The Hereditary Disease Foundation held a topic-specific workshop focused on "Therapeutically Targeting DNA Repair and Somatic Expansion" in New York City on October 28th and 29th, 2023. This was the HDF's first topical workshop in about a decade, reestablishing the tradition of a visionary model that helped lead to the discovery of the casual gene for HD. HDF workshops promote conversational research discussions to share ideas, establish collaborations, and advance the field's understanding of complex problems. The workshop brought together 27 of the world's leading experts on somatic repeat expansion and DNA repair from both academia and industry that work on Huntington's disease (HD) as well as other diseases and disorders. Following a clinical interview-style discussion with an HD family, workshop participants delved into deep discussions surrounding somatic repeat expansion and DNA repair, approaches and limitations, and therapeutic targeting for HD.

Huntington's disease: live for the moment

The workshop began with an individual living with and their partner sharing their journey with HD. All workshop participants introduced themselves and described what led them to work in the HD field. A common theme amongst the researchers was that others already working in the field drew them in, with a significant number saying they were personally recruited or inspired by Dr. Nancy Wexler. Our speaker opened their life to this group of researchers with an interview conducted by Dr. Sarah Tabrizi. Without a history of HD in their family, our speaker and their family were puzzled by their father's seemingly sudden changes in his late 40s. They shared an honest perspective about how HD affected their father's temper, causing violent, angry outbursts. While work and their job were once a central focus of their life, their inability to complete tasks and challenges around their working environment led to them leaving their career. The speaker is now an active member of the HD community, advocating for those living with HD. They also shared that they now see the effect that HD has had on their own memory, mood, and balance. They are currently taking part in the Sage Therapeutics clinical trial for SAGE-718. In a heartwarming and insightful moment, their partner recounted when their relationship first became serious. Our speaker living with HD shared their trepidation about a long-term relationship because of their HD gene status and what it would mean for their future, to which their partner responded, "Why are you going to let it stop you from living now?". Our speaker also bravely underwent a UHDRS exam by Dr. Michael Flower in front of the group to give a glimpse into what a clinical appointment is like for people living with HD.

Day 1 focused on the basic science of somatic repeat instability and the mechanisms driving that – structure of loop outs, mechanisms involved in repeat expansion, proteins that contribute to

One of the key themes that the group kept returning to over the morning session of day 1 was DYNAMICS – how dynamic are these structures, how long do they last, and is that sufficient for protein binding that allows for expansion. While the group noted the dearth of tools and techniques needed to assess these structures *in vivo* because of how dynamic these structures seem to be, it was stated by many that understanding this may be the lynchpin for unlocking the tie between structure and expansion.

The conversation was driven by a very lively debate surrounding non-homologous end joining, nicks, polymerases, and nucleases. There were conflicting theories surrounding the mechanism behind, and species of, DNA breaks that are the catalyst of expansion. Understanding this is perhaps the first step in uncovering the mechanistic cascade of expansion. The conversation was also driven by hypothetical models surrounding the timing of protein complex formation at loop outs and strand breaks that would allow for expansions or contractions.

Day 2 focused on in vivo findings from mouse and human studies, therapeutic intervention, biomarkers of somatic expansion and target engagement, and safety.

The discussion centered around opposing hypotheses for somatic repeat instability generated using human datasets and the timing of transcriptional dysregulation within this process. There are conflicting theories on when gene expression changes come into play pathologically – before or after the rapid expansion phase of somatic instability. The group also shared published and unpublished data on several mouse models, including the proteins that were targeted to modulate somatic instability, which included MSH3, PMS1, and FAN1.

There was a vigorous discussion about therapeutically treating somatic repeat instability and the gaps that need to be filled before we can reasonably move to the clinic with this approach. Many questions about what needs to be done were posed, for which the field currently has few answers, making it clear that clinical metrics and readouts need to be defined and elucidated before we can move forward.