

 Huntington's Disease
Society of America



50 YEARS OF SERVICE
1967-2017



2017 Research Report

Building a Road to a World Free of HD

“A world free of Huntington’s disease.” That is the vision of HDSA. Those six simple words describe a place all of us in the HD community would like to see. Making our vision a reality requires more than words and dreaming. It requires resources, strategic planning, trial and error, and collaboration where everyone rolls up their sleeves to do their part. The breakthroughs in developing treatments for HD that we seek are now closer than ever. This year in the clinic we saw exciting progress towards therapies for HD, including the first successful safety trial of a huntingtin lowering drug. I am confident that if we focus our efforts on *four* key areas, disease modifying therapies for HD can provide the relief for which families yearn.

The road to a world free of HD must begin with a focus on the patient. There is no more important patient study than Enroll-HD. This year the Enroll-HD observational platform enrolled its 14,000th participant and expanded to 15 countries. In 2017, research on thousands of human samples from Enroll-HD and similar observational studies allowed researchers to identify new drug targets that may be able to halt the onset of HD symptoms. Enroll-HD’s open access database is allowing researchers worldwide to answer questions about HD that simply were not possible until now. The potential of Enroll-HD is so great that HDSA has incorporated participation into our Centers of Excellence program.

HDSA has been seeking to better understand HD in people with our flagship research program, the HD Human Biology Project. Since 2013, HDSA has invested more than \$3.6 million in this program. The research we support is all patient-centric and done in collaboration with HD clinics from around the globe with the goal of understanding HD in the only place it naturally occurs, in *humans*. In this report you will find summaries of the four new HD Human Biology research projects for 2017 that will add to our understanding of HD.

Next, the real world perspective of the HD patient and caregiver will be an essential component in the development of meaningful therapies. To better provide this perspective to drug companies, HDSA, the Huntington Society of Canada and the European Huntington Association launched the HD-Coalition on Patient Engagement (HD-COPE) in 2017. The purpose of HD-COPE is to add quality to all aspects of clinical trials through patient representative input. At HDSA, we know that pharmaceutical and biotechnology companies, as well as regulatory agencies like the FDA, have a unique responsibility and opportunity to work with families to ensure that new treatments offer meaningful benefit to HD families. Together, Enroll-HD, the Human Biology Project, and HD-COPE are critical pieces of HDSA’s patient-focused strategy to support impactful HD research that will help build the road to a world free of HD.

Joining the patients and families on this journey will be our HD scientists. HDSA strongly believes it is our responsibility to ensure the next generation of HD scientists are prepared for what lies ahead. In addition to continuing the Human Biology Project, in 2017 HDSA awarded two Berman-Topper Family HD Career Development Fellowships into Dr. Tamara Maiuri (McMaster University) and Dr. Sarah Hernandez (University of California at Irvine). These three year grants are unlike any young investigator award in the world, providing \$80,000 of annual support for three years. In this report you will also read about the record number of Donald A. King Summer Research Fellows that were

awarded for 2017. Investing in these young scientists now should produce tangible benefits for the HD community in the future.

The third area of focus is on the expansion of care and research sites around the country. All people are entitled to receive expert care for their HD no matter where they live. To address this, HDSA has more than doubled the number of HDSA Centers of Excellence (COEs) in the US to 41 (plus an additional 5 partner sites) since 2015. At these 46 clinics, HD patients can receive multidisciplinary care and participate in HD research. HDSA must continue to provide adequate resources to our COEs to ensure they have the infrastructure in place to handle the HD clinical trials of the future.

The final leg of the journey will require novel drugs and rapidly recruiting clinical trials. In 2017, we all celebrated the approval of a second drug to combat the symptoms associated with HD. In April, the FDA approved Teva Pharmaceuticals' application for Austedo® to treat HD chorea. The importance of adding a new weapon to our clinical arsenal cannot be overstated.

We are encouraged by the December 2017 announcement from Ionis Pharmaceuticals that the first ever antisense oligonucleotide drug was found to successfully lower huntingtin in addition to being safe and tolerable in a Phase 1b/2a clinical trial. This is a tremendous step forward for the HD community, giving us hope for the future of this therapy and providing additional optimism for two new clinical studies that specifically target the expanded huntingtin gene..

Finally, the community must be ready to answer the call for research volunteers to get these disease-modifying trials completed as quickly as possible. There are more than six companies that are in the clinic, or will be shortly, testing huntingtin lowering treatments. To help facilitate participation, HDSA will continue to collaborate with our partners in HD education to increase utilization of HD Trialfinder and its accompanying call center, to match potential participants with studies in their area. The biggest hurdle to completing clinical trials to assess new therapies is how long it takes to recruit; time, and time is simply a luxury HD patients do not have.

As I look back on 2017, I am genuinely excited by the progress that has been made. There are scientific breakthroughs happening now in HD, with more around the corner, and it gives me hope that 2018 will bring us much closer to a "world free of Huntington's disease."

Thank you,



~ George Yohrling, PhD
HDSA Senior Director, Mission & Scientific Affairs





Table of Contents

- 5**
HDSA Awards \$481,000 to Four New HD Human Biology Project Fellowships
- 6**
Summaries of 2017 HDSA-Funded HD Human Biology Projects
- 8**
HDSA Awarded Four Donald A. King Summer Research Fellowships
- 9**
HDSA's 32nd Annual Convention
- 10**
Ensuring the Pipeline of HD Researchers is Primed & Ready
- 11**
HD-COPE - Global Huntington's Disease Patient Advocacy Organizations Unite
- 12**
HD Trialfinder & Dr. Leora Fox Joins the HDSA team
- 13**
How to Use HD Trialfinder
- 14**
Annual Huntington Study Group Meeting
- 15**
12th Annual CHDI Therapeutics Conference
- 16**
Berman-Topper Family HD Career Development Fellowships Awarded & HDSA Webinars
- 17**
Austedo™ Approved by FDA
- 18**
HDSA Announced Forty-one Centers of Excellence
- 19**
2017 HDSA Centers of Excellence Listing
- 20**
Penetrating the Blood-Brain Barrier
- 21**
HDBuzz
- 22**
Enroll-HD & STAIR trial
- 23**
Wave Life Sciences' PRECISION-HD
- 24**
IONIS HTTRx
- 26**
HDSA's Scientific Advisory Board
- 27**
Remembering Dr. Peter Como & Dr. Kimberly Quaid

Huntington's Disease Society of America Awards \$481,000 to Four New HD Human Biology Fellows

This October, the Huntington's Disease Society of America (HDSA) announced that four research grants have been awarded under the Society's largest research initiative the HDSA Huntington's Disease Human Biology Project. Totalling \$481,000, these grants represent HDSA's patient-centric research focus which brings basic and clinical researchers together to facilitate Huntington's disease (HD) science in the human condition, instead of in animal models, with the direct participation of people affected by HD.

"The 2017 HD Human Biology Project continues HDSA's history of providing the necessary resources to scientists

to better understand HD in the only true model of the disease, people", said George Yohrling, PhD, Senior Director, Mission and Scientific Affairs at HDSA. "Our 2017 fellows will pursue innovative and understudied lines of HD research. Their projects will expand our knowledge of HD by investigating topics related to cognitive reserve, GI disruption, biomarker development and novel neuroprotective mechanisms."

HDSA received applications from researchers from all around the world. Ultimately, grants were awarded to four research fellows, from England, Italy and the United States.

The winners and titles of the 2017 HDSA HD Human Biology Project Grants are:

- **Dr. Marta Biagioli**, Assistant Professor, University of Trento, Italy: *CircRNAs, non-coding, stable RNA circles as potential new biomarkers for Huntington's disease.*
 - This work will test the potential of a newly identified blood-based RNA to serve as a biomarker of HD.
- **Dr. Ali Khoshnan**, Senior Research Scientist, California Institute of Technology: *Exploring intestinal dysbiosis and developing Gastrointestinal-based therapeutics for Huntington's disease.*
 - This work will explore the effects the huntingtin gene has in the gut.
- **Dr. Marina Papoutsis**, Postdoctoral Research Fellow, University College London, England: *Variability in cognitive impairment in Huntington's disease: the effect of environment on cognitive reserve.*
 - This work will try to illuminate why there is variability in the degree of thinking capacity in HD.
- **Andrea Ruetenik**, Graduate Student, University of Miami Miller School of Medicine: *The protective role of NAD salvage pathway proteins against mutant huntingtin toxicity.*
 - This work seeks to identify new HD drug targets and novel mechanisms that could protect a person from harmful effects of the huntingtin protein.

"By funding important science from developing young scientists, HDSA's Human Biology Project is actively shaping the scientific progress to treat and ultimately cure HD. As HDSA marks fifty years of working tirelessly to improve the lives of people affected by Huntington's disease, our commitment to research is unwavering. We will not stop until HD no longer destroys families."

- Louise Vetter, HDSA's President & CEO



Summaries of 2017 HDSA-Funded HD Human Biology Projects

In Their Own Words

Dr. Marina Papoutsis,

Postdoctoral Research
Associate, University College
London

*Variability in cognitive impairment
in Huntington's disease: the effect
of environment on cognitive
reserve*



Although CAG repeat length is a strong predictor of when HD symptoms will begin, environmental and lifestyle factors can contribute to variability in the age of onset. Individuals with similar repeat length and pathology, even with identical genetic makeup, can show differences in disease severity, including cognitive impairment. The variability in cognitive performance that cannot be explained by neuropathy or genetic factors is attributed to cognitive reserve. Cognitive reserve builds up across one's lifespan as a result of a cognitively stimulating lifestyle. Research on animal models of HD has shown that exposing animals to an enriched environment during development slows disease progression. In addition, research on HD patients has provided promising results that lifestyle has an effect on disease progression. However, this work has been limited and there is a need for more research. The aim of the proposed project is to characterize the variability in cognitive ability in HD that is not explained by pathology, and understand the contribution of environmental factors to the build-up of cognitive reserve across the lifespan. We will analyze data already available in Track-HD, a longitudinal, observational study, which acquired detailed cognitive, motor and neuroimaging measures in addition to detailed environmental information from both symptomatic and pre-symptomatic HD patients. Our analyses will quantify cognitive reserve in HD, examine its effect on disease progression and, most importantly, identify the contribution of environmental factors to cognitive reserve. Our findings will have important implications for the design of lifestyle interventions and inform guidelines on neuroprotective lifestyle choices for HD patients.

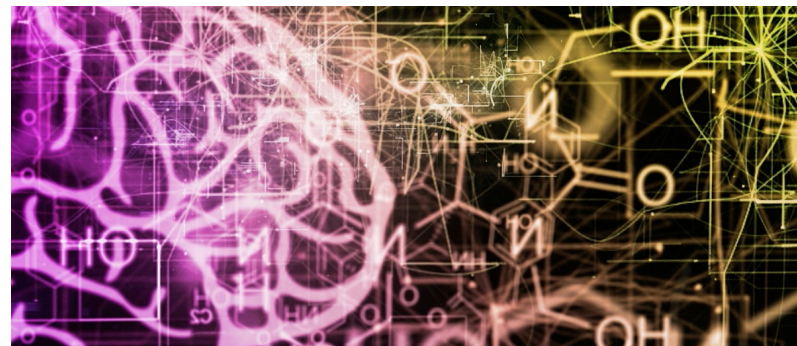
Andrea Ruetenik,

Graduate Student, University
of Miami

*The protective role of NAD salvage
pathway proteins against mutant
huntingtin toxicity*



Previously, our lab worked with a yeast model of Huntington's disease to discover that several proteins that form the NAD⁺ salvage pathway can protect against the adverse effects usually caused by mutant huntingtin. We further found that overexpression of NAD⁺ salvage pathway proteins helped to degrade 103Q oligomers in these cells, independent of NAD⁺ levels. Our preliminary studies have further demonstrated that these NAD⁺ salvage pathway proteins have an innate chaperone function in vitro and that catalytically inactive forms of these salvage pathway proteins can also protect against 103Q toxicity in vivo. We therefore propose that these NAD⁺ salvage pathway proteins have a previously undiscovered, dual function in the cell, and can moonlight as chaperone proteins. We propose to continue our investigations, with the help of this funding, to elucidate more specifically how these proteins are acting as chaperones, and how these findings translate to human patient-derived cells. This research will give us a greater understanding of the complexities of Huntington's disease, as well as other diseases of protein misfolding, and will potentially open the door to new therapeutic protein and pathway targets.



Dr. Ali Khoshnan,

Senior Research Scientist,
California Institute of
Technology

*Exploring intestinal dysbiosis and
developing GI-based therapeutics
for Huntington's disease*



Disruptions to the gastrointestinal (GI) tract and the homeostasis of intestinal microbiota are implicated in several brain disorders. HD patients display GI symptoms and metabolic abnormalities like extreme weight loss. However, the cause and contribution of GI dysfunction to the progression of neurological symptoms has not been investigated. We hypothesize that HD patients have altered intestinal microbiota (dysbiosis), which may contribute to GI dysfunction, systemic inflammation, mutant huntingtin (mHTT) aggregation, and brain pathology. In support of this hypothesis, we find that inflammatory bacterial products promote the oligomerization of mHTT in neurons, immune cells derived from HD patients, and epithelial cells. Moreover, in *Drosophila* models of HD, inflammation-inducing bacteria promote the aggregation of mutant HTT and exacerbate motor behavior. This project will explore whether the homeostasis of intestinal bacteria is altered in HD patients. We plan to profile the microbiome of pre-symptomatic and symptomatic HD patients by 16S RNA sequencing and identify bacterial species that could be overpopulated or eliminated. We also plan to develop qPCR protocols to quantify selected bacteria, which might be linked to different stages of clinical symptoms in HD. Finally, we propose to examine whether intestinal microbiota regulates the oligomerization of mutant HTT in the enteric nervous system and contributes to the development of CNS symptoms in a preclinical mouse model of HD. Studies on the microbiota of HD patients may ultimately identify novel pathogenic mechanisms, easy to access biomarkers, and GI-based therapeutics.

Dr. Marta Biagioli,

Assistant Professor,
University of Trento, Italy
*CircRNAs, non-coding, stable RNA
circles as potential new bio-markers
for Huntington's disease*



Although there are currently no available treatments that modify the onset or progression of HD, a number of therapeutic strategies are under investigation or even in clinical trials to reduce or block transcription from the mutant HTT allele. This includes antisense oligonucleotides, gene correction through CRISPR/Cas9, and other genetic techniques. Therefore, there is an increasing need to develop and validate biomarkers in accessible biofluids (such as blood) to either follow disease progression (prognostic biomarkers) and/or to predict treatment outcomes (predictive biomarkers). Since a valuable biomarker must be objectively measured and easily evaluated during the pathogenic process or therapeutic intervention, a variety of molecules such as small RNAs, proteins or metabolites can be taken into consideration. Here, for the first time in HD, we aim to focus, detect and characterize circRNAs in peripheral blood. CircRNAs are highly abundant and stable non-coding circular transcripts, enriched in brain districts and permeable to the blood brain barrier. We will investigate these molecules in a cohort of gender and age matched healthy and HD individuals in pre-manifest, in the first stages (stage I and II) and in the advanced stages (stage III and over) of disease. We aim to characterize the expression pattern of circRNAs in blood samples from HD patients, to correlate specific circRNAs with disease progression (prodromic vs early and late stages), and to develop a sensitive RT-qPCR assay for the detection and quantification of specific CAG-sensitive circRNAs to be used as reliable disease biomarkers in HD.



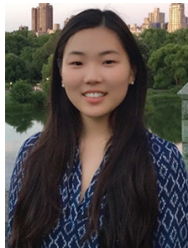
Huntington's Disease Society of America Awarded Four 2017 Donald A. King Summer Research Fellowships

The Donald A. King Summer Research Fellowship is a vital program to train the next generation of scientists with research expertise in Huntington's disease. HDSA established the Donald A. King Summer Research Fellowship program in 2005 in honor of Donald King who passed away in 2004. Don was a tireless advocate for HD families and served as HDSA's Chairman of the Board from 1999 to 2003.

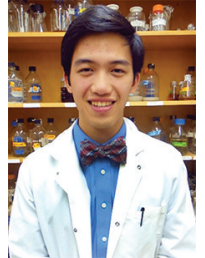
The purpose of this fellowship program is two-fold: First, to attract the brightest young scientists into the field of Huntington's disease research, and second, to facilitate meaningful HD research to clarify the biological mechanisms underlying HD pathology. Applicants are evaluated by the quality of their personal academic achievements, their mentoring plan, the scientific rigor of their experimental design, and feasibility to achieve significant deliverables in a short summer timeframe.

After rigorous review by the HDSA's Scientific Advisory Board, four young scientists were awarded 2017 Donald A. King Summer Research Fellowships. Fellows will present the outcomes of their projects to the HD community at the 2018 HDSA Annual Convention in Los Angeles.

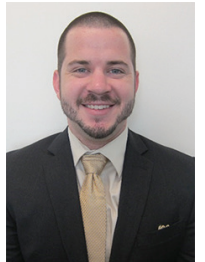
- **Ms. Kiryung Kim** (Columbia University) spent the summer working with Ai Yamamoto, PhD to elucidate the molecular mechanism of Alfy-mediated mutant huntingtin aggregate clearance.



- **Mr. Paul Elizalde** (The Catholic University of America) worked under the guidance of John Choy, PhD on a project that aims to better define the underlying mechanisms of neurodegeneration in Huntington's disease.



- **Mr. Christopher Yanick** (University of Central Florida) worked with current HDSA Human Biology Project fellow, Amber Southwell, PhD to investigate mutant huntingtin protein levels in the cerebrospinal fluid of HD patients to refine its use as a biomarker in future huntingtin lowering trials.



- **Ms. Teal Jenkins** (University of Washington Medical School) spent the summer working at the University of Wyoming in the laboratory of Jonathan Fox, PhD. She studied the effect of latent Toxoplasma gondii infection on neurodegeneration in the YAC128 Huntington's disease mouse model.



We look forward to hearing about their promising research at the 2018 HDSA Convention in Los Angeles.



Save the Date!

Join us for the **33rd Annual HDSA Convention** in the city of stars — Los Angeles, California — at the Los Angeles Airport Marriott.

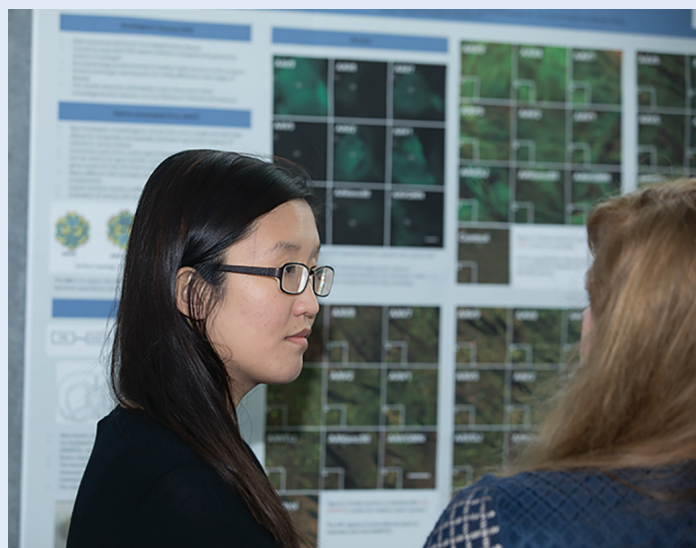
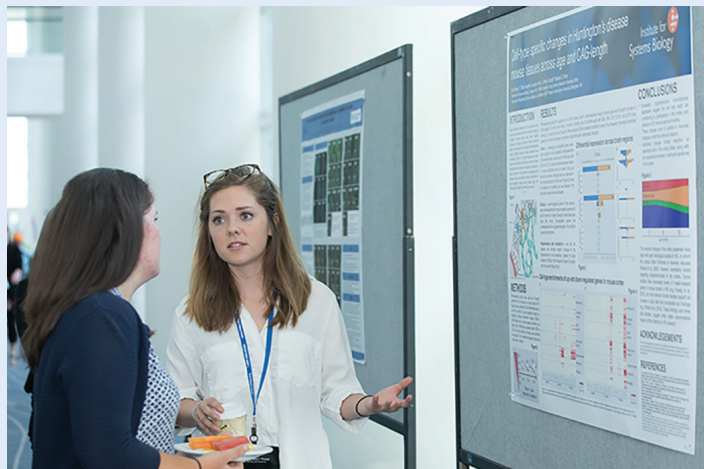


June 7-9, 2018 / Los Angeles, CA

Stay tuned for more details at HDSA.org



4th Annual Donald King Research Session at the 2017 HDSA Convention in Schaumburg, Illinois



2016 Donald King Fellows, Dani Bergey (above), ShuJuan Zheng (right) are shown presenting the findings of their research to the attendees of the 2017 HDSA Convention in Schaumburg, Illinois.

Drs. Cattaneo, Wild and Carroll speak at the 2017 HDSA Annual Convention



Keynote Address Speaker Dr. Elena Cattaneo (left), Director of the Laboratory of Stem Cell Biology and Pharmacology of Neurodegenerative Diseases at the Department of Biosciences at the University of Milan, addresses the nearly 1,000 attendees of the 2017 HDSA Convention in Schaumburg, Illinois at the annual Research Forum. Drs. Ed Wild and Jeff Carroll (right) provide Convention-goers with an entertaining review of the year in HD research.

Ensuring the Pipeline of HD Researchers is Primed and Ready

A goal of the HDSA research programs is to provide the resources and support to the brightest and best researchers around the globe to ensure they have what they need to bring impactful treatments to HD patients as quickly as possible. HDSA asked their current research fellows what the grant support from HDSA meant to them. Here is what they had to say.

“The HDSA does an amazing job of expediting the [grants] process. Support from the HDSA means that researchers can get to work on their ideas as fast as possible. Especially for diseases like HD, where patients are waiting for a treatment or cure, this is incredibly important.”

-Sarah Hernandez, 2017 Berman-Topper Fellow

“The HDSA grant support allows me to do what I most love in life (research) and gives me the motivation necessary to successfully carry out my research project. In addition, being awarded with the HDSA HD Human Biology Fellowship made me feel recognized as a good researcher, deserving the trust and support of a prestigious organization. This grant support will help me to become an independent investigator and increase my chances to be a professor, which, overall, is my main professional goal.”

-Natalia Pessoa Rocha, 2017 HD Human Biology Fellow

“The fact that I was now working with HDSA and invited to the Convention, it became more personal. You start developing a direct relationship with the patient community. Meeting the families that are funding me, putting that story into my daily work, creates new motivation.”

-Ricardo Mouro Pinto, 2016 Berman-Topper Fellow

“I'm very proud and grateful for this opportunity – it meant a lot to me to get this grant. It gave me the time to work on getting my results published, helped me to get attention and support from the HD community, and allowed me to understand whether the work could be impactful for patients. The Human Biology Project gave me the opportunity to establish collaborations with international researchers, and led me to think about my career goals. I have been supported by this grant and motivated by the expectations of the HD community during the process of applying for jobs, and right now I am establishing myself as an HD researcher with my own lab.”

-Rocio Gomez-Pastor, 2017 HD Human Biology Fellow

“The grant support from HDSA has allowed me to pursue a project that was in the early stages of development and has now developed to address important questions in HD and to provide the basis to pursue additional funding. Also, early in my career, family circumstances affected my career path such that my route to independence has been indirect and non-traditional. Grant support from HDSA has also given me the opportunity to establish myself as an investigator with independent funding.”

-Lisa Salazar, 2017 HD Human Biology Fellow

“Support from the HDSA Human Biology Project bolsters my development as a scientist. It allowed me to attend an international conference where I networked with leaders in my field and received invaluable feedback on my project. It allows me to pursue translational research in a department that is mostly focused on basic science. Finally, it allows me to work with the HD community which keeps me dialed-in to what this disease means to the people it affects.”

-Steven Marinero, 2017 HD Human Biology Fellow



Global Huntington's Disease Patient Advocacy Organizations Unite to Form Huntington's Disease Coalition for Patient Engagement (HD-COPE)

In September of 2017, the European Huntington Association (EHA), Huntington's Disease Society of America (HDSA) and Huntington Society of Canada (HSC) announced the formation of the Huntington's Disease Coalition for Patient Engagement (HD-COPE), a new global coalition to give families who are affected by Huntington disease (HD) a direct and impactful voice in HD clinical research.

HD-COPE will replace the current ad hoc approach to incorporate the patient voice in therapeutic development efforts in Huntington's disease with a coordinated and consistently knowledgeable mechanism to contribute HD community experience to regulators, industry and researchers. Patient-oriented input is highly needed to meet the needs of the patient community, speed up recruitment and increase retention for all HD clinical trials.

The HD-COPE Advisory Board, comprised of the senior staff of each member organization, will provide counsel to clinical research leaders on broad issues involving patient feedback, community needs and research recruitment. The Advisory Board will also manage a global HD-COPE Team of HD family representatives. Team members will be a select group of volunteers from HD families in each member region who meet the expectations of experience and availability to participate in global clinical research meetings.

"The most effective clinical research meets the therapeutic needs that patients and families have personally identified," said Louise Vetter, President and Chief Executive Officer

of the Huntington's Disease Society of America. "HD-COPE will ensure that HD affected families are true partners in clinical research by expanding their role from simply being trial participants to ensuring that the trials have their perspectives, values and thoughts on risks and benefits incorporated from the start. It fundamentally changes HD clinical research from being 'for' or 'about' HD families to being 'with' and 'by' them."

Astri Arnesen, President European Huntington Association added "Our voice matters and by uniting in a global coalition, we will make our voice stronger. I am convinced that contribution from HD-COPE will add value to all aspects of clinical research because we have a unique perspective and knowledge about HD."

"The global Huntington disease community is relatively small compared to other disease communities, which has created the need for us to work collaboratively with no borders. HD-COPE is an example of global HD lay organizations being the conduit of information between pharma and the HD communities to ensure the success of clinical trials. I am optimistic that the facilitation of equal collaboration between the key stakeholders will expedite the path to viable treatments for HD," said Bev Heim-Myers, Chief Executive Officer of the Huntington Society of Canada.



HD Trialfinder: A One Stop Shop to Find Currently Recruiting Trials

HD Trialfinder (www.HDTrialfinder.org) is an essential resource for all members of the HD community. HD Trialfinder is a free, easy-to-use clinical trial matching service that connects individuals with Huntington's disease, caregivers, healthy volunteers and physicians with current studies. Its continuously updated database includes interventional, observational and biomarker studies being conducted at clinical trial sites across North America. Since its launch, nearly 3,000 HD Trialfinder profiles have been established by people affected by HD looking for ways to make a difference.

In 2017, HDSA expanded access to the live call center component to HDTrialfinder. Now, HD families can call 866-890-6612 between 9:00 a.m. and 6:00 p.m. Eastern time and speak to an HDSA-trained Clinical Trial Navigator. The Navigator is there to assist families with customer service needs related to the HDTrialfinder.org website as well as to provide important clinical trial information to those who may not have access to a computer. For those who would prefer to search independently, HDTrialfinder is available online 24/7.

Currently, there are clinical research opportunities for every member of the Huntington's community to join. Unlike other websites like clinicaltrials.gov, which are not HD patient focused, HD Trialfinder works closely with corporate and

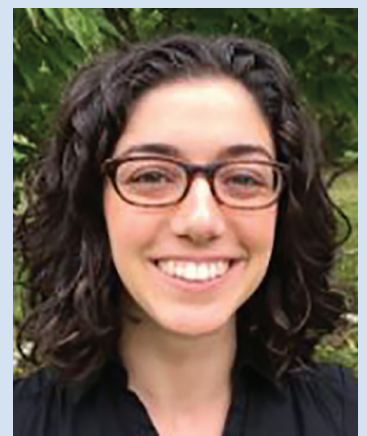
academic partners to provide information about all currently recruiting HD trials in lay language that is easy for HD families to understand.

"Generations of HD families have been waiting for the day when potential drugs to effectively treat this terrible disease would reach the clinic," says George Yohrling, PhD, Senior Director, Mission and Scientific Affairs at HDSA. "HD Trialfinder can empower the HD community to answer the call and join in the fight against HD by participating in today's clinical trials that could lead to tomorrow's cure."

HD Trialfinder was created to be a resource for the entire HD community. Numerous HD organizations such as HDBuzz have all joined HDSA as partners in clinical trial awareness and education by promoting use of HD Trialfinder among their constituents. Dr. Ed Wild of HD Buzz said "HD Trialfinder is one of the most valuable tools the HD community has at its disposal. I spend a lot of time and effort educating the HD community about HD research and try to get them motivated and excited to take part in clinical trials. HD Trialfinder brilliantly capitalizes on that motivation, supplying up-to-date, customized research opportunities and connecting patients to researchers in a few mouse clicks. It is a critical tool for recruiting the volunteers we need to help beat Huntington's disease."

HDSA Expands Research and Science Communications with a New Hire

As HDSA's research programs grow, so does our need for help to work on important projects like assisting HDSA supported scientists, coordinating the HDSA Scientific Advisory Board and raising awareness of clinical trials. In August 2017, Dr. Leora Fox joined the HDSA team as Manager of Research and Mission Programs. Previously an HD researcher, medical writer, and contributing author at HDBuzz, Dr. Fox works closely with Dr. George Yohrling to support HDSA's research efforts. She maintains HDTrialfinder.org by reaching out to clinical researchers throughout North America, works closely with HDSA fellows to support their progress and communicate their work, and creates oral and written materials to explain the science behind current trials. She is passionate about communicating science to the HD community so that families can keep abreast of scientific progress and make informed decisions about participating in clinical research.



How to Use HD Trialfinder

Step 1

Go to www.hdtrialfinder.org to create an account or log in if you already have a username and password or, dial 866-890-6612 between 9am and 6pm EDT to speak with an HD Clinical Trial Navigator.

Step 2


Complete a brief questionnaire about yourself or the HD impacted individual.

Step 3


Review your clinical trial match results. HD TrialFinder will compare your unique profile to its comprehensive, continually updated clinical trial database.

Step 4


Contact your nearest HD clinical center to speak with a study coordinator and get involved. As new clinical trial sites become active in your local area, HD TrialFinder will automatically notify you.



Hope for tomorrow begins with your involvement today!




[Request a Contact](#)
or
Search by Phone
[1-866-890-6612](tel:1-866-890-6612)
(local) [646-277-4062](tel:646-277-4062)
Monday - Friday, 9:00 am - 6:00 pm ET
Se Habla Español




[Search Online](#)
Complete our online questionnaire to identify trials nationwide looking for people with your exact diagnosis, stage and treatment history.


HD Trialfinder got a fresh new look in 2017 and expanded call center hours.



Convenience
In a few minutes you can identify all clinical trials that match your profile and the closest trial sites. We can also update you when new studies open that match your profile.



Support
Need help with your search or connecting with trial sites? [Request a Contact](#) to speak with a Clinical Trial Navigator today. We're here to help.



Privacy
Our commitment to privacy and security is uncompromising. Please read our [Privacy Policy](#).
HDSA will not have access to your name or contact information unless you specifically request HDSA to contact you.

Facts about HD Trialfinder

- Since its launch in 2015, more than 2900 people have signed up for HD Trialfinder.
- There are nearly 20 different HD clinical trial opportunities in the HD Trialfinder database that are looking for participants.
- HD Trialfinder listings are updated daily to provide HD families with the most up-to-date HD clinical trial information.
- Only North American trials that are currently recruiting participants are listed in the HD Trialfinder database. When a trial is full or recruitment has stopped, it is no longer promoted through HD Trialfinder.
- Unlike other resources, HD Trialfinder provides direct contact information to the sites nearest you (not just a national clearinghouse number) so that you have a name, phone number and email for a real person who you can contact and help you get involved.
- HD Trialfinder is the only HD-specific clinical trial navigation resource for HD families to offer customer support with Clinical Trial Navigators who are there to support you and follow-up with you to help you get involved.

Huntingtin Lowering Programs Showcased at Annual Huntington Study Group Meeting

In November 2017 a record number of approximately 500 researchers, clinicians, advocates and members of the local HD community convened in Denver, Colorado to discuss the latest breakthroughs in HD clinical research at the annual Huntington Study Group (HSG) conference entitled "HSG 2017: Elevating HD!".

Sessions covered topics from basic biology, as well as biomarkers, care and clinical trials. Of note, Dr. Jody Cory-Bloom, Director of the HDSA Center of Excellence at UCSD presented preliminary data on their investigation to see if they could accurately measure the huntingtin protein in the saliva of HD patients. To their surprise, they were able to detect huntingtin using antibodies. If they can confirm that the levels they observe in the saliva reflect brain huntingtin levels, this could spur the development of a less invasive way to collect patient biosamples in the clinic. One major goal of biomarker research is to determine if current therapies aimed at lowering huntingtin are working. More advanced biomarker work was presented by Dr. Blair Leavitt (University of British Columbia and HDSA Scientific Advisory Board Member) and Dr. Ed Wild (University College London). They took part in a workshop that discussed the recent advances in biomarker research, presenting their work on developing tests to measure huntingtin and neurofilament light chain in the cerebral spinal fluid (CSF) and plasma of HD patients, respectively.

As in years past, the HSG invited three HDSA Human Biology Project Fellows (Dr. Amber Southwell, University of Central Florida, Dr. Daniel Wilton, Boston Children's Hospital, and Dr. Lisa Salazar, UC-Irvine) to attend and present their patient focused research findings to the HD research community.



The first day concluded with a session completely dedicated to companies working on huntingtin lowering therapies. Ionis, Roche, Wave Life Sciences, Voyager, uniQure and Nuredis all presented overviews of their technologies and updates on their clinical progress.

The final day of the HSG conference was an HD Family Education Day. During the morning, attendees got an update on the drug development pipeline from Drs. Ed Wild and Jeff Carroll of HDBuzz. The meeting closed with an emotional recap of the HD advocacy event of the decade, the May 18th meeting of HD families with Pope Francis in Vatican City.

12th Annual CHDI Therapeutics Conference in Malta

In 2017, CHDI Foundation, a privately-funded, not-for-profit biomedical research organization devoted to HD, hosted approximately 350 HD researchers, clinicians and drug hunters in St Julian's, Malta for four days of scientific updates on the progress being made to bring effective therapies forward for HD. As in years past, the tone for the conference was set by an incredibly moving and deeply personal family story presented by Kate and Justin Miner, Jeff and Debbie Mulligan, Jenne and Blake Coler-Dark and Rebecca Johnson.

Over the course of the next three days, attendees were treated to five diverse scientific sessions on topics that covered: the use of unbiased systems biology to identify new targets for HD, the function/structure of the huntingtin protein, approaches to lower levels of the huntingtin protein, neuronal dysfunction in HD, and novel emerging opportunities for HD therapeutic development.

Scientific bias can be a big problem in research. To avoid introducing this into HD research, Leslie Jones presented recent work where her team used a computational approach to analyze a large amount of human genetic data associated with the moment an HD patient first has motor symptom onset. They reported that this unbiased approach revealed that biological pathways associated with how our bodies repair our own DNA may be involved in the onset of HD. Validation of a large number of genes in this pathway is now underway to see if a viable drug discovery program could eventually be developed to correct the DNA repair abnormalities in HD patients.

Despite the identification of the HD gene in 1993, there is still much we need to learn about its structure and function. Darren Monckton from Scotland enlightened the audience on the topic of somatic instability. Somatic instability in HD relates to the expansion of the CAG repeat over time. The HD CAG repeat is unstable, and can undergo progressive length increases over time, particularly in brain regions that are the targets of neurodegeneration. Kevin Meeks (University of North Carolina) presented work

on the actual structure of the CAG repeat within RNA. They have found that the CAG repeat forms long hairpin-like structures that can be toxic to neurons. His team is now looking for small molecules that could prevent these hairpin structures from forming. This would represent a completely novel approach to tackling HD.

Another novel drug discovery approach came from Liz Doherty from CHDI Foundation. CHDI is screening hundreds of thousands of compounds to see if they can find one that will decrease the amount of soluble huntingtin in HD patient-derived cells. Doherty reported that they have identified a number of novel "hits" in their drug screen. Additional studies are currently underway to determine the mechanism by which the compounds are lowering huntingtin. Current therapies in the clinic that target the huntingtin gene require invasive dosing such as a spinal tap or an injection directly into the brain tissue. In the future, approaches like CHDI's could offer a much less invasive and safer dosing paradigm when treating HD.

It was exciting to see non-traditional HD researchers using their technology to take a fresh look at HD. James Kozloski from IBM Research presented on work they are doing in partnership with CHDI Foundation, using computer models to understand how brain circuits become dysfunctional in HD. Using data from the TRACK-HD, ENROLL-HD and PREDICT-HD studies, IBM is creating a new model of HD progression. Their model can predict behavioral decline in pre-manifest HD over time using only MRI brain images.

Overall, the data presented at the 12th CHDI Therapeutics Conference demonstrate that the field is making dramatic progress in a uniquely collaborative manner. We are excited to hear about progress on all these projects at the 2018 CHDI Conference scheduled for February 26-March 1 in Palm Springs, CA.



Huntington's Disease Society of America Awards Berman-Topper Family HD Career Development Fellowships

In May of 2017, the Huntington's Disease Society of America (HDSA) announced that Dr. Tamara Maiuri (McMaster University) and Dr. Sarah Hernandez (University of California at Irvine) had been awarded HDSA Berman-Topper Family HD Career Development Fellowships for 2017.

These prestigious fellowships, made possible due to the generosity of the Berman and Topper families and the CHDI Foundation, provide up to \$80,000 of funding per year for three years to young scientists and clinicians who desire to make Huntington's disease (HD) part of their long-term career plan.

"On behalf of the Topper and Berman families, I would like to congratulate Drs. Maiuri and Hernandez on being named 2017 recipients of this fellowship," said Michael Berman. "Our hope is that the work of these two outstanding young scientists will lead to greater understanding of HD and accelerate the search for effective therapies for Huntington's disease. We sincerely appreciate the support of CHDI, HDSA and its Scientific Advisory Board."

HDSA received applications from researchers from all around the world for this competitive grant. Dr. Maiuri's project will investigate the role of the huntingtin protein in DNA repair and search for small molecules that affect



Dr. Tamara Maiuri and Dr. Sarah Hernandez

huntingtin and its oxidative stress interacting proteins. Dr. Hernandez's research will utilize patient-derived stem cells to elucidate the dysfunction of the extracellular matrix (the infrastructure of cells) in HD neurons and test ways to positively restore HD cellular function.

"Proposed cuts to the budget of the National Institutes of Health (NIH), a major supporter of HD research, have expanded the importance of non-profit disease organizations like HDSA, to ensure that the HD scientists and clinicians of the future have the resources and opportunities they need to succeed today," said George Yohrling, PhD, Senior Director, Mission and Scientific Affairs at HDSA.

HDSA Research Webinars Let Families Hear Directly from HD Researchers

HDSA remains committed to improving research communication between HD families, patients and scientists around the world. To achieve this, HDSA hosts a monthly HD Research Webinar Series. The webinars cover a variety of research topics presented by HD experts from around the globe. These webinars run for approximately 30-40 minutes, with 20-30 minutes dedicated to a question and answer session through a chat feature of the webinar software.

This year's topics included a research year in review, the PRIDE-HD and SIGNAL clinical trial results, identification of novel drug targets for HD and discussion on a potential new blood-based biomarker that could track HD progression. If you missed one, don't worry. Each Research Webinar is recorded and archived on HDSA's YouTube channel. Make sure you sign up for email alerts from HDSA to stay informed of more great webinars starting again in January 2018!

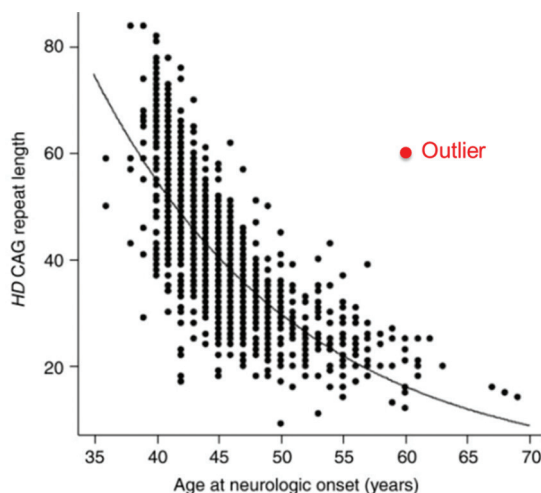


Tracking Down Genetic Modifiers of HD: Next Generation of HD Drug Targets

Ever wonder why one person with 42 CAGs develops symptoms at 40 years old, but another person with 42 CAGs in the same family might first show symptoms at 60? Well, so have scientists, and this year we are steps closer to better understanding reasons for these “outliers.” Dr. Davina Hensman-Moss, one of the lead authors of an exciting 2017 *Lancet Neurology* paper from the University College London HD Centre revealed that they have identified a new gene that could be a target for treating Huntington’s disease.

The research team used data from the recently completed TRACK-HD study to better understand the rates of HD progression. They then looked through the whole genome to see if changes in other genes could account for large differences in age of HD symptom onset or rate of progression. They found a significant result in their sample of 216 people, which they then confirmed in a larger sample of 1,773 people from the REGISTRY study.

The signal they found belonged to a variation in a gene



called MSH3. MSH3 is a DNA repair gene which has been linked to changes in size of the HD mutation. The researchers identified a variation in MSH3 that encodes an amino acid change in the gene. Interestingly, many years

earlier, MSH3 had been flagged as an influencer of HD behavior and damage in both mouse and cell studies. When researchers knock out or inhibit the expression of the MSH3 gene, expansion of the huntingtin gene is prevented. The group’s findings may also be relevant to all the other polyglutamine expansion diseases, such as spinocerebellar ataxia.

Work is currently underway to better understand the role of MSH3 in the context of HD and to determine if

inhibition of this gene is a viable path forward for HD drug discovery efforts. What gives us hope is the fact that Mother Nature has already performed the first validating experiment for MSH3 in HD patients to tell us that we can in fact modify the course of HD. Now it is up to researchers to see if they can develop safe drugs that can mimic the effects of the MSH3 mutation.

AUSTEDO™ (deutetrabenazine) approved by FDA for use in HD

On April 4th of 2017, Teva Pharmaceuticals announced the FDA approval of their drug deutetrabenazine, marketed as Austedo®. The second medication ever to be approved in the US for the treatment of Huntington’s disease, Austedo® treats symptoms of chorea in HD, and was tested in two Phase III clinical trials known as First-HD and ARC-HD. In these trials, Austedo® significantly improved chorea compared to a placebo and was shown to be safe for patients switching over from tetrabenazine (Xenazine®).

Both tetrabenazine (Xenazine®) and deutetrabenazine (Austedo®) are taken orally, and they act on the brain by quieting chemical communication between cells. Both drugs prevent the packaging of the chemical messenger

dopamine, so fewer impulses pass from cell to cell, leading to fewer involuntary movements. The difference is that Austedo® has a

structural tweak allowing it to stick around longer in the bloodstream. This means fewer doses, and in some cases, fewer side effects. Austedo® is a long-awaited new treatment option for managing chorea in HD. Its FDA approval also heightens awareness of HD and the need for further therapeutic resources.



HDSA Announced Forty-one Centers of Excellence in 2017

This February, the Huntington's Disease Society of America (HDSA) announced that forty-one outstanding Huntington's disease care facilities were being awarded the designation of HDSA Center of Excellence for 2017.

The 2017 HDSA Centers of Excellence program expanded to 41 Centers from 39 last year, 29 in 2015 and 20 in 2014 – a more than 100 percent increase in three years. The HDSA Centers of Excellence are multi-disciplinary care teams with expertise in Huntington's disease that share an exemplary commitment to providing comprehensive care.

With the growth of the program, HDSA is bringing more 'boots on the ground' to support HD-affected families across the United States with care locations in 29 states plus the District of Columbia. In addition, three Centers have partner sites to expand care in Oregon, North Dakota and South Dakota. In 2017, HDSA awarded a total of \$1,159,750 to the Centers of Excellence, an increase of \$67,750 from last year.

"We are deeply committed to helping families affected by HD access experienced care," said Louise Vetter, HDSA's Chief Executive Officer. "The expansion of the HDSA Center of Excellence program to more than forty

clinical care centers helps reduce the distance many families have to travel to find comprehensive HD services and increases access to the life changing treatment and research opportunities that drive us forward towards finding a cure for this disease."

The HDSA Centers of Excellence provide an elite team approach to Huntington's disease care and research. Patients benefit from expert neurologists, psychiatrists, therapists, counselors and other professionals who have extensive experience working with families affected by HD and who work collaboratively to help families plan the best HD care program throughout the course of the disease. Applications to become an HDSA Center of Excellence are open to all clinics in the United States who share HDSA's commitment to high-quality, comprehensive care and access to clinical research.

Ms. Vetter added, "HDSA Centers of Excellence share a common dedication to HD families. We are incredibly thankful to the clinical care teams who are able to provide incredible care with these modest awards and to the families whose generous support of HDSA's mission make these awards possible."

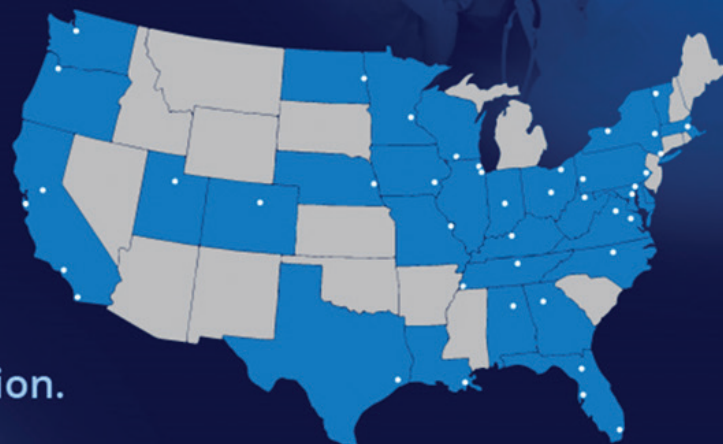


HDSA Centers of Excellence Directors

INCREASED SUPPORT

Huntington's Disease Society of America
Centers of Excellence

HDSA has expanded its Centers of Excellence program to forty-one clinics across the nation.



The 2017 HDSA Center of Excellence grantees are listed below alphabetically:

Blue = NEW COE for 2017

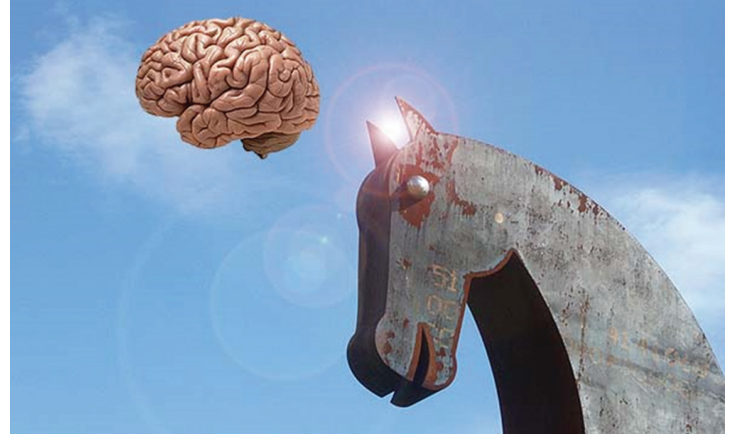
- Albany Medical College (NY)
- Beth Israel Deaconess Medical Center (MA)
- Cleveland Clinic (OH)
- Colorado Neurological Institute
- Columbia Health Sciences/NYS Psychiatric Institute (NY)
- Duke University (NC)
- Emory University (GA)
- Georgetown University (DC)
- Hennepin County Medical Center (MN)
- Indiana University
- Johns Hopkins University (MD)
- Massachusetts General Hospital
- **Northwestern University (IL)**
- Ochsner Health System (LA)
- Ohio State University
- Rush University Medical Center (IL)
- University of Alabama, Birmingham
- University of California, Davis Medical Center
- University of California, Los Angeles
- University of California, San Diego
- University of California, San Francisco
- University of Colorado
- University of Florida
- University of Iowa
- University of Louisville (KY)
- University of Miami (FL)
- University of Nebraska Medical Center
- University of Pennsylvania
- University of Pittsburgh Medical Center (PA)
- University of Rochester (NY)
- University of South Florida
- **University of Tennessee – Memphis**
- University of Texas Health Science Center – Houston
- University of Utah
- University of Vermont, Frederick Binter Center for Parkinson's Disease & Movement Disorders
- University of Virginia
- University of Washington (WA)
- **University of Wisconsin**
- Vanderbilt University Medical Center (TN)
- Virginia Commonwealth University
- Washington University School of Medicine (MO)

Building a Better Trojan Horse to Penetrate the Blood-Brain Barrier (Wall)

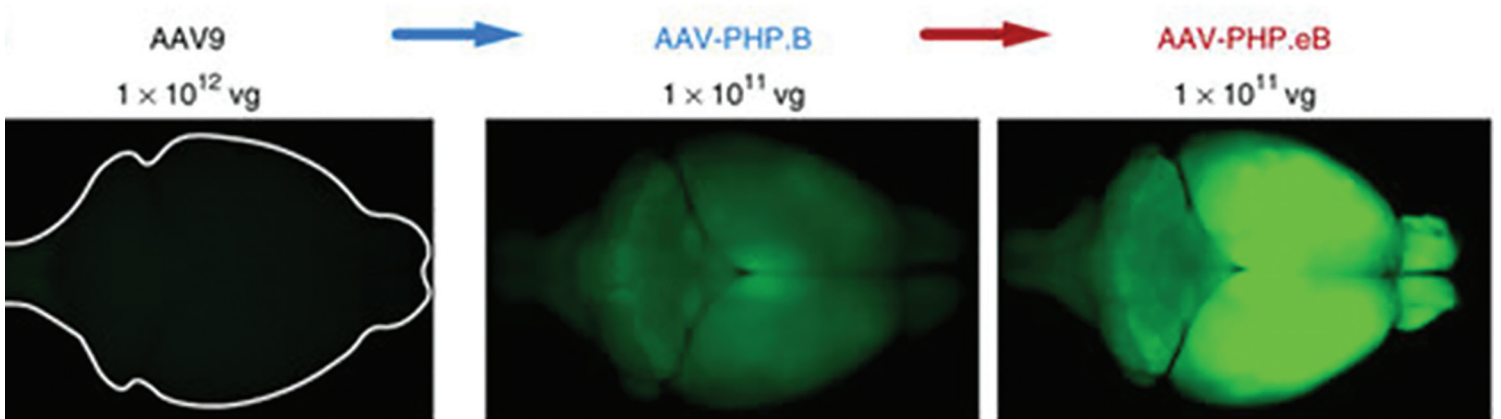
Treating neurological disorders such as HD is made more difficult by the presence of the blood-brain barrier (BBB). The BBB is there to defend our brain against unwanted invaders, like bacteria. However, when you want to get a drug into the brain, sometimes the BBB is just too good at its job. There are now three clinical trials underway testing the safety of antisense oligonucleotides as a potential treatment for HD. These are delivered via a spinal tap (lumbar puncture) in an attempt to get the drug into the brain via the spinal fluid that bathes the brain and avoid the BBB.

A new class of therapies advancing quickly in the HD pipeline will require an injection directly into the brain with adeno-associated viruses (AAV) that will deliver huntingtin RNA-interfering drugs. The administration of such drugs cannot be performed in a standard physician's clinic. This would require inpatient neurosurgery where precise needles would be directed into a specific brain region to deliver the huntingtin lowering agent. A potentially more palatable approach would be to administer these viruses via an intravenous infusion, much like chemotherapy is performed in an oncologist's office.

Until now, getting viruses containing gene silencing therapies into the brain with traditional dosing methods (orally or intravenous) was not possible, but new research in mice holds promise for the future. AAV9 has been the benchmark for reaching the striatum, the region of the brain



first affected in HD. However, as you can see in the figure, AAV9 does not readily cross the blood-brain barrier of a mouse upon intravenous administration. Recent work out of the California Institute of Technology has demonstrated that with some minor genetic modifications to an existing AAV called AAV-PHP.B, the ability of brain cells to take up the virus (transduction efficiency) with intravenous dosing was significantly improved. The researchers found that one injection of AAV-PHP.eB could enter 69% and 55% of the cortical and striatal neurons respectively in an adult mouse (Chan, KY et al, 2017, Nature Neurosci). This new virus is referred to as AAV-PHP.eB. This drug delivery technology could open many opportunities to treat a multitude of diseases of the brain in a much less invasive manner.



The increased green light indicates that the modified AAV-PHP.eB virus has dramatically enhanced brain penetration upon a single intravenous administration over AAV9 and AAV-PHP.B (figure from Chan KY et al).

HDBuzz HD Science...Simplified



Drs. Jeff Carroll & Ed. Wild presenting at HDSA's National Convention

HDSA is proud to be a founding supporter of HDBuzz, a website devoted to clear and effective communication of Huntington's disease science. At HDBuzz.net, scientists explain recent HD research and news reports in plain language. HDBuzz articles have been translated into more than ten languages to be read by the global HD community.

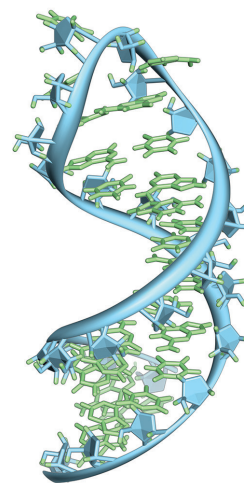
When press releases and media coverage of HD research hype up a scientific finding or claim a "cure," HDBuzz responds with concise explanations of the research and what they really mean to the HD community.

HDBuzz communications, through written articles and podcasts, are intended to bring clarity and context to the work of academic scientists, clinicians, and companies working on drugs and other interventions for HD. In 2017, HDBuzz featured live-tweeted updates from research conferences, unbiased explanations of results shared by pharmaceutical companies working on human HD trials, and today's up-and-coming basic research that will define tomorrow's HD therapeutics. Here are some hot HD research topics that were "Buzzed" about this year:

- **DNA repair**

Studies of the entire genome of thousands of individuals with HD are beginning to reveal that other genetic factors play a role in the age of onset. One important finding is that our cells' ability to quickly

fix damage to DNA may contribute to the age at which symptoms begin. HDBuzz reported on genetic factors influencing age of onset, and how the expanded huntingtin protein might interfere with DNA repair.



- **Genome editing with CRISPR**

CRISPR-Cas9 is a novel research technique used by scientists all over the world to edit DNA in laboratory experiments and in mice. While it is not currently safe to try as a therapeutic strategy, HDBuzz reported this year that HD researchers used CRISPR for the first time to edit the HD gene in the brain of a mouse. More articles explored how researchers are refining CRISPR-Cas9 to be more efficient, specific, and safe, so that one day, it might be used to combat hereditary diseases like HD.

- **Biomarkers**

With new huntingtin-lowering "gene therapies" in the clinic that have the potential to slow HD progression, how will we know that these drugs are working? We need non-invasive ways to determine brain health so that we can someday measure HD progression and use treatments even before a person becomes symptomatic. This is the concept of a biomarker. HDBuzz reported on how large animals are helping us to identify biomarkers and on a substance that can be measured in the blood that corresponds to HD progression.

From explaining the function of the huntingtin protein in growth and health of the brain, to exploring movement of molecules around the powerhouse of the cell, to investigating how sheep are helping us research HD, HDBuzz.net is a tremendous resource that is made available to all through support from HDSA and other HD organizations. All of HDBuzz's content is also available on HDSA.org and on the HDSA HD News App available for free on iTunes and GooglePlay.

HD Clinical Trials Update- After Five Years, Enroll-HD Creates New Vision for the Future

Enroll-HD is a global longitudinal, observational study of Huntington's disease with three major goals. It collects a common set of clinical data and biological samples that helps scientists better understand the disease. It also serves as a platform to support recruitment for clinical trials of potential new therapeutics for HD. Finally, it aims to inform us about the best standards of medical care for HD families around the globe.

Enroll-HD is sponsored and managed by CHDI Foundation, a not-for-profit biomedical research organization dedicated to rapidly developing therapies that slow the progression of Huntington's disease. As of November 1, 2017, there are over 14,000 active participants enrolled at 147 active sites in 15 countries around the world. Once an additional 60 or so clinical sites complete the start-up process, Enroll-HD will have over 20,000 participants in more than 200 sites.

After more than five years, the time has come to re-assess the study and make the necessary changes needed to ensure we are best prepared to handle the huntingtin lowering clinical trials that are now becoming reality.

Azevan Pharmaceuticals Continues Phase II STAIR Trial to Improve Irritability and Aggression in HD Patients

In 2016, Azevan Pharmaceuticals, a small biotechnology company from Pennsylvania, launched a Phase 2 clinical trial in partnership with the NIH to study a drug with the potential to improve symptoms of aggression and irritability in HD. The study, ongoing at 22 US sites, is known as STAIR, drawing on its official title, "An Exploratory Phase II Study to Test the Safety, Tolerability, & Activity of a Novel Vasopressin 1a Receptor Antagonist (SRX246) in Irritable Subjects with HD."

SRX-246 is an investigational drug that is believed to work by blocking a receptor in the brain called the vasopressin 1a (V1a) receptor. Vasopressin is a hormone made by the body that binds to the V1a receptor and triggers biological events that play a role in social and emotional behaviors. When a person makes too much vasopressin, which may be the case in the brain of an individual with HD, this can be associated with irritable or aggressive behaviors.

When SRX246 sticks to the V1a receptor, it interferes with vasopressin, and the Phase 2 STAIR study is an early step towards determining whether this could have a positive effect towards decreasing irritability in HD patients. SRX246 is taken by mouth

In the future, there will be three changes coming to the Enroll-HD platform.



- 1) There will be increased recruitment of at-risk, pre-manifest and early stage HD as these individuals will be most eligible for upcoming clinical trials.
- 2) To decrease the burden on later stage HD patients and their families, Enroll-HD will transition current participants in more advanced stages to an easier protocol ('Enroll Lite').
- 3) In the future, Enroll-HD will utilize mobile health applications to accommodate younger, working and remote participants ('Self-Enroll').

Despite these changes, Enroll-HD remains the HD study for all HD families. Whether you are at-risk for HD, gene positive or gene negative, symptomatic or asymptomatic, participation of the entire HD "family" is essential if we hope to continue to make progress towards development of better treatments for HD.

For a list of all current sites and more information about Enroll-HD, visit www.enroll-hd.org or www.HDfinder.org.

and is unique in that it can penetrate the blood-brain barrier to get access to the brain. During Phase 2 of STAIR, the primary goal is to test tolerability of 2 different doses of SRX246 in HD patients, and the secondary goal is to test safety. Finally, this phase includes some exploratory measurements in the clinic to see whether the drug has an effect on irritability, including the Unified HD Rating Scale (UHDRS); UHDRS Irritability and Aggression scale; Aberrant Behavior Checklist (ABC-I); Irritability Scale (IS), Cohen-Mansfield Agitation Inventory (CMAI); Clinical Global Impression Scale (CGI), Caregiver Burden Assessment, and even a novel eDiary.



The STAIR study is being conducted at 22 centers in the United States. They are looking to recruit 108 patients in total for this study. All 22 clinical sites are NeuroNEXT study sites for the National Institutes of Health and 17 of these sites are also HDSA Centers of Excellence. For a local study coordinator contact information, please visit HDfinder.org or call an HDfinder Clinical Trial Navigator at 866-890-6612.

A New “Wave” for Huntingtin Lowering Has Arrived



PRECISION HD

After a fast turnaround from therapeutic concept to study authorization, Wave Life Sciences has initiated a clinical trial called PRECISION-HD to test the safety of a new huntingtin lowering drug. Wave is a genetic medicine company based in Massachusetts that has created an antisense oligonucleotide (ASO) designed to target the expanded (mutant) huntingtin gene, while leaving the unexpanded (normal) copy intact.

Design of the Wave drug

Their ASO approach is similar to that of IONIS, interfering with the RNA message from the HD gene in order to lower levels of huntingtin protein in the brain. However, Wave's ASO recognizes single-letter differences between the two alleles, allowing it to specifically attack the mutant huntingtin message. Wave also uses a “stereopure” approach, meaning that the strings of nucleotide letters in their drugs have a set orientation, which could lead to a more targeted siege on harmful huntingtin. The single-letter discrepancy between the healthy and harmful alleles is called a single-nucleotide polymorphism (SNP, pronounced “snip”), and it is a common occurrence in many genes. Wave has identified two common SNPs that are found only on the mutant huntingtin gene, and they have designed two ASOs to match. Each ASO sticks to a SNP site in the mutant huntingtin RNA and forms a bulky complex that is targeted by the body for destruction.

More information about the Wave ASO trial

Unfortunately, not everyone with HD expresses these two SNPs. Wave estimates that approximately 70% of patients could benefit from this approach. Therefore, the first step of this study is a blood test for potential participants with early-to-mid-stage HD to see whether they have either of the two SNPs. SNP testing and administration of the ASOs in a Phase 1b/2a clinical study began in Europe and Canada in July 2017 and is projected to begin at several US sites in 2018. The drug will be administered similar to the IONIS drug, via lumbar puncture (spinal tap), to approximately 60 individuals each, provided that no red flags arise for safety. Among the very first group of patients, half will receive a single low dose of the drug, and half will receive a placebo. Because the Wave ASOs are in early experimental stages in the clinic, safety and tolerability are top priorities – effectiveness will be tested further down the road. Safety is taken very seriously: currently every early participant is monitored for two full days before another dose is given to anyone else in the world. If no immediate safety issues are identified, later participants in the study will be randomized 3:1 to receive multiple doses of the drug.

Watch HD Trialfinder for information about US based trial sites as they come online. Top-line safety results are expected in 2019.

December 11th, 2017: Groundbreaking Drug Provides Hope for Huntington's Disease

Since late 2015, the very first therapy aimed to combat the underlying genetics of Huntington's disease has been undergoing a safety and tolerability trial in around 40 adults with early-stage HD. The trial is testing a huntingtin-lowering therapy known as IONIS-HTTRx. On December 11th, 2017, Ionis announced that the completed Phase 1/2a study met its safety and tolerability endpoints and successfully lowered levels of mutant huntingtin protein. While the entire HD community is excited about this study, we must remember that its sole purpose was to evaluate the safety of Ionis-HTTRx in HD patients. A Phase III study is planned next to evaluate the effectiveness of the drug to improve HD symptoms.



Statement by Louise Vetter, President and CEO Of HDSA

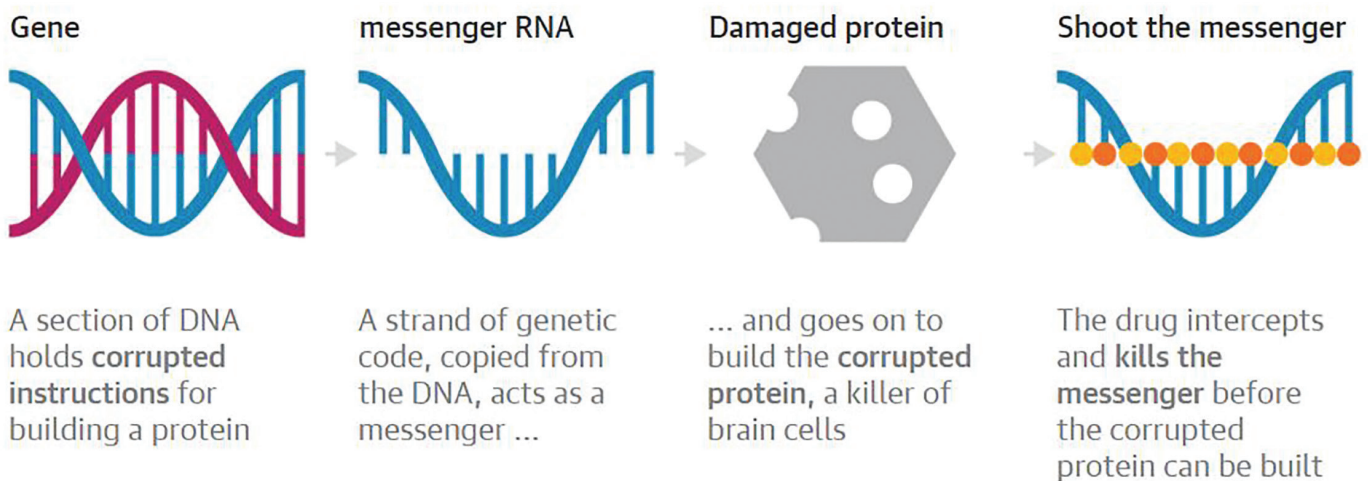
Today, the Huntington's disease community achieved a goal that would not have been possible without the support and dedication of the families, physicians and researchers who passionately pursue a treatment for Huntington's disease (HD). Ionis' announcement of the completion of the Phase 1/2a study of IONIS-HTTRx is a historic moment in the fight against HD as it represents the successful completion of the first trial to treat the underlying cause of Huntington's disease, the genetic mutation itself.

The fact that levels of mutant huntingtin were reduced in correlation to the dose of IONIS-HTTRx that was given is significant, and the fact that participants in this first Phase

1/2a study are able to continue on the drug through open label extension gives us optimism regarding its safety.

As the next phase of clinical study of IONIS-HTTRx gets underway, we look forward to continuing to partner with Roche and the many dedicated clinicians and scientists who work tirelessly to bring greater help and hope to Huntington's families everywhere. We know families will have many questions about what happens next. We always recommend you speak with your doctor about any medical questions you may have. HDTrialFinder.org and HDSA.org will continue to provide the timeliest information regarding development of meaningful treatments for HD.

How the drug slows the spread of Huntington's disease



Guardian graphic | Source: UCL



Statement from Ionis Pharmaceuticals

Dear members of the Huntington's community,

Today is an exciting day for the Huntington's disease community. The Phase 1/2a Study of IONIS-HTT_{Rx}, the first therapy in clinical development designed to target the underlying cause of HD, has been completed. We are pleased to share an update on the status of the IONIS-HTT_{Rx} program and its future.

Roche has exercised its option to license IONIS-HTT_{Rx} following conclusion of the Phase 1/2a randomized, placebo-controlled, dose escalation study of IONIS-HTT_{Rx} in people with Huntington's disease. In this study, reductions of the toxic mutant huntingtin protein (mHTT) were observed in study participants treated with IONIS-HTT_{Rx}, with the largest reductions in those who received the highest doses of IONIS-HTT_{Rx}. In addition, the safety and tolerability profile of IONIS-HTT_{Rx} observed in this study supports continued development of the drug. Ionis and Roche plan to present results from this study at medical conferences in the first half of 2018 and plan to submit the study results for publication in a peer-reviewed medical journal.

As we look to the future we want to share additional perspective on where we are headed in the coming months. Since 2013, when Ionis and Roche started their alliance, the teams in both companies have collaborated closely in advancing the clinical development of IONIS-HTT_{Rx}. Going forward, Roche will now become solely responsible for the further clinical development including trials to demonstrate the safety and efficacy of IONIS-HTT_{Rx}.

Roche's specific expertise in developing medicines to treat neurodegenerative brain diseases, along with their experience in bringing medicines to patients, has been instrumental in the success thus far and will be valuable as IONIS-HTT_{Rx} enters later-stage clinical development.

The next step for this program will be to conduct a safety and efficacy study to investigate if decreasing mutant huntingtin protein with IONIS-HTT_{Rx} can benefit people with Huntington's disease. Future studies for the program will be conducted globally, including in the U.S. Roche will announce details about future studies, including eligibility criteria and planned start dates, as this information becomes available. All relevant information on upcoming studies will also be posted on HDTrialFinder.org and ClinicalTrials.gov.

We thank you for your contributions to these ongoing efforts. We could not have reached this critical milestone without the support and dedication of the clinical study participants, their families, the study doctors who provide exceptional care for these individuals, and the entire HD community who inspire us to work diligently each and every day toward an effective treatment for HD.

Sincerely,
Your Ionis & Roche Team

FAQs about the Ionis Huntingtin-lowering trial

What is Ionis-HTT_{Rx}?

IONIS-HTT_{Rx} is an investigational drug being developed for the potential treatment of HD. IONIS-HTT_{Rx} offers a unique mechanism to moderate the underlying genetic cause of HD by decreasing the production of the toxic huntingtin protein. IONIS-HTT_{Rx} is an antisense drug designed to reduce the amount of huntingtin RNA in the brain, and with less RNA "message" available, less huntingtin protein is made. IONIS-HTT_{Rx} is designed to reduce the production of all forms of the huntingtin (HTT) protein, which in its mutated variant (mHTT) is responsible for HD. As such, IONIS-HTT_{Rx} offers a unique approach to treat people with Huntington's disease, irrespective of their individual HTT mutation.

What was the Phase 1/2a trial designed to do?

The Phase 1/2a study was a randomized placebo-controlled Phase 1/2a clinical study to evaluate the safety and tolerability of increasing doses of IONIS-HTT_{Rx} in people with early stage Huntington's disease. Phase 1/2a study participants who are eligible for the open-label extension (OLE) study will have the opportunity to continue on drug in this trial.

How was the study performed?

Each patient received multiple injections of a specific dosage of the drug, with different groups of patients receiving placebo and a range of doses. The treatment was administered as an intrathecal injection, commonly called a lumbar puncture or "spinal tap." The drug is injected into the lower back, enters the cerebrospinal fluid that bathes the nervous system, and reaches the brain. None of the patients or physicians participating in the study knew who was receiving active drug or placebo, known as a double-blind design.

Who participated in this phase of the study?

The study enrolled approximately 40 patients with early manifest, Stage 1 HD (defined as Total Functional Capacity of 11-13), aged 25 to 65 years. Participants were enrolled at six centers in Canada, the United Kingdom and Germany only. All patients had genetically confirmed HD by direct DNA testing, passed additional eligibility screening, and had informed consent. Participation in the Ionis-HTT_{Rx} study lasted for about 8 months.

What are the plans for further clinical development?

The next step for this program will be to conduct a safety and efficacy study to investigate if decreasing mutant huntingtin protein with IONIS-HTT_{Rx} can benefit people with Huntington's disease. Future studies for the program will be conducted globally, including the U.S. Roche will announce details about studies, including eligibility criteria and planned start dates, as this information becomes available. All relevant information on upcoming studies will also be posted on HDTrialFinder.org and ClinicalTrials.gov.

A Special Thanks to the HDSA Scientific Advisory Board

The HDSA Scientific Advisory Board (SAB) is comprised of leading experts in their fields. The Scientific Advisory Board's role is to provide scientific review of research proposals to ensure that the research programs at HDSA are scientifically sound, pertinent and provide a high impact to the HD research community. Additionally, the SAB advises the HDSA Board of Trustees and management on a range of issues influencing the scientific direction of the Society. The current members of the HDSA SAB are:

- **Michelle Gray, PhD**, Assistant Professor, University of Alabama-Birmingham (Chairwoman)
- **Neil Aronin, MD**, Professor and Chairman of Endocrinology and Metabolism, University of Massachusetts Medical School
- **Susan Browne, PhD**, Director, Teva Pharmaceuticals
- **Lucie Bruijn, PhD**, Chief Scientific Officer, ALS Association
- **Jang-Ho Cha, MD, PhD**, Global Translational Medicine Head, Neuroscience, Novartis Institutes for BioMedical Research
- **Kenneth Fischbeck, MD**, NIH Distinguished Investigator, Chief, Neurogenetics Branch
- **Sam Frank, MD**, Associate Professor, Beth Israel-Deaconess Hospital (ex officio)
- **David Howland, PhD**, Director, CHDI Foundation
- **Blair Leavitt, MD, PhD**, Professor, University of British Columbia
- **Marcy MacDonald, PhD**, Professor, Harvard Medical School, Massachusetts General Hospital
- **Melissa Moser**, Community Representative
- **Harry Orr, PhD**, Professor, University of Minnesota

The Committee's specific responsibilities include:

- Periodically reviewing HDSA's medical and scientific affairs strategy and recommending funding for research grant awards.
- Significantly expanding HDSA's research commitments.
- Define and administer HDSA's research program, including RFP development, proposal review and grant oversight.

We are grateful to the SAB members who so generously donate their time and talent as volunteers!



Remembering Dr. Peter Como & Dr. Kimberly Quaid

In 2017, the entire HD community mourned the loss of Dr. Peter Como and Dr. Kimberly Quaid. Their passing left behind large voids that will be difficult to fill.



Dr. Peter Como passed away unexpectedly on March 14, 2017. He began his career as a Clinical Psychologist practitioner at the University of Rochester Medical Center, and was in charge of research, grant writing, and oversaw several clinical trials worldwide. Peter helped start the HDSA Center of Excellence at the University of Rochester. Most recently, Peter was a member of HDSA's Centers Program and Education Advisory Committee that evaluates all HDSA Centers across the country. At the time of his passing, Peter worked as a Neuropsychologist in the Neurodiagnostic and Neurotherapeutic Devices Branch of the FDA.



On July 26, 2017, Dr. Kimberly Quaid also passed away suddenly. Kimberly was a Professor of Medical and Molecular Genetics, Co-Director of the Master of Science in Genetic Counseling, and Director of the Predictive Testing Program at Indiana University School of Medicine. As Director of this testing program she provided genetic counseling and testing for individuals with and at-risk for Huntington's disease. Dr. Quaid was also the Co-Director of the Genetic Counseling Program and was a faculty investigator at the IU Center for Bioethics. She also served as Director of the Huntington's Disease Society of America Center of Excellence at Indiana University.

Our Mission:
To improve the lives of people with Huntington's disease and their families.

Our Vision:
A World Free of Huntington's Disease

Huntington's disease (HD) is a fatal genetic disorder that causes the progressive breakdown of nerve cells in the brain. It deteriorates a person's physical and mental abilities often starting in their prime working years. Currently, there is no cure for Huntington's disease.

Every child of a parent with HD has a 50/50 chance of inheriting the faulty gene that causes HD. Today, there are approximately 30,000 symptomatic Americans and more than 200,000 at-risk of inheriting the disease.

The Huntington's Disease Society of America (HDSA) is the premier nonprofit organization dedicated to improving the lives of everyone affected by HD. From community services and education to advocacy and research, HDSA is the world's leader in providing help for today and hope for tomorrow for people with HD and their families.

Across the United States HDSA supports 54 volunteer-led Chapters & Affiliates, 41 HDSA Centers of Excellence, more than 60 social workers and 160 support groups specifically for HD families.

The Huntington's Disease Society of America (formerly known as the Committee to Combat Huntington's Disease) was founded on September 18, 1967 by Marjorie Guthrie, the wife of legendary folk singer Woody Guthrie. Woody died from HD complications when he was only 55 years old, but the Guthrie family legacy lives on at HDSA to this day.

 Huntington's Disease
Society of America



50 YEARS OF SERVICE
1967-2017

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