THE MARKER

THE 2021 HDSA RESEARCH REPORT

2021

A YEAR OF RESILIENCE

Huntington's Disease Society of America

THE MARKER

THE 2021 HDSA RESEARCH REPORT

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2021: A Year of Resilience

Dear Friends,

2021 was a year of unexpected highs and lows for the HD scientific community and the families that make HD research possible. We mourned the halt of a large global drug trial, welcomed many new industry partners into the HD research space, and with excitement await the start of upcoming trials, including testing the potential for oral gene therapies.

As we have navigated the peaks and valleys of the HD research landscape, HDSA's commitment to supporting and communicating about cutting-edge science has never wavered. Though we have continued to feel the weight of the COVID-19 pandemic, out of a global health crisis has emerged a set of new research approaches and techniques that will be applied to HD and a wide variety of diseases. And while we experienced setbacks on the journey towards disease-modifying therapies, we are empowered by the knowledge gained through unprecedented human trials aimed at combatting the genetic source of HD. The HDSA team and the entire scientific community are inspired by the resilience of HD families and their ongoing commitment to research progress and advocacy.

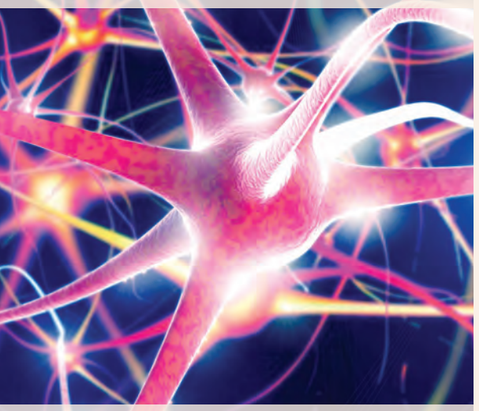
The global community banded together in an extraordinary show of support following the disappointing news this spring around the premature halt of dosing in the GENERATION-HD1 trial and the conclusion of the PRECISION trials.

As we continue to process and grieve these setbacks, we are heartened by the progress being made in many other realms of HD research. Clinical studies are underway to test novel genetic therapies for HD and to address many aspects of HD biology and symptoms. Dozens more companies are in the discovery or preclinical stages of developing HD therapeutics. This wide interest is powered by robust data generated through observational research, made possible by the thousands of participants who donate their time to studies like Enroll-HD.

This year saw unparalleled recruitment efforts and the worldwide expansion of virtual resources to reach more members of the HD community. We are enthusiastic about the steady progress of the first gene therapy trial for HD, as well as clinical studies of novel therapies to preserve brain health. We celebrate advances in CRISPR gene editing, and a host of new tools and discoveries that will power improved care in the near term and novel HD therapeutics in the future. We hope that this 2021 edition of *The Marker* provides a renewed sense of optimism about the year to come and the scientific developments on the horizon.

With hope,

Louise Vetter
President & Chief Executive Officer, HDSA



2021 Human Biology Project Fellowships

FELLOWSHIPS

In October of 2021, HDSA awarded five research grants under the Society's largest research initiative, the **HDSA Huntington's Disease Human Biology Project.** Totaling more than $728,000, 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 animal models, with direct participation of people affected by HD.

HDSA received impressive applications from researchers all around the world. After careful consideration by HDSA's Scientific Advisory Board, funds were ultimately granted to researchers from the United States, Canada, and Spain.

Ana Gámez-Valero, PhD

Postdoctoral Research Scientist
University of Barcelona

Plasma extracellular small RNAs as early biomarkers of Huntington's disease and indicators of dynamic changes in disease progression

Dr. Valero will analyze blood samples from pre-symptomatic and early-stage HD-carriers, as well as people without HD, to see if small pieces of the genetic recipe that creates mutant huntingtin protein, called small RNAs, can predict the onset of HD symptoms and how a patient responds to clinical interventions.

Tamara Maiuri, PhD

Research Associate
McMaster University

Poly ADP-ribose dysregulation in HD patient samples and potential for therapeutic intervention

Expanding upon a previous discovery that a step in the DNA-repair process called poly ADP-ribosylation involves huntingtin protein, Dr. Mairui's project will explore whether pre-existing therapeutics may be useful to target this pathway for treatment of HD in cell models of HD.

Joan O'Keefe, PhD, PT

Associate Professor
Rush University

Neural underpinnings of cognitive, balance, and gait deficits in Huntington's disease

Using cutting-edge brain imaging technologies, Dr. O'Keefe will investigate brain signaling patterns associated with cognitive and motor decline in Huntington's disease as a tool for developing preventative and rehabilitative therapies.

Alby Richard, MD, PhD

Assistant Professor and Neurologist
University of Montreal

Oculomotor learning as a biomarker in Huntington's disease patients

Dr. Richard will use noninvasive tracking techniques to measure changes in eye movements as a tool for rapid detection of subtle, early signs of motor and learning deficits in Huntington's disease.

Charlene Smith-Geater, PhD

Assistant Project Scientist
University of California, Irvine

Modulation of E3 SUMO-ligase PIAS1 in 3D cortico-striatal assembloids and investigation of the HD-relevant CSF SUMO-ome

Using cell structures resembling brain tissue and HD-patient-derived CSF samples, Dr. Smith-Geater will test how reduction of PIAS-1, a protein whose activity is altered in HD, will affect the progression of HD.

2021 Donald A. King Summer Research Fellowships

With the goal of attracting the next generation of bright young scientists to HD research and preparing them for the challenges of the field, HDSA established the **Donald A. King Summer Research Fellowship** in 2005 to support undergraduate researchers in their study of biological mechanisms underlying HD pathology. This program was established to honor Donald A. King, a tireless advocate for HD families who served as HDSA's Chairman of the Board from 1999 to 2003 before his sudden passing in 2004.

After careful review by HDSA's Scientific Advisory Board, two young scientists were awarded 2021 Donald A. King Summer Research Fellowships in April of this year.

Ratnesh Kesineni
University of Central Florida

Ratnesh was mentored by former HDSA Human Biology Fellow, ***Dr. Amber Southwell,*** *to explore a potential link between biological age and aggregation of misfolded mutant huntingtin (mHTT) for potential therapeutic targeting.*

Russell Wells
Whitworth College

Russell worked with ***Michael Sardinia, PhD, DVM,*** *to study the effects of dihexa, a small molecule that has previously shown positive effects in Alzheimer's and Parkinson's disease models, for the treatment of Huntington's disease phenotypes in mice models.*

2021 Berman-Topper Family HD Career Development Fellowships

FELLOWSHIPS

With a shared goal of bolstering opportunities for young HD researchers and generous support from the Berman and Topper families, HDSA launched the **Berman-Topper HD Career Development Fellowship** in 2016 to support future generations of passionate HD scientists and clinicians. These prestigious fellowships provide $80,000 of annual funding for three years to young scientists and clinicians who are motivated to make HD a focal point of their long-term career plans.

Since its inception in 2016, the program has supported seven emerging scientists in projects that have not only propelled them forward in their careers, but also made significant contributions to the HD research community. This year, after HDSA's Scientific Advisory Board carefully considered proposals from scientists across the globe, the Society was excited to name two 2021 Berman-Topper Fellows, **Dr. Eduardo Silva-Ramos** and **Dr. Adys Mendizabal.**

Under the mentorship of **Dr. Erich Wanker** at the Max Delbrück Center for Molecular Medicine, Dr. Silva-Ramos' project, ***"Characterization and targeting a novel HTT interacting E3 ligase protein complex,"*** will seek new insights into how the huntingtin protein is regulated in the body and what can be done to better target it for therapeutic development.

In her project entitled ***"HD epidemiology, healthcare utilization, and outcomes in racially and ethnically diverse populations in the US,"*** Dr. Mendizabal will study the actual prevalence of HD in racially diverse communities and how they utilize HD healthcare options. Dr. Mendizabal is the first clinician to be awarded the Berman-Topper fellowship and will be guided by **Dr. Yvette Bordelon** at The University of California, Los Angeles.

Dr. Adys Mendizabal

Dr. Eduardo Silva-Ramos

HDSA Center of Excellence Clinical Research Pilot Program

In 2021, HDSA awarded two grants under the **HDSA Center of Excellence Clinical Research Pilot Program.** These grants, totaling $25,000, represent HDSA's patient-centric research focus by fostering novel clinical research projects within the HDSA Center of Excellence network. These pilot projects will unite scientists with HD families through their direct participation in clinical research.

Two clinical research pilot grants were awarded this year. The first to **Leonard Sokol, MD,** at Northwestern University, for a study on Meaning-Centered Psychotherapy for treatment of psychosocial symptoms and improved quality of life in persons with Huntington's Disease. The second went to **Deb Kegelmeyer, DPT,** at The Ohio State University. This study will evaluate whether telehealth is an effective medium to implement a 12-week movement to music program designed to enhance physical, cognitive, and psychosocial health in adults, as well as whether the intervention leads to changes in these domains.

Leonard Sokol, MD
Northwestern University

Deb Kegelmeyer, DPT
The Ohio State University

HDSA Online Resources

HD Trialfinder: Premier Clinical Trials Matching for the HD Community

By continuing to build our understanding of HD and investigating new potential therapeutics to treat it, clinical trials enable HD researchers to bring us one step closer to treatments and cures for HD. Clinical trial participants are a critical piece of the process, which is why HDSA created **HD Trialfinder** in 2015. This online clinical trial matching service is a way for individuals with HD, caregivers, and healthy volunteers to learn what trials they may be eligible for, get notified of new trials in their area, and learn about ongoing trials across North America.

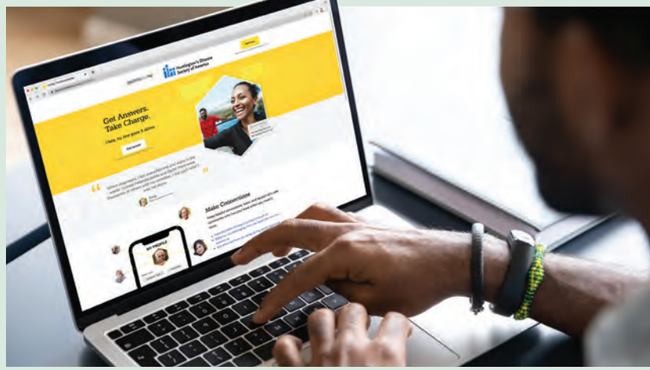
Through involvement in the worldwide HD research community, HDSA keeps track of national, international, and local clinical trials so that the HD Trialfinder listing stays up-to-date with studies that need participants. Anyone can visit the website to read about ongoing studies, and by creating a profile for yourself, a loved one, or a patient, users can find out which nearby studies they are eligible for and locate contact information to get involved directly.

To learn more, visit www.hdtrialfinder.org.
To speak with a trained HD clinical trial navigator, phone 1-866-890-6612.

HDSA Launches Online Community for Patients & Caregivers with *PatientsLikeMe*

In collaboration with **PatientsLikeMe (PLM),** HDSA launched a tailored community for HD families in June of this year. This virtual platform is not only a place for families to anonymously come together to find support and share experiences, but also a place to track day-to-day symptoms, ask questions, get answers, and find reputable information free from marketing schemes and misinformation. Additionally, PLM is a forum to empower the patient voice in the medical process and curate their perspectives for improved diagnosis, care, and treatment of HD. In this respect, PLM will serve as a catalyst to expand researchers' knowledge of the condition with patient-generated data. Through this partnership, PatientsLikeMe and The Huntington's Disease Society of America aspire to improve health outcomes and quality of life across the HD community.

Visit hdsa.org/plm to join the community today!



ENROLL-HD

Observational Research Drives Development of Therapeutics

Large-scale observational research, such as the **Enroll-HD** study, is an important driver behind the development of HD therapeutics. The ability to link genetic information gathered anonymously from blood samples with clinical data from neurological exams and family history information is enabling the identification of new aspects of HD biology to target for drug development. Since its inception in 2012, Enroll-HD has become the largest long-term observational study of people with HD and their families. An important recent milestone was reaching 25,000 participants worldwide, with more than 1000 recruited in the first half of 2021, despite the ongoing challenges of the COVID-19 pandemic. There are now several ongoing studies linked with Enroll-HD, addressing topics like composition of spinal fluid *(HD-Clarity)* and the economic burden of HD *(HD-Charge)*, with additional ones on the way. Although anyone in an HD family can participate in Enroll-HD, regardless of genetic status, the participation of pre-symptomatic and at-risk individuals is of the highest importance in the journey to prepare for future preventative drug trials. This demographic has increased steadily, a testament to the awareness and dedication of HD families to research worldwide.

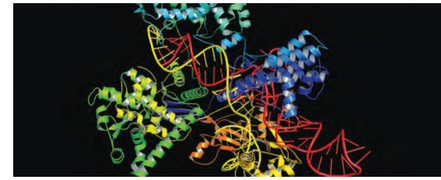
To learn more, visit enroll-hd.org

HOT TOPIC

Gene Editing Developments in 2021

Whereas many current genetic therapies target the RNA "recipe" that creates harmful huntingtin protein, a more permanent strategy being explored for hereditary diseases involves direct edits to DNA. **CRISPR gene editing** is one of these approaches. In late June of 2021 the first successful safety trial of direct-in-human CRISPR gene editing was announced. This was a very small safety trial for a genetic disease called TTR amyloidosis, which usually affects the liver, and the treatment lowered the toxic protein known to cause the disease. We don't know yet if it was effective for symptoms, but it was a first in gene editing, and it's a technology that could potentially be applied to other diseases. We are likely a long way from altering DNA in HD brain cells, as compared to the liver, but this news still represents a significant milestone for gene editing.

One of the major challenges for gene editing, especially in a brain disease like HD, is that once DNA has been altered, there's no going back, and so any mistake could have dire consequences. In July a research team from Philadelphia published their work on a way to gain more precise control of gene editing using oral drugs. They figured out a new way to turn on and off the gene editor in mice and regulate how active it was, so stopping administration of the oral drug would turn off the gene editor. A major reason that this story made waves in the HD community is that the leader of the team that developed this technology is **Dr. Beverly Davidson,** a well-known HD researcher, so it's likely that it might be applied to HD in future.



HDSA PERSON OF THE YEAR

Research Advocate Yvonne Sweeten

Yvonne Sweeten

Yvonne Sweeten, an HD gene carrier and active member of the HDSA Las Vegas Affiliate, was awarded the **HDSA Person of the Year Award** at the 36th Annual HDSA Convention. This award recognizes an advocate, voice for HD, and a leader who inspires others who are affected by Huntington's disease (HD) each and every day. As a member of the HD Coalition on Patient Engagement (HD-COPE), Yvonne has shared her story openly with pharmaceutical companies and scientists engaged in novel research so they can understand the complexities of HD and design clinical trials with families in mind. She has also been a part of many fundraising and educational events including the Las Vegas Team Hope Walk. Congratulations Yvonne!

2021 HDSA
Research Communications

As part of its mission and goal to provide help for today, hope for tomorrow for people with Huntington's disease and their families, HDSA's research communications provide community updates on clinical trials, research news, HDSA funded research activities, and more.

New HDSA Team Member

The HDSA staff family grew this year to include **Kelly Andrew,** who came on board as Coordinator of Mission and Research Programs to help support our expanding research and care programs. After earning her bachelor's degree from Wake Forest University in 2019, Kelly held a position in environmental policy and volunteered with an organization that is establishing a genetic registry for people affected by eating disorders. At HDSA she has applied her communication skills towards supporting our network of research fellows, blogging for "*This Week in HD Research*", growing the tailored PatientsLikeMe community, and supporting HDSA's Mission Team.

Kelly Andrew

This Week in HD Research

Published weekly, get the latest news in the HD research landscape with bite-sized briefings on HDSA's research activities, recent journal publications, clinical trial updates, and more.

To learn more, please visit ***hdsa.org/blog/***

Research Webinars

From clinical trials in the pipeline to emerging experimental biomarkers, HDSA's research webinars cover hot topics in the HD community with presentations from prominent HD clinicians and researchers.

To learn more, please visit ***hdsa.org/hd-research/hdsa-research-webinars/***

HDBuzz

HDSA proudly supports HDBuzz, a website where scientists write in plain language about HD research news, for the global community. HDSA's Assistant Director of Research and Patient Engagement, **Dr. Leora Fox,** is a contributing writer and editor. This year's topics included breaking clinical trial news, cutting-edge developments in gene therapy, novel biomarkers to track HD and prepare for prevention trials, COVID vaccines and HD, and live Twitter coverage of research conferences, among many others.

Dr. Leora Fox

To learn more, please visit ***HDBuzz.net***

HD-COPE

The Huntington's Disease Coalition for Patient Engagement (HD-COPE) has continued to provide patient and family input to help industry researchers better understand HD and to guide their clinical plans. Numerous companies met virtually in 2021 with members of the HD-COPE team to help shape their future clinical development plans.

To learn more, please visit ***hdsa.org/hd-research/hd-cope/***

HDSA's Virtual 36th Annual Convention

Researchers, clinicians, and family members came together virtually for a Convention that safely celebrated the progress we've made despite the challenges faced in 2021. As always, cutting-edge HD science was emphasized, with a focus on community engagement and clinical trial participation. Updates were presented by a variety of companies, including many of those mentioned above. Families had the opportunity to "*Ask the Scientist Anything*" live, to hear directly from HDSA-supported research fellows, and to learn more about gene therapy delivery, among many other topics in the realms of care, family planning, and social support.

All presentations are available at ***hdsa.org/convention***

Coverage of Virtual HD Research Conferences

Keeping our fingers on the pulse of HD science is essential to HDSA's ability to communicate timely and accurate information about HD research news. Important to this process is staff attendance and coverage of the major HD research conferences, which this year were all virtual and accessible to a global audience. These included the *16th Annual HD Therapeutics Conference,* hosted by CHDI, the *Congress of the European Huntington's Disease Network,* and the *Huntington Study Group Meeting.*

Conferences are highlighted on HDSA's research communication channels, like the blog, social media, and through our friends at HDBuzz.

Social Media

Follow HDSA on our social media platforms for immediate updates on relevant news in HD science.

Triumphs for HDSA-Supported Research

Novel PET Radiotracer Helps Visualize Protein Affected by HD

During his award period, 2018 HDSA Human Biology Fellow **Dr. Michael Placzek** developed

a novel PET radiotracer that can help to visualize a protein called COX-2, which is altered in HD. This could be used to track very early signs of disease progression and to assess the effectiveness of future HD therapeutics. Dr. Placzek's work has led to the recent submission of an Investigational New Drug application to continue developing this novel imaging strategy in humans.

Annexon Recruits Phase 2 Study of HD Investigational Drug, ANNX005

In 2021 **Annexon Biosciences** recruited a Phase 2 study of an investigational drug, ANX005,

to target a part of the brain's immune system that becomes overactive in HD. The pre-clinical studies that powered this work were originally conducted by **Dr. Daniel Wilton** during his HDSA HD Human Biology Fellowship, which is a testament to the impactful, human-centric work we fund.

Human Biology Project Initiative Forms Basis for HD Biomarker Discoveries

Research funded in the very first year of HDSA's Human Biology Project initiative formed the

basis for important recent HD biomarker discoveries. 2013 Fellow **Dr. Jun Hua** has been steadily working on ways to use blood volume as a means of tracking HD and response to genetic therapies. He co-led a 2021 study that provides hope for new biomarkers that could help identify participants and determine treatment response in future trials to prevent HD symptoms.

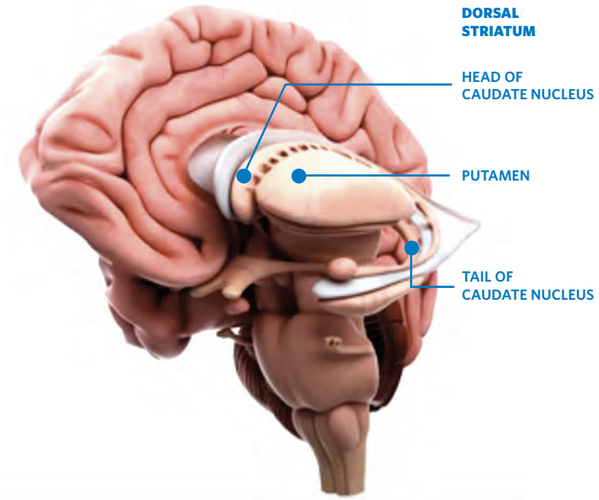
Clinical Trial Updates

CLINICAL TRIAL UPDATES

UNIQURE

First HD Gene Therapy Trial Safely Continues

Unlike ASO drugs which require repeated injections over time, gene therapy delivers new genetic material to a person's cells so that a single treatment could theoretically last a lifetime. **uniQure** is conducting the first trial of an HD gene therapy, called **AMT-130.** It is packaged inside a harmless virus and delivered via a brain surgery. This trial is planned to involve 26 participants at sites in the USA. Between mid-2020 and the end of 2021, 14 people with HD underwent the surgery, with no dangerous safety issues. 12 additional volunteers will be recruited to participate by mid-2022. A second trial will be conducted in Europe soon. The successful rollout of this first genetic therapy for HD is not only a triumph for uniQure but bodes well for dozens more drugs in the HD research pipeline.



AMT-130 is infused into two specific brain regions (caudate and striatum) under general anesthesia. This is done by drilling two to six small holes in the skull and administering AMT-130 by a micro-catheter.

Clinical Trial Updates

CLINICAL TRIAL UPDATES

NOVARTIS

Branaplam, An Oral Huntingtin-Lowering Drug to Enter Phase 2 Trial

Branaplam is an orally administered liquid drug originally developed to treat a fatal childhood disorder called spinal muscular atrophy (SMA). Unexpectedly, in early trials for SMA, branaplam was found to also lower levels of huntingtin protein. This discovery prompted **Novartis** to begin exploring its potential as a treatment for HD, and after early safety testing in healthy adults, a Phase 2 trial is expected to begin by the end of 2021. The trial will involve more than 100 people in about 10 countries, including the USA.

PTC THERAPEUTICS

Recruiting Trial of an Oral Huntingtin-Lowering Therapy

PTC Therapeutics is also developing an oral drug to lower huntingtin, which was also tested in healthy adults over the course of the year, and a Phase 2 clinical trial for HD patients is expected to begin by the end of 2021. The goal is to test safety and huntingtin lowering in HD gene carriers ages 25 and up, with a CAG repeat of 42-50. Eligibility will also depend on a new score called PINHD that will help to select people with very early symptoms. In September, PTC Therapeutics announced that they will be applying to the FDA for an accelerated regulatory pathway that could potentially enable approval following a successful Phase 2 trial.

NEUROCRINE BIOSCIENCES

KINECT-HD Trial Fully Recruited

The **KINECT-HD** trial and its extension, **KINECT-HD2,** is a Phase 3 trial of valbenazine as a treatment for HD chorea. Both trials fully recruited about 150 participants in 2021. This drug, similar to tetrabenazine and deutetrabenazine (Austedo®), was developed by **Neurocrine Biosciences** and is already FDA approved to treat people with a disorder called tardive dyskinesia (TD). TD causes facial and limb movements due to drugs prescribed for certain psychiatric conditions. The KINECT trials are designed to test whether valbenazine could also be effective for people with HD movement symptoms, and this treatment requires less frequent dosing than existing drugs for HD chorea.

PRILENIA THERAPEUTICS

PROOF-HD Trial of Pridopidine Fully Recruited

Pridopidine is a drug that has been in development for the treatment of HD for several years. **Prilenia Therapeutics** is currently conducting a Phase 3 clinical trial to determine whether it can help to preserve their day-to-day function. A shorter trial of pridopidine, PRIDE-HD, conducted by Teva Pharmaceuticals, did not meet its key goals of slowing movement symptoms. However, the drug showed promise for improving functional capacity for people with HD, and recent research has uncovered new information about its action on a type of brain receptor called sigma-1 that could help to protect brain cells. These scientific and clinical findings led to Prilenia developing a larger and longer trial, which is currently underway and has fully recruited with over 480 participating people with HD.

ANNEXON BIOSCIENCES

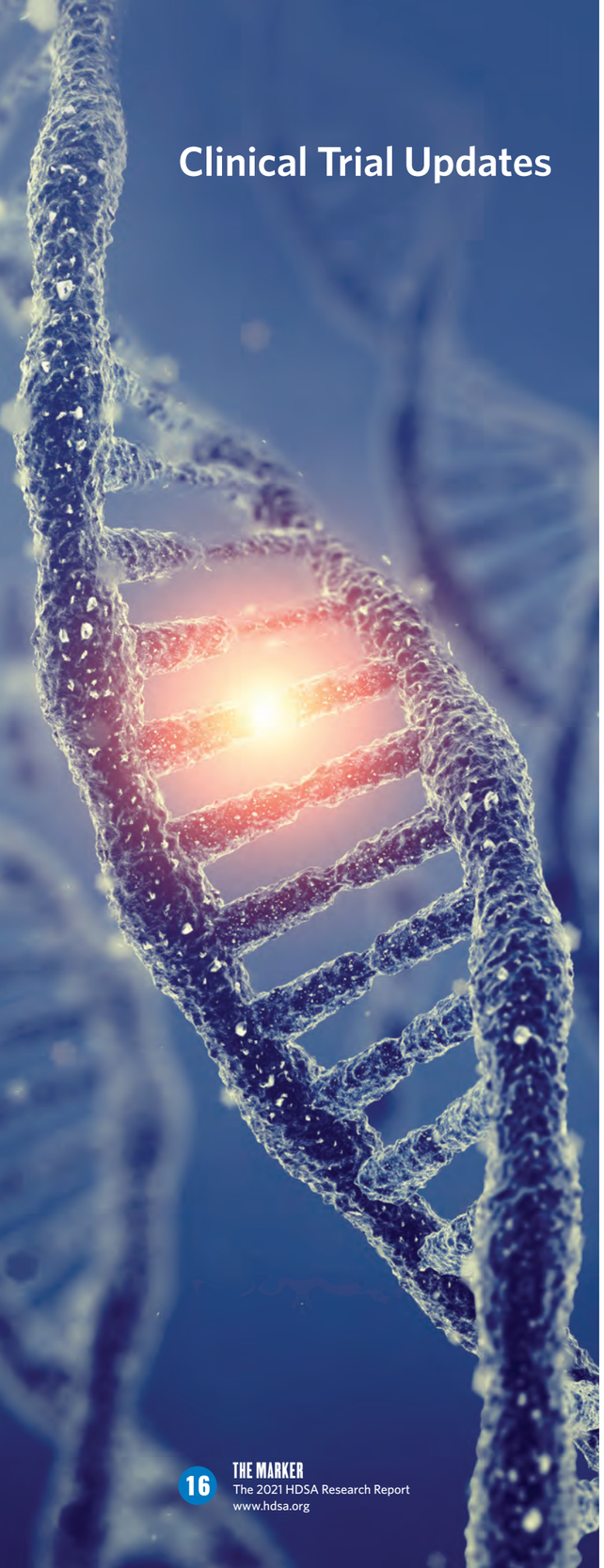
Targeting the Brain's Immune System In Huntington's Disease

Annexon Biosciences is focused on targeting a part of the immune system called the *complement system* which can become overactive in the brain as HD progresses, destroying connections between brain cells known as synapses. Annexon is developing a drug called **ANX-005** with the goal of preserving synapses in the HD brain. A Phase 2 trial has fully recruited in HD patients in the US, and is ongoing. Some of the early scientific discoveries behind this trial were made by **Dr. Daniel Wilton,** an HDSA Human Biology fellow.

SAGE THERAPEUTICS

Preserving Cognition for HD Patients

SAGE-718 is a therapeutic designed to increase activity of brain messaging through NMDA receptors. NMDA receptors are critical for tasks like combining and linking memories and effective decision making, and the chemicals that activate them are known to decline with the onset of HD. **Sage Therapeutics** is expected to initiate a Phase 2/3 clinical trial of SAGE-718 in the near future, and in late 2021 announced Fast Track Designation which could help speed development and review of the drug by the FDA.



Clinical Trial Updates

CLINICAL TRIAL UPDATES

VOYAGER THERAPEUTICS

New Scientific Direction Could Lead to Less Invasive Gene Therapies

In August of 2021, **Voyager Therapeutics** announced a major shift in their scientific pipeline. The announcement centered around an improved gene therapy delivery system and a proprietary discovery platform, which could allow Voyager to develop less invasive delivery methods (like IV injection) for HD gene therapies. Unfortunately, this means that Voyager will no longer be pursuing VY-HTT01, a therapy developed for HD that was meant to be the focus of a safety trial involving a brain surgery. The trial would have been called VYTAL, but no participants had yet been recruited. Although the loss of a gene therapy that was approaching the clinic is a significant short-term setback, Voyager's shift in focus now to accommodate a novel scientific development provides a new and potentially better therapeutic avenue for HD.

TRIPLET THERAPEUTICS

Slowing CAG Repeat Expansion

Triplet Therapeutics is approaching HD drug development from a novel genetic angle, by targeting DNA repair. When DNA repair goes awry in a person with HD, the number of CAG repeats in some brain cells can increase as they age, and this continued expansion is believed to accelerate the onset of symptoms. Triplet Therapeutics has developed a therapy called **TTX-3360,** which aims to slow the process to try and delay HD symptoms. A future clinical safety trial will involve a surgery to deliver the drug into the fluid-filled spaces of the brain.

ROCHE/GENENTECH

Roche/Genentech Halts GENERATION-HD1 Trial of Tominersen

In March of 2021, **Roche/Genentech** shared the disappointing news that the GENERATION-HD1 trial of huntingtin-lowering drug **tominersen** had come to a halt. This global Phase III trial of the first ASO drug to target the genetic source of HD had nearly 800 participants at 100 sites in 18 countries, who received spinal injections of tominersen or a placebo every two months. At an annual HD therapeutics conference hosted virtually in April by the private HD research foundation CHDI, Roche shared data showing that the drug did not benefit participants. This was a devastating blow to families, clinicians, and researchers alike, who had placed hope in tominersen. However, the global community came together in many virtual forums to support one another through this difficult news. In September, at a conference hosted by the European Huntington's Disease Network (EHDN), Roche shared that additional data is forthcoming by early 2022. As analysis continues, the knowledge gained from this trial will help to shape the HD gene therapies of the future.

WAVE LIFE SCIENCES

Disappointing Outcome of PRECISION-HD Trials; Hope in SELECT-HD

Just after the unfortunate news from Roche/Genentech, **Wave Life Sciences** also shared that they would not continue developing two ASO drugs for HD, which were tested in two Phase I/II trials known as PRECISION-HD1 and PRECISION-HD2. These genetic drugs aimed to lower harmful huntingtin while keeping healthy huntingtin intact. However, in these trials involving ~60 participants each, they did not achieve the goal of lowering huntingtin, so Wave will not be pursuing either drug.

However, using a redesigned chemical structure for their ASO drugs, Wave has developed a third ASO, **WVE-003,** which they began testing in Phase I/II trial called **SELECT-HD** in September of 2021. The study will involve 36 participants ages 25-60 with early HD symptoms at sites in Canada, Australia, Germany and Poland, who will receive monthly spinal injections for 16 weeks. The goal is to target just the harmful form of huntingtin, so eligibility also depends on having a certain genetic feature in part of the HD gene.

Preclinical Research Updates

In addition to the sponsors currently running clinical trials or anticipating them in the near future, there are dozens of companies working on the earlier stages of HD drug development. One example is **Atalanta Therapeutics,** which is working on RNA interference to target the recipe for huntingtin protein, using a design that could lead to better distribution of genetic drugs to the brain. Another is **LocanaBio,** which is developing RNA based therapies to lower levels of the harmful huntingtin protein while keeping the healthy form intact. Both companies presented updates at this year's Virtual HDSA Convention.

Fifty-Four HDSA Centers of Excellence Designated in 2021

In February HDSA was proud to announce that fifty-four outstanding Huntington's disease care facilities were awarded the designation of **HDSA Centers of Excellence** for 2021. 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.

The strategic expansion of the HDSA Center of Excellence program allows expanded access to expert HD clinical care and clinical trial opportunities to more families across the United States. With new Centers in Arizona, Arkansas, New Jersey, Mississippi, Ohio and South Carolina, HDSA now offers care locations in 35 States plus the District of Columbia. **This year, HDSA awarded $1,750,000 to the Centers of Excellence program.**

The 2021 HDSA Centers of Excellence program expanded to 54 Centers from 50 in 2020, and from just 20 in 2015. With the inclusion of eight regional partner clinics that expand access to expert HD care in various parts of the USA, this brings the overall number of HDSA-supported clinics to 62.

"The expansion of the HDSA Centers of Excellence program ensures that more families affected by Huntington's disease have increased access to expert and comprehensive care for this devastating rare brain disease," said **Dr. Victor Sung,** Chair of HDSA's National Board of Trustees and Director of the HDSA Center of Excellence at The University of Alabama, Birmingham. "Additionally, clinical research conducted at many HDSA Centers of Excellence is vital to the development of potentially life-changing treatments to improve the lives of everyone affected by HD."

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.

Louise Vetter, President and CEO of HDSA added, "HDSA Centers of Excellence share a common dedication to HD families. We are 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."

Huntington's Disease Society of America
Centers of Excellence

HDSA CENTERS OF EXCELLENCE

Albany Medical College (NY)

Barrow Neurological Institute (AZ)

Beth Israel Deaconess Medical Center (MA)

Cleveland Clinic (OH)

Columbia Health Sciences/ NYS Psychiatric Institute (NY)

Duke University (NC)

Emory University (GA)

Georgetown University (DC)

Hennepin County Medical Center (MN)

Henry Ford Hospital (MI)

Indiana University

Johns Hopkins University (MD)

Massachusetts General Hospital

Medical University of South Carolina

Northwestern University (IL)

Ochsner Health System (LA)

Ohio State University

Rocky Mountain Movement Disorders Clinic (CO)

Rowan University School of Medicine & Rutgers University RWJ Medical School (NJ)

Rush University Medical Center (IL)

Sanford Health (ND)

Stanford University (CA)

Stony Brook University Hospital (NY)

University of Alabama, Birmingham

University of Arkansas

University of Buffalo (NY)

University of California, Davis Medical Center

University of California, Irvine

University of California, Los Angeles

University of California, San Diego

University of California, San Francisco

University of Cincinnati (OH)

University of Colorado

University of Florida

University of Iowa

University of Kansas Medical Center

University of Louisville (KY)

University of Miami (FL)

University of Mississippi Medical Center

University of Nebraska Medical Center

University of Pennsylvania

University of Pittsburgh Medical Center (PA)

University of Rochester (NY)

University of South Carolina School of Medicine

University of South Florida

University of Texas Health Science Center at Houston, McGovern Medical School

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)

REGIONAL PARTNER CLINICS

Covenant Medical Group Neurology, Lubbock, TX

Kaiser Permanente (CA)

Oregon Health Sciences University

Cole Neuroscience Center, University of Tennessee Medical Center

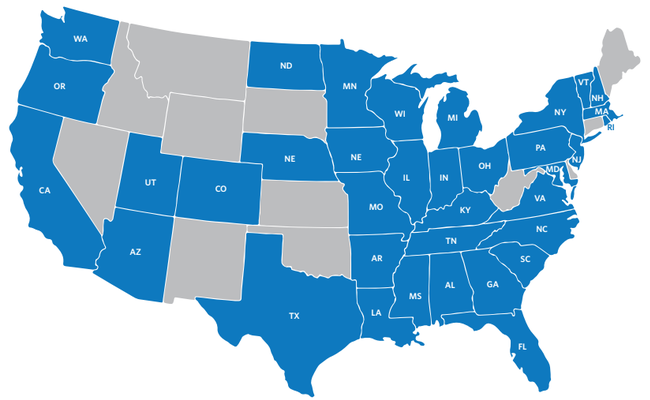
Texas Movement Disorders Specialist, PLLC

University of Tennessee, Erlanger Medical Center

University of Texas Health San Antonio

University of South Alabama

Bold type indicates 2021 additions.



HDSA 2021 Scientific Advisory Board

Huntington's Disease Society of America

A Special Thanks to the HDSA Scientific Advisory Board

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Community Representative

*We are grateful to the **HDSA Scientific Advisory Board (SAB)** members who generously volunteer their time and talent to ensure that HDSA's research programs are scientifically sound and maximally impactful for the HD community. The HDSA SAB is comprised of leading researchers and clinicians in HD and related fields, as well as HD community members with a passion for research. Additionally, the SAB advises HDSA management and its Board of Trustees on a range of issues influencing the scientific direction of the Society.*

With Hope,

We Can Be Together Again.

We are remaining cautiously optimistic that we will finally be able to see each other in-person at HDSA's most important and anticipated event — our Annual Convention. We miss being with you in-person terribly.

We must, however, remain diligent by following all federal, state, and local public health guidelines. The health and well-being of all our participants are our greatest priorities. We will continue to monitor current public health issues and will post Convention information and status updates regularly on our website, HDSA.org.

Fingers crossed, we'll see you in Atlanta!

Huntington's Disease Society of America

Huntington's Disease Society of America

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.

HD is known as the quintessential family disease, because every child of a parent with HD has a 50/50 chance of carrying the faulty gene that causes Huntington's disease. Today, there are approximately 41,000 symptomatic Americans and more than 200,000 individuals 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 50 volunteer-led Chapters & Affiliates, 54 HDSA Centers of Excellence, more than 60 social workers and 80 support groups specifically for HD families.

Huntington's Disease Society of America

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