

HUNTINGTON DISEASE Insights

AUTUMN 2019

SPECIAL EDITION

Look up!

Soaring Prospects for HD Youth

Also in this issue

- ▶ HOW THE HUNTINGTON GENE AFFECTS BRAIN DEVELOPMENT
- ▶ FAMILIES COPING WITH THE STRESS OF HD
- ▶ NEW HD INSIGHTS PODCAST + SOCIAL MEDIA

25
years

Features

14

An Informed Decision and a Prepared Mind

Clinical teams and patients navigate genetic testing.

20

HD Youth Find Their Voice

Kids-HD and juvenile onset HD programs foster deeper understanding of HD in youth

26

Building Resilience in the Face of Stress

Changing the landscape of Huntington's disease for HD patients and family members



DEPARTMENTS

10 ▶ HD RESEARCH
Profiles on current HD research

13 ▶ HD BY THE NUMBERS
Statistical highlights

30 ▶ SPOTLIGHT
Stories of Resilience

34 ▶ HD CLINICAL TRIALS
Status of HD clinical trials

35 ▶ HD THERAPEUTIC PIPELINE
Status of HD treatments



HD INSIGHTS PODCAST

The HD Insights Podcast is designed as a long form, one-on-one interview format. Our goal is the same as with the print publication: to promote, disseminate, and facilitate research and science education in HD by producing informative content that will be valuable to the global community of HD researchers in academia and industry. See page 6.



AVAILABLE ONLINE

Apple iTunes: [HTTP://BIT.LY/HSG-HDINSIGHTS](http://bit.ly/hsg-hdinsights)

Google Play: [HTTP://BIT.LY/HDINSIGHTSPOD](http://bit.ly/hdinsightspod)

“The cause of the child is the cause of humanity.”

MERLE S. SCHERR, FOUNDER | CAMP BRONCO JUNCTION

HUNTINGTON DISEASE Insights

AUTUMN 2019
HUNTINGTONSTUDYGROUP.ORG

Changing our approach

A recently, I was scheduled to dose a patient for an intrathecal antisense about one year ago, our clinic experienced a defining moment that caused us to reassess our practice. Our HD clinic occurs every Friday, and this Friday didn't seem very different. We saw a number of patients that day, and one patient in particular seemed to be doing quite well. He was tolerating his medications, had a good experience in physical therapy, had recently obtained disability, and was brought to clinic by his daughter and wife.

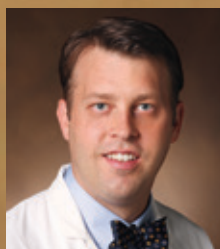
To our shock, we received a phone call three days later informing us that his daughter attempted suicide. This news was unexpected, and we realized that we had never talked to this patient's daughter and asked how *she* was doing. We needed to change our clinical approach.

The burden of HD in the lives of children is substantial. In this edition of *HD Insights*, we address this topic of children who live with HD. I am so grateful to Martha Nance, Peg Nopoulos and Bruce Compas, who have provided thoughtful articles that address genetic testing, imaging research in HD-kids, and novel approaches that assess stress and coping in children that live with HD. I have had the pleasure of working with Kat Martin, BJ Viau, and HDYO, and we are grateful for their personal stories about living with a parent who has HD.

Ed Wild, who is working front and center with HD youth in Great Britain, offers his perspective on the trends he sees and the strength and activism embodied by the young people across the pond. We continue to feature the clinical coordinator perspective, this time with Abigail Ciriégio telling us her experience about working with children. It is compelling, trust me.

I want to thank you all for the encouraging feedback you have given regarding the last couple of issues. We start the new academic year with a new deputy editor (welcome Margy Rockwood!) and new industry sponsors (we could not do it without their support!). We remain committed to providing an informative periodical that focuses on the clinical, research and life experiences around HD.

Listen in to the new podcast, and don't hesitate to drop us a note. (We may publish it!)



DANIEL CLAASSEN, MD

*Associate Professor
of Neurology
Vanderbilt University*

PUBLICATION STAFF

Margaret Rockwood, MA
Deputy Editor

Christina Ullman, MSJ
*Art Director,
Ullman Design*

Lise Munsie, PhD
Scientific Content Reviewer

EDITORIAL BOARD

Daniel Claassen, MD
*Editor
Vanderbilt University*

Donald Kennedy, PhD
Stanford University

Nobuyuki Nukina, MD, PhD
*Riken Brain
Science Institute*

Rodrigo Osorio
*Agrupación Chilena
de Huntington*

Ralf Reilmann, MD, PhD
George Huntington Institute

HUNTINGTON STUDY GROUP

Lauren Falanga
*Manager, Clinical
Collaborations*

Kevin Gregory
*Director, Education,
Communications
and Outreach*

Shari Kinell, JD
Executive Director

Janine Mercandetti
*Manager, Projects
and Contracts*

Kristin Strazdins
*Manager, Finance
and Special Projects*

Anne Van Dusen, CHC
Director, Operations



How clearing the air about HD brought me peace

BY CATHERINE MARTIN

Living with Huntington's Disease is hard. Regardless of your connection to HD, there are some really tough days. But what if you were 14 years old, you were the main caregiver for your dad, and your mom was struggling to pay the bills? How would you juggle school, friendships, caregiving responsibilities, all in the midst of hormonal changes? This is the reality that so many of the young people we work with face every single day. These are the family members who are often invisible to the outside world. This is why Huntington's Disease Youth Organization (HDYO) exists.



More information about the Huntington's Disease Youth Organization can be found on their website at:

WWW.HDYO.ORG



SECRECY IS NO FAVOR

In 2007 I spoke at the World Congress on HD in Dresden, Germany on why we needed to do more to educate and support children and young people impacted by HD. To say this wasn't a popular topic is an understatement. Family members, clinicians, scientists, patient group member all said "We shouldn't be talking to kids about this, it's too much for them," or "It is OK for them to provide care to their family members but don't tell them why they have to."

This was not my reality, and I knew they were wrong. I grew up with various family members sick with HD, was caregiving for my grandmother from a young age, and my mom developed symptoms when I was a teenager. This was my normal. In our family we spoke often about HD, about the symptoms different family members were having, about

our own risk, and about what we could do to help ourselves.

I was 13 years old when I first spoke to a geneticist. I had questions and needed to understand what HD was. Mom and Dad were supportive. They trusted me as an individual and wanted to give me the freedom to ask emotional and technical questions with a specialist so that I could grow. I was never scared of HD because of the education and support my parents provided to help me understand what was making people I loved sick. My childhood to me was normal and very happy.



SPREADING THE MESSAGE THROUGH EUROPE

My family was involved in establishing the Scottish Huntington's Association 30 years ago because they couldn't get the education and support they needed as adults. The reaction from people at the World Congress just made me more determined to prove to this community that children and young people needed and deserved age and stage-appropriate education and support about HD as much as adults did. Over the next five years, a number of events took place that changed this community for the better.

We have made good progress, following hundreds of years of secrecy and generational trauma. The question now is how do we continue to grow so that everyone understands and experiences the benefits of talking about HD? I know from my life growing up in an HD family and subsequently working with HD families in Scotland, that hiding HD isn't possible. Talking about it, finding specialists, educating ourselves about this disease and raising awareness changes the outlook of dying from HD to living with HD.



THE TRUTH MAY SET YOU FREE

As parents, protecting our children is a natural instinct. We don't want them to see how scared, tired, heart-broken and vulnerable this disease can make us. As clinicians, we may limit our care to making sure our patients get the right medicine to treat their symptoms so that we can keep them as well as possible for as long as possible.

HDYO challenges both of these schools of thought. Talking about this disease more honestly is a big part of the solution. Clinicians need to start asking emotional questions along with diagnostic questions. Parents need to encourage their children to ask questions and challenge the stigma they encounter. If we can all, as a singular HD community, help one another to talk about the true impact of HD and tailor the support and education needed by each member of the family to be age- and stage- appropriate, then think how different the perception of this disease would be!



HDYO OPENING BROAD CHANNELS OF COMMUNICATION

Providing education, support and events for young people under 35 years of age is the key objective of HDYO. In the seven years since we launched, HDYO has been viewed over seven million times; our educational resources (available in 14 different languages) have been shared 200,000 times. We have supported over 4,000 individuals from 96 countries and held 10 international youth camps in four regions (Europe, North America, Australia & New Zealand and South

America). In 2020 we will host the inaugural Young Adult World Congress for HD in Glasgow, Scotland.

Giving children and young people access to trustworthy educational resources will not harm them — it will strengthen them. I grew up knowing about HD, and I lost some of the most important people to me to HD, but it has taught me about being kind, compassionate, living life to the fullest and seeing the good in every situation. HD has given me more than it ever took from me and I have my parents' courage and strength in being honest and open with me to thank for that.



CATHERINE MARTIN

Catherine Martin is Executive Director of the Huntington's Disease Youth Organization.

OUR PROGRESS IN SPREADING THE MESSAGE

2008

- ▶ Audit of services for children and young people in Europe

2009

- ▶ Young people as speakers at World Congress, Vancouver
- ▶ First meeting of European Network to talk about establishing a working groups specifically about young people and HD

2010

- ▶ First European youth camp for HD
- ▶ The beginnings of HDYO and HD Buzz emerged

2011

- ▶ EHDN Young Adult Working Group established

2012

- ▶ HDYO launched its platform in four languages
- ▶ Second European youth camp for HD
- ▶ Young people on the main stage at EHDN conference



“Talking about it, finding specialists, educating ourselves about this disease and raising awareness changes the outlook of dying from HD to living with HD.”

HD Insights launches new podcast and social media pages



BY KEVIN GREGORY



KEVIN GREGORY

Kevin Gregory is Director of Education, Communication & Outreach at the Huntington Study Group.

The manner in which people consume information has changed drastically in the digital age, particularly over the past five to ten years. One of the channels experiencing a dramatic growth in user adoption is podcasts. They check all the right boxes for a generation of people on the go: ability to stream to your computer or mobile device, to listen on-demand — when you want and where you want — and to connect with topics or subjects on a personal level by listening.

According to the website MusicOomph, 165 million people in the United States have listened to a podcast. On a monthly basis, 32 percent of the U.S. population listen to a podcast, while the average weekly listener consumes seven different podcasts, totaling about six and a half hours! So, it made sense for HD Insights to expand our core platform of a semi-annual printed publication by creating a companion podcast series.

Interested listeners can find the HD Insights Podcast on Apple iTunes (<http://bit.ly/HSG-HDInsights>) and Google Play (<http://bit.ly/HDInsightsPod>), where they can download, subscribe, rate and review episodes. Listeners that subscribe to the podcast series automatically get the latest episodes downloaded to the device they subscribed from.

To help increase the potential reach for HD Insights content, the Huntington Study Group has created companion social media pages for HD Insights on Facebook and Twitter. Users can follow HD Insights on Facebook by the account name **@HDInsights.org**, or by searching for the handle titled **@HD_Insights** on Twitter. The social media channels are a great way to get quick-hitting updates on new articles, research, and our latest podcasts.

PODCAST EPISODES

▶ *First episode*

The first episode was an interview with Dr. Daniel Claassen, editor of *HD Insights*, about his journey in HD research, how he sees HD care evolving, and how he got involved in *HD Insights*. Listeners will also come away with some insight on a couple of his personal passions: the viola and golf.

▶ *Episode 2*

Episode 2 featured Dr. Joseph Higgins from uniQure who talked about their novel therapy, AMT-130.

▶ *Episode 3*

Dr. Vicki Wheelock joined the podcast for Episode 3 to talk about her work at UC Davis and the active community in the greater Sacramento area ahead of HSG 2019: Navigating HD.

▶ *Future episodes*

Future episodes already scheduled for release include an in-person conversation from the HDSA Annual Convention in Boston with Dr. Victor Sung from the University of Alabama at Birmingham, and a deeper discussion about the impact of HD on youth and genetic testing from Dr. Martha Nance.

A novel approach to Huntington's disease

Committed to listening, learning, and partnering with the Huntington's disease community

wavelifesciences.com



Defining juvenile Huntington disease

CALL FOR A COMMON DEFINITION OF EARLY-ONSET HD

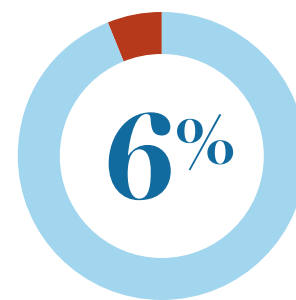
The European Medicines Agency (EMA) has removed a class waiver that allowed sponsors to exclude children and adolescents under 18 from clinical studies. This includes HD cohorts. Now, researchers will need to submit a pediatric investigation plan early in the drug development process, though they can still request an individual waiver or deferral.

This is a break from the U.S. policy, where the FDA continues to include HD as an adult-related condition that qualifies for a waiver because of HD's relatively rare onset in those under 21 (six percent of all cases).

Further confounding the issue are the differing definitions of "juvenile Huntington disease" (under 18) in Europe, versus "juvenile-onset Huntington disease" (under 21) and "pediatric Huntington disease" (under 18) in the United States.

The Juvenile Huntington Disease Working Group of the European Huntington Disease Network weighed in with comments in a recent publication of *Movement Disorders*, suggesting standardization of the terminology and age ranges. "We propose phasing out the term JHD... and introducing the term pediatric HD. This term is simpler to understand and means young people affected by HD who are currently aged <18 years," they said. This would align the pediatric definition with the U.S. FDA's.

With regard to Europe's removal of the waiver for children and adolescents, they caution that it will be challenging to obtain observational data following an intervention for this small, widely dispersed cohort.



The percentage of all HD cases

with onset under 21 years old.

Spreading information and hope

Dr. Ed Wild shares insights on the HD youth community

Dr. Ed Wild is editor-in chief of HD Buzz, an online source of research news, written “in plain language” for the global HD community. Since its inception in 2019, Dr. Wild, whose own research has been pivotal in the HD field, has been culling and clarifying HD news for this channel, spreading information and hope. We asked him for his insights on the current scene in the HD youth community.

▶ **We see announcements on HD Buzz about “zinc fingers,” new clinical trials and progress in ASO treatment. What recent news do you think might have the biggest impact on at-risk youth over the short term?**

I think it's the news that has been coming through, in drips, about the recruitment status of the RUSH generation HD1 trial of the drug RG6042. This is the first Phase III trial of a huntingtin-lowering drug that has ever happened.

We won't find out the results of that trial for a couple of years, but the trial is recruiting 660 volunteers. This recruitment has been unexpectedly rapid, and in fact, the trial is now fully recruited in the U.S.A. That is a huge testament to the dedication and determination of the HD community, and it also means that the trial will deliver its news, good or bad, in an unexpectedly rapid time frame, which is always good.

That news builds on several decades of successful work showing that lowering the huntingtin protein is possible and can be done safely and effectively in human patients. The question now is whether lowering the protein slows the progression of the disease. That is an answer the community is now going to provide for us in record time.

The bigger picture is that this is one of several huntingtin-lowering approaches, and while it is the one that is closest to success, there are at least half a dozen approaches being tried to accomplish the same thing. These include other ASOs, zinc fingers and gene therapies, so it's really kind of a diverse set of approaches to a problem that we know to be the cause of HD.

▶ **Do you see this news generating a spirit of optimism that wasn't there one, five or ten years ago?**

I do. I see it on social media and daily in my work with HD youth. A young person today knows that even if they do have a high HD risk, they may be symptom-free for 20 or 30 years, during which time, who knows what might happen?

And the hope is well-founded. We don't have an effective treatment for HD yet, but we are delivering on the things we have been promising. Ten, fifteen years ago we promised we would bring protein lowering drugs targeting HD to human trials, and we did that. We promised that we would deliver a drug that would lower the concentration of the protein, and we did that. Next, we promised we would test to see if that drug slows the progression of HD and we are in the process of doing that. And when I say “we,” I mean everyone — patients, families, healthcare professionals and scientists, together.

▶ **What can young people do if they want to participate in a trial or otherwise support the progress of HD research?**

Back in the 90s, the big news was the genetic test, but it didn't help you either way, you weren't any further ahead having had the test. Now people are starting to appreciate how much difference actively participating in research can make to their own future as well as the future of the next generation.

And that will have to happen in young people who have had a genetic test, but don't have symptoms yet. This is probably the next big thing in HD trials. This trial we are currently running is big. The effort to prevent HD will need to involve even more participants, because you need bigger, longer trials to prove that you can delay or prevent the onset of HD.

If young people want to know what to do next, I'd say there are two things. First, if you are not already seeing one regularly, you should see a genetic counselor to talk through the options and talk about how possible future research developments might factor into that.

The other thing is to sign up for the EnrollHD study, which is open to almost all family members and particularly open to at-risk people or people who are pre-manifest, people who don't have symptoms yet. That is the best way to make sure



DR. ED WILD

Ed Wild, MRCP, PhD, is principal investigator at UCL Institute of Neurology and a consultant neurologist at the National Hospital for Neurology and Neurosurgery, Queen Square, London. Wild studied medicine at Cambridge University and has worked in neuroscience since 2005. His PhD research was on biomarkers for Huntington disease. Wild's research team studies cerebrospinal fluid in Huntington disease and he is the global chief investigator of the HDClarity study. He also runs clinical trials of new treatments in HD including 'gene silencing' drugs. Since 2009 he has been collaborating with Dr. Jeff Carroll to make HD research news accessible to the global HD community.

“ Before social media, kids were completely alone and often bullied at school, and really didn't have any support, didn't know anyone else from an HD family.”

DR. ED WILD

that any future prevention trial gets recruited as quickly as possible, because EnrollHD is basically the squad from which the trial team will be picked.

The genetic test is part of enrollment, but the results are not revealed to anybody, including the participant or the sites. So the result is used for research but will never be conveyed to the person or the site. If people don't want to know that status, but want to help with the research, HDEnroll is a great way to do that.

► ***This issue includes an article by Dr. Martha Nance on predictive testing, which is, of course, the elephant in the room in the lives of at-risk youth and their families. What do you see most commonly when young people decide to get the test and learn they are at risk? Do they and their families cope better without the uncertainty? What constructive things do some of them do with the knowledge?***

We see a wide variety of reactions and that's what the whole genetic counseling piece is about, sort of giving people time and information to help them make a decision that is right for them.

Generally, people are psychologically better off having the test rather than not having it, and this has been studied, particularly in Canada. A positive test result is obviously devastating news, but it is a piece of information that can help people to come to terms with their future, it can help them plan their lives and decide what positive actions to take. So while it is not right for everyone, the decision to test, on the whole, turns out to be something people are glad they did. Obviously, it is something that takes awhile, and in some cases many years, to reconcile with.

► ***What strategies do you see the at-risk population using effectively to optimize their lives each day?***

What I have seen in the last 15 years is an absolutely seismic shift in the resources

that young people have to deal with, being at risk of HD. And it all comes down to social media. So when I joined HD in 2005, the cool thing that kids did was smoke cigarettes without their parents' permission. In my first five years, what I saw was that those cigarettes were replaced by mobile phones. And the way kids impressed each other was by having more followers on social media, by having the latest social media app.

As a result of that explosion, Huntington Disease Youth Organization came into being, and the National Youth Alliance in the U.S. has been hugely empowered by that.

Basically, before social media, kids were completely alone and often bullied at school, and really didn't have any support didn't know anyone else from an HD family. Now, kids at risk for HD have this huge support network from other kids and other HD family members in a very safe, curated space where families and their kids can help each other and they can engage on their own terms.

Essentially, an atmosphere of isolation and fear has completely transformed into one that is now about positivity, communication and taking specific actions to fight the disease. It's like the previous generation was tied up and blindfolded and put in an arena with an enemy to fight. And

now, the lights are on, everyone has their eyes open, and there are thousands of people fighting the enemy. Clearly everyone in that situation is in a much better position.

► ***How are some of these young people becoming activists for research and better understanding and support for people with HD in their communities?***

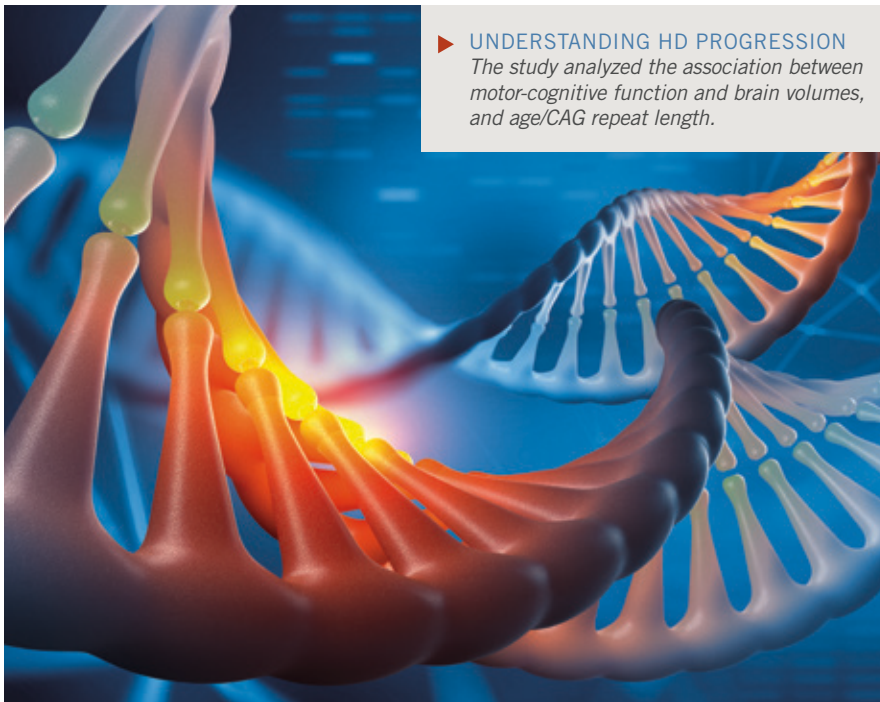
This is huge. On my Twitter feed, and on Instagram and Facebook and so on, I see selfies of young people taking part in research projects. It's become quite common to see a selfie of someone holding a tube of their own spinal fluid, or having an MRI scan, or at an EnrollHD visit. So social media has encouraged people to turn research into something that, in some cases, is even fun. It demystifies some of the fear that comes with the medical side it and helps to create something whereby research is celebrated and congratulated.

A lot of kids take part in fundraising to help in local research. I also see a lot of young adults who have piercings or tattoos that speak to raised awareness. These might be a DNA strand or a CAG block, or the number that is their CAG count. For these young people, it is partly awareness-raising and partly stamping on their own bodies their intention to fight the disease.



profiles

BY LISE MUNSIE, PH.D.



► **UNDERSTANDING HD PROGRESSION**
The study analyzed the association between motor-cognitive function and brain volumes, and age/CAG repeat length.

1

CAG Repeat Length Predicts Rate of HD Progression

A key aspect in the success of clinical trials is understanding the natural progression of disease. Although CAG repeat length is well-known to be associated with age of onset (AOO), there is conflicting evidence on whether disease progression is also impacted. The TRACK-HD and TrackOn-HD groups performed a prospective study over time¹ and analyzed the association between motor-cognitive function and brain volumes, and age/CAG repeat length. The outcomes of this study suggest that CAG repeat length not only predicts AOO, but additionally predicts rate of decline.

Adding more evidence that CAG repeat length is a predictor of AOO, the Genetic Modifiers of Huntington's Disease (GeM-HD) Consortium published results in

a recent *Cell* paper² that elaborated on specifics of this phenomenon. Since CAG repeat length only accounts for 60 percent of variation in AOO, GeM-HD looked for more complete explanations by carrying out genome-wide association studies (GWAS) in over 9,000 HD patients, seeking genetic modifiers.

During this study, the group found that the length of the translated polyglutamine tract is not the predictor of AOO; rather, it is the length of the uninterrupted CAG repeat at the DNA level, separate from its glutamine coding property. This highly powered study also identifies other genetic modifiers of disease onset, highlighting different therapeutic targets for multiple stages of disease.

Independently, Dr. Michael R. Hayden's group³ made the same conclusion about uninterrupted CAG repeats, by analyzing HD pedigrees that have a genetic variant resulting in longer uninterrupted CAG tracts. This group found a correlation between this extended, uninterrupted CGA tract (with earlier AOO) and individuals with the same translated polyglutamine tract length, but genetically with polyglutamine encoding CAA interruptions to the CAG repeat.

¹ Langbehn D.R. et al. (2019) Association of CAG Repeats With Long-term Progression in Huntington Disease. *JAMA Neurol.* .doi:10.1001/jamaneurol.2019.2368

² GeM-HD (2019) CAG Repeat Not Polyglutamine Length Determines Timing of Huntington's Disease Onset. *Cell* 178(4) 887-900

³ Wright, G.E.B et al. (2019) Length of Uninterrupted CAG, Independent of Polyglutamine Size, Results in Increased Somatic Instability, Hastening Onset of Huntington Disease. *AJHG*: 104(6) 1116-1126

2

ASO Phase I/II Trials Demonstrate Safety and Htt Impact

The highly anticipated results from the Ionis and Roche huntingtin (Htt) lowering phase I/II clinical trial have been published in the *New England Journal of Medicine*¹. The drug being tested is an antisense oligonucleotide (ASO) designed to lower Htt levels. The trial proved the safety of the drug with no serious adverse events, and found a dose-dependent decrease in the concentration of Htt found in cerebrospinal fluid (CSF). Larger studies will now be required to show if this decreased level of Htt found in the CSF correlates with decreased levels in the brain and the slowing or stopping of HD progression.

Researchers are exploring other methods for Htt lowering in pre-clinical models. A manuscript in *Nature Medicine* outlines the utility of zinc-finger protein transcription factors (ZFP-TFs) to selectively lower mutant-Htt (mHtt)². The current ASO methods are transient, require multiple doses and generally target both mHtt and wild type Htt alleles, which may have detrimental effects. Here, the test group designed and tested ZFP-TF that selectively silences mHtt over the long term after a single administration. They demonstrated its utility both in cell line and mouse models with fewer off-target effects.

Since Htt lowering is such a promising therapy, groups are exploring alternative ways to target mHtt in a allele-specific manner. Naturally occurring miRNAs, which regulate expression levels of genes, are another option for exploring therapeutic benefit if appropriate endogenous targets can be identified. Recently a group demonstrated that endogenous miRNA that can interact with Htt 3'-UTR exist. They created and validated a full length 3'-UTR reporter vector based on the most common mutant and wildtype Htt haplotypes.³ This vector can be used in concert with genetic information to identify targets for endogenous silencing of mHtt.

¹ Tabrizi, S. et al. (2019) Targeting Huntingtin Expression in Patients with Huntington's Disease. *NEJM* 380(24) 2307-2316

² Zeitler, B. et al. (2019) Allele-selective Transcriptional Repression of Mutant HTT for the Treatment of Huntington's Disease *Nature Medicine* 25:1131-1142

³ Kim, K et al. (2019) Full Sequence of Mutant Huntingtin 3'-untranslated region and modulation of its gene regulatory activity by endogenous microRNA. *Journal of Human Genetics* doi: 10.1038/s10038-019-0639-8



► **AFFECTING THE BRAIN**
While the striatum is significantly affected by HD, other areas of the brain, including the hippocampus, also undergo degeneration.

3

Synaptic Plasticity Deficits in HD Revealed Through iPSC Models

Juvenile-onset Huntington's Disease can be used as a surrogate to study the neurodevelopmental aspects of HD¹. Creating induced pluripotent stem cells (iPSC) from patient stem cells, followed by differentiation to neurons, makes a good in vitro model for studying disease and testing therapeutics on phenotypic reversal. During early timepoints in differentiation, there is a delay in neurodevelopment denoted by increased nestin positive neurons. Knocking down huntingtin (Htt) in iPSC decreases the nestin positive neurons at early stage differentiation towards the striatal lineage.

Non-cell autonomous effects are hypothesized to lead to some of the pathophysiology in HD. A group with a novel astrocyte differentiation process aimed to use the juvenile onset iPSC model to interrogate the effect of mutant Htt (mHtt) in this supportive cell type². The electrophysiological properties were conserved in astrocytes differentiated from HD or control iPSC, however the co-culture of HD astrocytes with neural precursor cells (NPC) showed distinct phenotypes. HD astrocytes are less supportive of the functional maturation of the co-cultured neurons, and in the presence of HD astrocytes, researchers found that co-cultured neurons exposed to chronic glutamine stimulation are not protected.

Also recapitulating juvenile or early onset HD, a comprehensive study was done on hippocampal synaptic plasticity³ in Q175 knock-in mice. Although the striatum is the most significantly affected brain region during the course of HD, it is well known that other areas of the brain, including the hippocampus (which is responsible for cognitive function), also undergo degeneration. This study examined heterozygous, homozygous and wild type littermates at different time points. A clear deficit in both short- and long-term synaptic plasticity was found to track with level of disease progression and mHtt expression.

¹ Mathkar, P. et al. (2019) Characterization of Neurodevelopmental Abnormalities in iPSC-Derived Striatal Cultures from Patients with Huntington's Disease. *Journal of Huntington's Disease*. doi: 10.3233/JHD-180333

² Garcia, V.J. et al. (2019) Huntington's Disease Patient-Derive Astrocytes Display Electrophysiological Impairments and Reduced Neuronal Support. *Front. In Neuro*: 13(669)

³ Quirion, J.G. and Parsons, M.P (2019) The Onset and Progression of Hippocampal Synaptic Plasticity Deficits in the Q175FDN Mouse Model of Huntington Disease. *Front. In Cell Neuro*. 13(326)

“Knocking down huntingtin (Htt) in iPSC decreases the nestin positive neurons at early stage differentiation towards the striatal lineage.”



SIGNAL studies update

Vaccinex, Inc., working with the Huntington Study Group (HSG) and the University of Rochester's Clinical Trials Coordination Center (CTCC), continues to advance SIGNAL, a potentially pivotal clinical trial for registration of pepinemab as a treatment for Huntington's disease (HD). Pepinemab (VX15/2503) is an antibody to semaphorin 4D, a molecule that is believed to trigger transition to an inflammatory state in the brain and may play an important role in HD disease progression. SIGNAL is a multi-center, randomized, double-blind, placebo controlled study designed to assess the safety, tolerability, and efficacy of pepinemab in subjects with early manifest and late prodromal Huntington's disease (HD).

The first 36 participants enrolled in the SIGNAL study, Cohort A, were randomized to receive monthly infusions of either pepinemab or placebo for six months in a double-blind fashion followed by open-label pepinemab for five additional months. No concerning safety signals were identified. Significantly, pepinemab treatment showed marked effects on FDG-PET imaging, a measure of glucose transport that is fundamental to brain metabolic activity.

Pepinemab increased glucose uptake in all cortical brain regions examined, with a median increase of 8.6 percent compared to placebo over just 6 months of treatment. Loss of FDG-PET signal is associated with underlying disease progression in HD as well as other neurodegenerative diseases, and has been shown to correlate with cognitive decline in Alzheimer's disease. Pepinemab is the first intervention shown to prevent loss of metabolic activity in the brain of subjects known to carry an HD gene mutation.

Cohorts B1 and B2, now fully enrolled, include 179 early manifest subjects in group 1 and 86 late prodromal subjects in group 2, for a total of 265 HD subjects. All subjects are randomized to receive monthly infusions of either pepinemab or placebo for 18 months in double-blind fashion, without crossover.

The last Cohort B subject visit is projected to be in June 2020, and topline results are expected in the fourth quarter of 2020. "Because of the efforts of HSG, CTCC, clinical site investigators and staff, and most importantly subject volunteers and their families, SIGNAL is several years ahead of any other ongoing advanced clinical trial testing possible disease-modifying effects in Huntington's disease. We are excited to be in the lead and hopeful of bringing relief to the patients and families who suffer this devastating disease," said Maurice Zauderer, president & CEO, Vaccinex, Inc.

“SIGNAL is several years ahead of any other ongoing advanced clinical trial testing possible disease-modifying effects in Huntington's disease.”

MAURICE ZAUDERER

HD *By the numbers*



131

TOTAL DOWNLOADS

of the initial HD Insights Podcast episode within the first week of launch

18-35

The age of young adults invited to attend HDYO's Inaugural Young Adults Congress in Glasgow, Scotland in May 2020



60

THE NUMBER OF CAG REPEATS MOST HD PATIENTS HAVE

15

The number of years

most people with JHD survive after becoming symptomatic



14,000

The approximate number of active patients at HSG sites in North America

3,615



The total number of followers

of Huntington Study Group and HD Insights on Facebook and Twitter

Facebook
[@HDInsights.org](https://www.facebook.com/HDInsights.org)

Twitter
[@HD_Insights](https://twitter.com/HD_Insights)

5 to 10%

OF ALL JHD CASES

exhibit symptoms before age 20

7

MILLION

The number of views in 7 years

of the HDYO.org website



Predictive Testing

for the HD gene

An Informed Decision and a Prepared

BY MARTHA NANCE

Mind

Clinical teams and patients navigate genetic testing.

The decisions we make as we move into adulthood are unavoidably impacted by our childhood experiences. For children living in families affected by Huntington's disease (HD), it is not surprising that experiences with HD color the transition from adolescence to adulthood.



MARTHA NANCE

Martha A. Nance, M.D., is Medical Director, Struthers Parkinson's Center in Golden Valley, Minnesota.

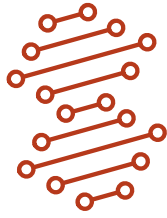
- ▶ Should I stay close to home so I can help with an ailing parent (or a struggling partner)?
- ▶ Maybe if I move far away, I can just be me and nobody has to know about this family secret.
- ▶ At what point should I tell a girlfriend/boyfriend about my family history?
- ▶ Why should I be serious about anything — for me there is no tomorrow, so I have to just try to enjoy today!
- ▶ Now that I am married, what about children?

One of those unique HD decisions is whether or not to have predictive genetic testing. Predictive (or pre-symptomatic) testing for HD has been widely available since the HD gene was identified in 1993, and should be performed in a clinical environment with the support of expert counseling. These may

include geneticists or genetic counselors, as well as neurologists, psychologists and social workers well-versed in the family challenges common to HD.

Guidelines for health professionals performing HD predictive testing were originally published in 1994, with subsequent revisions made by the European HD Network, and the Huntington's Disease Society of America.

Genetic testing for HD is an *irreversible* step; one cannot unlearn gene status. In that way, it is more akin to a surgical biopsy. For this reason, health professionals must help people who think they want to be tested to *carefully consider* the potential consequences of testing, and not just its benefits. Here are my top 10 recommendations for a predictive testing protocol.



Genetic testing for HD is an irreversible step; one cannot unlearn gene status.





Discuss visit logistics (Pre-visit phone call)

Initially, our clinic works with the patient to review the testing process, including how many visits they can expect to make, who they will see, what the cost will be, and insurance coverage or self-pay requirements. We suggest to patients that it is advisable to get life, disability, long-term care insurance in place before undergoing testing.

While the constraints and allowable practices vary from institution to institution, we discuss our own center's privacy, records retention and communications policies. We discuss "pseudonymous testing," and explain that health professionals are legally required to document our work in the chart and that "shadow files" are no longer a viable option because the laboratory requires retention of results for its own auditing purposes.

Often family members want to test together, and while we accommodate these requests, *we discourage siblings from testing together*. In our experience, the impact of any one test result is so profound for a family to absorb that they should space these out over many months.

Finally, we encourage, but don't require, patients to have a partner or companion as they go through testing.



Spend time on the family history

A second stage of discussion before testing involves looking at factors that may impact the person's risk. We ask if the family disease is genetically confirmed to be HD. If we have sufficient information, we calculate the patient's a priori risk (50% with an affected parent, 25% with an affected grandparent if parents' status is unknown, and much lower in the case where there is an affected sibling but no prior affected family members.)

If nobody in the family has ever had a gene test, the implications of a normal test result in an asymptomatic person are uncertain. Our group has tested patients who do not know their parent's gene status. In these situations, a positive test result means that the patient's parent will have an expanded CAG repeat. Some clinicians might decline to perform such a test, so much thought goes into this decision.

"A second stage of discussion before testing involves looking at factors that may impact the person's risk."



Become a genetic educator

An important part of our pre-testing counseling is educating the patient, at a level appropriate to their education and comprehension, about the biology of HD. We talk about chromosomes and genes, and autosomal dominant inheritance (50% risk to children of affected person). We need to introduce the CAG repeat expansion as the sole cause of HD. We discuss normal and abnormal CAG repeat ranges and the shades of gray — the high normal (mutable) range and the low abnormal (incomplete penetrance) range.

After setting the stage for a genetic understanding, we discuss meiotic instability of CAG repeats, particularly in male meiosis, and the relationship between CAG repeat length and onset age.

We make sure patients know, in advance of the moment that they receive results, that they should expect a result in the form of "two numbers" which correspond to two alleles (one from your mom, and one from your dad). In families with an older onset age, sometime the genetic testing result may not be conclusive, but in one of the "intermediate" ranges. Outlying issues like the possibility of two expanded repeats and nonpaternity (not readily proven with direct gene testing) may be explored if appropriate.



Review the limitations of a genetic result

Genetic results cannot predict the age of onset, the disease course, and there are currently no disease-modifying treatments. One potential benefit of testing is the surveillance of clinical symptoms (neurological or neuropsychological monitoring), but the primary benefit of predictive testing is patient-specific.



Predictive testing for HD

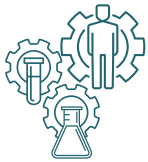
has been available since the HD gene was identified in

1993

“One potential benefit of testing is the surveillance of clinical symptoms (neurological or neuropsychological monitoring).”



Predictive Testing



Explore reasons for predictive testing

We spend time discussing why the patient wants to undergo predictive testing — Why now? Why not last year? Why not next year? We find that most patients have thought a lot about why they want gene testing, but not as much about why they may not want testing. We discuss the potential negative impact of test results on self-perception, status of relationships within the family and community, employability, and insurability. We remind the patient that they still have the option to postpone testing, or not have testing at all. Some patients come for testing at a time when they are overtly symptomatic. Symptomatic and asymptomatic patients may return to talk about testing several times before getting gene tested.



FIND OUT MORE ONLINE

ABOUTGENETICCOUNSELORS.COM
HDSA.ORG
PREDICTIVETESTINGFORHD.COM

“We discuss the potential negative impact of test results on self-perception, status and relationships within the family and community, employability and insurability.”



Assess psychosocial status

A critical aspect of our pre-testing process is determining, as best we can, how the patient is likely to manage new knowledge that will come with the test results. It can be useful to have a trained psychologist address these issues. They will look at demographic information (marital status, employment status, age, general health, alcohol and drug use), the support system, their life history with HD, psychiatric history, and personal and family history of suicidal thinking or suicide attempts.

As the major potential adverse effects of genetic testing are psychosocial, understanding the patient's current psychological status and support system are important, and knowing whether he or she is among the approximately 20 percent of at-risk patients who have had suicidal ideation, helps the medical team to plan a support system appropriate to that patient. We encourage the patient to establish a relationship with a local counselor, if needed, before results are given.



“The patient should have time to reconsider the decision to be tested.”



Allow time for reflection

If the patient wants to proceed, the genetic counselor and psychologist usually meet with the patient first, and the neurologist a week later. This provides time to consider the preceding discussions, and opt out of testing, if desired.

We appreciate pre-test meetings to ensure that the patient fully understands what they are asking for, and the potential implications of the results. They may change their perspective; sometimes there are more questions, or they may need a local counselor. The patient should have time to reconsider the decision to be tested.



Provide hope

Even gene-positive results can be surrounded with a backdrop of hope and an action plan for the future. Gene-negative results sometimes come as a surprise or shock, and need to be worked through. We encourage patients, whatever their outcomes, to participate in research, advocacy, HD community educational support and fundraising activities.



Ensure a clear timeline for results

With a go-ahead decision, we document consent and promise to communicate that results can be given to the patient in two weeks. When the patient comes in to learn the results, they meet with the genetic counselor and/or the neurologist, who assure ample time for discussion. Follow-up may incorporate neurologic examination, neuropsychological testing, and/or support and counseling, as well as scheduling of a follow-up phone call.



Stick to a protocol

We have found that this framework provides patients with the understanding and support that they need to optimize the benefits of testing, or to support them in the decision not to be tested. Our predictive testing team of genetic counselors, psychologists, and neurologists, utilize the skills and perspectives each has to educate, evaluate, and guide the patient to the testing decision that is best for them.

BY PEG NOPOULOS

HD Youth Find Their **VOICE**

Kids-HD and juvenile onset HD programs foster deeper understanding of HD in youth



Peg Nopoulos, MD, is a Professor of Psychiatry, Neurology, and Pediatrics and Chair of Psychiatry in the University of Iowa Carver College of Medicine.

Whether it be watching family members suffer, carrying the burden of caring for family members, feeling the weight of living with the knowledge they are at risk for HD, or even suffering from the juvenile onset form, HD youth carry a unique emotional load. However, it has been only recently that the youth affected by HD have found their voice and come together. The establishment of the National Youth Alliance (NYA) in 2001 (as part of the Huntington's Disease Society of America or HDSA) and the international organization Huntington's Disease Youth Organization (HDYO) in 2012 have provided world-wide opportunities for youth affected by HD to have a platform to learn, support others, and help in the fight against HD.

One piece of the fight against HD is the opportunity to participate in research. Children and young adults at risk for HD had few, if any, options to enroll in studies until a unique initiative was developed at the University of Iowa in 2009: the Kids-HD and Kids-JHD research programs. Funded by the National Institutes of Health and the private foundation, CHDI, the Kids-HD and Kids-JHD programs offer a unique opportunity for young people enroll and participate in research. The two 'arms' of the research protocol (Kids-HD and Kids-JHD) are very similar, but have unique aspects and are described below separately.



FIND OUT MORE ABOUT
KIDS-HD AND KIDS-JHD

CALL 1-866-514-0858 OR
EMAIL KIDS-HD@UIOWA.EDU

Youth organizations have provided world-wide opportunity for youth affected by HD to have a platform to learn, support others, and help in the fight against HD.

Kids-HD



This program is a single-site protocol based at the University of Iowa in Iowa City, Iowa. The population studied is children (ages 6-18 years old) at risk for HD (have a parent or a grandparent with HD).

All participants undergo genetic testing for research purposes only — there is no release of this information to the subjects or their families. Each subject's CAG repeat is made anonymous by assigning a research number rather than their name to the genetic results so even the research team is blind to the genetic results of any particular subject. Those subjects whose CAG repeat is greater than or equal to 36 are termed Gene Expanded (GE) and those with 35 or less are termed Gene Non Expanded (GNE).

The assessment protocol includes cognitive testing, motor examination, and behavioral assessment (scales filled out by parents that quantify behavioral traits). There is also a brain MRI to evaluate brain structure (volumes of global and regional brain tissue) and brain function such as connectivity of regions using resting state functional MRI.

An important feature of our program highlights the notion that the striatum and the cerebellum are integrated, connected via the indirect pathway.¹ Given the integration of the cerebellum into striatal circuitry, is it a vital component in the growth and development of striatal circuitry, and therefore may also play a key role in the pathophysiology of the disease, acting in compensation for a dysfunctional striatum.

The primary goal of the Kids-HD research program is to evaluate how the Huntingtin gene (HTT) affects brain development. Although the primary focus is to better understand its role in disease, it is important to try to understand how HTT normally functions. Therefore, we evaluate how HTT affects brain development in both normal (below disease threshold) and pathologic (above disease threshold) states.

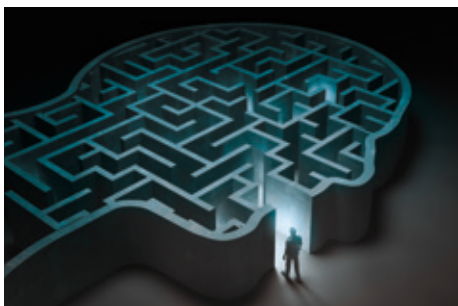
EFFECT OF HTT BELOW DISEASE THRESHOLD:

HTT is a very important gene for brain development. One way we know this is because when HTT is 'knocked-out' of mouse models, it is lethal — and in particular, development of the brain is affected. The other reason why HTT is thought to affect brain development comes from studies in evolutionary biology. HTT is highly conserved, which means that even simple creatures such as the sea urchin have HTT.

The CAG repeats in this gene increase as species become more evolutionarily advanced.² Rodents have a few repeats, primates a few more. The large number of repeats in humans is thought to represent a unique mechanism for genetic variability — the foundation of evolution. In order for natural selection to occur, there must be a variety of phenotypes for nature to choose from. In a typical genetic mutation mechanism, that phenotype is binary — mutated or not mutated. However, with genes that have variation, such as triplet repeats, each triplet added to the gene may effect a subtle change in the protein, manifesting in different phenotypes, based on numbers of repeats.³

The scientific question of the effect HTT has on brain development below disease threshold is to determine if the number of CAG repeats have an effect on brain structure and function in children who will not develop HD — the GNE group. We found that the number of CAG repeats did indeed impact basic brain functioning such as IQ; the greater the CAG repeat, the higher the IQ.⁴ We also found evidence of assortative mating,⁵ meaning that there was a tendency for those with higher CAG repeats in the HTT gene to marry those with similar repeat counts (supportive of the IQ finding, since it is well known that one of the strongest factors in assortative mating is similar IQ).

In regard to brain structure, we found that the CAG repeat effect was different for males and females. For males, higher repeats impacted the growth and development of the striatal-cerebellar



The primary goal of the Kids-HD research program is to evaluate how the Huntingtin gene affects brain development.

► *The population studied is children ages*



6 to 18 years old

at risk for HD (with a parent or a grandparent with HD).

The design of Kids-HD is based on the gold-standard method in brain imaging in children.

circuitry, while in females, higher repeats impacted the thickness of the cortex. This was also recapitulated when looking at sex differences in the relationship of brain structure to IQ — in males, IQ was directly related to the volumes of the striatal-cerebellum circuit, where in females, IQ was related to cortical thickness.⁶

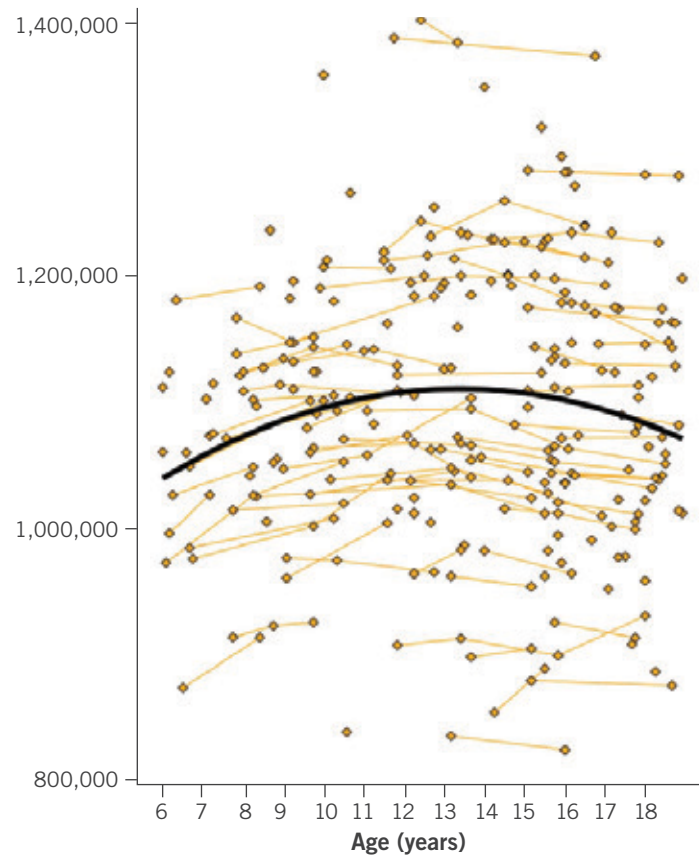
In general, our findings of how the HTT gene effects brain development below disease threshold provide evidence that there are advantageous changes to brain structure and function with increasing CAG repeats. This supports the theories that this gene — and others like it — may have undergone positive selection for human brain evolution. However, this advantage is coupled with the disadvantage that if the repeats are too long, the devastating disease of HD occurs.

EFFECT OF HTT ON BRAIN DEVELOPMENT ABOVE DISEASE THRESHOLD

In the same way we conceptualize HTT affecting brain development below disease threshold, the evaluation of HTT effects above disease threshold begins with the understanding that expanded or mHTT may adversely affect brain development. This is the basis of the neurodevelopmental hypothesis of degenerative diseases first posed by Mark Mehler.⁷ The concept is that mHTT affects the development of the striatum. The striatum is therefore abnormal in its growth and development. However, it is not dysfunctional early in life because there is compensation. We believe the compensation for the developmentally abnormal striatum is the cerebellum. Therefore the abnormal striatum is held in 'mutant steady state' through childhood and then later in life — when compensatory mechanisms fail — disease begins to manifest. Thus, the primary roots of degeneration lie in abnormal brain development.

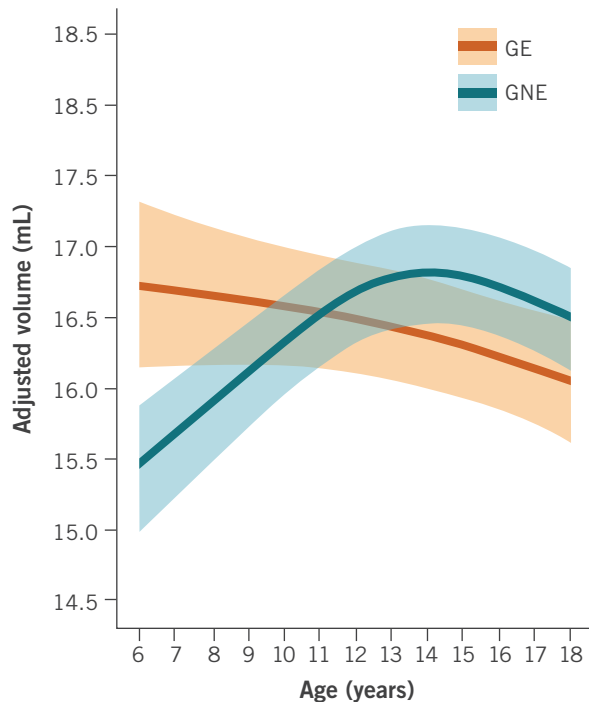
The design of Kids-HD is based on the gold-standard method in brain imaging in children — an accelerated longitudinal design or ALD. This is not a traditional time1-time2 longitudinal study, but instead a mechanism to evaluate how the brain develops over a large age range — from 6-18. With an ALD design, we can show the trajectory of development. Although many children come for repeat visits, the goal of analysis is to fit one line that represents how the brain changes across the range, as shown in Figure 1.⁸

Our most recent publication shows that in GE children, the striatum is indeed markedly different in its development compared to the GNE children. In fact, the time in which the striatum is the most different is in the earliest time point we assessed — age 6. At this age, the striatum is enlarged compared to the GNE group (Figure 2⁹). Then over time, it has a linear decrease in volume.



► **FIGURE 1**
Age is shown on the x-axis and cerebrum volume (gray and white matter combined) is shown on the y-axis. Single diamonds represent a single observation in an individual, while connected diamonds show repeated observations within the same individual. The thick, black line illustrates the growth curve across age based on a combination of cross-sectional and longitudinal components. To preserve gene status confidentiality, the figure illustrates the combined gene-expanded and gene-nonexpanded groups.

The Kids-HD program is unique and the only study in the world evaluating at-risk children.



► **FIGURE 2**
Mean estimated age-dependent change of striatal volume in the GE (red) and GNE (green) groups.

► *Brain development and maturation changes can last from*



**adolescence
to age 30**

This decrease in volume is a normal developmental phenomenon called “pruning,” and occurs in the typically developing brain beginning in adolescence; however it begins much earlier in the GE children.⁸ In more recent (unpublished) analysis using resting state functional MRI, we also show that the connectivity between the cerebellum and the striatum in the GE children is higher than normal. This supports the neurodevelopmental hypothesis of the striatum having abnormal growth and development, with the cerebellum developing a compensatory role through greater connectivity.

In the era of gene knock-down therapy for HD, it is important to highlight how the findings of the Kids-HD study impact future trials.

One thing to emphasize is that the process of brain development in humans is very long — there are development and maturational changes that are robust in adolescence and last until roughly age 30. If gene knock-down therapy is successful in the current trials, the ultimate will be disease prevention — administering the drug prior to disease onset. However, given that HTT affects brain development, and brain development is prolonged, administering a drug that would affect brain development needs to be addressed with an abundance of caution.

The Kids-HD program is unique and the only study in the world evaluating at-risk children. The study has recently been favorably scored by the NIH for renewal to extend the study an additional five years. The renewal will expand the program to five sites: Iowa, University of Texas, Houston; University of Pennsylvania/Children’s Hospital of Philadelphia; University of California, Davis; and Columbia in New York. The new sample will attempt to replicate the initial findings in a larger sample. In addition, the age range of the sample will be increased to 6 to 30 years of age in order to capture the entirety of brain development.

Given that the age range now extends beyond children, the program has rebranded itself and will now be called CHildhood to Adult Neurodevelopment in Gene Expanded — HD or CHANGE-HD. In addition to continued brain imaging, we will also be evaluating quantitative motor assessments (Q-Motor), along with Dr. Ralf Reilmann from Germany, as well as the utility of serum neurofilament light (NfL) as a potential biomarker, along with Dr. Wild from London.

Kids-JHD



Alongside the Kids-HD program, we have also been assessing children and young adults who have already been diagnosed with juvenile onset Huntington's Disease (JHD), in the first ever brain imaging study of JHD. Given the rarity of JHD, there is still little known about basic things such as symptomatology, let alone details of the disease process (and how that might differ from adult onset HD). So one of the first things we did was to learn about symptoms.

Using an online survey, we queried caretakers around the country on presence and severity of JHD symptoms. In particular, we focused on several that were considered to be important, based on conversations with JHD parents: sleep, tics (not chorea), pain, "itching" and psychosis. We found that these symptoms were remarkably prominent, frequent, and severe in many cases as shown by Table 1.⁹

At Iowa, the protocol for the Kids-JHD subjects is essentially the same as for the Kids-HD, where families travel to Iowa City, Iowa, to get cognitive, motor, and behavioral assessments as well as an MRI. The findings of our first analysis in the structure of the

JHD brain were recently published.¹⁰ As might be expected, one of the main findings was that children with JHD have an overall much smaller intracranial volume (ICV), a measure of maximal brain growth. This supports a generalized phenomenon. However, after accounting for the smaller ICV, there was a very specific effect on the striatum, which was simply devastated in terms of volume, being several standard deviations below the mean of the comparison group. Interestingly, the cerebellum was proportionately larger — meaning that it was either completely spared from the disease or potentially grew in size in a compensatory phenomenon.

Finally, the cortex, though thinned in some areas (such as the insula) was surprisingly intact. In this paper, we also evaluated the MRI findings of several mouse models of HD which, in many ways, recapitulate JHD, given the length of their repeats. The mouse models had the same pattern of findings in which striatum and cerebrum were decreased in volume, but the cerebellum was proportionately enlarged. These findings in JHD support the Kids-HD findings of cerebellar hyperconnectivity, and may reflect the compensatory role that it plays in the disease. ●

► TABLE 1 Symptom prevalence and severity of JHD

SYMPTOM	% REPORTED (N=33)	NUMBER OF SUBJECTS	MILD	MODERATE	SEVERE
Sleeping	87	25	12%	40%	48%
Tics	78	19	47%	32%	21%
Pain	69	18	28%	50%	22%
Itching	60	17	18%	41%	41%
Psychosis	39	7	57%	29%	14%

¹ Bostan, A.C. and P.L. Strick, The cerebellum and basal ganglia are interconnected. *Neuropsychol Rev*, 2010. 20(3): p. 261-70.

² Candiani, S., et al., Characterization, developmental expression and evolutionary features of the huntingtin gene in the amphioxus *Branchiostoma floridae*. *BMC Dev Biol*, 2007. 7: p. 127.

³ Fondon, J.W., 3rd, et al., Simple sequence repeats: genetic modulators of brain function and behavior. *Trends Neurosci*, 2008. 31(7): p. 328-34.

⁴ Lee, J.K., et al., Effect of Trinucleotide Repeats in the Huntington's Gene on Intelligence. *EBioMedicine*, 2018. 31: p. 47-53.

⁵ Nopoulos, P., et al., Correlation of CAG repeat length between the maternal and paternal allele of the Huntington gene: evidence for assortative mating. *Behav Brain Funct*, 2011. 7: p. 45.

⁶ Lee, J.K., et al., Sex-specific effects of the Huntington gene on normal neurodevelopment. *J Neurosci Res*, 2017. 95(1-2): p. 398-408.

⁷ Mehler, M.F. and S. Gokhan, Mechanisms underlying neural cell death in neurodegenerative diseases: alterations of a developmentally-mediated cellular rheostat. *Trends Neurosci*, 2000. 23(12): p. 599-605.

⁸ van der Plas, E., et al., Abnormal brain development in child and adolescent carriers of mutant huntingtin. *Neurology*, 2019.

⁹ Moser, A.D., et al., A survey-based study identifies common but unrecognized symptoms in a large series of juvenile Huntington's disease. *Neurodegener Dis Manag*, 2017. 7(5): p. 307-315.

¹⁰ Tereshchenko, A., et al., Brain structure in juvenile-onset Huntington disease. *Neurology*, 2019. 92(17): p. e1939-e1947.

Building Resilience in the

Face of Stress

*Changing the landscape of Huntington's disease
for HD patients and family members*



Bruce E. Compas is the Patricia and Rodes Hart Professor of Psychology and Human Development and Professor of Pediatrics at Vanderbilt University.





BY BRUCE E. COMPAS AND ABAGAIL CIRIEGIO

The landscape of Huntington's disease is rapidly changing for HD patients and family members. Significant progress has been made in the ability to diagnosis the disease at earlier stages, tools are now available to chart the progression of HD with greater precision and, most importantly, there are therapeutics that show promise to slow disease progression.

In spite of these changes and advances, one aspect of HD remains constant — the diagnosis, management, and progression of Huntington's disease is highly stressful for patients and their families, including siblings, spouses, children, and other loved ones. These stresses can take a significant toll on the mental health of patients and family members, create challenges in interpersonal relationships, and potentially lead to compromises in the body's ability to fight against the progression of the disease. In spite of the importance of understanding these effects, relatively little research has been conducted on the sources of stress, psychological and physical effects of stress, and the ways that HD patients and family members cope with stress. As a consequence of the paucity of research in this area, there are no evidence-based psychological or behavioral interventions to help improve coping and communication in HD patients and their families.

We are relative newcomers to the world of HD. In our short but intense time, three aspects of this experience have been most powerful. First, the emotional and psychological aspects of HD are compelling. Second, our experience conducting psychological research with patients with other medical and psychiatric conditions (e.g., cancer, depression) has positioned us to bring new perspectives that we can apply to our work with HD. And third, HD has unique features that will challenge us as we strive to better understand its psychological and emotional impact and develop new ways to provide support, enhance resilience and improve quality of life for HD patients and their families.

In spite of these changes and advances, one aspect of HD remains constant — the diagnosis, management, and progression of Huntington's disease is highly stressful for patients and their families.



The stories that families have shared with us have been both poignant and inspiring. One primary aim of our research is to better understand the nature and consequences of these sources of stress.

The Stress of HD

Members of the Vanderbilt HD Center of Excellence first reached out to as potential collaborators in the study and improved understanding of the effects HD has on the children of patients. The neurology team shared with us their observations of the challenges faced by adolescents and young adults whose parents have HD. One of the first families that they described included an adolescent girl whose father was in the late stages of HD. She had shared her fears and acute sadness that she was experiencing about her father's condition. But she also shared her sense of hopelessness for the future — his future and more painfully, hopelessness about her own future. Even though she had not undergone genetic testing, she felt sure that she was a gene carrier and that she saw her own future in her father.

We have also seen and heard about the challenges faced by spouses of patients who struggle to support their husbands and wives, care for their children, and manage stresses and strains related to lost income and mounting medical bills. The stresses for patients are pervasive, and include the physical and mental changes that result from the disease, the impairment in the ability to work, and the loss

of autonomy (inability to drive, challenges in self-care). The stories that families have shared with us have been both poignant and inspiring. One primary aim of our research is to better understand the nature and consequences of these sources of stress.

Applying Research from Other Medical Conditions

As we have learned more about HD, we have been struck by some powerful similarities to families who are faced with other significant mental and physical disorders. Over 30 years ago we began our work with families faced with a parent's cancer and we have continued in our research with families a parent has major depressive disorder. We have also studied hundreds of families of children with serious illnesses including cancer, brain tumors, sickle cell disease, and congenital heart disease.

Several findings from this research have guided our initial work with HD. First, physical and mental disorders present families with both acute and chronic stress. Acute stresses include the moment that a diagnosis is made, the administration of specific treatments, and a sudden change in a patient's condition. Acute stressors require immediate responses and create short-term but intense demands on the emotional and behavioral functioning of patients and family members. For example, the unexpected diagnosis of cancer in a child presents children and their parents with a challenge that turns life upside down and can trigger intense fear and anxiety. However, the most demanding sources of stress for families faced with physical and mental disorders are chronic in nature.

Second, most of the significant stressors for these families are uncontrollable. Children and parents feel helpless when faced with a cancer diagnosis and a long, arduous course of treatment. Similarly, children cannot control the symptoms and course of depression in their mother or father. Uncontrollable stress presents the greatest risk for problems of anxiety and depression in families faced with physical and mental illness.

Third, we have identified specific coping strategies that are associated with resilience in children and parents. These include cognitive and behavioral coping skills that are best suited for uncontrollable stress and are encompassed in the category of "secondary control coping." These skills involve the ability to accept (rather than deny) the source of stress, use cognitive reappraisal to think about stress in ways that makes it less negative, and the ability to use positive ways to distract oneself from and gain some relief from uncontrollable stress.

The Unique Stresses and Challenges of HD

Although HD shares many common features with other conditions, it presents patients and their families with unique stresses and challenges. HD differs from other diseases we have studied in that it is transmitted through an autosomal dominant gene that has complete penetrance. Further, children and adolescents are not eligible for genetic testing to know whether they carry the HD gene, and many young adults choose not to pursue testing. As a consequence, offspring of parents with HD may be faced with prolonged stress of uncertainty about their gene status and their futures.

Our work has also identified important aspects of disruption and impairment in cognitive development and functioning. Problems in cognitive executive function are widely documented in patients with HD. Our research has found that these problems may emerge



Our findings, which require much more extensive investigation, suggest the HD may be a neurodevelopmental disorder with the first signs of cognitive impairment arising long before signs of the disease.

much earlier than previously thought, including during early adolescence in children of HD patients.

Our findings, which require much more extensive investigation, suggest that HD may be a neurodevelopmental disorder, with the first signs of cognitive impairment arising long before signs of the disease. Further, we have found that impairment in executive function are associated with disruptions in the ability to use the secondary control coping skills (acceptance, cognitive reappraisal) that are central to adapting to the uncontrollable stress experienced by children of parents with HD.

Our Goal: Support and Build Resilience

We have begun the process of carefully documenting the significant sources of stress for HD patients and their families and loved ones. We have also taken the first steps towards understanding the ways that patients and families can cope with these stressors to reduce or mitigate the emotional and physical toll that they can take. Our goal is to continue to document these processes to provide the basis for developing programs to strengthen and develop communication and coping skills for HD patients and their families.

We have achieved significant success in developing evidence-based interventions for parents who suffer from depression and their families. Today, we are committed to developing similar resources to contribute to resilience in families who are coping with HD. ●

My experience working with children

CLINICAL COORDINATOR'S CORNER BY ABAGAIL CIRIEGIO

I have been involved in research with families impacted by Huntington's disease for about 14 months. Looking back, HD research was not something that I foresaw in my career path, but now looking ahead it is hard for me to imagine not being involved in research with this population. As a research coordinator, my interactions with these families can be very brief (a few hours for one or two study visits), and yet I am captivated and inspired by every single family that I have come in contact with.

Huntington's disease is a medical condition characterized by a specific set of motoric, cognitive, and psychiatric symptoms, but the way each HD patient presents with these symptoms can be variable. Similarly, every HD family that I work with is unique; each family, and each member within that family, copes with, talks about, and adjusts to the stress of the disease in their own way. What ties all of these families together, however, is that they are all impacted by HD.

What does that mean, to be impacted by Huntington's disease? To understand the impact HD has on families, I think it is first important to understand the types of stressors these families are facing. HD patients themselves are faced with various levels of symptoms that progress over time, which are eventually accompanied by a loss of independence. I've talked to various patients who describe how devastating it is to lose their driver's license, the ability to maintain their job, or communicate effectively. For many patients, the loss of these abilities and privileges not only signifies a loss in autonomy, but a loss in their ability to function as the parent and spouse they once were. Other stressors for HD patients include emotional concerns about their personal future (i.e., learning to live with a progressive disease that results in a shortened life expectancy) and the future of their loved ones.

Spouses and caregivers of HD patients are faced with the stresses associated with increased caretaking responsibilities and financial concerns. Oftentimes there is a shift in the household dynamic, and families are forced to readjust as the responsibilities of the home transfer from two caregivers down to one. Many spouses have reported to us how burnt out they feel, just completely overwhelmed with the continuing needs of their partner with HD and children. Balancing the needs and concerns of your spouse and children can be a very burdensome task for any caregiver, but HD adds into the mix the stress

of having to watch the progressive decline of your partner, while at the same time worrying and fearing for the "status" of your children.

I can remember conducting a study visit with one family, in particular, that included a mother who was caring for her recently diagnosed daughter (in her mid-20's) and her young infant grandchild in the months after the death of her husband, who had HD. For a portion of the visit, we asked the mother and young adult daughter to sit together and discuss a positive memory that the two of them had shared together recently. After about 10 minutes I re-entered the room to a distraught, tear-stricken mother who was being comforted by her young adult daughter. This mother was brought to tears throughout the conversation, as she realized that the last happy memory she could recall was nearly five months ago, when her husband was still alive. In that moment I was emotionally struck by how much this mother had been through. In a few short months she watched HD take away the husband that she loved and was clearly still mourning, and seeing her young adult daughter be diagnosed with the same disease. For this mother, in particular, HD colored her memories. In a sense HD took away her future, but in this case it was also taking away from her past.

In my time working with families impacted by HD, among the most compelling moments that I have experienced, by far, have been with the adolescent and young adult children in these families. Adolescent and young adult children of HD patients face a wide

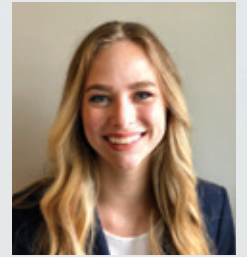
array of stressors and they can be particularly vulnerable to them because, compounded on top of an already taxing developmental period in their lives (puberty, school, peer relationships), these young people are forced to navigate the hardships associated with HD. A majority of the young people in HD families that I have come in contact with report having to take on more responsibilities within their family unit. That can mean taking on more of a caretaking role with their siblings, to helping manage the care of their affected parent, to cleaning, cooking, and chores around the home. The stigma that these young people face is also something I have heard a lot about; they carry the burden of having to deal with the judgments or insensitive assumptions others make about their parent with HD because of a lack of understanding. These young people bounce back and forth between chaos and instability at home, to feeling isolated and different from their peers and community members. All the while, these young people are faced with the decision of whether to get genetically tested and make decisions that will affect the rest of their future.

It can all seem overwhelming. Learning from and talking to these young people, it can seem that it would be easy for them to get bogged down with the stress, to cower in the face of such uncertainty. The truth is, I have never met a group of individuals so strong and resilient and hopeful. For all of the negative experiences I have seen and heard from these young people, I have doubly experienced positive ones. The young people from HD families that I work with embrace life from a much younger age than the vast majority of people I meet. They are optimists for life. They find the joyful things in life and go after them because they know how precious life can be.

In our psychology research lab we strive to conduct "compassionate science"—we utilize the most rigorous and up-to-date methods to conduct research that benefits and improves the lives of others. Comparably, I like to think of the young people from HD families that I have worked with as "compassionate advocates." They are loving, supportive, and hopeful individuals who fight to advocate for HD, for their parents, and for themselves. They embody the attitude of "this disease ends with me," and volunteer to participate in research, knowing that it all contributes to the greater cause of finding a cure for the disease. These young people are set and determined to change the way Huntington's disease affects their future and the future of others like them. I feel honored to be a small piece of their journey and can't wait to watch all that they accomplish!



The young people from HD families that I work with embrace life from a much younger age than the vast majority of people I meet.”



ABAGAIL CIRIEGIO

Abigail Ciriegio is a research assistant in the Stress and Coping Research Lab in the Peabody College at Vanderbilt University.

My HD community involvement— not done yet!

BY BJ VIAU

I first heard the words Huntington’s Disease when I was around nine years old after my parents came home from a doctor’s appointment and shared my mom’s positive results with my sister and me. I had spent some time in my early years with my grandfather, who had it as well, but I was too young to understand anything was wrong, and he passed away when I five. The decision my parents made to be up front about HD with my sister and me at a young age made a positive impact on my life from every angle. Learning about HD so young gave me the opportunity to ask questions over a long period of time, to process what it all meant slowly, and to find ways to support my mom over time as HD took away her abilities to live a “normal” life.

DISCOVERING FUN IN FUNDRAISING

Soon after her diagnosis, my parents got involved in our local Huntington’s Disease Society of America (HDSA) chapter in Minneapolis and slowly started dragging me to education days, support groups and fundraisers. I was typically the youngest person in the room and always felt like an outsider until they brought me to a fundraiser called a Hoopathon (think basketball). Basketball was my sport at 10 years old so I felt right at home. ...Huntington’s disease & basketball!!! I had so much fun at this event that before we got home I asked my dad if we could hold our own Hoopathon the following year. Without much external hesitation (I am sure my dad hesitated internally) he said yes, and we agreed as a family to hold our own event.

Note, this was in 1995, so the world wide web was a limited resource. We stuck to basic principles by picking a date/location, and creating a one-sheet flier and handing it to our friends, family and classmates. We held the first event, raised a couple thousand dollars and felt like we made a big difference! The feeling you get after raising funds is infectious, so before the event was even complete, we had people offering to help for next year.

“Next year?” We hadn’t really thought of that yet. Well, next year happened, as well as 13 years after that. We tried our best to grow the event each and every year in an attempt to raise more money, create more awareness, and connect more families with HD to our local resources. The Hoopathon provided a lot of good to many people, but one person sticks out for receiving more benefits from the event than anyone else. That someone was me.

The Hoopathon gave me an outlet that I wish all young people who live in an HD family had. It gave me an outlet to talk to my friends, classmates and coaches about what I was dealing with. It gave them the opportunity to provide support that I really needed in these tough years by simply showing up to the event. It provided me an outlet to do something good with a situation that most would think is dark and untouchable. I am forever grateful to every single person who had any hand in putting on the Hoopathon, because that event gave me the life I have today.



▶ **NEW OPPORTUNITIES**
BJ Viau (right) with Huntington’s Disease Youth Organization board member Seth Rotberg.



“The Hoopathon provided me an outlet to do something good with a situation that most would think is dark and untouchable.”

BJ VIAU

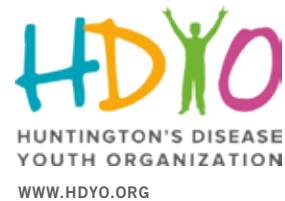
▶ **MAKING A DIFFERENCE**
BJ Viau (left), sister Emily, father Bryan (right) and mother, Debbie (front) at a Hoopathon event.



▶ HDYO'S INAUGURAL YOUNG ADULTS CONGRESS IN GLASGOW, SCOTLAND IN MAY 2020

WWW.HDYOCONGRESS.ORG

▶ HDYO
Participants in the 2012 European HD youth camp in Sweden strike the HDYO logo pose.



HOOPATHON ENDS, HDYO LAUNCHES

In 2011, my mom passed away and we called it quits on the Hoopathon. Over 15 years this little community event was able to raise close to one million dollars, educate thousands, connect hundreds of HD families in Minnesota, and provide an opportunity for our community to understand what my mom was going through.

Fundraising is very tiring, so it was time to deflate the basketballs, but look for the next opportunity to make a difference. That opportunity for me came from an invitation to attend a international Huntington's Disease Congress (thanks Dr. Martha Nance). Through this meeting I connected with many other young people from HD families who were all doing their own work to fight back against HD. One young man, Matt Ellison, and I stayed connected after the conference and he shared his vision to create a non-profit organization that specifically supports young people living in HD families. I obviously knew firsthand that this was an unmet need, so I jumped right in and wanted to create the same type of platform for young people that I felt with the Hoopathon.

A few years of work from 2010-2012 led to the launch of the Huntington's Disease Youth Organization. HDYO is an international non-profit that provides needed support, education and motivation to young people across the globe.

HDYO TACKLES CHALLENGES AND NEW OPPORTUNITIES FULL-ON

Since HDYO launched, we have worked to change the paradigm for what it is like for young people growing up in a family with HD. HDYO now has three full-time employees and an army of volunteers around the world who provide daily support, host yearly camps, maintain our online and social media presence, and help strategically run the organization. The effects of HDYO have been remarkable as we've continued to grow our reach and resources. The lives HDYO has been able to positively impact — regardless of language or location — makes my heart explode. We have a lot more work to do in order to end HD, so we continue to fight each day at HDYO to do more.

The HD community is approaching a very unique time with multiple disease-modifying and symptom treatments coming to clinical trials. We at HDYO are doing our best to connect with these companies and trial sites to make sure they have the voice of young people at the forefront of their thinking. I can't encourage readers enough to connect with your local HSG trial site, HDSA Center of Excellence and our team at HDYO to stay in the know about all the promise on our horizon.

One way to get connected is to accept this as an invitation to all the young adults out there (18-35 years old) to attend HDYO's Inaugural Young Adults Congress in Glasgow, Scotland in May 2020.

VIAU'S ADVICE FOR PARENTS AND KIDS IN HD FAMILIES:

▶ *Tell your kids about HD as soon as you can.*

Use www.HDYO.org as a resource.

▶ *Don't be afraid of getting involved.*

There isn't a playbook, so just do it!

▶ *Connect with others from the HD community.*

There are so many amazing people to meet!

▶ *Tell everyone you know about HDYO.*

More people should be utilizing our resources or joining our volunteer team!

BJ Viau is the board chairman of the Huntington's Disease Youth Organization, a nonprofit that focuses solely on the support for young people impacted by Huntington's Disease.

CLINICAL TRIALS

► UPDATES AND ADDITIONS

To update or add a clinical trial, please e-mail HDInsights@hsglimited.org.

	SPONSOR	IDENTIFIER	AGENT	PHASE	DESIGN	SITES
CURRENTLY ENROLLING	Sage Therapeutics	SAGE-718	718-CLP-102 B	I	A Phase 1, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Study to Determine the Safety, Tolerability, and Pharmacokinetics of SAGE-718 Oral Solution in Healthy Adults With an Open-label Cohort of Patients With Huntington's Disease	United States: Long Beach, CA and Berlin, NJ
	Roche/ Genentech	BN40423	RG6042	III	A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Phase III Clinical Study to Evaluate the Efficacy and Safety of Intrathecally Administered RO7234292 (RG6042) in Patients With Manifest Huntington's Disease	102 Total: Worldwide
	Wave Life Sciences Ltd.	PRECISIONHD2	WVE-120102	I / II	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 1b/2a Study of WVE-120102 Administered Intrathecally in Patients With Huntington's Disease	5 Total: Canada and Europe
	Wave Life Sciences Ltd.	PRECISIONHD1	WVE-120101	I / II	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 1b/2a Study of WVE-120101 Administered Intrathecally in Patients With Huntington's Disease	5 Total: Canada and Europe
	Azidus Brasil	ADORE-DH	Cellavita	II	Dose-Response Evaluation of the Investigational Product Cellavita HD After Intravenous Administration in Patients With Huntington's Disease	Sao Paulo, Brazil
ACTIVE	Vaccinex, Inc.	SIGNAL	VX15/2503	II	A Phase 2, Multi-center, Randomized, Double-Blind, Placebo Controlled Study in Subjects With Late Prodromal and Early Manifest Huntington's Disease (HD) to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of VX15/2503	30 Total: United States and Canada
	Ultragenyx Pharmaceutical	TRIHEP3	Triheptanoin oil	II	A Comparative Phase 2 Study Assessing the Efficacy of Triheptanoin, an Anaplerotic Therapy in Huntington's Disease	2 Total: France and Netherlands
	Neurocrine Biosciences	KINECT-HD	Valbenazine	III	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Valbenazine to Treat Chorea in Subjects with Huntington's Disease	55 total: United States and Canada
RECENTLY COMPLETED	Prilena Therapeutics Development Ltd.	OPEN-HART	Pridopidine	II	A Multi-Center, North American, Open-Label Extension Study of Pridopidine (ACR16) in the Symptomatic Treatment of Huntington's Disease (Open-HART)	12 Total: United States and Canada
	Teva Pharmaceutical Industries	LEGATO-HD	Laquinimod	II	A Multicenter, Multinational, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Laquinimod (0.5, 1.0 and 1.5 mg/ Day) as Treatment in Patients With Huntington's Disease	52 Total: Worldwide
	Azevan Pharmaceuticals	AVN011	SRX246	I / II	An Exploratory Phase II Study to Determine the Tolerability, Safety, and Activity of a Novel Vasopressin 1a Receptor Antagonist (SRX246) in Irritable Subjects With Huntington's Disease (HD)	22 Total: United States

Sources: www.clinicaltrials.gov and apps.who.int/trialsearch

pipeline

TREATMENT TYPE

- Disease-modifying therapies
- Symptomatic treatments
- Gene-targeting therapies



Preclinical

- Adeno-associated virus - short hairpin RNA (AAV-shRNA) (Spark Therapeutics)
- Adeno-associated virus - short hairpin RNA (AAV-shRNA) (Genzyme / Sanofi / Voyager Therapeutics)
- Anti-C1q monoclonal antibody (Annexon Biosciences)
- Peptide-nucleic acid (PNA) antisense oligonucleotide (Neubase Therapeutics)
- zinc finger DNA-binding protein (ZFP) (Shire and Sangamo Therapeutics)



Phase 1

- VY-HTT01 (Voyager Therapeutics)
- AMT-130 (uniQure)
- SAGE-718 (Sage Therapeutics)



Phase 2

- WWE-120101 (Wave Life Sciences)
- WWE-120102 (Wave Life Sciences)
- Pepinemab – VX15/2503 (Vaccinex)



Phase 3

- RG6042 (Roche/Genentech)



To Patients

- Deutetrabenazine (Teva)
- Tetrabenazine (Lundbeck)

Sources: www.clinicaltrials.gov, HDSA's Therapies in the Pipeline, and company/developer websites.

A novel approach to Huntington's disease

Committed to listening, learning, and partnering with the Huntington's disease community

WAVE[™]
LIFE SCIENCES

wavelifesciences.com

VACCINEX

Vaccinex Inc.
1895 Mount Hope Avenue,
Rochester, NY 14520
585.271.2700
info@vaccinex.com
Vaccinex.com

Science in the Service
Of Medicine
Unique Targets.
Novel Mechanisms.
New Medicines.

Vaccinex is committed to innovation in the way we approach drug discovery and development.

Vaccinex, Inc. (VCNX) is a clinical-stage biotechnology company pioneering investigational antibody therapies in cancer and neurodegenerative diseases, including Huntington's disease.

SIGNAL

Vaccinex's **SIGNAL** trial is a clinical study of its investigational antibody, pepinemab (VX15/2503), in Huntington's disease. For more information concerning the **SIGNAL** trial, please visit Vaccinex.com



HUNTINGTONSTUDYGROUP.ORG

We Make Quality Healthcare Accessible

Teva Pharmaceuticals is working every day to make quality healthcare accessible around the world. As a manufacturer of specialty and generic pharmaceuticals, Teva provides both new therapies and greater access to quality, affordable medicines.



teva

tevausa.com