Gene Positive: Now What?

Sasha Duffy
Department of Neurology
Objectives

• We are living in a very exciting time
• Getting and processing the news
• Putting the pieces together
• Do I have HD? When will I get HD?
• Living positively: getting connected and involved
• HOPE in now and what is coming down the pipeline
Addressing the crowd on 18 May, Pope Francis spoke warmly, telling people that they are all precious in the eyes of the church. He then spent nearly an hour with about 150 patients, their families and their caretakers, greeting and hugging them one by one.
Anyervi, 13, and Brenda, 15, who both have early-onset Huntington’s.

*Photograph: Pier Paolo Lisarelli*

Excitement as trial shows Huntington's drug could slow progress of disease

Hailed as ‘enormously significant’, results in groundbreaking trial are first time a drug has been shown to suppress effects of Huntington’s genetic mutation

A landmark trial for Huntington’s disease has announced positive results,
Getting the news

• Getting life altering news. This is a process. Let it settle in.
  – All or none of the above.

• Be kind to yourself

• Slow and steady
  – Start putting your pieces together
  – Start to educate yourself: Know your support team, your resources and your options. Learn about HD.
Sharing the news

• This is your information
  – Who to tell? When to tell? How to tell?
• Family? Friends? Coworkers?
• Take your time to answer this question for you. It will be different for everyone.
Identifying self

- From a HD family
- Daughter or son of a person with HD
- Family member
- At risk
- Gene positive
- I have HD
- All of the above
- Who am I?
Gene Expanded

Manifest HD
The results

• Autosomal dominant
• Huntingtin gene localized to Chr 4p in 1983 then discovery of location 1993
  – Genetic testing programs: 1986 with linkage testing and direct genetic testing in 1994
• The results:
  – Repeat of 26 and smaller = normal
  – 27 – 35 = not associated with disease, “anticipation” (Rare, 3.2%)
  – 36 – 39: reduced penetrance (Rare, 2.7%)
  – 40 or more: HD
FIG. 1. Huntington’s disease onset ages. The age at onset distribution in Huntington’s disease is very broad and may vary from as young as 3 or 4 years of age to as old as 85. Onset presented here represents initial signs of motor impairment.

FIG. 2. Normal and expanded HD repeat sizes. The distribution of repeats for Huntington’s disease may be divided into four categories. Repeats of 26 or fewer are normal. Repeats between 27 and 35 are rare and are not associated with the expression of the disease, but occasionally fathers with repeats in this range will transmit a repeat to descendants that is expanded to the range for expression of the illness. Repeats between 36 and 39 are associated with reduced penetrance whereby some individuals will develop HD and others will not. Repeats of 40 or larger are associated with the expression of HD. Persons carrying repeats in this range will develop HD, assuming they do not die of other causes before onset.
The # of CAG repeats accounts for about 60% of the variation in age of onset, with the remainder represented by modifying genes and environment.
Clinical Presentation

- **MOTOR**: chorea, slowed ocular movements, bradykinesia, dystonia, balance and gait changes
- **MEMORY**: Cognitive impairment
- **MOOD**: Behavior and psychiatric problems
- And so much more...
- Each patient has a unique course
Disease Presentation

- Chorea present in 90% of patients initially
- Motor symptoms will progress
- Cognition difficulties will develop
- Psychiatric/behavioral issues less predictable

Figure 1: Progression of Huntington's disease over a patient's lifespan
Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington’s disease in the TRACK-HD study: analysis of 36-month observational data

Sarah J Tabrizi, Rachael I Scali, Gail Owen, Alexandra Durr, Blair R Leavitt, Raymund A Roos, Beth Borowsky, Bernhard Landwehrmeyer, Chris Frost, Hans Johnson, David Crawford, Ralf Reilmann, Julie C Stout, Douglas R Langbehn, and the TRACK-HD Investigators*
Prodromal HD

- **Prodromal phase**
  - TRACK HD (2007): changes in function and imaging up to 16 years prior to diagnosis
  - PREDICT-HD (2012): clear changes in cognition up to 15 years before motor diagnosis
Threshold for diagnosis

The Unified Huntington’s Disease Rating Scale (UHDRS)

To what degree are you confident that this person meets the operational definition of the unequivocal presence of an otherwise unexplained extrapyramidal movement disorder (e.g., chorea, dystonia, bradykinesia, rigidity) in a subject at risk for HD?

- 0 = Normal (no abnormalities)
- 1 = Nonspecific motor abnormalities (<50% confidence)
- 2 = Motor abnormalities that may be signs of HD (50%-89% confidence)
- 3 = Motor abnormalities that are likely signs of HD (90%-98% confidence)
- 4 = Motor abnormalities that are unequivocal signs of HD (≥99% confidence)
Figure 4: Life cycle in Huntington’s disease

This figure depicts the sequential evolution of events and ultimately recurrent nature of Huntington’s disease from the perspective of a child born to an affected parent. The family events timeline shows events that might occur in different sequences for different individuals; irrespective of timing, such events can have clinically significant implications.
Am I having symptoms?

- Not every trip or dropped item is HD
- There are emotional responses that are situationally appropriate and you have A LOT going on
- It is natural to be distracted when we have A LOT going on
- So it is not always HD
- But it can be
Anosognosia
Your Medical Team

• HD COE: Neurologist, Psychiatrist, Social Worker, Genetic Counselor, Therapist, Research Coordinator
• Therapy: Physical, occupational and speech
• Dietician
• Primary care physician
• Dental care
Medical Team

• Routine Care with PCP
• Seeing your neurologist or HD team on a regular basis
  – Memory, motor and mood
  – Early diagnosis = early intervention
  – Prodromal intervention
• This is a journey together
• We are here to educate, support and care for you and your care partners
Taking care of yourself

• Physical Health
  – Heart healthy diet
  – Routine cardiovascular exercise
    • Find what you enjoy
  – Regular follow-up with PCP

• Mental Health
  – Wellness
    • Feed your soul
  – Mental health provider
  – Support groups
Creating Your Community

• Build your support network
  – Family, friends, HD family
  – HD warriors
  – Meeting others who have walked in similar shoes

• Your point person

• Consider telling someone at work

• Support groups

• Social media

• Outreach
Understanding HD

• Sources of Education
  – Your medical team
  – Many resources out there
  – Attending events like this and others

• Learning about the symptoms of HD
  – What is HD?
  – What are the symptoms?
  – How do they affect individuals?
  – Is what I am experiencing normal?
  – What treatments are available to me?
  – What research is out there for me?
Future Planning

• Relationships
  – Do I date? Do I get married?

• Family planning
  – Do I want to have kids? What are my options?

• Work

• Disability

• Long-Term Care
Resources

• Huntington’s Disease Society of America (HDSA): http://hdsa.org/
  – Support Groups
  – Team Hope Walks
  – Annual Convention
  – HD Trial Finder
• Help4HD: https://help4hd.org/
• HD Buzz: https://en.hdbuzz.net/
• UC Davis Center of Excellence: https://www.ucdmc.ucdavis.edu/huntingtons/
Raising Awareness

• Telling people about HD
• Sharing your story
• Greater in numbers
• Be a part of the solution: educating others, building awareness, fundraising for care and research
Treatments for HD

- **Supportive**: HDSA support groups, counseling, benefits programs
- **Advocacy**: Patients, families, HDSA (HD warriors)
- **Symptomatic**: Palliative treatments for HD symptoms
- **Research**: Huntington Study Group, Euro HD Network, US government and pharmaceutical funding

No effective treatments exist to slow progression or prevent death from HD. On the search for effective treatments and, ultimately, a CURE!
FIG. 1. Schematic depicting current priority preclinical therapeutic targets under investigation for Huntington’s disease. HTT, huntingtin; KMO, kynurenine monoxygenase; NMDA, N-methyl-D-aspartate; PDE, phosphodiesterase; BDNF, brain-derived neurotrophic factor; HDAC, histone deacetylase; Trk, tropomyosin-related kinase. Adapted from Ross et al.36
<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Study Identifier</th>
<th>Study Agent</th>
<th>Phase</th>
<th>Contact</th>
<th>Design</th>
<th>Trial Length</th>
<th>Sites</th>
<th>Status</th>
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<tr>
<td>Beijing Pins Medical Co., Ltd</td>
<td>NCT02263430</td>
<td>PINS Stimulator System</td>
<td>I</td>
<td>Jia Funan, PhD 010-59361265 <a href="mailto:pina_medical@163.com">pina_medical@163.com</a></td>
<td>Randomized, double-blind, parallel-group, sham-controlled trial of Globus Pallidus Deep Brain Stimulation in HD</td>
<td>1 year</td>
<td>Beijing, China</td>
<td>Not yet enrolling</td>
</tr>
<tr>
<td>Areevan Pharmaceuticals</td>
<td>STAIR</td>
<td>SRX246</td>
<td>I/II</td>
<td>Neal Simon, PhD 610-419-1057 <a href="mailto:ngsimon@asevan.com">ngsimon@asevan.com</a></td>
<td>Randomized, placebo-controlled, double-blind, 12 week, 3-arm dose-escalation study of SRX246 in individuals with immobility and suicide/homicide symptoms</td>
<td>12 weeks</td>
<td>22 total - United States</td>
<td>Currently enrolling</td>
</tr>
<tr>
<td>Innoce Pharmaceuticals</td>
<td>NCT0342055</td>
<td>IONET-HTTRs</td>
<td>II</td>
<td>Ionics Pharmaceuticals 300-679-4747 <a href="mailto:patients@ionicsph.com">patients@ionicsph.com</a></td>
<td>An open-label extension study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of IONET-HTTRs for patients who participated in prior IONET-HTTR studies.</td>
<td>74 weeks</td>
<td>9 total - Canada, Germany, and the UK</td>
<td>Not yet enrolling</td>
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<tr>
<td>Wave Life Sciences Ltd</td>
<td>PRECISION-HD1</td>
<td>WVR-120101</td>
<td>I/II</td>
<td>Clinical Operations 355-215-4607 <a href="mailto:clinicaltrials@wavelifesci.com">clinicaltrials@wavelifesci.com</a></td>
<td>Randomized, double-blind, placebo-controlled study to evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics of WVR-120101 in adults with early manifest HD</td>
<td>2 years</td>
<td>Toronto, Ontario, Canada</td>
<td>Currently enrolling</td>
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<tr>
<td>Wave Life Sciences Ltd</td>
<td>PRECISION-HD2</td>
<td>WVR-120102</td>
<td>I/II</td>
<td>Clinical Operations 355-215-4607 <a href="mailto:clinicaltrials@wavelifesci.com">clinicaltrials@wavelifesci.com</a></td>
<td>Randomized, double-blind, placebo-controlled study to evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics of WVR-120102 in adults with early manifest HD</td>
<td>2 years</td>
<td>Toronto, Ontario, Canada</td>
<td>Currently enrolling</td>
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<tr>
<td>Arludus Brasil</td>
<td>NCT03252535</td>
<td>Collavita HD</td>
<td>II</td>
<td>Joyce Macedo, PI +55(19)3828-6100 <a href="mailto:joyce.macedo@arldusbrasil.com.br">joyce.macedo@arldusbrasil.com.br</a></td>
<td>First-in-human, dose-escalation study to evaluate the safety of the stem-cell based therapy Collavita HD in HD</td>
<td>5 years</td>
<td>None listed</td>
<td>Not yet enrolling</td>
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<tr>
<td>Heinrich-Heine University</td>
<td>ACTIVA® PC neuro-stimulator</td>
<td>ACTIVA® PC</td>
<td>II</td>
<td>Susanne Harnisch +49 6421 206653 <a href="mailto:harnisch@uni-marburg.de">harnisch@uni-marburg.de</a></td>
<td>Randomized, double-blind, parallel-group, sham-controlled, multi-centre trial of Globus Pallidus Deep Brain Stimulation in individuals with HD</td>
<td>3 months</td>
<td>10 total - Germany, Austria, and Switzerland</td>
<td>Currently enrolling</td>
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<tr>
<td>Institut National de la Sante et de la Recherche Medicale</td>
<td>TRIRP3</td>
<td>Triheptanol oil</td>
<td>II</td>
<td>Fanny Mochel, MD, PhD <a href="mailto:fanney.mochel@upmc.fr">fanney.mochel@upmc.fr</a></td>
<td>Randomized, double-blind, controlled study of Triheptanol oil, an anaplastotic therapy, in early manifest HD</td>
<td>12 months</td>
<td>2 total - France and Netherlands</td>
<td>Currently enrolling</td>
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<tr>
<td>Teva Pharmaceutical Industries</td>
<td>NCT02215616</td>
<td>Laquinimod</td>
<td>II</td>
<td>Sarah Bee, Teva 610-772-3486</td>
<td>Randomized, double-blind, placebo-controlled trial evaluating efficacy and safety of Laquinimod (0.5 or 1.0 mg/day) in HD</td>
<td>12 months</td>
<td>92 total - worldwide</td>
<td>Active, not enrolling</td>
</tr>
<tr>
<td>University of Auckland</td>
<td>VCA6-HD</td>
<td>Varenicline</td>
<td>II</td>
<td>Ailsa McGregor, PhD +64 2 479 4239 <a href="mailto:ailsa.mcgregor@adho.ac.nz">ailsa.mcgregor@adho.ac.nz</a></td>
<td>Randomized, double-blind, placebo-controlled trial of varenicline using the standard dosing regimen for smoking cessation in patients with HD</td>
<td>16 weeks</td>
<td>1 total - New Zealand</td>
<td>Currently enrolling</td>
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<tr>
<td>Vaccines Inc.</td>
<td>SIGNAL</td>
<td>VX15/2003</td>
<td>II</td>
<td>Andrew Feigin, MD, Huntington Study Group: 300-457-7671</td>
<td>Randomized, double-blind, placebo-controlled study to assess the safety, tolerability, pharmacokinetics, and efficacy of VX15/2003 in individuals with late postural and early manifest HD</td>
<td>12-21 months</td>
<td>30 total - United States and Canada</td>
<td>Currently enrolling</td>
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<tr>
<td>Hopitaux de Paris</td>
<td>RIVHD</td>
<td>Resveratrol</td>
<td>III</td>
<td>Fanny Mochel, MD, PhD <a href="mailto:fanney.mochel@upmc.fr">fanney.mochel@upmc.fr</a></td>
<td>Randomized, placebo-controlled study to evaluate the therapeutic potential of Resveratrol on sebula volume in HD patients using volumetric MRI</td>
<td>1 year</td>
<td>1 total - France</td>
<td>Currently enrolling</td>
</tr>
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</table>
HD THERAPEUTIC PIPELINE

As of January 2018

Disease-modifying therapies

- Cellavita HD (Azidus Brasil)
- SRX246 (Azevan)
- Laquisalmod (Teva)
- VX15/2503 (Vaccinex)

- Preclinical
- Phase 1
- Phase 2
- Phase 3
- To patients

Neuroprotective compounds

- Rucaserin
- Triheptanoin oil

- Preclinical
- Phase 1
- Phase 2
- Phase 3
- To patients

Symptomatic treatments

- Varenicline
- Pradopidine (Teva)
- Deutetrabenazine (Teva)
- Tetrabenazine

- Preclinical
- Phase 1
- Phase 2
- Phase 3
- To patients

Gene-targeting therapies

- AAV-miRNA (aniQure)
- AAV-RNAi (Voyager/Genzyme)
- AAV-shRNA (Spark Therapeutics)
- WVE-L20101 (WAVE Life Sciences)
- WVE-L20102 (WAVE Life Sciences)
- IONIS-HTTRx (Ionis)

- Preclinical
- Phase 1
- Phase 2
- Phase 3
- To patients

Sources: www.clinicaltrials.gov, HDSPA's Therapies in Pipeline, and company/developer websites.
To add or correct a therapy in development, please email HDInsight@haslunited.org.
Figure 2. Antisense
Antisense DNA or RNA binds to a specific mRNA and prevents it from being translated into protein.
The first ASO drug for neurological disease approved by FDA December 2016!
IONIS-HTTRx

- A randomized, double-blind, Placebo-controlled Phase 1/2a study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple ascending doses of intrathecally administered ISIS 443139 in patients with early manifest Huntington’s disease
- 46 participants, ages 25 – 65
- Locations: Canada, Germany, UK
Study results

- 13-week study with four intrathecal injections of increasing doses for a total of four doses of IONIS-HTT<sub>Rx</sub> (RG6042) or placebo, given monthly.
- **Significant, dose-dependent reductions in mHTT were observed in CSF** with 40 - 60% reduction of mHTT of treated participants
- **mHTT levels were continuing to decline at the last measurement** with further decreases in mHTT anticipated; maximum reduction expected by approximately six months after first dose.
- At the last measurement, levels of mHTT were continuing to decline
- The magnitude of reduction of mHTT in CSF is within the range predicted to provide clinical benefit based on evidence from animal models
- **No serious adverse events** were reported and most adverse events were mild and considered to be unrelated to study drug. No participants discontinued from the study.
- **An open-label extension study** for patients who participated in the Phase 1/2 study is ongoing.

Gene Editing Techniques Show Promise in Silencing or Inhibiting the Mutant Huntington’s Disease Gene

THE UNIVERSITY OF CALIFORNIA, DAVIS RESEARCH TEAM is shown here: Dr. Kyle Fink (center) with (left to right) Peter Deng, Anvita Komarla, Dr. Audrey Torrest, and Joseph Aprille.

THE MECHANISM BEHIND TALES: Panels A, B, and C describe the different effector domains that can be attached to DNA-targeting proteins. Panel A represents obligate heterodimeric variants of the nuclease FokI (TALEN); the rationale for using a heterodimeric nuclease was to reduce potential off-target nuclease activity by necessitating complementary binding of the two TALE arrays to elicit a double-stranded break. The breaks were expected to be repaired by the highly efficient single-strand annealing pathway, resulting in the deletion of CAG repeats. The B panel represents a transcriptional activator that can turn on or enhance gene expression, though this was not used for Huntington’s. Panel C represents a transcriptional repressor that would silence or block gene expression. To achieve the allele-specific transcriptional repression of mutant huntingtin, the researchers designed TALEs to target unique DNA sequences in the mutant allele.

Gene-targeting Therapies
Evaluate efficacy of transplanting GMP-grade human embryonic stem cell-derived neural stem cell line into striatum of HD modeled mice.

In two separate mouse models:
- R6/2 mice: Improved motor behavior, cells showed potential synaptic connections, good cell survival
- Q140 mice: Improved pole test performance and behavior outcomes, good cell survival

They are electrophysiologically active

Improve motor and late-stage cognitive impairment

Overall, disease-modifying activity is suggested by the reduction of accumulation of mutant HTT protein and expression of BDNF

These findings hold promise for future development of stem cell-based therapies
Be kind to yourself.

You can do anything but not everything.
In the moment...

• Attempt to take pause and live in the moment
• Enjoy the simple things in life
• Have the moment be NOT about HD
HDSA Center of Excellence at UC Davis
Thank You to JHD & HD Patients and Care Partners!

Our work in HD has been inspired and generously supported by HD patients and family members.

We are grateful to the Joseph P. Roberson Foundation, the Charles and Margaret Pue Charitable Foundation, HDSA, Help4HD and many others who have contributed to our HD care and research programs at UC Davis.

https://www.ucdmc.ucdavis.edu/huntingtons/
Key Points

• Education
• Know where to turn for help and support
• Advocate (HD warriors)
• And maintain hope through research!
Thank you to our JHD & HD families for your strength, courage, and inspiration!