Kennedy's Disease Association

# Kennedy's Disease (KD), also known as Spinal and Bulbar Muscular Atrophy (SBMA)

# *Voice of the Patient* Report

**Report submitted to the United States Food and Drug Administration (FDA)**

**Meeting hosted by: Kennedy's Disease Association**
**as part of the 2022 KDA Conference**

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**Kennedy's Disease (KD), also known as Spinal and Bulbar Muscular Atrophy (SBMA)**

***Voice of the Patient* Report**

The Kennedy's Disease Association's (KDA) mission is to inform, support, educate, fund, research and find a cure for Kennedy's Disease (KD), also known as Spinal and Bulbar Muscular Atrophy (SBMA). This *Voice of the Patient* report was prepared on behalf of KDA as a summary of the input shared by patients and caregivers, both virtually and in-person, during the KD Externally-Led Patient Focused Drug Development (EL-PFDD) meeting, held on November 9, 2022. The EL-PFDD was hosted by the KDA as part of the 2022 KDA conference, in San Diego California, November 9-11, 2022.

**Disclosures**: KDA is a non-profit 501(c)(3) organization. KDA receives almost all its funding from patients, family members, and friends. In 2022, KDA received two unrestricted grants from pharmaceutical and life science companies in support of the Great Road Trip fundraiser.

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## Message from the KDA President

Kennedy's Disease (KD), otherwise known as Spinal Bulbar Muscular Atrophy (SBMA), is a rare, genetic, multisystem disease that affects men beginning in their 30s and 40s and gets progressively worse for the remainder of their lives. The gene mutation causing the disease is carried on the X-chromosome, on the androgen receptor gene, and is activated by androgen (testosterone). KD primarily affects males. Some females with the gene mutation also experience symptoms. Dr. William R. Kennedy first identified the characteristic symptoms of KD in the 1960s. In 1991, Dr. Albert La Spada in the lab of Dr. Kenneth Fischbeck at the University of Pennsylvania discovered the gene mutation causing the disease. In 2023, over 30 years since the gene mutation was discovered, there is no cure and no effective treatment for Kennedy's Disease.

The Kennedy's Disease Association (KDA) was founded in 2000 to inform, support, educate, fund research and find a cure for Kennedy's Disease. KDA today includes 1,685 members from over 20 countries, and about half of our membership identify as KD men.

On November 9, 2022, KDA was privileged to host an externally led, Patient Focused Drug Development (EL-PFDD) meeting. We welcomed a range of individuals living with this devastating disease, including some who were newly diagnosed as well as many who have lived with KD for years. We also heard from caregivers and family members including women who are carriers of the genetic variation that causes the disease.

This KD/SBMA *Voice of the Patient* report contains important patient and caregiver insights and perspectives which we hope the FDA and the research community will use to ensure that patients have a voice in therapies developed for their disease and in the evaluation of clinical trial results. We believe our *VOP* report accurately captures all the voices and experiences of those who contributed, both in person and virtually. We intend our report to also represent the voices of the many members of our global KD community who have difficulty speaking because Kennedy's Disease has made it nearly impossible to speak and be understood.

We're all hopeful that effective treatments for Kennedy's Disease are on the way and look forward to new clinical trials for therapies to treat this devasting disease that, although rare, affects so many people and their families.

Thank you for giving us your attention.

Terry Thompson, PhD, President, Kennedy's Disease Association

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## Kennedy's Disease: Key Meeting Insights

1. **Most individuals experience symptoms long before receiving a formal diagnosis of Kennedy's Disease. KD progresses slowly and diagnosis is often delayed**. One reason for delayed diagnosis is the lack of knowledge about KD in the medical community.
2. **Initial KD symptoms can include lower body weakness and fatigue, muscle cramping, muscle spasms and tremors.** Kennedy's Disease is caused by a mutation in the Androgen Receptor gene and is activated by androgen (testosterone) during puberty. Initial symptoms of KD typically include tremors, muscle spasms, muscle cramping, and fatigue. As the disease progresses, patients experience more severe muscle weakness in limbs and the bulbar (neck and throat) region. The former can result in balance instability and mobility difficulties and the latter produces problems with swallowing and speaking. The disease often has metabolic and non-muscle symptoms including neuropathy, gynecomastia and sexual dysfunction.
3. **Kennedy's Disease symptoms are variable both with respect to age of onset, and severity in individual patients**. Patient testimony during the PFDD is consistent with findings in natural history studies about the variability of initial symptoms and in disease progression. Disease progression is generally slow with some studies suggesting patients lose about 2% of muscle mass per year. [1] In addition, disease symptoms are variable with regard to age of onset, location of initial weakness and severity.
4. **Kennedy's Disease impacts all activities of daily living**. These impacts intensify as the disease progresses, further diminishing quality of life. Mobility and balance issues can result in falls and injuries. Fatigue and muscle weakness impact physical activities and employment. Speech difficulties interfere with communication, leading to social isolation. Swallowing challenges interfere with eating and cause choking. The disease has profound mental health impacts including depression and anxiety. As KD progresses, the burden of disease increases and patients become dependent on their caregivers to perform basic activities of daily living. The burden of KD on caregivers is particularly heavy. Men and their caregivers live in fear of the next catastrophe and have many worries for the future.
5. **Women may also experience KD symptoms**. As an X-linked disease, KD affects primarily men, however many women who are carriers also experience symptoms. This issue needs wider recognition in the medical community.
6. **There are no effective or disease-modifying treatments for KD.** Instead, patients rely on supportive interventions to help manage symptoms. These can include physio, speech and occupational therapy, assistive devices, home modifications, nutritional management, respiratory management, symptomatic pharmaceutical therapy, supplements, strategies, adaptations and other approaches.
7. **Despite much effort, none of these supportive interventions fully address KD symptoms nor do they halt the progression of Kennedy's Disease.** Most men speaking at the KD EL-

[1]Grunseich and Fischbeck, "Molecular pathogenesis of spinal bulbar muscular atrophy (Kennedy's Disease) and avenues for treatment" (Current Opinions in Neurology 2020 October; 33(5): 629-634.

PFDD were highly functioning, much more so than many who suffer from this disease who can no longer walk and have difficulty being understood when speaking.

8. **Short of a cure, individuals living with KD would like a treatment that stops disease progression, slows muscle deterioration, maintains balance, and improves swallowing and speech.** Individuals with KD would like to be able to maintain their independence for as long as possible. They would like faster access to potentially effective medications, and would prefer an imperfect treatment now, rather than to wait for a future perfect treatment.
9. **Many individuals living with KD likely remain undiagnosed**. This highlights the need for increased awareness and medical education about KD.

## Clinical overview of Kennedy's Disease or Spinal and Bulbar Muscular Atrophy[2]

**Kennedy's Disease, also known as X-linked spinal and bulbar muscular atrophy (SBMA),[3]** is caused by a CAG repeat expansion in the androgen receptor gene, located at Xq12. In normal alleles, CAG repeat numbers range from 9 to 34, however in a sample of 129 men diagnosed with KD, the mean number of CAG repeats was 46 (range 39-64)[4]. Although those with a larger CAG repeat tend to have an earlier onset of SBMA motor symptoms, the rate of disease progression is not influenced by repeat length.

**KD is inherited in an X-linked recessive pattern.** Affected males will pass the affected X chromosome to their female offspring, who then become obligate carriers. Females who inherit the gene mutation have a 50% chance of passing the gene to their male or female children. Some female carriers experience KD symptoms, but with less severity than male patients. Although the prevalence of KD was previously estimated to be 'fewer than 1:150,000 males and very rare in females,'[5] recent research has estimated that the prevalence of KD/SBMA is 1:6,887 males and that the frequency of the gene mutation may be as high as 1:3,182 people.[6]

**KD causes the cranial nerves from the brainstem and motor and sensory nerves from the spinal cord to gradually atrophy, resulting in both sensory and motor deficits**. Symptoms are wide-ranging and variable and can involve the bulbar muscles in the head and neck, as well as muscles in both the upper and lower extremities.

**KD diagnosis is often delayed**. While KD can be diagnosed based on a family history, the time between the appearance of first symptoms until diagnosis is often lengthy for people with no family history of SBMA. During this period, KD can be considered an "invisible disability," a period in which KD men may be reluctant to discuss their symptoms with family, friends or employers.

**The disease is progressive and different symptoms emerge with time**. While there is a lot of variation in age of onset and progression of symptoms, muscle cramping and hand tremors often appear in the mid-30s, followed by leg or arm weakness in the mid-40s. By the early 50s, patients often require a handrail when going up stairs and experience fatigue and sensory neuropathy. They also begin to experience bulbar symptoms including dysphonia (vocal

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[2] This clinical overview is extracted from the presentation of Dr. Christopher Grunseich, Staff Clinician in the Neurogenetics Branch, National Institute of Neurological Disease and Stroke, NIH, provided at he EL-PFDD meeting on November 9, 2022. Other references are shown.

[3] In this report, the abbreviations of KD and SBMA are used interchangeably.

[4] Alqahtani A, Kokkinis A, Dilek N, et al: Patient Reported Impact of Symptoms in Spinal Bulbar Muscular Atrophy (PRISM-SBMA) In Press, 2023

[5] Spinal and bulbar muscular atrophy: MedlinePlus Genetics (Last accessed 22 May 2022)

[6] Matteo Zanovello, et al: Unexpected frequency of the pathogenic AR CAG repeat expansion in the general population. Brain, in press, 2023

changes), dysarthria (difficulty speaking), fibrillations (small contractions within a muscle), atrophy of the tongue, fasciculations (twitching of muscles) around the chin and mouth, and laryngospasms. Some experience head drop. Dysphagia (difficulties swallowing) typically follows in the mid 50s along with trouble chewing. Often patients will require the use of a cane or wheelchair by the age of 60. KD also includes many non-neurological symptoms including gynecomastia (breast enlargement, which can occur at an early age), erectile dysfunction, infertility, testicular atrophy, insulin resistance, liver damage (including fat deposition and scarring), Brugada syndrome (abnormal heart rhythm), and elevated serum levels of creatine kinase, cholesterol, and triglycerides.

**Although men living with KD are reported to have a normal lifespan, their later years are anything but normal**. Many KD men eventually require 24-hour care and assistance with all activities of daily living including feeding, dressing and toileting. Traumatic injuries from falls, aspiration pneumonia from swallowing difficulties, heart and lung issues and breathing-related issues decimate quality of life and can reduce life expectancy.

**At this time, no KD disease-modifying therapies are available.**

## Meeting Summary and Overview

**Terry Thompson**, **PhD**, Kennedy's Disease Association (KDA) President opened the 2022 KDA Conference and EL-PFDD meeting by providing welcome and introductory remarks on behalf of the KDA. He welcomed the 73 live attendees present in San Diego as well as 285 participating virtually on Zoom, including individuals living with KD, their caregivers and families, members of the FDA as well as clinicians, researchers, and pharmaceutical companies. Terry Thompson highlighted a very important point:

Note: Most men speaking at the KD EL-PFDD were still highly functioning, much more so than many who have suffered from this disease much longer. Most speakers were ambulatory and had little difficulty speaking. They were not representative of others whose disease has progressed to where they're confined to a wheelchair, have difficulty speaking and making themselves understood, require care 24/7 and have a feeding tube inserted due to the continual choking on food.

**Dr. Christopher Grunseich**, Staff Clinician in the Neurogenetics Branch, National Institute of Neurological Disease and Stroke, NIH, provided a thorough clinical overview of SBMA, which served as a scientific foundation for the rest of the meeting. **Michelle Campbell, PhD**, Senior Clinical Analyst Stakeholder Engagement and Clinical Outcomes, Division of Neurology Products, and the Center for Drug Evaluation and Research (CDER), provided opening remarks from the FDA. **Dr. Brian Ahangar**, a physician and KD patient**,** shared the results of the pre-meeting patient survey.

The meeting continued with two patient/caregiver panels. ***Topic 1: Health Effects and Daily Impacts of KD*****,** moderated by **Dr. Brian Ahangar,** focused on the experiences of those living with KD or who are caring for a KD patient. During ***Topic 2: Patient Perspectives on Potential Treatments*****,** moderated by **Ed Meyertholen**, **PhD**, patients discussed the different medications, medical treatments, therapies, or other approaches used to manage KD symptoms. They also shared their views of an ideal future treatment. Both panels were followed by open discussions between individuals in the room and those who were participating on Zoom. To conclude the meeting, Terry Thompson provided a summary of the key meeting points. The meeting agenda is in **Appendix 1**.

## About the Voice of the Patient Report

This *Voice of the Patient* report includes the key themes, and patient insights and comments captured at the KD EL-PFDD meeting, as well as from a video prepared for the 2021 KDA conference, featuring 10 KD patients from six countries talking about their lived experience with KD. The names of meeting panelists and speakers are listed in **Appendix 2**. A video link to the meeting recording as well as links to other presentations made at the 2022 KDA meeting are included in **Appendix 3**, along with additional important resources that informed the VOP, and are referenced throughout.

To include as many voices as possible, KDA members were invited to submit additional written comments, which are included in **Appendix 4**. Selected comments from the pre-meeting survey are also included in this report. The input received from the EL-PFDD meeting reflects a wide range of Kennedy's Disease experiences, however not all symptoms and impacts may be captured in this report.

This *Voice of the Patient* report is provided to all KD stakeholders including the US FDA, other government agencies, regulatory authorities, medical products developers, academics, clinicians, and any other interested individuals. The final VOP report, is available on the KDA website at https://kennedysdisease.org.

*Kennedy's Disease Association recommends that all individuals living with Kennedy's Disease (KD)/Spinal and Bulbar Muscular Atrophy (SBMA) consult their physician before starting or changing any treatments or supplements. Kennedy's Disease Association does not endorse any of the supplements or products described in this report.*

## Topic 1: Health Effects and Daily Impacts of KD

Key insights and themes are captured below and illustrated with selected patient comments.

### Most individuals experience symptoms long before receiving a formal diagnosis of Kennedy's Disease. KD progresses slowly and diagnosis is often delayed.

Diagnosis stories were a powerful foundation of most patient testimonies and revealed many insights about the patient experience. Many men, who were athletic throughout their early lives, described bewildering experiences with muscle weakness, fatigue, swallowing and speech challenges, cramping and balance issues.

> *"My son, after college and during his early working years, started noticing that he was having trouble with cramping, with not being able to walk as fast as some of his colleagues. Tripping over things, falling and so he went to a neurologist at a big hospital and the neurologist told him, 'Well, you need to work out harder at the gym.' And so of course doing that just made him, well… like spaghetti. He was just limp after working out. ... Finally, he was diagnosed at age 32 with spinal bulbar muscular atrophy, which we now know as Kennedy's Disease."* – Lou, carrier and mother of Bob, diagnosed at age 32, living with KD for 17 years (mother and son both have 50 CAG repeats)

Underdiagnosis and misdiagnosis are challenges for KD patients. A diagnosis of KD is sometimes made based on family history. For those without a history of KD in the family, the time between the first symptoms until diagnosis is often lengthy, an average of five years[7]. Some patients have been misdiagnosed as having amyotrophic lateral sclerosis (ALS), while others initially dismissed their symptoms because they were young or were in denial, because of cultural beliefs or because they didn't think there was anything they could do to treat the symptoms. Others misattributed their symptoms to aging, overwork or deconditioning, including many who had a family history of the disease. Some were unable to obtain insurance coverage for the genetic tests.

> *"I've pretty much known I have KD from the time I was a teenager because I had an uncle who had Kennedy's Disease. And I never did anything, I never went to get diagnosed, I didn't try to find out too much about it. And the reality was it was because there weren't too many people that had it or knew they had it, and there wasn't much going on to treat it, so I just ignored it."* – Lew, diagnosed at age 57, living with KD 15 years (44 CAG repeats)

[7] Alqahtani A, Kokkinis A, Dilek N, et al: Patient Reported Impact of Symptoms in Spinal Bulbar Muscular Atrophy (PRISM-SBMA) In Press, 2023

*"Growing up, I was told that my father had ALS or Lou Gehrig's disease and he had two years to live. When he was first diagnosed with ALS, he was still in his 30s. After a few years and he was still alive, he was rediagnosed with spinal muscular atrophy and for the rest of his life, we believed that's what he had."* – Lou, carrier and mother of Bob, diagnosed at age 32, living with KD for 17 years (mother and son both have 50 CAG repeats)

"*For about 20 years, I had bounced back and forth between a number of neurologists and no one was able really to accurately diagnose what I had. I thought it was in my head, I thought I was going crazy, tried to work out more. That certainly didn't work, that was actually quite detrimental*." – George, diagnosed at age 53, living with KD for six years

*"I then saw a local neurologist a number of times and was repeatedly told that he couldn't find anything wrong with me. And in the last visit, he suggested that my symptoms were largely psychosomatic, and I should really go and see a shrink. Anyway, I took him up on that suggestion, and after only three sessions with a very good local psychologist, I was told there is nothing wrong with my mind and that as far as the psychologist was concerned, it was very obvious that I had a medical issue*." – Kim, diagnosed at age 63 after living with symptoms for more than 20 years

After years of their increasing symptoms being misdiagnosed, many patients are relieved to finally have a correct diagnosis.

After seeking answers for many years, Scott was correctly diagnosed at the NIH. "*I can't say enough about what that workup meant to me in terms of having doctors who finally recognized what the issue is."* – Scott, diagnosed at age 51, living with KD for three years (46 CAG repeats)

Dale's symptoms kept getting worse before a diagnosis was finally made. "*I was glad to know the cause of all the problems. It was a big relief that it was KD, not ALS. I am still relieved even today."* – Dale, diagnosed at age 52, living with KD for 12 years

## Initial KD symptoms often include lower body weakness and fatigue, muscle cramping, spasms and tremors. Symptoms become worse as disease progression continues.

Kennedy's Disease symptoms include a wide range of neuromuscular as well as other symptoms

### Lower body weakness

Lower limb weakness is often one of the first KD symptoms noted and is eventually experienced by almost all individuals with KD. Some experience problems running, which progresses to challenges when climbing stairs and getting up from the floor. Some start to notice a leg drop, some experience loss of muscle mass and muscle wasting. Many men will try to counteract this weakness by working out more, but unfortunately, excessive training only breaks down muscle mass in those living with KD.

> *"My son throughout his young life was always an excellent athlete, all sports. …In his senior year of high school, his running was slowed from what it had been in his freshman year. And thinking back, we realize now that that was due to this disease, but we didn't know that then."* – Lou, carrier and mother of Bob, diagnosed at age 32, living with KD for 17 years (mother and son both have 50 CAG repeats)

> "*I noticed that when I was at work, I started struggling. If I had to kneel down for something, getting back up, getting in and out of the car, getting into the car, my right leg would consistently drag across the threshold of the car. I started tripping up stairs."* – James, diagnosed at age 51, living with KD for five years (39 CAG repeats)

> *"The biggest thing that I experience is muscle weakness in my legs, that seems to be getting worse. I can no longer lift heavy objects with my legs and carry things upstairs from the basement. Although my upper body strength is good, the legs are giving out. I also can't really do long walks anymore. And as the previous panelists have said, once you break down your muscles, there's no building them back up.*" – Jurgen, living with KD for five years (44 CAG repeats)

### Balance issues

A loss of balance and repeated falls was a symptom that led many men to seek medical care.

> "*I've fallen about 15 times just this year*." – James, diagnosed at age 51, living with KD for five years (39 CAG repeats)

> "*When I was diagnosed, it was after really a series of falls on my bicycle. …I thought I was getting weaker, but I would crash all the time and I never revealed this to my wife. I didn't want her to worry but eventually, I knew something was really wrong and I had to*

*make more of an effort to push my neurologist to find an answer to this*." – George, diagnosed at age 53, living with KD for six years

### Fatigue

Most men living with KD experience fatigue and endurance issues, and for many this is one of their first KD symptoms. Fatigue can result from muscle weakness, medications, subclinical respiratory weakness, poor sleep or low caloric intake[8].

"*I was definitely showing symptoms a few years leading up to my diagnosis. … feeling a little extra exhausted after playing sports or just the general feeling of heaviness in my ability to move, kind of like wearing cement shoes*." – Randy, diagnosed at age 31, living with KD for seven years (51 CAG repeats)

*"The fatigue some days makes it so I don't even feel like moving."* – KD patient (online survey response)

### Upper body weakness

KD can affect strength in the arms, including the shoulders, elbows and hands and fingers. This can interfere with lifting objects, holding or handling objects like keys and cutlery, handwriting and most activities of daily living.

*"I can't lift anything over my head. It's sometimes hard enough just to get my arms up. So that's my exercise. I'll lift my arms and I'll do multiple reps of that."* – Mike, diagnosed at age 62, living with KD for seven years (44 CAG repeats)

Randy experienced a stark decline in upper body strength between the birth of his two children. "*I was able to rock, lift and lay my first daughter into her crib. But with my second daughter, I wasn't able to do any of that, due to the weakness in my arms."*
– Randy, diagnosed at age 31, living with KD for seven years (51 CAG repeats)

### Muscle cramping and spasms

Muscle cramping and spasms are often early KD symptoms disregarded or overlooked by patients and/or physicians. These symptoms can be extremely painful and can occur throughout the body, including the diaphragm.

*"It was in my late thirties, early forties when I started having a lot of issues associated with cramping and shaking."* – Scott, diagnosed at age 51, living with KD for three years (46 CAG repeats)

[8] Pradat P-F, Bernard E, Corcia P, et al: The French national protocol for Kennedy's Disease (SBMA): consensus diagnostic and management recommendations. Orphanet Journal of Rare Diseases 15:90, 2020

> *"My cramps are really bad. I'll just cramp up on my hamstring or my neck or my stomach."* – Micah, diagnosed at age 46, living with KD for 7 years

Laryngospasms were mentioned frequently throughout the meeting. These vocal cord spasms temporarily interfere with speaking or breathing and are extremely alarming.

> *"I've experienced laryngospasm, … you know how terribly frightening that is. It's intense when it first happens, … it's just overwhelming."* – George, diagnosed at age 53, living with KD for six years

### Muscle tremors

Again, tremors are often early KD symptoms which can be dismissed by patients.

> "*My hands were shaking, and tremoring, and lots of muscle cramps, even when I was a swimmer in high school. And so, I definitely had early symptoms at 14, 15, 16, 17 [ years old]*." – Jim, diagnosed at age 25, living with KD for 20 years

> "*In my mid thirties I started having cramps in my legs and some fasciculations after intense physical activity which I wrote off as overdoing it. I noticed tremors in my hand but was told that they were likely intention tremors that many have and was not concerned.*" – Brian, diagnosed at age 46, living with KD for two years (44 CAG repeats)

### Bulbar weakness–related symptoms including dysarthria, dysphonia, and dysphagia

Bulbar weakness in the head and the neck results in many characteristic Kennedy's Disease symptoms, including fasciculations (muscle twitches) around the chin, and mouth and tongue fibrillations (small electrical impulses). Symptoms can also include tongue atrophy, head drop, facial drooping, as well as difficulty speaking, vocal changes, difficulty swallowing and choking.

> Head drop and weakness were Mike's first symptoms. *"I couldn't hold my head up. I had a head drop pretty severe."* – Mike, diagnosed at age 62, living with KD for seven years (44 CAG repeats)

> *"I've been diagnosed in 2018 when I first went to my new eye doctor and he said, 'The side of your face seems to be drooping.' I said, 'I never noticed it. I thought I always looked like this.' He thought it might be Bell's palsy, so I went and got an appointment with a specialist."* – Jurgen, living with KD for five years (44 CAG repeats)

Difficulty speaking (dysarthria) and vocal changes (dysphonia). As a result of bulbar weakness, many of the speakers the EL-PFDD meeting displayed a characteristic vocal quality. Despite their hoarse, slightly quivering voices, their words were still comprehensible. As the disease

gradually progresses, speech becomes harder to understand, and eventually other communication modalities are required. Some experience challenges with drooling or spitting.

> "*As two or three years have gone by, the swallowing, choking, drooling, and voice changes have become very, very impactful*." – Brian, diagnosed at age 46, living with KD for two years (44 CAG repeats)

> *"A few years ago, I started feeling it's getting tougher and tougher to climb up stairs, run, walk/stand long hours, pronounce certain English words (mostly EX-words such as excuse me, expect, expensive, etc.)."* – Kunihiko, KD patient

Difficulty swallowing (dysphagia) and choking. An initial discomfort when swallowing progresses to challenges with clearing the throat and choking.

> Scott's sister, a carrier, is affected. "*She has some issues as well with swallowing and with some muscle issues*." – Scott, diagnosed at age 51, living with KD for three years (46 CAG repeats)

> *"Choking on food and saliva has been an issue. I do all I can to prevent that, and as you can hear, my speech is compromised*." – George, diagnosed at age 53, living with KD for six years

### Breathing challenges

Breathing difficulties in KD progress from a shortness of breath (dyspnea) when exercising, to shortness of breath even during slight activities and then shortness of breath at rest. For some, a tracheostomy and respiratory assistance may eventually be required.

> *"My symptoms progressed very quickly from my diagnosis primarily attacking my upper respiratory system. My voice box collapsed resulting in a permanent tracheostomy after prolific tests to ensure there were no other underlying issues other than Kennedy's."*
> – Angus, living with KD for almost two years

For patients with advanced disease, breathing issues become crises and take precedence over all other issues.

> "*Recent crises have been revolving around respiratory – not so much the weakness and the falling obviously anymore – but more respiratory and pulmonary issues such as RSV, pneumonia, two bouts of COVID-19, other non-respiratory issues*." – Maria, caregiver for her husband Gerry, aged 64 and living with KD for over three decades

### Symptoms of androgen insensitivity – gynecomastia, sexual dysfunction and infertility

Gynecomastia, or breast enlargement, is an androgen-related issue and for many, was an early symptom of the disease.

*"I was in my late teens and early 20s, when I had the typical symptoms of muscle cramping, twitching, the twitching that goes on, and enlarged breasts. I noticed this but I didn't think anything of it. I mean, big deal, you go on. It was not debilitating."* – Tim, diagnosed at age 52, living with KD for 12 years

*"I got gynecomastia, had that really bad. I had a plastic surgery that took care of that. I think that was my sophomore or junior year."* – Jim, diagnosed at age 25, living with KD for 20 years

While few spoke openly about sexual dysfunction, symptoms including erectile dysfunction, reduced sex drive, impotence, testicular atrophy and infertility affect many. One man spoke about a significant decrease in his libido and potency. Several experienced years of infertility, which caused a lot of grief. These complications amplify the impact of the physical symptoms and cause anxiety and relationship challenges for KD men, as discussed below.

### Other KD symptoms

Other important symptoms of KD mentioned at the EL-PFDD meeting include gastrointestinal (GI) motility issues (related to core muscle issues), peripheral neuropathy, metabolic syndrome, muscle paralysis, thermoregulation challenges, extreme light-sensitivity and incontinence.

### Other significant points from patient testimony

#### Kennedy's Disease symptoms are variable with respect to age of onset and severity.

One of the challenges for researchers and pharmaceutical companies is the variability of symptoms. Not all patients experience all the symptoms described, and the symptoms do not always occur in the same sequence or with the same severity.

#### Symptoms change as Kennedy's Disease progresses.

Rather than a continual decline, some patients reach "plateaus" where symptoms remain stable for awhile before progressing again. Some patients described that some symptoms such as muscle cramping and spasms eventually disappeared as the muscles and nerves atrophy. Again, it is important to emphasize that many of the men who spoke at the meeting were fairly early in the course of their disease.

*"Since [diagnosis] I've seen progression from simple stuff like tremors, hand cramping, inability to do little things around the restaurant, to I have nowadays I can't really walk long distances without assistance of an AFO (ankle foot orthosis) on my right leg."* – Dan, diagnosed at age 39, living with KD for six years

"*For a long time, the disease would plateau, and we could adapt and create a new normal. In the beginning, those plateaus were longer, sometimes up to a year if we were lucky…. Many of you will know what I mean by that plateau, where you normalize,*

*adjust, and then that's status quo for a while and then things change and you go into adjustment mode and then another plateau*."– Maria, caregiver for her husband Gerry, aged 64 and living with KD for over three decades

"*I have not had a laryngospasm in quite sometime, and hope these do not return*."
– KD patient (online survey response)

### Women may also experience symptoms of Kennedy's Disease.

Woman who are carriers may also get symptoms. Many carriers report some problems with cramping. Scott's sister experiences both swallowing and muscle issues. Elaine summed up the situation:

"*I'm very affected by the symptoms which are Kennedy's. I have peripheral neuropathy and just all kinds of neurological [challenges], so I have huge mobility issues. Being a carrier is not just being a carrier with no side issues*." – Elaine, carrier and mother of Nick, diagnosed at age 24, living with KD for 20 years

## Kennedy's Disease impacts all activities of daily living, and these impacts intensify as the disease progresses, further diminishing quality of life.

*"KD now impacts quite dramatically on every aspect of my life."* – Kim, diagnosed at age 63 after living with symptoms for more than 20 years

*"[KD impacts] all the little things in life that you took for granted."* – Jameson, living with KD

### Mobility impacts: walking, standing, stairs, getting up from sitting

Mobility impacts intensify as the disease progresses. Patients are unable to walk as fast as they would like, and they increasingly experience challenges with being able to walk and even stand without support. Many experience challenges with going up and down stairs, getting out of low seats and entering and exiting some vehicles.

"*For many years, I didn't experience impacts of the disease, but recently have experienced difficulties in walking, taking the stairs and steps, and also with stability in the legs as I lose my balance*." – Gianni, diagnosed at age 43, living with KD for 16 years

"*He has no mobility, he can walk a few steps, that's about it. He uses a power chair, he uses scooters, we've got all the devices in the world. He has a wonderful caregiver in his wife, Tara. And they just moved into a more livable space, and they just make it work*."
– Harvey, father of Nick, diagnosed at age 24, living with KD for 20 years

"*Finding it difficult to get up and down, I need assistance sometimes if I'm sitting on a chair to get up."* – Andrew, diagnosed at age 40, living with KD for more than 30 years

### Trips, falls and injuries

Challenges with walking, neuropathy and balance can lead to trips, falls and serious injuries, which can lead to further declines in abilities and quality of life.

*"I fell and broke three bones in my foot and needed surgery. I had abdominal complications after the surgery, more deconditioning and I was out of work for almost three months, and now I have to make other adjustments as I transitioned."* – Brian, diagnosed at age 46, living with KD for two years (44 CAG repeats)

"*About three years ago, he fell and broke his hip. It was a major disaster for him. …It set him back of course*." – Lou, carrier and mother of Bob, diagnosed at age 32, living with KD for 17 years (mother and son both have 50 CAG repeats)

"*Gerry fell again. He broke more toes than the usual one or two. He was able to walk about 20 feet or so before that fall, but then from that point on, he was only able to do pivot transfers from his bed to the scooter, from the scooter to the toilet. … And then in 2017, he fell during a transfer, … he broke both of his legs below his knees.*" – Maria, caregiver for her husband Gerry, aged 64 and living with KD for over three decades

### Inability to do what they want or need, including activities of daily living

KD patients spoke about the daily frustration of being unable to do things that they once took for granted, including picking things up, fixing things, or lifting and carrying things. They spoke about challenges with buttons and zippers, dropping things and how their handwriting is deteriorating. Simon cannot raise his arms as he used to, so often will brush against or knock over wine glasses.

*"I was in NIH last year and I bought a Diet Coke and I couldn't open it. So I asked one of the guards actually, that was kind of embarrassing, to 'please open my diet coke'."* – Ed, diagnosed at age 44, living with KD for 24 years (46 CAG repeats)

*"It's the little things for me. Being able to walk on the beach, being able to walk out in the waves, go for a hike. Button your shirts, all the little things seem to weigh on me more than the big things."* – Dale, diagnosed at age 52, living with KD for 12 years

*"My dexterity is getting worse by the month and deteriorates in colder weather making simple tasks like doing up buttons quite difficult. But while my fine motor neuron skills continue to diminish my gross motor neuron skills are still ok."* – Angus, living with KD for almost two years

Randy described the "Spoon Theory"[9] which explains how those with disabilities have to make very conscious choices about how they budget their energy by analogy to the limited number of "spoons" they are allocated each day. This story resonated with many at the meeting.

> "*Sometimes, it's hard to explain what we go through, and this is a really great way for me to say, 'Hey, here's how my day goes*.'" – Randy, diagnosed at age 31, living with KD for seven years (51 CAG repeats)

### Challenges with eating independently

Patients have greater challenges with chewing and swallowing as KD progresses. They need to concentrate more when eating so that they don't choke, take a longer time to eat their meals, start to require their food to be chopped or pureed, and eventually have problems handling utensils. Eventually they require assistance with eating and enteral or IV nutrition is often required.

> Dale has no jaw strength left, so he chews with his chin supported by back of his hand, with his elbow supported on the table. *"I have no jaw strength so I will sit there and use my wrist to manipulate [my mouth] when I am in public or even at my home. With that, I can chew."* – Dale, diagnosed at age 52, living with KD for 12 years

> *"I have big problems with eating and swallowing. Talking is still manageable."* – Giancarlo, diagnosed at age 56, living with KD for 11 years

> *"Swallowing/choking affected how I eat and the types of food I eat and causes anxiety. It is dangerous and socially embarrassing at times."* – KD patient (online survey response)

### Challenges participating in sports, exercise and other hobbies

Limited abilities to participate in sports and exercise are even more impactful as many patients were athletic prior to their diagnosis. Many had to drop other important hobbies as well.

> "*I was 55 when I gave up yoga classes, and it was because I couldn't keep up, because I was cramping going into different positions.*" – Tim, diagnosed at age 52, living with KD for 12 years

> *"I no longer run or ski and don't engage in sports that require quick lateral movement (tennis)."* – KD patient (online survey response)

> *"Music was central to my life, though never a professional. I can no longer play trumpet and can barely play piano. My singing voice has become nearly nonexistent. I used to be*

[9] https://butyoudontlooksick.com/articles/written-by-christine/the-spoon-theory/

*an avid skier, both Nordic and alpine, and also an avid hiker. I now cannot climb stairs."* – KD patient (online survey response)

### Travel impacts

Travel challenges are an early KD impact; later in the course of the disease, travel is impossible.

*"If there's a beach, how do you get down to the beach? Because sand, snow and grass, it's horrible. How can you do it? I've been to Hawaii where it took me and my wife two hours to get from here to the door because there was sand and it was just so stressful."* – Fred, diagnosed at age 40, living with KD for eight years

"*My wife and I like to travel.... We stayed at some hotels and some inns that didn't have elevators, and the reality becomes real clear when you're struggling to get up the stairs, but [at least] I'm still able to take stairs*." – Tim, diagnosed at age 52, living with KD for 12 years

*"In the past I used to travel a lot, now need airport assistance off and on the plane. I can't explore new cities on foot anymore, but I can still drive around by car."* – Giancarlo, diagnosed at age 56, living with KD for 11 years

### Changes in family roles and relationships

Some men are unable to pick up their children or grandchildren or play and care for them as much as they want, and some are unable to express affection with hugs.

"*I can't just lean in and hug somebody, or I might fall over."* – Jameson, living with KD

"*What has impacted me the most is just involvement with my two children. They're very robust kids who want to wrestle all the time. They want to play soccer, they want to play basketball. I think emotionally, that really affected me the most, just not being able to participate with them*." – Brian, diagnosed at age 46, living with KD for two years (44 CAG repeats)

Gerry stopped working at the age of 40 to become a stay-at-home dad. "*He was determined to do as much as he could with her and us as a family while he still could, but as our daughter grew and developed and became more independent, Gerry regressed and declined and became more dependent on those around him."* – Maria, caregiver for her husband Gerry, aged 64 and living with KD for over three decades

### Losing sexual function

A significant topic that was only briefly mentioned during the EL-PFDD meeting is the issue of sexual dysfunction. Erectile dysfunction, reduced sex drive and impotence can impact

relationships and marriages. Some couples are able to deal with this, but in some cases, it can have a devastating effect on relationships, leading to marriage breakups.

> *"Sexual function and desirability were top concerns of mine. Fortunately, my wife has been very, very supportive and lovely, but that was the top concern of mine."* – Brian, diagnosed at age 46, living with KD for two years (44 CAG repeats)

> *"Loss of sexual function.*" – KD patient (online survey response)

> *"Not being able to do the things I truly enjoy such as sex with spouse, eating and socializing with others properly, traveling."* – KD patient (online survey response)

### Impacts on employment, retirement and financial stability

KD has an enormous impact on employment and careers, as many men have to change direction or retire early, which can cause financial hardship.

> *"I taught for many years in academies and in the Navy and spoke publicly. I have recently had to get out of some of those because I have the drooling issues. …I can't talk longer than about five or six minutes straight."* – James, diagnosed at age 51, living with KD for five years (39 CAG repeats)

> *"Following diagnosis, I decided to retire at the age of 49, when the challenges of my job, combined with the KD symptoms were starting to be too much."* – Rod, diagnosed at the age of 43, living with KD for 16 years (43 CAG repeats)

> *"KD robbed me of my well-structured retirement plans, which included golf, tennis and sailing to New Zealand.*" – Kim, diagnosed at age 63 after living with symptoms for more than 20 years

KD also impacts the careers of family members and caregivers.

> "*I would oftentimes get called home from work when he couldn't get up or had a fall*." – Maria, caregiver for her husband Gerry, aged 64 and living with KD for over three decades

### Social isolation

Most KD symptoms eventually lead to social isolation. Mobility difficulties mean that patients are unable to ascend the stairs to a friend's home, or participate in social activities like golf, tennis or dining out. Individuals living with KD have an increasingly difficult time articulating words and making themselves understood. Friends and family members, not wanting to keep asking them to repeat themselves, stop asking and then stop listening.

After being diagnosed, Fred initially didn't go out. "*I did not want to eat with people because of choking, because of falling. If they get a reservation and there's no elevator...*" – Fred, diagnosed at age 40, living with KD for eight years

Simon is self-conscious about others seeing him eat. *"Going out for dinner is hard. Moving food around inside my mouth is extremely difficult."* – Simon, diagnosed at age 47, living with KD for 24 years

*"If I'm at parties or group gatherings, it's hard. It's difficult to talk loud, especially if there's a lot of background noise or if you're speaking with somebody for more than two minutes of time."* – Micah, diagnosed at age 46, living with KD for 7 years

*"I don't like to talk about this, so I tend not to tell people. I'm still at that phase, if you will."* – Tim, diagnosed at age 52, living with KD for 12 years

Some are stigmatized because of their condition.

*"I had pretty immense tremors and I had to convince people – despite the fact that I probably had one or two glasses of wine a week – that really, I wasn't a drinker and I was not experiencing DTs (Delirium tremens). Some people didn't believe me."* – George, diagnosed at age 53, living with KD for six years

### Mental health impacts including anxiety and depression

For many, the mental health impacts of KD are more severe than the physical disability. Many individuals with KD experience mental health challenges as a result of their diagnosis and as the symptoms progress. When faced with a progressive disease without a cure, many experience different stages of grief, some experience anxiety and depression, decreased attention and short-term memory, as well as difficulties concentrating. Some are reluctant to share their diagnosis with their families and friends.

Dmitry lives in what he describes as a *"chronic moderate depressive state. …I couldn't work, I couldn't think about the future.*" – Dmitry, diagnosed at age 46, living with KD for five years (45 CAG repeats)

Randy was unable to lift and care for his second daughter. *"Mentally, that really got me, it got me down…. I'm a very positive person but when that came along, and I noticed it, it really put me in a difficult situation, where I was cursing out KD."* – Randy, diagnosed at age 31, living with KD for seven years (51 CAG repeats)

Applying for a vehicle handicap sticker was a trigger for Tim. *"When I was sitting down and filling out the application, it was very emotional. So, my wife and I are trying to find therapists now."* – Tim, diagnosed at age 52, living with KD for 12 years

*"It was screwing my mental health and I was in this state of depression because I just didn't go out."* – Fred, diagnosed at age 40, living with KD for eight years

### Loss of independence

KD eventually has an incredible disease burden on patients and their families and caregivers. As KD progresses, activities of the daily living become impossible without caregiver help. Maria described how KD patients require assistance for every single aspect of their life.

*"At this point, our daily routine is practically 24/7 involvement on my part from getting him out of bed, onto the commode to the toilet, cleaning him up, showering him, dressing him, moving his equipment cart from the bedroom to the living room, making sure it's plugged in so that the BiPap breathing machine doesn't die in the day and I have to run home from work to plug it back in. Getting food for him that won't choke him or create more phlegm issues, putting on his BiPap mask, analyzing to see if he needs a cough assist treatment or a nebulizer treatment. Emptying his urinal, getting dinner for him, more cough assist treatments, getting ready for bed, rolling him over during the night, looking to see if any pressure sores have developed, and then dealing with techniques I've learned to how to address those. Then there's also behind the scenes type of things, like getting ready his medications, coordinating the doctor's appointments, grocery shopping, paying bills, ordering various medical supplies, doing the laundry, going to work, perhaps being called back or not even being able to go in for the day at all, and so many other little details that need to be done each and every day."* – Maria, caregiver for her husband Gerry, aged 64 and living with KD for over three decades

### Caregiver and carrier impacts

Maria's quote above, illustrates the immense amount of work and attention required to keep individuals living with KD alive. Maria spoke about how both the physical and emotional burden of caring for her husband has increased as his disease has progressed.

*"Early on the symptoms were more physical, and I felt like I could fill it in and take care of what needed to be done. …But the decline now is more internal. I refer to the respiratory kind of stuff and so filling in the gap isn't something I really can do. I can't breathe for him, I can't swallow for him. I'm a fixer and I just don't feel like I'm fixing as much as I could before but we're at the point right now where we're working to make each day manageable and meaningful."* – Maria, caregiver for her husband Gerry, aged 64 and living with KD for over three decades

Many KD carriers grew up watching their fathers with KD slowly deteriorate, and now experience tremendous guilt about passing the gene on to their children.

> *"Before I ever got married, I asked my doctor and his doctor if that disease was something that I was going to pass on to a future generation. And I was assured it would not pass on unless the person I married had that disease in his family. I questioned my future in laws and I was assured there was no neuromuscular disease in their family. So, I felt assured that I had a safe future."* – Lou, carrier and mother of Bob, diagnosed at age 32, living with KD for 17 years (mother and son both have 50 CAG repeats)

### Living on the edge of catastrophe

At some point in the disease, men with KD are just one step away from catastrophe: a fall that results in a traumatic brain injury, an immobilizing stroke leading to early death, aspiration pneumonia from which one can't recover.

> After Gerry broke both of his legs in a fall, "*Life from that point was in crisis mode, as we spent the next month and half or so in the hospital and then in rehab. That was a very stressful time. I was constantly overseeing his life in the hospital, in the rehab, overseeing his medications, his food, so he would not choke on it, educating each new staff person as they came on shift so they would understand the details of this disease.*" – Maria, caregiver for her husband Gerry, aged 64 and living with KD for over three decades

> *"My parents lived well into their 80s and 90s. My brother, Frank, who had KD, died at age 71 from a catastrophic fall. He was forced to ride a scooter because of an earlier fall that resulted in a broken leg. The scooter tipped over and Frank suffered traumatic brain injuries from which he never recovered."* – Kathy Thompson, addressing the point that KD men do not always have a normal lifespan

Although the medical literature says that KD victims have a normal or near-normal lifespan, this is not necessarily accurate as many of these men are taken much too soon.

### Other impacts

Bulbar weakness and breathing challenges create a risk for anesthesia and surgery.

## Individuals living with Kennedy's Disease have many worries, especially about the loss of independence.

Worries about the future very much reflect the KD impacts. In addition to loss of independence and becoming a burden, individuals with KD have many other worries.

### Losing independence and becoming a burden on others

> *"But at the stage I'm at right now, my worry is my independence. I like to be able to get up and go, and be able to do what I want without having to have assistance or rely on*

*other people, and I also don't want to be a burden to the family always asking them for assistance."* – Andrew, diagnosed at age 40, living with KD for more than 30 years

*"[KD] interferes with my normal daily life, with my work, public relations and social life. I hope it doesn't get so serious to the point that I won't be able to look after myself and will need assistance in my normal daily life in the future."* – Gianni, diagnosed at age 43, living with KD for 16 years

*"I really do not want to have to be in a position of having my wife have to perform the duties that [caregivers represented at the meeting] so capably and lovingly do*."
– George, diagnosed at age 53, living with KD for six years

### Financial insecurity, employment and providing for their family

"*Not being able to provide for my wife. I worry about maintaining my current employment level."* – KD patient (online survey response)

*"I have a farm and worry that someday soon I won't be able to do the regular tasks I do routinely around the farm*." – KD patient (online survey response)

*"Early death and disability, financial insecurity due to disability. Not being able to participate and do the things I consider essential to my life like work or do things with my sons."* – KD patient (online survey response)

### Being unable to swallow and eat

*"My biggest fear is not eventually being in a wheelchair, but it's not being able to eat. ... Now, there really isn't anything I can do about it."* – Ed, diagnosed at age 44, living with KD for 24 years (46 CAG repeats)

"*Not being able to swallow food at all.*" – KD patient (online survey response)

### Experiencing a catastrophic event including a fall

*"Our biggest fear was a fall, which could result in a serious injury and accelerate past several next plateaus.*" Gerry experienced many falls which changed the trajectory of his disease. *"From that point on, he was only able to do somewhat pivot transfers from his bed to the scooter, from the scooter to the toilet. But even those were with some great difficulty and worry."* – Maria, caregiver for her husband Gerry, aged 64 and living with KD for over three decades

*"I joke about falling a lot, [but] I'm really worried about it, and I'm trying to figure out ways to fall less."* – Jim, diagnosed at age 25, living with KD for 20 years

### Worry about passing KD on to children and grandchildren

*"What troubles me most, is the fact that this is a genetic disease and I now know that my grandson has a 50% chance of getting it, and my two granddaughters have a 50% chance of being carriers."* – Kim, diagnosed at age 63 after living with symptoms for more than 20 years

## Topic 2 –Patient Perspectives on Potential Treatments

Patients and caregivers discussed all the different types of therapies, supplements and assistive devices they use to manage KD symptoms. Some shared the results of their extensive research into potential treatments and described how well each of these treatments worked for them. KD patients discussed their thoughts of what an ideal future treatment for KD would need to address. They identified other areas for research and improvement.

### There are no effective or disease-modifying treatments for KD. Instead, patients rely on supportive interventions to help manage symptoms.

The absolute lack of any type of effective treatment was emphasized throughout the EL-PFDD meeting. Instead, patients are forced to rely on supportive interventions for their KD-associated symptoms. Patients described their distress and disappointment at finding that their disease had no cure and no disease-modifying therapies.

> *"I was quite disappointed to find out that there were no treatments for Kennedy's. That WAS a disappointment."* – Kim, diagnosed at age 63 after living with symptoms for more than 20 years

#### Physiotherapy and exercise

Physiotherapy and exercise were one of the main modalities used to maintain physical function and strength and to support their overall well being. The ability to exercise independently diminishes as the disease progresses; many of the comments about exercise were made by men who are still early in the disease process.

> "*I found a physiotherapist who actually knew about Kennedy's Disease, and she provided a program of exercise which is largely stretching of all your appendages, keep them limber without overworking them*." – Jurgen, living with KD for five years (44 CAG repeats)

> *"Swimming has been one of those things that's really been really great for me personally. I feel stronger, I feel less sore after I work out."* – Dan, diagnosed at age 39, living with KD for six years

> *"I try to do as much physical activity as I can while keeping that balance, knowing that if I lift weights or I break down muscle, I'm never going to get it back again."* – Lew, diagnosed at age 57, living with KD 15 years (44 CAG repeats)

> *"My personal trainer really understands what I need to do. Not to strengthen my muscles but to keep my spirts up and to keep my body in shape."* – Giancarlo, diagnosed at age 56, living with KD for 11 years

In addition to physiotherapy, many patients mentioned keeping active by working in the garden, spending time outside or going for walks. Many patients budget or manage their fatigue by taking frequent breaks.

A downside of exercise is that it should not be done too strenuously. Many patients reported that their first response to experiencing the KD symptoms of muscle weakness and fatigue was to work out more; unfortunately, excessive training breaks down muscle mass in those living with KD. One of the online survey respondents said, *"I need to exercise more, but when I do, I have excessive soreness even with mild exercise."*

### Speech therapy

Speech therapy is another essential rehabilitative therapy for those with KD, conducted to mobilize and maintain muscle function in the bulbar area, to assist with speaking and eating and to help to prevent choking and aspiration.

> Ed saw a speech therapist, "*She gave me these little straws as an exercise to try, so at least I have something to try and do for the swallowing*." – Ed, diagnosed at age 44, living with KD for 24 years (46 CAG repeats)

### Occupational therapy and assistive devices

Occupational therapy helps individuals maintain autonomy with regards to activities of daily living and can include strategies as well as assistive tools. These need to be refreshed each time disease status or disability changes. While many patients were initially reluctant to use assistive devices, they felt grateful once they realized that this would significantly improve their lives.

**Neck supports including supportive collars and neck braces.** Neck supports help to counteract head drop. These range from regular cervical supports from the local drug store to more customized approaches. Some patients use different neck supports in different situations, but downsides include the fact that neck supports which support the head under the jaw can't be used while eating, some don't allow patients to turn their heads easily and others are just uncomfortable.

> "*Neck braces of a few sorts help in my neck weakness as well as careful attention to ergonomics at my desk."* – KD patient (online survey response)

**AFO (ankle-foot orthosis).** AFOs are often one of the first devices used to support mobility.

> "*Without the AFO, I don't think I could do my work. I don't think I could walk around the block*." – Dan, diagnosed at age 39, living with KD for six years

> "*I'm getting braces the week I get back so that I can hopefully not fall as much*." – James, diagnosed at age 51, living with KD for five years (39 CAG repeats)

**Canes, walking sticks and walkers.** These aid walking, standing, or going up stairs.

> *"I went to a football game a couple weeks ago with some friends and it was packed and everybody was standing the whole time. If I hadn't had taken my cane with me, it would've been really, really difficult and I would've been afraid of falling or somebody knocking me over in that crowd."* – Micah, diagnosed at age 46, living with KD for seven years

> *"Walking is getting more difficult and I find the use of a walking stick gives me the confidence to go further than without it. I hope not to ever require a wheelchair but have to manage my expectations regarding this matter as it may happen."* – Angus, living with KD for almost two years

**Scooters, powerchairs and wheelchairs.** These options are for those who are easily fatigued and can't walk long distances. As KD progresses, individuals require more and more mobility support.

> "*I'm currently at the stage where I need a walker to get around. I have a scooter that I use when I go to the mall or out anywhere."* – Andrew, diagnosed at age 40, living with KD for more than 30 years

> *"I like the power chair inside the home because their maneuverability is phenomenal."* – Jim, diagnosed at age 25, living with KD for 20 years

> *He's full time in a wheelchair. …He has three different wheelchairs.* – Lou, carrier and mother of Bob, diagnosed at age 32, living with KD for 17 years (mother and son both have 50 CAG repeats)

### Home modifications and adaptations.

Many individuals living with KD require home modifications like ramps, handles and railings. As the disease progresses, additional adaptations are necessary: lift chairs and *SitnStand* devices to stand from a seated position, stair lifts or elevators for getting up and down stairs, fall recovery devices to help lift someone who has fallen on the ground, hospital beds, barrier-free showers, commode products such as toilet seat lifts, adapted vans. Some men have had to call 911 to request help to get up after a fall.

> *"He has a hospital bed, he has a lift chair that will lift him to a standing position to transfer to his wheelchair. He has a shower chair, he has a raised toilet seat chair, he has a van with a lift. Anything that will help him, he's got."* – Lou, carrier and mother of Bob, diagnosed at age 32, living with KD for 17 years (mother and son both have 50 CAG repeats)

Extensive renovations were required for Gerry to return home after his latest fall. "*Ripping out carpet, putting in new flooring, getting commercial grade flooring, ordering a lift because we didn't have one at that point*." – Maria, caregiver for her husband Gerry, aged 64 and living with KD for over three decades

*"I used to have to step over something and up a few inches in order to get into the shower. Getting in wasn't too bad because I could always push myself against the windowsill. But getting out, I was always afraid that as I step out and step down, my knee would give way. …We recently got that barrier-free shower and, man, it is a dream. Every time I come out if it, I'm telling my wife: "I love our new shower."* – Jameson, living with KD

### Nutrition management

Nutritional management is essential for those living with KD. While there is no clinically approved diet for KD patients outside of the French National Protocol, food supplements are used by some patients to ensure they consume enough protein, energy and vitamins[10]. Some make dietary changes including keto diets and time-restricted feeding to prevent the development of metabolic syndrome and diabetes. For those with problems swallowing, smoothies, meal replacement and thickening powders may be required, as well as GI tubes.

"*The doctors at the ALS clinic had said that I need to try and get 70 grams of protein a day, which doesn't seem like a lot, but that's a lot of protein. So high protein diet, I try to do low carbs, high protein, lots of vegetables*." – Dan, diagnosed at age 39, living with KD for six years

*"As far as managing the disease, diet-wise, I think it's important to maintain a healthy diet; I prefer one that's lower in fat, higher in protein*." – Jurgen, living with KD for five years (44 CAG repeats)

### Respiratory management

Respiratory management is focused on the detection and treatment of bronchial obstructions as well as the prevention of aspiration pneumonia[7]. Patients described using BiPap breathing machines, cough assists, Trilogy ventilators, nebulizers and one even had a trach.

"*I have a paralyzed left diaphragm, so my lung capacity is severely limited, it's around 50%. I use a BiPap at night, that has done wonders. The BiPap, and I sleep on my side,*

[10] Pradat P-F, Bernard E, Corcia P, et al: The French national protocol for Kennedy's Disease (SBMA): consensus diagnostic and management recommendations. Orphanet Journal of Rare Diseases 15:90, 2020

*and I rarely have a bad night's sleep*." – Mike, diagnosed at age 62, living with KD for seven years (44 CAG repeats)

*"I am grateful for what I have …without the trach I would not be here."* – Angus, living with KD for almost two years

### Symptomatic pharmaceutical therapy

This includes medications to manage pain as well as for endocrine and metabolic interventions, antidepressants, anti-inflammatories, blood pressure medications, statins and other cholesterol-lowering drugs, medications for fatigue, sleep and mood disorders. Some tried alternate therapies for cardiovascular health such as Zetia and curcumin.

*"Our neurologist recommended metformin, which I've taken low dose to prevent muscle wasting and help with the insulin sensitivity. But I know that there's controversy around whether it actually accelerates muscle wasting or prevents it."* – Brian, diagnosed at age 46, living with KD for two years (44 CAG repeats)

"*I was prescribed Primidone to help with my tremors, but stopped after a couple days due to how it made me feel. … For now, I just live with the tremors. Frankly, the potential side effects of Primidone are scary."*– KD patient (online survey response)

*"Gabapentin helps keep me asleep and from waking due to movements."* – KD patient (online survey response)

**Pain management is required for muscle cramping and neuropathic and myogenic pain.** These can include quinine derivatives, mexiletine, alpha-lipoic acid, magnesium, analgesics and CBD.

Jim experiences pain in his neck due to his weak neck muscles. "*The thing that's helped me more than anything is a CBD roll-on stick onto my neck. None of the other stuff seems to help me."* – Jim, diagnosed at age 25, living with KD for 20 years

### Supplements and vitamins

During the meeting, patients discussed supplements as a way to potentially manage Kennedy's Disease symptoms. Many conducted extensive literature research to understand the biochemical pathways affected by this disease and to find ways to address neuromuscular degeneration and fatigue. The evidence supporting the use of some of these products ranges from unproven to controversial.

**Creatine and other supplements to support muscle maintenance and reduce neurodegeneration.** Many individuals living with Kennedy's Disease use creatine, an amino acid

commonly used as a body building supplement. They also mentioned many other supplements. Despite the lack of evidence, several patients have tried androgen substitution therapy, selective androgen receptor modulators or anabolic steroids.

> James was advised by his uncle, who was "*in his mid to late seventies, still walking with canes. He said, 'Take creatine.' I've been taking it since. I don't know if it's placebo effect or not. I don't care. As long as it keeps me functioning, that's fine*." – James, diagnosed at age 51, living with KD for five years (39 CAG repeats)

> *"I started experimenting. I have literal tubs of supplements that I tried and set aside and a cocktail that I've been taking now that seems to work okay for me. I do actually feel like I have fewer cramps, fewer fasciculations, and my muscles are a bit stronger than they were thanks, potentially, to that."* – Chris, diagnosed at age 25, living with KD (46 CAG repeats)

**Vitamins.** Some of the different vitamins used by individuals living with KD included nicotinic acid (a NAD precursor), Coenzyme $Q_{10}$, fish oil, magnesium, B vitamins, vitamins C and D.

> *"Coenzyme Q10 is something that's been recommended overall, and I've checked with the pharmacies and there's no interaction with that or any other supplements, and the cardiologists all say it's good for you as well."* – Jurgen, living with KD for five years (44 CAG repeats)

> *"I take a cocktail of additional vitamins, fish oil, magnesium, vitamin B12, C, ashwagandha."* -– Dan, diagnosed at age 39, living with KD for six years

> *"I've taken a ton of supplements like amino acids, like arginine, carnitine, berberine, coenzyme Q... I'm not sure if any of those things have had an impact. I think my fish oil and my vitamin Bs and vitamin D supplements that I take are my go-to."* – Brian, diagnosed at age 46, living with KD for two years (44 CAG repeats)

### Adaptation: strategies and attitudes

In the absence of any effective ways to treat KD symptoms, individuals living with KD are left with adaptation strategies and attitude adjustments to cope. These includes adapting activities and taking more frequent breaks, maintaining a positive mindset, adapting eating and swallowing activities, asking for help, planning well in advance, maintaining a strong faith, adaptations to speech activities, breathing and relaxation techniques, and relying on social support including support in the KD community, counselling and psychotherapy. For many patients, however, positive attitude adjustments are difficult, especially as the disease progresses, and depression may become more pronounced.

### Other approaches to address symptoms.

Other symptom management approaches mentioned during the meeting include surgery, primarily for gynecomastia.

## Despite much effort, none of these supportive interventions fully address symptoms nor do they halt the progression of Kennedy's Disease.

Despite enormous amounts of therapies, assistive devices, supplements and adjustments, patients reported very little effect on KD symptoms. This may be due to the variability and severity of symptoms in individual patients.

> *"I take a number of supplements to help overcome the fatigue but some days that doesn't help."* – KD patient (online survey response)

> *"Hard to say whether it provided me with actual improvement, but it makes me feel like I am doing what I can to preserve those functions that I still possess*." – KD patient (online survey response)

> *"Hope is that I am doing my best to maintain my existing functions and slow further declines."* – KD patient (online survey response)

## Short of a cure, individuals living with KD would like a treatment that stops disease progression, slows muscle deterioration, maintains balance, and improves swallowing and speech.

Individuals living with Kennedy's Disease want a cure for their disease, not only for themselves, but for their families as well. In the absence of a cure, they discussed some of the things that they hoped a future therapy would help address.

### Slows or stops disease progression

Ultimately, individuals would like to maintain their independence, and even stopping the disease at the current point would be beneficial. Maria described how this would make both her husband's and her life more manageable and meaningful.

> *"The most immediate impact or benefit that I see to us, me and my husband and my family, is one that would create longer plateaus and slow down the progression so that the patient and the caregiver could adapt to the challenges in a more planned, careful, safe approach rather than as a crisis response, so that their everyday life in the meantime – until there is a cure – is more manageable and meaningful."* – Maria, caregiver for her husband Gerry, aged 64 and living with KD for over three decades

> *"Anything I can do to keep where I am now. I don't have a lot of problems with swallowing. I don't have a lot of problems with eating. I don't want to get worse. I don't*

*think any of us want to get worse, I think we all want to either find a way to reverse it or find a way to get better."* – Dan, diagnosed at age 39, living with KD for six years

*"What we're looking for right now is not so much a cure, but at least some kind of a treatment that will stop the disease so that at least we don't have to worry about muscle degeneration so much."* – Jurgen, living with KD for five years (44 CAG repeats)

### Slows muscle deterioration and maintains mobility and balance.

This would help to maintain activity levels and independence.

*"One of the outcomes I would like to see is really to help stop the muscle deterioration."* – Lew, diagnosed at age 57, living with KD 15 years (44 CAG repeats)

*"For me [an ideal treatment] would be assisting and slowing the progression of quad and calf weakness, which would also help with mobility, and assist with bulbar and swallowing dysfunction*." – Brian, diagnosed at age 46, living with KD for two years (44 CAG repeats)

*"I believe that for me, my quality of life is most inhibited by my lack of balance. …And so that would be one of my primary areas of concern to any people that would develop therapies or drugs."* – George, diagnosed at age 53, living with KD for six years

### Makes improvements in swallowing and talking

*"It's critical that I maintain my ability to speak and to be understood, not just speak and slur my words… to communicate with my friends, my adult children, my wife and importantly, to remain social and engaged."* – George, diagnosed at age 53, living with KD for six years

### Other therapeutic focuses

Individuals living with KD would like therapies that decrease fatigue, effectively address erectile dysfunction (ED), provide mobility improvements, help lose visceral fat, reduce cramping and tremors. They emphasized that different treatments are necessary at different stages of the disease.

*"My perspective is I'll take whatever they got, at this point, but I think it really depends on the stage of your disease. Early on, before I knew I had KD, I was cramping up and I had a lot of tremors in my hands. So, at that time something that would've stopped the cramps and stopped the tremors would've been nice."* – Andrew, diagnosed at age 40, living with KD for more than 30 years

*"Less fatigue. Allow me to walk long distances again. I would love an effective treatment for ED. I would love to climb stairs again."* – KD patient (online survey response)

## Other important needs within the KD community.

Throughout the meeting, individuals with KD identified several other important needs.

### Individuals living with KD would like to obtain treatments sooner

Some KD patients are willing to tolerate more risk in exchange for a more immediate treatment. This includes opportunities to try potentially efficacious treatments off-label. They also asked the FDA to consider alternate clinical trial designs with fewer of subjects, and accelerated approval processes.

> "*If a treatment is showing some promise and is safe, I think it's more important to get it out faster than it is to wait 10, 20 years for the perfect treatment. And we all want a miracle cure, but we also want relief now*." – Mike, diagnosed at age 62, living with KD for seven years (44 CAG repeats)

> *"We get excited about research, but nothing is making it to trials. A slightly successful treatment today is better than a perfect treatment that is forever five years from trials."* – KD patient (online survey response)

### Increased awareness and education about Kennedy's Disease are needed

KD underdiagnosis was a recurring theme; many individuals are living with KD whose symptoms are not recognized or who do not have a diagnosis because of a lack of medical knowledge, fear, denial, lack of insurance or cultural reasons. Many have already participated in medical education.

> *"The reality is the more people hear about Kennedy's, know about Kennedy's, maybe get diagnosed with it, the better chance we have of continuing that momentum to find a treatment or find a cure for it."* – Lew, diagnosed at age 57, living with KD 15 years (44 CAG repeats)

> "*I believe that Kennedy's is severely underdiagnosed. I think it's not nearly as rare as we think it is. And I think it's because of it not being [included in medical training] or not [enough patients] being seen by neurologists."* – Mike, diagnosed at age 62, living with KD for seven years (44 CAG repeats)

### Greater recognition of symptoms and a greater inclusion of women in studies

Female carriers may experience symptoms. This is an underserved KD population that deserves more research.

### Insurance coverage for genetic testing

Several individuals living with KD described challenges in obtaining insurance coverage for KD genetic testing.

### KD multi-disciplinary clinics

*"I suggest that even for us, it's nice to go to a clinic all day where you can get a swallow specialist, an exercise specialist, but just everybody sees you for five or 10 minutes at a time."*
– Mike, diagnosed at age 62, living with KD for seven years (44 CAG repeats)

## Incorporating Patient Input into a Benefit-Risk Assessment Framework

The FDA's Benefit-Risk Assessment Framework includes decision factors such as the analysis of condition, current treatment options, benefit, risk, and risk management. The Framework provides an important context for drug regulatory decision-making and includes valuable information for weighing the specific benefits and risks of a particular medical product under review.

**Table 1** describes the challenges of having a lifelong disease burden that patients living with Kennedy's Disease also known as spinal bulbar muscular atrophy (SBMA) endure. It serves as the proposed introductory framework for the Analysis of Condition and Current Treatment Option that could be adapted and incorporated in the FDA's Benefit-Risk Assessment. This may enable a more comprehensive understanding of this unique condition for key reviewers in the FDA Centers and Divisions who would be evaluating new treatments for Kennedy's Disease. The data resulting from this meeting may help inform the development of KD-specific clinically meaningful endpoints for current and future clinical trials, as well as encourage additional researchers and industry to investigate options for treatments.

Note that the information in this sample framework is likely to evolve over time.

The collective hope of the KDA is that this meeting will encourage future research and successful new product development for people living with KD/SBMA who urgently need treatment options.

**TABLE 1: Benefit-Risk Table for Kennedy's Disease/SBMA**

| | EVIDENCE AND UNCERTAINTIES | CONCLUSIONS AND REASONS |
|---|---|---|
| ANALYSIS OF CONDITION/ IMPACTS ON ACTIVITIES OF DAILY LIVING | **Most individuals experience symptoms long before receiving a formal diagnosis of Kennedy's Disease. KD progresses slowly and diagnosis is often delayed**. Knowledge of KD in the medical community is lacking.<br><br>**Initial KD symptoms can include lower body weakness and fatigue, muscle cramping, muscle spasms and tremors.** Bulbar-related symptoms include orofacial fasciculations and difficulties swallowing and speaking. Additional symptoms include upper body weakness, balance challenges, neuropathy, gynecomastia, sexual dysfunction and breathing challenges.<br><br>**Symptoms worsen and can change as the disease progresses.** Kennedy's Disease symptoms are variable both with respect to age of onset, and severity in individual patients**.**<br><br>**Women can also experience KD symptoms**. Many women who are carriers also experience symptoms; an issue that needs wider recognition in the medical community | **KD impacts all activities of daily living**. Impacts intensify as the disease progresses, further diminishing quality of life. Mobility and balance issues can result in falls and injuries. Fatigue and muscle weakness impact activities and employment. Speech difficulties interfere with communication, leading to social isolation. Swallowing challenges interfere with eating and cause choking. The disease has profound mental health impacts including depression and anxiety. As KD progresses, the burden of disease increases and patients become dependent on their caregivers to perform basic activities of daily living. The burden of KD on caregivers is particularly heavy. Men and their caregivers live in fear of the next catastrophe and have many worries for the future. |
| CURRENT TREATMENT OPTIONS/ PROSPECTS FOR FUTURE TREATMENTS | **There are no effective or disease-modifying treatments for KD.** Instead, patients rely on supportive interventions to help manage symptoms. These can include physio and speech therapy, occupational therapy and assistive devices, home modifications, nutritional management, respiratory management, symptomatic pharmaceutical therapy, supplements, adaptation, and other approaches.<br><br>**Despite much effort, none of these supportive interventions fully address symptoms nor do they halt the progression of Kennedy's Disease.** While waiting for comprehensive therapies and a cure, KD patients are most interested in therapies that would slow the progression of the disease and allow them to retain the mobility and level of independence they have today. | **Short of a cure, individuals living with KD would like a treatment that stops disease progression, slows muscle deterioration, maintains balance, improves swallowing and speech, and sexual function.**<br><br>They would like faster access to potentially effective medications, and would prefer an imperfect treatment now, rather than to wait for a future perfect treatment.<br><br>Many individuals living with KD remain undiagnosed. This highlights the need for increased awareness and medical education about KD. |
| | ***See the Voice of the Patient report for a more detailed narrative.*** | |

## Acknowledgements

The Kennedy's Disease Association (KDA) thanks all KD patients, female carriers, and caregivers who participated in this meeting, as well as those who contributed online and in the 2021 Patient Stories video. We appreciate you all for so openly sharing your honest and authentic experience of living with this condition. We want to acknowledge all the families and especially the caregivers who work so hard to ensure that KD men are able to maintain a sense of independence for as long as possible.

We wish to thank the many staff members from the US Food and Drug Administration who attended our EL-PFDD meeting to hear what our amazing patients, carriers, and caregivers had to say. We are so grateful to have this opportunity to ensure that patient perspectives are considered in the drug development and regulatory processes. Thank you to Michelle Campbell, PhD, from the FDA for her opening comments. Thank you to Shannon Sparklin from the FDA's Patient Focused Drug Development staff who expertly guided us through this process over the many months of planning.

Thank you to Dr. Christopher Grunseich, from the NIH, for such an insightful presentation about KD. Thank you to our moderators, Brian Ahangar, MD and Ed Meyertholen, PhD, for so expertly moderating our panel sessions and for generating so many amazing insights from our participants.

Thank you to the many researchers, clinicians and representatives from pharmaceutical companies and federal agencies, who attended and listened to the voices of the KD community. We want to especially express our appreciation to the investigators working in labs all around the world, striving towards a better understanding of Kennedy's Disease and who will help to move us towards future therapeutics.

The caregiver burden of KD is enormous and men living with KD eventually require full time care. Thank you to all of the caregivers who so tirelessly care for our patients.

Thank you to our KDA Board of Directors, our staff, our many volunteers for making this meeting possible.

## Appendix 1: EL-PFDD Meeting Agenda

| Wednesday, November 9 | |
|---|---|
| 8:15 am | **Welcome and Introductory Remarks**<br>*Terry Thompson, PhD, KDA President* |
| 8:30 am | **Patient Focused Drug Development (PFDD) Meeting**<br>Introduction<br>• KDA Welcome and PFDD overview<br>*Terry Thompson, PhD, KDA President*<br>• FDA Welcome and Opening Remarks<br>*Michelle Campbell, Sr Clinical Analyst Stakeholder Engagement and Clinical Outcomes, Division of Neurology Products, FDA*<br>• Clinical Overview of Kennedy's Disease<br>*Christopher Grunseich, MD, Staff Clinician in the Neurogenetics Branch, National Institute of Neurological Disease and Stroke, National Institutes of Health* |
| 8:50 | **Introduction of Panels and Overview of Discussion Format** (Terry)<br>*Terry Thompson, PhD, KDA President* |
| 9:00 | **Panel 1: Health Effects and Daily Impacts of KD**<br>Participants discuss their experiences living with KD or caring for a KD patient.<br>Moderator/Discussant: *Brian Ahangar, MD*<br>Panelists: *Fred, Micah, Scott, James (in person); Maria, George, Lou, Randy, Tim, Jim (via Zoom)*<br>Open Discussion |
| 10:30 am | **Break** |
| 11:00 am | **Panel 2: Patient Perspectives on Potential Treatments**<br>Participants discuss how they manage their KD and their views of an ideal treatment.<br>• Moderator/Discussant: *Ed Meyertholen, PhD*<br>• Panelists: Lew, Chris, Mike (in person); Andrew, Jurgen, Dan, Harvey, Elaine, Jim (via Zoom)<br>Open Discussion |
| 12:25 | **Closing Remarks (Terry)** |

## Appendix 2: Meeting speakers and panelists

**Panel 1: Health Effects and Daily Impacts of KD**

- Brian, diagnosed at age 46, living with KD for two years (44 CAG repeats)
- Fred, diagnosed at age 40, living with KD for eight years
- Micah, diagnosed at age 46, living with KD for seven years
- James, diagnosed at age 51, living with KD for five years (39 CAG repeats)
- Scott, diagnosed at age 51, living with KD for three years (46 CAG repeats)
- Maria, caregiver for her husband Gerry, aged 64 and living with KD for over three decades
- Lou, carrier and mother of Bob, diagnosed at age 32, living with KD for 17 years (mother and son both have 50 CAG repeats)
- George, diagnosed at age 53, living with KD for six years
- Randy, diagnosed at age 31, living with KD for seven years (51 CAG repeats)
- Tim, diagnosed at age 52, living with KD for 12 years
- Jim, diagnosed at age 25, living with KD for 20 years

**Panel 2: Patient Perspectives on Potential Treatments**

- Ed, diagnosed at age 44, living with KD for 24 years (46 CAG repeats)
- Lew, diagnosed at age 57, living with KD 15 years (44 CAG repeats)
- Mike, diagnosed at age 62, living with KD for seven years (44 CAG repeats)
- Chris, diagnosed at age 25, living with KD (46 CAG repeats)
- Andrew, diagnosed at age 40, living with KD for more than 30 years
- Jurgen, living with KD for five years (44 CAG repeats)
- Dan, diagnosed at age 39, living with KD for six years
- Harvey, father of Nick, diagnosed at age 24, living with KD for 20 years
- Elaine, carrier and mother of Nick, diagnosed at age 24, living with KD for 20 years
- Jim, diagnosed at age 25, living with KD for 20 years

**Patients who spoke in the 2021 video**

- Simon, diagnosed at age 47, living with KD for 24 years
- Matt, diagnosed at age 18, living with the disease for 28 years
- Dale, diagnosed at age 52, living with KD for 12 years
- Rod, diagnosed at the age 43, living with KD for 16 years (43 CAG repeats)
- Andrew, diagnosed in early 20s, living with KD for more than 30 years
- Dmitry, diagnosed at age 46, living with KD for five years (45 CAG repeats)
- Giancarlo, diagnosed at age 56, living with KD for 11 years
- Gianni, diagnosed at age 43, living with KD for 16 years
- Kim, diagnosed at age 63 after living with symptoms for more than 20 years
- Jameson, living with KD

## Appendix 3: Additional Kennedy's Disease Resources

**(1) EL-PFDD meeting videos**

These recordings include speaker presentations, patient testimonies as well as panel discussions.

- **Part 1: Health Effects and Daily Impacts of KD.** https://youtu.be/26p7qsPgCbY. (2 h 18 min) This video contains the KDA 2022 conference opening, the introduction to the Patient Focused Drug Development (PFDD) meeting, a clinical overview of SBMA by Dr. Christopher Grunseich, and PFDD Panel 1, Health Effects and Daily Impacts of KD.
- **Part 2: Patient Perspectives on Potential Treatments.** https://youtu.be/vm0JvtXCn1Y (2 h 2 min). This video includes Panel 2 of the Patient Focused Drug Development meeting held at KDA 2022. It also includes a presentation by Dr. Abdullah AlQahtani of the NIH on the SBMA Quality of Life Study he is conducting[11], and a presentation by Jason Resendez of the National Alliance of Caregivers.
- **Patient video produced for the 2021 KDA Annual Meeting.** KDA21 Patient Stories - YouTube. This 90-minute patient video features patient perspectives from ten patients from six countries, moderated by Jameson Parker, KDA Vice-President. Some of the patient quotes were included in this *Voice of the Patient* report.

**(2) The French National Protocol for Kennedy's Disease (SBMA): Consensus Diagnostic and Management Recommendations.[12]**

This manuscript provides an SBMA/KD overview, and includes recommendations to help both physicians and patients with the diagnosis of this disease. These guidelines were created by a group of 22 individuals including patients, and are based on "participatory medicine", involving patient representatives, associations and advocacy groups. It includes a summary for the general practitioner, non-specialists, patients and the general public.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7149864/pdf/13023_2020_Article_1366.pdf

**(3) KDA patient registry at Center of Rare Diseases Sanford (CoRDS).**

The Center of Rare Diseases Sanford (CoRDS) registry was started about two years ago. At the time of the EL-PFDD meeting, 316 individuals had enrolled in the registry and complete data was obtained from 197 individuals, including some female carriers. This database is used for research and may potentially be used to recruit patients for clinical trials.
https://research.sanfordhealth.org/rare-disease-registry

[11] Alqahtani A, Kokkinis A, Dilek N, et al: Patient Reported Impact of Symptoms in Spinal Bulbar Muscular Atrophy (PRISM-SBMA) In Press, 2023

[12] Pradat P-F, Bernard E, Corcia P, et al: The French national protocol for Kennedy's Disease (SBMA): consensus diagnostic and management recommendations. Orphanet Journal of Rare Diseases 15:90, 2020

## Appendix 4: Additional Patient Comments

These comments were submitted in response to requests on the KDA Facebook page.

**Kunihiko, living with KD**

***1: How does KD affect your life?***

I used to work 12 hours a day, 5 to 6 days a week. From a few years ago, I started feeling it's getting tougher and tougher to climb up stairs, run, walk/stand long hours, pronounce certain English words (mostly EX-words such as excuse me, expect, expensive, etc....). And most recently, my neck is becoming more easier to get tired.

This causes us a lot of financial damage. With less work hours and less gain, but still have to pay more and more medical expenses. Fear of going out and hanging out with friends like before. I try to not cause any trouble to other people who might have to take care of me if something happens to me while we are together. I feel preoccupied sometimes thinking about something for hours, and that causes insomnia occasionally. So my life is affected, physically, mentally, socially and of course financially.

***2: What are you doing to help manage the disease with medication and/or supplements?***

Medication / supplements

- Etodolac (anti-inflammatory)
- Creatine
- Alpha Lipoic Acid
- Selenium
- Vitamin D
- Vitamin E
- Magnesium

How to manage

- Trying to take more rest than ever
- Exercise program about an hour every day
- Physical therapy and occupational therapy
- Trying to take more time for hobby like painting and playing guitar as stress management
- Trying to tell about pain to my family and some close friends so they can understand more
- Trying to get less physical position at work

**Angus, living with KD for almost two years**

I was diagnosed in Nov. 2021 along with my only sibling, my older brother.

We have both suffered niggling health issues from our early 20s ranging from mild anxiety, cramps, twitches (facial) and balance. Having compared notes over the years and coming to the realisation that we were both suffering similar symptoms we put it down to genetics

(uncoordinated genes) and part of the aging process, so we didn't take it any further until required.

My brother suffered a serious case of hemi facial palsy early in 2021 leading to a genetic test later in the year which disclosed Kennedy's Disease as the culprit. I was then tested, and the results came back positive.

I didn't suffer from hemi facial palsy (similar to Bell's Palsy) but have had ongoing issues with facial twitching for many years along with balance-reflex issues and extreme light sensitivity even at night. My symptoms progressed very quickly from my diagnosis primarily attacking my upper respiratory system. My voice box collapsed resulting in a permanent tracheostomy after prolific tests to ensure there were no other underlying issues other than Kennedy's.

My dexterity is getting worse by the month and deteriorates in colder weather making simple tasks like doing up buttons quite difficult. But while my fine motor neuron skills continue to diminish, my gross motor neuron skills are still ok allowing me to work around my small farm in South Australia.

Walking is getting more difficult and I find the use of a walking stick gives me the confidence to go farther than without it. I hope not to ever require a wheelchair but have to manage my expectations regarding this matter as it may happen. This, coupled with the progression of swallowing issues, may also eventuate in a PEG. But while I am alive I am grateful for what I have with the understanding that without the trachy I would not be here. I do not take any tablets other than general medicine for common colds and I still hold hope that there will be a solution for sufferers in the not-too-distant future.

**Dmitry, diagnosed at age 46, living with KD for five years (45 CAG repeats)**

1. I am 51 years old, diagnosed with KD (45 CAG repeats) for 5 years. My physical condition still allows me to walk limited distances, but during these 5 years I could not maintain morning runs, I note a decrease in coordination, a significant decrease in libido, potency, sensitivity of the genital organs, some (still insignificant) difficulties with chewing and swallowing, aphasia, chronic moderate depressive state.

2. It seems to me that I have found a mode of life that allows me to somewhat curb the rate of development of the disease (maybe I'm wrong):

- keto diet, avoidance of sugar, fast carbohydrates, fructose restriction;
- complete refusal of alcoholic beverages and smoking;
- systematic physical activity with an emphasis on strength exercises (similar to physiotherapy for sarcopenia) in combination with walking, cycling, swimming, sauna;
- bioadditives (I don't have my own observations and conclusions on their effectiveness): L-carnitine, Coenzyme Q10 (CoQ10), Creatine (with physical exertion), vitamin D, Micellar Curcumin.
- antidepressants.