Taking aim at HD

Antisense oligonucleotides hold promise for treating Huntington disease.

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In honor of the Huntington Study Group’s (HSG’s) founder, Ira Shoulson, the HSG established in 2015 the Shoulson Scholar Fund. The fund recognizes outstanding junior investigators for promising research in Huntington disease. The award supports recipients’ travel to the HSG meeting. See page 8.

FIND OUT MORE ONLINE
HUNTINGTONSTUDYGROUP.ORG/ABOUT/OUR-ANNUAL-MEETING
Collective excitement

Recently, I was scheduled to dose a patient for an intrathecal antisense oligonucleotide (ASO) study. As usual, I was running from one end of campus to another (fashionably late as my team would put it), but when I came to the clinical research center, I noticed a crowd of about 20 people standing in the lobby. Aside from a momentary frustration that their presence slowed me down, I nonchalantly thought the Clinical Research Center was full of participants, thus explaining the crowd. To my surprise, after talking to my patient, I discovered that this crowd had accompanied her to this visit. They were aunts, uncles, cousins, and friends from her home town. They took off work, skipped school, and left their daily routines to support her participation in this experimental procedure.

To me, nothing captures the excitement and potential of these new ASO disease-modifying trials like this experience. These trials have been a long time coming, and as a community, can you sense the collective excitement?

In this edition of *HD Insights*, we highlight stories, perspectives, and considerations to clinical trial design of ASO studies that define this new era of HD care. I want to introduce a new clinical coordinator section, authored by Danielle Buchanan, a fantastic coordinator who works with me at Vanderbilt. Danielle talks about her experiences as a coordinator managing patient expectations in disease-modifying studies. Also, I hope you enjoy the wonderful story of a psychology student (Jessica Klein) meeting her first HD support group, and the insightful article about the “Right to Try” legislation by Alma Farooque. I find the article by Mark Guttman about his experiences with intrathecal drug delivery to be a testament to how, as clinicians, we need to adapt and learn new techniques, like ultrasound-guided lumbar punctures. Our feature story is on the subject of ASO trials, and I learned much from the insights provided by Karl Kieburtz and Amber Southwell.

Please also let me introduce you to Kevin Gregory, the new Director of Education, Communications, and Outreach at the Huntington Study Group. In this issue, Kevin reviews the recent HSG meeting. He helps in the outreach efforts of the HSG, including working with *HD Insights*. Finally, this will be the last periodical with our deputy editor Sara LaJeunesse. Sara is such a delight to work with, and we will miss her presence at the HSG and EHDN meetings, and I will miss her insightful guidance for *HD Insights*. We wish her well as she begins her new role at Penn State.

Keep your suggestions coming! I look forward to more of your comments and articles for *HD Insights*.

**DANIEL CLAASSEN, MD**
Associate Professor of Neurology
Vanderbilt University
CME4HD: Bridging the HD Knowledge Gap

BY KEVIN GREGORY

With its classification as a rare disease, there is a strong possibility that most healthcare providers have never treated patients affected by Huntington disease (HD). About 30,000 people in the United States have HD and another 200,000 are at risk of developing the condition. This means that in total, only 0.07% of the entire population of the U.S. has or is at risk for developing the symptoms of HD.

So, it is not uncommon for a general practitioner or family medicine practice to have little or no experience with HD beyond what was briefly covered in school or residency. In the same way, caregivers can be at just as much of a disadvantage. While the math itself reduces the likelihood of treating or caring for a patient with HD, other factors – such as geography, population density, stigma, and the resemblance with other symptoms such as Parkinson’s, Alzheimer’s, or ALS – make HD challenging to identify and deal with.

A NEW EDUCATION PROGRAM

Enter the Huntington Study Group (HSG) and the CME4HD educational program. Several years ago, the HSG recognized the gap between educational foundation and practical experience in HD. An effort was launched to develop a professional education curriculum through which providers could attend and learn from experts in the field. Mary Edmondson, chair of the HSG Provider Education Committee, credits Lavonne Goodman with the foresight to create CME4HD to help educate community-based colleagues.

“People with HD need a variety of care providers across their life span,” explains Edmondson. “They need more than just a HD doctor; they need a team of different providers, including primary and acute care specialists. Ancillary providers like nurses, social workers, physical therapists, speech therapists, and behavioral health therapists make a big difference in the lives of patients and family members. It’s hard to find knowledgeable care providers for patients outside specialty HD centers at tertiary care centers.”

In 2012, the first in-person CME4HD training session was delivered at the Huntington Study Group’s annual meeting held that year in Seattle, Washington. By attending the day-long accredited session on the Saturday following the general meeting agenda, providers could earn continuing education credits while gaining a deeper understanding of the course and symptoms of Huntington disease.

Edmondson says that it is also important for care providers to be aware that there is much that can be done to ease the burden on HD patients. “The core message that CME4HD offers is that Huntington disease is a highly treatable disease. Although we search for treatments to modify the course of the disease, the goal at HSG is to seek meaningful treatments, including treatment of current symptoms.”

The CME4HD program continued with that approach for the next four years, with HSG faculty members teaching attendees and any interested local providers in the city where the meeting was held. However, to further expand the reach of CME4HD, the curriculum was adapted for presentation in an online, self-paced format beginning in February 2018. By hosting the content online, learners can now take the same training anywhere, at any time. The types of credits learners can earn is also expanded, and currently includes CME, CNE, and IPCE credits for 2019.
POSITIVE RESULTS

Early returns on the 2019 update to CME4HD have been very positive. In one month following announcement of the launch date, 87 new users had signed up for accounts – a 15% increase in total registered learners. In 2018, CME4HD learners completed a total of 1,070 courses. After the first month, the Huntington Study Group has had learners earn credits on nearly 150 courses, already matching 13% on the prior year’s total.

Jamie Hatcher-Martin, assistant professor of neurology at Emory University School of Medicine and fellow CME4HD faculty presenter added, “I appreciated discussing actionable topics that can help in every day care. I think my topic may have included subjects that many providers do not know as much about [end of life concerns, options for managing patients with advanced disease]. I really enjoyed interacting with the other faculty.”

One of the best things about CME4HD Online is that it is completely free. And while the content is specifically geared as training for healthcare providers, there are definitely benefits that caregivers and family members can gain from the material.

As Furr-Stimming mentions, “This is an easy, readily accessible mechanism to hear from care providers that are familiar with HD about the challenges that HD families face throughout the lifecycle of HD. The program is excellent because it addresses clinically relevant challenges that care providers frequently face when caring for individuals with HD.”

CME4HD CURRICULUM

An independent educational grant was provided by Teva Pharmaceuticals in 2018 to help develop and deliver the most recent version of the CME4HD curriculum.

If you are interested in taking the online courses, information and links to register can be found on the Huntington Study Group’s website at HTTPS://HUNTINGTONSTUDYGROUP.ORG/CME4HD-ONLINE

TRANSITIONING ONLINE

In order to make CME4HD work in an online delivery setting, the HSG faculty presenters are recorded on camera presenting their course content in its entirety. But instead of a large classroom audience, they are speaking directly to the learner through the lens of the camera. In the initial 2018 CME4HD Online launch, a total of five courses were offered for credit. In the 2019 update, which launched on February 1st of this year, three additional courses were added, but the duration of each course was shortened to a TED Talks style of 20-30 minutes in length.

“This program disseminates important educational, practical information about a rare disease that can be intimidating to treat for those unfamiliar with the disease,” says Erin Furr-Stimming, a CME4HD faculty presenter and HSG investigator at the University of Texas Health Science Center at Houston. “The content hopefully adds value to the clinician’s knowledge base and reframes some older concepts, for example, considering functional independence and the importance of a multidimensional diagnosis.”

This year, CME4HD learners also were treated to the incorporation of real-world examples and references from the documentary The Inheritance, which chronicles the story of Bridget Lyon and her family’s history with HD. As an added bonus, anyone that registers for CME4HD Online has access to watch the full-length documentary at their leisure.

“Reducing the burden of symptoms and improving quality of life makes a difference not only for HD gene expansion carriers but the entire family living with HD, including caregivers, at-risk children, and family members,” says Edmondson, who is extremely grateful for Bridget’s desire to share her family’s experiences with the HD community. “An often-overlooked fact about HD is that the mental health aspects of the disease are often the hardest aspect of the disease. Our secondary goal with CME4HD is to share practical interventions that non-mental health practitioners can implement with their patients.”
At the end of it, there was no doubt about the fact that this support group had more than fulfilled its mission—to make all of its participants feel connected and inspired, supported and hopeful, comforted and nurtured.”

JESSICA KLEIN
My first support group

BY JESSICA KLEIN

As a psychology intern, meeting Huntington disease (HD) patients and caregivers and witnessing their interactions with clinicians and social workers has been enriching in many ways. Some of the most eye-opening experiences I’ve had include witnessing patients’ sometimes-unpredictable behavior, perceiving their frustration with the inability to communicate, and acknowledging their sources of anger. I have also enjoyed being part of a team that seeks to bring contentment through therapeutic interventions, including non-pharmacologic (organizational and logistical adjustments at home) and pharmacologic interventions.

I had never before attended a HD support group—a group in which participants can share whatever they feel the need to share. My observation until this point was that the subject matter of HD is often held within the family boundaries. Whether it is because of fear, embarrassment, modesty, isolation, or its multi-faceted effects, being able to break through these barriers and confide in individuals whose experiences are similar brings candor, openness, and relief, especially when the group is led by a trustworthy and experienced person who knows when and how to intervene, ask the right questions, rephrase, and redirect when appropriate.

Jessica Klein is a graduate student in the Department of Psychology at Paris Diderot University.

One cold and rainy Saturday, I ventured out to attend one of these groups. One might have anticipated that the attendance would be rather limited: not so! Some people drove for hours to be there, while others lived only thirty minutes away; some were completely new to the disease while others had lived with it for decades; some were affected mostly by the physical aspects of HD while others suffered most from its mental and psychological effects; some were represented by three generations while others showed up unaccompanied. Whatever their place and their state in the HD journey, it was obvious that none of the fifteen people present would have imagined being anywhere else at this precise moment.

In this open group that meets every third Saturday of the month, anyone is free to come, so the attendees don’t know in advance who will be there, whether they will be young or old, at the onset of the disease or well into it already. So why does it ‘work’? Why does it feel so natural for everyone—even the seemingly most introverted participants—to speak up, talk about their concerns, and reveal pieces of their lives, including ones so intimate that they may have never disclosed them to anyone before?

The first reason is that they don’t need to explain HD because everyone around the table is already aware of it. Second, they all come with the same two-folded goal in mind: to support others and to get support for themselves. This dual objective creates in each and every person a common readiness to be just as he or she is, in his or her raw vulnerability, as truthful as it gets.

The issues raised vary widely: A lady who had just learned that her son-in-law has HD wondered what changes would be coming as her son-in-law and his daughter would most likely move into her house when his condition deteriorated. A man who had recently discovered that his father-in-law had HD wanted to be as knowledgeable as possible about the disease in order for he and his wife to take the best possible care of him. In the meantime, his wife needed to accept what it meant to have a father with HD who exhibited sudden outbursts of irritability when he had previously been then the gentlest man on Earth. As for their 14-year-old daughter, who wrote an essay about her grandfather’s disease at school and received an award, she was just starting to figure out how to live with the idea of her grandfather being such a different version of his former self. Many other stories were shared, including by those more familiar with the disease and whose experiences helped the newest members of the group understand how one can learn to live with HD over the years and what ‘strategies’ prove effective in the long run.

After two hours of uninterrupted dialogue, I was under the impression that everyone in the room had been given the freedom to say—or keep quiet about—whatever was on their mind, and had been given the privilege to listen and to be listened to in an empathetic, nurturing, non-judgmental way. At the end of it, there was no doubt about the fact that this support group had more than fulfilled its mission—to make all of its participants feel connected and inspired, supported and hopeful, comforted and nurtured.

Above all, the group empowered participants to muster the energy to carry on, despite the difficulties and the obstacles lying ahead on their challenging journeys.
Meet the scholars

Shoulson Scholar Fund recognizes outstanding investigators for promising HD research

NANCY DOWNING

► How did your receipt of a Shoulson Scholar Award help you in your career?
Receipt of a Shoulson Scholar Award was a great honor because it recognized the contributions I had made to HD research. It is important as a researcher to demonstrate impact of your research beyond your academic institution. Although I did not continue with HD research, I believe I helped bring attention to research on lifestyle factors and quality of life in HD. This research is being continued by others with whom I collaborated, and I’m confident they will continue to make progress in those areas.

► Please describe the research that you conducted in HD.
I was involved with Exercise-HD, a trial to determine if exercise may slow the progression of brain degeneration and motor impairment caused by HD. Areas of the brain most affected by HD (striatum and white matter) have been shown to be responsive to exercise.

► Please describe the work you are doing now in forensic health care.
My research focuses on improving health outcomes for persons impacted by interpersonal violence. I currently have five funded projects, ranging from a National Institute of Justice-funded study examining use of alternate light sources to visualize bruises in different skin colors to a study investigating how emergency contraception impacts fear and extinction learning associated with development of PTSD. Working on two large NIH-funded HD studies (PREDICT-HD and HD-QLife), I learned many research skills that prepared me for my current work.

The HD research in which I was involved was interdisciplinary, and included large multi-site research teams. This type of research collaboration is essential to success these days. Collaboration with psychologists, psychiatrists, biostatisticians, and nurse researchers in HD has translated well into my current practice, which also involves working closely with those disciplines. My involvement in HD studies prepared me to work with large data sets, to be involved in measurement development and validation, and to have interdisciplinary discussions about data analysis and interpretation. These are essential tools that have prepared me well for my current program of research. I’m very grateful to HSG and the HD researchers who contributed to my development as a researcher.

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Nancy Downing, associate professor of forensic health care at Texas A&M University and commissioner of the Texas Forensic Science Commission, was the first recipient of a Shoulson Scholar Award in 2015.
In honor of the Huntington Study Group’s (HSG’s) founder, Ira Shoulson, the HSG established in 2015 the Shoulson Scholar Fund. The fund recognizes outstanding junior investigators for promising research in Huntington disease. The award supports recipients’ travel to the HSG meeting.

NORA FRITZ

How did your receipt of a Shoulson Scholar Award help you in your career?

The Shoulson Scholar Award provided support for presenting my work early in my career. This recognition has contributed to ongoing collaborations within HSG, including working with an international group of rehabilitation researchers to develop guidelines for exercise in HD, and the opportunity to present our ongoing work at HSG 2018.

Please describe your current research.

In addition to many other projects, I am currently leading an international team of rehabilitation researchers in the development of a formal Clinical Guideline for Exercise in Huntington’s Disease. We have received support from the HSG, the European Huntington’s Disease Network, and The Griffin Foundation for this effort. To date, we have completed a systematic review of the literature, drafted the clinical guidelines, met with stakeholders for review and revisions, and put the guidelines forward for public comment. Presently, the guidelines are being reviewed by the American Academy of Neurology and the Academy of Neurologic Physical Therapy for possible endorsement. We anticipate submission of these Clinical Guidelines for Exercise in Huntington’s Disease in the coming months. These guidelines will provide evidence-based recommendations for healthcare providers and persons with HD.

FILIPPE RODRIGUES

How did your receipt of a Shoulson Scholar Award help you in your career?

Since the presentation of these two posters at the HSG 2017 meeting in Denver, Colorado, we have been working hard to produce relevant information to help optimize clinical trials in Huntington’s disease. The work on cerebrospinal fluid dynamics has been published in the European Journal of Neuroscience, and the Enroll-HD analysis on Parkinsonism & Related Disorders.

Last year, we had the opportunity to present our work on biofluid biomarkers from a London-based cohort of 80 participants at the HSG 2018 meeting in Houston, Texas, where we showed that mutant cerebrospinal huntingtin, and blood and cerebrospinal neurofilament light can be a helpful tool to empower clinical trials. At the moment we are working on longitudinal analyses from the same cohort, which we hope to present at HSG 2019.


Nora Fritz, assistant professor of physical therapy at Wayne State University, received a Shoulson Scholar Award in 2016.

Filipe Rodrigues, clinical research fellow at UCL Huntington’s Disease Centre, received a Shoulson Scholar Award in 2017.
New clinical trials
a welcome arrival

BY DANIELLE BUCHANAN

ew clinical trials, especially ASO therapies, are a welcome arrival to the Huntington Disease (HD) community. As a clinical research coordinator, one of my responsibilities is to answer patient and family inquiries about clinical trial participation. I have noticed major misconceptions regarding these upcoming trials. Many consider participation in a trial as a long-term treatment, but of course we truly don’t know the final story, as it can be a long time before a compound has clinical relevance.

As of now, most of the inquiries to our center concern GENERATION-HD (Genentech-Roche) or PRECISION-HD (Wave Life Sciences). The former includes a two-year commitment with a monthly intrathecal injection; the latter is a Phase I study. Participation in either of these trials could exclude you from another ASO clinical trial. Despite these restrictions, I have encountered a frenetic urgency for participation. Most patients equate participation in these studies as an opportunity “to be cured.” I have even encountered some patients wanting to drop out of a study, to get into another.

Months before GENERATIONS-HD was announced, I received calls from patients inquiring about this study, asking to “save their spot.” How, as a community, can we help our patients and families navigate this stressful time of feeling like they may be left out? How do we, as HD coordinators, manage expectations? These are difficult interactions, and I believe we need to discuss as an HD community how to navigate these challenging situations.

When I receive calls from patients, I make sure that each patient has established care in an HD clinic. I still receive calls about studies that have closed enrollment. If coming from another HD center, our policy is to make sure we know the patients clinically before we engage them regarding a research study. We want to meet the patients, understand their HD story, ensure they are getting the proper care, and establish a therapeutic relationship. We set out, at the beginning, to remind our patients. “How do we, as HD coordinators, manage expectations? These are difficult interactions, and I believe we need to discuss as an HD community how to navigate these challenging situations.

When I receive calls from patients, I make sure that each patient has established care in an HD clinic. I still receive calls about studies that have closed enrollment. If coming from another HD center, our policy is to make sure we know the patients clinically before we engage them regarding a research study. We want to meet the patients, understand their HD story, ensure they are getting the proper care, and establish a therapeutic relationship. We set out, at the beginning, to remind patients that we have a limited number of slots for clinical trials, and make extra efforts to explain that clinical trials are not treatments. I think, as a coordinator, you must stress that there is never a guarantee for participation in a clinical trial, but the most important action is making sure the patient is getting good clinical care.

Several months ago, I met a man with HD during an ENROLL-HD appointment. This appointment was made soon after he received the news that he was gene positive. The patient and his wife were devastated, but amazingly had never heard of clinical trials before. I told them about SIGNAL and how it was testing the hypothesis that infusions of this therapy may slow the progression of HD. They were thrilled and ecstatic to think they could possibly be a candidate. When I called to confirm his screening appointment, they had read more about clinical trials in HD, and decided to wait to consider participation in a potential upcoming ASO trial. The man may or may not be a candidate for a future trial, but the potential for receiving a gene-silencing treatment grabbed his attention.

Despite the small amount of promising data in humans, it was enough for him to choose to wait to see if he could participate in an ASO study. His story echoes other stories of participants who believe participation in a certain trial will deliver a better outcome for their HD.

I believe we are still early on the therapeutic timeline of HD. We can’t predict the future of gene-silencing studies, as there is no sure thing in clinical research. This is the beginning of an era and a new strategy for clinical trials in HD, but remembering the difference between a trial and a therapy is an important reminder as we speak to our patients. We need to counsel our patients not to jump to conclusions about the potential outcomes of these studies before they are completed. I also think we need to make sure patients understand every aspect of what they are signing up for in the consent. Retention is really important for giving us the best chance to accurately interpret clinical trial data. While a patient may be eager to jump on board a study, it may be challenging for them to commit to two years, and participation in a trial should not be threatened if another trial seems more interesting.

Managing the expectations of our patients is one of the main battles I experience as a coordinator. Until we understand what these treatments can actually do for patients, we must encourage participation to help figure out future treatments—and this is just the beginning. Better treatments are the light at the end of the tunnel. HD is finally getting the societal attention it needs, which means more of an opportunity for coordinators, and the HD team, to take the lead in these discussions.

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DANIELLE BUCHANAN

Danielle Buchanan is a clinical research coordinator at Vanderbilt University Medical Center.
2018
The year that Roche licensed RG6042, an ASO-based drug, from Ionis

The number of years
the U.S. FDA has overseen the responsible commercialization of new drugs and therapies

200,000
The number of people at risk of developing Huntington disease in the United States

SRX246
The new drug developed by Azevan Pharmaceuticals shown to help to alleviate symptoms of irritability in HD patients

120 MILLIGRAMS
The amount of RG6042 that participants in the Roche ASO trial will receive either every 2 or 4 months

1,800
The number of individuals or groups who apply to the FDA each year for “expanded access” to experimental therapies outside of clinical trials

1,070
THE NUMBER OF COURSES TAKEN IN 2018 by participants in CME4HD, an in-person continuing medical education program designed to teach healthcare providers how to care for and manage individuals with HD, hosted by the Huntington Study Group
1 Imaging in a Mouse Model

An ex vivo imaging study was performed on fixed brains from the R6/2 Huntington disease (HD) mouse model. White matter integrity was analyzed by using diffusion imaging (DTI) and 17.6T high-field MRI, followed by fluorescent and electron microscopy to visualize associated cellular changes. The model used in this study was called continuous random walk and complements the standard DTI model. The group identified axonal degeneration in the corpus callosum (CC) and increased axonal density in both the MRI and microscopy imaging, consistent with the volume reduction of the CC in HD patient MRIs. The conclusions from this paper include early axonal degeneration as a biomarker for HD and the use of anomalous diffusion models in future clinical trials.

The valuable resource of MRI images from TRACK-HD continues to be utilized in studies globally. Bock’s group from Canada used this resource to investigate cortical microstructure in biomarker for HD and the use of anomalous diffusion models in future clinical trials. The model used in this study was called continuous random walk and complements the standard DTI model. The group identified axonal degeneration in the corpus callosum (CC) and increased axonal density in both the MRI and microscopy imaging, consistent with the volume reduction of the CC in HD patient MRIs. The conclusions from this paper include early axonal degeneration as a biomarker for HD and the use of anomalous diffusion models in future clinical trials.

The valuable resource of MRI images from TRACK-HD continues to be utilized in studies globally. Bock’s group from Canada used this resource to investigate cortical microstructure in patients at different stage of disease. Even though these images were not optimized for this type of analysis the researchers were still able to use $T_1^WWT$ ratio images to map the changes in cortical composition. They identified an increase in intensity with HD progression before disease onset.

2 Human Pluripotent Stem Cells

Neurons differentiated from human pluripotent stem cells serve as an important model for studying Huntington disease (HD).

Induced pluripotent stem cells (iPSC) from the HD iPSC consortium are available to the research community. The consortium recently published a study in which they differentiated the iPSC lines into neuronal cells and analyzed bioenergetic phenotypes. They found that ATP levels were decreased in cells derived from HD patients in undifferentiated iPSC as well as in cells at different stages of neuronal differentiation. Treating the cells with glycolytic late pathway intermediates led to increased ATP production. The group performed LC-MS and identified a lower expression level of glycolytic enzymes in HD iPSC-derived neural cells. These data indicate that defects in glycolysis may contribute to HD bioenergetics and metabolism phenotypes.

The Kiselev lab uses a subset of the HD iPSC consortium lines in their studies on mitochondrial trafficking in differentiated neurons. Their recent manuscript examined mitochondrial density in neurons. They found a decrease in the density of mitochondria in HD neurons. When the cells were artificially aged by inhibiting the proteasome, the mitochondrial density decreased proportionally in both HD and wild-type neurons, suggesting this impairment occurs before disease onset.

Another useful stem cell model is creating isogenic lines from a single donor. The Pouladi group used gene editing to create isogenic human embryonic stem cell lines with different CAG repeat lengths. The group differentiated the lines into different cell types (neural precursor cells (NPC), neurons, hepatocytes, and muscle myotubes) and performed whole-transcriptome and/or whole-proteome analysis. They found mitochondrial alterations in NPCs recapitulated known HD mitochondrial phenotypes, including reduced ATP production. Mitochondrial defects were additionally noted in the myotubes and hepatocytes, meaning the bioenergetics phenotype is not limited to neuronal cells. Importantly, the group has provided a web portal to provide query-based access to the transcriptional and proteomic data generated in this study.

![MRI IMAGING](https://example.com/mri_image)

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Cell and mouse models are an important tool for studying the normal function of huntingtin (htt) and the selective vulnerability of neurons due to the insult of mutant htt (mHtt).

An elegant study published in *Cell Stem Cell* used human embryonic stem cells (hESC) derived from embryos harboring mHtt, or wild-type sibling controls. The group differentiated the hESCs into glial progenitor cells (GPC), performed RNA-seq, and identified a downregulation in transcription factors (TF) that regulate astroglial and oligodendrogial differentiation and downstream myelin synthesis in the mHtt GPC’s. These GPC’s were transplanted into mice that were both myelin-deficient and immunodeficient. The mHtt GPC resulted in slower and incomplete myelination *in vivo*. The mHtt-induced hypomyelination was rescued by overexpression of the TF’s SOX10 and MYRF, demonstrating that the white matter failure in HD is a product of a mHtt-dependent block in differentiation by affected GPCs.

Early Huntington disease (HD) is hallmarked by altered neurotransmission. The Park group examined synaptic vesicle release in real time in primary cortical neurons isolated from the Q175 mouse model. Neurons were loaded with FM1-43, a membrane-impermeable liphophilic styryl dye, and using electric field stimulation mHtt was observed to affect excitatory neurotransmission. Presynaptic terminals were shown to have an increased released probability which can be modulated through controlling voltage gated Ca2+ channels. This modulation may be a therapeutic avenue to explore to rescue the vulnerability of these excitatory neurons and stop subsequent neuronal loss.

There are many studies that support Htt involvement in cell trafficking and interaction with the cytoskeleton which may explain the selective vulnerability of neurons that have unique morphology and special trafficking requirements. To further probe Htt involvement in the cytoskeleton, a study in *PLOS ONE* features an imaging-based study in fibroblasts using growth factor cytoskeletal stimulation as a model. Htt was required for proper cell morphology and adhesion, and when mHtt was present, cell remodeling was inhibited upon stimulation, further supporting the normal function of Htt in these processes.

Once considered to be unsuitable for therapeutics because of their ineffectiveness in reaching their target and lack of tolerability in patients, antisense oligonucleotides (ASOs) have made a big comeback and now hold promise for altering the course of Huntington disease (HD). ASOs are short pieces of chemically modified DNA that bind to RNA transcripts. Those designed to engage the huntingtin gene seek to prevent generation of the toxic mutant huntingtin protein (mHTT) by inducing degradation of the transcript. This is the protein that is thought to be responsible for neurodegenerative progression of people with HD.

There are two RNA-targeted approaches currently in development for HD. Both seek to reduce HTT gene expression, but they contrast in their delivery and dosing.
Why ASOs?

There are two RNA-targeted approaches currently in development for HD. Both seek to reduce HTT gene expression, but they contrast in their delivery and dosing. siRNAs (small interfering RNAs), such as those used in RNA interference (RNAi), are delivered via viral vectors. siRNAs must be delivered directly into the brain, and dosing is targeted to subcortical regions like the thalamus and striatum. This procedure only has to be performed once.

In contrast, ASOs are able to be delivered throughout the nervous system using an intrathecal injection. While this is a chronic, long-term dosing schedule (approximately every 2 months), “you just put these molecules into cerebral spinal fluid and they distribute throughout the CNS where they enter cells and do their magic,” says Amber Southwell, assistant professor at the University of Central Florida. ASOs appear to be better at getting to the cortex than to subcortical areas.

ASOs in Development

In 2018, Roche licensed an ASO-based drug, which is now named RG6042, from Ionis Pharmaceuticals. RG6042 is a non-selective ASO, meaning that it will reduce both mutant huntingtin and wild-type huntingtin. The company has initiated a Phase 3 clinical trial in Europe, Canada, and the United States. Preliminary data demonstrate that the drug successfully reduces the amount of mHTT in the cerebrospinal fluid, suggesting that it may be reduced in the brain—the first time any medicine has done so—and that it may even result in clinical improvements.

In the double-blinded study, participants will undergo intrathecal injections every two months and be randomized to one of three treatment study arms: 120 mg of RG6042 every two months (eight weeks), 120 mg of RG6042 every four months (placebo during alternating procedures), or placebo every two months.

According to Scott Schobel, associate group medical director and clinical science leader for the HD program at Roche, this study design was recently amended following preliminary nine-month data from the open-label extension of the Phase I/IIa study, which showed effects on lowering mutant huntingtin protein levels in the cerebral spinal fluid that support the exploration of less frequent dosing. “Based on the totality of the data, including safety and tolerability, there appears to be no overall advantage to treating monthly versus every two months,” says Schobel. “We believe this will make study participation less demanding for patients, families and healthcare providers.”

Schobel adds that if the clinical development program is successful and RG6042 is ultimately granted regulatory approval, the entire HD community will need to transform itself to be able to effectively and efficiently administer this treatment. “This will require a lot of work, and strong collaboration across patient groups, medical societies, medical institutions, and companies like Roche and Genentech,” he says. “We look forward to partnering with the entire HD community to think about and address these challenges at the appropriate time.”

The issue of whether reductions in wild-type huntingtin will result in clinically relevant safety concerns is somewhat in question, but encouraging results from Phase I work have not shown clear safety issues to date. “There’s a complex interplay between loss of wild-type huntingtin and toxicity from mutant huntingtin,” says Southwell. “I think that getting rid of mutant huntingtin is more important than preserving wild-type huntingtin in terms of being...
beneficial to disease in the short term; however, over the long term, I think reduction in wild-type huntingtin has the potential to reduce the beneficial effect of lowering mutant huntingtin.”

Other approaches attempt to use selective ASOs that only suppress mHTT. Wave Life Sciences, for example, has two selective ASOs under development. Both are currently in Phase I, with results expected by the end of 2019.

**Challenges of Disease Modifying Clinical Trials and the Border Wall**

Clinical trials that test the hypothesis that any therapy will slow or stop the progression of disease are challenging on many fronts. How long should the trial go? How is disease progression defined? How can one account for biological variability in disease presentations and course? What methods are best for defining clinical changes?

A clinical trial outcome should be a measure that is clinically meaningful. By the FDA’s definition such an outcome measures how a patient feels, functions, or survives. Unfortunately, with Huntington disease, measuring such an outcome can take years or even decades to show a clear difference. Historically, the UHDRS motor score has

“This will require a lot of work, and strong collaboration... We look forward to partnering with the entire HD community to think about and address these challenges at the appropriate time.”

SCOTT SCHOBEL
“There’s no such thing as a cure for Huntington disease... The only cure would be full-body genome editing to correct the mutation, which is complete science fiction.”

AMBER SOUTHWELL
been used as a marker of motor progression in HD, and has been useful in VMAT-2 inhibitor trials. In the case of ASO trials, this outcome measure fails to capture the breadth of HD symptoms, like the cognitive and psychiatric changes that are well described.

Karl Kieburtz, professor of neurology, likens this problem to the current border security debate. “When we talk about ‘disease modification’ it’s a little bit like talking about a ‘border wall,’” he says. “Patients, families, investigators, regulators…everybody knows that with Huntington disease, the disease gets worse over time, people become disabled, and die. Everyone wants a treatment that stops or slows this process. That is like saying everyone wants border security. When we start saying a treatment slows or stops the inexorable progression to disability and death, needs to be a ‘disease-modifying’ treatment, it is like saying we need a ‘border wall’ for border security. Then the debate becomes about the ‘wall,’ rather than focusing on how to define and measure HD disability. It’s like saying the only way to get border security is to build a wall, and we start debating something; in my view, that is a distraction.”

How do we measure, in aggregate, the disabling quality of Huntington disease? Or turn it around, how do we measure the abilities that are important to patients over time so we can say this group of people is doing better than that group of people? “Total motor score alone probably does not fit the bill,” says Kieburtz. Because if the motor score gets better, what does that mean? How do we know if a person is doing better just because their scale score is better? This issue is a very important hurdle to cross in order to get therapies that improve HD in the long run.”

We also want to think about treating HD before it becomes disabling, perhaps before symptoms even begin, says Kieburtz. Accelerated approval, one of the FDA’s expedited approval programs, is one mechanism that allows for use of an outcome which is not a clinically meaningful outcome, but which is reasonably likely to predict a clinically meaningful outcome. Such outcomes could be used in individuals before symptoms develop. “In Huntington disease, one could imagine reducing the production of mutant huntingtin could be a biological measure which might be reasonably likely to predict a clinical outcome,” says Kieburtz.

For instance, a trial in pre-manifest patients with no observable clinical symptoms to manage may use mutant huntingtin levels as a measure that is reasonably likely to predict a clinical measure. “That can, in certain circumstances, be used as a substantial measure of efficacy, which is used in lieu of a clinical outcome measure,” says Kieburtz.

### A Worldwide Problem

Further complicating global studies are apparent differences of opinion between the U.S. (FDA) and European Medical Agency (EMA) on what is needed for drug approval. The FDA and EMA are largely aligned but have definitively different perspectives on the issues of how to determine clinical efficacy. For example, European approval of a therapy for marketing considers the magnitude of benefit of a drug versus approved drugs for that indication, as well as versus placebo. In the U.S., the standard of evidence is a comparison to placebo alone.

In HD, the differing approach of the FDA and EMA is evident in the differing endpoints for the GENERATION-HD1 study in Europe and the U.S. The primary outcome in the U.S. will be the Total Functional Capacity (TFC) compared to placebo. In Europe, the primary outcome will be the composite Unified Huntington’s Disease Rating Scale (UHDRS) versus placebo. This score combines the TFC, UHDRS motor score, symbol digit modality test, and Stroop Word Reading. “There’s usually a different perspective on composite measures at the FDA, with concerns about how to interpret them,” says Kieburtz. “EMA is traditionally not so concerned with the potential shortfalls of a composite measure.”

### The Future...

There is certainly a lot of optimism for ASOs. “Reducing mutant huntingtin is the only thing I would expect to have benefit to every aspect of HD,” says Southwell. “I think with an effective huntingtin-lowering therapy, we may even see recovery of function in people with HD. Studies in mouse models of HD show that stopping or reducing production of mutant huntingtin in mice that are already symptomatic results in their recovery, sometimes all the way to normal function.”

Southwell reminds us that these approaches, while promising, are not cures. “There’s no such thing as a cure for Huntington disease, and even if you have a therapeutic treatment that completely prevents onset of disease, you haven’t cured it,” she says. “The only cure would be full-body genome editing to correct the mutation, which is complete science fiction.”

Are ASOs an answer that the HD community has been waiting for?

Everyone, around the world, and across all borders, hopes so.

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“We also want to think about treating HD before it becomes disabling, perhaps before symptoms even begin.”

KARL KIEBURTZ
Reflections on Right to Try

Policy aims to provide terminally ill patients access to experimental therapies

The U.S. Food and Drug Administration (FDA) has overseen the responsible commercialization of new drugs and therapies since 1938. Pre-clinical (laboratory and animal) and clinical (human) trials data must provide sufficient proof to convince the FDA that a new therapy is both safe and effective before it is approved for marketing. Over time, the FDA’s responsibility has been better defined and expanded into a distinct process, in which drug developers must be approved with their pre-clinical data before they continue into the standard four phases of human trials.

It is not a simple feat to be accepted as a participant into a clinical trial for a new drug. Spots are limited and enrollment criteria can be very strict. Old age, being under- or overweight, and common comorbid conditions like heart disease or migraines can all be exclusionary. The drug-developing companies or their sponsors set these criteria to remove as many competing influences as possible to obtain the clearest picture of the safety and efficacy of their treatment. Ideally this expedites the process to market. Setting these criteria can significantly decrease the chances of serious adverse events like death or disability from occurring during a trial that can cripple a drug’s development, whether by FDA ruling or by plummeting investor confidence. However, this rigidity leaves many ineligible patients to face their fate without access to options and without hope. This is especially true in an incurable disease population like Huntington’s, where some first-of-their-kind therapies are undergoing clinical trials with limited eligibility and a demand that far surpasses the available spots.

As a study coordinator involved with the newest clinical trials in HD, I speak to patients and loved ones about research possibilities daily. Limited spots, challenges in travelling to our site, and, of course, exclusionary criteria are the most common reasons we must turn hopeful people away. These are difficult conversations to have with those suffering from a terminal illness, especially when many are willing to go to extreme lengths to participate. Families that are willing to leave their jobs, move across the country, or spend enormous sums of money in order to travel to our site have become a norm in our center. But about six months ago, when discussing a patient’s prospects for a popular new clinical trial, the patient’s husband told me something I had yet to hear: he said that, by law, his wife had the “right to try.”
Limited spots, challenges in travelling to our site, and, of course, exclusionary criteria are the most common reasons we must turn hopeful people away.
On May 30, 2018, the S.204 Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act was signed into federal law by President Donald Trump. This policy aims to help terminally ill patients in the United States access experimental therapies that are otherwise only available through clinical trials.

Eligible therapies must have passed at least a Phase I clinical trial, which are typically small studies that test basic safety of a drug by measuring side effects at increasing dosages. Patients who qualify for Right to Try (RTT), in addition to having a diagnosis of a life-threatening condition, must also have exhausted approved treatment options and be unable to participate in a clinical trial for the drug they are trying to access. A licensed physician must certify these qualifications and appeal to the developing company or sponsor directly to exercise a patient’s Right to Try. However, RTT does not mandate companies to provide their product, nor to bear the financial burden if they decide to do so, which brings up a couple questions: how effective is the policy really at reaching its goals, and are those goals truly desirable for patients and the medical community at large?

Expanded Access

The idea of improving access to experimental therapies outside of highly controlled clinical trials is actually not new. In fact, 41 U.S. state legislatures had passed a version of an RTT law in the years leading up to the federal motion. But even before RTT, the FDA itself had established a “compassionate use” program to accomplish the same goal, albeit with some distinct differences. Formally called expanded access (EA), this program began informally in the 1970s and has been codified and overhauled over the decades.

Under EA, a patient’s physician must submit a formal request to a company to provide the drug to either a single patient, an intermediate-size group, or a large “widespread” population. If the company agrees, which they are not required to do, the FDA must then approve an application for a proposed treatment protocol, which is usually drawn up by the requesting physician. This application must clinically describe the patient or group and explain the rationale for compassionate use. It also must detail a treatment plan that ensures patients give fully informed consent, explains the methods and timeline of treatment, and outlines how patients will be monitored for safety. An application must also be approved by an Institutional Review Board (IRB) of the institution where the patients will be treated, and IRBs typically have their own sets of local policies and requirements. If both the FDA and the IRB approve, which may require some protocol modifications, a physician can begin treating his or her consented patient(s) per that approved protocol, making sure to document treatment outcomes and adverse events to report back at regular intervals to both organizations.
Similar to RTT, companies are not financially responsible for providing their product under EA, and they also are not permitted to turn a profit from a product pre-market approval. Under either program, companies can charge the patient to recoup costs directly associated with making the drug available to them. This does not include indirect costs like administrative effort or IRB fees and expenses. However, to avoid revealing the actual cost of their drug and impacting potential profits post-approval, the few companies who do agree to provide their product under EA do so for free. As these compounds can be incredibly expensive, it may not be possible for companies to supply both clinical trials and compassionate use cases with their product. When companies do charge, insurance companies, Medicare, and Medicaid are not required to cover the cost of accessing therapies obtained through EA or RTT, creating financial uncertainty for all patients seeking compassionate use, save for the significantly wealthy.2,4,6

**A New Model**

If both EA and RTT provide a pathway to experimental therapies, but neither program can force companies to comply or foot the bill, why was RTT instated? The main difference lies in oversight. With EA, a physician works with both the FDA and an IRB to bring an investigational therapy from industry to patient in a process that prioritizes safety, accountability, and rationalized risk. RTT’s attractiveness lies in its simplicity; it is a direct agreement between a physician and a company that does not require FDA or IRB approval. This cuts out not only the administrative burden traditionally associated with these organizations, but also the business risk from reporting safety data.

Industry refusal to participate is cited often as the greatest obstacle to accessing investigational therapies through compassionate use.
Indeed, proponents of RTT criticize the FDA’s program as fraught with obstacles that complicate and delay access. According to a May 2018 FDA report, surveyed physicians reported that the total time taken to complete the entire EA approval process was approximately 30 hours, and that it was a notably challenging experience, especially for first-time applicants with less familiarity working with IRBs, manufacturers, and the FDA. While 30 hours of typically unreimbursed time is no small commitment for a physician and his or her staff, the FDA did do their part to reduce this burden, overhauled their piece of the application (the form that physicians must use to request FDA approval of a proposed treatment protocol), and created a new form in 2016, which now takes 45 minutes to complete instead of eight hours. It is important to note this form is specifically for individual patient protocols and EA applications to the FDA for intermediate-size groups and larger populations, and expectedly takes longer – around 120 hours – by a 2009 FDA estimate. The FDA also concedes that they have numerous areas of improvement in terms of providing more resources to help patients and physicians understand and navigate the program and in terms of easing the use of FDA systems that navigate EA. It is difficult to compare RTT’s application process with EA’s due to the recency of the RTT legislature and because RTT’s access process differs by company.

Once an EA application is submitted, the FDA has a surprisingly speedy turnaround. Various factors can shorten or lengthen the review time, including known risks of the investigational therapy, whether it’s an emergency, and whether modifications to the application need to be made for safety purposes. Emergency requests for single patients are generally reviewed in less than one day, as they have much less stringent oversight requirements. Non-emergency requests take approximately eight days for single patients and roughly 30 days for groups. Roughly 1,800 EA applications, individual and group, are received by the FDA annually, and this number has been growing consistently, with an overall approval rate of 99%. Of course, there is no way of knowing how many patient requests for EA are denied by a physician or company before an application is prepared for the FDA. Neither physicians nor drug companies are required to keep track of how many requests they receive, let alone how many are rejected or why.

Industry refusal to participate is cited often as the greatest obstacle to accessing investigational therapies through compassionate use. This is where RTT’s essential difference of limited oversight is once again key. Not only does RTT include a blanket “no-liability provision” to protect companies from facing patient litigation when providing their investigational drug, but they are also not required to report serious adverse events, including death or disability, immediately. Instead these are compiled in an annual report to the FDA. The FDA is only allowed to use this data to slow or halt review or approval of the drug if it is determined to be “critical to determining safety.” In contrast, EA requires companies to immediately report any serious and unexpected event that may be causally related to the study drug, which can provide early identification of important risks. While EA data are taken into consideration when the FDA reviews clinical trial data for continued development, safety labeling, and market approval, the FDA does state that it is “not aware of instances in which adverse event information from expanded access has prevented FDA from approving a drug.” The FDA must take into account the less controlled environment of EA treatment and that EA participants are often more advanced in their condition, making them more likely to experience adverse events than their corresponding clinical trial subjects.
In reality, Right to Try is only another right to ask to try, which translates to false hope when key players do not participate.

RTT thereby seems to remove one of the perceived disincentives of the EA program to industry, though it has not yet effected industry participation. The first patient received an investigational drug under RTT just in November 2018, under the California state RTT law set in 2017.13 As a relatively recent federal legislation, time will tell how RTT is developed and redefined, and whether it will change the landscape of compassionate use. There is no doubt that the passage of RTT is an ideological win for those in favor of individual freedoms and government deregulation, but at what cost?

Returning to my patient’s husband who invoked her Right to Try, to my knowledge, none of the companies sponsoring the newest, most promising HD investigational therapies are participating in any compassionate use. In reality, Right to Try is only another right to ask to try, which translates to false hope when key players do not participate. Not only does that request come with no guarantee of physician or industry cooperation, but it disrupts an existing system by bypassing significant measures developed over decades to ensure human safety on a larger scale. This may be attractive to some drug companies looking to gain public approval, but it can pose catastrophic and almost entirely unregulated risk to desperate, easily exploited patients. The EA program is by no means perfect, but the FDA has proven to be willing to balance the interests of seriously ill patients with those of the industry. The agency shows a commitment to adapting and improving EA appropriately, while prioritizing safety of clinical trial participants and, later, consumers. •

2 http://righttotry.org/about-right-to-try
3 http://righttotry.org/in-your-state
5 https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/ucm431774.htm
7 http://righttotry.org/dead-on-arrival
9 https://www.fda.gov/news-events/newsroom/pressannouncements/ucm504579.htm
11 https://fas.org/sgp/crs/misc/R45414.pdf
The times they are a-changin’. Up until recently, the skillsets of neurologists and psychiatrists who treat Huntington disease (HD) patients were focused on assessing and treating motor and psychiatric problems, keeping up with recent research, and maintaining a compassionate approach to dealing with a progressive chronic disease that affects entire families. In 2019, however, our field is now advanced to the point that we perform lumbar punctures (LPs) and intrathecal infusion therapies for delivering antisense oligonucleotides (ASO) to lower mutant huntingtin protein.

I first heard about RNA-lowering strategies at research meetings approximately five years ago. They were an entirely new approach with the potential for developing disease-modifying therapies directed at solving the central problem in HD: the genetic mutation. In what seems like a very short time, researchers developed antisense oligonucleotide (ASO) programs, the ability to accurately measure mutant huntingtin protein concentration in the cerebral spinal fluid (CSF), and a successful program to develop ASO treatment for spinal muscular atrophy.

Almost three years ago, after listening to more exciting presentations about RNA-lowering strategies at the CHDI Foundation’s annual meeting, I realized that this treatment could be the future for HD clinical research.
New Tricks

I made a decision to prepare for the next generation of HD research by developing my own expertise and facilities to participate in research projects that involved LPs and eventually intrathecal administration of research products. I also decided to take the plunge and become the first international site for HDClarity, a multi-site cerebrospinal fluid collection initiative to facilitate therapeutic development for HD. As a neurologist who finished training in 1986, I had experience performing LPs as a resident and felt reasonably competent in administering this procedure. During the 1990s I was proud to be able to perform LPs when other physicians were unable and rarely had to send patients for fluoroscopic guidance. However, in 2016, when I opened HDClarity, I had not performed a lumbar puncture in approximately 10 years.

It’s not easy to transform oneself from a typical HD specialist to a LP expert with the confidence and experience to carry out intensive phase 1 and 3 research studies. First, the technical aspects of performing LPs has changed. In the past we used LP needles that had a cutting edge and were either 18, 20, or 22 gauge. Now we are using atraumatic needles that have a blunt pencil point end and collect fluid through a small opening on the side just proximal to the end. We are using either 22-gauge needles (HDClarity), or for the intrathecal infusion studies, 24-gauge needles that require a 20-gauge introducer since the needles are so small that they cannot be passed through the soft tissues easily. We perform the procedure.
with the patient either in the seated position or the lateral decubitus position, depending on the study. We are required to collect up to 20 ml of CSF either by using a syringe to suction or by slow drip. We also have to attach a syringe and push the study medication through an intrathecal bolus administration. These techniques are all very different than what we have been taught.

How did I make this transition? It was my impression that the best way to become proficient was to do as many LPs as possible. I decided to participate in HDClarity and dedicated time and space at my clinic to offer this study to as many Enroll HD patients as possible. It took at least 10 LPs to get used to the new needles and at least 50 LPs to deal with the different issues that arose. These challenges included when to replace needles during the procedure, what happens if CSF flow stops in the middle of collection, when to change levels when you are having difficulty getting in, determining how to recognize and deal with vaso-vagal symptoms, and obtaining better lighting sources and fans for hot days. Other issues included figuring out how many people should be required in the room, and what the emergency plan would be? I found that my level of stress improved with getting more comfortable with the procedures. My staff was excellent in supporting LPs, and their input was very useful.

Diving In

The next step was to take the plunge into the intrathecal administration research studies. For me, being involved with phase 1 projects, frequent assessments and the technical aspects of delivering intrathecal products were new experiences. We were asking a lot from our patients by subjecting them to repeated LPs, MRIs, and frequent assessments without any guarantees about safety. Having the experience with HDClarity was helpful but I was very concerned about the potential of failing to perform an LP and not being able to administer the research product. I did not want to be the limiting step in a potentially successful treatment.

A colleague suggested using spinal ultrasound, which has become a standard of practice in obstetrical anesthesia in performing epidurals. I was fortunate to be able to organize a day of training at a local teaching hospital’s obstetrical ward to get familiar with this procedure. I obtained an ultrasound machine dedicated for this purpose at my site and now use ultrasound guidance for all LPs. This strategy has been transformative. It is my impression that spinal ultrasound reduces the procedure time, morbidity for the patient, and stress for the physician. It took about ten patients to get used to the ultrasound technique; it adds no risk to the patient; and it is easy to use.

It was my impression that the best way to become proficient was to do as many LPs as possible. I decided to participate in HDClarity and dedicated time and space at my clinic to offer this study to as many Enroll HD patients as possible.
Fast forward to February 2019. My site is now involved in five studies that require LPs. We have just opened a suite dedicated to LPs and intrathecal study drug administration. The suite includes two LP procedure rooms with stretchers that can go into Trendelenburg positions; adequate lighting and ventilation; BP machines; a recovery room with two infusion chairs that can also go into reclining and Trendelenburg positions; nursing and physicians offices; and a full lab with centrifuges, a -80 degree freezer, and a specialized refrigerator for drug storage. With this new facility, we can perform two LPs at the same time. To date we have performed up to four per day, but have the potential capacity for up to eight procedures per day. We anticipate with the current studies that we may have as many as 30-to-50 patients requiring intrathecal administration each month by the end of the recruitment. We have added staff and will continue to add staff as our needs evolve.

**Lessons Learned**

What are the lessons learned? When doing procedures, you should anticipate complications. The new LP needles are less likely to cause post-dural puncture headaches, but they still occur. We have a protocol to telephone every patient the day after the procedure, and all patients are given my cell number if problems should occur. We have had approximately eight post-dural puncture headaches with the 22-gauge needles (less than 10%), but no post-dural puncture headaches with the 24-gauge needles to date. We have had to arrange a blood patch in one patient with a successful outcome. We have had approximately five patients have vaso-vagal attacks during the procedure. We have had two times when the patient has rapidly gone unconscious with low pulse and BP. Presyncope has occurred in two normal control subjects. We now make sure that we have automated BP cuffs in the LP rooms and have stretchers that can be put into Trendelenburg positions.

As a neurologist performing LPs, you have to be prepared for failures. Although we have had only one failure since we started using ultrasound guidance, this will occur. We have to make sure that the patients always can identify when they have had enough if they are experiencing discomfort. These are research studies and the patient experience always is a priority. If the patient is anxious or having a bad day, it is best to just stop the procedure.

My advice is for HD physicians is to do whatever it takes to become comfortable performing these procedures. The HSG, EHDN, and CHDI have been involved in offering LP workshops that many have found helpful. I have personally reached out to the pioneers in this area, including Ed Wild, clinician scientist at UCL Institute of Neurology, and his fellows, as well as Blair Leavitt, professor at the University of British Columbia. They have been very generous in answering questions and giving helpful hints.

I believe that using ultrasound should be the standard. We are planning a research study to be able to assess the benefits of spinal ultrasound for this patient population. If you are not comfortable with LPs and do not want to embark on this journey, enlist someone at your site who will take that role. It took time and experience for me to develop the confidence in performing LPs. I think that we need to develop a support network for physicians performing LPs and intrathecal infusions. The HSG, EHDN, and sponsors of these trials should be approached to help to develop these networks.

This is an exciting time for HD research. I anticipate that in the next 3-to-5 years that a vast network of sites will be required to perform the current and future studies involving intrathecal administration. It is important as HD physicians that we develop the skills needed to carry out this research and that the studies do not fail because of a lack of technical expertise. Hopefully our research will be successful. We will then need to be pioneers in developing a network of infusion sites after the drugs are approved.
### CLINICAL TRIALS

**UPDATES AND ADDITIONS**

To update or add a clinical trial, please e-mail [HDInsights@hsglimited.org](mailto:HDInsights@hsglimited.org).

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<tr>
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<td>Sage Therapeutics</td>
<td>SAGE-718</td>
<td>718-CLP-102 B</td>
<td>I</td>
<td>A Phase 1, Double-blind, Placebo-controlled, Multiple Ascending Dose Study to Determine the Safety, Tolerability, and Pharmacokinetics of SAGE-718 Oral Solution in Healthy Adults With an Open-label Cohort of Patients With Huntington’s Disease</td>
<td>Long Beach, CA and Berlin, NJ</td>
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<td>Roche/Genentech</td>
<td>GENERATION HD1</td>
<td>RG6042</td>
<td>III</td>
<td>A Randomized, Multicenter, Double-Blind, Placebo-Controlled, Phase III Clinical Study to Evaluate the Efficacy and Safety of Intrathecally Administered RG7234292 (RG6042) in Patients With Manifest Huntington’s Disease</td>
<td>30 Total: United States and Canada, 19 Total: Europe</td>
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<td>Wave Life Sciences Ltd.</td>
<td>PRECISIONHD1</td>
<td>WVE-120101</td>
<td>I / II</td>
<td>A Multicenter, Randomized, Double-blind, Placebo-controlled, Phase 1b/2a Study of WVE-120101 and WVE-120102 Administered Intrathecally in Patients With Huntington’s Disease</td>
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<td>Ultragenyx Pharmaceutical</td>
<td>TRIHEP3</td>
<td>Triheptanoin oil</td>
<td>II</td>
<td>A Comparative Phase 2 Study Assessing the Efficacy of Triheptanoin, an Anaplerotic Therapy in Huntington’s Disease</td>
<td>2 Total: France and Netherlands</td>
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<td>Azidus Brasil</td>
<td>ADORE-DH</td>
<td>Cellavita</td>
<td>II</td>
<td>Dose-Response Evaluation of the Investigational Product Cellavita HD After Intravenous Administration in Patients With Huntington’s Disease</td>
<td>Sao Paulo, Brazil</td>
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<td><strong>ACTIVE</strong></td>
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<td>Vaccinex, Inc.</td>
<td>SIGNAL</td>
<td>VX15/2503</td>
<td>II</td>
<td>A Phase 2, Multi-center, Randomized, Double-blind, Placebo Controlled Study in Subjects With Late Prodromal and Early Manifest Huntington’s Disease (HD) to Assess the Safety, Tolerability, Pharmacokinetics, and Efficacy of VX15/2503</td>
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<td>Azevan Pharmaceuticals</td>
<td>AVN011</td>
<td>SRX246</td>
<td>I / II</td>
<td>An Exploratory Phase II Study to Determine the Tolerability, Safety, and Activity of a Novel Vasopressin 1a Receptor Antagonist (SRX246) in Irritable Subjects With Huntington’s Disease (HD)</td>
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<td>Teva Pharmaceutical Industries</td>
<td>OPEN-HART</td>
<td>Pridopidine</td>
<td>II</td>
<td>A Multi-Center, North American, Open-Label Extension Study of Pridopidine (ACR16) in the Symptomatic Treatment of Huntington’s Disease (Open-HART)</td>
<td>12 Total: United States and Canada</td>
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<td>Teva Pharmaceutical Industries</td>
<td>LEGATO-HD</td>
<td>Laquinimod</td>
<td>II</td>
<td>A Multicenter, Multinational, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Laquinimod (0.5, 1.0 and 1.5 mg/Day) as Treatment in Patients With Huntington’s Disease</td>
<td>52 Total: Worldwide</td>
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Sources: [www.clinicaltrials.gov](http://www.clinicaltrials.gov) and [apps.who.int/trialsearch](http://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.

### To patients
- Deutetrabenazine (Teva)
- Tetrabenazine (Lundbeck)

### Phase 3
- RG6042 (Roche/Genentech)

### Phase 2
- WVE-120101 (Wave Life Sciences)
- WVE-120102 (Wave Life Sciences)
- SRX246 (Azevan Pharmaceuticals)
- VX15/2503 (Vaccinex)

### Phase 1
- VY-HTT01 (Voyager Therapeutics)
- AMT-130 (uniQure)
- SAGE-718 (Sage Therapeutics)

### Preclinical
- PTC small molecule (PTC Therapeutics)
- MTC-1203 (Mitoconix)
Teva Pharmaceuticals is working every day to make quality healthcare accessible around the world. As a manufacturer of specialty and generic pharmaceuticals, Teva provides both new therapies and greater access to quality, affordable medicines.