Huntington's Disease - Pre-Symptomatic

FDA Patient Listening Session
Monday July 25th, 2022

Led by:
HD Community Advocates:
Seth Rotberg, BJ Viau, Tyler Orem, Lauren Holder, Danielle Valenti, Gia Mannone and Chris Brown

Financial Interest Statement

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.

THANK YOU

Huntington's Disease Society of America

HUNTINGTON'S DISEASE YOUTH ORGANIZATION

CHDI FOUNDATION

Pharma / Biotech

Connected with over 10 companies currently working in HD community trying to understand their views on pre-symptom population. As professionals in this space their insight is incredibly valuable.

Help 4HD

HUNTINGTON STUDY GROUP

seeking treatments that make a difference

hdreach

Helping families with Huntington's disease

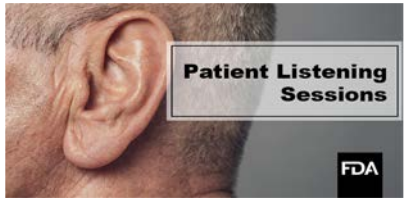
Optio Biopharma Solutions

Supported Market Research Data

No financial stake

Huntington's Disease Patient Listening Session 2022

Pre-Symptom Community



Goals for Today's PLS

- Help the FDA team understand the impact that HD has on people's lives before symptoms ever occur.
- Help the FDA better understand the urgency and needs of pre-symptomatic young adults, along with their desire and willingness to participate in clinical trials.
- Share with the FDA collected data from this sub-population of at-risk/pre-symptomatic about risk/benefit of participation in a clinical trial and needs for treatments for disease before symptom onset.
- Find a way to start a real discussion with the FDA and other stakeholders about accelerating treatments options for pre-symptomatic individuals

Huntington's Disease

Neurological brain disorder with typically symptom onset as adult (30s/40s)

Progressive triad of cognitive, behavioral and movement symptoms slowly taking away individual's ability to do everything. Impacts about ~40,000 today

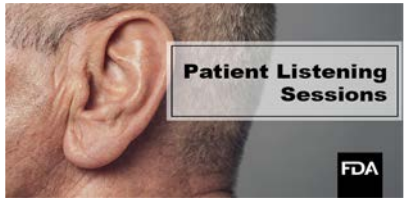
Autosomal dominant condition giving children of affected parent a 50% chance of inheriting condition. ~200,000 at-risk today.

Genetic testing allows individuals to learn if they have genetic mutation

Research shows that 90% of those at-risk (not yet tested) choose not to get tested, with top reason being *"no available treatments to do anything about course of disease"*

Family disease with major impacts to partners, children and surrounding family and friends

2015 FDA Held an HD PFDD Meeting Focused on Care Partners and Symptomatic Individuals



Pre-Symptom Population - Topic for Today!

Pre-Symptomatic / Prodromal / At-Risk = the population we are speaking about today.

Individuals who do yet have diagnosable symptoms, but carry the HD genetic mutation (whether they know it or not)

Fully independent, full-time jobs, home owners, professionals, parents of young children, community leaders, for the most part not seeing any HD doctors.

Until more recently this population has been hidden in a closet. Times are changing, but we need to move faster.

Research shows that there are biomarker changes happening 25 years before symptom onset

Although no “HD symptoms”, HD plays a MAJOR role in the lives of young people

VERY VERY VERY LITTLE this population can do today to stop their disease onset

B.J. Viau - HD's Past Impact

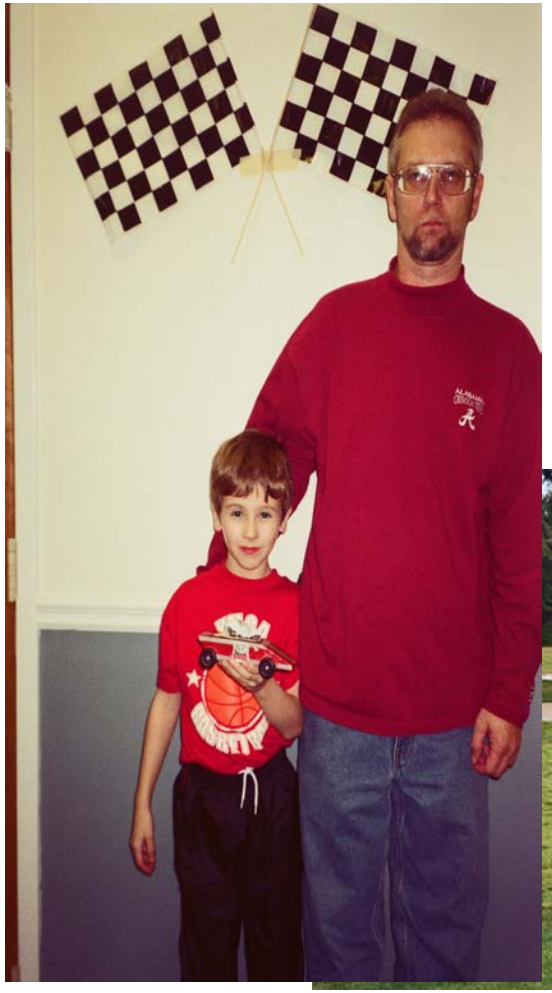
- 1995: Mom was diagnosed when she was 36.
- 2011: Mom passed away (BJ was 23)
- Childhood: outside looking in "sad, but fine". Inside was a rollercoaster every single day.
- 95 - 2012: Viau family held annual basketball fundraiser helping raise over 1M USD for HD
- 2010: first job post college was at pharmaceutical company marketing FDA approved treatment for chorea associated with HD
- 2010: Co-Founded Huntington's Disease Youth Organization (www.HDYO.org)

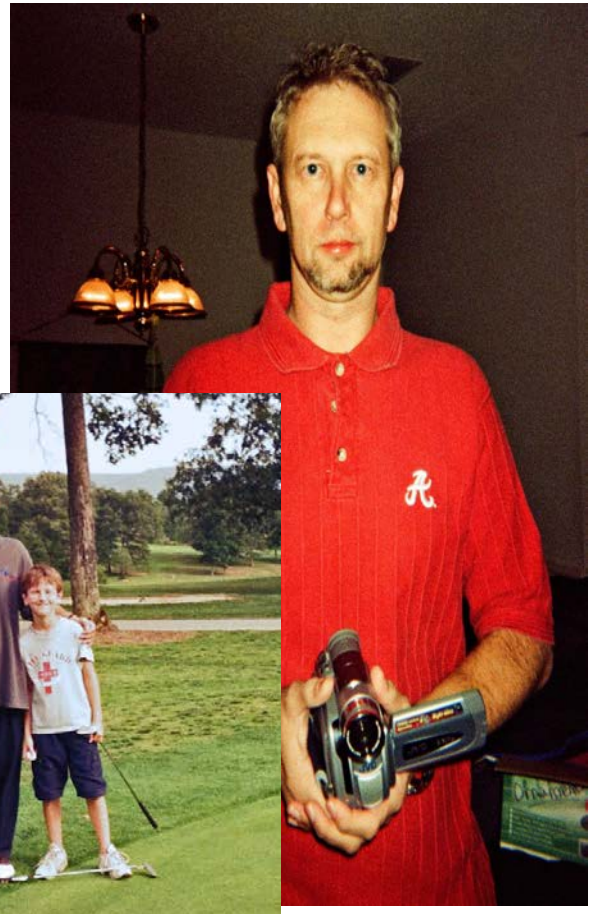
B.J. Viau - HD's Current Impact

- Current age: 35
- Professional career in pharmaceutical industry, personal career as HD Advocate
- Genetic test in 2010 (23 years old)
- Gene status: gene negative
- Technically HD is "out" of Viau family, only sister also tested negative
- Many friends will one day get HD, **IF nothing is done about it!**

"Clinical trial and treatment options for individuals who aren't yet symptomatic NEED to be accelerated.
What can FDA do to help accelerate this?

Tyler O - HD's Past Impact





- Dad was diagnosed in 2008, age 52
- Dad passed away in 2011 (Tyler was 16)
- Impact on childhood: Became distanced from father
- Founded Birmingham Team Hope Walk in 2016
- Presented research on cost of presymptomatic genetic testing at Huntingtons Study Group in 2019
- Graduated from UAB in 2017 with neuroscience degree then graduated from medical school in 2021

Tyler O - HD's Current Impact

- Current age: 26
- Resident physician, Neurology
- Genetic Test in 2016 (20 years old)
- Gene status: gene positive
- Would join clinical trial today? **Yes**
- Utilization of new biomarkers so that pre-symptomatic patients may participate in trials AND ensure pre-symptomatic patients have access to disease-modifying therapies once available

Seth R - HD's Past Impact

- Mom was diagnosed for 17 years
- Mom passed away in 2015 (Seth was 25)
- Impact on childhood: Informed about mom's diagnosis at the age of 15 and was in denial for several years.
- Put together 3-on-3 basketball charity event, took on leadership roles with HDSA and HDYO
- Did a TEDx talk on my story in 2018 which led to a career in the healthcare space

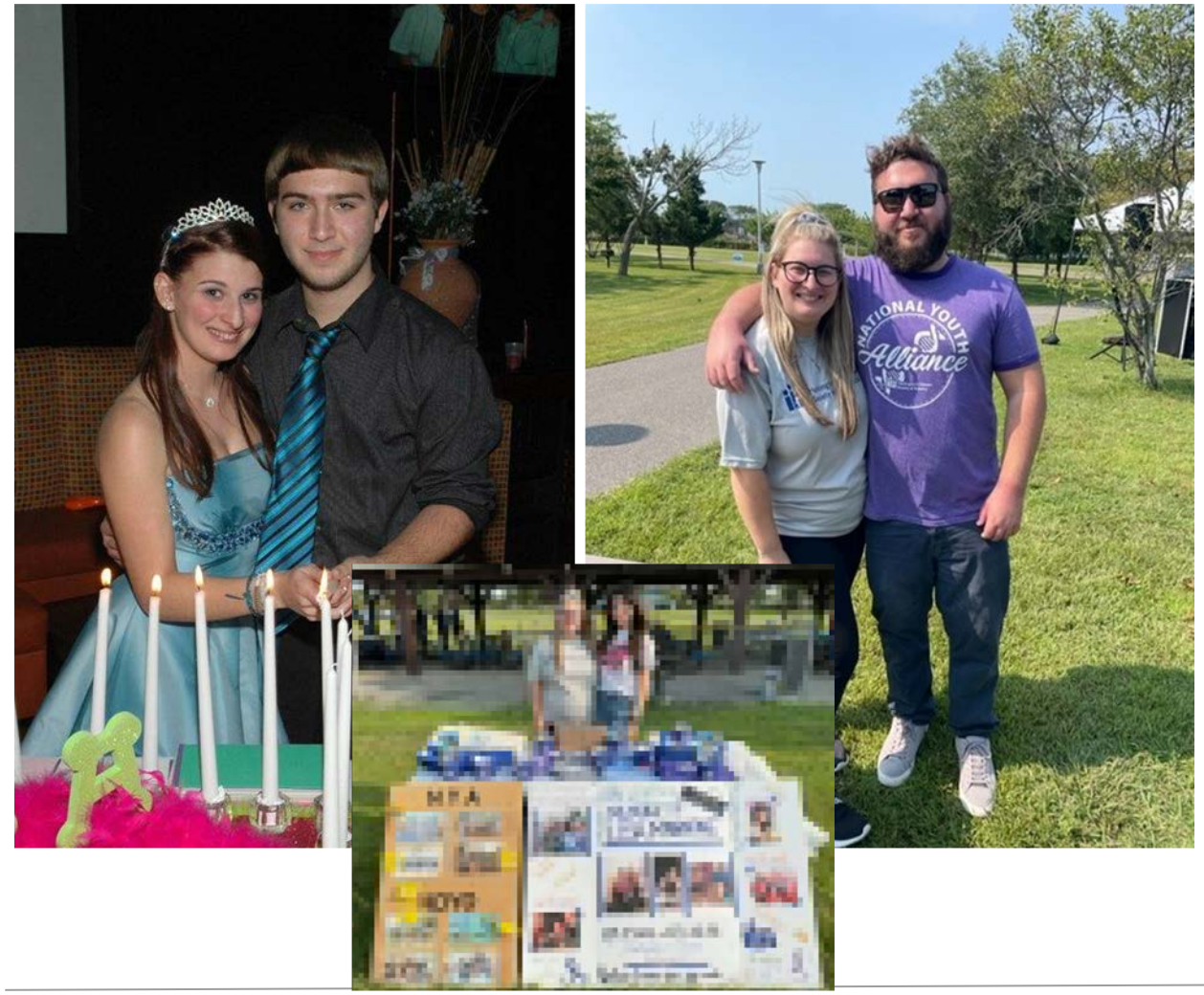
Seth R - HD's Current Impact

- Current age: 31
- Professional career in healthcare industry
- Genetic test in 2011 (20 years old)
- Gene status: gene positive
- Would join clinical trial today? **YES**
- Would like the FDA to figure out a way to better support clinical trials in pre-symptomatic patients **so I have more options to participate in studies prior to showing symptoms**

Gia M - HD's Past Impact

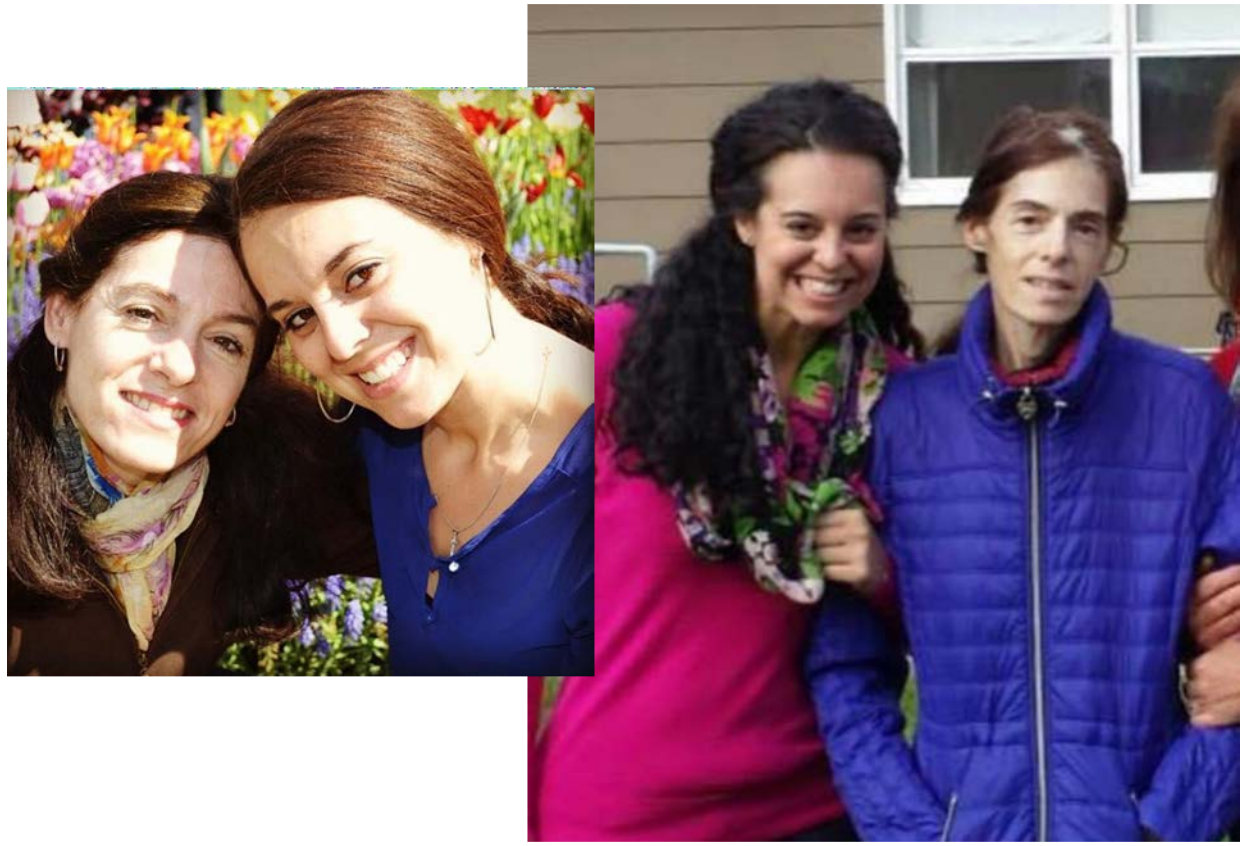
- Mom was diagnosed around 2005, approx. 35 years old
- Mom passed away in 2016 (Gia was 21)
- Impact on childhood: Was informed about mom's diagnosis and risk at age 10. **Caregiving took away a lot of childhood.**
- Family moved to FL in 2013 for easier living for her mom. Gia stayed in NY for her education and mental health.
- Family has attended HD fundraisers since 2012, HDSA Conventions since 2016, Gia has spoken on panels each year since 2016. Board member of HDSA's National Youth Alliance since 2017.

Gia M - HD's Current Impact

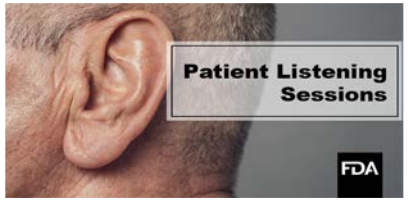


- Current age: 27
- Career: Social Worker in the Alzheimer's & Dementia space
- Gene status: At-risk
- Would join clinical trial today? **Yes!**
- Would like pre-symptomatic clinical trials to be more widely available because it would alleviate my fear and anxiety. **It would provide me the ability to move forward with my relationship. We need inclusivity!**

Danielle V - HD's Past Impact



- Mom was diagnosed in 2009, age 50
- Mom passed away in 2014 (Danielle was 29)
- Impact: Completely changed my life. Being a caretaker caused so much stress that I developed autoimmune issues.
- Gave a TEDx talk on my story in 2015
- Leadership roles with local HDSA Chapter
- Involved in Enroll-HD and Predict HD observational studies



Danielle V - HD's Current Impact

- Current age: 37
- Career: Director at a tech company
- Gene status: gene positive
- Tested in 2015 (age 29)
- Would join clinical trial today? **Yes!**
- Ask to the FDA: Find a way to better allow pre-symptomatic patients to participate in trials and have access to therapies when available. **Fighting HD means finding therapies BEFORE symptoms show.**

Lauren H - HD's Past Impact

- Dad was diagnosed at age 50, in 2009.
- Dad passed away in January 2021 (age 62).
- Impact on childhood: Grandfather diagnosed when I was 15, I became obsessed with understanding HD. When father was diagnosed, I became determined things would be different for my father.
- Published a book after grandfather's death, in 2008.
- Became very involved in HD community – HDSA Person of the Year in 2014, took over Help 4 HD podcast in 2018.

Lauren H - HD's Current Impact

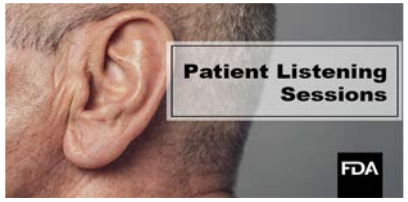
- Current age: 36
- Professional career with Alzheimer's Association, personal career as a podcaster and advocate for HD community.
- Genetic test in 2005 (age 20)
- Gene status: Gene positive
- Would join clinical trial today? **YES**
- Would like the FDA to support pre-symptomatic people with HD the choice to take on the risk of participating in clinical trials.

Chris B - HD's Past Impact

- Mom was diagnosed in 2006 at age 43
- Mom passed away in 2014 (I was 29)
- Impact on childhood: Mom developed symptoms when I was 16 and got diagnosed 5 years later due to an aneurysm.
- Moved to DC after mom passed and got involved in HD community through fundraisers, education days, and support groups.
- In 2018, I participated in an 18 month HD clinical trial.
- Still actively involved in the HD community as a public speaker to nonprofits and healthcare companies.

Chris B - HD's Current Impact

- Current age: 37
- Professional career in the restaurant industry
- Gene status: gene positive (tested in 2016)
- Would join clinical trial today? **YES**
- Would like the FDA to think of us as humans who have no other options finding ways to make trials easier and more inclusive to early-stage HD patients.



BURDEN OF HD SURVEY RESULTS AND ANALYSIS

The Perspective of Pre-Symptomatic Individuals Living in the USA

Methodology

- Authorship and review
  - Survey strategy by Seth Rotberg and BJ Viau
  - IRB review and approval by WCG Clinical Services
  - Survey contents and questions authored by Seth Rotberg, BJ Viau, and Optio Biopharma Solutions (*pro bono* work by Eric Miller and Debbie Neville)
  - Secondary analysis by Debbie Neville, draft report by Eric Miller, BJ Viau and Seth Rotberg
- Online survey predominantly targeting pre-symptomatic or at-risk for HD individuals living in the United States
- Software: SurveyMonkey
- Recruitment
  - Dissemination to by all HD Patient Advocacy Organizations (HDSA, HDYO, Help4HD, HD Reach)
  - Personal interaction with HD families at Huntington's Disease Society of America (HDSA)
    - Flyers with QR codes
    - Dissemination of survey links
  - Social media
    - Personal Facebook pages, private HD community groups
    - Instagram and twitter personal accounts
  - Personal email
- No honorarium or prize was offered as an incentive

Survey design, implementation, and completion rates

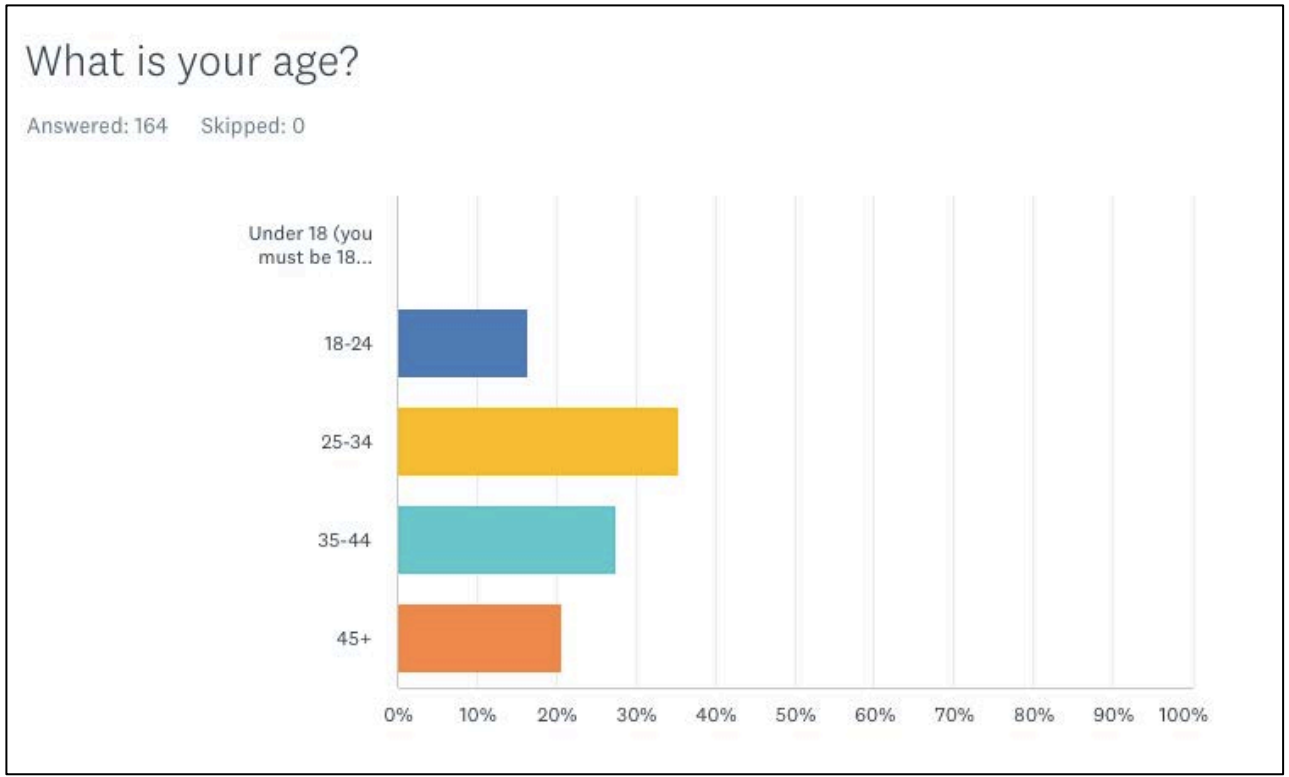
- Survey was opened on 6 June 2022
- Survey was closed on 5 July 2022
- Exclusions:
  - Those residing outside of USA
  - Respondents under age 18
  - Diagnosed symptomatic individuals

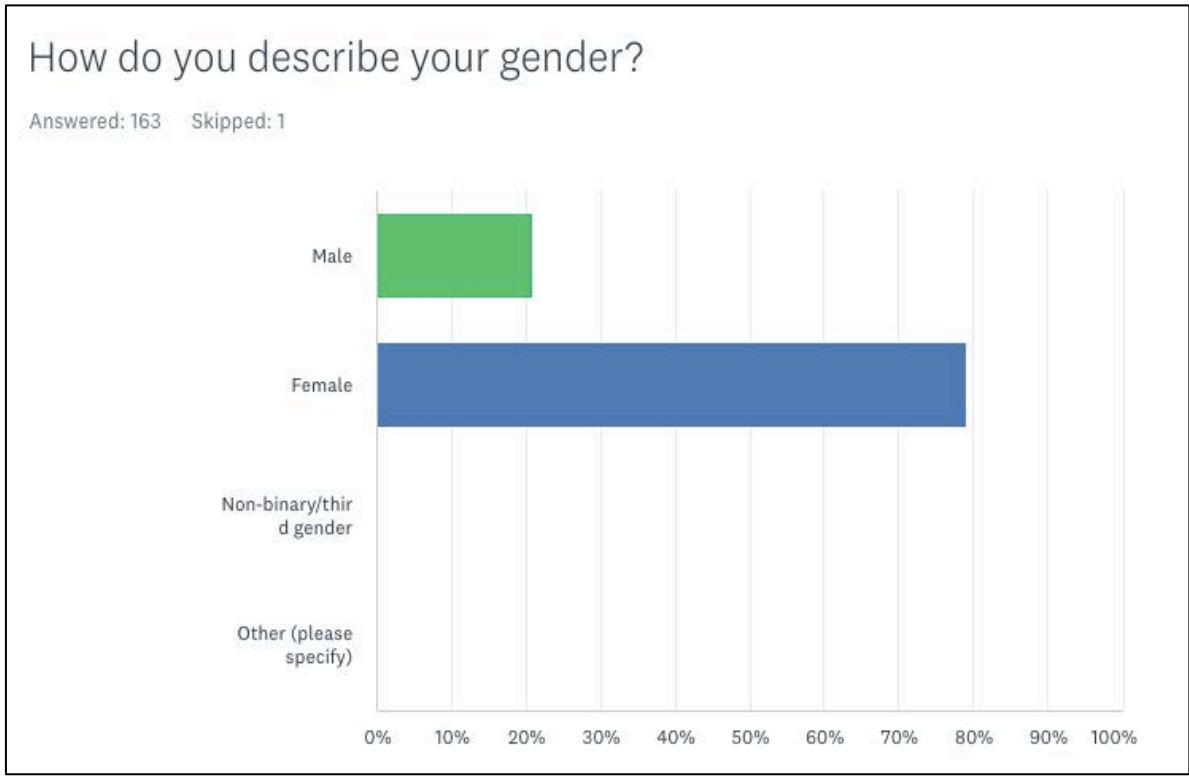
- Study completion:
  - 164 respondents reached the mandatory progress point (Q16)
  - 128 respondents completed the main survey (questions up to Q 34)
  - 112 respondents completed the optional questions regarding a hypothetical scenario of a “near cure” treatment versus treatment mortality risk trade-off designed to provide a novel perspective on HD burden of illness (Q 35 - Q 38)
  - It is estimated the average respondent took roughly 10 minutes to complete the survey

DEMOGRAPHICS

General Demographics

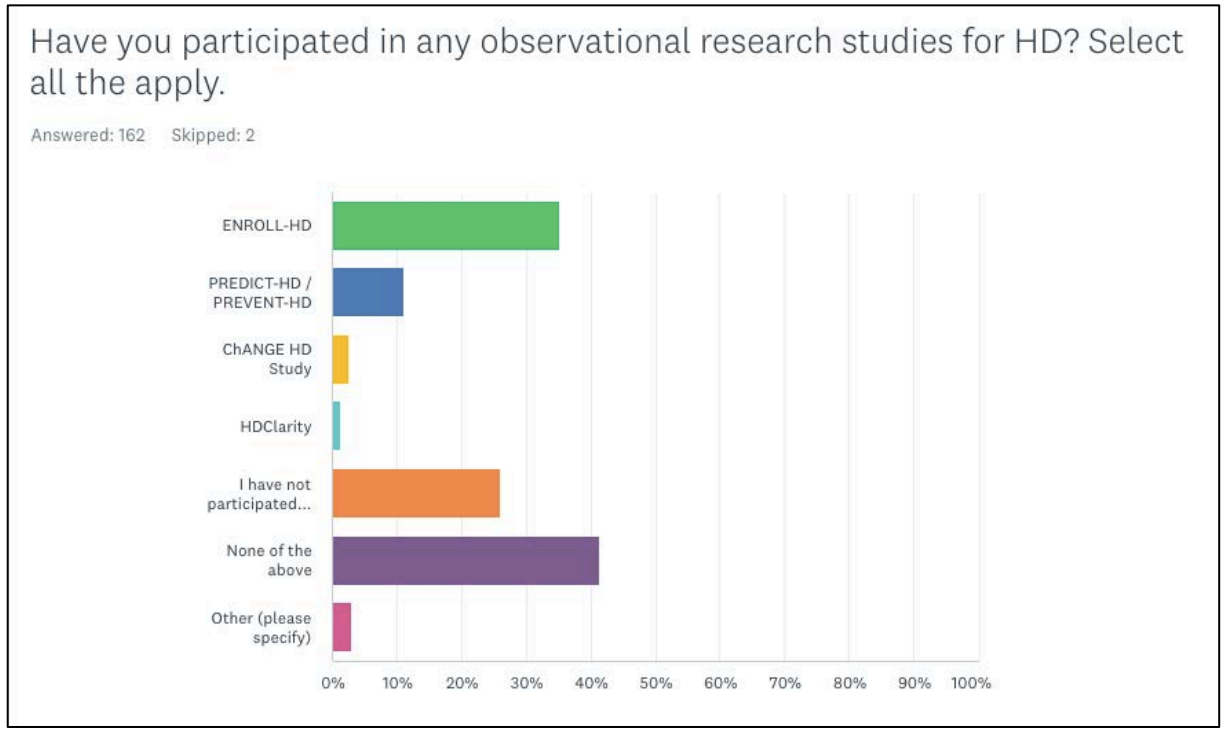
- 52% of respondents were under 35 years of age
- 79% of respondents were female
- 47% were married, 20% in a relationship, 20% single.
- 74% reported as being employed with 55% full-time employment
- 48% reported having one or more biological children
- 92% reported they had a biological sibling also at-risk or who had tested for HD

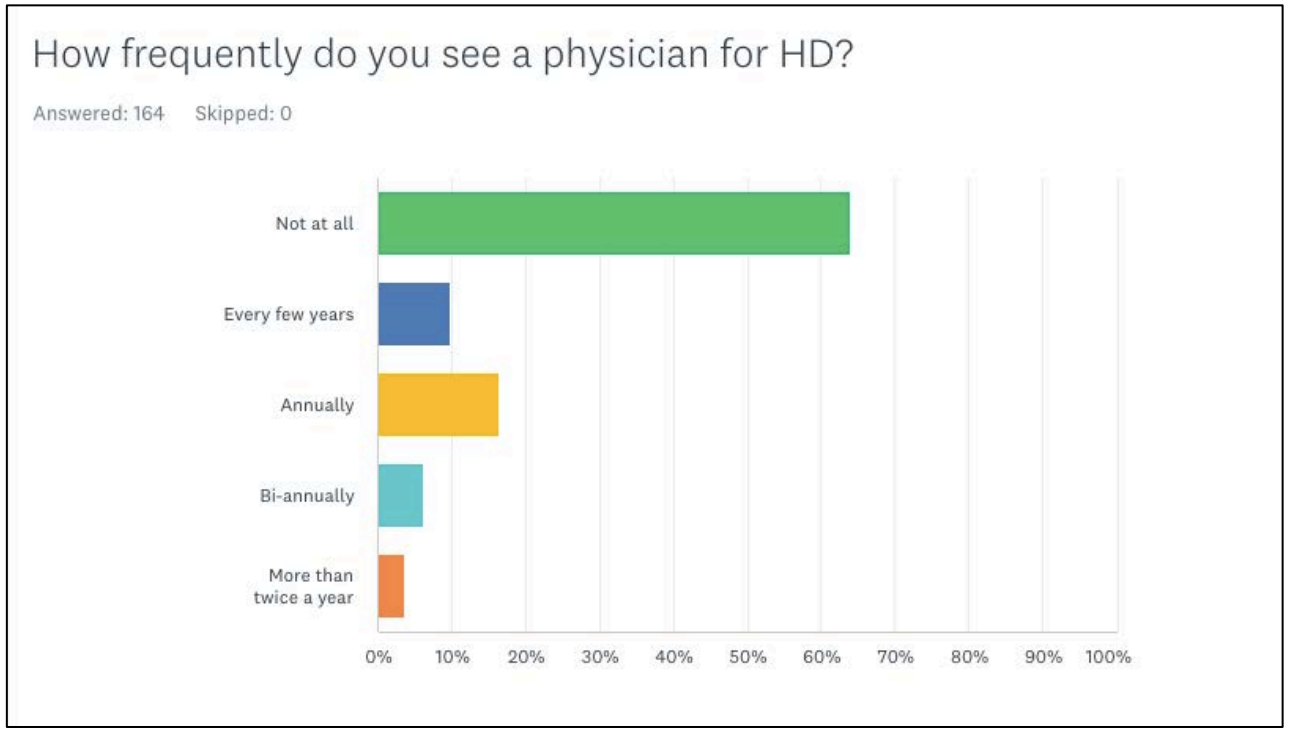




HD Demographics

- 50% had undergone genetic testing, 50% are still at-risk with unknown genetic status
- 50% of respondents have already participated in observational HD research studies
- 73% of respondents are seeing a clinician less than annually or not at all for HD-related evaluation or care





Respondents represent a mix of at-risk, pre-manifest, or diagnosed with only subtle or minor symptoms

ANSWER CHOICES	RESPONSES	
I am at-risk for HD, but I don't know if I carry the genetic mutation of HD (because I have not tested for it yet)	44.51%	73
I think I may have some symptoms but have not been genetically tested nor diagnosed clinically by a physician	4.88%	8
A genetic test confirmed that I have HD but I do not show symptoms of the disease, and have not been clinically diagnosed by a physician (referred to as pre-manifest or pre-symptomatic)	36.59%	60
I have been clinically diagnosed with HD by my physician within the last few years but have only subtle or minor symptoms	11.59%	19
I have been diagnosed (clinically or genetically) and have significant symptoms	2.44%	4
None of the above or I do not understand.	0.00%	0
TOTAL		164

76 percent of respondents were "somewhat open," "open," to "highly motivated" toward enrolling in an HD clinical trial

ANSWER CHOICES	RESPONSES	
I am highly motivated to enroll in an HD trial	37.80%	62
I am open to enrolling in an HD trial	23.78%	39
I am somewhat open to enrolling in an HD trial	14.63%	24
I am neutral regarding enrolling in an HD trial	11.59%	19
I am somewhat reluctant to enroll in an HD trial	3.66%	6
I am reluctant to enroll in an HD trial	3.05%	5
I am highly unlikely to enroll in an HD trial	5.49%	9
TOTAL		164

ATTITUDES TOWARD HD, CLINICAL TRIALS AND THE FDA

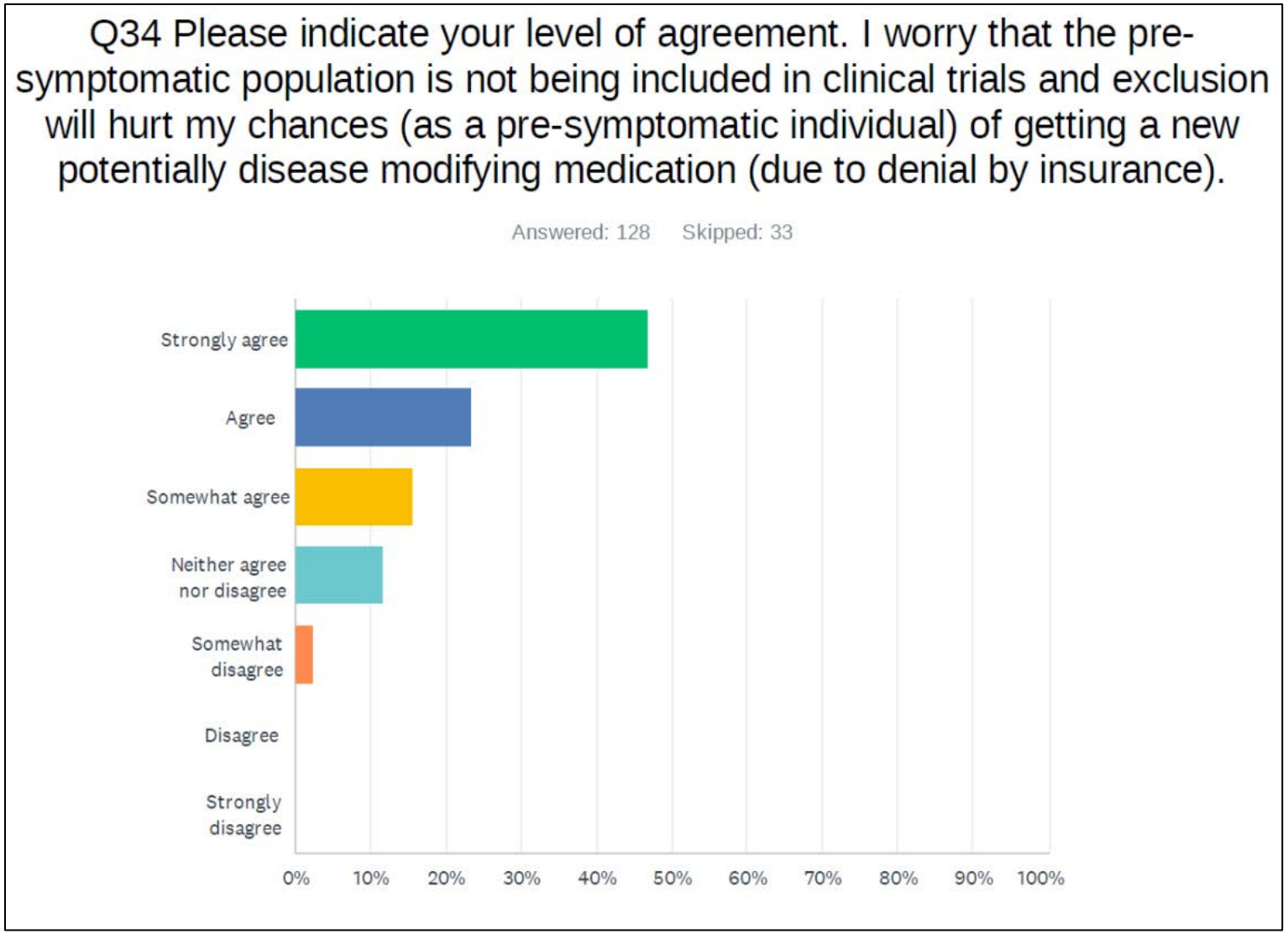
Concern about the potential effects of HD seem relatively distributed among symptom domains

ANSWER CHOICES	RESPONSES	
Financial effects – loss of income and cost of care leading to financial burdens for yourself and others	22.98%	37
Loss of independence – inability to do daily activities such as drive, cook, bathe, dress, etc.	52.80%	85
Social effects – impaired communication, loss of friends, strained family relationships, social isolation, etc.	35.40%	57
Psychiatric effects – depression, anxiety, apathy, anger, mood swings, etc.	32.92%	53
Cognitive effects – loss of executive function, memory, slowed thinking, etc.	39.75%	64
Living in a long-term care facility	6.21%	10
Total Respondents: 161		

The perceived "hassle factor" associated with a clinical trial is a major consideration for potential enrollees

- # of clinic visits, financial costs & amount of travel time were top barriers to join a trial in the future
- Treatment methodology (oral pill, vs brain surgery, vs spinal tap) was top consideration affecting clinical trial participation
- 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
- 75% indicated sites/investigators can improve trial communication, facilitation, and motivation of candidates

80+ percent are concerned low trial participation of pre-symptomatic individuals may lead to denial of treatment



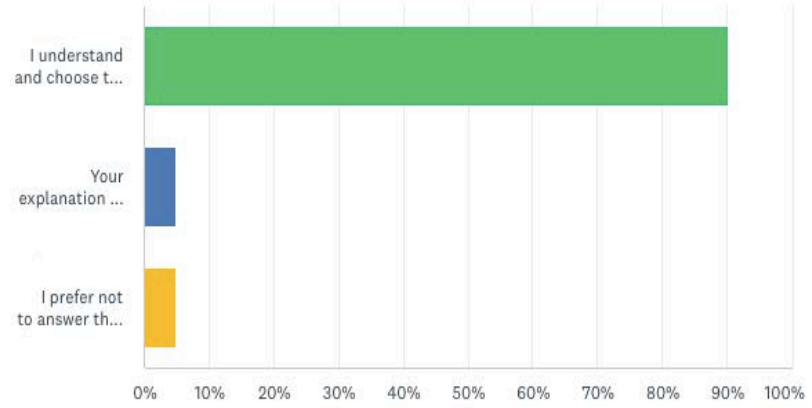
TREATMENT MORTALITY RISK TOLERANCE SCENARIOS

Exploratory questions providing a different measure of HD burden of illness from the perspective of predominantly pre-symptomatic or at-risk respondents

Exploratory (and optional) questions attempting to gauge HD burden of illness via risk vs. benefit scenario

Q35 This last question is designed to be a hypothetical Thought Experiment. A thought experiment is a hypothetical (imaginary, made up, not real) situation in which a hypothesis is described for the purpose of thinking through its consequences. It is a surrogate question to gain an understanding of the level of clinical trial risk you are willing to accept based on the potential benefit you would gain. Again, this scenario is totally hypothetical and is not linked to any real-world clinical trial or drug. When answering this question, please write in the blank the percentage of risk of mortality (death) you would take to receive a highly effective HD gene therapy that slows disease progression by 90%. As a reminder this is a thought experiment only. This question is not associated with the FDA, any pharmaceutical company, or any real-world investigational drug or therapy in clinical development. It is highly unlikely the FDA or pharmaceutical companies would be comfortable asking this type of surrogate question; but as patient advocates with a strong connection to the HD community we felt it may be a potentially valid measure of risk-to-benefit thinking for patients. NOTE: Again, this is hypothetical, but please try to imagine if such a gene-modifying drug able to slow progression by 90% was available, estimate the level of mortality risk you would take to gain access to the drug. The treatment would be a one-time administration with a permanent effect. Please consider this thought experiment at 3 different disease timepoints reflected in 3 different questions to follow:Please indicate as a percentage, the level of mortality (death) risk you would hypothetically be willing to take to receive a highly effective HD gene therapy that slows disease progression by 90%.

Given the controversial and complex nature of the risk versus benefit scenarios, they were included as optional



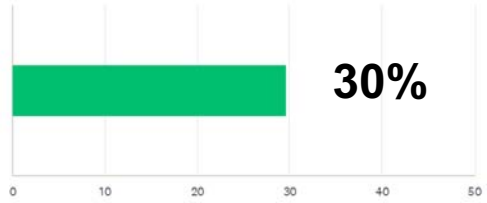
ANSWER CHOICES	RESPONSES	
I understand and choose to continue and answer the last 3 questions. (Please scroll down.)	90.16%	110
Your explanation is too unclear or this situation is too hypothetical and I choose not to answer the last 3 questions. (There is no penalty for this response and your previous responses will be anonymously preserved and provided to the FDA for the benefit of the HD community.) Thank you!	4.92%	6
I prefer not to answer the last 3 questions. (There is no penalty for this response and your previous responses will be anonymously preserved and provided to the FDA for the benefit of the HD community.) Thank you!	4.92%	6
TOTAL		122

Willing to accept _____% of mortality risk to receive a highly effective gene therapy that slows disease progression by 90%

Pre-symptomatic

Q36 Please consider this thought experiment at the disease timepoint where you are gene positive but have no clinical symptoms. This is when you are pre-manifest or pre-symptomatic (genetically confirmed with no clinically detectable symptoms, but MRI results identify disease onset where there is some brain volume loss/brain shrinkage).At this time point I would be willing to accept __% risk___ to receive a highly effective HD gene therapy that slows disease progression by 90%.

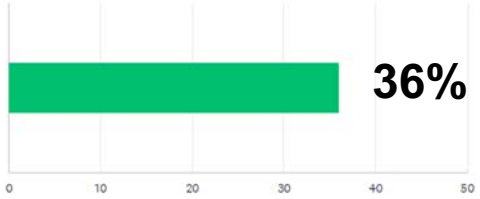
Answered: 113 Skipped: 48



Subtle/early symptoms

Q37 Please consider this thought experiment at the disease timepoint where you are gene positive and have mild/early symptoms. This is when you are experiencing subtle/early HD symptoms such as some difficulty concentrating, subtle motor symptoms such as occasional stumbling, clumsiness, and occasional irritable mood, or bouts of mild depression.At this time point I would be willing to accept __%__ risk to receive a highly effective HD gene therapy that slows disease progression by 90%.

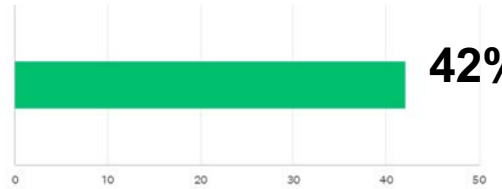
Answered: 112 Skipped: 49



Moderate symptoms

Q38 Please consider this thought experiment at the disease timepoint where you have moderate/significant symptoms. This is when you are experiencing moderate HD symptoms such as chorea, your ability to think has been impaired so you may be working at a lower capacity or are no longer able to work and some daily activities are becoming meaningfully difficult, and any psychiatric symptoms are becoming more pronounced. At this time point I would be willing to accept __% risk___ to receive a highly effective HD gene therapy that slows disease progression by 90%.

Answered: 112 Skipped: 49



Risk-acceptance increased as symptoms progressed indicating most seemed to understand the scenarios

Average scores progressed from 30, to 36, to 42

(50 was maximum percentage risk)

In Closing

- This is a multi-stakeholder effort and collaboration to save the lives of those living with HD.
- Speakers today and those who participated in the data represent a small portion of all involved.
- **Thank you for your time today to listen and hopefully learn a few things!**
- Our major ask today is for this to just be the start of this conversation & to allow the FDA and other stakeholders to all participate in a future discussion.
- **The presenters plan to re-group with other stakeholders and organize a formal request for future CPIM meeting.**
- Please keep an eye out for this request Fall 2022 and consider the opportunity to continue the dialogue and push treatment options for the pre-symptomatic HD community!

Reference & Resource Slide

1. A biological classification of Huntington's disease: the Integrated Staging System *(just published June 2022)*
2. Volumetric MRI-Based Biomarkers in Huntington's Disease: An Evidentiary Review
3. Mutant huntingtin and neurofilament light have distinct longitudinal dynamics in Huntington’s disease
4. Biological and clinical characteristics of gene carriers far from predicted onset in the Huntington’s disease Young Adult Study (HD-YAS): a cross-sectional analysis
5. Huntington's Disease - The Impact on Young People