National Ataxia Foundation
Ensuring no one experiences Ataxia alone, until no one experiences Ataxia, period.
www.ataxia.org

Spinocerebellar Ataxia type 3 (SCA3)
FDA Patient-Led Listening Session

September 22, 2023

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Session Objectives

- To educate FDA staff on the complex issues, variety of physical manifestations, and body systems affected by this rare disorder.
- To educate FDA staff on the serious impacts of SCA3 disease manifestations on patients and their quality of life.
- To educate FDA staff on the scarcity of currently available treatments, tremendous unmet medical need, and preferences for future treatments and outcomes.

Topics Discussed

- An overview of SCA3, including the cause of disease, disease progression, symptomology, and the impact on families and caregivers.
- The symptoms and health effects most burdensome to people with SCA3.
- The inadequacy of current treatments and unmet medical needs of patients with SCA3.

Patients and Caregiver Representatives

- Derek, a 35-year-old SCA3 patient from Massachusetts
- Doug, a 51-year-old SCA3 patient, and his brother David, a 55-year-old caregiver from Texas
- Karen, a 61-year-old SCA3 patient from Colorado
- Keenan, a 35-year-old SCA3 patient from Texas
- Lucy, a 28-year-old SCA3 patient from California

Partner Organizations

National Ataxia Foundation (www.ataxia.org)

- Andrew Rosen, Executive Director, National Ataxia Foundation
- Dr. Lauren Moore, Chief Scientific Officer, National Ataxia Foundation
- Dr. Celeste Suart, Patient Engagement Manager, National Ataxia Foundation
- Kelsey Trace, Clinical Services Manager, National Ataxia Foundation
- Beth Bowerman, Clinical Services Coordinator, National Ataxia Foundation
- Aimee Alcott, Research Services Assistant, National Ataxia Foundation

African Americans with Ataxia Association (www.aawataxia.org)

- Letitia Diggs, Executive Director, African Americans with Ataxia Association

Ataxia UK (www.ataxia.org.uk)

- Dr. Julie Greenfield, Head of Research, Ataxia UK

Israeli MJD Association (www.mjd.org.il)

- Tomer Hillel, Chairman, Israeli MJD Association

MJD Foundation – Australia (www.mjd.org.au)

- Libby Massey, Director of Research and Education, MJD Foundation

FDA Divisions Representatives

Office of the Commissioner (OC) – *1 office*

- OC/OCPP/PAS – Office of Clinical Policy and Programs/Patient Affairs Staff *(organizer)*

Center for Biologics Evaluation and Research (CBER) – *3 offices/divisions*

- CBER/OCD – Office of the Center Director
- CBER/OCD/PS - Office of the Center Director/Policy Staff
- CBER/OTP/OCE/DCEGM/GMB2 - Office of Therapeutic Products/Office of Clinical Evaluation/Division of Clinical Evaluation General Medicine/General Medicine Branch 2

Center for Drug Evaluation and Research (CDER) – *4 offices/divisions*

- CDER/OND/ODES/DCOA –Office of New Drugs/Office of Drug Evaluation Science/Division of Clinical Outcome Assessment
- CDER/OND/ON – Office of New Drugs/Office of Neuroscience
- CDER/OND/ON/DNI - Office of New Drugs/Office of Neuroscience /Division of Neurology I
- CDER/OND/ORDPURM/DRDMG -Office of New Drugs/Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine/Division of Rare Diseases and Medical Genetics

Center for Devices and Radiological Health (CDRH) – 6 offices/divisions

- CDRH/OPEQ/OHT1/DHTIC – Office of Product Evaluation and Quality/Office of Health and Technology 1/Division of Health and Technology IC
- CDRH/OPEQ/OHTIII - Office of Product Evaluation and Quality/ Office of Health and Technology III
- CDRH/OPEQ/OHTIII/DHTIIIB - Office of Product Evaluation and Quality/Office of Health and Technology III/Division of Health and Technology IIIB
- CDRH/OPEQ/OHTIII/DHTIIIC - Office of Product Evaluation and Quality/ Office of Health and Technology III/Division of Health and Technology IIIC
- CDRH/OSPTI/DAHRSSP - Office of Strategic Partnerships and Technology Innovation/ Division of All Hazards Response, Science and Strategic Partnerships
- CDRH/OSPTI/DAHRSSP/PSE - Office of Strategic Partnerships and Technology Innovation/ Division of All Hazards Response, Science and Strategic Partnerships/Patient Science and Engagement

Non-FDA Attendees

- NCATS – National Center for Advancing Translational Sciences
- Reagan Udall Foundation

Session Speaker Notes

An Overview of SCA3 – Dr. Lauren Moore

Good afternoon, my name is Dr. Lauren Moore, and I am the Chief Scientific Officer of the National Ataxia Foundation. We are the largest non-profit organization that supports patients with all forms of ataxia and we represent more than 13,600 members around the globe. I'd like to quickly acknowledge a few other patient organizations; the African Americans with Ataxia Association, Ataxia UK, the Israeli MJD Association, and the MJD Foundation of Australia, that have provided helpful guidance in preparation for this meeting.

I'm very grateful for the opportunity to speak today about one of the most prevalent genetic diseases that we represent, called Spinocerebellar ataxia type 3 or SCA3. This is a disease that has defined my personal and professional career for the past decade. I am both a PhD-trained neuroscientist with a background in SCA3 gene silencing therapeutics, as well as a member of a large SCA3 family in which many of my direct relatives are impacted. So today, I'll be referring to my research background as well as to my own personal experience with this disease to hopefully provide a fuller picture of its real-world impacts.

Through today's patient and caregiver testimonials, we hope to bring to the forefront the profound impact that this devastating disease has on the daily lives of SCA3 patients and the large unmet medical need of this population. We also hope to provide the FDA with the knowledge necessary to guide drug developers working in the ataxia space, and to help inform future regulatory decisions.

Let's begin with what is SCA3. SCA3 is the most prevalent autosomal dominant ataxia, with an estimated worldwide prevalence of about 1 in 40,000. I'll note that it is difficult to accurately assess the prevalence of this disease due to low testing rates, delayed or incorrect diagnoses across all ataxias, and a historic lack of patient registries. There is also high regional variability in SCA3 incidence, with high prevalence noted in Portugal, Brazil, China, the Netherlands, Japan, United States, Canada, Germany, and Australia.

Symptom onset in SCA3 typically occurs in adulthood between the 2nd and 5th decade of life. I'd like to emphasize here at the beginning of this meeting that SCA3 is a devastating, severely disabling, and life-shortening disease for which there are no existing treatments to slow or stop disease progression.

SCA3 is caused by a CAG repeat expansion in the gene ataxin-3, which encodes a protein of the same name. In all individuals, both ataxin-3 alleles contain a repetitive sequence of the trinucleotide CAG, which encodes the amino acid glutamine. In unaffected individuals, this repetitive tract ranges in length from about 12-44 repeats. However, in individuals with SCA3, this repetitive sequence expands to above 60 repeats in one of the ataxin-3 alleles, and can expand to longer than 80 repeats. Because the repeat is located within an ATXN3 exon, this results in an expanded polyglutamine sequence in the translated mutant ATXN3 protein. This mutation has been shown to disrupt a number of neuronal homeostatic processes through a likely toxic-gain-of-function mechanism.

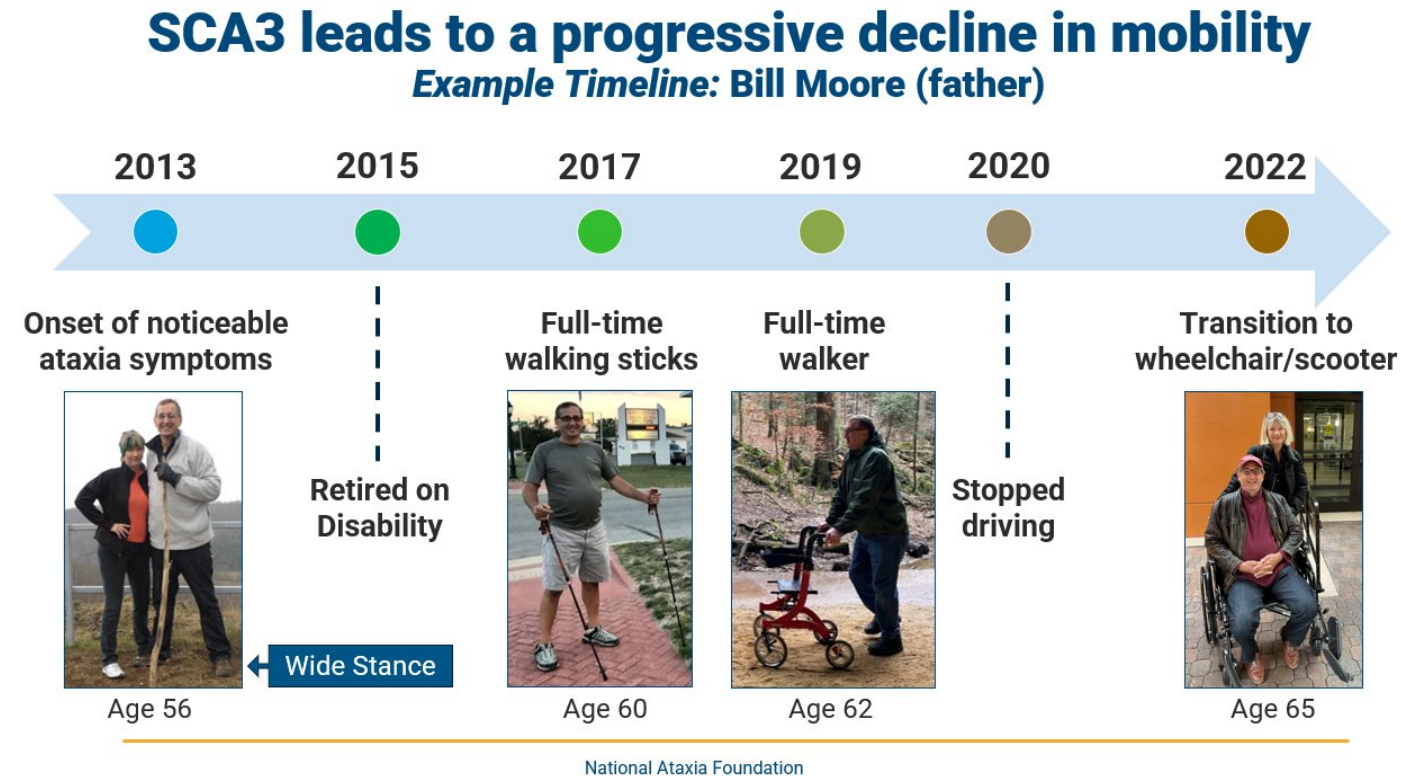
Despite expression of ATXN3 throughout all cells in the body, SCA3 is characterized by selective, progressive loss of neurons primarily within the pons, cerebellum, and brainstem, as demonstrated by significant thinning in these regions in the MRI image shown here relative to a healthy control brain.

The most prominent clinical feature of SCA3 is progressive cerebellar ataxia. You can see a typical ataxic gait in the video shown here. The ataxic gait is marked by poor balance, wide stance, lateral veering, stuttering starts and stops and general uncoordinated movements. In addition to ataxia, many SCA3 patients also experience a number of other distinct progressive motor symptoms including deterioration of fine motor skills, tremors, parkinsonism, rigidity, and dystonia.

The gentleman in this video happens to be my Dad, Bill. In the next slide, I'd like to spend a few minutes focusing on his personal journey to illustrate how SCA3 leads to a progressive decline in mobility.

My Dad's first noticeable symptom, which I'd estimate began around 2013, could best be described as a general increase in klutziness. Although he was still very mobile, you can see in this photo of him and my mom that he had already developed a wide stance while standing still to overcome his imbalance.

This picture in 2013 was taken from a week-long backpacking trip that I took with my parents that year. These annual 50 to 75-mile hiking trips used to be a favorite tradition of me and my incredibly outdoorsy Dad, but unfortunately, this ended up being our last hiking trip.



Progress of ataxia symptoms. Diagram by Lauren Moore.

Just four years later, my Dad was forced to use walking sticks full-time to help safely get around and by 2019 he had transitioned into using a walker. Today my Dad is going through the difficult transition from a walker to a wheelchair or scooter. I want to point out that this decline in mobility went alongside major milestones that decreased his independence and quality of life. My dad retired on disability at age 58 and gave up his driver's license in 2020. Both of these decisions were directly due to the progression of his ataxia and other SCA3-related symptoms.

In addition to impairments to gait and other voluntary movements, SCA3 has broad impacts on other body systems that can greatly impact quality of life. Notably, many of these symptoms are progressive, becoming increasingly debilitating over time. And as you'll hear from today's panelists, a patient's severity of symptoms can vary greatly from person to person.

Oculomotor dysfunction can significantly impair patient's vision. Common issues include diplopia or double vision and nystagmus. Most patients will require prism glasses with increasing prescriptions throughout their lifetime. Double vision was in fact the ultimate reason that my dad decided to quit driving.

Urinary incontinence and bowel symptoms can lead to further isolation for patients, and daily reliance on adult diapers, portable urinals, and self-catheterization are not uncommon.

SCA3 can lead to a variety of sleep disturbances that inevitably contribute to daily fatigue and poor quality of life. Several common issues include REM sleep disorder, restless legs, insomnia, and painful nightly cramping.

Patients will exhibit progressive dysarthria characterized by gargled and slurred speech, greatly diminishing one's ability to work and communicate as the disease progresses.

Dysphagia leading to swallowing impairments is one of the most dangerous symptoms in SCA3 as it can lead to frequent choking and puts patients at a high risk for aspiration and pneumonia.

Peripheral neuropathy can lead to severe neuropathic pain and tingling. Interestingly, recent studies point to the possibility of the peripheral nervous system playing a more significant role in disease progression.

Finally, the direct and indirect impact of SCA3 on mental health cannot be overlooked. SCA3 patients are at high risk for a variety of psychiatric disorders including mood disorders, depression, complaints of cognitive fog, and suicidal thoughts.

Individuals with SCA3 are also at a very high risk of falls and fall-related injuries as a result of their ataxia and other symptoms. Studies have shown that more than 80% of patients experience at least one fall per year. Additionally, one study found that 85% percent of fallers reported injuries, and 31% of fallers had suffered a fracture or joint dislocation.

I know personally I have seen my Dad fall probably over a hundred times. Most of these falls have thankfully led to only minor bruises and scrapes, but a few major falls have led to serious injuries that have put him in the ER with a broken ankle, shattered knee, concussion, or need for stitches. I've highlighted just a few of the acute and sustained injuries that he has accumulated as a direct result of his ataxia here.

Unfortunately, there are no approved treatments capable of slowing or stopping the relentless progression of symptoms in SCA3. Most patients will start and stop a wide variety of medications and rehabilitative therapies throughout their lifetime in the hopes of attenuating the impact of their symptoms on activities of daily living. I've listed just a few of the major categories of treatments that patients are typically prescribed. Note that most of these prescriptions are going to be prescribed off-label for these patients, and their utility and appropriate dose for the treatment of SCA3-related symptoms have not been assessed in a clinical trial.

SCA3 is ultimately fatal, with death typically occurring 15-20 years after first symptom onset. Unfortunately, about all patients experience a very low quality of life towards the end stages of their disease, which will be marked by very poor vision, inability to communicate, sit independently, eat or drink independently, or perform basic personal hygiene. They will often struggle with maintaining weight due to frequent choking. Psychiatric disorders such as clinical depression also are very common.

Grandmother, Liz Moore, in 1998 (left) and in 2013 (right), two months before her death, demonstrating long-term physical effects of SCA3. Images from Lauren Moore.

I know that each of these points was true of my grandmother during her last years. Here I'm showing pictures of my grandmother taken about 15 years apart, at the beginning of her symptoms and only a few months before her death. She was bedridden for about the last year or two of her life, unable to communicate or perform any independent tasks. She ultimately succumbed to complications related to aspiration pneumonia, which is one of the most common causes of death in SCA3.

Thankfully, there has been have been advances in understanding of SCA3 accompanied by a marked increase in drug development for this devastating disease. Here I'm showing some of the progress that has been made towards the development of treatments for SCA3. There are several programs that have advanced into clinical trials, however, there remain no treatments for SCA3 patients like my Dad whose symptoms continue to get worse every day.

Before I pass the mic on to our fantastic panelists, I want to quickly discuss what I think is one of the most difficult aspects of this disease. SCA3, like many dominant diseases, is a disease of families, not individuals. Due to its later onset, it is often marked by decades of fear, guilt, dread, and often shame by those with the disease, their spouses or partners, the unaffected siblings, and those who remain at-risk and untested. In my family's case, my grandparents had 8 children, and half of those children including my dad inherited the SCA3 mutation. Those four adults have gone on to have a combined total of 14 children who are considered at-risk for this disease, and from those 14 children, there are now 9 great-grandchildren. Only four of those 14 adult children have been tested for the disorder. Only one of those grandchildren has tested positive so far. My older sister Jess is thankfully still pre-symptomatic and is doing all that she can to get involved in SCA3 clinical research while maintaining a healthy lifestyle as she waits for a treatment that might prevent her onset.

I'd like to close by quoting my mom, Sue, from a recent presentation that she gave as the wife and caregiver of someone with SCA3: "The generational impact of ataxia sets it apart from illnesses without a genetic component. There's tremendous emotional fatigue for many of us over concern for our children. We have friends with ataxia who have children experiencing symptoms at a younger age than their own onset. This level of emotional pain can't be adequately put into words."

Community Perspectives – Past, Present, and Future

Derek

Past

Hi, my name is Derek. I was born into a loving family in Quincy, Massachusetts (just south of Boston). I remember both of my parents being hard workers. I remember my dad's slow decline in his physical health. At first, it appeared as if he were just clumsy. My mom was very concerned about my dad's worsening condition. She was able to eventually find out what he had: SCA3. She found a general neurologist to care for my dad, without knowledge of NAF.

Later, he had to transition to use a cane, which he definitely did not want to use. Then a walker for a longer period of time, and then eventually a wheelchair all within approximately a 10-year span.

The hardest part of ataxia is seeing your parents suffer through it. But at least I did not have to worry about it, right? I remember feeling quite depressed when I found that I had a 50-50 chance of inheriting this disease. What would become of my life if I carried this disease? Would I have to go through this disability that slowly eats at you, making you lose all independence?

I met my wife, then girlfriend, after college in 2013. I finally mustered up the courage to tell her about ataxia and my chances of getting it. She stayed by my side and we got married in 2016. Before thinking of starting to have kids, I got tested and diagnosed with SCA3 in late 2016. I was grateful that I had been able to get diagnosed earlier than my dad, just so I can be more prepared, but I still tried to live my life as if I did not have ataxia since symptoms were still not severe, and I did not want to face the impending issues. I first noticed that the ataxia was getting worse when I noticed that my gait was off while walking in 2018.

That's when I started using walking sticks. "A young man's cane", as my neurologist at the time described it. One day after a church service, one of my wife's friend's father noticed that I had them. My wife was wondering what he was thinking so she asked her friend. Her friend said that the father was thinking that "Derek must've gone for a hike".

The issue that I had with the walking sticks was that my disability was not as obvious to others, for example, I could have just been hiking. I also remember not wanting to use the walking sticks at all. Now, looking back at it all, I realize that it was definitely my sense of pride, but at that time, I did not want to admit that ataxia was going to be a part of my life.

I started speech therapy, to gain good habits, in speaking slowly and clearly. I started doing speech therapy early, before symptoms arose because I was afraid of losing my ability to speak clearly, something that my dad and many others with SCA3 struggle with. I joined a local NAF support group around 2019, which helped me meet others who have experienced the same issues that I have been having.

I started using a rollator, or a walker with 4 wheels, in 2020. The biggest difference that I noticed was that I wasn't bumped into as much at Costco, when using the rollator versus the walking sticks. That and I noticed how ataxia would change me. I also did physical therapy to help me use the rollator more effectively. I started using a wheelchair in 2022, after having a fall and breaking my collarbone. We also went from renting an inaccessible place to owning an accessible home, which has been very helpful.

Present

Now, as a 35-year-old married man, having ataxia does prevent my family's decision to have kids, even though we did hear about pre-implantation to screen for ataxia. If my mom and dad had pre-implantation done, I would not have been born.

SCA3 requires me to work fully remotely, because of my situation. Having that opportunity to still be working helps me mentally and financially.

I participate in a clinical trial at Mass General Hospital, an Ataxia Center of Excellence from NAF. I am very grateful to be seen by an ataxia center versus a general neurologist. Currently, I've been seeing a physical therapist who has been helping me a lot with transferring from one seat to the floor or back into my wheelchair. We have been trying to walk again, with an upright rollator.

I constantly want to complete tasks but I've had to learn to slow down and be OK with not having things 100 percent complete. My wife helps me a lot and I feel bad about not being able to help with many of the chores, but I am able to handle less physically intensive things like the finances, budgeting, and folding laundry. I also enjoy the adaptive sports programs, like wheelchair basketball, cycling, and rock climbing.

I find joy in living as a child of God, knowing that I was knit together in my mother's womb. That I was created by Him without mistakes. As even what I think might be a mistake may be God's way of showing that there is hope.

Future

I am very grateful to participate in clinical trials and to get travel reimbursement.

Ataxia is a progressive disease, meaning that it affects my life more and more over a long period of time. I think prioritizing speech and balance is very important for me. Reducing these declining symptoms over time would be very helpful. Having speech therapy and physical therapy may be helpful, but it only helps build good habits. It does not delay the onset of losing your balance, ability to talk, or ability to eat.

Even if it does not cure the disease, slowing down the progression of this disease is what I am looking for in treatment options.

Doug and David

Past (David)

Doug and I come from a large family with an extensive history of SCA3. My earliest memories of my grandmother were of her in a wheelchair. Grandma had two girls and two boys. 3 of the 4 had SCA3, including our Dad. In a strange twist, my mom and her sister both met and married distant cousins who were both descendants of an individual with SCA3, my Dad and my uncle. Unfortunately, both men became symptomatic with SCA3. So Doug and I have generations of cousins on both sides of our family with SCA3. Family photos from years past tell the tale. There are always people in pictures in various states of progression; with some pre-symptomatic, others using assistance devices, and finally, those not pictured because they couldn't get to the event, or they had succumbed to the disease. Needless to say, the social and economic costs have been devastating.

I remember being at a community dance hall when I first recognized symptoms in my father. He was dancing with Mom at the time and his movements were so stiff, rigid, and uncoordinated. I remember feeling embarrassed, and later ashamed for that embarrassment.

I was fortunate to have the chance to go to college and serve in the army. While away, it became increasingly difficult to understand my Dad over the telephone. His speech was uncoordinated, and when he would get excited, the volume would often change dramatically. To a bystander, he may have appeared mad, but he just couldn't control it.

Perhaps most devastating, was when I recognized the symptoms in my sister Peggy. We were at a Christmas gathering and she was passing out gifts. She stammered, then found her balance, and proceeded. But I had seen that stammer before, and the fact that my sister was just in her 20s was devastating. Until that point, I thought of ataxia as a distant possibility. But seeing it in Peggy made it very real, and very present. Not long after that, Peggy told me she thought of ending her life.

SCA3 had a devastating impact on Dad, Peggy, and all of us. My Dad was a businessman and a volunteer firefighter. Peggy became a school teacher and a mother. But Dad was forced to retire at 54 and Peggy quit teaching in her 30's because the demands were so great. In their own way, my Dad and my sister both went from being reliable leaders in the community and family to being someone who needed to rely on the community and family.

I lived most of my life in fear of having SCA3. For the longest time, I put off getting tested. Why would I? Having lived the multi-generational struggles with SCA3 there is one resounding message that the medical community made clear . . . There is no treatment for SCA3!

The clinical manifestations of SCA3 materialize over a long time, sometimes decades. This is a blessing of sorts. In the early days, the disease progresses slowly. The curse, of course, is that in the end, the disease progresses slowly as well. Peggy was in her 40s when she passed away. But for the ataxia, she was in splendid shape. This makes for a sinister, prolonged, and painful end. As a final gift to her children, Peggy committed her brain tissue to the University of Michigan for research. Her hope was that this final contribution might, in some small way, provide the insights needed to ensure that *future* family members would not have to hear . . . There is no treatment for SCA3.

Present (Doug)

I work for [US-Based Bank] as a Project Manager. They have been good with respect to accommodating my challenges. But it has not been easy. SCA3 is a rare disease so I constantly have to educate my

managers, coworkers and human resource staff at [US-Based Bank] about the progressive nature of the disease. As recently as a few years ago, I would travel to different project sites to supervise the progress. However, because SCA3 has diminished my mobility and energy levels, I no longer do that. Further, I no longer travel to the downtown office for my daily routine. This is certainly beneficial to me, but it comes with costs. I miss the camaraderie of working with my colleagues, and I know I miss out on bonuses and compensation increases because of the nature of being "out of sight, out of mind".

One of the most devastating things about ataxia is its effect on my family. Not long ago, I was happily married, taking regular family vacations and visiting relatives. However, as my symptoms advanced, it put pressure on my relationship with my wife, where previously there was none. Ultimately, she filed for divorce 2 years ago.

I now live on my own and have routine visits with my boys L and B. L is 15 and he's learning to drive a car. This is timely. I can still make short trips driving, but my response times have slowed. Hopefully, when L turns 16 in November, he will be ready and willing to drive more, providing some much-needed mobility to our lives.

Getting to my Special Ataxia Neurologist appointments downtown can be difficult. I'm fortunate that thus far David has been able to make that work within his busy schedule.

One of the things I'm proud of doing is that I participate in the READISCA study. This means that every year for the last 4 to 5 years I've endured a series of tests at Methodist Hospital downtown. I also travel 1 to 2 times per year for an MRI at the University of Minnesota. I'm hopeful that these efforts will help lead to a treatment. I'm tired of hearing . . . There is no treatment for SCA3.

Future

David: Doug and I have a lot in common. One of the things we have in common is hope.

Doug: Scientists have been studying SCA3 for decades. We are encouraged that pharma companies are now involved as well. More than anything, we are hopeful that they will find a cure for SCA3.

David: We expect a cure is still years in the making. In the meantime, we are hoping for effective treatments to help reduce the devastating effects SCA3 has on speech, balance, swallowing, and more.

Doug: When I think about treatments, they don't need to be perfect. Everything I do right now involves tradeoffs and risks. If I want a glass of water, getting to the sink involves risk. I would gladly collaborate with my doctor to discuss the tradeoffs of various treatment options. Unfortunately, as we've said several times, there is no treatment for SCA3.

I'm also not too squeamish about treatment options. Given the choice, I would prefer a pill over a shot. I would also prefer a shot over a spinal tap. But at this point, that's really a matter of convenience. It's important for me to maintain my independence. To do that, I need to retain my current level of mobility, as well as the ability to swallow without choking. I need a treatment option soon! Ideally, it would be great if future treatments included the ability to interact with doctors remotely via telemedicine.

David: This brings us to an important point: finding a doctor that specializes in SCA3 is difficult.

Doug: It takes a lot of time and energy to travel to appointments. For rare diseases like SCA3, I'd rather talk to a knowledgeable doctor in another state, *over Zoom*, than to speak to a local doctor who is clueless.

David: Finally, it's important not to neglect the mental health impacts of SCA3. We've observed multiple generations of our family deal with ataxia. With no treatments, the outlook is very bleak, and that can be tremendously straining with respect to mental health.

Doug: It can be so bleak that some patients just want to give up.

David: I told you earlier about Peggy considering ending her life. Fortunately, Peggy became infected with the same hope that Doug and I share, and that never happened. Together, we are hopeful that we will soon be able to say . . . there is a treatment for SCA3!

Karen

Past

I am presenting on behalf of my Great grandfather, my grandpa, my father Hugh, my sister Diane, and unfortunately, I need to now add to this list my son. I grew up hearing that Multiple Sclerosis runs in our family. Family reunions were full of canes, walkers, and wheelchairs.

When my father started experiencing neuropathy and loss of balance, he wasn't satisfied with that explanation and he started a multi-year journey of seeing every neurologist he could find to get a diagnosis in 2008. The quest finally took him to a neurologist 6 hours from his home. The doctor administered the genetic test and got the diagnosis of SCA3 in 2008. But the neurologist didn't know anything about the disease – they just said "Get a cane."

My father told me his diagnosis and the genetic implications, so when I first experienced neuropathy at age 48, I knew what it was. I was formally diagnosed in 2016 so I could enroll in the READISCA natural history study.

I am one of 3 daughters. My sister Diane has been symptomatic since age 28, but she refuses to get a formal diagnosis. That is her way of dealing with this. I have 3 sons. I didn't know when I conceived them that I could give them this terrible condition. Unfortunately, one of my sons was diagnosed in June.

Present

I am currently 61 years old, and living in Colorado. I was trained as a hydrogeochemist, and I am currently the Chief Business Development Officer of an environmental clean-up consulting firm. People ask me all the time, Why do I work? Two reasons – first, insurance, and second, to distract myself from pain.

Managing pain is my biggest challenge. I have to deal with neuropathy from my feet up my legs and into my hips, and in my hands. There is a common misconception that Neuropathy isn't numbness – it's intense pain. My neuropathic pain changes character with time of day, temperature, and amount of recent exercise. Sometimes it's like sandpaper rubbing on your legs, or if you banged your funny bone but doesn't fade. It can also be intense cold or feeling like you are "on fire". I can't sit for more than an hour and not on hard surfaces at all. I can't wear shoes, and as such I can't go out much. I am very hampered in my job as I can't sit still to meet with clients.

Other symptoms I experience include double vision, wobbly gait, nystagmus, choking, and muscle weakness. My work is impacted as I can't see well or get around without wobbling. I can no longer attend conferences. I have never been a recreational drug user, but I need cannabis to be able to sleep.

I work very hard to maintain a positive mindset – but that is hard when I know I will never experience another pain-free minute for the rest of my life.

I am blessed to be close to UC Anschutz so it's logistically easy to participate in clinical studies. I participate in a natural history study. There have only been 2 trials for drug therapies I have tried to participate in. I couldn't get into the first because my symptoms aren't easily measurable. I am currently enrolled in the second, but enrollment has been paused and I'm worried they will cancel the study.

Future

As a person living with ataxia and understanding what my future looks like, I'm obviously hoping for a cure in time to benefit me. Or at the very least, new medication that will alleviate or mitigate symptoms to make my life easier to live. I'm not sure there's time to help me. But I need this hope to be realistic for my son.

We know so much more about disease progression based on private research and we know the opportunity exists to treat or even cure this disease before symptoms manifest. We need to find more ways to take advantage of these early treatment opportunities.

And we don't need to only be shooting for a cure – the benefit to my family would be enormous from a medication that would just slow progression or ease pain or alleviate symptoms like tremors or choking. Small improvements are worthwhile goals as well.

As an ataxia patient, I am at risk every day of losing more and more movement and cognitive abilities. To me, the risks associated with a clinical trial pale in comparison. I've already demonstrated my willingness to support trials and I will be in this trial for at least another year.

But more importantly, as a mother, I would move heaven and earth to find a cure before my son has to live with the pain that I live with. He has so much potential to give back to humanity if given the chance. I know I can't save him from all of life's challenges, but I want to save him from this.

Keenan

Past

The quality of life hasn't been the greatest for me or my family throughout our lifetime. My grandfather took care of my grandmother, which affected his quality of life while the Ataxia affected hers gradually, but dramatically until she passed in 2010. I saw my father's and mother's quality of life slowly diminish over the years. Growing up watching my dad lose his ability to walk has been traumatizing, to say the least. My older sister is asymptomatic, and I have two untested kids. I got a vasectomy at age 31.

Also, the quality of my life has been in question from time to time with all the falls, balance, and coordination issues that I have constantly that have a significant impact on my physical, emotional, mental, and financial health. I use a cane quite often now which helps. I was raised around traumatic events that were made to seem normal and now I'm trying to navigate my own journey on how to raise my kids.

For the last 4 years, once a year, I've been a test subject in a Natural History study for SCA3. I drive to Houston each year for an annual "progress check" of how my Ataxia has progressed. They do the same tests every year, and then right after I have to drive another 4+ hours back home which is not easy.

I've tried to participate in multiple clinical trials, but they haven't worked out. There was a Phase 1 trial where I was strung along for a month at a time for 5 months, after waiting a year for the study, just to never hear back from them. After waiting a year for the study, they never got back to me. I was turned down for another Phase 1 trial after flying to Phoenix, taking time off work, and covering some of the costs myself.

The most recent study, for an injection medication, lost funding at the very last moment. This was frustrating because I had so much hope and then it was all taken away from me. Frustrating because I had been hearing for years there is no treatment, then this was taken away from me.

Present

This is how ataxia affects me in my daily activities.

Physical: I fall often, sometimes causing other injuries, and there is an immense amount of chronic pain, normally at night, when I stand, all the way from the tops of my knees to the balls of my feet. As well as there is a sharp chronic pain on the bottoms of my feet every time, I take a step. Running and jogging aren't possible anymore, my knees lock and I fall when trying to run or walk fast and my brain is having issues coordinating the multiple movements it takes to run. I have to do some type of physical exercise daily. Ataxia doesn't take a day off, so neither can I. Handling utensils and cups and stuff is possible but causes a lot of spills while eating and making food. and spills happen quite often when making food and eating. I fall back down quite often when going from sitting to standing and I plop into chairs when I sit down. Driving is difficult, with blepharospasms that I treat with OnabotulinumtoxinA (Botox®) injections in my eyelids, and I also have persistent double vision that I've had to adapt to as well. I get styes because my eyelids don't work great. Also, even while on the medication that I'm prescribed, I still have a real urgency to urinate frequently daily. I think yesterday it was 15-16 times. I'm a very busy person so I don't always have access to a restroom immediately, so I'll pee a little in my pants, not on purpose, attempting to hold it quite often. To that point, I'm currently prescribed 14 different medications.

Mental: I've become more and more reclusive and when I do go out I feel like a burden to anyone I'm with because I'm a "fall risk" at all times and things can get awkward around new people. Goes to NA meetings just for the company.

Emotional: I've become more and more introverted and allowed a lot of folks to use me because of the lack of attention or affection that is put out there anymore. I go to NA meetings just to get out of the house and be around people. I know I'm different and it's frustrating when someone tells me that I'm not special and they can't empathize with me and my current situation because it's so rare. It's a very alienating disease. I feel even more alienated working from home but honestly, I believe that commuting in would be even worse. You already feel alienated, because no one can really empathize with you, which is already hard enough. You're also at the mercy of having to rely on a substance to change how I feel every day just to function.

Financial: I pay over 2k a month to insure myself as well as my kids. I'm starting to accumulate debts from multiple hospitals and on top of that I get double billed or incorrectly billed by a lot of my providers, so I have no idea how much I owe to whom.

Performing almost any task is difficult, SCA3 affects literally everything that I do. If I let it, it impacts the quality of my life/attitude/demeanor, drastically to the point of self-harm. I've considered suicide to end the pain which is really hard. The fact that you're slowly losing your ability to do things that were once routine is depressing, frightening, frustrating, and disheartening.

Future

As ataxia patients, we are more than test subjects, we have been diagnosed with an untreatable, uncurable, invisible, disease that slowly takes away our quality of life, and that lowers public perception of us due to the nature of its effect on the cerebellum. You add the fact that most people (physicians included) have never heard of SCA3 and it can get pretty depressing dealing with these symptoms every day all day and no one has said they could help in 30+ years, fosters a feeling even of being more alienated than the day before.

So, what would help? First, having funding for travel, it has to come out of pocket right now. There are only ~150k of ataxia patients (with different types) in the US. So for clinical trials to be accurate there needs to be more available funds to travel these patients nationwide and even some internationally. The SCA community is ready to sign up for a possible treatment, even if it's just a clinical trial. Hope is hope. And I know every single patient I talk to is ready to help.

Second, make future and current clinical trials (recruiting, ongoing, and completed) data more available. I understand it goes to the clinical trials website, but that is difficult to navigate. Having somewhere where you could go to see real-time data would be helpful. That's all from me.

Lucy

Past

Being the last speaker, my heart goes out to every speaker and their stories. It is 9 minutes of storytelling, but for us it is the rest of our lives. With that, I will start my story.

My name is Lucy. I am 29 years old with SCA3. I live with my husband in California, but now I am in Vancouver with my Mom. My family comes from China, and my maternal family is the gene carrier. My grandmother, my mom, and all her three siblings show symptoms of SCA3. Then there's me.

My grandmother passed away at the age of 72 in China, from causes attributable to SCA3. Five years prior to her death, her quality of life had already declined to the point where she attempted suicide. By that time, she couldn't eliminate her bowels independently, she couldn't swallow food, and she was wheelchair-bound. Living in rural China, on the 4th floor of a building without an elevator, her living environment didn't offer her a way out.

My mother is now 56, and lives in Vancouver, Canada. Her discovery to SCA3 started from injuries. At 43, she fell on the stairs to the basement and fractured her toes. She rested like any good patient, not knowing that that would be the last time she could walk independently. It all started from this fall, and then another, and then another. After a couple injuries, her imbalance caught up to her from being immobile for so long. After a year, she went from canes to a walker, and after another year, from walker to the wheelchair she's in now. In that period, she learns of her shrinking cerebellum. And after a decade, she's finally diagnosed with SCA3.

I was diagnosed at age 25, 5 years after the first sign showed. There were many signs, but I didn't take them seriously. For example, I was called out for my poor balance while hiking with friends. Soon after, I dislocated my elbow while running. Then, there was the ski trip, where my then boyfriend got so frustrated with me after spending the entire time patiently teaching me, and I just kept falling and couldn't stand up. My boyfriend, now husband, knew something was wrong at the time. This led me to seek medical help, which then led me to a diagnosis.

Ataxia Past. Image created by Lucy.

Present

As I watched ataxia eating away at my grandmother and mother's lives, it was terrifying to think about my own future. The thing about SCA is that it's a slow-acting agent. In the early days, it fools you into thinking that you are perfectly normal. It's just another bruise on the knee, right? As it progresses, it sneaks up on you and eats away at your quality of life.

On a daily basis, nobody understands how much humility and strength it takes for a person to go through life risking falls every day. The physical instability accumulates immense exhaustion in the body and the mind. Basic things everyone needs to do to live becomes a mechanical challenge. How do I bend down to pick up the laundry basket without falling into the basket? How do I get up from the toilet without sitting back down several times? How do I stop wobbling back and forth when I'm standing waiting in line? And because my body works extra hard just to keep me afloat, I get fatigued a lot quicker and most days, I feel like I am in a fish tank drowning in dizzy spells. They add up.

Social encounters also became a luxury after my SCA3 progressed. I try to plan restaurant visits where the food won't make me cough and look like a COVID hazard. I decline invitations later in the day where poor vision makes it harder to balance. In the end, you give up trying to socialize. People don't want to hear you complain, people don't want to always accommodate you. We who have this disease know that even our loving partners and family have limits to their compassion, and need a break from the attention and needs we have. My husband described it as "having to constantly worry about a part of your body that you have no control over, but it keeps getting hurt".

I carry a cane when I go outside, so most of my falls happen at home. So the bad times are mostly hidden from the public. It took me 3 years since diagnosis to build up enough mental immunity against this disability. Since then, I've joined an oral medication clinical trial for ataxia, and have been on it for two and half years. And most recently, I finished three In vitro fertilization cycles and now have three ataxia free embryos in the freezer. Getting an early diagnosis made it possible for a chance to curb progress and plan appropriately for what's to come.

Ataxia Present. Image created by Lucy.

Nowadays, my mother is wheelchair bound raising my teenage brother alone without a caregiver. I have monthly calls with my mother where she cries and tells me she's trying her best to live but doesn't have the strength to continue. A day in her life looks like this – wakes up and meditates, then gets tired, tries to cook, then gets tired, tries to read, then gets tired. As the days go by, her will to continue to try to do "something" diminishes. And she ends the day feeling defeated. And the next day the same defeatedness returns and compounds. She has daily home support workers to help her shower. That's her only source of social connection and some happiness. She attributes ataxia to everything, including her divorce. For her, ataxia is a life sentence that she's living.

Future

As I look ahead, I am hopeful but also scared. I am scared that being pregnant will cut my life short because the chance to continue receiving treatment on a clinical trial will end as soon as I am pregnant. This mere nine months can mean a rapid progression that I cannot reverse.

If possible, I recommend giving female patients a chance to rejoin a given clinical trial after they are relieved from their mother duty and is clinically safe to do so.

I hope in the future there is equal access to the same clinical trial across different study locations. One way to increase equal access to studies is to centralize the upfront recruitment process. Deadlines and available spots per location should be communicated timely and with clarity.

Interventional studies where half of the patients never actually receive the treatment, but are on placebo the entire time are challenging. For those that do not receive the treatment, the value of the study is significantly lowered unless they go on to receive the treatment after a placebo.

With early diagnosis, patients have a better chance to protect their future just like I do. I hope future clinical trials will encourage early diagnosis, champion equal access, and are designed to balance the value to the pharmaceuticals and the value to the patients.

Ataxia Future. Image created by Lucy.

Summary of Key Points – Dr. Lauren Moore

I want to thank each of our speakers for sharing their extremely personal stories today. Everyone's story and experience with SCA3 is unique and these are just a sampling of the over 5,000 individuals likely affected in the US. As we close this portion of the session, I want to highlight a few key points that I hope each of you will take away from today's session.

First, **SCA3 is a disease of families and there are generational impacts** that ripple out across generations. For me and my siblings, SCA3 has meant having to come to terms with two fates --- eventually becoming a burden to my partner and family and suffering the same disease journey as my dad OR carrying the life-long guilt of testing negative while watching your parent, aunts and uncles, siblings and cousins suffer that fate instead.

Second, **SCA3 causes a wide variety of symptoms**, and patients are interested in treatments that can target multiple symptoms. Third, for folks facing a SCA3 diagnosis, **small changes in symptoms can make a big difference**. The community is interested in treatments that slow down disease progression, even if it is only an incremental change. In addition, as more and more patients are getting tested earlier in their lives, people are very interested in the development of pre-symptomatic treatment options.

And finally, having **a SCA3 diagnosis means living with risk**. The life-threatening, life-shortening, debilitating nature of SCA3 means that just surviving day to day comes along with increased risk. This patient community is more comfortable than others may be with participating in clinical trials that may have increased risk or may only lead to incremental slowing of disease.

FDA Q&A Discussion with Panelists

Q1. I heard a lot of people mention pain as a common symptom. Is pain a common or less common symptom for SCA3? The type of pain that you have, is that typically neuropathy or something else?

- Two of five patients identified neuropathic pain as their most debilitating symptom. They described it as being constant (24/7).
- From the research literature, there are estimates that between 30-50% of SCA3 patients experience neuropathic pain. However, there has been limited research in this area as motor and balance symptoms have been the primary focus.
- There was discussion of how the current largest, ongoing natural history study for SCA3 has minimal tracking of non-motor symptoms. This has largely been due to feedback from neurologists and regulators, who have not been interested in non-motor symptoms. Based on this patient feedback, the National Ataxia Foundation team will be recommending that non-motor symptoms, including neuropathy, are incorporated into the natural history study protocol.

Q2. One of you said that pain was your biggest symptom. How many of you experience pain, but it's not your predominant symptom?

- One patient mentioned that he experiences muscle pain from trying to maintain his balance all day. Another agreed, saying that now that he uses a wheelchair, he has less pain than when he was on his feet.
- Patients shared how completing certain physical activities – such as exercise – can make their pain worse. This is especially difficult, since exercise is recommended for SCA3 patients to maintain their balance and muscle tone.

- There was a discussion about if you could pick one symptom to treat, poor balance or pain, which would patients choose. The consensus amongst patient speakers was that both were important, and that they wouldn't be able to pick between them.

Q3. Would you say your symptoms are similar day-to-day, or is there fluctuation? Both in your own experience and for your family members?

- Patients shared how symptoms vary day to day, for both themselves and their family members. One described the better symptoms days not as 'good' but as 'less worse' than the bad days. However, even with these fluctuations, nearly all symptoms get progressively worse over time.
- There was discussion about how different symptoms progress at different speeds. In addition to motor symptoms, the speakers discussed how symptoms like pain, speech modulation, coughing/choking, cognitive decline, depression, and suicidality impact their quality of life.

Q4. Can you share a bit about your challenges with fine motor coordination? Do you all have hand movement issues?

- All patients shared that they had issues with fine motor coordination. Depending on their stage of disease, different patients reported different degrees of impairment. Examples of challenges included difficulty typing, not being able to use utensils, being unable to cook for yourself, and inability to handwrite.
- The patients discussed how they would need to actively focus on trying to do fine motor tasks in order to have a chance at completing them. However, if you are focused on a fine motor task, then you can't pay attention to balance or gross motor tasks. This has led to accidents where patients tried to focus on too many things at once, leading to dropped items, bumping into things, or falls.
- One patient shared how their family member experiences tremors due to SCA3, which also makes fine motor skills difficult.

Q5. Can you talk about how symptoms have varied in your family from generation to generation?

- Patients shared how SCA3 symptoms tended to start earlier and be more intense in each subsequent generation of a family. Although there are exceptions to this trend, this is consistent with what we know in the research literature.
- When the mutation causing SCA3 is passed from parent to child, the CAG tract expansion tends to get longer. Individuals with longer CAG tract expansions, on average, report earlier age at onset of symptoms.

Disclaimer

Discussions in FDA Patient Listening Sessions are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants. This report reflects the National Ataxia Foundation's account of the perspectives of patients and caregivers who participated in the Patient Listening Session with the FDA. To the extent possible, the terms used in this summary to describe specific manifestations of Spinocerebellar Ataxia type 3, health effects and impacts, and treatment experiences, reflect those of the participants. This report is not meant to be representative of the views and experiences of the entire Spinocerebellar Ataxia type 3 patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.

Letters of Support from Charity Partners

The following are letters of support that were provided to the FDA staff ahead of the SCA3 FDA Patient Listening Session. We asked each charity partner supporting the development of this patient listening session to share a bit about their organization, as well as answer one or more of the following questions about SCA:

- How does SCA3 impact the lives of patients and their families?
- What are the most important needs of SCA3 patients, caregivers, and family members right now?
- What barriers exist to the development and testing of SCA3 therapeutics?

National Ataxia Foundation
Ensuring no one experiences Ataxia alone, until no one experiences Ataxia, period.
www.ataxia.org

SCA3 FDA Patient Listening Session
Statement from the National Ataxia Foundation

Who We Are

The National Ataxia Foundation was established in 1957 to help persons with Ataxia and their families. As a patient advocacy organization, our mission is to accelerate the development of treatments and a cure while working to improve the lives of those living with Ataxia. NAF's vision of a world without Ataxia will be accomplished through our primary programs of funding Ataxia research, providing vital programs and services for Ataxia families, and partnering with pharmaceutical companies in the search for treatments and a cure. We work closely with the world's leading Ataxia researchers and clinicians, promoting exchanges of ideas and innovation in Ataxia discovery.

SCA3 Impact on Patients and Families

Impaired balance is usually the first symptom of SCA3, followed later by incoordination of the hands and slurring of speech. Some individuals with SCA3 will notice double vision, limitation of eye movements, abnormally slow eye movements, or a "staring" appearance of the eyes. As the disease progresses, it is common to experience spasticity, rigidity, loss of muscle bulk and strength, and slowness of movement. In general, SCA3 symptoms tend to be more wide-ranging than those in many other forms of Spinocerebellar Ataxia.

SCA3 profoundly impacts many aspects of life, both for those directly affected by the disease and for their family members who are either unaffected or at-risk but as-of-yet untested. The emotional toll of witnessing this disease course through generations of families is a common experience with SCA3. For example, LeRoy watched the disease kill his grandmother, father, brother, uncle, and cousin. He has to live with the dread of not knowing if the same fate awaits him. He is at-risk for SCA3 but has not yet been tested. He said, "I hope and pray that I don't become that statistic."

Patients who have SCA3 experience negative impacts on everyday living including communication, walking, performing household tasks, driving, personal hygiene, socialization, and many other aspects. These are just a few personal perspectives from the SCA3 families that we serve:

- Gina, who lives with SCA3, remarked, "I lost my balance and crashed into the wall at work. Some laughed and asked me what I had been drinking. That was really embarrassing and hurtful. I'm afraid to have a glass of wine when having dinner with friends because my condition is not familiar to most and I can never pass a sobriety test, even if I had nothing to drink." In the past, Gina was the caregiver for her father. She said that she would rather end her life than depend on others to attend to her every need for feeding and bathing.

- Chihyang said, “As a husband/caregiver with a spouse that has SCA3, I have seen firsthand the aggressive nature of this disease. In the span of 6 years, my wife has gone from running to now requiring assistance with a walker, and soon she’ll require a wheelchair.”

- Jessica learned about her family’s history of SCA3 when she began to think about starting a family with her husband. It was then that her father informed his four children that they may have inherited the SCA3 gene. Jessica said it was a challenging time. “We were ready and excited to start a family - and this put everything on hold.” After meeting with a genetic counselor and undergoing testing, she learned that she also had SCA3.

Families affected by SCA3 face a grim reality: no treatments available to stop or slow progression of the disease. During an Externally-Led Patient-Focused Drug Development Meeting, SCA3 families indicated that the symptoms that most impacted their life were lack of balance, impaired mobility, loss of speech, decreased coordination, and loss of fine motor skills. These families are relying on researchers, drug developers, regulators, and patient advocacy organizations to deliver treatments for SCA3.

What We Do

NAF offers a variety of programs and services to the Ataxia community. There are many unmet needs of those who are diagnosed with SCA3. NAF works diligently to provide solutions to help them live better with their disease and inspire research toward treatments.

We support SCA3 families in a number of ways, including:

- Providing direct funding for SCA3 research.
- Educating neurologists to improve clinical care for SCA3 patients.
- Leading collaboration efforts for those involved in SCA3 research and drug development.
- Connecting people affected by SCA3 to create an atmosphere of support, education, and sharing.
- Advocating to policymakers to amplify the voice of the SCA3 community.
- Educating SCA3 patients, their families, and their caregivers about research, treatment development, and best practices for clinical care.

A Statement from the African Americans with Ataxia Association

An action that I believe would make this disease a bit easier to deal with would be to receive unlimited therapies. Be it occupational, physical, physio or speech all three work together believe it or not. Not everyone has a support system in place to ask if they have been exercising, but when we do have such a support system in place it makes a world of difference. To have someone on your case daily about exercising can really become bothersome. So, to have unlimited therapy 2- 3 times a week all year round will keep us with SCA3 around a little bit longer.

Namely, I have the hereditary gene SCA3 or Machado Joseph Disease (MJD). To choose between any two therapies would be difficult but any instance would be acceptable for me. I believe that there are more people with SCA3 than any of the other SCA's. Personally, I think that all persons with the diagnosis of SCA3 should at least be given the opportunity to choose which therapy try. This will also allow us to be our own advocate.

The African Americans with Ataxia Association is a support group for people dealing with the rare disease called Spinocerebellar Ataxia (SCA). This illness is considered rare because it affects about 150,000 people in the US. Our membership is over 300 and growing. We started this organization because Black people were underrepresented in the Ataxia community. This disease attacks the cerebellum, which is the part of the brain that controls movement. This impaired control by the cerebellum, which impacts 50 types of SCA, is quite debilitating to say the least. Not having control of my muscle movement is most disheartening.

From the action of swallowing to emptying my bladder to writing this paper all depends on muscle movement.

We hold monthly meetings in which we talk about the disease and its progression and tips from one to the other on dealing with the different progressions. For at least 6 months annually, we hold meetings with individuals who are experts in their field. Whether it's the physical therapist teaching exercise plans for persons with Ataxia showing us how to get up from a fall. To a mental health therapist telling us how to deal with our diagnosis. Or an attorney letting us know what we can and cannot do for our loved ones when the time comes for our demise.

I hope this information is helpful to your team.

Respectfully Submitted,
Letitia M. Diggs
Founder/Executive Director

SCA3 FDA Patient Listening Session - Statement from Ataxia UK

Ataxia UK is a research active patient organisation supporting people affected by the ataxias. It is a charity registered in the UK. Ataxia UK's mission is to fund and promote research to develop treatments and cures for the ataxias. Until this is achieved, the charity will do all it can to provide support to people affected by ataxia, and improve the quality of treatment and care they receive, to enable them to have the highest possible quality of life.

Ataxia UK is a membership organisation and as such its members are affected by a range of different ataxias. The majority of members are living in the UK, and currently there are currently around 130 individuals affected by SCA3 living in the UK who are members of Ataxia UK. We work closely with National Ataxia Foundation and are grateful for the opportunity to be able to contribute to this important event focused on SCA3.

SCA3 is a debilitating progressive neurological condition with a lack of treatments to slow or stop the deterioration. Patients with SCA3, as with other progressive ataxias, have an urgent need to have treatments that either slow or stop the progression or even provide some relief of the symptoms they experience. When we surveyed people with progressive ataxias, they highlighted mobility, coordination of movement and speech as the top burdens for their condition (Lowit et al. Health Open Research 2023). Fatigue can have a significant impact on daily life, reducing the activities people can be involved in. It is a relentless condition, but we are here to give hope that treatments will be developed for people with SCA3 and their families.

It is encouraging to see more companies with research development programmes on SCA3 and making use of the years of important research undergone by researchers worldwide that have laid the foundations for the future success of trials. The usefulness of natural history and biomarker studies, such as those run by the European Consortium (ESMI) or the US READISCA and CRC-SCA (run by NAF), is being recognised. The availability of clinical data, biomaterials, cell and animal models and therapeutic opportunities is testament to the dedication of researchers who have focused their efforts in this area. Importantly, we have a very engaged patient community who respond to the need to take part in research and come forward to help advance research. Ataxia UK is always amazed at the enthusiasm people show when there are opportunities to take part in research. This was seen in a recent study we collaborated on with researchers at the London Ataxia centre, where the ataxia community was

surveyed to ask about their attitudes to risk in clinical trials (Thomas-Black et al. Orp J Rare Dis 2022) It was interesting to note that a large proportion were prepared to have invasive procedures such as intrathecal drug administration in trials in order to benefit research and also a large proportion would take part in all phases of trials (including phase I) showing willingness to participate even with more limited evidence for benefit. There is indeed a great desire to help in research efforts.

The excitement in the ataxia research field could be seen clearly at the recent International Congress for Ataxia Research held in Dallas in November 2022. Ataxia UK had the privilege of working together with two US patient organisations, NAF and FARA, in organising this important congress that attracted over 400 delegates from around the world. Ataxia UK is also an active member of Euro-ataxia, the federation of ataxia charities in Europe and together we promote and facilitate research developments.

Ataxia UK is actively involved in the Ataxia Global Initiative, a global network with the aim of achieving trial readiness and leading to the development of successful treatments for the ataxias. All these important activities give the patient community much hope that treatments will be developed for the progressive ataxias, and SCA3 is one of the conditions leading the way within the ataxias, due to its higher prevalence and its further advancement in research.

Given the rarity of the condition, and the urgent need to develop treatments, it is extremely important to recognise that traditional trial design may not always be possible in SCA3, and it is essential to consider alternatives to traditional placebo-controlled trials. We hope that regulators around the world recognise this and help the patient community get access to treatments as early as possible. Ataxia UK also believes strongly in involving patients and their advocates in all stages of research and we very much welcome how regulators and funders are also recognising this crucial role patients can make to ensure better trials are run.

For further information on Ataxia UK visit www.ataxia.org.uk or contact the Head of Research, Julie Greenfield (jgreenfield@ataxia.org.uk)

9/1/2023

Dear FDA Team.

I am writing on behalf of the Israeli Machado Joseph Association, an organization established in 2009 by families of MJD patients and carriers. Our primary objectives encompass advancing clinical research to find a cure for MJD, providing essential support to patients, carriers, and families, and raising public awareness regarding this disease.

It is noteworthy that all diagnosed MJD patients in Israel trace their ancestry to Yemenite descent. Our association operates as a non-profit entity, functioning solely through the dedicated efforts of volunteers.

Vision

- A better future for us and for our children

Mission

Research

- Seek remedies and treatments for MJD.
- Prepare for upcoming clinical trials.
- Promote research endeavors within Israel.
- Foster communication and collaboration with relevant scientists and organizations on both national and international fronts.

Support

- Disseminate valuable information to MJD patients and their families.
- Encourage the adoption of healthier lifestyles.
- Cultivate a network of mutual aid and assistance for patients and their families.
- Elevate awareness of the condition among medical practitioners, researchers, and the public.

Clinics

- Establish a National MJD clinic at Meir Medical Center.
- Launch an Ataxia clinic at Tel Aviv Sourasky Medical Center.

Patients

- There are 117 patients from 18 families.

How does SCA3 impact the lives of patients and their families?

Machado Joseph Disease takes a significant toll on the lives of patients and their families:

- Symptoms relentlessly worsen over time, prompting patients to explore various treatment options, conventional and non-conventional, in pursuit of relief.
- The dynamics of families evolve as older members experience a gradual decline in health, necessitating adjustments in roles and responsibilities.
- The financial burden intensifies due to the escalating costs of medical care, specialized support, and assistive devices.
- In the advanced stages of the disease, speech impairment presents a formidable communication challenge for patients and their families.

What are the most important needs of SCA3 patients, caregivers, and family members right now?

Considering these challenges, we emphasize the pressing needs of MJD patients, caregivers, and families:

- Foremost among these needs is the urgent requirement for a definitive cure or treatment that can arrest or slow down the progression of MJD. This breakthrough would provide not only medical benefits but also instill a sense of control and hope for those affected.
- Comprehensive social and financial support systems are essential to alleviate the emotional, financial, and physical burdens experienced by patients and caregivers alike.
- Recognizing the strenuous demands of caregiving, respite, and support mechanisms for caregivers are of paramount importance.

What barriers exist to the development and testing of SCA3 therapeutics?

We acknowledge that there are barriers hindering the development and testing of SCA3 therapeutics:

- The rarity of MJD poses a significant challenge in identifying enough eligible patients to meet clinical trial criteria especially for parallel clinical trials, particularly when focusing on therapies with specific mechanisms such as antisense oligonucleotides.

Thank you for your time and attention.

Tomer Hillel Chairman
Israeli MJD Association

SCA3 FDA Patient Listening Session - Written Statement from Non-Profit Partners

The MJD Foundation is an Australian-based not-for-profit serving Australian Aboriginal families with Machado-Joseph Disease SCA3 and SCA7 in the remote north of Australia. https://mjd.org.au/ We are a grassroots community organisation. Our mission focuses on working in partnership with our clients, families and communities affected by MJD and SCA7.

Mission Statement

The MJD Foundation partners with Aboriginal & Torres Strait Islander communities to support families living with Machado-Joseph Disease (MJD) and Spinocerebellar Ataxia Type 7 (SCA7) by providing specialised knowledge and supports. We collaborate to conduct research providing hope for the future, and use our influence for change, so people living with MJD and related conditions can live stronger for longer

Strategic Plan

1. Our programs and services are designed and delivered following "Our Way", being client/family led, with "Our Way" being embedded throughout all parts of the organisation.
   MJD Foundation's 'Our Way' approach is based on a strong Aboriginal Community Worker two-way engagement model. View the 'Proper Approach' video and the 'Our Way' publication to learn more about how our clients and families are at https://mjd.org.au/strategic-plans/
2. Our service provision is equitable across locations, with a focus on overcoming the barriers of remote service delivery so that our clients can choose to stay living in, and cared for in their community.
3. The clinical and community services we deliver to our clients/families are best practice, based on evidence through robust research.
4. Our clients are prepared and eligible to participate in clinical trials

Initiatives

Research

Our 'Research Cycle of Knowing' ensures MJD and SCA7 families have the best information about the disease and the ways to manage it. We listen to families to find out what's important to them. We both lead research and collaborate with experts, embedding 'Our Way' to ensure cultures and values are respected. We talk with MJD researchers around the world and share the latest news with our families. We are always looking to make life better for people with MJD and SCA7. We know that it is important to keep searching for a treatment and cure.

Education

We believe that our clients and families receive better support if people in their lives understand more about MJD and SCA7, and are confident, capable and knowledgeable. We

provide education to clients, their families, health professionals, care workers and other support organisations.

Clinical Services

We provide specialist clinical services including:

Genetic Care – providing culturally safe genetic education and counselling so that families better understand how MJD and SCA7 are passed down through families and have the knowledge they need to make decisions about their future.

Neurology clinics – ensuring our clients have access to a specialist neurologist to track their disease progression and direct best practice interventions.

Therapy program – delivering multidisciplinary, specialised knowledge and therapeutic services.

Community Services

Our families are supported by a highly skilled multidisciplinary team comprised of Aboriginal Health and Community Workers, Health Professionals and Family Support Workers. Our team listens from the heart and responds with holistic family-centred practice working in partnership with families living with MJD and SCA7, by valuing and respecting an "Our Way" approach. We provide supports under the National Disability Insurance Scheme (NDIS), but do not limit our support to NDIS constraints.

Advocacy

We strive to improve outcomes for our clients by ensuring the people who can make a difference, understand about MJD and SCA7, and understand how policies impact people's lives. We use our influence to encourage meaningful and practical changes to relevant policies and practices. We raise awareness of the impacts of MJD and SCA7 on families and communities.

Governance/Management

We are an Aboriginal controlled organisation. We have a strong and dedicated Board who support the Strategic goals of the MJDF. Our staff strive for excellence bringing their best every day in: teamwork, the delivery of our programs, financial & legal regulatory compliance, fundraising & income generation. Our workforce strategy honours "Our Way" working, partnering Aboriginal and non-Aboriginal staff across MJDF activities.

Organisational Statement

Machado-Joseph disease/SCA3 impacts every element of life. The disease's impacts are felt in the patient's body through effects on multiple systems, eroding vision, balance, mobility, sleep and continence, and making even the most mundane of tasks first difficult, then dangerous and eventually impossible. MJD shortens and dramatically reduces life and its quality. The disease's reach extends to family carers, who are often at risk of developing the disease themselves or veterans of caring for other family members and the community at large, especially in small remote communites where many people are related to each other and resources are scarce.

For Australian Aboriginal families living with MJD/SCA3 the hope of treatment burns bright but the reality is complex. Their remote locations, language and worldview are barriers to truly understanding and engaging with therapeutic trials conducted in English in major metropolitan centres. Their will to be involved, however, is a strong and powerful incentive for the MJD Foundation to advocate and facilitate their inclusion.