or who cannot find or do not seek a transplant, rely on dialysis to sustain life.

## Conclusions and Reasons

ACE inhibitors and ARBs provide sub-optimal treatment to AS patients. These medications may delay, but do not halt or reverse disease progression. They are limited, in part, by hypotensive and hyperkalemic effects. ACE inhibitors and ARBs do not target the defects in type IV collagen that cause AS. They are contraindicated in pregnancy.

There is an urgent unmet need for effective treatments for AS. The AS community seeks therapies that will be safe, with tolerable side effects for administration over the course of the disease, and that will:

- Slow, stabilize, or reverse decline in kidney function
- Reduce fatigue
- Prevent or slow hearing loss
- Address co-morbidities associated with pregnancy in AS
- Be safe during pregnancy.

New agents that address the root cause of the disease are needed (i.e., agents that restore normal type IV collagen to basement membranes).