Huntington's Disease Pre-Symptomatic Population
FDA Patient-Led Listening Session
July 25, 2022
3-4:30 PM EST

Session Objectives

- Share with the FDA collected data from pre-symptomatic & at-risk Huntington's Disease (HD) sub-population regarding risk/benefit of participation in a clinical trial and needs for treatments for disease before symptom onset.
- Help the FDA better understand the urgency and needs of HD pre-symptomatic young adults, along with their desire and willingness to participate in clinical trial.
- Plant seed with the FDA about Critical Path Innovation Meeting (CPIM) request coming their way before the end of 2022 for opportunity to continue this conversation with other HD community stakeholders in hopes to accelerate treatments into the future.

Topics Discussed

- Risk/benefit of participating in trials during pre-symptomatic stage of HD
- Current impact HD has on quality of life today and for the future

Agenda

- Hellos, Greetings & Introductions, FDA Opening Statement
- B.J. Viau: History of the HD community and how there has been a major paradigm shift in the communication and willingness to talk to young people about HD
- Patient Stories
  - Tyler Orem, MD
  - Seth Rotberg
  - Gia Mannone
  - Danielle Valenti Mahoney
  - Lauren Holder
  - Chris Brown
- Analysis of IRB approved survey highlighting the benefit-risk assessment of this population around clinical trials and future treatments.
- FDA and Advocate Discussion/Questions
- Closing / Wrap Up Remarks by FDA

Session Requesters/Leaders & Patient Advocates

Seth Rotberg
BJ Viau

Patient Advocate Attendees

Tyler Orem, MD
Gia Mannone
Danielle Valenti Mahoney
Lauren Holder
Chris Brown

Listening Attendees:

Jenna Hellman, HDYO
Katie Jackson, HDSA
Emily Gantman, CHDI
Jennifer Simpson, HDSA

Eric Miller, Optio Bio
Kristin Keyes, HSG

FDA Representatives

FDA staff from a total of 24 different offices from across 5 FDA Centers attended the session (50 total people).

Office of the Commissioner (OC) – 5 *offices*

- OC/OCPP/OPA – Office of Clinical Policy and Programs/Office of Patient Affairs *(organizer)*
- OC/OCPP – Office of Clinical Policy and Programs
- OC/OCPP/OOPD – Office of Clinical Policy and Programs/Office of Orphan Products Development
- OC/OCPP/OPT – Office of Clinical Policy and Programs/Office of Pediatric Therapeutics
- OC/OCPP/OCliP – Office of Clinical Policy and Programs/Office of Clinical Policy

Center for Biologics Evaluation and Research (CBER) – 3 *offices/divisions*

- CBER/OCD – Office of the Center Director
- CBER/OCD/PS - Office of the Center Director/Policy Staff
- CBER/OTAT/DCEPT/GMB2 - Office of Tissues and Advanced Therapies/Division of Clinical Evaluation and Pharmacology/Toxicology/General Medicine Branch

Center for Drug Evaluation and Research (CDER) – 8 *offices/divisions*

- CDER/OCD/PFDD – Office of the Center Director/Patient Focused Drug Development
- CDER/OGD/ORS – Office of Generic Drugs/Office of Research and Standards
- CDER/OND/ODES/DCOA – Office of New Drugs/Office of Drug Evaluation Science/Division of Clinical Outcome Assessment
- CDER/OND/ON – Office of New Drugs/Office of Neuroscience
- CDER/OND/ON/DNI – Office of New Drugs/Office of Neuroscience/Division of Neurology I
- CDER/OND/ON/DNII – Office of New Drugs/Office of Neuroscience/Division of Neurology II
- CDER/OND/ON/DP – Office of New Drugs/Office of Neuroscience/Division of Psychiatry
- CDER/OTS/OB/DBI – Office of Translational Sciences/Office of Biostatistics/Division of Biometrics I

Center for Devices and Radiological Health (CDRH) – 6 offices/divisions

- CDRH/OPEQ/OHTI/DHTIA - Office of Product Evaluation and Quality/Office of Health Technology I/Division of Health Technology IA
- CDRH/OPEQ/OHTI/DHTIC - Office of Product Evaluation and Quality/Office of Health Technology I/ Division of Health Technology IC
- CDRH/OPEQ/OHTIII - Office of Product Evaluation and Quality/Office of Health Technology III
- CDRH/OPEQ/OHTIII/DHTIIIB - Office of Product Evaluation and Quality/Office of Health Technology III/ Division of Health Technology IIIB
- CDRH/OPEQ/OHTIII/DHTIIIC - Office of Product Evaluation and Quality/Office of Health Technology III/ Division of Health Technology IIIC
- CDRH/OSPTI/DAHRSSP - Office of Strategic Partnership and Technology Innovation/Division of All Hazards Response Science and Strategic Partnership

Office of Regulatory Affairs (ORA) – 2 offices

- ORA/OMPTO/OPQO/DPQOIII/PQIB – Office of Medical Products and Tobacco Operations/Office of Pharmaceutical Quality Operations/Division of Pharmaceutical Quality Operations III/Pharmaceutical Quality Investigation Branch
- ORA/ORS/OMPTSLO/NMPL - Office of Regulatory Science/Office of Medical Products and Tobacco and Specialty Laboratory Operations/Northeast Medical Products Laboratory

Huntington's Disease Pre-Symptomatic Population Listening Session Summary

Hellos, Greetings & Intros, FDA Opening Statement

The FDA Office of Patient Affairs welcomed everyone and thanked the participants for bringing together advocates from across HD Communities to help the FDA better understand the urgency and needs of pre-symptomatic, HD gene-positive young adults, along with their desire and willingness to participate in clinical trials.

Patient listening sessions are non-regulatory, non-binding meetings that provide a forum for the FDA to listen to the patient community.

Disclosure

There are no financial interests to disclose for any of the participants prior to today's Patient Listening Session. All participants are here today as individuals from the HD community who have invested their own time and money to put this session together.

Following the opening statement from the FDA, BJ Viau led the discussion and the advocates voiced their experiences and perspectives to better inform the FDA about what's important to the Pre-Symptomatic HD Community and why their help is needed. They thanked the FDA for their guidance in presenting this information, as well as the clinicians, advocates, and industry supporters for sharing their views, providing feedback, and sharing their survey among the community.

History of the HD community and how there has been a major paradigm shift in the communication and willingness to talk to young people about HD

BJ Viau | HD Community Advocate, Co-Founder of Huntington's Disease Youth Organization, Tested Negative for HD

Mr. Viau provided a high-level overview of Huntington's Disease (HD):

- HD is a rare neurological disorder with symptoms typically presenting in adulthood (30s/40s).
- It involves a progressive triad of cognitive, behavioral, and movement symptoms that slowly impact an individual's ability to function. It currently impacts about 40,000 people.
- HD is an autosomal dominant condition that give children of affected parents a 50% risk of inheriting the condition. Around 200,000 people in the USA are at-risk today.
- Research shows that 90% of those at-risk (not yet tested) choose not to get tested with the top reason being "no available treatments to do anything about course of disease."
- HD is a family disease that impacts partners, children, surrounding family, and friends.

He noted that there are typically 15 years of disease progression prior to death. Whether or not to get tested for HD is a very personal decision in the HD Community and many choose not to do so because of the lack of involvement and treatments they have post-diagnosis.

There are many HD patients who have tested positive for the gene but remain pre-symptomatic. This is the population that will be focused on during this listening session; those who carry the mutation and have seen parents, relatives, and or/friends suffer from the disease. These patients are underserved physically, socially, and emotionally and are here today as a cohesive community asking for help.

BJ's first memorable experience with HD was when he attended a local fundraising event back in 1994. His mom had recently been diagnosed with HD and he and his family wanted to get involved. After the event, BJ asked his dad to help him host his own basketball fundraiser which led to over $1 million raised and over 15 years.

As BJ got older and his mom's disease progressed, he felt the mental toll that young people with HD-positive family members experience, knowing they could have the disease. As he watched his mom suffer with psychiatric issues, physical limitations, suicide threats, and public issues, he decided that he would never allow himself to live to that point if he was gene positive. BJ thought about this every day and decided to undergo genetic testing at age 23 with a fake name and a cash payment. His results came back negative, meaning he wouldn't develop HD symptoms in his lifetime. Two years later, his sister also tested negative.

BJ witnessed firsthand the cruelty of HD and the impact it begins having on people at a young age. Being an advocate has helped him cope, but he wants to do something more to help accelerate treatments for HD positive pre-symptomatic people who aren't currently battling HD, but are constantly symptom hunting throughout their daily life wondering when HD will arrive. He noted that research shows negative biomarker changes well before symptom onset. He asked, "If we know negative changes are happening, why aren't we doing something about it sooner?" He pointed out that we've never even asked pre-symptomatic individuals about their desire to be treated when symptoms have already arrived. He concluded that now is the time to encourage more pre-symptomatic studies to give people the opportunity to save their own life.

Patient Stories

Tyler Orem, MD | Neurology Resident Physician & HD Family Member

Dr. Orem is a member of the HD community and is sharing his story today for the first time publicly. He hasn't been open about his experiences because of the pain that comes with sharing them.

Tyler's father was diagnosed with HD in 2008 and passed away only three years later, when Tyler was 16. In those few short years, his father had to stop working for the company he was with for almost 25 years, almost set the house on fire, and experienced the suicidal thoughts that are common among HD patients.

Dr. Orem's pains and experiences led him to pursue a degree in Neuroscience. When he tested positive for HD in 2016, he considered changing his path since his future was unknown. Ultimately, his experiences and the patient stories he heard inspired him to attend medical school. Tyler thinks about the disease every time he experiences a potential symptom and wonders if it is the beginning of his HD progression.

Dr. Orem noted that there are only two medications currently available for HD, both of which treat chorea movements, an HD symptom. There is nothing available that treats the underlying cause of the disease. Based on what we know about the disease progression, it makes sense to treat it as early as possible. Even though the brains of pre-symptomatic patients show changes 25 years before symptoms are visible, there are essentially no clinical trials for them to participate in, causing them to feel helpless. The phase three TOMINERISEN clinical trial that failed in 2021 was a very big blow to the HD community that still stings today. Every failed study is a crush of the future. He and the many other pre-symptomatic individuals are willing to take risks to be involved and want to be part of the fight.

Seth Rotberg | Gene positive, currently pre-symptomatic, active community leader and rare disease advocate, Board Member of HDYO

Seth's mom was misdiagnosed for seven challenging years, and each day was unpredictable. After she was finally diagnosed with HD, he was in denial for several years. Seth is not alone in his experiences and knows the challenges teens and caregivers face.

Only about 10% of the at-risk population gets tested for the disease, because many feel that there's no point since no further action can be taken. By the time Seth was 20 years old, he was exhausted and mentally drained. He decided that he needed to know what potentially lay ahead for him, so he was tested anonymously and found out that he is gene positive. He immediately got involved in the HD community by hosting fundraisers, volunteering for HDSA and HDYO, and doing a TEDx talk on his genetic testing story.

Like many others, Seth feels that he is in a race against time to figure out what can be done and wants to act now rather than waiting years for something to happen. He doesn't want to go through 10-20 years of his life with the same disease that took his mom and friends' lives. He can only participate in observational studies but wants to be able to participate in interventional trials that involve a potential treatment, including 3 clinical trials that are currently enrolling right now. If he and other pre-symptomatic patients aren't given the opportunity to participate in trials today, then by the time there is a possible treatment to slow down HD or halt the disease in its tracks, it will be too late.

Seth emphasized that he himself and the HD community are willing to take the risks to participate in these studies. He also mentioned how pharma still needs to make it accessible for someone like him who is still fully independent and working full-time. His ask is for the FDA to provide more guidance to pharmaceutical companies when it comes to including pre-symptomatic patients into their studies. The fairly new HD Integrated Staging System can help with this, while also letting pharmaceutical companies know that the community is willing to take the risk to participate in their studies.

Gia Mannone | Untested person at-risk for HD who struggles with decisions about staying untested while moving forward with life.

Gia's mom was diagnosed with HD in 1999 and passed away in 2016. She learned about her mom's diagnosis and her own risk when she was only 10 years old in 2005. Gia has been with her partner for 12 years and feels that her life is stagnant and cannot move forward because of her "at-risk" status. She described how HD has taken away her ability to make choices and how important it is to intervene early and fight the disease at every stage. Gia feels that if the FDA assisted the pre-symptomatic HD community by accelerating the opportunity for them to engage in clinical trials, the community would feel a sense of hope. She echoed the sentiments of others who spoke today that having the opportunity to participate in a clinical trial would be worth the risk of possible side effects. She also stated that if there was something she could participate in,

she would be much more comfortable getting the genetic test and moving forward with her life and relationship.

Danielle Valenti Mahoney | Gene positive, currently pre-symptomatic, mother and HD Community Volunteer.

Danielle described how her life changed when her mom was diagnosed with HD in 2009 and she became her mom's primary caretaker at a young age. Her mom chose to end her life in a nursing home in 2014 by refusing to eat. Danielle experienced so much stress that she developed autoimmune issues. She decided to get tested for HD to be proactive, and the results came back positive. Danielle recalled becoming pregnant and the emotional testing process she underwent while her child, whose test results were negative for HD, was in utero. Danielle is here today to ask the FDA to help accelerate the process of HD trials for pre-symptomatic individuals and noted how much more willing to get tested people would be if they knew there would be potential opportunities to participate in research.

Lauren Holder | Gene positive, currently pre-symptomatic, mother of two young children, active research participant, and Help4HD Volunteer

When Lauren was a teen, her grandfather was diagnosed with HD. She did everything she could to learn about the disease and immersed herself in the HD Community until she had to shift gears to take care of her father after his diagnosis at age 50. Lauren decided to have genetic testing done when she was 20 because she believes knowledge is power and wants to be as proactive as she can. She has participated in every available observational study and hosts an HD podcast. Lauren has two children. One is gene negative, and the other is untested. Lauren is sharing her story with the hope that it will impress upon those here today the urgency of supporting pre-symptomatic HD patients by providing guidance and helping them participate in clinical trials before it's too late.

Chris Brown | Gene positive. Has participated in a clinical trial in the past and is willing to participate in more despite the pain and commitment endured.

Chris is a patient advocate whose mom was diagnosed with HD in 2006 after experiencing an aneurysm. Her family history was largely unknown due to her mom being a foster child. They later learned that five of her biological siblings also had HD. Chris tested to go through genetic testing at the age of 32 and learned he was gene positive. It was shortly after that where he decided to participate in an 18-month clinical trial. He mentions how he knew he had to participate because when you have nothing else, and you're approaching your date of being clinically diagnosed with HD, you're willing to take that risk.

He shares about the challenges of the trial and how it was mentally draining to go in each month for his visit. Chris emphasizes the importance of providing resources and a good support system for each patient participating in a trial since, without his support group, social worker, doctor, and therapist, he wouldn't have stayed in the study.

Although the trial failed to meet its sought after endpoints and he faced a lot of personal challenges as a participant, he would take the risk again to participate in another study because he doesn't want to wait until he gets sick and end up like his mom. He is here to ask the FDA to help find ways to make clinical trials easier and more inclusive of pre-symptomatic HD patients.

Analysis of IRB approved survey highlighting the benefit-risk assessment of this population around clinical trials and future treatments.

An IRB approved online community survey aimed to capture the perspective of pre-symptomatic individuals living in the USA was conducted from June 6, 2022 – July 5, 2022. The methodology and general demographics of the survey were briefly reviewed. 164 respondents reached the mandatory progress point (Q16), 128 respondents completed the main survey (up to Q34), and 112 respondents completed the optional survey questions regarding a hypothetical scenario of a "near cure" treatment versus treatment mortality risk trade-off that was designed to provide a novel perspective on the HD burden of illness (Q35-38).

The study showed that the concerns about the potential effects of HD were relatively distributed among the symptom domains.

Other key takeaways from the survey results were that 90% of respondents felt that the pharmaceutical industry and 95% felt that the FDA could have higher sense of urgency to treat this population, 50% feel that both the FDA and pharmaceutical industry could make it easier to enroll in a trial, and 75% indicated sites/investigators can improve trial communication, facilitation, and motivation of candidates.

The optional, exploratory questions that were included in the survey attempted to gauge the HD burden of illness via a risk vs. benefit scenario. The participants were given a hypothetical scenario in which they were asked what percentage of mortality risk (maximum of 50%) they would be willing to accept to receive a highly effective gene therapy that slows disease progression by 90%. Individuals answered that when there were pre-symptomatic they would accept a 30% mortality risk, when they had subtle/early symptoms they would accept a 36% mortality risk, and when they had moderate symptoms they would accept a 42% mortality risk.

This is the first time a question of this magnitude and emotion has been asked to the HD community so further research is needed to better understand different treatment scenarios and situations that could be possible in the future. Mr. Viau shared that although the questions were not perfectly asked, it does show early evidence that the pre-symptomatic population is willing to take large risks to get access to an effective treatment.

The full results of the study will be made public in August 2022.

Summary & General Theme

The stories shared today highlight the negative mental and emotional impact HD has on people long before symptoms occur. The participants of today's session as well as those in the larger HD communities don't want HD in their lives and are willing to take risks to keep it from continuing to cause suffering and death. There is an urgent need for the FDA to act now to help pre-symptomatic HD patients participate in clinical trials before it's too late for this generation.

The speakers here today would like to continue discussions and bring in additional stakeholders to be part of the conversation that's just beginning. Today's presenters plan to organize a formal request for a Critical Path Innovation Meeting (CPIM) that should hit the FDA's inbox in Fall 2022.

On behalf of the speakers here today and the HD community, Mr. Viau thanked the FDA and everyone on the call for taking the time to listen to the information shared and for considering the opportunity to continue the dialogue to push for treatment options for the pre-symptomatic HD community.

FDA and Advocate Discussion/Questions

The FDA expressed their gratitude to today's participants for taking the time to lead the discussion and share their stories. They assured the group that the points discussed today are not unfamiliar to the agency and that they've been advocating for similar things. This disease presents the opportunity for early intervention and the end goal is to fully ameliorate it.

It was suggested that the survey questions be reviewed to determine if there was contextualization regarding the "90% slowing progression" hypothetical. It was also noted that it would be helpful to add a more inclusive non-gene therapy question as well as a broader scenario that correlates degrees of progression and willingness to take risks.

Closing / Wrap Up Remarks by FDA

The CPIM meeting request is welcome, and the group should continue providing relevant information to the FDA, who is willing to do all they can to assist these efforts.

If anyone has questions or comments regarding today's session, they should email patientaffairs@fda.gov.

Disclaimer

Discussions in FDA Patient Listening Sessions are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants. This report reflects the account of the perspectives of patients and caregivers who participated in the Patient Listening Session with the FDA. To the extent possible, the terms used in this summary to describe specific manifestations of [disease or condition], health effects and impacts, and treatment experiences, reflect those of the participants. This report is not meant to be representative of the views and experiences of the entire [disease or condition] patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.