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Overcoming a 'heartbreaking' moment for the Huntington's disease cause (Coping with disappointing clinical trial results – Part I)

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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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THURSDAY, APRIL 01, 2021

Overcoming a 'heartbreaking' moment for the Huntington's disease cause (Coping with disappointing clinical trial results – Part I)

In the wake of two deeply disappointing clinical trial updates in just one week, the Huntington's disease community is collectively grieving the loss of drugs that might have provided the first effective treatments for this incurable disorder.

As reported here, on March 22 Roche announced that it was halting dosing in the firm's historic Phase 3 clinical trial of its gene silencing drug tominersen because of unfavorable efficacy data, as seen by an independent review committee.

On March 29, Wave Life Sciences revealed that a similar effort – gene silencing drug candidates in two small, earlier-stage trials – had failed to lower the level of the mutant huntingtin protein in trial participants.

Whereas Roche partner Ionis Pharmaceuticals' success in using tominersen to reduce the protein represented a milestone and moment of euphoria in the HD community, the stall in the effort to transform this type of drug into an actual treatment in both the Roche and Wave programs has created one of the most frustrating moments of the last several decades.

With its usual resilience, the community and its leaders have responded quickly, organizing outreach events and furnishing resources to put the Roche results in perspective and provide ways to cope with the shock and disappointment.

Grieving because of lost hope

Huntington's Disease Society of America
International Huntington Association
Huntington's Disease Drug Works
Huntington's Disease Lighthouse
Hereditary Disease Foundation
Huntington's Disease Advocacy Center
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HDSA Orange County (CA) Affiliate
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"It has been heartbreaking," Katie Jackson, the president and CEO of Help4HD International, said of the Roche stoppage, which, she added, has "rocked the HD community." Jackson's husband Michael Hinshaw died of HD in 2019 at age 40, and she has three children at risk for being carriers of the HD mutation.

Jackson spoke during a March 24 panel discussion on Help4HD TV titled "Grief – When a clinical trial doesn't go as hoped it is a loss."

"I'm definitely grieving," said Help4HD activist and podcast host Lauren Holder, 35, like me a carrier of the HD gene. The mother of two young at-risk children, Holder lost her father Stephen M. Rose, Jr., 62, to HD in January.

Holder said that she felt "extremely sad and disappointed and terrified" by the Roche news. The possibility of a treatment was "huge for us to have – to get so close to where it did and have all of the information so good on it" over the past several years, but then suddenly that hope "was taken away."

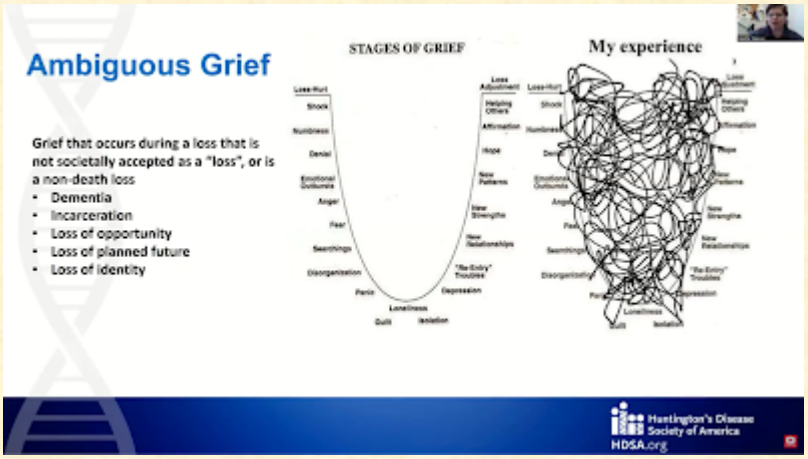
HD gene carriers "don't have time to just go back to the beginning" of another trial, "because that could mean symptoms" might have already started, she lamented.

"Everyone is human," observed Help4HD vice president and CFO Katrina Hamel. "We all are feeling something because of this news."

"I felt like someone punched me in the stomach," said MaryAnn Emerick, an HD family member, in a March 25 webinar on the Roche announcement and grief sponsored by the Huntington's Disease Society of America (HDSA), where she works as the manager of youth and community services. "I started hysterical crying."

Emerick had built "more hope" in the potential of the Roche trial than she had realized, she added.

About 500 people took part in the webinar, including clinicians, scientists, social workers, and HD family members – a sign of both the impact of the Roche announcement and of community solidarity.



A slide from the HDSA webinar that focuses on the concept of ambiguous grief and compares the textbook-version stages of grief with how grief can actually be experienced by an individual. Presenting the slide is Jennifer Simpson, LCSW, HDSA assistant director of youth and community services (screenshot by Gene Veritas, aka Kenneth P. Serbin).

Tracking the project since 2008

I, too, have grieved the outcome of the Roche trial. I began tracking the program in April 2008, less than a year after tominersen developer Ionis (formerly Isis Pharmaceuticals) had initiated the search for a gene silencing compound. I reported on every key turn of the project, with many visits to the Ionis facility in Carlsbad, CA, about 30 miles from my house.

The prospect of taking an Ionis-Roche drug developed in my own community has long felt like a protective blanket shielding me from Huntington's. Now, that blanket has been ripped away.

Like other HD family members, the Roche announcement has led me to relive the difficult moments in my family's HD history, including my mother's inexorable decline and then death in 2006. Since the day of the Roche news, I have aggravated the unhealthy, usually unconscious habit of clenching my teeth.

I *do* add my deep thanks to the chorus of gratitude for the participants in the Roche trial and their families and – once the data is analyzed in the coming months – for their contributions to a greater understanding of HD science. In Emerick's words, "They are the foundation for the future."

The team effort was not a 'failure'

Other perspectives on clinical trials can perhaps help the community overcome the grief and disappointment.

In 2005, when I was preparing articles for the HDSA-San Diego chapter newsletter on a research project in San Diego sponsored by the Hereditary Disease Foundation, a scientist educated me on a key point: if a scientific experiment does not produce the desired result, that does not mean it failed. On the contrary, such an experiment is valuable in its own right because it brings forth new information and helps point the way for future experiments.

Clinical trials *are* scientific experiments, a fact underscored by the scientific and medical personnel at the HDSA webinar. Interestingly, nobody said "failure" at that event nor at the one by Help4HD.

Indeed, the Roche and Wave trials should *not* be considered failures – especially because of the very large team efforts involving not just the scientists and the participant families, but many kinds of support staff from inside and outside those firms.

Riding – and learning from – the clinical trial roller coaster

Emerick described another common feeling that can ultimately help the community move forward in the search for effective treatments: "I'm going on this roller coaster ride of emotion and feeling super-motivated and resilient and then all of a sudden just wanting to cry and wanting to know why – give us answers."

Leading HD scientist Robert Pacifici, Ph.D., anticipated this scenario in February 2020. At that point, Roche was approaching

the midpoint of its trial and, significantly, other clinical trials were also ramping up – as others do today.

"Getting to this stage – which we've all so been hoping for – is still a bit of a roller coaster ride," Dr. Pacifici told me in an interview at the 15th Annual HD Therapeutics Conference, sponsored by CHDI Foundation, Inc., the nonprofit virtual biotech dedicated solely to finding HD therapies and headed by Pacifici. "You have to be able stay in our seats and weather the ups and downs. I think we're well-poised for some great news, as some of these trials hopefully report out. Even a whisper of efficacy would be just amazing."

However, there will also be "disappointments, where, despite our best attempts, some of the things that showed so much promise didn't end up meeting their endpoints," he cautioned. "But it's going to be a learning roller coaster. So hang in there. Don't lose hope."

The HD-affected (and their caregivers) should keep informed about the trials by consulting their physicians, attending meetings of patient organizations, and keeping abreast of developments in such sources as HDBuzz and this blog, Dr. Pacifici advised.

Become knowledgeable, he urged, "so that you are not disproportionately spooked or elated when these bits of information come out."

Many of us *are* scared. However, in the words of my "HD sister" Holder, now is the time to reach out to one another, and remember that the scientists have continued their quest.

Nobody has to ride that roller coaster alone.

(The second part of this series will examine other key programs in the Huntington's disease drug pipeline.)

(Disclosure: I hold a symbolic amount of Ionis shares.)

Posted by Gene Veritas at 3:08 PM

Labels: clinical trials , HDSA , Help4HD International , huntingtin lowering , Huntington's disease , Ionis , Lauren Holder , MaryAnn Emerick , Roche , stages of

grief , tominersen , treatments , Wave Life Sciences

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