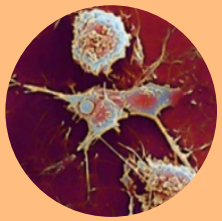
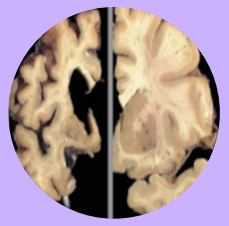
LIHR

La ricerca sulle malattie rare e le prospettive di cura per la malattia di Huntington

Neuroscience, the Future is Bright

Mauro Patroncini, MD
Pipeline Product Strategy Leader
Luisa De Stefano
Head of Patient Advocacy

Neuroscience Disease Areas of Focus

	Neuroimmunology	Alzheimer	Neuromuscular	Psychiatry	Movement Disorders	Others
Marketed/ late stage (Ph3/Pivotal)	 **Multiple Sclerosis** Ocrevus™ **Neuromyelitis Optica** Anti-IL6R mAb (SA237)	 **Alzheimer Disease** Crenezumab Gantenerumab	 **Spinal Muscular Atrophy** Olesoxime SMN(2) splicer **Duchenne Muscular Dystrophy** Anti-myostatin	 **Autism Spectrum Disorders** V1a receptor antagonist		
(Ph1-2)		Tau mAb	**Amyotrophic Lateral Sclerosis** DLKi	**Schizophrenia** basmisanil TAAR1(4)	**Huntington Disease** ASO HTT (IONIS) **Parkinson Disease** Alpha-Syn mAb	**Pain** Nav1.7 ant **Stroke recovery** Basmisanil

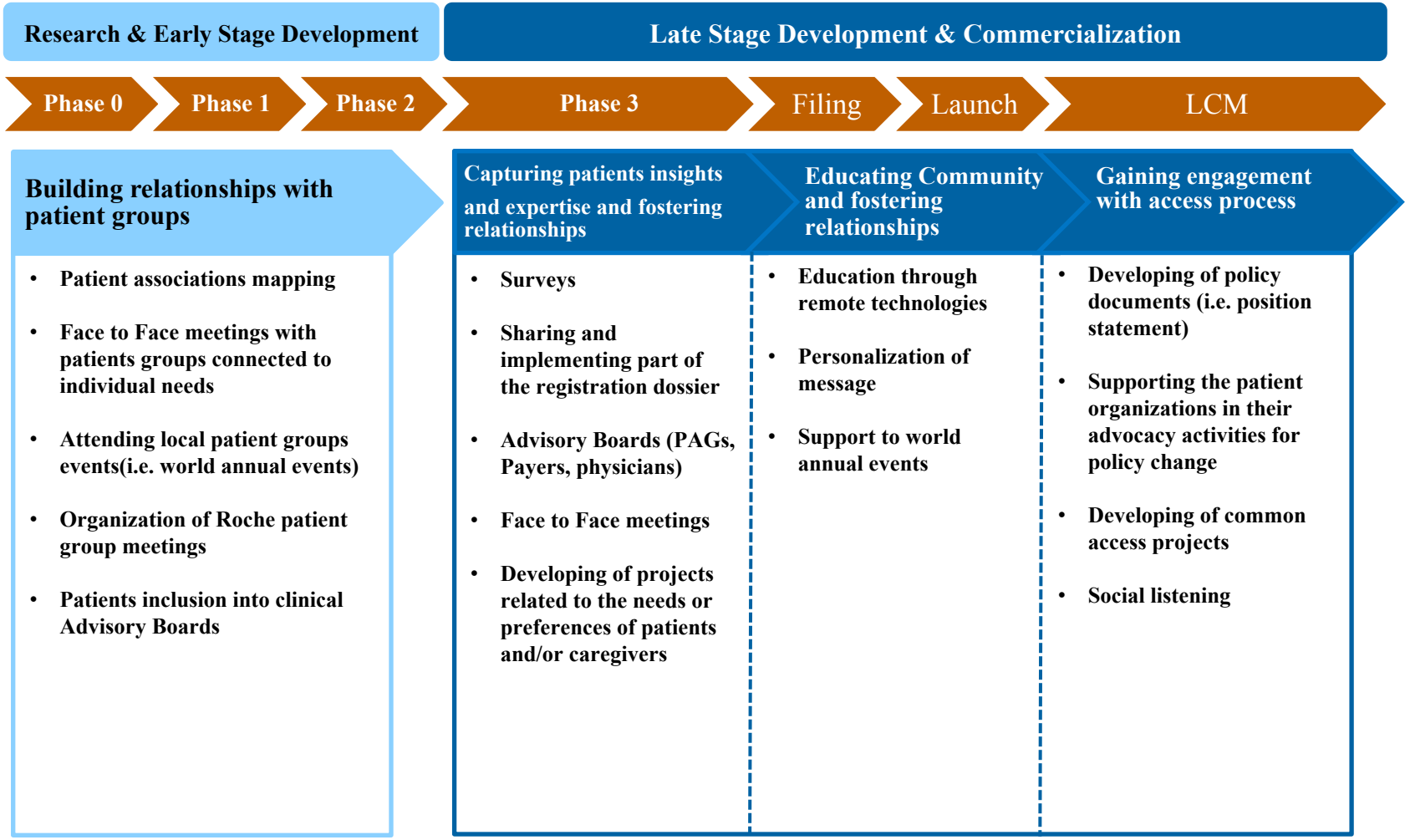
Collaborations

- Collaboration is essential to advance science and develop new treatments.
- Diverse groups bring different perspectives on the burden of nervous system disorders and potential solutions to ease this burden.
- Clinical trials would not be possible without patients and caregivers who volunteer their time and participation.
- Patients and caregivers can provide a more complete picture of the disease and treatment effects.
- **Patient groups are increasingly important partners for Roche**

Some data can only be obtained through patient or caregiver reports and advocacy organizations, such as frequency of symptoms and their impact on daily life.

Roche Working with patient groups

Engagement activities along the lifecycle



Huntington Disease

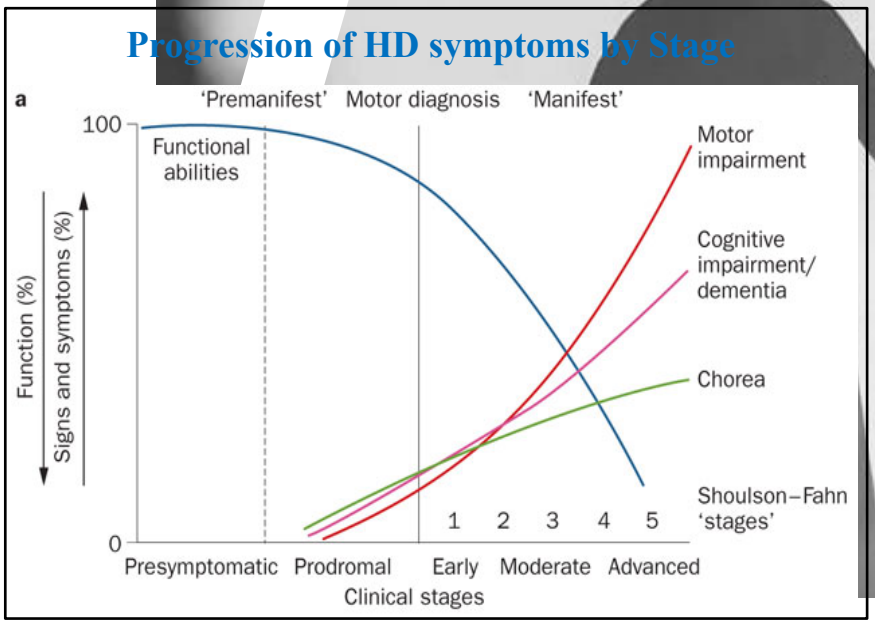
A genetic progressive, highly debilitating neurological disease

HD is a rare disease for which no cure is available

Currently available therapies are symptomatic

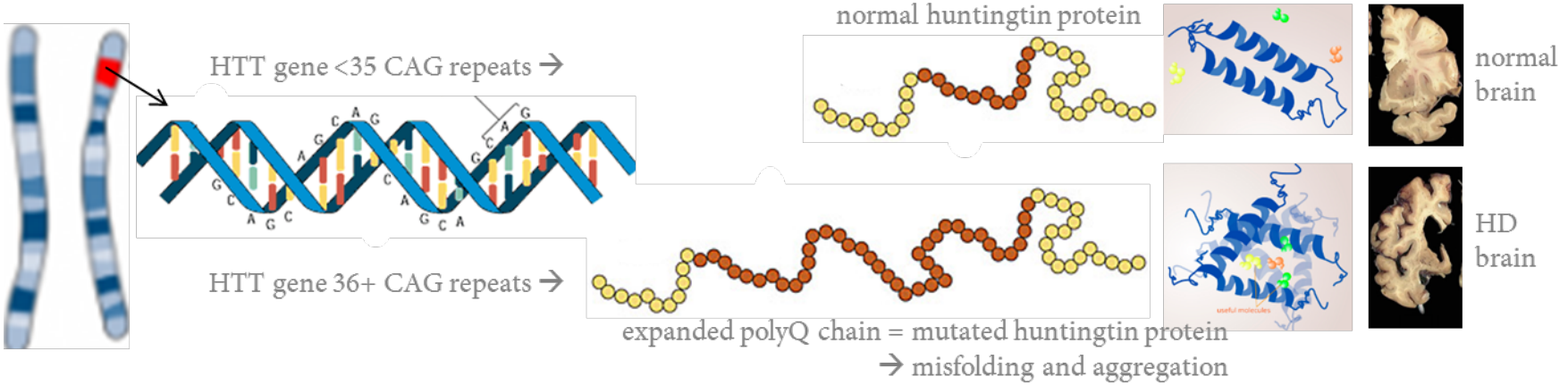
HTT-ASO (IONIS-Roche)

Progression of HD symptoms by Stage

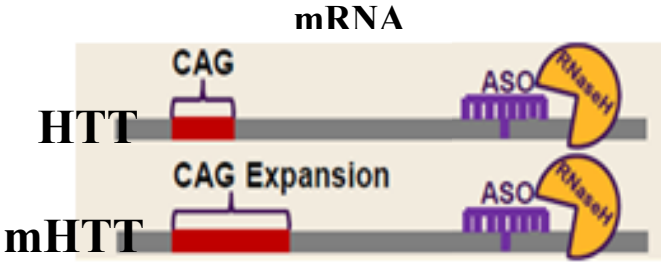


HTT-ASO directly targets causal pathway of HD

Mechanism of action suppresses toxic mutant protein production



→ *impaired axonal transport; mitochondrial dysfunction; transcriptional deregulation; proteasome inhibition; exocytotoxicity; synaptic dysfunction; caspase/protease activation…* ***neuronal dysfunction & death***



- **ASO binds its complementary *HTT* mRNA** (non-allele selective)
- *HTT* mRNA-ASO duplex recognized by RNaseH which selectively degrades HTT mRNA, suppressing total HTT (mutant and normal HTT) Interrupts toxic gain of function

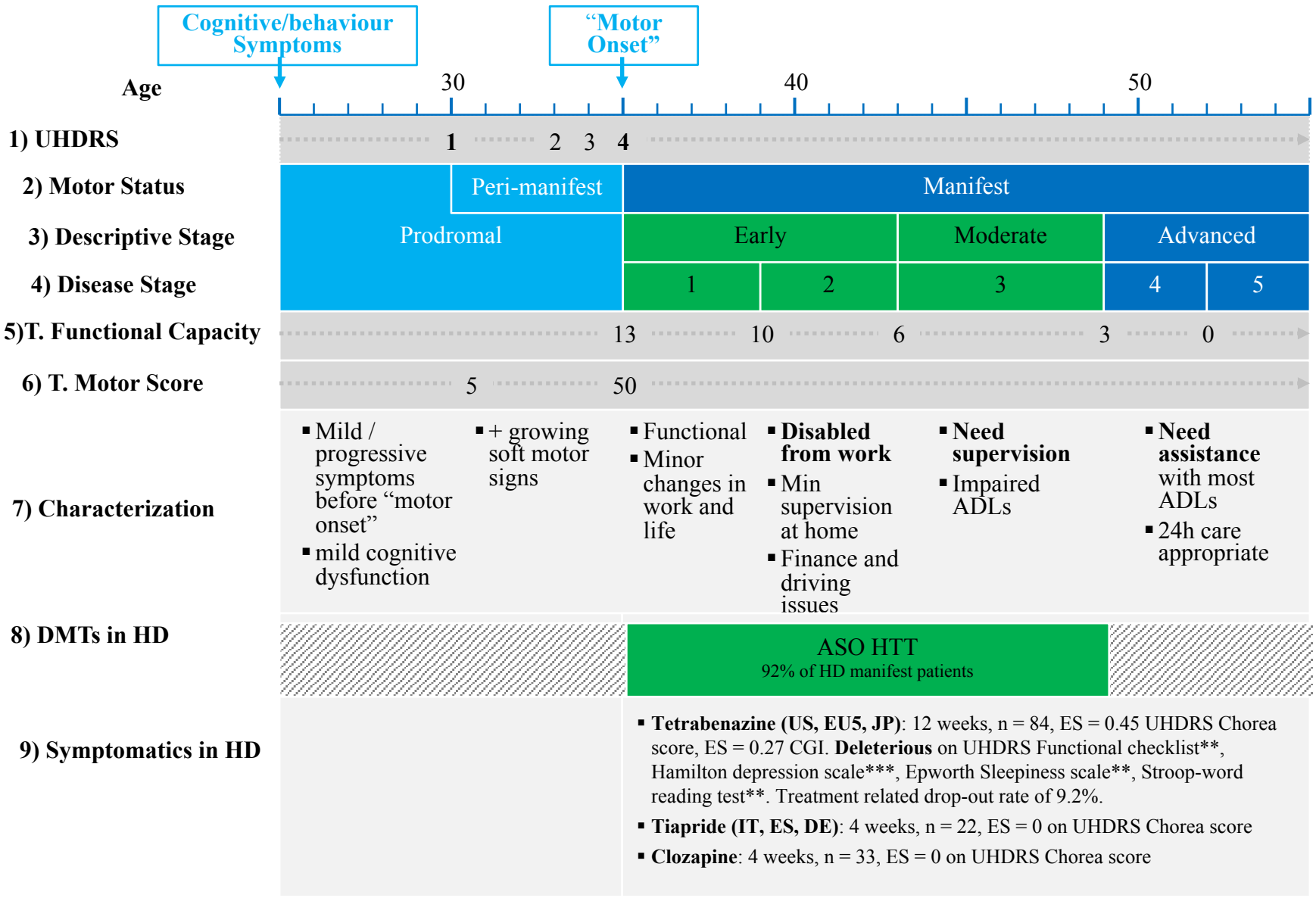
What makes this program “rare”

#1 Aetiology and biology well understood

#2 MoA linked to THE causative pathogenic pathway

#3 BM changes correlated with disease progression

HTT ASO is the first-in-class disease modifier for the treatment of manifest HD patients



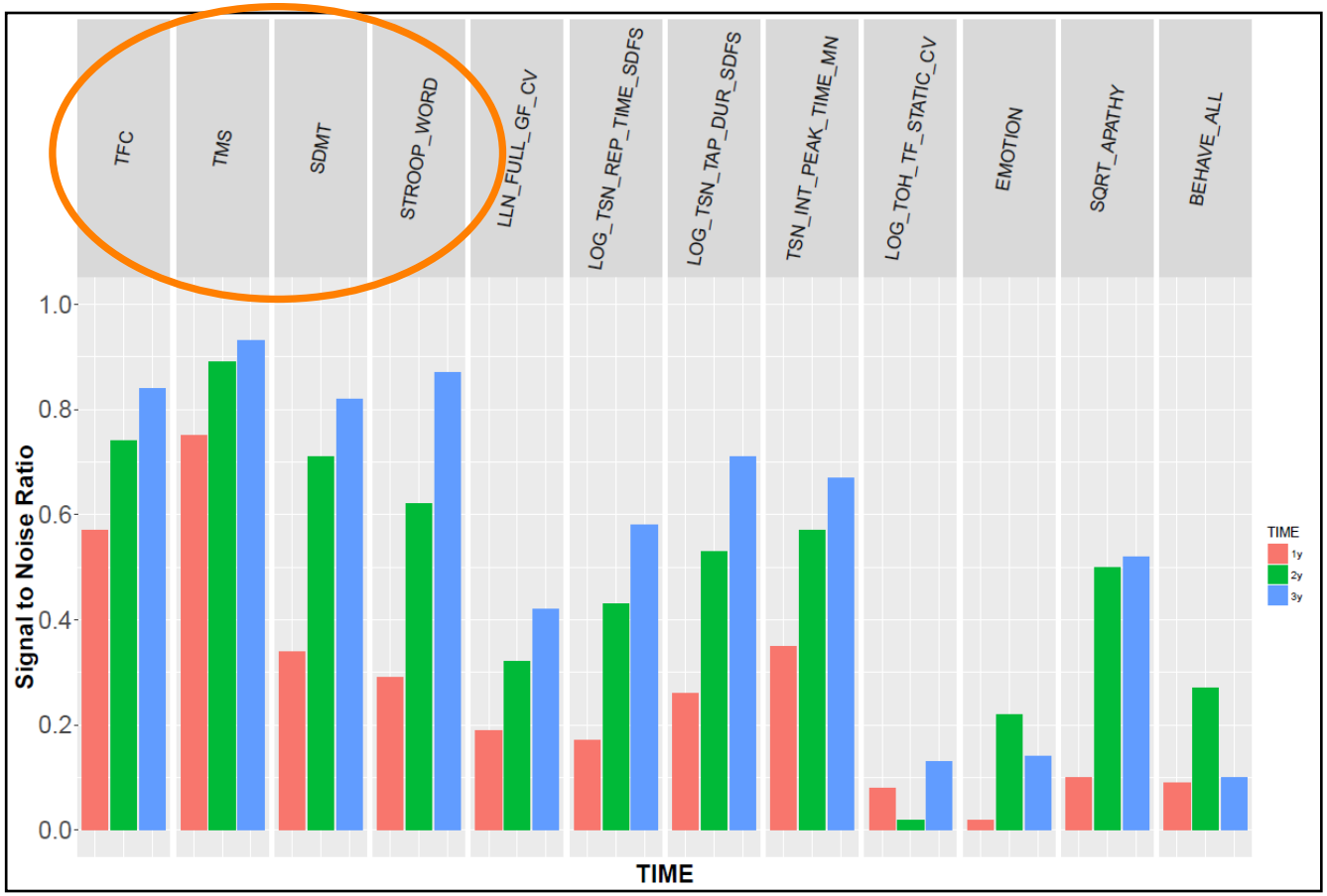
Formation of cUHDRS concept from UHDRS

Discovery of a linked pattern of longitudinal clinical change in individual UHDRS items

Discovery of a 'cognitive-motor-functional' progression factor (TMS, TFC, SDMT, Stroop word)

Behavioral and quantitative motor variables less well performing, with the exception of apathy

TRACK-HD trial



Composite Unified Huntington's Disease Rating Scale (cUHDRS)

Primary goal: better understand clinical progression across domains & identify improved outcome measures

The composite UHDRS scale would not be new but would be a **composite** built by assembling the **most sensitive instruments** from the existing UHDRS to track disease progression across motor, cognitive, behavioural and functional symptoms. The aim is to use an established scale to better capture disease progression concept.

CUHDRS Development

Method: Data were analysed from many individuals across four multi-site and multi-national studies of early HD.

Results: Relative to the TMS or TFS alone, a composite variable comprising

- TMS (motor)
- TFC (function)
- Symbol Digit Modality Test
- Stroop word score (cognition)

best fulfilled clinical meaningfulness criteria in an early HD population.

Several additional supportive analyses have also been conducted.

The use of the composite UHDRS is heavily supported by therapeutic area experts.
Roche will establish and pursue clinical and regulatory validation of a composite based on the UHDRS which will be used in clinical trials (paper published on Neurology).

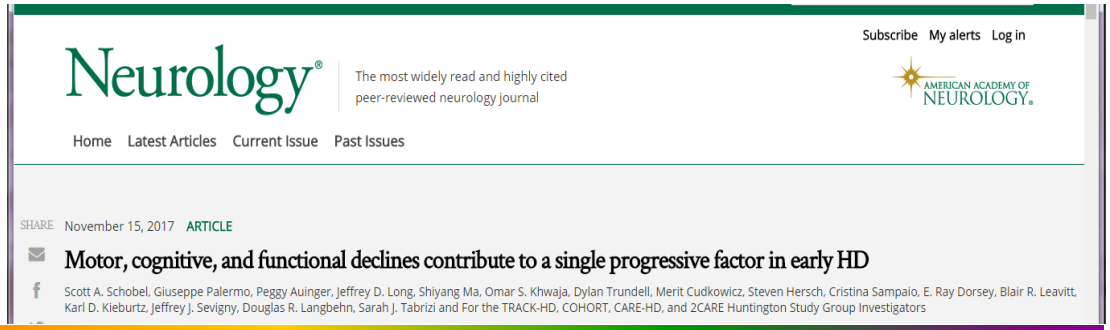
What is a meaningful change on the cUHDRS?

- **25% treatment effect on composite**: progression rate slowed by **3 months for every 12 months**
- **50% treament effect on composite:** progression rate slowed by **6 months for every 12 months**
- **Consistent treatment effects** between composite & individual variables expected for treatment impacting core pathophysiology

Extensive academic collaborations for cUHDRS endpoint development

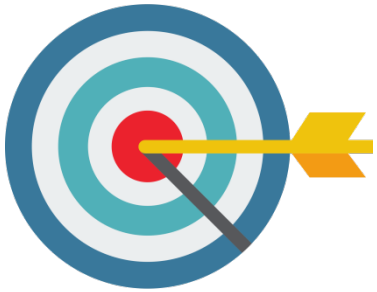
- ***Primary goal: better understand clinical progression across domains & identify improved outcome measures***

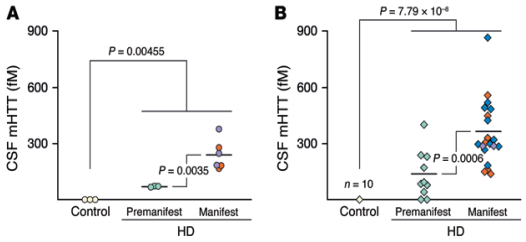
- HD biostatistics working group and data sharing between Roche, academia & HSG (2015/2016)
  - ~4,000 baseline cases, from 6 mo-11 yrs longitudina follow-up of UHDRS data
  - Prospective cohort study data: TRACK-HD, PREDICT-HD; PADDINGTON; COHORT; PHAROS
  - Placebo group trial data: CARE-HD, 2-CARE, TREND-HD, HORIZON
  - **Paper published on Neurology**



Biomarker for Huntington ASO

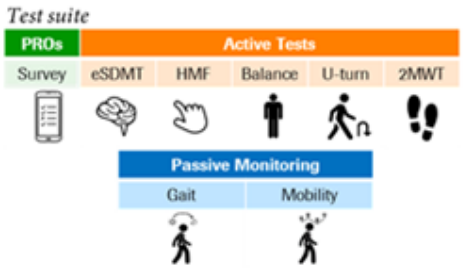
- **Target engagement**
  - Levels of mutant and total HTT in CSF after treatments
    - Singulex assay validated
    - Cobas Assays feasibility under evaluation
- **Proof of concept /proof of mechanism**
  - Downstream markers of pathology in CSF and plasma (e.g. Tau, NF-L, Neurogranin)
  - MRI (structural, functional)
  - PET imaging of ASO distribution using zirkonium labeled ASO
  - PET imaging using ligand for aggregated mHTT (collaboration with CHDI)
  - Continuous monitoring of motor function and cognition using smartphone technology
- **Diagnosis**
  - Diagnosis of family members straight forward (genetic testing)
  - Diagnosis can be issue in patients w/o family history – early genetic testing needed





Roche leadership in digital biomarkers

Providing enhanced patient insights and novel endpoints



- **Clinical trials utilizing mobiles, wearables and gaming devices:**
  - Parkinson's Disease, Multiple Sclerosis
  - Spinal Muscular Atrophy, Stroke Recovery and **HD**
- **More sensitive, precise and objective**
- **Continuous and longitudinal measurement captures episodic and rare events**
- **Reduced assessment burden and greater real-world relevance – post-marketing applications**
- **Potential beyond neuroscience indications**

ASO-HTT a DMT for HD

- **1) Clear mode of action**
- **2) Biomarker correlation with clinical features ?**
- **3) Sustained effect duration ?**

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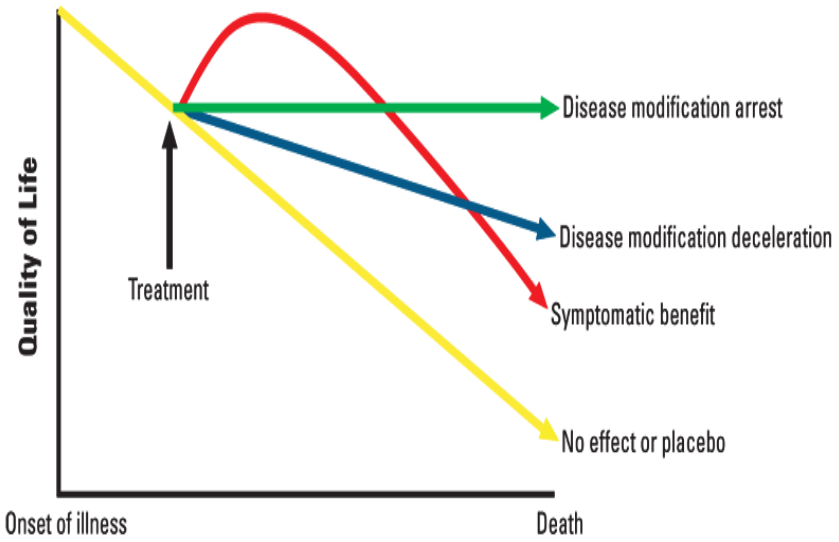
Quantification of mutant huntingtin protein in cerebrospinal fluid from Huntington's disease patients

Edward J. Wild,[1] Roberto Boggio,[2] Douglas Langbehn,[3] Nicola Robertson,[1] Salman Haider,[1] James R.C. Miller,[1] Henrik Zetterberg,[1,4] Blair R. Leavitt,[5] Rainer Kuhn,[2] Sarah J. Tabrizi,[1] Douglas Macdonald,[6] and Andreas Weiss[2]

[1]University College London (UCL) Institute of Neurology, National Hospital for Neurology and Neurosurgery, London, United Kingdom. [2]IRBM Promidis SRL, Pomezia, Italy. [3]Carver College of Medicine, University of Iowa, Iowa City, USA. [4]Institute of Neuroscience and Physiology, Department of Psychiatry and Neurochemistry, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden. [5]Centre for Molecular Medicine and Therapeutics, Department of Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada. [6]CHDI Management/CHDI Foundation, Los Angeles, California, USA.



Building On Our Legacy

We have a history of transforming scientific insights into breakthrough medicines for cancer.
We want to do the same for nervous system disorders with the greatest need, whether they affect millions of people or thousands.

Doing now what patients need next