



KDA/KD-UK 2020 Conference Questions and Answers

Questions and Answers from Wednesday, 14 October	
Questions for Ed Meyertholen	Response
Is it possible to get a copy of the article, "Onset Manifestations of Spinal and Bulbar Muscular Atrophy (Kennedy's Disease)," by Finsterer and Sorau? Without paying the \$40 the journal is asking?	Hi - We'll save this one until after the webinar and try to get you an answer then. Email me: emeyerth@yahoo.com
Does after diagnosis of KD CAG repeats increase over the years?	Live answered Additional response: Repeat expansion after diagnosis occurs in other repeat expansion diseases, not so much in KD. (K. Fischbeck)
Do the protein accumulations occur in both nerve nuclei and muscle nuclei?	Live answered Additional response: Nuclear inclusions are found in muscle as well as nerve cells. (K. Fischbeck)
<ul style="list-style-type: none"> • Can CRISPR be used to modify DNA sequence? • What about the use of CRISPR as a possibility? <p>Note: This question also came up during the Roundtable discussion on 15 October. See below.</p>	<ul style="list-style-type: none"> • Certainly, that is what it does. The problem is doing it in a living person is not yet possible. There are two major problems, first, the technique is not specific enough (yet) so there are errors - it could change the sequence of the wrong gene (very bad) Secondly, the proteins that 'do' CRISPR have to be put into the right cells and there currently no way to do this yet. CRISPR is amazing but the technology is not currently advanced enough to use it in a living being. I would guess that we are 10 years of more away, I am a fan of the ASO at this time. • Not at this time, there are major problems with specificity and getting the CRISPR proteins into cells. Crispr is great in a test tube but we cannot (yet) do it safely in a living person. Let me know if you need more info.

<ul style="list-style-type: none"> • Does the higher number of CAG repeats have any correlation to the onset of the disease or the severity of the weakness? • Is the number of CAG repeats indicative of severity of the disease? • I'm 68, have a CAG rate of 42, and for the past 6 -8 years have experienced many of the negative KD symptoms. My brother is 61 with a CAG of 37. He's experienced little or no symptoms. His neurologist stated he did not have KD. Mine says he has it mildly. Is his daughter a KD carrier and if so could the children have a higher CAG rate? 	<ul style="list-style-type: none"> • Live answered • Yes and no - there is a slight correlation, but it is not really predictive on the individual level. Ed, John and I all had just about the same repeat but seem to have quite different severity, and we were essentially the same age.
<p>if a carrier mother has 2 sons and one has KD, what is the percentage that the other son also has KD?</p>	<p>It's always a 50% chance prior to testing, based on the inheritance pattern. The one son's status does not affect the other. The chance of having KD for each individual son of a carrier is 50/50.</p>
<p>I am recently diagnosed with KD As an aside, I have NASH. In order to improve my liver I started to run 5-6 km 2-3 times a week. Can it harm me in the long term? or should I keep walking? Not that I lose a few "walking years". The liver has gotten better</p>	<p>I cannot speak for everyone, but I was diagnosed with KD in 1999 when I was 45 but had almost no symptoms. I started running at that time - between 20-30 miles per week and in the next 10 years ran 7 marathons - I was amazed how good I was at long distance running (I wish I knew this when I was younger). At 66, I still run albeit quite slowly, 15-20 miles per week, 6 (10K) or more miles per run. I have not found that it harmed me, but of course, I do not know how I would have been if I did not run. If I could, I would not do anything different except lose more weight! My advice would be to run if you feel good doing it. If you have any questions, please email me at emeyerth@yahoo.com. Ed Meyertholen</p>
<p>Questions for Carlo Rinaldi</p>	<p>Response</p>
<p>Carlo have you read the following papers suggesting a link between Covid-19 severity and androgen activity and the AR CAG repeat count? Could this be relevant to those of us with SBMA? Receptor Genetic Variant Predicts COVID-19 Disease Severity: A Prospective Longitudinal Study of Hospitalized COVID-19 Male Patients https://onlinelibrary.wiley.com/doi/epdf/10.1111/jdv.16956 Our data suggest that longer AR CAG score is associated with more severe COVID-19 disease. ... The results of this study suggest that the AR CAG repeat length could potentially be used as a biomarker to identify male COVID-19 patients</p>	<p>Yes, I have seen these works. In the first case the observation did not take into account the pathological expansions, so we really don't know if applies to SBMA. Regarding the second paper, it is an interesting finding that certainly deserves more study.</p>

at risk for ICU admissions. Anti-androgens may protect against severe COVID-19 outcomes: results from a prospective cohort study of 77 hospitalized men https://onlinelibrary.wiley.com/doi/epdf/10.1111/jdv.16953 These results should encourage larger studies of anti-androgens in COVID-19 patients. A large double-blinded interventional study with dutasteride is ongoing.	
Would you recommend that all KD patients, even younger relatively asymptomatic KD men isolate from Covid? As in stay at home as much as possible?	Live answered
When the vaccine comes out, should we take it?	So far the data published on the vaccines in development are showing excellent safety profiles and good immune response, which are good indicators.
Are those on ACE inhibitors at increased risk?	This is still being investigated. Some recent studies have shown that ACE inhibitors do not make coronavirus worse, but it might be too early to draw any conclusions.
//Question about the relationship between Covid and KD// In a prospective study it has found that the risk of hospitalization was about three times higher if a patient has more than 22 CAG repeats (still in normal range, not KD patients). Maybe we are therefore in a lot higher risk?	A direct link between polymorphisms in the androgen receptor and COVID-19 disease severity has not yet been established.
Does it imply that AR could be a potential therapeutic target for CoV-19, such as virus entry and the cytokine storm?	The risk of male to female is quite marginal, so it is unlikely that AR will be a therapeutic target for COVID-19 but we need to do further studies.
Is there a procedure to apply for being followed up by the London KD institute?	If you live in UK, we would simply need a referral from your GP or general neurologist.
For Dr. Rinaldi. Why does having a tracheostomy increase the risk of Covid-19 and what measures can be taken to lessen the risk?	This has to do with the general increased risk of infection that tracheostomy carries.
I have no sense of smell or taste. Is this a symptom of KD?	If this is something that has developed acutely, I would prompt you to get tested for Covid, as these may well be symptoms of a mild infection.
I am a Native American. Does there seem to be a connection between KD and Native Americans?	This connection is unknown, as far as I am aware.

Questions for Joe Shrader	Response
Will you address severely affected patients, ones in powerchairs, etc.?	Live answered.
Can elaborate on what you mean by strength training?	Muscle strength training. Any methods intended to preserve or improve strength. Keep in mind that you don't have to lift weights at all, but if you do, you don't have to see an increase in peak strength in order to see functional performance improve. I hope this helps, let me know if you wanted more information.
My speech and language therapist has recommended the use of an Expiratory Muscle Trainer machine, EMST150, to improve vocal tone. Have you found this helpful for KD patients?	Hello, I have not recommended this technique but will look into it and get back to you. Please feel free to send the same question to Beth Solomon also. Beth's response: "I use the expiratory trainers in my clinical practice for goals of increasing expiratory respiratory support for voice/swallowing. However, have not used with KD patients. Discuss this with your speech pathologist with the discussion of what is the goal and objective for using the device for your specific situation."
Do you have advice to help get back up in case of a fall - this is almost impossible to do when you live alone...?	Live answered
Are there exercises that may help drop-head?	Live answered
Can you make these videos available to us? I'd like to share with my PT.	Absolutely- the whole presentation will be linked on the KDA website. The videos we showed will be accessible and other videos by us are on the Resource Slide of the presentation. But the whole thing will be available on the KDA website.
I have had physiotherapy before and have been limited because of some serious cramps. Any advice?	Live answered
How can you get your muscles tested to tell what percentage they are currently at? Can all physical therapists test this?	This is a great question. We have a special lab for these purposes. The clinical equivalent is called hand held dynamometry. This is an inexpensive tool that is found more frequently. You may be able to get some of the medium to small body muscles tested with this method. I'll warn you, It's not simple to interpret. You can get some muscles tested and then return a year later and see how your exercise plan may have helped.
Any PT help for neuropathy? No one talks about neuropathy, numbness and pain. It affects my feet, legs, shoulders and back. Especially bad at night lying down. A burning pain and sometimes a skin crawling feeling. Neurologist always same answer: Gabapentin. Over time Gabapentin creates more issues that what it is treating, not a long-term solution.	We do recognize this is a problem for people with KD. Sorry you aren't getting the help you need. I hope some of these suggestions help. Try to make sure any edema in you feet or lower legs is managed. You can do this with elevation when resting and with compression socks when upright. There is also a technique called edema reduction massage. try socks that are cooling socks, that wick away sweat. We generally find that keeping skin cool and dry is preferable to reduce symptoms. You can try soft shoe inserts to reduce shock as you walk. Keep in mind, anything you add to your shoes requires room so you may have to upsize your shoe to allow room. You may try visiting a pediatrist. This person will assess your shoe fit. Many people with PN fit themselves with shoes slightly too tight since it give more sensory feedback and "feels" like a better fit. Shoe should not be tight. Even if you don't have swelling, performing circulation enhancing exercises can be vauable to increase blood flow to area needed for nerves.

	I don't have much to add to Joe's answer. Gabapentin may be worth trying. Similar pain occurs in other disorders, particularly diabetes. A visit to a pain specialist might be helpful.
Do you gauge exercise intensity by heart rate, perceived effort or other metrics? Do you see value in hot yoga and sauna strength training to increase heart rate or blood flow restriction training to increase effort at a given load?	We may use a percentage of target heart rate for aerobic exercise but also you can use a method called the talk test if heart rate isn't available. For strength training or functional training we may change to the rating of perceived exertion and other visible unwanted signs or responses to exercise (pain, lasting soreness, cramping, loss of form, etc), indicating a decrease in intensity may be needed. We currently have no experience with blood flow restriction and wouldn't try it without getting more experience or beginning a trial. Love saunas for health benefits but haven't recommended strength training combined.
Questions for Beth Solomon	Response
What happens to me is that, by aspiration, something (water, mucus, food) enters the channel and touches the vocal cords, that provokes them to close beyond my control, and I can't breathe. It's pretty stressful, fortunately not very frequent.	You may want to try the straw technique to see if it helps. Try and stay as calm as you can.
Are there exercises specific for throat muscles?	As with any exercise, it is always best to check with your physician or therapist in order that you are targeting the specific goal you are trying to achieve. Basic range of motion exercises are always a good place to start, e.g. head turns to each side, slow head rolls.
Excess phlegm on my vocal cords causes speech and aspiration concerns. Is there anything I can do to help reduce phlegm?	Live answered
French fries are very difficult for me to swallow. They ball up at the back of my throat and cause me to choke.	Live answered
When yawning the muscles in my neck/throat tighten and close affecting my breathing afterward until they relax. Is this typical in KD?	Live answered
I'd like to hear the proper procedure for a KD patient choking on food lodged in the throat and unable to breathe. A while back, we were advised never to use the Heimlich maneuver on a KD patient. What is the current advice?	If you are actually choking on a piece of food, following the precursors to the Heimlich maneuver by an individual asking you the specific questions what should be done. Also, consulting with your primary physician is beneficial.
Is there a drug that reduces problems with swallowing and talking for ALS patients that has finished phase 3 clinical trials and is currently being reviewed by the FDA? If yes, what does this mean for patients with KD?	I am not aware of any specific trials that address the swallowing and speech outcomes.

Questions and Answers from Thursday, 15 October	
I meant to ask Dr. Rinaldi this yesterday and forgot. It may have come up and I just missed it. Have any KD patients gotten Covid-19? If so how severe were their symptoms?	I know KD patients have gotten Covid. Since Carlo will be on the roundtable, we could ask him today or have him answer this separately with other questions that came in yesterday.
Questions for Kurt Fischbeck	Response
Why does this condition of the androgen receptor only effect leg, arm and bulbar muscle and not breathing , etc?	Live answered
Does it affect the heart?	Not usually. A cardiac conduction problem called Brugada syndrome has been described in KD patients in Japan, but not so much in the US & Europe.
Is the severity and progression of the disease dependent upon the number of CAG repeats?	There may be some correlation of repeat length with severity & progression, but more with age of onset. The number of CAG repeats correlates with the age of onset, but there is no clear evidence that the disease progression is associated with the CAG number.
Hallo I am from Belgium Have heard about „Enzymatic degradation of RNA causes widespread protein aggregation.” Could it be a solution to our disease? Your opinion interests me very much. Thanks for the good work!!! Most proteins in cell and tissue lysates are soluble. We show here that in lysate from human neurons, more than 1,300 proteins are maintained in a soluble and functional state by association with endogenous RNA, as degradation of RNA invariably leads to protein aggregation. The majority of these proteins lack conventional RNA-binding domains. Using synthetic oligonucleotides, we identify the importance of nucleic acid structure, with single-stranded pyrimidine-rich bulges or loops surrounded by double-stranded regions being particularly efficient in the maintenance of protein solubility. These experiments also identify an apparent one-to-one protein-nucleic acid stoichiometry. Furthermore, we show that protein aggregates isolated from brain tissue from myotrophic	I am not aware of the study you mention. Do you know the authors and journal in which it was published? Feel free to follow up with me about it by email at kf@ninds.nih.gov

Lateral SclerosisPlease read also: https://www.embopress.org/doi/epdf/10.15252/embr.201949585	
if you are born with genetic defect why does it take years to "show up"? Is the effect cumulative?	Good question. Yes, the effect of the mutant protein is cumulative, and it gradually overwhelms cellular protective mechanisms.
Questions for Gianni Soraru	Response
For the Clenbuterol trial how frequently is the primary 6MWT done? Have KD men been analyzed for consistency of 6MWT performance. In my own testing I find my performance highly variable influenced by many factors and it takes many tests over a long time period to have a meaningful signal.	Hi. 6MWT will be performed every 3 months during the study period (one year).
How does white matter atrophy manifest itself?	Not that I know of. The main problem is loss of motor neurons in the gray matter of the spinal cord and brainstem.
Questions for Katy Meilleur	Response
Thank you for your hard work! Is the efficacy of ASO's dependent on treating patients *before* onset of symptoms? Will ASO's work on adult SBMA patients well after onset of symptoms has begun?	Live answered
In the ASO mice test that is being referenced, did the mice exhibit symptoms of SBMA prior to the ASO treatment?	Live answered
Questions for Andy Lieberman	Response
Do we think Artificial Intelligence and Cloud Computing will speed up research?	Live answered
Dr. Lieberman, are there ways for those of us with KD to test for HSP activation direct or by proxy through orderable labs?	Great question. The hospital clinical lab does not typically run a test to assess HSP activation.
Questions for the Roundtable	Response
Dr Fratta suggested last year that KD might be much more prevalent than currently thought. If he doesn't cover this in today's presentation can he give us an update?	Live answered
1. Are there any news about an international KD register? It may be an important resource. 2. There are some animal results (in C. elegans) with low dose metformin + ASA in reducing of number of polyq aggregates. It	Live answered

sounds to be a quite safe strategy. Efficacy is a question. Any human experience? Please kindly comment it.	
I was 44 when with a CAG = 43 when diagnosed in 2004. Is there a correlation with age of onset and number of androgen receptor repeats?	//Please see answer to a similar question under Ed Meyertholen, above.//
Is the ultimate goal a cocktail like aids with several drugs mixed to help several ways?	Live answered
<p>CRISPR:</p> <ul style="list-style-type: none"> • Will the panel be able to discuss efficacy of Crispr? • I have read several articles recently about CRISPR and gene editing and have also seen programs on PBS and Nova. Is CRISPR technology a possible cure or treatment for Kennedy's disease and if so, when could it become available to patients? Thanks. • What about CRISPR CAS 9 ? 	<ul style="list-style-type: none"> • Live answered • //Please also see answer from Ed Meyertholen, above. // • Ed also provided this link to an ABC News item about CRISPR: https://abcnews.go.com/Health/wireStory/lab-tests-show-risks-crispr-gene-editing-embryos-73902820
Dr. Fischbeck, if age of onset is correlated with severity, has anyone discovered what factors determine age of onset?	There is a loose but not definitive correlation with age of onset and CAG repeat. We assume that other genetic factors are at play but there has not yet been enough study to support a conclusion.
Has there been any studies on healthy non affected siblings or family members of KD?	Live answered
I took Nuedexta for 6 months and did not notice any improvement in my swallowing.	<ul style="list-style-type: none"> • Live answered • I heard from one patient that they used Neudexta and they saw improvement. Had improvement on swallow studies. (Angela Kokkinis)
I was originally diagnosed with Kulgeberg-Wheelander in 1990 and finally with KD in 2000. can KD be diagnosed earlier now?	There is a genetic test for Kennedy's Disease, and that is the only way the disease can be diagnosed.
Is there any benefit in using carriers for research since we have half the mutation in our cells?	Live answered
My Brother also had KD. Are siblings rare ?	Live answered. Also see Ed Meyertholen's earlier comment about his cousins.

What would be your best guess on the timeline for the next clinical trial for Kennedy's Disease and what would the drug candidates be?	Live answered
Kurt: Is it possible that there are significantly more patients than 1 in 50,000-100,000?	Live answered
Carlo Rinaldi: Any progress on your submission for gene therapy submitted to FDA that you discussed last year?	We are planning to submit this work to a peer-reviewed scientific journal very soon and are very excited to share the data with the SBMA community. Meanwhile, we are trying to get funding and to engage with pharmaceutical companies to perform toxicology studies, that are necessary before this gene therapy can enter the clinical stage.
Re: Testing: The word needs to go out to Neurologists to make the genetic test more of a standard test when KD symptoms appear in patients. Here in Ontario, the cost is not covered by OHIP and costs about \$125. They need to recognize the symptoms (through education) and to confirm the POSSIBILITY of KD to start with...	Live answered
Can anyone speak to the prevalence of diabetes with SBMA and why that occurs?	Live answered
In my experience as a KD patient who has significant pseudo bulbar symptoms in a sense anxiety, or over mental stimulus, I do benefit from Nuedexta in helping with speech and physical coordination such as affecting balance.	Live answered
Wondering if a ketogenic diet could help with the insulin resistance and other factors of the disease?	<ul style="list-style-type: none"> • Live answered • Benjamin C. reach out to me and I can supply you with a vast quantity of info on keto dieting which I have been following for 4+ years with great benefit. TAllen@KennedysDisease.org
I was diagnosed a year ago with type 2 diabetes I realize it comes with KD but last month I was diagnosed sugar diabetes free I have not changed my diet and I still use sugar normally I have not come back on anything does that happen to other Kennedy disease patients	Live answered
What about an increase in proteins in diet... is there a benefit to increasing proteins to help retain muscle mass or muscle building?	I do not think there is any data on the effects of a high protein diet on KD, but I'm not an expert. There can be kidney issues with such diets so one should consult with their physician before starting.

General Comments from Both Days	
Metformin can possibly play a role in reducing visceral body fat which would improve health profile of KD patients.	Response not required.
A few years ago we performed a study in transgenic SBMA mice with metformin and did not observe any motor function benefit. But it was limited to one dose (in mouse food). So I'm not sure if it is off the table yet (or should be kept on it).	Response not required.
Anyone interested in remote coaching a KD patient collective effort seeking better approaches to monitoring disease trajectory to facilitate future clinical trials? I suggest looking at tests which anyone can perform often without specialized equipment such as a 10 second sprint or using a bathroom scale to measure force of isolated muscle groups. As a patient group we could explore non-pharma interventions and gain experience potentially useful to the KD research community.	Response not required.
I have more of a comment. My dad participated in the research study on Kennedy's and exercise at the NIH. He passed away in 2017. It is good to see the results of the study he participated in.	Response not required.
I am so thankful for KDA. My father was diagnosed with Kennedy's when I was 28 and he was 61. I am a nurse. The KDA website has been my main source of information ever since his diagnosis and I am so appreciative. My father passed away in 2017 and he did not let KD stop him.	Response not required.