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The Holy Grail of Huntington's disease research: the gene-positive, drug trials, and treatments

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At Risk for Huntington's Disease

HD is a genetically caused brain disorder that causes uncontrollable bodily movements and robs people's ability to walk, talk, eat, and think. The final result is a slow, ugly death. Children of parents with HD have a 50-50 chance of inheriting the disease. There is no cure or treatment.

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About Me

WEDNESDAY, NOVEMBER 30, 2011

The Holy Grail of Huntington's disease research: the gene-positive, drug trials, and treatments

Living in the gray zone between my genetic test for Huntington's disease and the inevitable but indefinite onset of this devastating brain disorder, I frequently feel forgotten in the excited discussion about impending clinical trials to test potential treatments.

HD researchers *want* to include people like me in trials, but haven't yet found a way to do so.

I am a victim in waiting, but without any of the noticeable, classic symptoms that would qualify me for participation in a clinical trial.

Because so much of the effort against HD is geared to helping the affected and the caregivers, I sometimes sense that we, the asymptomatic (or pre-manifest) gene-positive, have been relegated to second priority.

Emotional impact

I recognize that I am, for the time being, relatively fortunate, but the situation of perceived neglect, although unintentional, impacts me emotionally.

I wonder if symptomatic people feel jealous towards me – just as I have occasionally reacted with a furious inner jealousy when I learn that someone has tested negative. In other instances, I have briefly felt smug when I'm around or am thinking about people with symptoms.

In yet other instances, I feel compassion – and even profound guilt. I tell myself, "You have no right to worry! You're not even sick! Your life hasn't even been affected by the disease!"

Mostly, I just feel lucky to function normally and to have the opportunity to enjoy daily life.

But then I remember, "Yes, I *have* been affected by this disease. It took Mom's life at only age 68, and it has robbed me and my family of so many dreams."

I literally dreamt about my status last night as my mind worked on this article: a team of HD medical specialists put me through a series of exams to see whether symptoms had begun, and, as I awaited the results, I used a large red marker to edit this text.

Not coincidentally, it's time to set up my annual checkup at the Huntington's Disease Society of America's Center of Excellence for Family Services and Research at the University of California, San Diego.

So far, those checkups have not turned up any of HD's classic, outwardly noticeable symptoms.

But I am hyper-conscious of the fact that HD affects the brain ten or more years *before* those symptoms start. If an effective treatment isn't found in the next few years, I will be doomed to follow in my mother's footsteps.

Unable to reach the finish line?

The feelings of vulnerability and abandonment are magnified when I remember that no current or impending HD clinical trial includes participation of those of us who are pre-manifest.

In short, everything is currently focused on *stopping* HD already in progress. Nobody has yet developed a workable strategy for *preventing the onset* of HD.

Along with the scientists I have interviewed over the years, I am confident that a significant treatment or series of treatments will become available in the next decade or so to ameliorate the symptoms. Of course, I also hope for a "cure," but scientists don't use that term. They talk of controlling or managing the disease, because, of course, the defective HD gene cannot be removed from the body.

But I'm deeply worried that scientists will still take many more years beyond that to discover treatments for people like me, treatments that can stave off onset and/or minimize symptoms.

Ever since I tested positive in 1999, I have been racing against my own interior genetic clock to avoid symptoms and support the HD movement.

But the probability that my symptoms will start in the next few years leaves me with the sensation of the marathon runner who glimpses the finish line but ultimately cannot reach it.

Participation in studies

For now, pre-manifest people can participate in research *studies*. Whereas clinical trials aim specifically to test the safety, tolerability, and efficacy of a drug, studies seek to provide further information about a disease and/or strategies for treating it.

Studies can also include a test of safety and tolerability of a substance, as exemplified in the PREQUEL study, an investigation of coenzyme Q-10 exclusively in a pre-manifest group of 90 individuals. PREQUEL also aims to "assess the usefulness of certain markers of HD in the blood, which may help measure the rate of the disease progression or effects of medication." Its coordinators aim to use it as precursor to a clinical trial of coenzyme Q-10, an antioxidant produced in the brain and that has led to the improvement of symptoms in HD mouse models.

Major studies involving pre-manifest people include PREDICT-HD, COHORT, and the forthcoming Enroll-HD, a new, worldwide HD database expected to start gathering information in early 2012. (Click here to read my previous article on Enroll-HD). Enroll-HD is sponsored by the CHDI Foundation, Inc., the so-called "cure Huntington's disease initiative," a multi-million-dollar effort backed by a group of anonymous donors.

Through the above-mentioned Center of Excellence, I have participated in a number of studies, including COHORT, MRI studies, research involving HD and the sense of smell, and an experiment with instruments designed to measure loss in mobility. (Click here and here to read more.) I have also given blood and, for many years, participated in cognitive batteries and a Dementia Rating Scale study. I also took part as the only pre-manifest individual in the Huntington's Disease Drug Works program's "treatment now" observational trial of supplements, a rare opportunity for someone in my situation.

A 'long time' to gene-positive trials

The federal Food and Drug Administration (FDA) will not permit pre-manifest people to participate in clinical trials until beneficial results have first been demonstrated in symptomatic patients. The FDA also requires that researchers come up with useful ways to measure benefits in the pre-manifest.

I became acutely aware of the challenges of designing a drug for the pre-manifest during a July 2009 interview with Dr. Frank Bennett, the senior vice president for research at Isis Pharmaceuticals, Inc., in Carlsbad, CA. Along with CHDI, Isis is planning a clinical trial of a revolutionary drug that, if successful, would attack HD at its genetic roots and slow or perhaps even stop the progression of the disease in the brain.

Dr. Bennett told me that although the clinical trial will focus only on symptomatic patients, he was "optimistic" that a way could be found to help the pre-manifest, too.

Exhilarated by the promise of a potential "cure," I wrote several enthusiastic articles about Isis.

But privately I also felt somewhat desperate, because, as Dr. Bennett explained, finding a solution for the pre-manifest would take a "long time."

"Identifying when to start treating those patients is going to be a little tricky, as you might imagine, because you don't want to do it too soon," he said. By the same token, Dr. Bennett added, waiting too long would miss the opportunity to protect brain cells, which, once damaged, could not recover. "This is not a short-term fix but it's something that's going to take a large number of years to figure out how to optimally treat these patients."

Other path-breaking clinical trials face similar hurdles. Alnylam Pharmaceuticals, which is close to starting its own clinical trial for a similar attack on the disease's genetic causes, plans to inject its drug directly into the heads of patients, but they must first undergo an operation so that a very fine needle can be inserted into their brains (click here to read more). Medically, scientifically, and ethically speaking, only symptomatic patients can undergo the many risks of such a trial.

As Dr. Bennett and others have noted, the FDA will display great caution with these new kinds of drugs as well as the highly invasive delivery systems. Isis and Alnylam are striving to minimize levels of risk and invasiveness.

Seeking the Holy Grail

HD researchers face a major challenge in finding a treatment for the pre-manifest. It's really the Holy Grail not only for HD, but also for other neurological diseases such as Alzheimer's in which brain damage occurs many years before symptoms appear. Ideally, researchers want to design medications that will completely prevent these diseases.

In a recent e-mail to me, CHDI President Robi Blumenstein elaborated on this point with an analogy.

"The purpose of a cholesterol-lowering drug is to prevent heart disease, *not* lower cholesterol for its own sake," he explained. "Cholesterol-lowering drugs were tested on people *at risk* for heart disease. By analogy, we would like to test HD drugs on gene-positive people (like you) *at risk* of developing symptoms of HD *to see if the intervention prevents the appearance of symptoms* (that is, slows or arrests the progression of the disease)."

So, as researchers ramp up to clinical trials, this challenge is gaining greater attention. At the World Congress on Huntington's Disease in Melbourne, Australia, in early September, several scientists revealed their research into areas directly related to this challenge, including a study of brain changes in the pre-manifest, the development of measurements from MRI brain scans to predict and track symptoms, and a report on how functional MRI scans can detect brain activity changes before brain shrinkage occurs. (For details click here.)

In his remarks at the World Congress, Blumenstein pointed out that researchers need both gene-positive and affected individuals to participate in research studies now in order to prepare adequate measurement tools for clinical trials.

"It would be a shame if we have potential drugs to test but lack the tools to conduct the tests to see if they are having the desired effect," Blumenstein wrote to me.

"What the FDA will accept for regulatory purposes (i.e., to approve a drug) and whether we can satisfy ourselves that we are on the right track *scientifically* to modify the disease are two different questions," he added. "We will need people like you to participate in studies and, yes, trials to establish the latter. When we are successful with that the former may require some education and lobbying of the regulators to convince them that new approaches to approving drugs for genetic diseases are appropriate."

Waiting in the wings

For the beleaguered Huntington's disease community, clinical trials of potential treatments provide a ray of hope.

Looking back to my mother's diagnosis in 1995, I recognize that researchers have made stunning progress. But big hurdles remain, especially in developing preventive treatments for the pre-manifest.

I share the researchers' optimism, but I temper it with a sober assessment of the complexity of the challenges.

For me, time is ever more precious.

Once again, it's crystal clear that researchers ultimately rely on the participation of HD-affected families. Everybody can play a part – the untested at risk and the pre-manifest in research studies, and the affected in clinical trials.

The affected will bravely pioneer treatments by initiating the trials.

For the time being, however, gene-positive individuals like me must wait in the wings.

But we can assist immensely by supporting the affected, advocating for the cause, and, perhaps most importantly, taking part in the appropriate studies and experiments.

Together we dream of the day when we can all declare: "I'm HD-free!"

Today, being gene-positive for Huntington's disease threatens the well-being of me and my family. But if the science continues to accelerate, it will provide hope that carrying the HD gene will become little more than an inconvenience.

Posted by Gene Veritas at 9:51 PM

Labels: asymptomatic , brain , caregiver , CHDI , clinical trial , coenzyme Q-10 , Enroll-HD , FDA , gene-positive , genetic test , Huntington's , onset , pre-manifest ,

symptomatic , symptoms , treatment

2 comments:

Sean Thompson, PREDICT-HD Public Relations Coordinator said...
Hi Gene,

Great post; I admire the honesty with which you write. This is the kind of feedback that we on the research side need to hear from people in the HD community. The desire of people such as yourself who don't exhibit the clinical signs of HD to take part in clinical trials would be well received by researchers and reinforces what we're trying to discover in PREDICT-HD. This observational trial for people not showing clinical signs of HD is attempting to identify the earliest signs of HD to learn more about the progression of the disease, identify areas that can be targeted with treatments to slow or prevent onset before people's health starts to be affected, and validate measures that can be used in the very clinical trials for people not showing clinical signs of HD that you speak of.

Your dedication to doing whatever you can to contribute to HD research and fight against this disease shines through in the fact that you aren't lamenting the fact that you're being asked to participate in too many research trials and studies, rather, not enough clinical trials. The desire of yourself and others who want to do more (and we hear it often) is what is going to help researchers meet enrollment goals for clinical trials and observational studies. And difficulty meeting those goals is often what holds research up the most.

Thanks again for the post, and keep sharing your thoughts!

8:31 AM, December 01, 2011

Beverly said...
Hi Gene:

I've been busy with teaching duties at end of my semester, so I got behind in reading your blog. You know all about that. I just caught up and read several blogs at once. I want you to know how much I depend on you to share not just ideas and information, but also your emotional responses to what's going on. I'm the support person for someone in the early stages of being symptomatic, and your blog sometimes opens up ways for us to discuss HD.

I feel guilty telling you that because of your encouragement to participate in clinical trials, my fiance was able to participate in the trial of ACR-16. When I thanked you for that

encouragement before, I did not realize that you were not eligible to be in such trials.

I'm sorry if I rubbed salt in the wound.

Funny story: the doctors and I thought he did really well in the double-blind part of the trial. Guess what he was on? Placebo!

8:37 AM, December 05, 2011

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