# *Enroll!*

**Updates from the Enroll-HD global community**

**SUMMER 2019**

# STEPPING INTO THE FUTURE OF HD RESEARCH
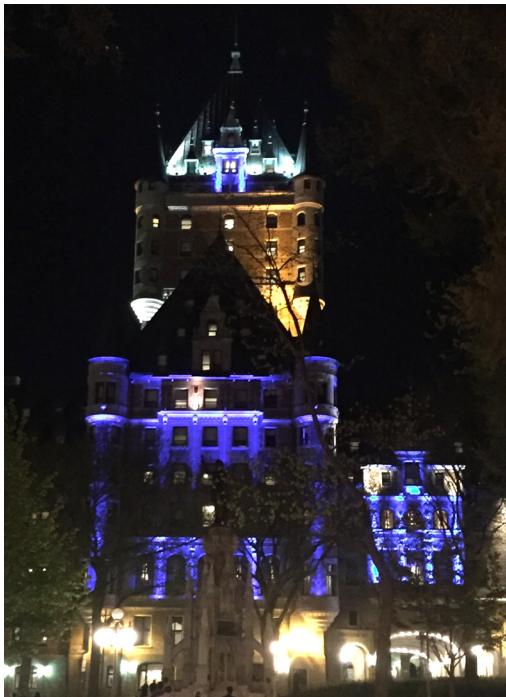
**A lot has happened since the last issue of *Enroll!***

It's good to be back! This latest issue of *Enroll!* lands at an especially promising time in HD research. Everywhere you look, from the lab bench to the clinical exam room, the excitement about the latest scientific advances is palpable. With promising drug candidates either approaching or currently in clinical trials, there has never been a more important time to become a part of research.

Our Enroll-HD community continues to grow—today, we have more than 20,000 participants from 19 different nations located across 174 clinical sites on four continents. Every Enroll-HD participant and clinical staff member has been instrumental in reaching these impressive milestones. But there also remains much more for us to accomplish.

Together, this vibrant network of participants, their families, clinicians, site staff, and researchers must continue to expand and evolve to meet the research challenges of the next decade. Enroll-HD is now providing a wealth of clinical data to researchers, and as these datasets continue to grow they will allow us to better describe HD, further understand the genetics that contribute to disease progression, and offer new ideas about how to develop effective treatments.

Scientific discovery is accelerated when people collaborate and share knowledge. In May 2018 clinicians and researchers from the worldwide Enroll-HD network gathered for the first ever Enroll-HD Congress in Quebec City, Canada. It was a unique



*Le Chateau Frontenac in Quebec City, the conference center and hotel for the Enroll-HD Congress in May 2018, was lit up blue in honor of HD Awareness Month*

opportunity to learn, connect, and express ideas that will propel HD research forward. Some of the highlights discussed included new initiatives and studies for the Enroll-HD platform, advances in HD research, and clinical findings that have provided novel insights into how HD develops, affects the body, and manifests in patients.

## *Noteworthy accomplishments*

Since our last issue researchers have made remarkable progress in drug development. Medications known as antisense oligonucleotides that can lower levels of the huntingtin protein that causes HD are now in phase III clinical trial—the last step of testing before regulatory authorities approve a medication—to evaluate whether or not the lowered amount of huntingtin translates into clinical benefit. Other interventions of various types that aim to lower huntingtin protein are also rapidly approaching clinical trials (see the Postcard from Palm Springs video on the www.enroll-hd.org homepage for further details).

To accelerate the development and approval of new drugs, the Huntington's Disease Regulatory Science Consortium (HD-RSC) has been established by CHDI in collaboration with the Critical Path Institute, a nonprofit organization that works with drug developers and regulatory authorities like the Food & Drug Administration (FDA) and the European Medicines Agency (EMA). Made up of pharmaceutical and biotechnology industry partners, academic institutions, government agencies, patient-advocacy organizations, and

technology industry partners, the HD-RSC works in coordination with regulatory officials to plan the approval process for new drugs.

Progress is already underway. The HD-RSC has established data standards that are required when new drugs are submitted to regulatory agencies for approval. These data standards will maximize and streamline how the information contributed by Enroll-HD participants is gathered, shared, and compared. With these standards in place, the Enroll-HD database will become an even more powerful resource for researchers.

### Expanding and sharing our database

During the Congress, researchers had the opportunity to learn about the extensive datasets and associated biosample resources available to test new ideas and design experiments. More than 150 researchers around the globe are now using the Enroll-HD database, which has also been used to help design 10 platform studies and five clinical trials, with more currently being planned.

Enroll-HD now has a collection of over a million HD biosamples available; these include DNA and blood cells from Enroll-HD, cerebrospinal fluid and plasma from HDClarity, and will soon extend to plasma from Enroll-HD and sperm from the Origin-HD study. Some of the most notable platform studies are looking to develop two vital tools: biomarkers for drug development that measure a disease-related process going on in the body, and clinical assessment tools tailored to different stages of HD.

### The future of HD research

To accelerate the pace of discoveries it is imperative that data continues to be shared openly and made available to the HD research community. In November 2017 Enroll-HD introduced a new strategy to recruit premanifest participants as early as possible (see article page 3), even

*Some of the many staff who manage and centrally coordinate the Enroll-HD platform at the Congress held in Quebec City, Canada, in May 2018*

if they have not been tested for the gene. Studying behavior and collecting samples from people before disease onset will enable the development of better biomarkers and detailed characterization of the earliest stages of HD. As new drugs are developed, it will be essential to have insight into this critical window before disease begins. It will also prepare for a future where premanifest people can be treated early so that they only develop symptoms late in life, or not at all.

*With promising drug candidates either approaching or currently in clinical trials, there has never been a more important time to become a part of research*

*Enroll-HD now has a collection of over a million HD biosamples available*

We hope you enjoy this issue of *Enroll!* After you learn about the new premanifest recruitment strategy, meet some of the faces of HD who are advocating on the frontlines. Then see some of the ways leading HD researchers use participant data and take an inside look at some of the research studies that use the Enroll-HD platform. Working together, the HD community is making a difference for patients and families.

# STAYING AHEAD OF THE CURVE
## *The benefits of getting involved in research early*

When Anna*, 23, found out she had the expanded HD gene three years ago, her doctor said there was nothing they could do but wait. Yet Anna, who was getting ready to start a graduate program in social work, refused to sit around and watch the clock. She enlisted in any study that would accept her, including Enroll-HD.

Study participants like Anna are the lifeblood of HD research. But Anna also represents a particularly important population in the HD community: premanifest individuals who do not yet show clear signs or symptoms of disease but may


*Anna with her dog, Murdoch*

have very subtle but measurable changes. Over the past couple of years there has been a shift in Enroll-HD recruitment strategy to encourage more young people from HD families to step out of the shadows and embrace the opportunity to be involved in research.

There are several reasons premanifest individuals are essential to Enroll-HD. Researchers need to study and finely characterize the very earliest stage of disease so they can better understand the full spectrum of HD. Knowing more about the subtle changes that occur in premanifest people could inspire further ideas for new therapeutics.

Early-manifest patients who show the initial motor signs of disease are the current target population for most of the

*"Engaging premanifest patients who are asymptomatic is beneficial from a clinical, research, and patient perspective"*
*– Suresh Komati*

clinical trials that are ongoing or planned. This is because the early-manifest stage is where the current crop of drugs in development will likely have the best chance of having a measurable benefit. If there are more premanifest people in Enroll-HD these individuals will be engaged and available to be invited into clinical trials as soon as they start to have symptoms. Eventually, as scientists develop a better understanding of HD and effective therapeutics become available, the aim will be to treat premanifest individuals before these symptoms begin and slow disease progression even further. In order to do that, the premanifest phase of the disease needs to be fully characterized.

"Engaging premanifest patients who are asymptomatic is beneficial from a clinical, research, and patient perspective," says Suresh Komati, MD, consultant neuropsychiatrist at Walkergate Park Hospital and principal investigator at the Enroll-HD site at St Nicholas Hospital in Newcastle, UK. "Investigators can develop insights into when this population first develops symptoms and what is the best time for interventions."

### *More is better*

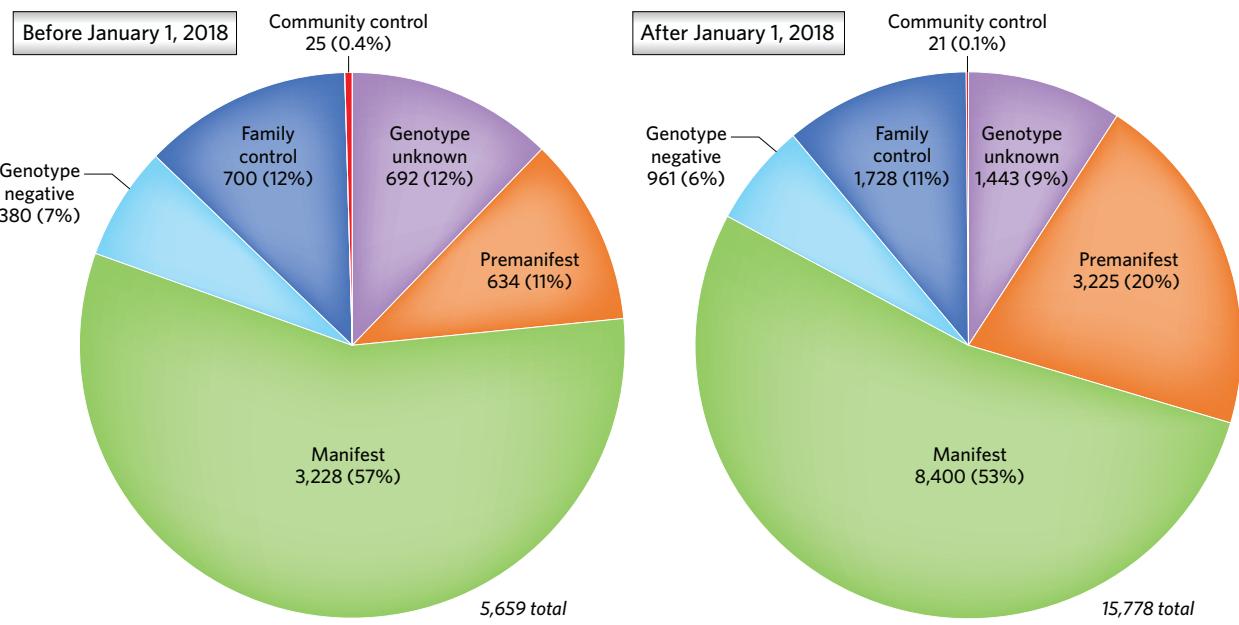Since November 2017 Enroll-HD has been spearheading an effort to recruit more people in the premanifest stage. There are currently 18,688 active participants in Enroll-HD; 9,711 of those are in the manifest stages of disease while only 3,701 are from the premanifest population (see pie chart, page 4). Enroll-HD sites are learning how to encourage more premanifest individuals to come forward. Komati's site, for example, which has been at the forefront of this endeavor, is now made up of around 30% premanifest individuals.

*\*Anna's last name has not been included at her request*

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## RESEARCH IN LATE-STAGE HD

Every participant in Enroll-HD, regardless of their stage of disease, has made an invaluable contribution to the field. Investigators recognize, however, that being part of a study can be particularly burdensome to individuals in the later stages of HD, as well as their caregivers. Researchers have also found that the current assessments are not sensitive enough to accurately describe the characteristics of this stage of disease. As part of a new platform study, called Later Stage Assessments (LSA), rating scales that will accurately measure the moderate-to-late stages of illness are being developed. For more information read about some of the Enroll-HD platform studies on page 10.

**Before January 1, 2018**

- Community control 25 (0.4%)
- Genotype unknown 692 (12%)
- Family control 700 (12%)
- Genotype negative 380 (7%)
- Premanifest 634 (11%)
- Manifest 3,228 (57%)

5,659 total

**After January 1, 2018**

- Community control 21 (0.1%)
- Genotype negative 961 (6%)
- Family control 1,728 (11%)
- Genotype unknown 1,443 (9%)
- Premanifest 3,225 (20%)
- Manifest 8,400 (53%)

15,778 total

*Percentages of the disease category of participants at their most recent visit - before and after January 1, 2018*

"If we could double this premanifest number it would do a world of good," says Steve Horvath, PhD, professor of human genetics and biostatistics at University of California, Los Angeles and avid user of the Enroll-HD database (see Who's Using My Data? article, page 7). "Studying premanifest individuals allows you to dissect the causal change linking the HD mutation to downstream bad effects. If we only look at manifest individuals, we might miss a critical window in the disease etiology [cause]."

HD is one of the more common rare diseases, with around one in every 10,000 people affected. This rarity means that every HD-affected person that takes part in research makes a big difference, and there can never be too many volunteers. As a clinical research platform, Enroll-HD is also a doorway into other studies as participants can be invited by their local site to join other studies and clinical trials that are appropriate for them.

Some individuals like Anna have already been tested and know they carry the HD gene. But other premanifest indi-

viduals are still at risk because they have decided to not yet undergo predictive testing to find out their gene status. Anyone from an HD family, even if they have not been tested, is critical to research and can join Enroll-HD.
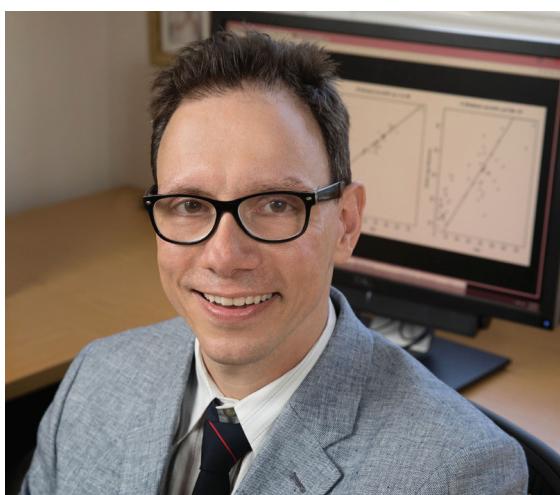
## Characterizing disease

To advance medicine, researchers need to better understand what comes first. By studying HD families early on, researchers can see how the disease progresses from its earliest stages. They can pinpoint what biological processes inside the body are involved and what changes occur first.

Typically, individuals are not diagnosed with HD, and in many cases do not even visit a neurologist, until they develop clear motor symptoms. But subtle behavioral and cognitive changes may occur 10 to 15 years before this motor onset. Recruiting more premanifest individuals is the key to identifying those very first signs of disease. By characterizing the symptoms early on, researchers can make the case that treatment should begin early too.



*"Studying premanifest individuals allows you to dissect the causal change linking the HD mutation to downstream bad effects"*
*– Steve Horvath*

"We are missing a large chunk of patients who have symptoms in other non-motor domains. We need to catch them sooner and gain insights into exactly how and when these symptoms develop," explains Komati.

With a better understanding of disease that indicates when signs and symptoms are expected to occur, researchers can develop more sensitive rating scales that are essential to the success of clinical trials. Without an accurate scale for the premanifest stage it is impossible to say whether a particular drug has worked in that population. Developing a finely tuned scale for the premanifest stage will enable researchers to eventually conduct clinical trials in that phase and convince regulatory authorities to approve treatments (see Furst 2.0 article, page 12).

*"The hope is that in the future disease-modifying treatment trials may be offered to people even earlier in the disease process"*
*– Rhona MacLeod*

### Advancing clinical trials

Insights into the earliest stage of disease will also help researchers develop new drug targets. One way to measure whether a drug is making a difference is to identify biomarkers. A biomarker can be anything measurable that specifically and accurately reflects a process going on in the body. For example, a diabetic's blood glucose level is a very good measure of how well they are metabolizing and managing energy.

The best biomarkers are like a window into the body, allowing a physician or researcher to understand how things are going and what has changed. Scientists are studying premanifest individuals that carry HD mutations to identify biomarkers reflecting certain signs and symptoms of early disease. Finding such biomarkers will be central to developing and evaluating new drugs in clinical trials, and eventually to making available therapeutics that can be started earlier in the premanifest phase of disease.

*"When someone contributes to a research study they are not just doing it for themselves but for generations of people after them"*
*– Sarah Edwards*

"The hope is that in the future disease-modifying treatment trials may be offered to people even earlier in the disease process," says Rhona MacLeod, PhD, lead genetic counsellor at the Manchester Centre for Genomic Medicine in the UK. "It is important that we have as many people as possible participating in Enroll-HD to help progress research."

Early-manifest patients who have recently developed motor symptoms are currently the target population for most of the clinical trials ongoing or planned. In this stage a drug has the best chance of making a measurable difference. If there are lots of premanifest people already engaged in research through their involvement in Enroll-HD, they can be invited to take part in studies as soon as their symptoms begin.

The current goal is to develop effective treatments that will slow disease progression to such an extent that symptom onset is delayed for as long as possible, ultimately it is hoped for a person's whole lifespan. Once these therapeutics are found to be effective in early-manifest people the next goal will be to get approval from regulators so that they can be prescribed in the premanifest stage.

### How researchers use data

Thanks to Enroll-HD participants, researchers already have a goldmine of information at their fingertips. Over time, this data only becomes more valuable, explains Sarah Edwards, study coordinator at Komati's Enroll-HD site at St Nicholas Hospital in Newcastle. A premanifest participant, for example, may contribute a decade or more of data before they experience any signs or symptoms.

"When someone contributes to a research study they are not just doing it for themselves but for generations of people after them—their children and the children of other families," says Edwards, who notes her voicemail is full of eager participants whenever exciting HD research news is announced. "People are engaged—they come back year after year because they feel what they are doing matters. They trust the investigators and know that their information is benefiting genetics research."

When a study participant completes a cognitive test or gives a biosample, such as blood, that information becomes part of the Enroll-HD database. After a biosample is collected it is sent to a facility in Italy where it is checked, processed and stored. Researchers like Horvath can request access to the database. Enroll-HD, they say, makes their jobs easier and faster.

"The Enroll-HD study is extremely well designed and the data quality is absolutely superb," says Horvath. "There is very little friction between the people who generate the data and the people who consume the data. We lose a lot of time on other studies when the variables are not clear."

## Recruiting premanifest individuals

From youth organization leaders to study site staff, clinicians, and affected families, it is imperative that the HD community joins together and spreads the message that more premanifest participants are needed for studies. The advent of social media like Facebook and Twitter has helped break down some of the social stigma of HD, especially among young people who have so enthusiastically adopted using these platforms. This has prompted youth organizations to form and flourish, including the Huntington's Disease Youth Organization (HDYO), the Huntington's Disease Society of America's National Youth Alliance, the Huntington Society of Canada's Young People Affected by HD (YPAHD), and the European Huntington's Disease Network's Young Adults Working Group (YAWG). Anna encourages anyone from an HD family to embrace the opportunity and be part of the HD community by participating in Enroll-HD.

Genetic counselors like MacLeod are also research recruitment champions. In the clinic she counsels individuals and families who are either at risk for HD or undergoing genetic testing, and she has encouraged and guided many HD families to become involved in research.

Participants do not need to know their genetic status to be a part of Enroll-HD. MacLeod assures her patients that the information in Enroll-HD is de-identified and safeguarded. An individual's gene status is tested anonymously and associated only with a code that cannot be accessed by anyone at the site (to learn more see www.enroll-hd.org/where-does-my-data-go/). Even the staff running the study and drawing blood samples do not know the individual's genetic status.

"It is made very clear that no one on the team has access to the genetic results," explains MacLeod, "but for many participants at 50 percent risk there is a psychological barrier. There is still this feeling deep down inside that the test has been done and someone knows the results."

> **"The Enroll-HD study is extremely well designed and the data quality is absolutely superb"**
> – Steve Horvath

However, taking part in research can be extremely helpful for HD families. People who test positive or are still at risk feel empowered from contributing to research that may change the course of their disease, while individuals who do not have the mutation are comforted that they get to be involved in something that can help their family and friends. "Patients have a lifeline—they feel extremely valuable when they contribute to a global study." says Komati.

"It can help pull them away from feelings of isolation and be a boost for their resilience to do something positive that contributes to research and connects them to the wider community," adds MacLeod, who along with her clinical and research team colleagues has hosted an open day at Manchester Town Hall to explain HD research and genetic counseling.

But there are still several recruitment challenges. Since many premanifest people have full-time jobs, Komati's site tries to make the appointments as convenient as possible. Participants can make their Enroll-HD appointment at the same time as their regular visit with the clinician.

> **"...this is one of the only ways to give information directly to the scientists. It is empowering to leave knowing that my little data point is there forever"**
> – Anna

While there are some individuals who do not want to be reminded of their disease until they develop symptoms, Edwards says most of the HD community is motivated to participate in research.

"Every time I leave a site visit I feel like I have contributed something to the HD community," says Anna. "There are a million ways you can tell your story or explain HD to someone, but this is one of the only ways to give information directly to the scientists. It is empowering to leave knowing that my little data point is there forever."

# WHO'S USING MY DATA?

*Ever wondered what happens to your data? Some insight into how researchers are using the Enroll-HD datasets and biosamples, and what we might learn.*

## Power in numbers

We know that HD is caused by an inherited expansion mutation in the *huntingtin* gene, and that the average age of onset within a population is related to the length of that expansion. But at the individual level there can be very different outcomes from the same CAG length; for instance, one person with a 40 CAG repeat may be lucky enough not to have onset until age 65, whereas another person with the same 40 CAG repeat may develop motor symptoms at age 25. This huge 40-year difference tells us that there must be other genes in everyone's cells that also play a role in disease onset.

In genome-wide association studies (GWAS) researchers try to find these other genes by comparing the whole genomes (all of the DNA sequence that makes up a person) of thousands of individuals across all disease stages. They look for people who have disease onset at ages outside the expected average and compare all of their genes. If lots of these people have a particular gene then that might be what is known as a genetic modifier.

Once we know the gene we can begin to understand what that gene does and what biological processes cause certain symptoms to develop and the disease to progress. Peter Holmans, PhD, professor of biostatistics and genetic epidemiology at Cardiff University, is one of many investigators around the world who studies genetic data. Recently, the researchers identified a variant in a gene, known as *MSH3*, which is associated with an earlier age of disease onset. This gene mutation could possibly act as a biomarker for drug targets.

Psychiatric symptoms are less well studied than cognitive and motor presentations in HD. Using both manifest and premanifest samples, Holmans is also trying to identify genetic variants that are associated with common behavioral traits such as irritability, depression, and psychosis. When Holmans finds a pattern, he tries to determine whether these variants are associated with these traits in the general population or are unique to individuals with HD.

The key to finding these genetic variants, Holmans says, is a large sample size. Many thousands of participants are needed to identify genetic associations and avoid false-positive results. "Without premanifest patients we would have a much less powerful sample. We can discover new variants, show which ones are the strongest, and confirm the ones we have," he explains.

## Clues within the blood

Almost all Enroll-HD participants give blood samples during each of their visits, and these samples provide the DNA samples that are essential to so many studies. Steve Horvath, PhD, professor of human genetics and biostatistics at the University of California, Los Angeles, and his colleagues are using some of that DNA to study epigenetic age. Epigenetic factors are influences outside the DNA that can affect whether a gene is turned on or off, which affects the biology of a cell. Horvath has developed the idea of an 'epigenetic clock' that measures an individual's epigenetic age as reflected in the epigenetic factors in their DNA. He compares this to their actual age, the number of years since they were born.

Horvath has found that the DNA in the blood of individuals with HD in the manifest stage is an average of three years older than their biological age. The goal of his research is twofold: to determine how epigenetic changes in the DNA in blood cells indicate when a premanifest individual will develop HD; and how fast HD will progress in a manifest patient that already has motor impairment.

"For me, HD is a disease of accelerated aging," explains Horvath. "We want to see whether epigenetic changes in the blood of Enroll-HD participants relate to HD conversion and progression. This could lead to novel insights into what genes or pathways can be targeted to delay the onset of HD conversion."



*"Without premanifest patients we would have a much less powerful sample"*
*Peter Holmans*

## NOW AVAILABLE

Fourth Enroll-HD periodic dataset (PDS) now available! This de-identified and privacy-protected dataset was made available to researchers around the world on December 14, 2018. Visit *www.Enroll-HD.org* to learn more.

# THE FACES OF ENROLL-HD

**HD** family members who participate in research studies and clinical trials are essential to advancing science, with the ultimate goal being effective treatments that substantially improve the lives of those that have HD. Meet two proactive and passionate members of the National Youth Alliance (NYA) at the Huntington's Disease Society of America, young women who are contributing to Enroll-HD in different but equally important ways.

## Anna

*Three years ago, Anna\* found out she carried the HD gene. The 23-year-old had lost a grandfather to HD, her father started showing signs in his mid-30s, and as many as 40 of her relatives in her large family are at risk. Empowered by her desire to help researchers, Anna joined Enroll-HD and became an advocate for the NYA.*

**What motivates you to be a part of HD research?**
My main motivator is that I want to be able to help my family. There are a lot of people at risk. I want to find a treatment that can help us before my friends and family get really sick.

**You tested positive for the HD gene a few years ago but do not have any signs of the disease. Why is it so important for individuals to be involved in research early on before those symptoms start?**
My body holds information that so few people can give. I do not want to waste that knowledge if it could help a researcher better understand how the disease works. We know the HD gene interacts in different ways—my positive result, and the way my body acts, will be different from anyone else in my family. As a result, we need to gather as much data as possible, as early as possible, to help scientists find those patterns. The HD community is very small compared to a disease like cancer, which makes it even more critical for young people, and others impacted by HD, to share this information.

**How has being a part of Enroll-HD helped you personally since you tested positive?**
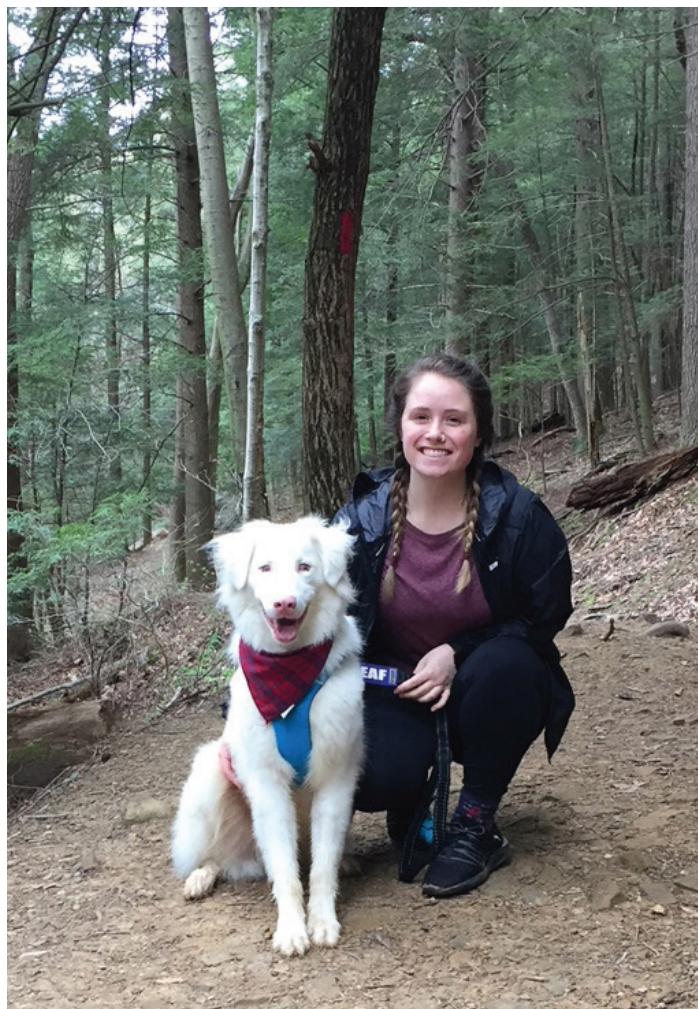I was always interested in how the symptoms start and being a part of research is a way for me to better understand the disease. When I do start getting sick or showing signs, I want to be as comfortable as possible and have the resources and physicians I need to be less scared.

**What would you say to someone else who was tentative about joining Enroll-HD?**
I would tell them that I was worried too. I was nervous the researchers would make it obvious that I was showing signs of HD. The site staff is very understanding and educated about the disease and they do not know anyone's gene status. You can skip certain portions if you feel uncomfortable. Any amount of information you can provide is helpful.

**What is your hope looking forward?**
My biggest goal is to make people less scared of HD and give them the sense of hope they need to keep going. Things in research are happening faster than we would have imagined. Any treatment that works long-term would be beneficial for people my age and younger so they potentially do not have to face symptoms at all, or until a normal elderly age.



*Anna, with Murdoch*

## Miranda

*Miranda\*, 24, was getting ready to start nursing school when she learned several of her family members had HD. Growing up, Miranda watched helplessly as her grandmother slowly deteriorated and her great-aunt gradually lost the ability to walk. A few years later, Miranda's mother decided to be tested; since her test was negative, thankfully her children were also no longer at risk. Miranda joined Enroll-HD, became an impassioned advocate for HD, and serves today as chair of the NYA.*



*Miranda*

### Why is it important to become involved in research?

Science does not move forward without participants. You can have all the doctors in the world, but if no one is participating in research studies they can't learn anything or make progress. Many larger studies pull from Enroll-HD data so I hope my contribution will help another researcher learn something.

### There are many clinical studies out there. What makes Enroll-HD special?

You do not need to know your gene status to participate in Enroll-HD. A lot of other studies require that you are gene positive to participate. Even if you do not have the gene, you can still join Enroll-HD and help out in some way.

### People at risk who do not want to know their gene status may be reluctant to participate in Enroll-HD. What advice do you have for them?

What makes people nervous is that they are afraid the researcher conducting the assessment will see a red flag and allude to their status one way or another. To ease their concerns, we try to connect them with another member in Enroll-HD who has a similar status so they can share experiences. I remind them no one in the room knows their genetic status. And even if they do a blood draw, that vial is sent to another lab and plugged into a computer with a random number. Everything is anonymous.

### Why is it so important that more young people like yourself join?

It is also beneficial to see someone over a long period of time so they can see how the disease evolves. Scientists learn more when they know people longer. There are so many different ways that HD presents itself—the more types of presentations we study, the more we learn.

### Can you describe a typical site visit? You recently moved from Michigan to Pittsburgh, was it easy to find a new site?

There are many sites around the country [there are 50 in the US] that participate in Enroll-HD. My initial visit was about two hours, but future visits will be less than an hour. I went through my family tree, had a cognitive evaluation, and took a physical exam.

### You're active in the NYA—how has it enriched your life?

When you are part of the NYA, you are never alone. We are each other's chosen family. Many of us have lost our family to HD, and unfortunately a lot of our friends and coworkers do not know anything about the disease. I joined after attending an HD convention because I thought it was the most welcoming group of people I had ever met.

### Your mother was on the fence about being tested for the HD gene. What made you want to know your status?

We encourage people not to let their genetic status change how they feel about their lives. But I was in nursing school when everything happened and I had this fear that since my grandma's disease affected her cognitively, I would follow the same pattern. Most HD patients do not realize they are starting to show cognitive symptoms. I feared I would be at work and mix up medications or give a patient the wrong dosage. If I were gene positive I would probably still have finished nursing school but I may have changed my focus.

*\*Anna's and Miranda's last names have not been included at their request*

## 22,197
### PEOPLE FROM 19 COUNTRIES ON 4 CONTINENTS ARE IN THE ENROLL-HD DATABASE
#### (AS OF AUGUST 26, 2019)

# A PLATFORM FOR SUCCESS
*There's more to Enroll-HD than meets the eye*

Enroll-HD is much more than just a single study, it is what researchers refer to as a platform and is at the core of many projects in HD research today. A platform means that the rich database—which includes information from more than 20,000 participants—and all the sites and staff that make up Enroll-HD serve as the foundation for numerous new studies, ideas, projects, and questions in HD research. Enroll-HD is there to make all other research easier.

"Enroll-HD is like a launchpad— it enables new projects to explore the unknown," says Olivia Handley, PhD, platform manager for Enroll-HD. "With this strong hub of expertise serving as our research foundation we can continually add new studies, including providing an existing infrastructure to support collaborators. The aim is to expand the global HD research community and enable more collaboration."

> *"Enroll-HD is like a launchpad— it enables new projects to explore the unknown"*
> *– Olivia Handley*

When a researcher wants to design a study, Enroll-HD is often where they start. First, they request support from the platform. Each request is carefully reviewed by the Enroll-HD governance committees. Studies given the green light then relay details about the type of participants they need (age, HD stage, CAG repeat length, etc.). Enroll-HD staff will then search the database to locate de-identified individuals who meet their study criteria. Each Enroll-HD participant is given an HDID code so that only the staff at the clinical site where that participant is registered knows their name (to learn more visit www.enroll-hd.org/where-does-my-data-go/). These individuals can then be invited by the staff at their Enroll-HD site to take part in the new study. Often the same initial assessment that was conducted for Enroll-HD can be used for the new study, so participants do not have to repeat certain steps.

"The real beauty and strength of Enroll-HD is in the size and scope of the platform," says Handley. "The more scientific questions we can answer, the more HD families can benefit."

Some of the current and planned platform studies include Later Stage HD Assessments, Enroll-HD Lite, HDClarity, and Furst 2.0.

## Later Stage HD Assessments & Enroll-HD Lite – Better, faster, simpler

Measuring and understanding the progression of disease in the moderate to late stages is an important focus for HD research. But the current clinical assessments that researchers use were not designed to measure these later stages and are not sensitive enough to do so accurately.

The aim of Enroll-HD Later Stage HD Assessments (LSA) is to develop shorter, more targeted, and less burdensome assessment tools that are specific to participants in the moderate to late stage of disease. The overall goal is two-fold: to have a more accurate way to measure late stage disease and to ease the burden on late-stage participants and their caregivers.

LSA is an 18-24 month pilot study designed to better understand the disease characteristics and milestones that occur in these later stages, and will begin enrolling in 2020. Participants will be given a shorter assessment, and caregivers can also be interviewed to give their insight into how the participant is doing. "We are mindful of the fact that it may be difficult for patients in the moderate to late stages of disease to get to the clinic and that much of the current assessment may need to be completed by the caregiver," says Handley.

Once the LSA has been developed and validated in late-stage participants, the current plan is to then launch Enroll-HD Lite. "Enroll-HD Lite will be designed to streamline the assessment for moderate- to late-stage participants while obtaining a richer amount of more relevant data," says Handley. "Our task is to better capture this phase of disease by reducing the questions and focusing on the topics that provide valuable information, such as the use of assistive devices, history of hospital admissions, and communication difficulties."

Enroll-HD participants in later stages will be able to transition into Enroll-HD Lite so that their visits are simpler and less time consuming. There may even be a way to participate remotely.

"There is a lot we still don't know about HD in the moderate to late stages of disease. We want to harness a better understanding of this stage of disease and identify the characteristics and milestones that occur," says Handley. "Enroll-HD Lite will focus on developing questions to more accurately assess these later stages of illness and reduce the burden on the participant."

## HDClarity - Looking for a clear advantage

One of the best ways to understand what is happening inside the brain is to look at cerebrospinal fluid (CSF)—a clear liquid that surrounds and protects the brain and spinal cord. Unlike blood or urine samples, CSF is enriched with chemicals that come directly from the brain.

With more than 400 completed sampling visits, HDClarity is the largest collection of CSF in HD research today. Researchers are using these CSF samples to look for what are known as biomarkers—proteins or other chemical substances that provide clues about the changes that happen in the body due to disease.

The goal of HDClarity is to identify biomarkers that change over time in people with HD. These biomarkers can then be used to predict the progression of HD, which is a vitally important first step in designing clinical trials for new drugs.

"Biomarkers are measurements that can tell us if we have protected or improved the health of the brain. They can help us decide if a drug is doing what it was intended to do," explains Ed Wild, MD, PhD, associate director of University College London's Huntington's Disease Centre and principal investigator for HDClarity.

These measurements are also important in preventive trials, adds Wild. Say you give an experimental new drug to a gene-positive individual who currently does not have any HD symptoms. Two years later that same person is still symptom-free. Without biomarkers to measure the underlying biology of HD there is no way to know if the drug worked or if the disease has progressed but is still not yet detectable.

HDClarity is an ongoing study that continually accepts new participants at any stage of disease. Gene-negative participants can also participate as part of the control group. Participants have a minimum of two site visits—an initial screening and then a lumbar puncture or spinal tap, which is similar to the epidural injections routinely given to mothers during childbirth. Wild says the procedure is well tolerated with a local anesthetic.

There are currently 15 HDClarity sites and an additional 25 are being set up. If your Enroll-HD site is not taking part in HDClarity you can visit another site.

To better study HD over time, participants will soon be able to donate CSF as often as every year. "The samples we collect today will continue to be used in research studies for decades to come," says Wild. "We don't know all of the possibilities these samples hold and how technology will advance in the future. My advice is to not wait around for the 'home-run' research trial—get involved now and good things will happen."

## 56,828
### PARTICIPANT VISITS IN TOTAL SINCE ENROLL-HD BEGAN
#### (AS OF AUGUST 26, 2019)



*"My advice is to not wait around for the 'home-run' research trial— get involved now and good things will happen"*
*– Ed Wild*

## FuRST 2.0 - Translating the voice of the participant

Intervening early with effective treatments is likely to be the most promising approach to slowing down the progression of HD. Researchers are working to develop therapeutics that can be given in the earliest stages of disease, as well as in premanifest patients who may not yet have clears signs and symptoms of disease.

Before researchers can test potential new drugs they need to have reliable assessments that can accurately measure the clinical changes during these beginning stages of disease. While there are several rating scales for HD there is not yet one that measures functional ability and specifically targets the premanifest and early-manifest population.

The goal of FuRST 2.0 (Functional Rating Scale) is to develop a clinical assessment that reliably measures functional ability and can detect the very first signs of functional decline in the premanifest and early-manifest population. This scale will be used in clinical trials to measure whether a drug is effective in alleviating that functional decline. HD can manifest in a variety of ways—from motor to cognitive or psychological changes—and all of these can affect function, such as ability to manage finances or complete daily activities. The assessment scale needs to be extremely sensitive to subtle changes.

"It is of utmost importance to hear the voice of the participant," says Pua Feigenbaum, PhD, who managed the FuRST 2.0 cognitive pretesting study. "We listen to the participant and the family members, collect data, and identify the most important areas of interest. They tell us what should be included on the rating scales."

There are several stages in the development of FuRST 2.0, including focus groups and cognitive pretesting, which involve gathering input from the participants. The goal of a cognitive interview is to receive feedback on the quality of the instrument being measured, such as a survey or rating scale. The participants' feedback from the interviews helps improve the wording of the scale to ensure the questions and instructions are easy to understand.

*"It is of utmost importance to hear the voice of the participant"*
*–Pua Feigenbaum*

"FuRST 2.0 is a patient reported outcome measure, which means the information is reported exactly how the participant describes it without input from a physician," says Feigenbaum. "Participants are paramount in helping us determine how the scale should be worded and what information is meaningful to them."

FuRST 2.0 will include two rounds of cognitive pretesting. The first was completed in only five months because participants were recruited from the Enroll-HD study. Researchers interviewed 40 premanifest and 40 early-manifest participants as well as 35 of their caregivers, using the feedback to refine the assessment scale.

The modified rating scale will be given to a second group of premanifest and early-manifest participants together with their companions later this year to get further feedback on the refined scale. HD participants for the second cognitive pretesting study will also be recruited from Enroll-HD.