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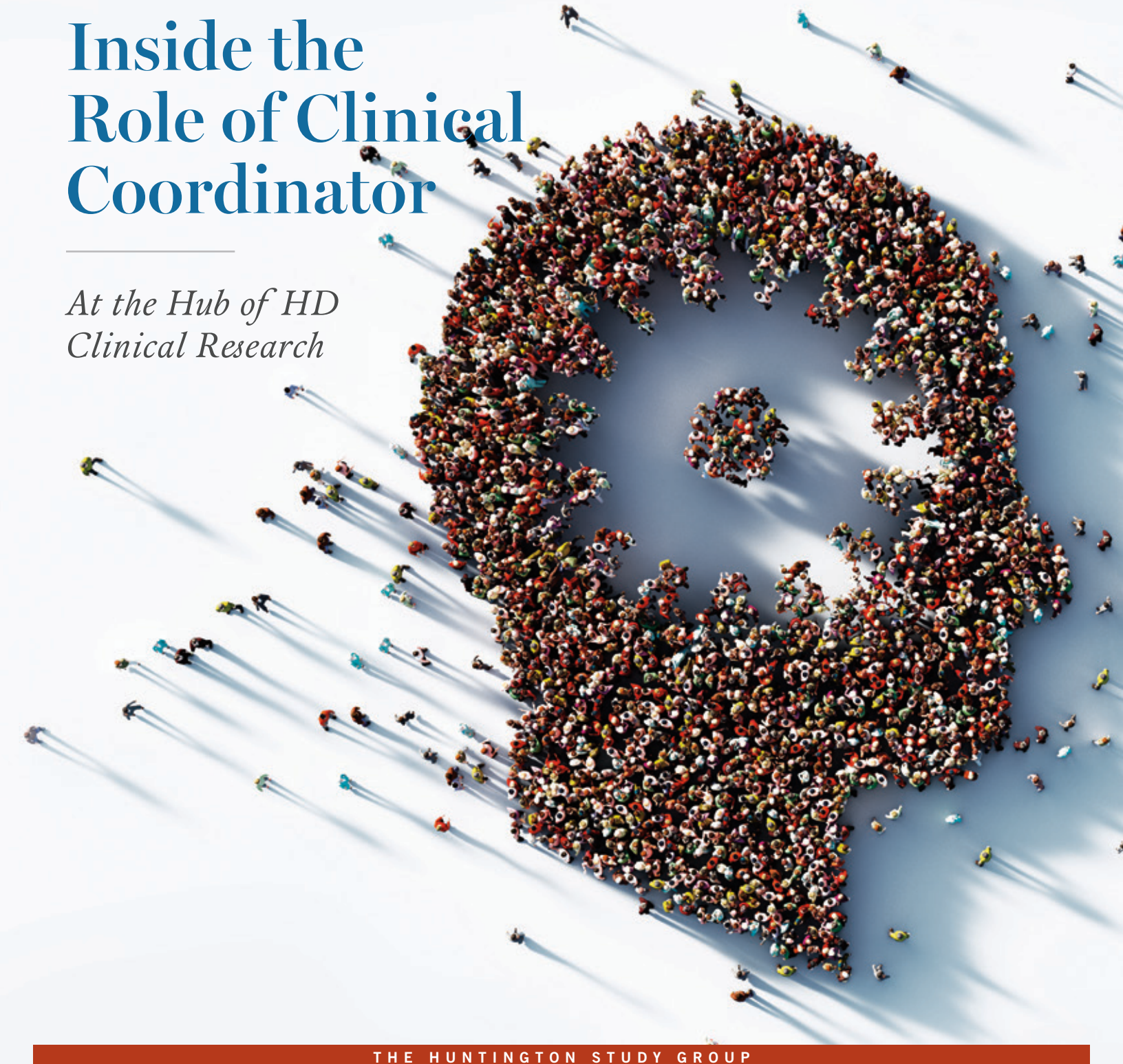
HUNTINGTON DISEASE

Insights

SPRING 2021

Inside the Role of Clinical Coordinator

At the Hub of HD Clinical Research



THE HUNTINGTON STUDY GROUP

Features

DEPARTMENTS

HDINSIGHTS podcast

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 5.*

AVAILABLE ONLINE

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Resilience

"*Thinking of everyone today. I'm sure you are all stressed. Thank you for all you do.*" This was the text message I woke up to the morning after the announcement that Roche instructed the investigators of GENERATION-HD to stop dosing. I can summarize the mood in our group as frustrated, upset, and weary.

We called all our patients that morning, and the mood on the other side of the phone was similar. *And yet*, I also heard comments that reflect the incredible resilience of our patients and families. "This is a setback, but thank you for continuing to work on finding a cure." "I was so hopeful, but I'm glad we found out now." "What are the research options for me now?"

One of the most challenging aspects of running clinical trials, is the reality that the trials are not treatments. When our site was named as a participating site for GENERATION-HD, the phone rang off the hook. Some families promised to move to Nashville in order to be in the study, others said they would donate money in order to get accepted into the trial. We had to remind participants that this was a trial, not a treatment. You can get placebo, there is a chance that it won't work, there is a risk that the therapy would have side effects.

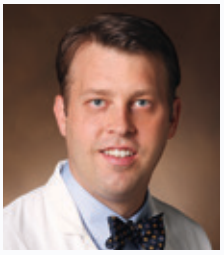
These are discussions that happen with any clinical trial, and you know who was fielding these calls? The clinical research coordinator.

In this edition of *HD Insights*, we highlight the important role of the clinical research coordinator. It is a role that is sometimes taken for granted, but one that needs to be elevated, honored, rewarded, respected, and appreciated. Many of our academic centers don't consider this a career path, and yet, our coordinators are the linchpin of our clinical research programs. They are asked to wear so many hats, from understanding regulatory details to managing patient expectations.

We look at how the HSG has outlined a new credentialing mechanism that is coordinator-centric, we reflect on the attributes of an excellent coordinator and what makes a strong research team. We also consider the career story of Jody Goldstein (who I like to refer to as the coordinator's coordinator!)

Oh, and we also have so much more: new trials, scientific discoveries, new methods — all that speaks to our communal effort to serve our patients and families that suffer from HD. Learn about Seth Rotberg's personal HD story, and how he is providing social support to hundreds of young adults with rare diseases.

Yes, we are in this together. It's OK to be frustrated, but hope will always win.



DANIEL CLAASSEN, MD
Associate Professor
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HD RESEARCH

Kinect-HD Trial in Progress

BY ERIN E. FURR-STIMMING, M.D.

KINECT-HD is conducting ongoing enrollment of a total of 120 subjects with motor manifest HD from North America and Canada at 46 HSG study sites. The study duration is approximately 18 weeks and includes nine study visits. KINECT-HD2 is an open label rollover study that will allow participants from KINECT-HD to receive valbenazine for up to 104 weeks while assessing safety, tolerability and efficacy.

Why should we study yet another VMAT2 inhibitor for HD related chorea? I believe there are a number of reasons:

1. EXPANDED APPROVED TREATMENT OPTIONS FOR INDIVIDUALS WITH HD

There remains an unmet medical need for the symptomatic treatment of chorea. Schultz et al. studied the Enroll-HD dataset as of April 2018 and found only 137 of 1,612 eligible subjects received tetrabenazine, while 104 used risperidone and 158 olanzapine.[1] A more recent Enroll-HD analysis found that <25% of HD patients with chorea actually receive treatment.[2]

The unique pharmacokinetic profile of valbenazine allows for once daily dosing and low peak to trough fluctuations. The terminal half-life for valbenazine and its metabolite is approximately ~20 hours, which differs significantly from deutetrabenazine (~8 hours) and tetrabenazine (~4 hours).[3] Importantly, valbenazine's sole metabolite (+ alpha DHTBZ) has the highest affinity and selectivity for VMAT2.[4]

Medications are often cost-prohibitive or cost-offensive at best. We have a higher likelihood of achieving cost coverage for medications that are prescribed on label. This is yet another reason — even within the same class — to provide patients with additional therapeutic options.

2. MORE OPPORTUNITIES FOR INDIVIDUALS WITH HD TO PARTICIPATE IN CLINICAL TRIALS

The process of pursuing an approval for a new indication is arduous. However, it provides a chance for individuals with HD to participate in the process, be part of the solution and to feel empowered. Das Mahapatra et al. published results from an online patient directed survey that found the most important considerations in trial participation were altruistic: an opportunity to improve one's own health and that of others.[5]

3. EXPLORE NEW OUTCOME MEASURES FOR HD CLINICAL TRIALS EXPLORED

A subpopulation of study subjects in KINECT-HD will apply wearable sensors to help objectively determine how study participants are responding while not in the clinic. This enhances our understanding of the impact of chorea in a "real world" setting. Moreover, applying scales that assess quality of life (QoL) can help us better determine the impact chorea has on various QoL measures.

We are profoundly grateful to the HD community for their participation in KINECT-HD and KINECT-HD2. Every trial is important in advancing our knowledge of and treatment for HD. We must continue to strive for improved symptomatic treatments for individuals currently struggling with HD.

Erin E. Furr-Stimming, M.D., is Director of the HDSA Center of Excellence and Associate Professor of neurology at The University of Texas Health Science Center at Houston.

[1] Shultz, JL, Kamholz, J, Nopoulos, P, Killoran, A.Comparing Risperidone and Olanzapine to Tetrabenazine for the Management of Chorea in Huntington Disease: An Analysis from the Enroll-HD Database, Movement Disorders Clinical Practice 2019; 6(2): 132–138. doi: 10.1002/mdc3.12706

[2] Furr-Stimming, E Claassen, D, Farrar, M, Jethwani, D, Carmack, T, Yonan, C, Haubenberger, D. Characteristics and Treatment Patterns in Patients with Huntington Disease: Current Data from Enroll HD, Huntington Study Group Annual Meeting, Virtual Poster Presentation 2020

[3] Grigoriadis, D, Smith, E, Hoare, S, Madan, A, Bozigian, H, Pharmacologic Characterization of Valbenazine (NBI-98854) and Its Metabolites, Pharmacol Exp Ther 361:454–461, June 2017 https://doi.org/10.1124/jpet.116.239160

[4] DasMahapatra, P., Raja, P., Gilbert, J. et al. Clinical trials from the patient perspective: survey in an online patient community. *BMC Health Serv Res* 17, 166 (2017). https://doi.org/10.1186/s12913-017-2090

KINECT HD

WHAT IS KINECT-HD?

KINECT-HD is a phase 3, randomized, double-blind, placebo-controlled trial to assess the efficacy, safety, and tolerability of valbenazine for the treatment of chorea associated with HD. FDA approved in 2017 for tardive dyskinesia, valbenazine is a VMAT2 inhibitor, the third in this class being studied for chorea in HD.

The primary endpoint of KINECT-HD is the change in the total maximal chorea (TMC) score from screening/baseline to maintenance (the average of the Week 10 and Week 12 assessments).

Secondary study objectives include the Clinical Global Impression of Change (CGI-C), the Patient Global Impression of Change (PGI-C), and the Quality of Life in Neurological Disorders (Neuro-QoL) Upper and Lower Extremity Function Short Form.

FIND OUT MORE ONLINE
WWW.HUNTINGTONSTUDYGROUP.ORG/CURRENT-CLINICAL-TRIALS/KINECT-HD

The Scoop on Credentialing Site Coordinators

Readiness for a Reason

BY DR. BONNIE HENNIG-TRESTMAN

More than two decades ago, the Huntington Study Group initiated credentialing of its sites, primary investigators (PIs), and study coordinators (SCs) to ensure consistency of clinical readiness. Over the past few years, however, the HSG has seen an increased number of candidates applying to become credentialed PIs and SCs who have limited clinical and/or trial experience.

To address this issue, the HSG Credential Committee has revised their standard operating procedures (SOPs) and application process. The goal of the revisions is to ensure that HSG-credentialed PIs and SCs are trained to work with people who are impacted by HD and are skilled at conducting clinical trials.

The Huntington Study Group (HSG) is the largest clinical research organization focused solely on clinical trials designed for people impacted by Huntington Disease. Sponsors such as pharmaceutical companies rely on the HSG to set the standard for conducting these studies. While each site's principal investigator (PI) is ultimately responsible for the conduct of specific trials, their sponsors look to HSG to provide a pool of potential sites where the staff are knowledgeable and experienced.

Dr. Bonnie Hennig-Trestman is the Director of the Carilion Clinic Huntington's Disease Program and Co-chair of the HSG Credentialing Committee in Rochester, New York.

If you would like more information about how to become a credentialed SC (or PI or site), please contact the Huntington Study Group at **info@hsglimited.org** or toll-free in North America at **1.800.487.7671**.

CREDENTIALING CENTERS ON PREPAREDNESS

Preparedness is primary for success as a clinical coordinator. Personally, I can tell you that going into a study with a "trial by fire" mentality is not the best option. Over a decade ago, when I initially became a site coordinator (SC) on a drug trial, I was armed with only experience as a back-up coordinator for an observational study. Although at the time I felt confident as a SC, looking back I realize my limitations.

My site IRB conducted an audit that proved to be a huge learning experience for me. While my initial perception of the audit result felt like a slap on the wrist, I realized later how beneficial it really was. The audit wasn't a punishment — it was implemented to assure the research was documented properly.

A side benefit was that it taught me how to do my job properly and how to keep participants safe.

In fact, following the audit, I asked for ongoing support in order to improve the quality of my documentation. The knowledge I gained from that support was invaluable. Since that time, I have served as a SC for other successful studies, and I credit these to this auditor who became a mentor to me. She made me a better SC, and more confident in my role.

MODIFICATIONS TO MEET MORE COMPLEX DEMANDS

While mentors play a vital role in each person's development, the purpose of the HSG Credential Committee is to ensure that SCs (and PIs) are qualified and ready to take on these respective roles. Current studies are increasingly more complex. To enhance the success of these SCs and PIs, the HSG Credential Committee actively works to support the credentialing process.

In addition to other requirements, the Credential Committee has made revisions to the application which now requires completion of the latest CME4HD courses and case studies. These are offered on demand (**https://huntingtonstudygroup.org/cme4hd-online**/). Along with providing CMEs, CNEs, or IPCE, these lecture courses and interactive case studies provide an overview of clinical care for people with HD.

Another modification is that the online credential application itself is now more streamlined and efficient. This change allows you, the SC candidate, to focus on the most relevant aspects of your experience and helps committee members to better understand whether you are prepared to conduct clinical trials in your specific roles.

THE QUALIFIED SITE COORDINATOR CANDIDATE

The committee reviews each application and pays close attention to the SC candidate's clinical and research experience. When you submit an application, be sure to include all relevant clinical practice and specifics of any involvement in trials which you have participated.

If you do not have adequate experience, the HSG Credential Committee will send you a letter recommending additional training and mentorship, along with a checklist of recommendations. These include: reviewing the HSG Educational Training Videos, which cover topics such as budgeting, Unified Huntington's Disease Rating Scale (UHDRS) insights, audits, and evaluation of suicidal behaviors; attending HD clinics at your institution; participating in the HSG Study Coordinator Council, which meets virtually weekly and provides mentorship; shadowing a PI or coordinator at your site; and other suggestions.

Of course, if you are able to complete some of these prior to submitting your application, we strongly encourage you to do that!

It is our hope that HSG members applying for certification take the time to review the credential application thoroughly and understand that receiving approval is much more than just a "rubber stamp." Becoming a HSG-credentialed SC means that you have met strict standards to ensure the safety of study participants and to assure sponsors that your site is well-prepared and able to "hit the ground ready" when chosen to participate in a study.

PROOF-HD:

New clinical trial in the United States, Canada, and Europe

BY SANDRA K. KOSTYK, MD, PhD

PROOF-HD is an acronym for a new Huntington's disease clinical trial that has recently begun in the United States, Canada and Europe. This acronym comes from the study title, Pridopidine Outcome On Function in Huntington's Disease. PROOF-HD is an international Phase 3 randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of 45 mg of pridopidine taken orally twice a day in patients with early-stage HD. The study is sponsored by Prilenia Therapeutics and is being run in conjunction with the Huntington Study Group and the Total Functional Capacity.

The agent under study in this trial, pridopidine, is not new to our HD community. Its potential effects, benefits and safety in HD have been studied in several earlier clinical trials in more than a thousand subjects, most recently in 408 individuals in the PRIDE-HD trial. PRIDE-HD is a phase 2 randomized placebo-controlled multicenter, dose ranging and safety and efficacy study of pridopidine in patients with Huntington's disease. It was originally thought that this drug's primary mechanism of action was as a dopamine modulator. As dopamine is involved in coordinating movements, the initial trials were focused primarily on looking at pridopidine effects on motor performance over time in individuals with HD and specifically its effect on the Unified Huntington's Disease Rating Scale (UHDRS)-Total Motor Score. The study did not meet the primary outcome measure of an improvement over placebo on the Total Motor Score (TFS). However, by using a more sensitive motor assessment tool, the Q-Motor system, an improvement in motor function over placebo was suggested.

As more was learned about pridopidine from ongoing preclinical trials, it was found that its greater potential benefit in HD was its activation of a receptor that is widespread in areas of the brain affected by HD. This receptor is the Sigma 1 receptor (S1R). Activation of the S1R has multiple effects in brain cells and on specific cellular activities that are implicated in the progression of HD. These include effects on mitochondrial function and cell energy production, and control and beneficial effects on neuronal plasticity — the ability of neurons to establish and maintain new connections in the brain to adapt to changes in the environment and preserve integrity of neural pathways.

Sandra K. Kostyk, MD, PhD is the Medical Director of the HDSA Center of Excellence at The Ohio State University Wexner Medical Center. She is also the North American co-primary investigator for this international trial.

> “The potential effects, benefits and safety in HD of the agent under study in this trial, pridopidine, has been studied in several earlier clinical trials.”

Activation of S1R also triggers an increase in levels of Brain Derived Neurotrophic Growth Factor (BDNF), a molecule that is a key player in modulating cell function, and thought to have the potential to slow the degenerative processes associated with HD.

Analysis of data from the past trials of pridopidine in HD patients has predicated the design and outcome measures of the PROOF-HD trial to maximize sensitivity to changes over time and increase the likelihood of establishing the efficacy of pridopidine as a beneficial agent for HD. Pridopidine has already been shown to be safe and well-tolerated compared to placebo in individuals with early-stage disease.

Few side effects have been reported and almost all study subjects completed the earlier studies, with few dropping out. This suggests that continuing on the study drug for over a year or more poses no difficulties. The prior studies also helped in choosing the most efficacious dose for the current trial, 45 mg, to be taken twice daily. In addition, data from the earlier trials helped identify the choice of outcome markers for the PROOF-HD trial beyond its possible benefits on sensitive measures of motor control, but also perhaps more importantly and primarily, its potential global effect on slowing the rate of overall disease progression.

The FDA has identified the Total Functional Capacity (TFC) score as one of the measures that has the greatest impact on patients’ lives and independence levels. The main objective of the PROOF-HD trial is to see if pridopidine can stabilize or reduce the rate of decline in HD over the course of a more than a year or longer. The TFC score, which ranges from 13 (little effect of HD on life activities) to 0 (end stage disease), usually declines by about one point every year in the earlier stages of the disease. Evidence from the prior HD trials suggests that pridopidine may slow

PROOF HD

WHO IS ELIGIBLE?

- *Male or female, 25 years of age and older, capable of giving informed consent.*
- *Have a diagnosis of HD based on clinical features.*
- *Have confirmed presence of CAG repeats of 36 or greater in the huntingtin gene.*
- *Must have adult-onset HD with onset of signs and symptoms at, or later than 18 years of age*
- *Must be willing and able to comply with the study instructions.*

STUDY SCHEDULE

- **Screening:** *After signing informed consent, participants will undergo screening assessments to determine eligibility.*
- **Treatment Period:** *The screening period will be followed by a double blind treatment period that will last between 65 to 78 weeks (Main study).*
- **Open-Label Extension (OLE):** *Eligible participants who complete the Main study will have the option to enroll into an OLE period and receive pridopidine (no patients will receive placebo during the OLE).*

FIND OUT MORE

- Further information about the study, including study site locations, can be found online at:

www.huntingtonstudygroup.org

www.clinicaltrials.gov

PROOF-HD *(continued)*

this rate of decline. However, we need to prove to the FDA (i.e. prove this hypothesis through the PROOF-HD trial) that pridopidine has this effect in a carefully designed and well-controlled study.

The TFC assesses five measures of function, including ability to continue employment, ability to manage finances, ability to attend to activities of daily living (such as bathing and dressing and taking medications idependently), ability to do housework, and ability to continue to live at home.

Individuals eligible to participate in the trial must be in the early stages of disease and age 25 years or older with symptom onset after age 18. There is no upper age limit for participating in this trial. Participants must be on stable doses of medications but there are a few medication restrictions in the trial. There are several other inclusion and exclusion criteria that must be met and will be assessed at the first screening visit.

The study will last at least 65 weeks and will include 8-9 study visits. Mitigations have been included in the trial design to accommodate exigencies, such as those that might be caused by Covid-19, to allow some visits to be done virtually, if necessary. It is essential that the baseline and last visit be done in person. A total of 480 subjects are expected to enroll worldwide. Subjects will be randomized 1:1 to be on study drug or placebo.

In addition to the TFC as the primary outcome measure, other assessments will also be completed in the PROOF-HD trial. These will include the UHDRS-Total Motor Score, the more sensitive Q-Motor system assessments (as these showed potential efficacy in the earlier HART and MERMAID pridopidine trials).

It seems likely that clinical features that contribute to overall TFC score will include aspects of motor function. Several safety and additional quality-of-life measures will also be assessed. These additional measures will be used to support and help prove the efficacy of pridopidine for HD.

There will be 30 study sites in the United States and Canada and 30 sites in Europe. At the end of the study, all subjects, both those who were on pridopidine and those who were on placebo can continue in the OPEN-LABEL extension of the trial, where everyone will take 45 mg of pridopidine twice a day. This open-label extension will help prove the long-term safety and benefits of pridopidine.

The PROOF-HD study will last at least

65 *weeks*

8 TO 9

study visits are included

480 *individuals*

are expected to participate in the PROOF-HD clinical trial worldwide

> “Analysis of data from the past trials of pridopidine in HD patients has predicated the design and outcome measures of the PROOF-HD trial to maximize sensitivity to changes over time and increase the likelihood of establishing the efficacy of pridopidine as a beneficial agent for HD.”

Q-Motor in PROOF-HD

Objective evidence for effect of pridopidine

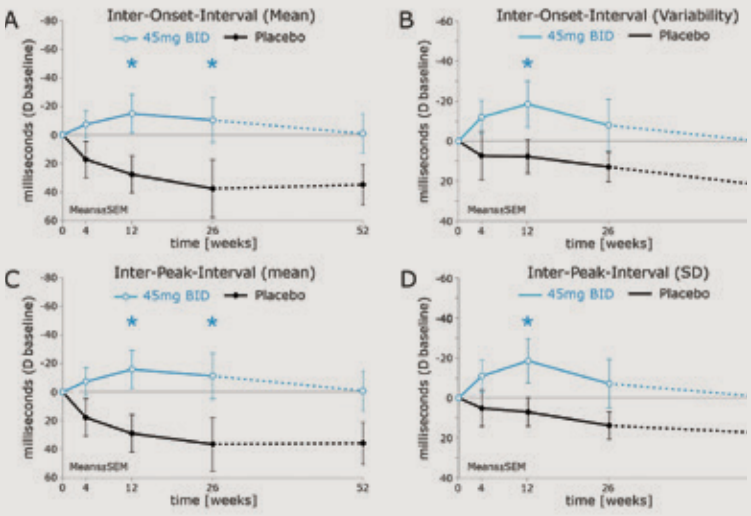
BY RALF REILMANN, MD, PhD

Q-Motor (Quantitative-Motor) assessments have been applied in multiple clinical trials and biomarker studies in HD. In PRIDE-HD, several Q-Motor measures provided evidence for a motor benefit of patients treated with pridopidine — particularly in the 45 mg BID arm — see Figure 1 below (modified from Reilmann et al., 2019). In contrast, the placebo group showed deterioration, i.e. progression of motor symptoms. This observation corroborated the Total Functional Capacity (TFC) effect observed at 45mg BID.

Jointly, the data supported a central effect of Pridopidine and provided the rational for embarking into the PROOF-HD phase III study. It was very helpful to have these observations at hand, particularly in light of the changes seen in the Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS). The standardized, objective Q-Motor data supported the interpretation that a strong placebo effect had driven the large TMS benefits observed in the placebo group in PRIDE-HD. While Q-Motor measures are not yet validated and accepted as a primary endpoint by regulatory bodies, agencies such as the Federal Institute for Drugs and Medial Devices (BfArM) in Germany did acknowledge the supportive evidence they may provide for a primary endpoint in pivotal clinical trials. Therefore, Q-Motor assessments were also implemented in PROOF-HD.

Q-MOTOR IN PRIDE-HD

Speeded Tapping Hand (Digitomotography)



Q-Motor speeded tapping measures in PRIDE-HD revealed an improved motor coordination in patients treated with 45mg BID pridopidine compared to placebo, while the TMS showed no benefit.

Q-Motor is an outpatient clinic-based assessment that is easy to use at no relevant risk or burden for patients. Assessments selected for PROOF-HD will take approximately 5-10 minutes. The data is transferred automatically online to the George-Huntington-Institute/ QuantiMedis Q-Motor team in Germany for ongoing quality control and blinded analyses. It can be used for efficacy and safety analysis and help trigger decisions in adaptive clinical trial designs (not implemented in PROOF-HD). Online training to study coordinators in live sessions is provided by the Q-Motor team, available 24/7. Changes in Q-Motor were observed in premanifest HD gene carriers up to two decades before HD onset in the Cure Huntington's Disease Initiative (CHDI) funded study TRACK-HD.

In essence, Q-Motor was developed in the HD community and originally explored at the HDSA Center of Excellence at Columbia University in New York during a post-doc I did between 1997 and 2001. Encouraged by early results, the development of more refined assessments and setups was initiated and funded by several sources. After implementation in TRACK-HD, Q-Motor was employed in clinical trials, e.g. the AFQ056 study (Novartis), AMARYLLIS (Pfizer), LEGATO-HD (Teva), PRIDE-HD (Teva) SIGNAL (Vaccinex), and the first HD gene therapy trial, HD-GeneTX1 (uniQure).

Feedback from the over 100 sites that used Q-Motor globally allowed the development of "Q-Motor 2.0." It is installed on a mobile cart and can easily be moved to different places. The novel platform was expanded to also provide cognitive assessments such as the Trail-Making Test A and B and others such as the "Q-Cog" assessments that were developed with funding from the European Union.

Correlation of Q-Motor measures with MRI volumes, CAG repeat-based disease burden scores, and clinical assessments such as the TFC or UHDRS-TMS were observed in multiple trials. Evidence of the clinical significance of these measures is evolving, and studies like PROOF-HD help us learn what contributions these measures may make. Besides use in symptomatic HD cohorts, the sensitivity in prodromal and premanifest groups holds promise to facilitate development of preventive HD therapies in prodromal stages, which could also be interesting for a well-tolerated drug as pridopidine.

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Ralf Reilmann is the Global Coordinating Principal Investigator – Europe, for PROOF-HD.

Stronger Than the Sum of Their Parts

Thoughts on Building a Clinical Research Team

BY DANIELLE BUCHANAN

Danielle Buchanan has a bachelor of science in biology from Eckerd College in St. Petersburg, Florida and eight years of research experience. Currently, she is a Clinical Translational Research Coordinator III at Vanderbilt University Medical Center.

There is no "I" in the word team, as the famous quote says. Teamwork is the most important aspect of clinical research. You work as a team at the site, or program level, in order to bring discoveries to patients.

In reflecting on my life experiences, I have been on a number of teams: in volleyball, symphony orchestra, as a student resident advisor, and now as a clinical research coordinator. Some teams did not succeed. Others did. Each team I have been a part of has taught me about many different qualities for success. These experiences have created a curiosity about what components make a clinical research team and program successful.

Before my current job, I worked on a large team of 13, running oncology clinical trials. Over those years, about 90 percent of that group had resigned, and been replaced. This seemed to be high, for such a critical work-flow. Why did this team in particular fall apart? As I started exploring other positions, I formulated a list of desirable attributes to help guide my employment decision. My current role allows me to reflect on those team attributes I find most compelling.

HIRING FOR SUCCESS

Over the past decades, the clinical research coordinator role in the U.S. has changed from one with fairly long tenure, to one where there is high turnover. As I enter my third year working at Vanderbilt University Medical Center, I have had the freedom and responsibility to define key characteristics in new hires that would help ensure a long and productive tenure. Informally, I believe that there are certain characteristics necessary for clinical research: a self-starter, organized, a positive personality, great communication skills, passion for patient care, a commitment for excellence, and a love of teamwork.

In our group, we often use a quote from de Saint-Exupery, who wrote *The Little Prince*, to capture these attributes: "If you want to build a ship, don't drum up people together to collect wood and don't assign them tasks and work, but rather teach them to long for the endless immensity of the sea." We could train people on how to run a clinical trial, or how to perform a motor exam, but what we cannot teach anyone is how our passion for patients informs our desire to run excellent clinical research trials. This passion must develop from within.

RETENTION IN A "STEPPING STONE" PROFESSION

You can hire the right person, but retaining them is a different matter. The clinical coordinator role is still a transitional one for many, and top people are presented with ample opportunities for other positions. We want people to stay a long time, but losing a great team member is a risk we recognize and accept.

Currently, I am in charge of hiring four clinical research coordinators. These positions are available because current coordinators are leaving for graduate school, medical school, and other careers in health care. We are so happy and proud of them for moving to the next step in their journey, but this means finding and training new people, which is time-consuming. It also means a loss of valuable knowledge about our program.

To help guide us in how to keep excellent clinical research coordinators, I have worked with colleagues on a study where we identified statistically significant predictors of retention for this role. We found these nine top factors to be key: work environment, clinical research coordinator (CRC) level, perception of competitive salary, role appreciation, input in protocol development, engagement, collaborative opportunities, respect, and a close working relationship with the principal investigator.*

Since multiple predictors connect back to the principal investigator, it showed us that in order for the team to work as a well-oiled machine, not only do the coordinators have to have to meet a certain standard for success, but the PI needs to engage and support the team.

TEAMS SINK OR SWIM ON OUTLOOK AND MATURITY

Positivity is something that can keep a team from sinking when the disappointments, setbacks and emergency deadlines hit. If one person starts to bring bad energy into the office, it can act like a virus and spread quickly. We are constantly working on ways to improve our positive work environment. One of those strategies includes a "zero gossip" policy. If there are

*Danielle A. Buchanan, Jody Goldstein, Anna C. Pfalzer, Ya-Chen Lin, Hakmook Kang, Daniel O. Claassen, "Empowering the Clinical Research Coordinator in Academic Medical Centers," Mayo Clinic Proceedings: Innovations, Quality & Outcomes, 2020.

https://mcpiqojournal.org/article/S2542-4548(20)30197-1/fulltext

any conflicts to be discussed, this needs to be done with a supervisor — and in private, not in front of other employees.

Alongside positivity, we all have to work on conflict management. We work as a multidisciplinary team and must interact with many different types of people, so this job takes maturity and critical thinking skills. Yet, since a clinical coordinator has been labeled as an entry-level position in the research community, it ultimately attracts recent graduates or those without much relevant work experience. Maturity beyond someone's years, the ability to resolve conflicts are qualities we look for while hiring.

We have learned to be on the lookout for evidence of this before we hire, no matter how qualified a candidate is on paper. In each interview, we stress that we need long-term commitment, a strong work ethic, attention to detail, interpersonal communication skills and critical thinking and problem-solving skills — all qualities that speak to maturity. We know that it is not a process we should rush. Finding the best candidate is worth the wait and may avert serious problems resulting from a poor choice.

MARRYING ATTRIBUTES TO FORGE A STRONG TEAM

Reflecting on our coordinators who have come and gone, I realize they have taught us some things about what we can change as we forge future groups of coordinators. Different people shine in different areas and that can often be managed, as long as a "weaker strength" doesn't translate into real weaknesses.

Running clinical trials is often "organized chaos," requiring coordinators to have a steady vision of the big picture, yet be quick on their feet — planful, but able to respond quickly and appropriately to a change of plans. These high "executive function" qualities may not always coexist in someone who has a strong empathetic side. Yet we need people with naturally supportive and patient personalities. Our patients and their families need to know we are committed to them — they need to know we are here to care for them. That takes someone who has compassion and conveys a sense of hope to these families who are dealing with incurable diseases.

Expecting all these attributes within one clinical coordinator is not always realistic. What we are finding, though, is that we can build a team with complementary strengths. While everyone on the team must have a base level of empathy and ability to juggle priorities, different members can take up the slack for one another when needed. Plus, they can teach each other. This can occur naturally or as part of a deliberate leadership strategy.

Looking ahead at training a new group of coordinators, I realize we may never be perfect *individuals*, but we can work to develop a near-perfect *team*, making us more and more effective as we move forward.

> "Looking ahead at training a new group of coordinators, I realize we may never be perfect individuals, but I can work to develop a near-perfect team."
>
> **DANIELLE BUCHANAN**

PART OF THE TEAM
Danielle Buchanan, left, works with the Cognitive and Movement Disorders group led by Dr. Daniel Claassen, right.

profiles

BY LISE MUNSIE, PH.D.

Lise Munsie is Senior Development Manager and Project Leader, Pluripotent Stem Cell Therapies at CCRM, a Canadian, not-for-profit group that is focused on developing and commercializing regenerative medicine, cell and gene therapy technologies.

1 Studies on Modulating Transcriptional Dysregulation

There is substantial data to support that there are many changes to how normal gene — and thus proteins — are expressed in cells of HD patients. This is called transcriptional dysregulation. Work still needs to be done to parse cause vs. effect of this transcriptional dysregulation. We need to determine if the transcriptional alterations can be tracked over the course of HD, and if modulating them may be therapeutic.

Epigenetic Alterations Explored

Most reports looking at changes in gene expression focus broadly on transcription, with fewer studies focusing on epigenetic alterations. Epigenetic alterations are a kind of change that happens to the DNA without changing the DNA. A study published in *Nature Communications* investigates temporal dynamics and mechanisms underlying epigenetic changes contributing to HD.[1]

Q140 heterozygous mice were used because they are a slow-progressing disease model, and therefore useful for examining early disease markers. The main technique used to detect epigenetic changes is called ChIP-Seq. ChIP-Seq was used to detect certain DNA changes, specifically H3K27ac, RNAPII and H3K27me3. These markers keep DNA in different structures that lead to different expression of genes. ChiP-Seq data for these changes were generated at two and six months in neuronal and non-neuronal populations in this mouse model.

This extensive and detailed study indicated that there are age-related epigenetic and transcriptional striatal changes that are exacerbated by mHtt. The group shows a structural change of the DNA in the nucleus (called chromatin) that correlates with the transcriptional changes. This data indicates that mHtt leads to an accelerated epigenetic aging phenomenon.

Impact of Histone Deacetylases Alterations on Somatic Expansion

A phenomenon called somatic expansion occurs in HD. This is where the mutation that causes HD actually increases over time in certain cells of HD patients and is a hallmark of disease. Histone deacetylases (HDACs) are chromatin-remodeling enzymes responsible for transcriptional regulation and epigenetic modifications. HDACs have been shown to correlate with disease-causing gene expression alterations in HD.

A group led by Dr. Vanessa Wheeler investigated whether alterations in HDACs and their chromatic remodeling abilities had any effect on the increased somatic expansion seen in HD.[2] Using the HD Q111 mouse model, and conditionally knocking out Hdac2 or Hdac3 from the striatum, the group found a trend towards decreased somatic expansion and altered nuclear pathology. This supports the theory that HDACs may enhance CAG expansion in striatal neurons, and warrants further studies.

Lamin Proteins Track with HD Pathology

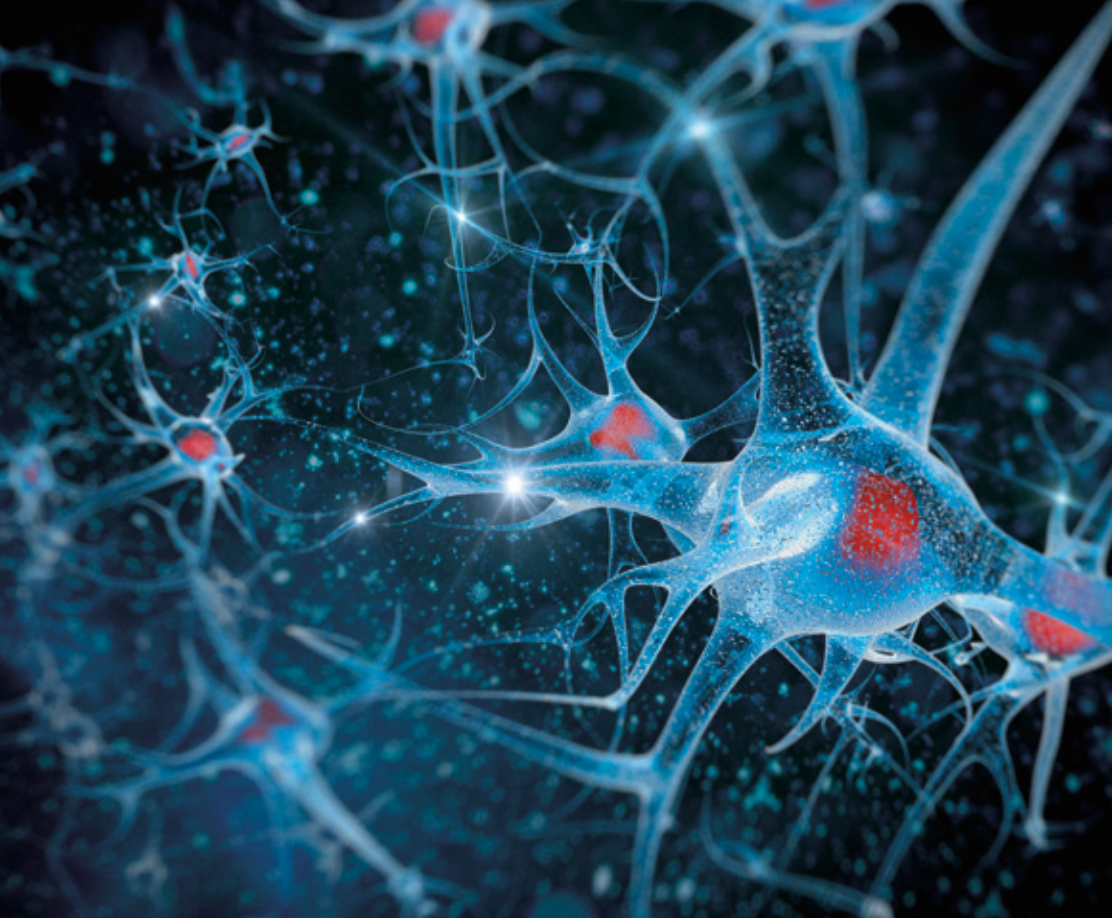
Lamin proteins assist in maintaining nuclear structure and function. They are critical for RNA nuclear export which, with transcription, are altered in HD. A recent paper looked at lamin alterations in the R6/2 mouse model and post mortem HD tissue.[3] There are many different lamin isoforms, but this study highlighted how lamin B1 affected the brain in both models. They found increased levels of lamin B1 tracking with pathology, and these changes were not age-related.

The group generated Lamin B1 ChIP-seq data in the mouse and showed changes in the nuclear lamina heterochromatin organization and lamin B1 chromatin binding. This data shows another avenue that can be explored with respect to transcription, chromatin and epigenetic-related pathophysiology in the brain during HD.

[1] Alcala-Vida, R., et.al. (2021) Age-Related and disease locus-specific mechanisms contribute to early remodelling of chromatin structure in Huntington's disease mice. *Nature Communications* 12(364)

[2] Kovalenko, M., et.al. (2020) Histone deacetylase knockouts modify transcription, CAG instability and nuclear pathology in Huntington disease mice. *Elife DOI: https://doi.org/10.7554/eLife.55911*

[3] Alcala-Vida R., et.al. (2021) Neuron type-specific increase in lamin B1 contributes to nuclear dysfunction in Huntington's Disease *EMBO Mol Med* 13:e12105



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Basic Research Impacting Htt-Lowering Therapy

▶ A PREDICTIVE TOOL
Dr. Ed Wild's team has examined the correlation of Mtt and neurofilament light, which correlated with clinical prognosis of HD.

Huntingtin (Htt) is the protein, that when mutated (mutant huntingtin (mHtt)), causes Huntington's Disease (HD). Lowering the levels of Htt in the brain is a promising therapeutic avenue. To track success of these therapies, it is important to have the ability to detect if the levels of Htt in the brain are decreasing after the therapy has been administered. Ideally, scientists and doctors would like to have non-invasive procedures, like blood collection, to achieve this.

The CNS-CFS Connection

This effort has been assisted by a recent study published in *Neurobiology of Disease*, which describes an investigation of how Htt moves from the central nervous system (CNS), or the brain, to cerebrospinal fluid (CSF), a fluid that can be easily collected and analyzed by doctors.[1] Using ultrasensitive protein detection techniques, researchers were able to detect mHtt in CSF at levels that correlate to that in the CNS.

Using a variety of cellular and animal models and a sensitive protein detection technique called immunoprecipitation flow cytometry (IP-FCM), the group finds that the neurodegeneration that causes HD leads to increased mHtt in CSF. However, interestingly, in the absence of neurodegeneration, mHtt is still detectable in the CSF.

Findings showed that both wildtype Htt (wtHtt) and mtHtt are secreted from neurons, the cells in the brain that are affected by Htt, indicating the movement of Htt from CNS to CSF may be a normal function. However, during neurodegeneration, an increase of mHtt is found to be actively moved into the CSF by a cellular system called the glymphatic system. These findings tell researchers that Htt is found in the CSF normally, but in HD is also actively moved into the CSF. This will help them understand how and why they see changes in Htt levels in the blood and correlate this back to treatments.

Finding the Best Methods to Detect Htt

To assess how best to detect low levels of Htt using immunoassays, another manuscript systematically assesses how different molecules and antibodies used to detect Htt perform. This is done through using one of the best detection methods for proteins: the single molecular counting (SMC) assay.[2]

This assay requires antibodies that detect a certain part of the Htt protein called the N-terminus, to be immobilized on magnetic particles that capture the protein. Then detection of Htt is based on another antibody that detects a different part of the protein conjugated to a fluorphore — a molecule that can light up and be quantitated by researchers.

This paper tests different antibodies and produces a summary table which displays their ability to detect different Htt fragments and whether there is specificity for the assay to detect mHtt . The paper makes a reference table for other researchers to use when designing their assays that tells them the specificity of the antibody, the ability to pick up Htt in different species and how sensitive the antibody is. The group also makes different recommendations on which antibodies to use or avoid in certain situations.

Neurofilament Light as Predictive Tool

While detecting mHtt levels is important for tracking the success of Htt knockdown therapies, finding other markers in the blood (biomarkers) that indicate whether lowering Htt is having a positive outcome on disease progression is also required.

Neurofilament light (NfL), is an axonal protein indicative of brain injury or neuronal injury, which is what happens to individual with HD. NfL levels have been shown to track with HD progression in blood, however NfL spikes in the CSF of patients who have undergone Htt-lowering therapy.

Dr. Ed Wild's group examined the correlation of Htt and NfL levels in HD patients.[3] Both NfL and mHtt increased in this cohort of patients over a two-year period, and this correlated with clinical prognosis. NfL proved to be a more sensitive readout than just looking at levels of mHtt, and has potential to be sensitive enough for clinicians to track in the blood and determine when a patient is moving from PreHD (no symptoms) to manifest HD (starting to have symptoms).

[1] Caron, N., et.al (2021) Mutant Huntingtin Is Cleared from the Brain via Active Mechanisms in Huntington's Disease. *Neurobiology of Disease* 41(4) 780-796

[2] Fodale, V., et. al. (2021) Analysis of mutant and total huntingtin expression in Huntington's disease murine models. *Scientific Reports* 10(22137)

[3] Rodrigues, F.B., et. al. (2020) Mutant Huntingtin and Neurofilament Light have Distinct Longitudinal Dynamic in Huntington's Disease *Sci.Transl.Med* 12(eabc2888)

BY LISE MUNSIE, PH.D.

3 Identifying Peripheral Markers for Htt

Because Huntingtin (Htt) is difficult to detect peripherally (in blood or other non-invasive tests) as a marker for Htt knockdown in the brain, it is important to have other markers that correlate with disease. Additionally, these are important for future therapies that do not involve knockdown of Htt, as clinicians will need ways to know their therapy is working in patients.

BDNF Level Differences Ruled Out as Biomarkers

A study published in *Scientific Reports* investigates if Brain Derived Neurotropic Factor (BDNF), a protein whose expression levels in the brain are known to be associated with HD progression, can be detected in CSF and track with disease.[1] Conventional ELISA assays, which are standard protein detection assays, were not able to detect BDNF in the blood.

Using an ultra-sensitive detection method, the group was able to detect BDNF in plasma and CSF. However, when examining HD patient cohorts of premanifest and manifest HD, no differences in BDNF levels were detectable in the blood between control and HD patients, nor between patients at different stages of disease. Although BDNF levels decrease over the course of HD in the brain, this decrease cannot be detected peripherally. Therefore, BDNF can be ruled out as a peripheral biomarker.

> “Although BDNF levels decrease over the course of HD in the brain, this decrease cannot be detected peripherally. Therefore, BDNF can be ruled out as a peripheral biomarker.”

DETECTING BDNF
Using an ultra-sensitive detection method, the group was able to detect BDNF in plasma and CSF.

Dynein Light Chain Expression Correlates to Disease Progression

There is a lot of genome-wide data from HD mouse models, providing clues to pathways and genes/proteins that may be affected during disease. Large studies on this data lead to many potential biomarkers. Many changes in gene and protein expression have been validated as up- or down-regulated in HD patients. Dynein light chain Tctex type 1 (DYNLT1) is a motor protein with a gene expression that is regulated by mHtt.

A group aimed to determine if changes in DYNLT1 could be detected in human blood.[2] The patient cohort studied included patients at different stages of disease. Some patients were sampled twice, three years apart. The group shows that expression of DYNLT1 by qPCR, a sensitive technique that detects changes in level ofgene expression, is correlated with disease progression. The study was not powered enough to make any correlations to age of onset or disease stage. However, it does indicate that DYNTL1 should be further studied as a biomarker in larger cohorts.

Prodynophin as Potential Biomarker

Prodynorphin (PDYN) is a gene that is highly enriched in the striatum, the area of the brain affected in HD. It has been shown to have decreased expression in HD brains as neurodegeneration occurs. Based on this, a group set out to see if PDYN-derived peptides could be correlated with HD onset in CSF.[3]

The detection of PDYN protein in CSF was performed using a detection technique called liquid chromatography mass spectrometry. The levels of PDYN-derived peptides was significantly decreased in the HD cohort compared with controls and compared to patients with other neurodegenerative disorders. This decrease was trending down with disease severity and did not correlate with age, indicating this is another potential biomarker for HD progression and treatment.

[1] Andy Ou, Z., et. al. (2021) Brain-derived neurotrophic factor in cerebrospinal fluid and plasma is not a biomarker for Huntington’s Disease. *Scientific Reports* (11)3481

[2] Rosseto, S.M., et.al. (2020) DYNTL1 gene expression is downregulated in whole blood of patients at different Huntington’s disease stages. *Neurological Sciences doi/* s10072-020-04772-0

[3] Al Shweiki, R., et.al (2020) Cerebrospinal Fluid Levels of Prodynorphin-Derived Peptides are Decreased in Huntington’s Disease. *Movement Disorders* doi. org/10.1002/mds.28300

BY VICTORIA SEGRO, ANP-C

Clinical Perspective

Reflections on Twenty YEARS OF TRIALS

Vicki Segro is a nurse practitioner and a rater and sub-investigator at the Rocky Mountain Movement Disorders Center in Englewood, Colorado.

I have had the pleasure of participating in the care of patients with Huntington's disease for the last 20 years, and now working with multiple generations of these families.

The approach in how we care for patients participating in clinical trials is certainly different compared to routine clinical care, but the quality of the care should be the same. In our work, good care of a person with HD participating in a clinical trial appreciates both the science of the study and the human being willing to volunteer for the study.

The team members must all understand the course of clinical illness in HD to provide excellent care, of course. This includes the motor symptoms of HD, cognitive symptoms, as well as the emotional symptoms of the illness. This becomes more challenging as the science behind the studies becomes more complex over time.

Team members must all understand the course of clinical illness in HD to provide excellent care.

Understanding the basics of the science is still critical. "God is in the details," they say. When I was learning to participate in clinical trials as a nurse practitioner, I was assisted by a seasoned research coordinator who impressed on me how important it was to pay attention to the details, and helped me learn how to do that in the context of a study. This saved me and others from rework, embarrassment, trial delays, and most importantly, potential harm to participants.

Organization skills are a must, particularly scheduling visits within time windows. We have some studies that we pre-schedule over six months ahead to keep within those windows. Our office schedules a mix of routine clinic follow-up patients, new clinic patients, and study participants on every day of the week, so scheduling far in advance is preferable.

Caring at the Center of It All

The best study coordinators I have worked with have a deep commitment to the care of the entire family that is affected by HD. They are in "for the long haul" with a long-term commitment to HD. I think this leads to a greater willingness for patients to commit to participation in studies. We must always remind ourselves that patients with HD and their families bring a lot of hope and commitment to this — they are providing us with the ability to perform the research through volunteerism.

Personal relationships often come with the territory. Some research studies allow us to spend more time with patients and their caregivers because of more frequent office visits through the course of the study. As a result, you learn more about their personal interests and, in some cases gain a deeper understanding of how HD affects their lives and relationships.

We may then connect people to resources, if needed, through the local Huntington's Disease Society of America or other community groups. I am amazed by the extent families will go to to provide care for their loved one — whether a parent, sibling, or a child. More frequent contact with patients allows me to appreciate their commitment to research and finding a cure for this disease.

I once had a gene-positive, asymptomatic patient who was participating in an observational study tell me about the anxiety that came with annual visits. Each visit, she worried that there would be a formal diagnosis of HD. It made me realize that

At the end of her visit, the excitement and hope that she and her family expressed was overwhelming. I was grateful to have participated in her care that day. This kind of experience affirms the whole reason I love to participate in research.

even observational studies put a lot of stress on participants. I can now have open conversations which validate anxiety and fear over coming in for what may be somewhat routine visit.

I remember a young lady who came to our site to administer the first open label (no placebo) dose of tominersen in the GEN-EXTEND study. She was uncomfortable because this was a single visit at our site and she had never met any of our staff. The visit and the procedure went smoothly, for which I was thankful. At the end of her visit, the excitement and hope that she and her family expressed was overwhelming. I was grateful to have participated in her care that day. This kind of experience affirms the whole reason I love to participate in research.

A Partner to the Provider

Our research coordinators spend a great deal of time with patients and caregivers and then report important interval history events to the provider prior to their being seen by the providers. Tracking medication changes and health events that occur between visits is tedious in some cases, particularly when the patient may have seen other providers in the interim.

Providers greatly appreciate our organizing the study tasks during the visit, so they may complete their portion efficiently. It isn't the most exciting aspect of the job, but everyone wins when you double-check that the paperwork is properly

completed, with everything signed and dated correctly. My advice is to do your job as though there will be no second set of eyes on it — then get a second set of eyes on it! I cannot count the times that I filled in the wrong date on paperwork, particularly in the new year, and the study coordinator helped me to fix it right away.

Bonding Around Tasks and the HD Mission

Communication with the larger study team is vital. We have monthly research meetings with all of the coordinators and providers in the office. We discuss study recruitment as well as larger working issues related to each individual study. In addition, study coordinators have a separate monthly meeting to discuss specific details and coordinator specific challenges.

After we have enrolled a few patients into a new study protocol, the coordinators and providers become more comfortable with the "flow" of procedures. We can expect some organized chaos for the first patient participating in their first study visit, but somehow, we manage to get through it all in one piece. I have learned to expect this over time, and we will counsel participants that this may happen. To minimize the snafus, our seasoned HD study coordinators mentor new coordinators and those transitioning from care of patients with other diagnoses to HD.

In this process, a cohesive team begins to develop. Further strengthening it, teams also participate in local community events and fundraisers. It is a pleasure getting to participate in hoop-a-thons and walks and other local fundraising activities. These activities help build a strong team of caregivers and create an excellent work environment.

Meeting a Ballooning Complexity Challenge

The biggest challenge of research in HD is trying to keep up with the science behind the research, which is moving at a faster pace over time. This includes observational studies, studies of new medications for the treatment of symptoms of HD, and new treatments meant to slow the progression of this disease. We are studying medications that may be administered via many routes, including pill forms, intravenous infusions, intrathecal infusions (through a lumbar puncture process), and even through direct injection into the brain.

Every year, the science is advancing to provide better treatments of symptoms of HD with fewer side effects. Ultimately, the goal of treatment is to slow or even stop the progression of HD. I look forward to the future when we see the day that we find a cure and will be proud to have contributed to the cause. ●

To minimize the snafus, our seasoned HD study coordinators mentor new study coordinators and coordinators transitioning care from patients with other diagnoses to HD.

The biggest challenge of research in HD is trying to keep up with of the science behind the research, which is moving at a faster pace over time.

Coaching the Point Guards

HD Insights interviewed Jody Goldstein, who reflects on being a "coordinator of coordinators." Yes, it's complicated, but the rewards are rich.

JODY GOLDSTEIN

Jody is the Director of Clinical Operations for HSG, she is the Chair of the HSG Member Education Committee, Co-chair of the HSG Executive Coordinator Council, and a member of the HSG Research Advisory Board.

Her expertise in study start-up (protocol and consent development), innovative patient recruitment, and clinical trial site education has led to the successful initiation and implementation of over 15 HSG clinical trials.

She has served as a member of the HSG Executive Committee, Project Aware Committee, and HD Communications Committee. Due to her commitment to educate and support coordinators, Jody was recognized with the 2015 HSG Coordinator Mentorship award.

MCAT scores in hand, Jody Goldstein was set to pursue a career as a physician, when the love of an HD clinical research coordinator job interfered. Twenty years later, she is helping scores of new or rising clinical coordinators realize some of the success, contribution and gratification she has known

15

The number of HSG clinical trials

that Jody Goldstein has helped to initiate and implement.

A Rapid-fire Onboarding

Jody's career path in clinical research began when she met Dr. Jody Corey-Bloom, Director of the University of California at San Diego (UCSD) Huntington's Disease Clinical Research Program, in 2001, and was introduced to the Huntington disease community. She recalls her first days as a clinical research coordinator at UCSD: "The HD team members heaved a sigh of relief when I arrived, and gave me a stack of charts as big as I was to review," she said. "I remember their saying, 'Let us know if you have any questions,' as they walked out the door."

Well, she had quite a few. While she had experience in patient care and a business background, Jody didn't know much about HD. Thankfully she had a very supportive team who welcomed her questions. To this day, Jody tells coordinators, "Don't ever be afraid to ask questions — it is one of the most important things you can do to learn and become effective."

Jody immersed herself in HD by reading books, scouring charts, reviewing patient videos, and learning about HD symptoms and medications. She immediately forged strong bonds with families impacted by HD and began to develop top-notch skills as a clinical research coordinator.

During her time at UCSD, Jody participated in other activities, including genetic counseling and testing, running HD support groups, and educating the community about HD. In addition, due to her bicultural background (her mother is Mexican), she was able to engage the HD Hispanic community to come to the clinic and participate in research.

Coordinating Coordinators

In 2012, Jody was presented with an opportunity to use her experience as a clinical research coordinator to enter a project management role, running global clinical trials with another of her mentors, Elise Kayson, M.S., ANP, at the University of Rochester in Rochester, New York. "It wasn't an easy decision to leave my UCSD team and San Diego HD families," she said. "They were family to me."

It was her colleagues and HD families who ultimately encouraged her to accept the job. "They knew I could make a larger footprint in the HD world through this new position. I took the job on the condition that I could be a project manager who would be there for all of the sites, so that they could concentrate on their research participants and studies. I wanted to teach, coach, and help sites to become successful at running clinical trials and bringing study results faster to the HD community."

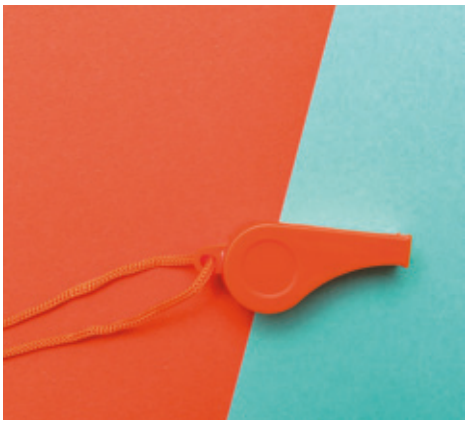
An Audit-ready Preparation

Preparation for a clinical trial starts well before the site is selected for a study. Having been been part of a successful FDA site audit for the tetrabenazine study, helped prepare Jody to teach coordinators the importance of being audit-ready. Part of the coordinator's responsibility is to work with the investigator to learn about the study design, understand the requirements of the protocol and determine if the site has enough appropriate patients who meet the eligibility criteria.

"Your job is to learn every aspect of the study — what it requires, what staff you need (pharmacy, laboratory, imaging, etc.), the budget side of things, and the regulatory side of things (IRB)," she said. "The questions you need to ask yourself include: what elements does the study require, what staff is needed (pharmacy, laboratory, imaging), is there sufficient budget to cover your costs, and do you understand the regulatory requirements and IRB timelines?"

ON THE FRONT LINE
Jody speaks with a patient at a research and treatment center.
Photo: Sam Hodgson

In addition to navigating conversations with potential and established trial participants, another role of the clinical research coordinator is to ensure protocol compliance. "You have to be obsessive about documentation. If you don't document that you ask all the required questions, every time, it's like it never happened." This balancing act is one of the arts Jody teaches. "I remind coordinators that it takes time to train yourself to do this gracefully."



Secrets of a Point Guard

Jody says her love of basketball and her experience as a point guard contributed to her ability to handle multifaceted projects, anticipating and managing what may lie ahead. "As a point guard, you have to know where someone's going to be before the ball is passed — you have to know what's going on before it happens. It is very similar in the clinic. You have to be aware of everything," she said.

"You have to know what will make somebody want to participate in a clinical trial but you also have to know when it's not the right choice. You have to know when somebody is anxious about a research visit and how to put them at ease. You have to know how to position your team to run an effective research visit."

"Your job is to learn every aspect of the study — what it requires, what staff you need (pharmacy, laboratory, imaging, etc.), the budget side of things, and the regulatory side of things." **JODY GOLDSTEIN**

Goldstein believes recruitment starts with empathy, and understanding that patients are participating not only for themselves, but for the next generation.

Rapport Matters

Once these questions are answered, Jody says the success of each trial depends largely on the relationships you create. "One of the things that I learned very early on is that you need to build a rapport with everyone". This includes not only patients and families but also other health care professionals.

A clinical coordinator depends on myriad people who work outside the clinic to get the trial done. Working to be "top of the list" for those who control trial resources means first earning their respect. "You are in a situation where there are competing contracts. My mentor, Dr. Corey-Bloom, and I made sure our applications were straightforward and without gaps. That way, the finance team or the IRB analysts, for example, would see our names on the application and feel comfortable committing resources to our project because they knew we were well-prepared."

Not only did this benefit Jody's team, but it made the other groups' jobs easier. "Time is saved on their side when you fill in all of the gaps in advance, provide the teams with all necessary

information to complete their side of the project, and provide clean and accurate information," she explained.

The Trial Participant at the Center of it All

After the preparation, the most important part — recruitment — begins.

"You have already worn your scientist hat, learning about the drug and knowing the protocol backward and forward so you can answer any question participants might have," Jody said.

Then, a different hat becomes primary. "Recruiting starts with empathy," she said. "You really have to put yourself in the shoes of the person, whether they are at-risk, pre-manifest, prodromal, or manifest. They are the ones who are courageously willing to try a drug that is not approved by the FDA. They may be nervous or scared. You have to understand that they are participating not only for themselves but to benefit the next generation." Jody says that successful clinical research coordinators learn to present the study in a positive, truthful light and provide as thorough an explanation as the patient can understand.

Coordinating Coordinators Worldwide

Today Jody is the Director of Clinical Operations for the Huntington Study Group, and has shared her experience and wisdom with over 200 HSG site coordinators, traveling to work with new coordinators and help establish what Ira Shoulson, M.D., coined "tiger teams." Tiger teams are well-prepared clinical research sites that are ready to take on a clinical trial at a moment's notice. When sponsors ask the HSG to conduct a clinial trial, Jody has confidence that the tiger teams are ready to roll.

Jody's commitment to research and her passion for the HD community are stronger than ever. Her goals for the future include continuing to mentor new and rising coordinators so they can realize the importance of their contribution and the gratification of knowing successful clinical trials will eventually lead to new treatments for the HD community.

"I love the fact that I have been a part of helping to support, mentor, and encourage people to become prepared for future endeavors and build career coordinators,"she said. ●

LEARN MORE

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JODY'S TOP 10 RECOMMENDATIONS TO BECOME AN EFFECTIVE AND HAPPY CLINICAL COORDINATOR

- *Immerse in HD science, regulations and research*
- *Become an expert in each study before it starts*
- *Develop good relationships with everyone you work with*
- *Find a great mentor*
- *Learn to wear all your hats well*
- *Relish your point guard role*
- *Love and respect each participant*
- *End each research visit by saying thank you*
- *Know what you do is important*
- *Know that finding a treatment for HD is possible because of your dedication*

"I love the fact that I have been a part of helping to support, mentor, and encourage people to become prepared for future endeavors and build career coordinators." **JODY GOLDSTEIN**

An Odyssey Shared is Not Lonely

An Interview with Seth Rotberg

Seth Rotberg is a disciplined exerciser and "social" athlete, an avid sports fan, and a businessman in the healthcare nonprofit space. He is also the co-founder and Board President of Our Odyssey, an organization dedicated to connecting young adults in the rare and chronic disease communities.

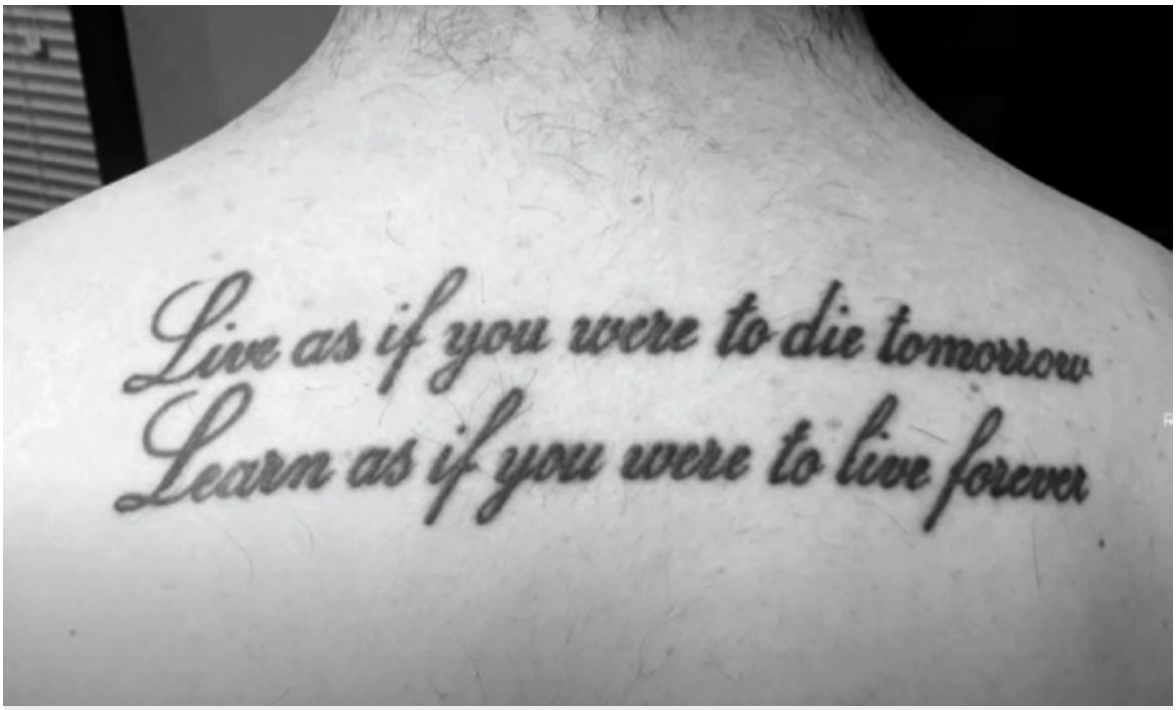
As a young man of 30 who tested positive for HD ten years ago, Seth's mission is to ensure that his peers in the rare disease community develop strong social and emotional supports through in-person and virtual meet-ups, as well as friendships "off-line."

On National Rare Disease Day, which, he points out, is the last day of the "rarest" month — February — Seth talked with HD Insights. He shared his journey from watching his mother begin to deteriorate from HD when he was 15, to learning about his own status at 20, and then deciding how that news would influence his outlook and path in life.

This decision began to gel on the day he summoned the courage to tell his dad and sister his test results. Instead of panicking or grieving, his dad said, "Okay," and proceeded to talk about the research and all the valid reasons for hope. His sister reacted in a similar way, with the net effect of defusing the sense of impending doom Seth was feeling. Since then, Seth has grown to be a rock for hundreds of others with uncertain futures, though he is the first to say, he relies on a support network as well…and a tattoo that reminds him we have choices, every day.

> "Seth has grown to be a rock for hundreds of others with uncertain futures, though he is the first to say, he relies on a support network as well…and a tattoo that reminds him we have choices, every day.

SETH ROTBERG



▶ SETH'S TATTOO
Seth became determined to live by his friend Jake's motto following his death.

▶ Seth, let's dive right into the story behind the tattoo. What was your life like before your mother got sick and how did you get from there to where you developed these words to live by?

I was a kid who grew up loving sports, because who doesn't if you're from the Boston area?!

I played soccer and I played basketball, which was and remains my favorite game to watch. At 15, my pretty normal life changed when my mom was diagnosed with HD. I went to off to college at 18, and midway through, came to grips with the fact that I had to know my own HD status. My life changed again when I decided to get tested at the age of 20 and the results came back positive. I knew from that point on, I would have to live wondering if and when I am going to show symptoms, am I going to have enough time to do the things you are supposed to do in life — have a house, get married, have children, become financially sustainable?

Around that time, I lost two friends my age — Jake, to a housefire the day before my last semester in college, and Meghan, to the juvenile version of HD. Along with the shock and loss I felt, I also became determined to live by my friend Jake's motto: "Live as if you were to die tomorrow, learn as if you were to live forever."

After I graduated from college, it became clear to me that living this motto meant a number of things, but first and foremost, it meant doing meaningful work that can help others facing challenges. Also, my dad really inspired me by taking good care of my mom until she passed six years ago. And he's been great, always staying positive about where things are going with the research.

▶ FAMILY STRUGGLES
Seth poses with his mother Debbie, center, and sister Julie. Debbie died in 2015 after a 17-year battle with Huntington's disease.

How did that translate into a career track for you?

It started during college, really, with fundraisers like my own 3-on-3 basketball charity event, Hoops for HD. After college, I joined Americorps City Year, working with freshmen and sophomore high school students on math and English, trying to help them stay on track to graduate. Shortly after that, I worked for a nonprofit that focused on student athletes. I had majored in sports management because I was excited about the concept of how we can use sports to teach life lessons, how we use that platform to encourage people to learn about different aspects of life. So that opportunity was right up my alley.

Later, doing meaningful work also came to mean sharing my story, and helping support others who are facing adversity. I knew I wanted to focus on young adults. What I found is that there was no national organization that helped connect them. That ultimately led me to start Our Odyssey.

Would you tell me more about the backdrop to Our Odyssey?

Well, Our Odyssey was launched in 2019, so it is still in its infancy. By that time, I had spent a few years in the non-profit world and had gotten a master's in non-profit management from DePaul. At that point, my career focus had really shifted to the healthcare world. It started with my work at a digital health company that had these online communities that connected people to one another. So I became familiar with that realm, and it allowed me to dive deeper into the rare disease community, and ultimately, to start Our Odyssey.

It started informally, though. I was working for the digital health company, Inspire, at that time, and I was trying to figure out a way to support young people who are impacted by any rare or chronic condition. I was very involved with HDYO supporting young people impacted by HD, which was awesome. But then I thought, I wonder if other kinds of communities have something like this, and I found out they didn't. So I did a little homework and asked young adults between the ages of 18 to 35 if they would be interested in connecting with people outside of their specific disease, and the response was overwhelmingly, "YES!" I remember it was Rare Disease week in 2019, and one young adult said, "It's a great idea — who's going to do it? Are you going to do it?" So I said sure, I'm going to do it.

So that's kind of how it started, to provide this social and emotional support to young adults, connect them with one another, and really empower them to not feel that sense of isolation that many of us feel, especially as a young adult who's trying to fit in with your peers and fit in with society. There is this feeling like I can let my guard down and just be myself again, because these people get what I'm going through, they understand the harder challenges of college or career or family planning or dating.

What is the structure for Our Odyssey and how has COVID-19 impacted the group?

Prior to COVID, we were hosting in-person meet-ups in different cities such as D.C., Philadelphia and Boston. We were already planning on doing virtual meet-ups prior to COVID-19, since we knew we could increase our accessibility to young adults. Due to the pandemic, we had to shift to fully virtual, and ended up supporting over 460 participants in about 35 states and some other countries as well. These are young adults with 130 different rare conditions.

CLINICAL TRIAL
Seth participated in the PREDICT-HD 3.0 observational study, which involved a full day of cognitive and motor tests, getting blood drawn, two different MRI scans, and a spinal tap (also known as a lumbar puncture).

A fellow young adult, Anna Laruent, who lives with another rare disease, is my colleague in Our Odyssey. We make sure one of us is at each of these zoom events. We've hosted 36 virtual meetups and seven topic-specific meetups running since the COVID lockdowns began.

I think the cool thing is that you can connect with others and just learn from one another, and build up those relationships. If it's a very rare disease, the closest person to you could be on the other side of the country or even the other side of the world. All this gives people the opportunity to actually connect with other young adults who maybe won't understand some of the specific details of your health condition, but at least understand the general challenges that we all face when living with a rare disease.

Who sponsors Our Odyssey?

Our main sponsors right now are in the pharmaceutical biotech space. They're the ones who have really helped us along the way. We hope to have other potential sponsors, perhaps medical centers, hospitals, foundations, and individual donors. It's one step at a time, though. We are still a young organization and want to manage our current set of stakeholders well before we go to the next level.

What is your current job and does it relate to your mission to help young adults living with health challenges?

I'm currently a Patient Leader Recruitment Manager with WEGO Health. This job grew out of a patient advocacy consulting business I started last August. I wanted to help bring the patient voice into medical research early and

▶ OUR ODYSSEY—A GROUP SOCIAL

throughout the drug development cycle. I saw a need for the pharmaceutical companies to build the relationships with participants earlier on and recruit thoughtfully, explaining expectations more thoroughly, and wherever possible, building in some flexibility for the participants' schedules and lifestyle. I also promoted giving feedback to the participant, something that is often sparce or totally absent!

Having my own consulting company had plusses, but I missed being part of a team. Fortunately, my work in advocacy led me to WEGO Health, which actually connects healthcare companies to patient advocacy leaders for insights, and provides opportunities to get that patient voice heard and established within these companies. With WEGO, my role is to identify these different advocates who can help us with projects and programs we are working on. So, if we're working on lupus, for example, we find advocates we feel might have a compelling story or might be interested in this opportunity.

We also provide resources and content on our platform to help educate and empower these different advocates to learn more, and to really take that next step in being a patient advocate or patient leader.

One of the things I fight for is compensation for the advocate's time. I'm a big believer that if you're on an advisory board of any type as a patient advocate, you deserve to get compensated. These people are usually passionate about their mission, so they are often willing to do the work for free, but they should be seen as key opinion leaders (KOLs) who are taking time out of their worklife to provide valuable insight to organizations studying a therapy or for clinical trial design feedback. A stipend or honorarium is the right thing to do, especially since patients and caregivers need to be seen beyond their condition.

> "Doing meaningful work also came to mean sharing my story, and helping support others who are facing adversity."
>
> **SETH ROTBERG**

▶ ***So you work on the social support end, but you also advocate for patients and caregivers. Do you also work on changing national policies through lobbying Congress?***

As you say, our space is social supports, but we partner with YARR, which is Young Adult Representatives of RLDA (Rare Diseases Legislative Advocates– an acronym within an acronym) because they have a big focus on policy and advocacy space. We work together to answer

questions about how to empower young adults in these different advocacy realms — policy-related or otherwise — and how they can take their advocacy game to the next level. We are currently partnering with them by co-hosting advocacy meet-ups once a month for young adults to connect and learn from one another. This is a stepping stone, and we are excited to continue growing this partnership.

One of the issues I think really needs to be addressed at the policy level is insurance payment for mental health support. Having a support system of family and friends and having something like Our Odyssey is huge, but it's not the whole picture. Most everyone living with a rare disease deals with mental health challenges at various points, if not throughout their lives. But access to therapy is expensive. Under most health plans, coverage is very restrictive in terms of the provider choices, and copays are high. Often, the therapist doesn't accept certain health plans.

We are all acutely aware of the mental health challenges the COVID lockdowns have posed. How have you tried o live your axiom during this time when living fully does not always feel like a daily option?

You're right. It's hard to do when you are isolated. Day to day, during the pandemic, I've not been able to do a lot of what I want to do to enjoy life, whether that's just going out, hanging out with friends, or having a chance to go travel.

Everyone's going to have their bad days and there are more of them when we are isolated. It's a matter of what your resources are to get through it. You know, for me, it may be going out on a walk or journaling, working out, or meditation, and really just trying to just accept what it is happening. It's also a matter of who's going to be your support? This includes getting professional support through therapy. Some people say there is a stigma with that. I say, why not try it if you can? Again, insurance coverage can be a barrier.

Last year, I was dealing with some bad anxiety, and I decided to just be more open about it, share it with my dad, my sister, my cousin and get their support. I also have some really great friends and a great therapist. Plus I have strong relationships within the HD community — people I can rely on and they can rely on me. So I'm fortunate. I can call on these different resources at different times so I'm not always going to the same person.

How do you plan for or think about your future in terms of dating, marriage and children?

I hope to find a woman who sees me for who I am, and it's a challenge. I can't choose a "best" time to disclose my HD status with a woman I might date, because they can google my name and my story is out there. This makes it hard to establish a relationship based on the two of us as people.

I hope to marry and I'd love to be a dad. While it's a personal choice I wouldn't make for anyone else, I don't want to pass this gene on, so for me it might mean adoption, or IVF with pre-implantation genetic testing, or maybe sperm donation. I joke with my friends that one of them will have to help me out. Better yet, could I get a famous athlete like Tom Brady to help?

With the current pace of research, are you, like your dad, optimistic that there will be a cure or other therapy that changes the whole face of HD in the coming decade?

I am — because I kind of have to be — but I also believe it is justified by the science, the pace of the research. When I was 15, there were probably one or two companies coming out with therapies. Now there are over 20 or 25 companies, with different approaches to symptom management and cures. I hear there are now four patients in the uniQure trial who have been injected. I try to stay up on the research and stay patient. There are a lot of questions that will come up. Hypothetically speaking, do I do the one-and-done gene therapy, do I wait a few years for an oral pill, or do I wait until there's an IV? Lots of decisions ahead.

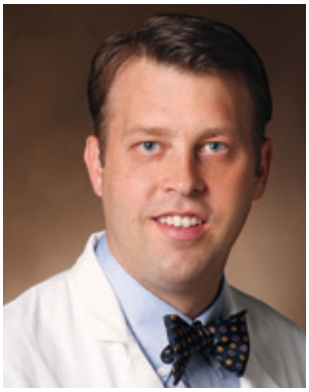
The future looks promising for those of us in the HD community, but I would remind people to try to live one day at a time and in the present. By the way, this doesn't mean you have to do something audacious like bungee jumping — which I highly recommend not doing if you're scared of heights (been there, done that)!

What is the easiest way for people learn more about your story, Seth?

I'd love readers to visit Our Odyssey. If they want more, they can also check out my TEDxNatick talk, which is a quick lowdown on my life, and get more information about my journey by visiting: **www.sethrotberg.com**. ●

VIRTUAL CONNECTIONS
Due to the pandemic, Our Odyssey shifted to fully virtual, supporting over 460 participants in about 35 states and some other countries as well.

Closing thoughts on GENERATION-HD



BY DANIEL CLAASSEN, MD

Daniel Claassen is an Associate Professor of Neurology at Vanderbilt University and Editor of HD Insights.

The disappointing news of 2 halted programs reverberated around the HD community this past month. Tominseren, and WVE-120101/2 were proposed as antisense oligomer (ASO) treatments for HD patients. These treatments do not presently appear viable options for therapies, but for different reasons. It's difficult to express the profound hype and the hope that accompanied these trials. ASO treatments appear promising for neurologic disease: Nusinersen was approved for the treatment of spinal muscular atrophy, and the videos of children who can now walk are miraculous. I was at a European HD program, and when watching these videos, I remember a comment from the audience microphone, … "Can we imagine a world where HD patients will have a treatment like this?" Fast forward to 2021, and the mood is … flat.

GENRERATION-HD was a massive undertaking. Over 800 HD patients were dosed with Tominersen. The global scope of this trial, speed at which it enrolled, and effort to methodically follow the protocol was simply astonishing. Participants were dosed initially every 4 or 8 weeks, then later the schedule was delayed to every 8 or 16 weeks. There was a lot of enthusiasm about this program, despite the sacrifice involved. The criteria ensured a motor manifest population, rather independent in ADLs, and without substantial comorbidities. For the Wave program, dosing was every 4 weeks, with similar clinical criteria for inclusion, but was a dose finding and safety study.

Phase 1 data from Tominersen showed dear reductions in mutant Huntington protein, in a dose dependent level. This non -selective allele approach would also theoretically reduce wild-type Htt expression. (Remember, there are 2 alleles, a mutant expanded CAG-repeat and a wild-type allele). Several early concerns regarding elevation of neurofilament light chain, and increased ventricular size were noted, but the treatment seemed to 'hit the target.' The Wave program was much earlier, and took a different approach, using a single nucleotide polymorphism targeted approach to reduce only the mutant huntington (Htt) protein, leaving the wild-type protein alone. Side by side, the pros and cons of selective or non-selective approach appear to have encouraged a vigorous debate regarding the role of wild-type Htt in neurodevelopment, response to stress, and safety. Several recent reports have emphasized the potential deleterious effects of wild-type Htt reductions, but overall these programs have forced the field to consider what role, if any, wild-type Htt has in humans. This has been a welcome discussion in the field, and one that will continue long after these trials. It appears that Wave has developed a promising method to assess wild-type Htt, and we hope that Roche and others will test this method on their stored samples.

The endpoints of GENERATION-HD deserve consideration. It is clear that regulatory agency across the globe cannot agree what endpoint is considered useful for HD. The FDA only allowed the Total Functional Capacity (TFC) scale, a crude marker of ADLs in persons with HD. In Europe, acceptance of a composite endpoint which includes objective motor (Unified Huntington Disease Rating scale), cognitive, and TFC measurements were accepted as a primary endpoint. Htt is fair to say that coming to a 'global' agreement on endpoints is crucial for rare diseases. However, it's easier to agree on an endpoint like COVID-19 infection, but harder for one like disease progression in a neurodegenerative disorder. It does not help patients to have bickering between countries on which endpoint to pursue. Hopefully, we will see regulatory bodies work in tandem, and not in opposition, for drug development. It's a tall order, but would make for better science and an assessment of treatments.

On the topic of endpoints, there is a movement in neurodegeneration to find better, reliable endpoints, that are quantifiable, and not subject to noise.

The promotion of quantitative digital biomarkers appears to be a way forward. GENERATION-HD employed a secondary outcome measure assessing digital outcomes. As a global community, we would anticipate data from this study to be publicly available for use in developing better biomarkers of disease progression in HD. There is always a tension with private company's collecting data, but allowing for algorithm development., hypothesis testing, and analytic approaches to this vast data set will only help the field.

Where do we go from here?

Given the potential issues with outcomes, treatment side effects, and patient inclusion, it is not fair to say we should abandon mutant Htt protein reductions. There is no reason, at present, to believe that the pathophysiologic progression of HD is not driven by mutant Htt protein expression. Undoubtedly, a deep dive into the data from GENERATION-HD will allow us to look at patient subtypes, clinical safety, variation in treatment responses, longitudinal clinical progression., and sub-analysis on imaging, digital, and other secondary biomarkers. These will be important and help us move forward. For Wave, it appears that there are continued advances in the SNP targeted therapy, with promise of an improved allele-specific ASO in development. This approach is touted to provide improved drug distribution and efficacy.

It is worth reminding the community of current and future studies in HD. Uniqure is testing the hypothesis that AAV-mediated gene therapy can reduce mutant Htt, and is currently in the midst of a Phase 1 sham controlled study. Several other companies, Voyager and Spark, are pursuing similar approaches. These are invasive treatments, requiring surgical delivery of the AAV virus to the striatum. There are a number of potential impediments to scalability of this method, but the potential benefit of 'direct-to-striatum' delivery appears promising.

Aside from these studies, there are others that are of interest. One of the more compelling ideas is the concept of somatic instability in HD (increasing CAG repeat number over time). This is now an important treatment target, and companies like Triplet Therapeutics are pursuing therapies that may stabilize this instability. Oral medications offer an important convenience for patients. Here, novel approaches including RNA splicing (PTC Therapeutics), and repurposing of Branaplam {Novartis), are in early stages of development. These offer additional opportunities to assess how reductions in mutant Htt will potentially alter the disease course in HD.

“At the end of the day, clinicians, and patients, are sailing together. The grief, frustration, disappointment, and dread of a failed trial has left many of us searching for what gives us hope.

At the end of the day, clinicians, and patients, are sailing together. The grief, frustration, disappointment, and dread of a failed trial has left many of us searching for what gives us hope. Many of my patients have reminded me that our hope is not in the immediate promise of treatments, but in things like family, faith, nature, and in the support of the HD community. I always find that my HD patients remind me of what is important, and they exemplify resilience in the face of adversity. We will continue to serve this population with steadfast resolve.

CLINICAL TRIALS

UPDATES AND ADDITIONS

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

	SPONSOR	IDENTIFIER	AGENT	PHASE	DESIGN	SITES
ACTIVE	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 disease	55 Total: United States and Canada
	uniQure Biopharma	CT-AMT-130-01	AMT-130	I / II	A Phase I/II, Randomized, Double-blind, Sham Control Study to Explore Safety, Tolerability, and Efficacy Signals of Multiple Ascending Doses of Striatally-administered rAAV5-miHTT Total Huntingtin Gene (HTT) Lowering Therapy (AMT-130) in Early Manifest Huntington Disease	United States
	Georgetown University	Tasigna HD	Nilotinib	I	An Open Label, Phase Ib, Proof of Concept Study to Evaluate the Impact of Low Doses of Nilotinib Treatment on Safety, Tolerability and Biomarkers in Participants with HD	United States
	University of Texas Health Science Center, Houston	NCT03854019	Dextromethorphan/ Quinidine	I	An Interventional Study to Assess Efficacy and Safety of Dextromethorphan/Quinidine 20mg/10mg (DM/Q 20mg/10mg) in Patients with Irritability Due to Huntington Disease	United States
	Prilienia Therapeutics	PROOF-HD	Pridopidine	III	A Phase 3, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Pridopidine in Patients with Early Stage of Huntington Disease	60 Total: United States, 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 disease	Brazil
	Ultragenyx Pharmaceutical	TRIHEP3	Triheptanoin oil	II	A Comparative Phase 2 Study Assessing the Efficacy of Triheptanoin, an Anaplerotic Therapy in Huntington Disease	2 Total: France and Netherlands
RECENTLY COMPLETED	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 disease	20 Total: Canada, Europe, and Australia
	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 disease	21 Total: Canada, Europe, and Australia
	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 Disease	United States
	Roche/ Genentech	GENERATION HD1	Tominersen	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 disease	97 Total: Worldwide
	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 Disease (HD) to Assess the Safety, Tolerability, Pharmacokinetics and Efficacy of VX15/2503	32 Total: United States and Canada

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

HD THERAPEUTIC

pipeline

TREATMENT TYPE

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

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

Preclinical

- VY-HTT01 (Voyager Therapeutics)
- TAK-686 (Takeda and Sangamo Therapeutics)

Phase 1

- MP101 (Mitochon)
- AMT-130 (uniQure)
- SAGE-718 (Sage Therapeutics)
- PTC small molecule (PTC Therapeutics)

Phase 2

- SRX246 (Azevan Pharmaceuticals)
- Pepinemab – VX15/2503 (Vaccinex)

Phase 3

- Pridopidine (Prilenia)
- Valbenazine/NBI-98854 (Neurocrine Biosciences)

To Patients

- Deutetrabenazine (Teva)
- Tetrabenazine (Lundbeck)

Bringing home the gold —6X

Our own Christina Ullman, the graphic designer and illustrator behind the beautiful, thematic images you see in HD Insights, has just proven she can defend her 2020 world championship title in women's powerlifting. She competed in the World Powerlifting Alliance (WPA) World Championship meet in Pabianice, Poland, on April 14. She won six gold medals, setting five world records, two American records, and eight Ohio records at the competition.

Ullman won gold medals in the overall meet in the bench press only, deadlift only, and push-pull competitions. She also took first place in those categories within her age group.

Ullman began powerlifting less than two years ago. In that time, she has set 12 world records in WPA, as well as nine American records and 13 Ohio records in the American Powerlifting Association federation.

A sport where strength, technique and discipline rule, powerlifting has brought a new perspective to her life. "Amazing things can happen with patience and perseverance," says Ullman. "The first step is to trust your abilities and take that leap of faith to try something new. You never know what you can achieve."

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