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Research Updates in Huntington's Disease

Ochsner Neuroscience Symposium 2026

Victor Sung, MD

Director, Division of Movement Disorders and HD Center of Excellence

Professor, UAB Dept. of Neurology

May 9, 2026

Disclosures

- I have received research support (site PI) from Roche/Genentech and UniQure, but no confidential information will be shared
- I am on the Steering Committee for the UniQure AMT-130 trial
- I have served as a consultant for Genentech (not for HD), Teva Neuroscience, and Neurocrine, with no relevant conflicts for this talk

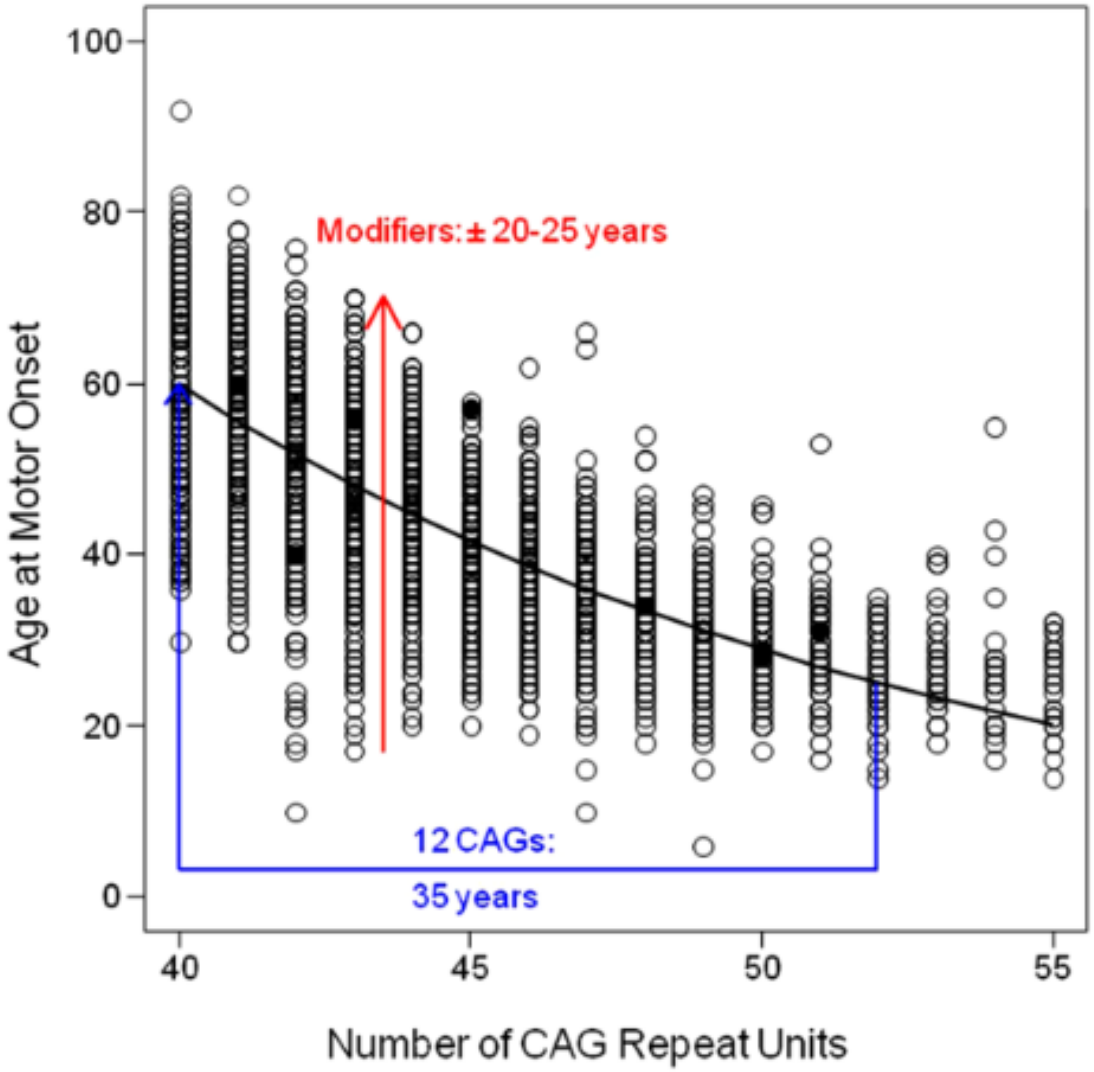
- Note: All data shown without citations is taken from public press releases from those companies

HD Research Updates 2026

- Updates on HD Pathophysiology
  - New understandings to guide DMT research in HD and beyond
- Biomarkers in HD
- Clinical DMT Research
  - Antisense Oligonucleotides (ASO's)
  - Gene therapy
  - Small molecule splicing modifiers
  - Other mechanisms
- Applications for other diseases

HD Overview

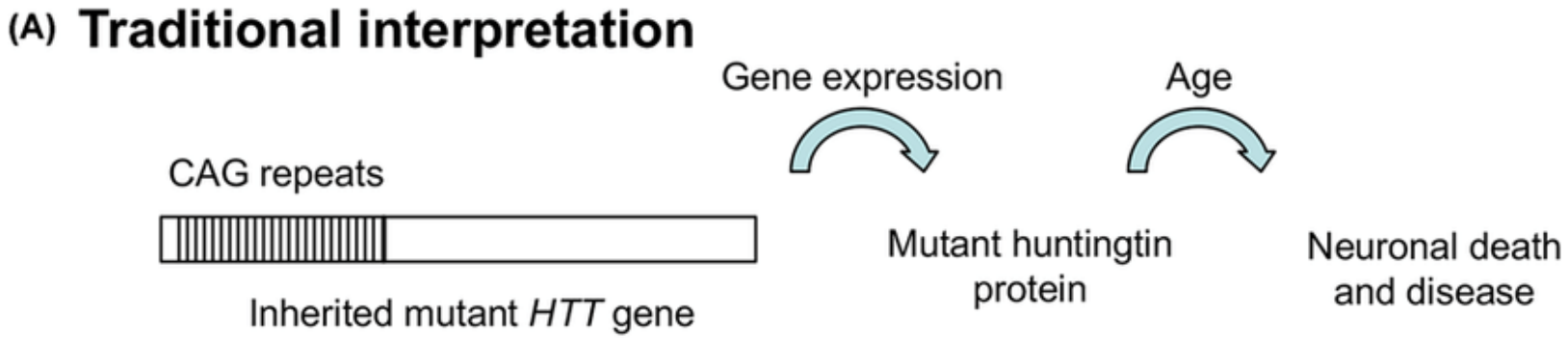
- Autosomal dominant trinucleotide repeat (CAG) disorder causing neurodegeneration
- Clinical phenotype includes triad of motor, cognitive, and behavioral symptoms
- Age of symptom onset in the 30-40 range
- Correlation between CAG repeat length and age of onset



Gusella, et al 2014

HD Pathophysiology

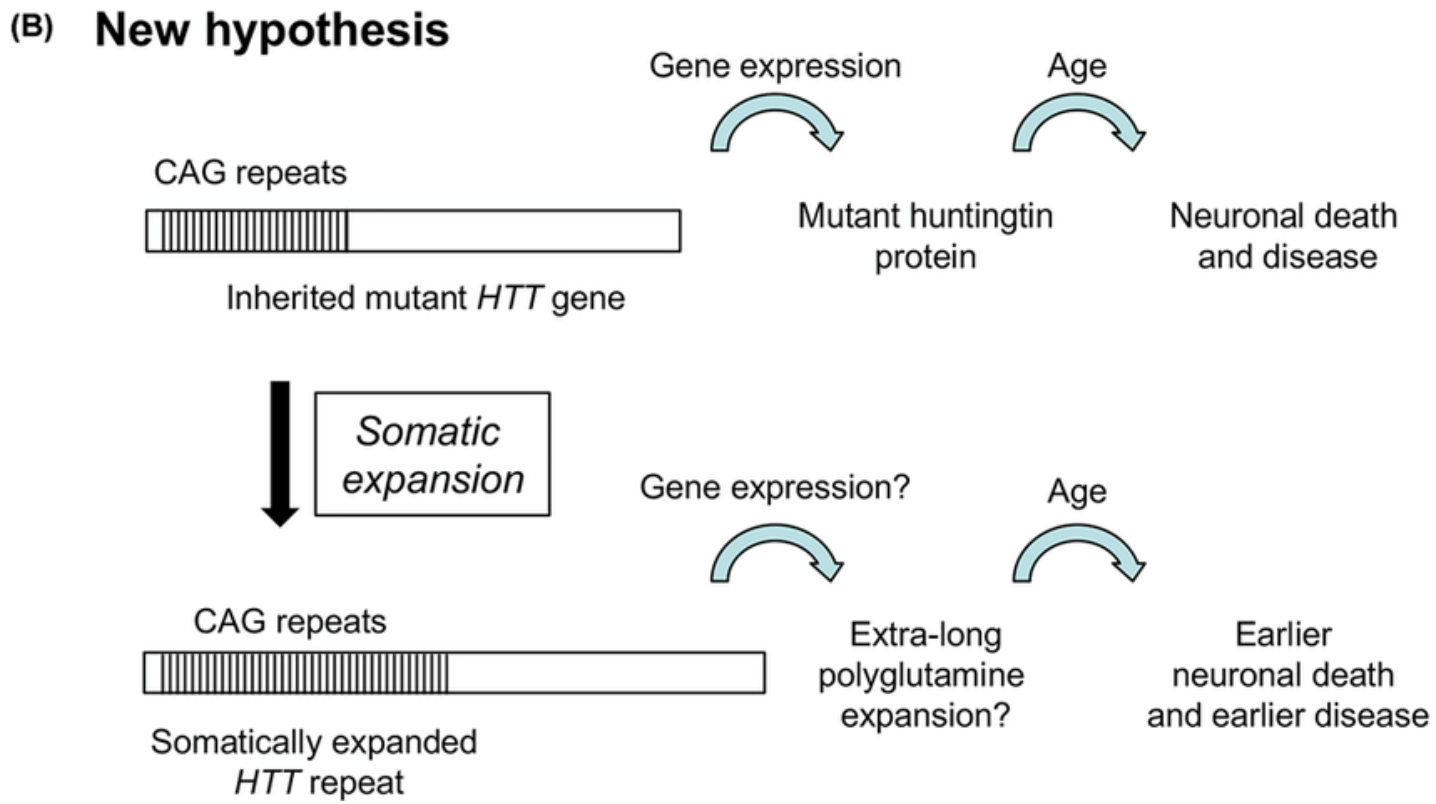
- But what are these modifiers of expression?
- Traditional model is simple toxicity of mHtt protein causing cell loss
- All previous therapies focused on *huntingtin*-lowering



- But this is not the whole story…

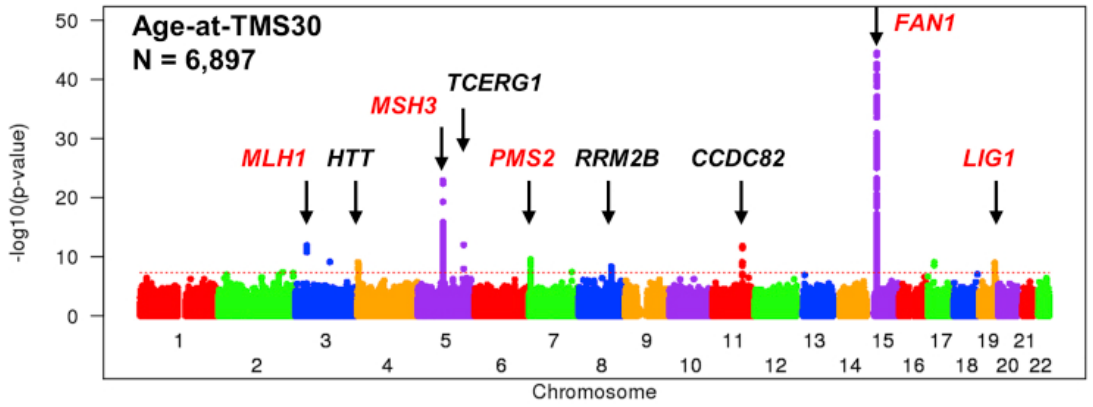
HD Pathophysiology

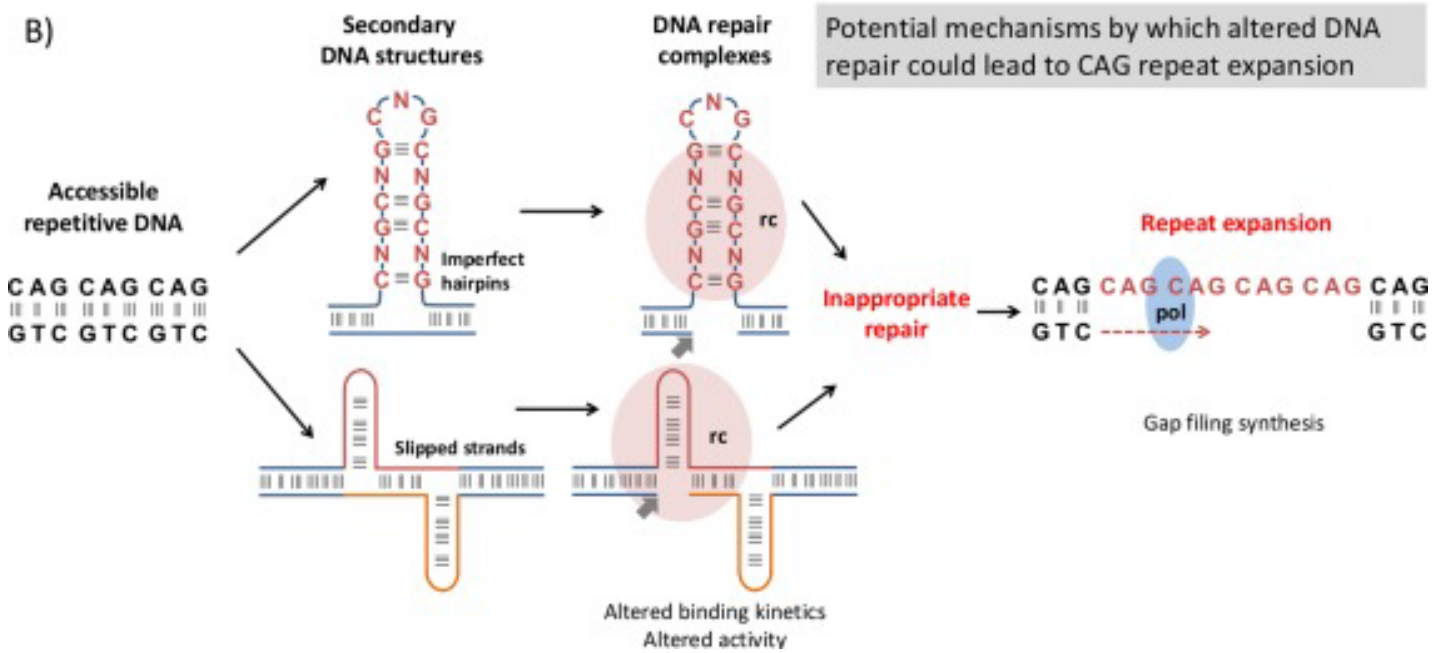
- New understanding that somatic instability through mismatch repair (MMR) is a key mechanism



HD Pathophysiology

- GWAS showing key modifiers of HD phenotype are MMR genes

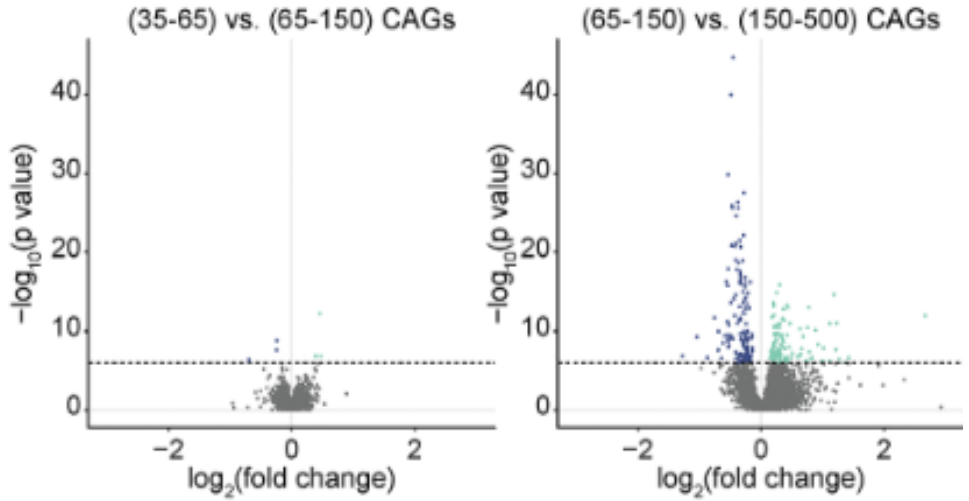




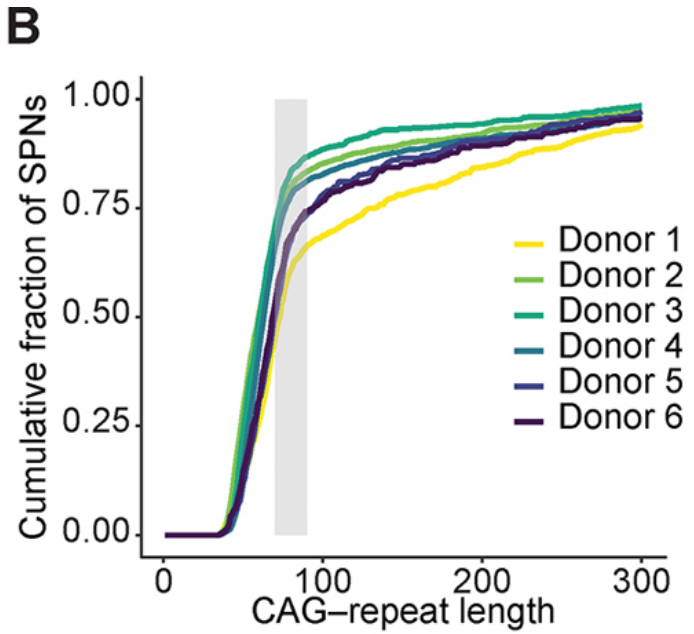
JM Lee, et al *Am J Hum Gen* 2022
Bettencourt et al *Ann Neurol* 2016

HD Pathophysiology

- Somatic instability occurring in all cells but disproportionately so in striatal neurons

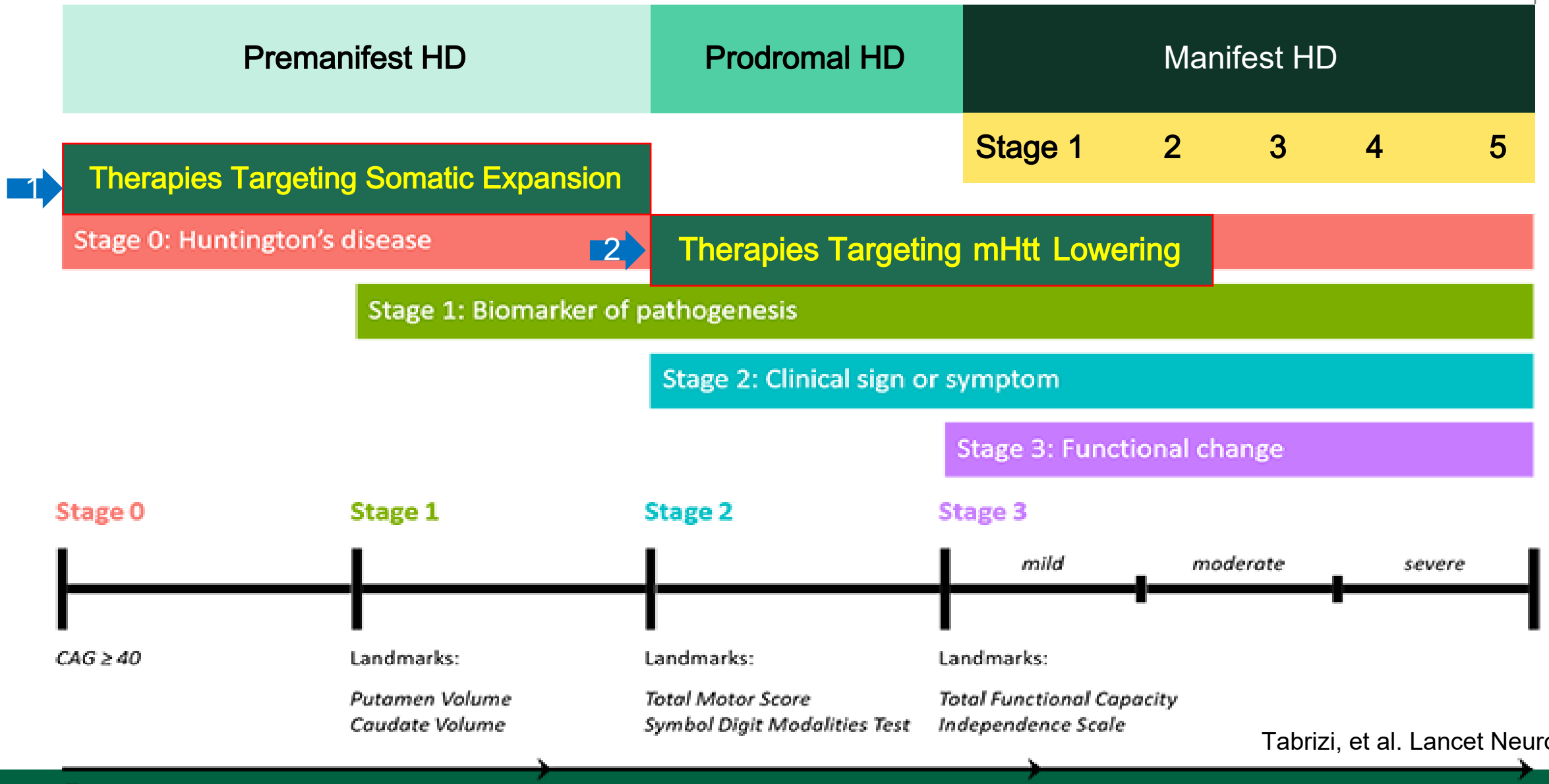


- Two key inflection points where CAG repeat expansion increases rapidly



Handsaker, B. et al.*Cell,* 2025

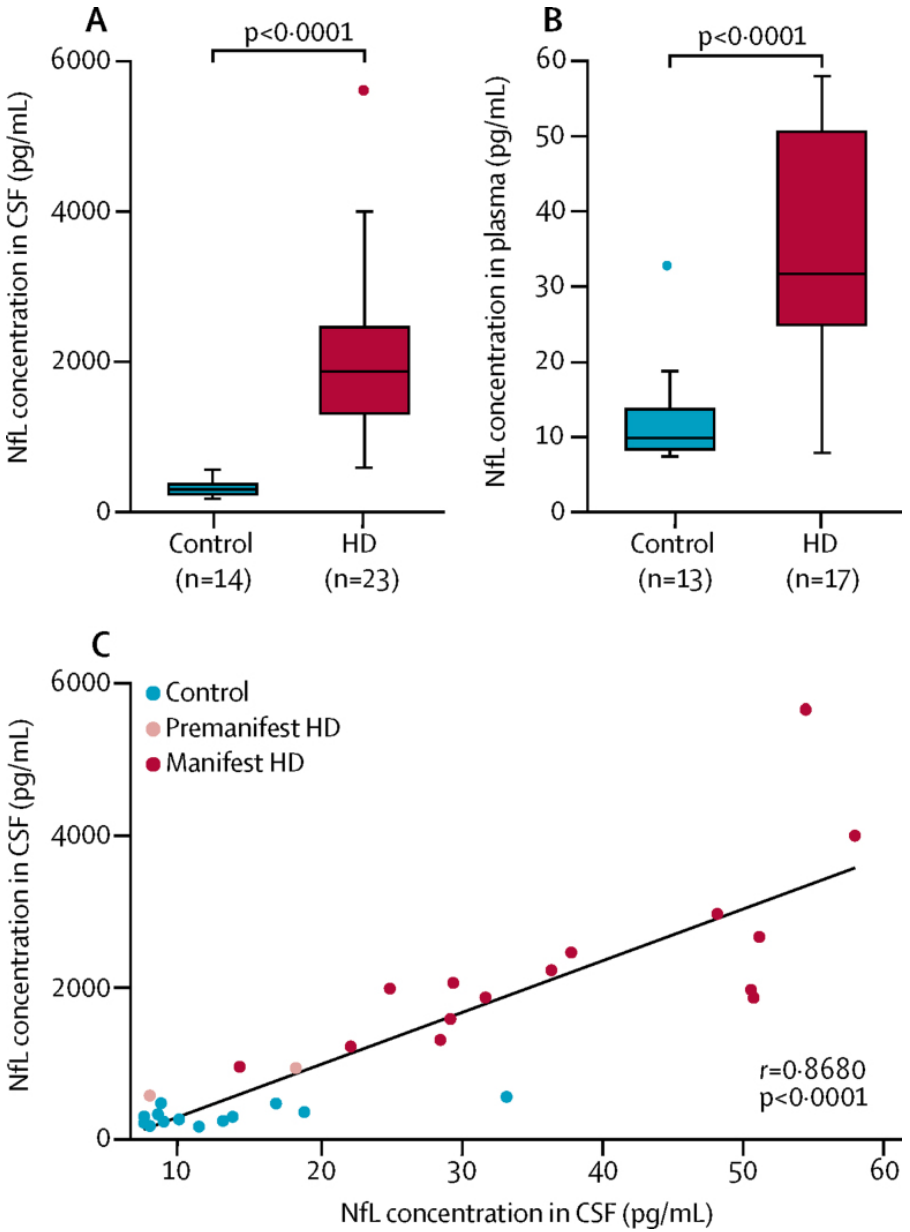
Pathophysiology of HD and Staging



Tabrizi, et al. Lancet Neurol, 2022

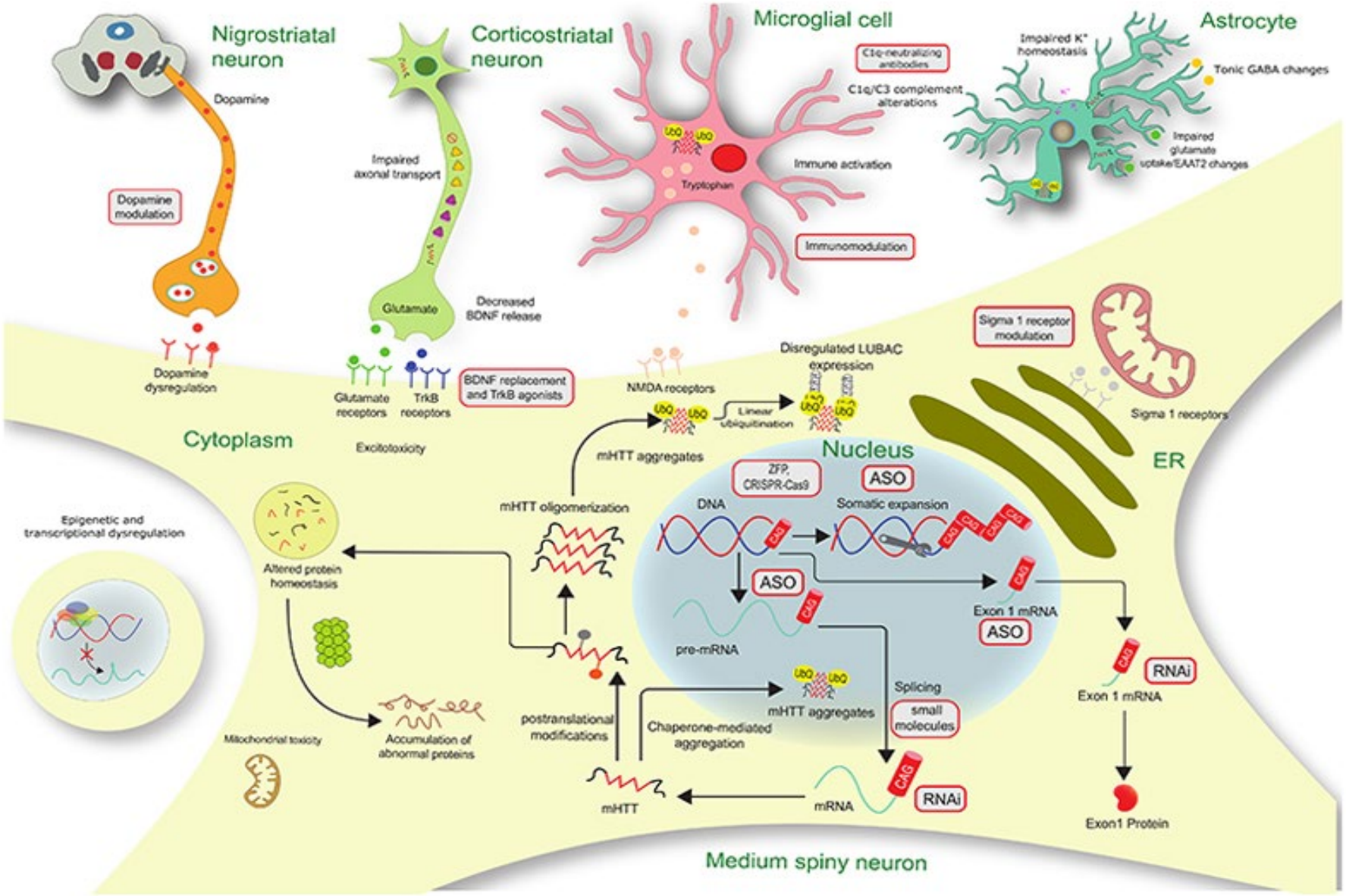
NfL in HD

- Plasma and CSF concentrations of NfL significantly higher in HD patients than controls
- CSF NfL concentration also tracked with disease stage
- Suggests that plasma NfL has CNS origin and is a good biomarker in HD
- Widely accepted as a safety biomarker in HD
- Growing acceptance as a biomarker for disease progression



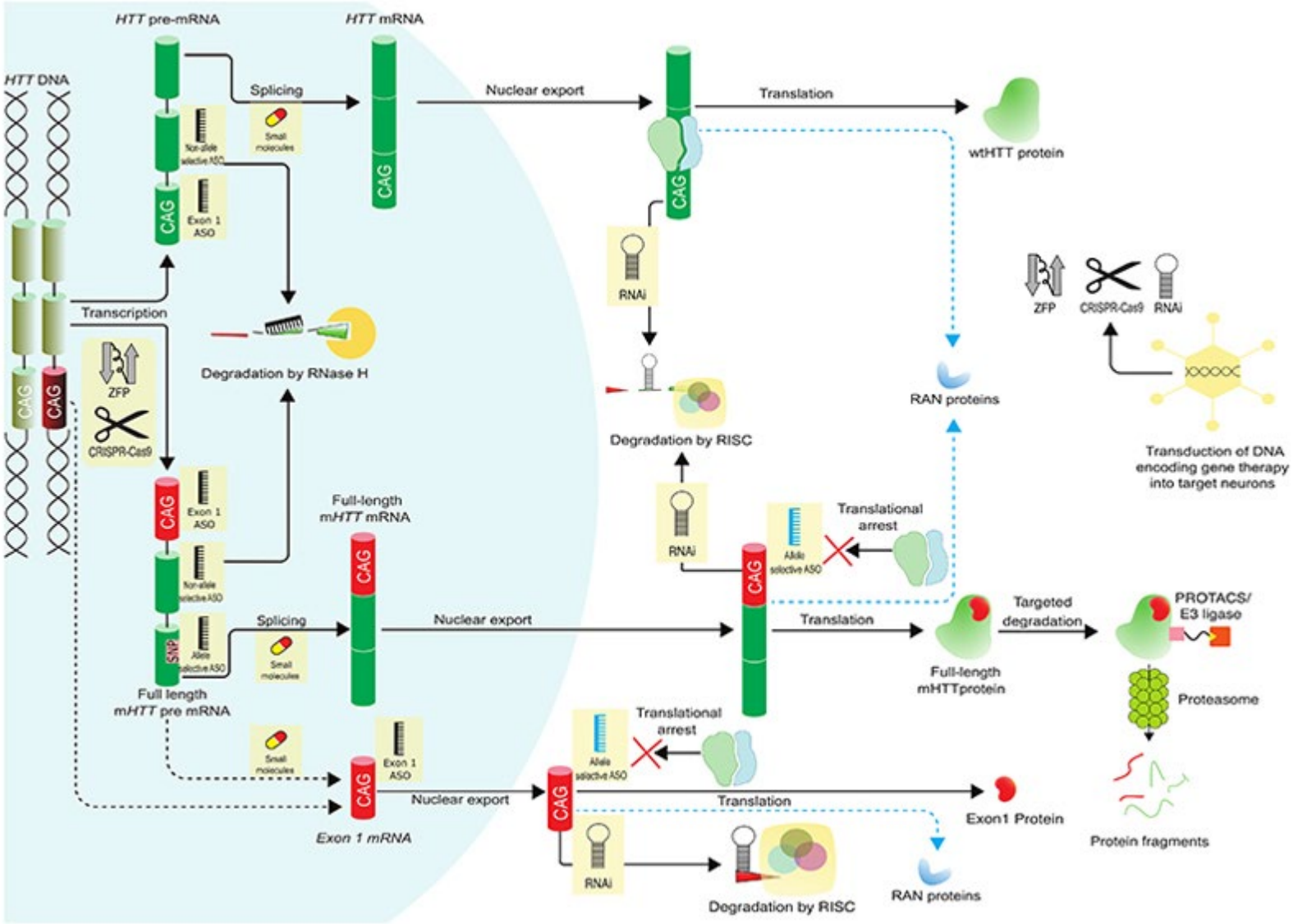
Byrne, LM et al, LancetNeurol, 2017

DMT's on the horizon for HD



Tabrizi, et al. Lancet Neurol, 2022

Htt-lowering Strategies in HD



Tabrizi, et al. Lancet Neurol, 2022

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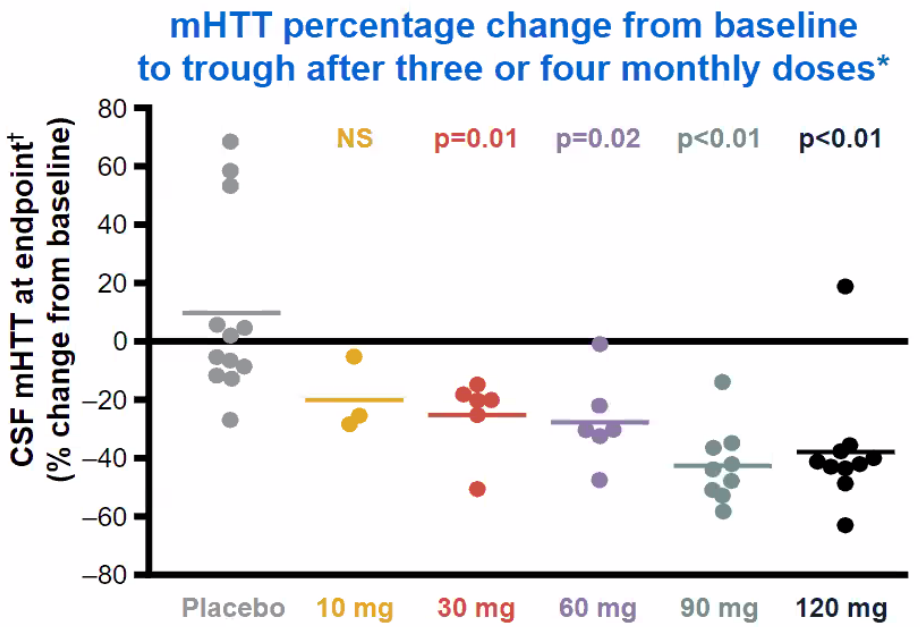
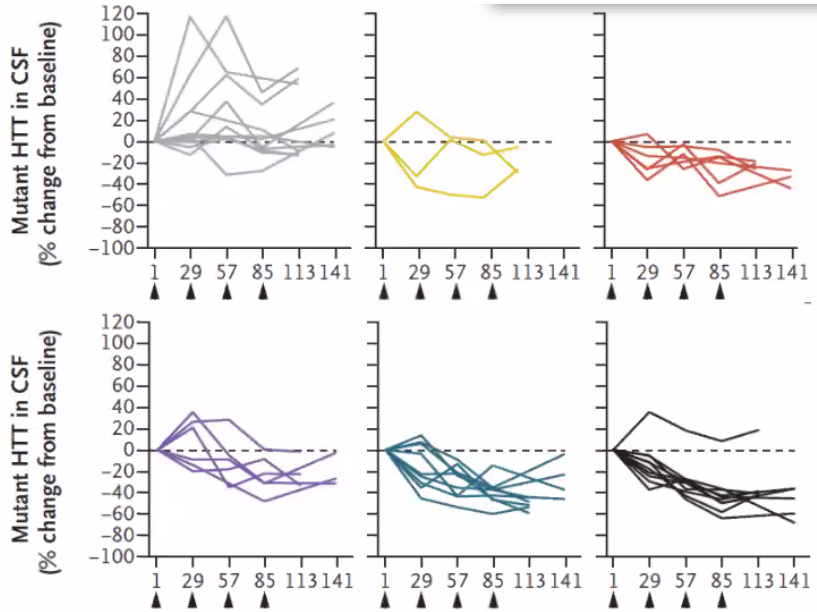
ASO’s

Tominersen Recap

- Intrathecal non-allele specific ASO
- Older generation ASO backbone
- Reached Phase 3 trial based on positive data at right
- Dose dependent lowering of Htt



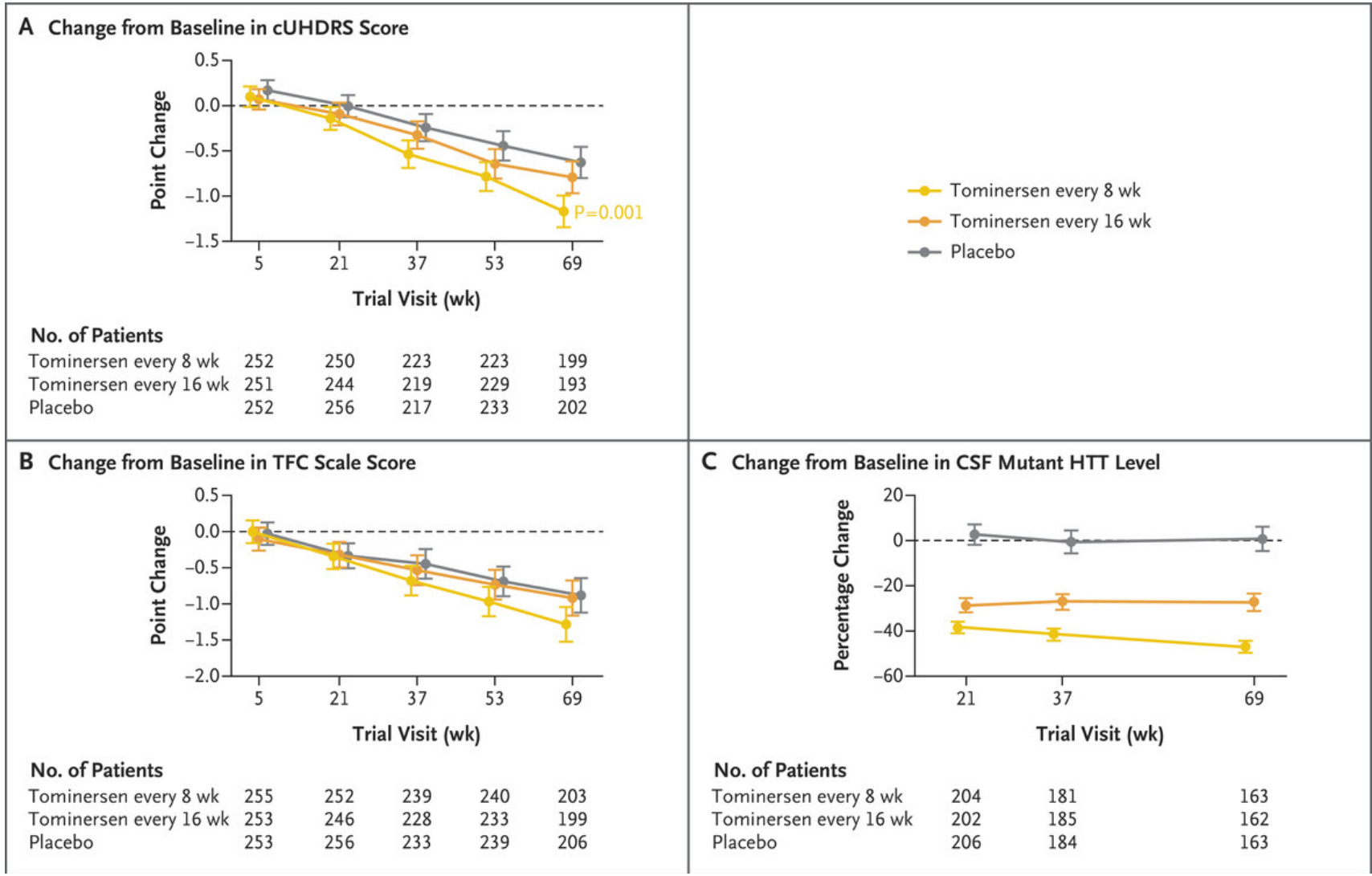


% CSF HTT KD‡	Predicted % HTT KD in cortex	Predicted % HTT KD in caudate
20–30	30–55	5–20
30–40	40–70	15–35
40–50	55–80	25–45

McColgan, et al. NEJM, 2023

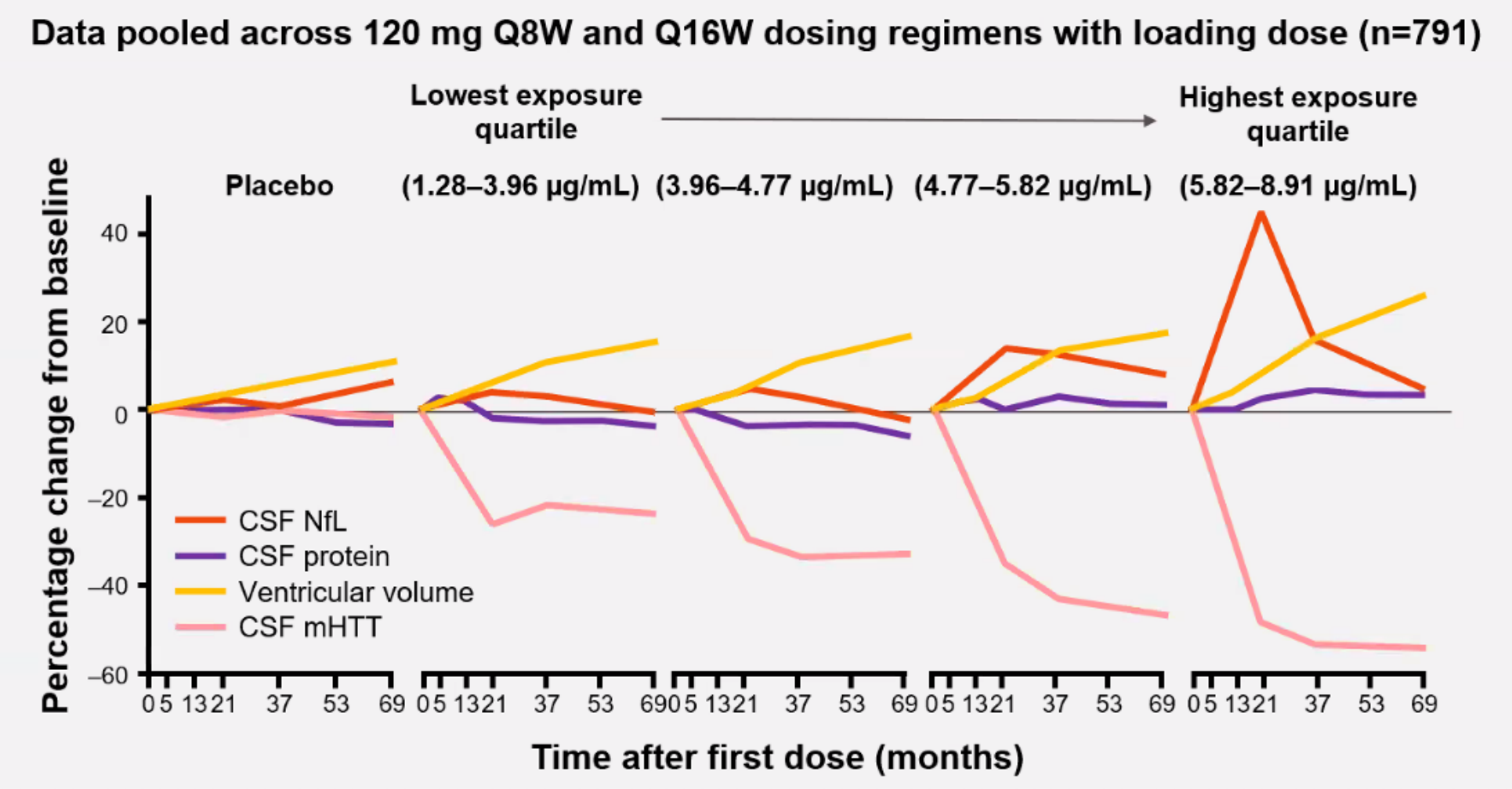
Tominersen ASO

- Phase 3 trial enrolled >600 patients in less than 2 months
- At interim data analysis, DSMB stopped trial early
- Treated patients doing worse on all clinical measures



McColgan, et al. NEJM, 2023

Tominersen ASO Safety Data



McColgan, et al. NEJM, 2023

Key Learnings

- 45% of ~600 subjects aged 55-65 – perhaps DMT trials should be done in younger populations
- Higher dose patients did worse
  - Too much lowering of wtHtt?
  - Toxicity of ASO backbone?
- NfL spikes appear to be a really negative sign in HD DMT trials
- Roche proceeded with phase 2 re-trial of low dose tominersen in a younger/milder population
  - Study completed, awaiting data readout this summer

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Gene Therapy

BBC

Huntington's disease successfully treated for first time

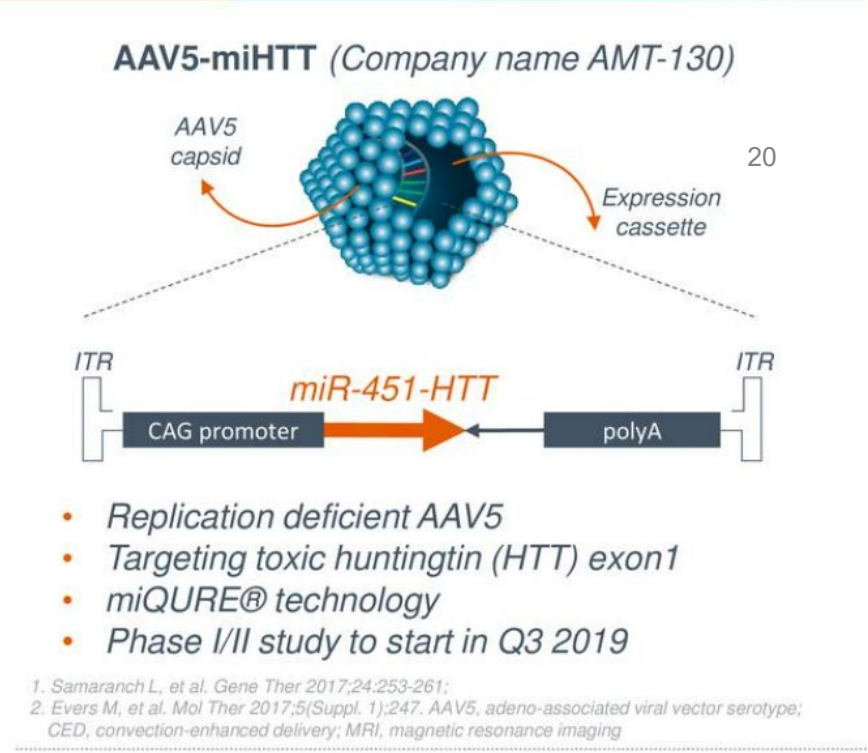
3 days ago

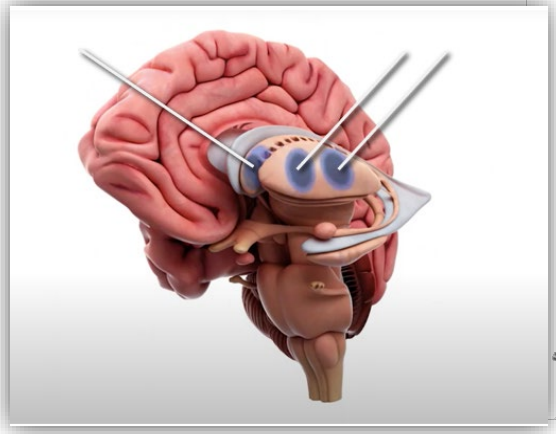
Share Save

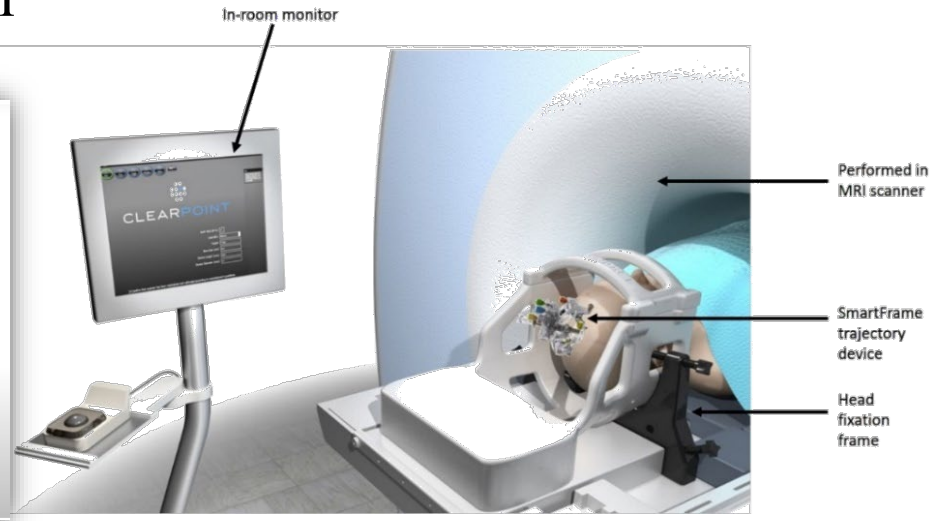
James Gallagher Health and science correspondent

AMT-130

- uniQure AMT-130 (AAV5 + miHTT - miRNA)
- Non-allele specific, targets within exon 1 so lowers both full length Htt and exon 1 fragment
- Single injection intended to have lifelong effect
- IMRI-guided powered injection into bilateral striatum
  - 3 infusions per hemisphere
  - Procedure duration 12-14 hours





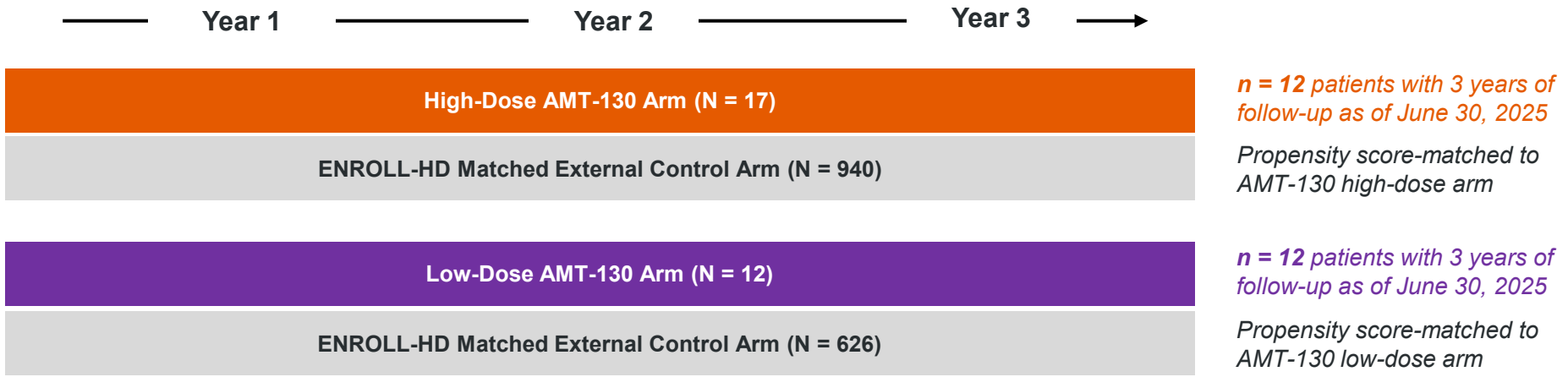


uniQure AMT-130

- Phase 1b/2a Study EU and US
  - Active treatment vs. sham at one of 4 US surgery sites
    - Double blinded for first year
  - Active treatment only (open label) at 3 UK/EU surgery sites
  - 5 years of follow-up visits
- 39 patients (17 high dose active drug, 12 low dose active drug, 10 sham surgery)
  - Symptomatic, age 25-65, TFC 9-13, CAG>=40
  - Striatal volume screening requirements by MRI
    - Leading to ~25% of patients able to screen into study
  - All subjects unblinded at 12 month follow-up, sham subjects allowed to cross over if met same initial volumetric criteria

uniQure AMT-130 Analysis Plan

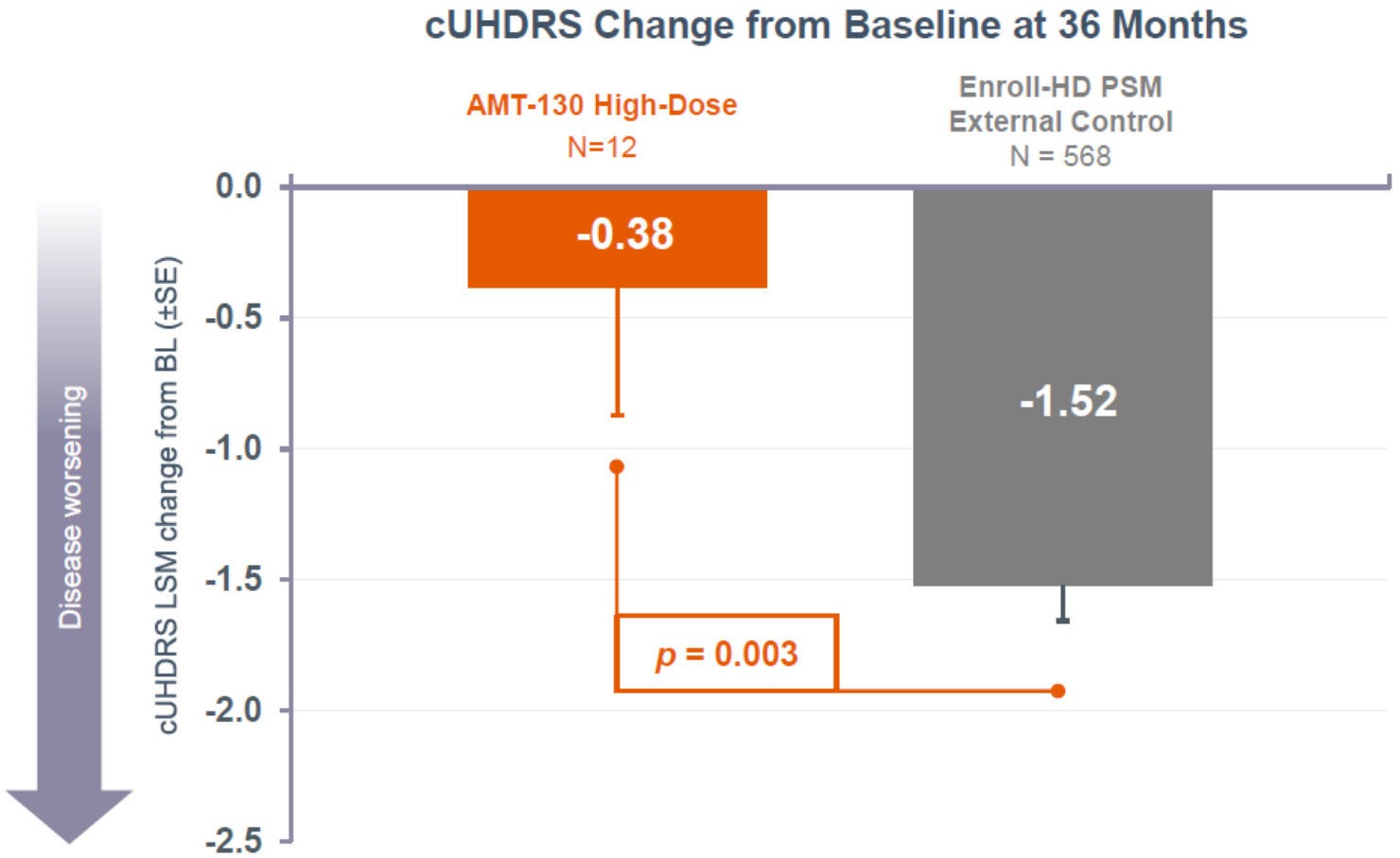
- Prespecified/submitted/approved by FDA



PRIMARY ENDPOINT	• Composite Unified Huntington's Disease Rating Scale (cUHDRS)	Change from baseline at 3 Years in High-Dose AMT-130 Arm vs Enroll-HD propensity score-matched external control
SECONDARY ENDPOINTS	• Total Functional Capacity (TFC) • Symbol Digit Modalities Test (SDMT) • Stroop Word Reading Test (SWRT) • Total Motor Score (TMS)	
EXPLORATORY ENDPOINT	• Cerebrospinal fluid (CSF) Neurofilament light chain (NfL) change from baseline at 3 years	

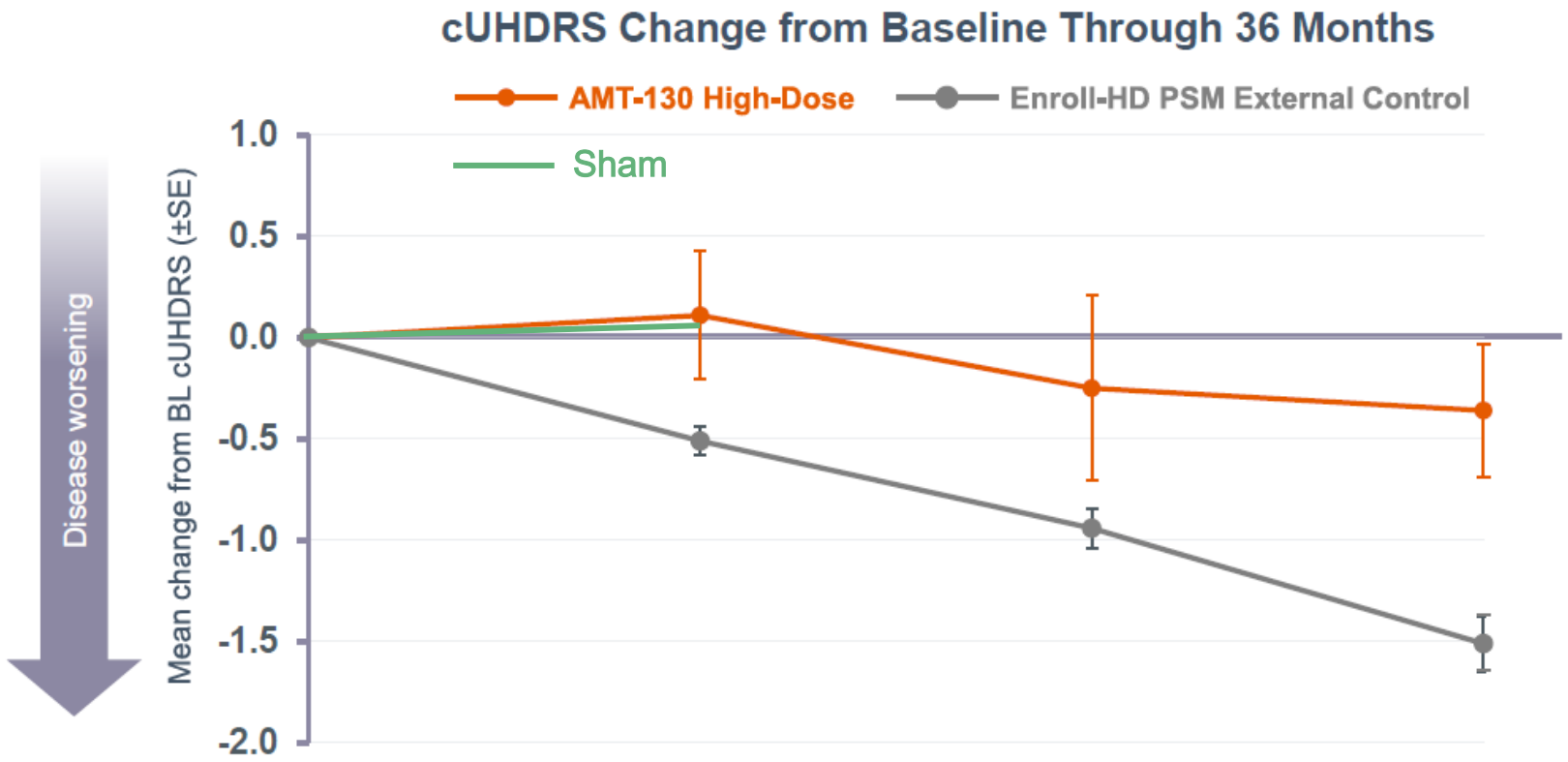
AMT-130 Primary Endpoint

- This difference is the 75% slowing claimed in uniQure press release
- Why comparing to an external control?
- What happened to sham subjects?



AMT-130 Press Release

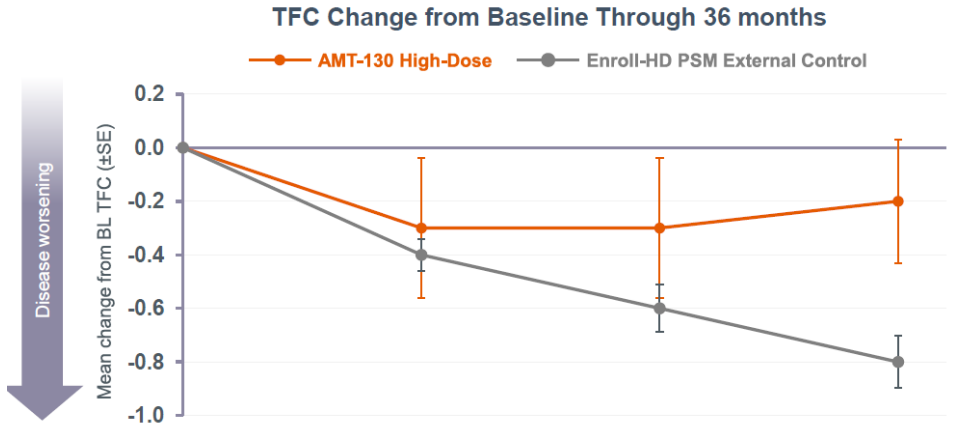
- Further separation over time
- Sham subject data not published, but added superimposed based on previous press releases

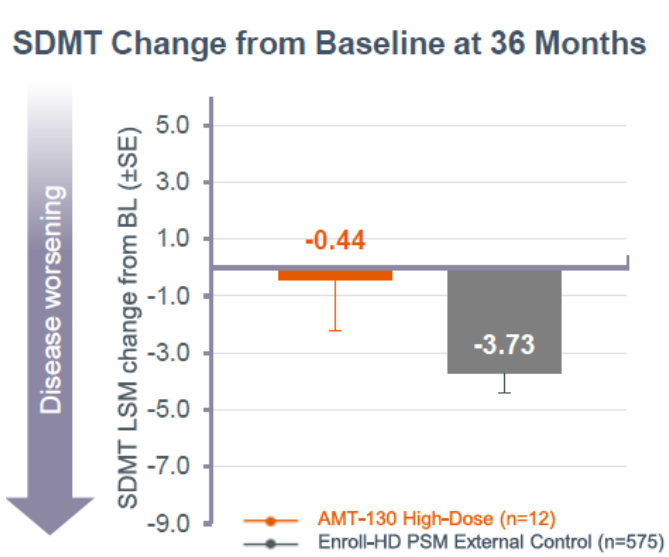


Participants	Baseline	12 months	24 months	36 months
AMT-130 High-Dose	17	17	15	12
PSM External Control	940	715	586	568

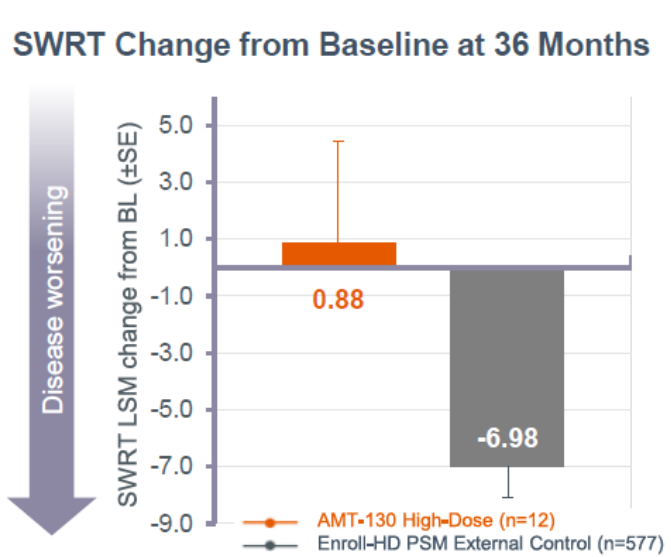
AMT-130 Secondary Endpoints

- All components of cUHDRS individually also separated from external control group at 36 months

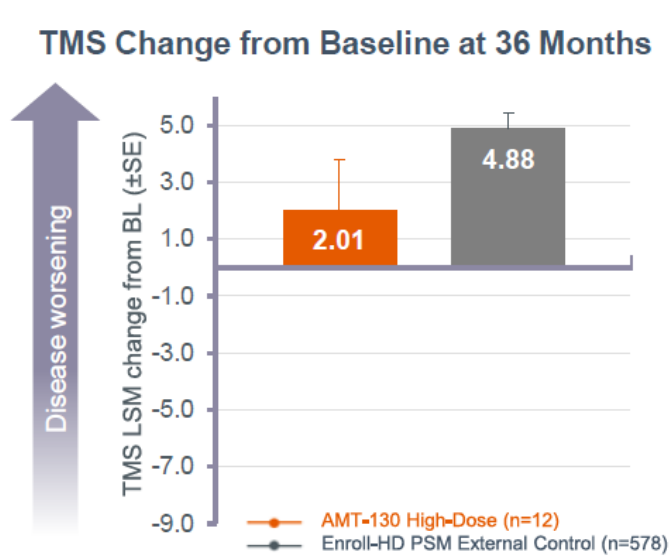




Reduced HD progression by 88% based on SDMT at 36 months (p=0.057)

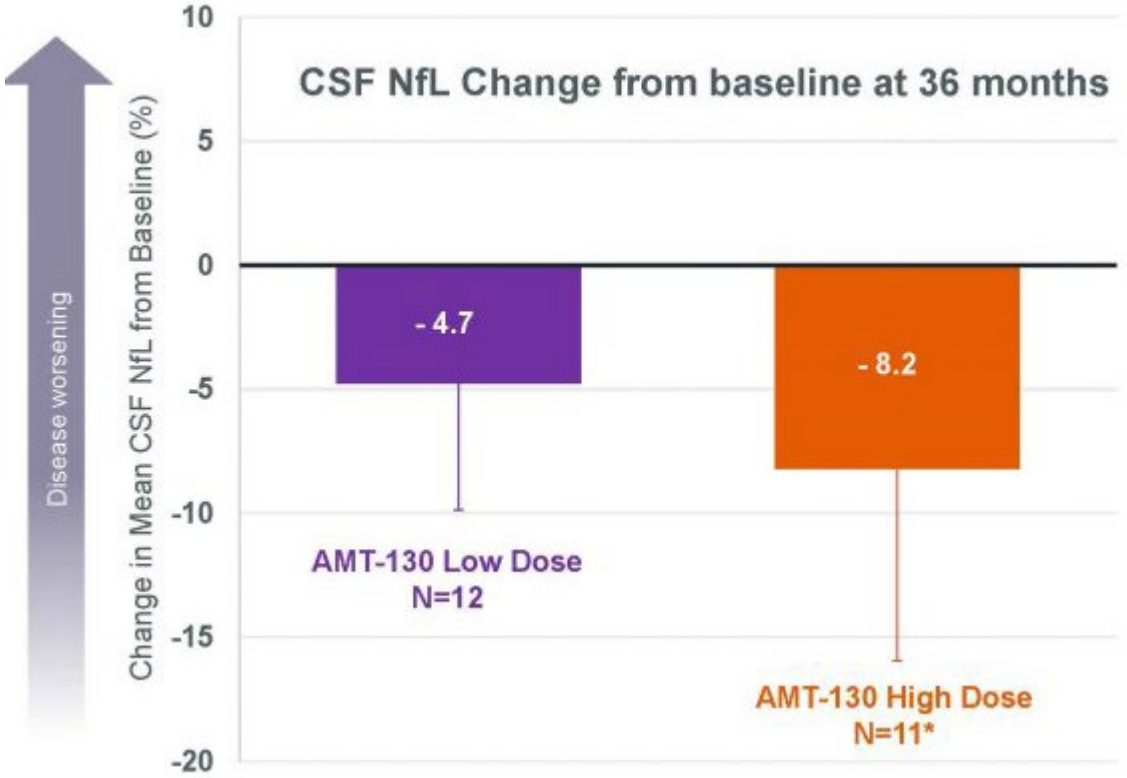


Reduced HD progression by 113% based on SWRT at 36 months (p=0.002*)

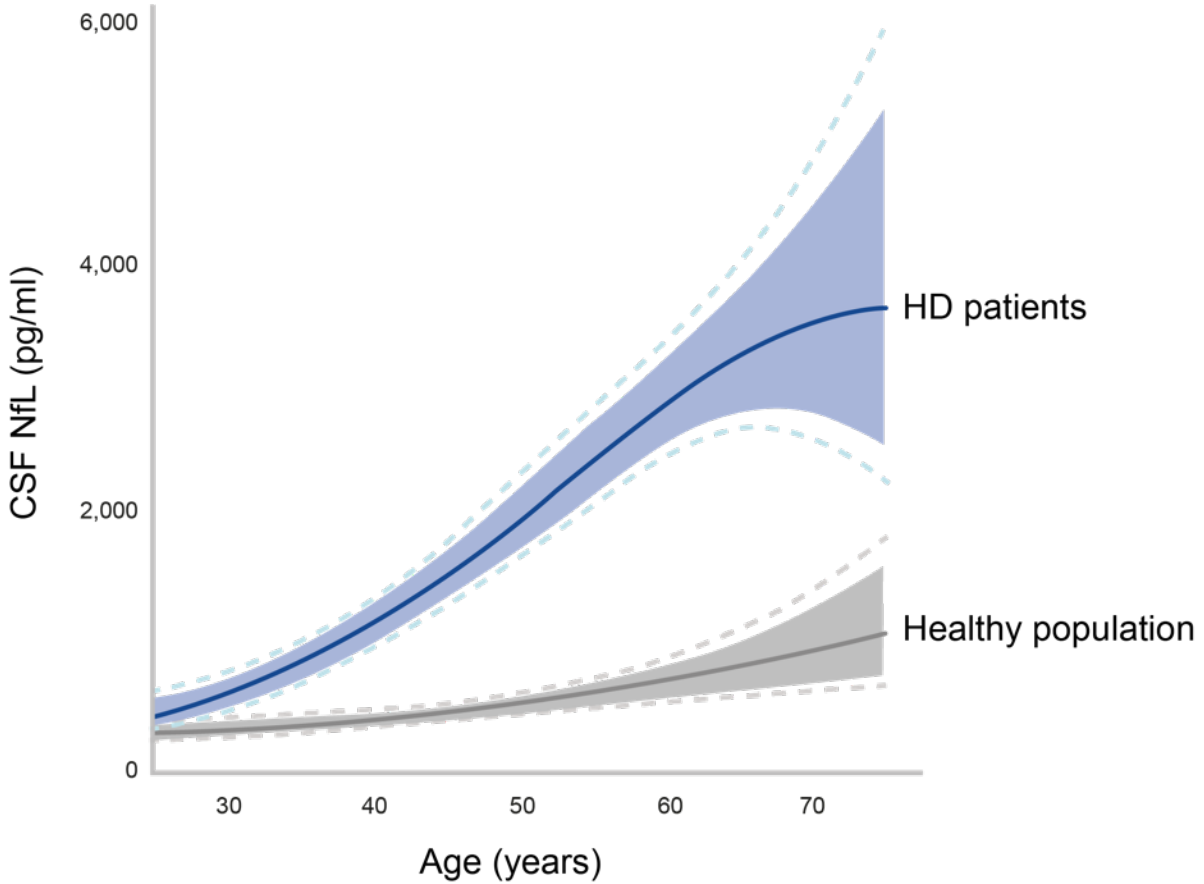


Reduced HD progression by 59% based on TMS at 36 months (p=0.174*)

AMT-130 Biomarker Data



The relationship between NfL and age in HD [1]



1. Rodrigues et al. *Sci Transl Med* 2021

AMT-130 Safety Data

	Control (n=10)		Low-dose AMT-130 (n=13[&])		High-dose AMT-130 (n=20[&])	
	N	(%)	N	(%)	N	(%)
Any TEAEs	10	100.0	12	92.3	20	100.0
Any SAEs (peri-operative)	1	10.0	2	15.4	6	30.0
Any Drug-Related TEAE	0	0.0	0	0.0	6	30.0
Any Drug-Related SAE	0	0.0	0	0.0	4	20.0
CNS Inflammation	0	0.0	0	0.0	4*	20.0
Most Common TEAEs (≥30% in at least one group)						
Procedural headache	5	50.0	4	30.8	10	50.0
Procedural complication	4	40.0	4	30.8	5	25.0
Headache	3	30.0	3	23.1	8	40.0
Post lumbar puncture syndrome	6	60.0	2	15.4	6	30.0
Procedural pain	6	60.0	2	15.4	7	35.0

UniQure AMT-130 Key Learnings and Next Steps

- Htt-lowering can still be effective
  - ?Importance of engagement of exon 1
- FDA meeting takeaways
  - Dislikes external controls
  - Preference is wet/imaging biomarkers all in alignment/positive and subtle clinical benefit
  - Accelerated approval pathway may not be viable at this time
- Planning to submit in UK for approval, likely headed for large sham-controlled Phase 3 trial in US
- Ethics of long duration sham surgery with long duration blinded followup remain challenging
- Stay tuned!

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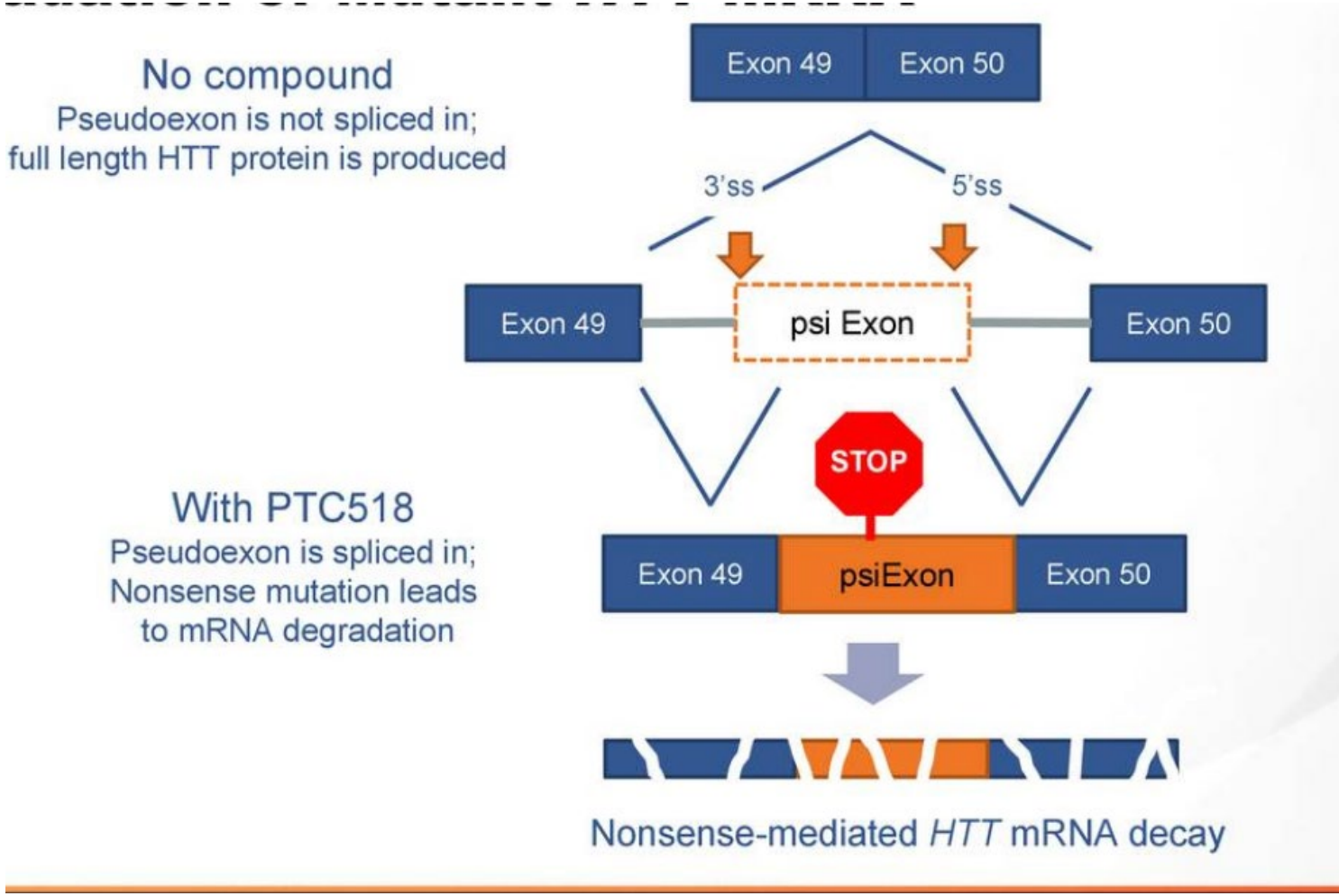
Splicing Modifiers

Novartis Votoplam

- Oral small molecule splicing modifier inserts pseudoexon between exon 49 and exon 50 on Htt mRNA
- Htt-lowering approach



PIVOT-HD Votoplam Phase 2 Study Results

- Achieved primary endpoint of mHtt lowering

Stage 2

Biomarker	Month 12 Mean (SD) Treatment Effect	
	PTC518 5 mg	PTC518 10 mg
mHTT Blood (95% CI)	-23.4% (-34.4, -12.4)	-39.1% (-49.4,-28.7)
mHTT CSF (95% CI)	-23.2% (-51.4, 4.9)	-26.3% (-53.7, 1.1)

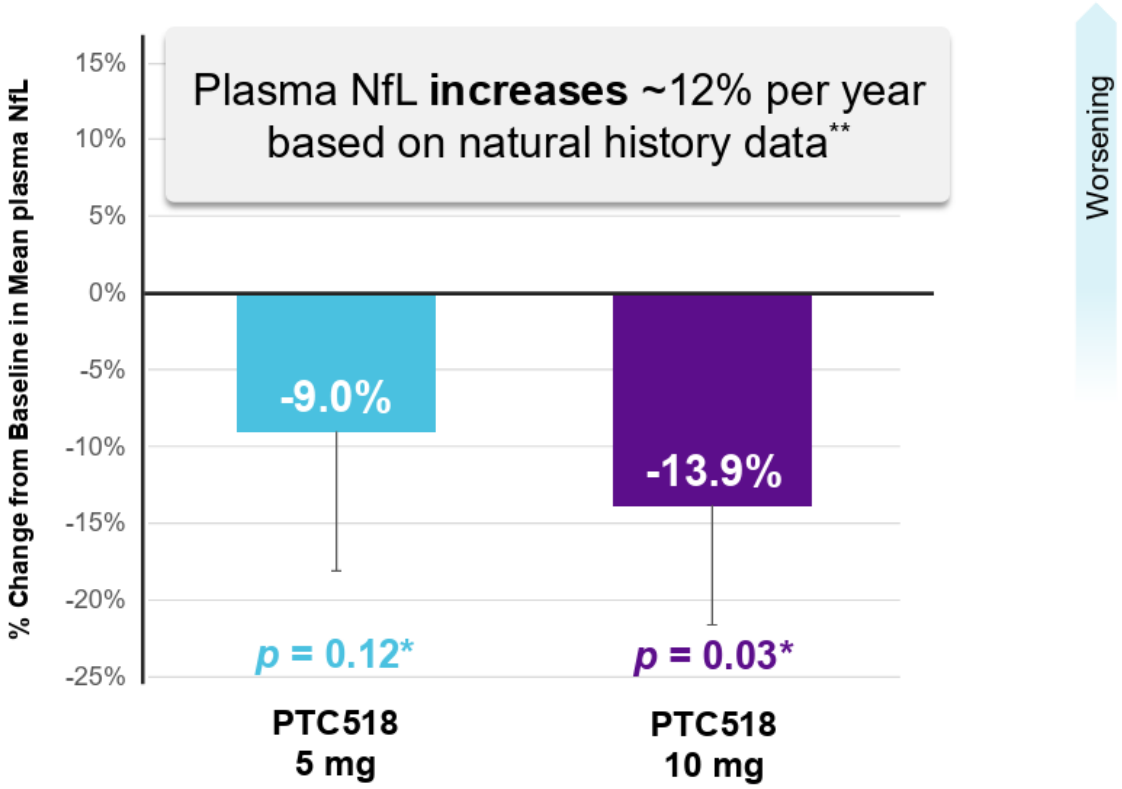
Stage 3

Biomarker	Month 12 Mean (SD) Treatment Effect	
	PTC518 5 mg	PTC518 10 mg
mHTT Blood (95% CI)	-23.3% (-33.4, -13.2)	-36.1% (-45.9, -26.4)
mHTT CSF (95% CI)	-20.8% (-47.4, 5.7)	-22.3% (-48.3, 3.6)

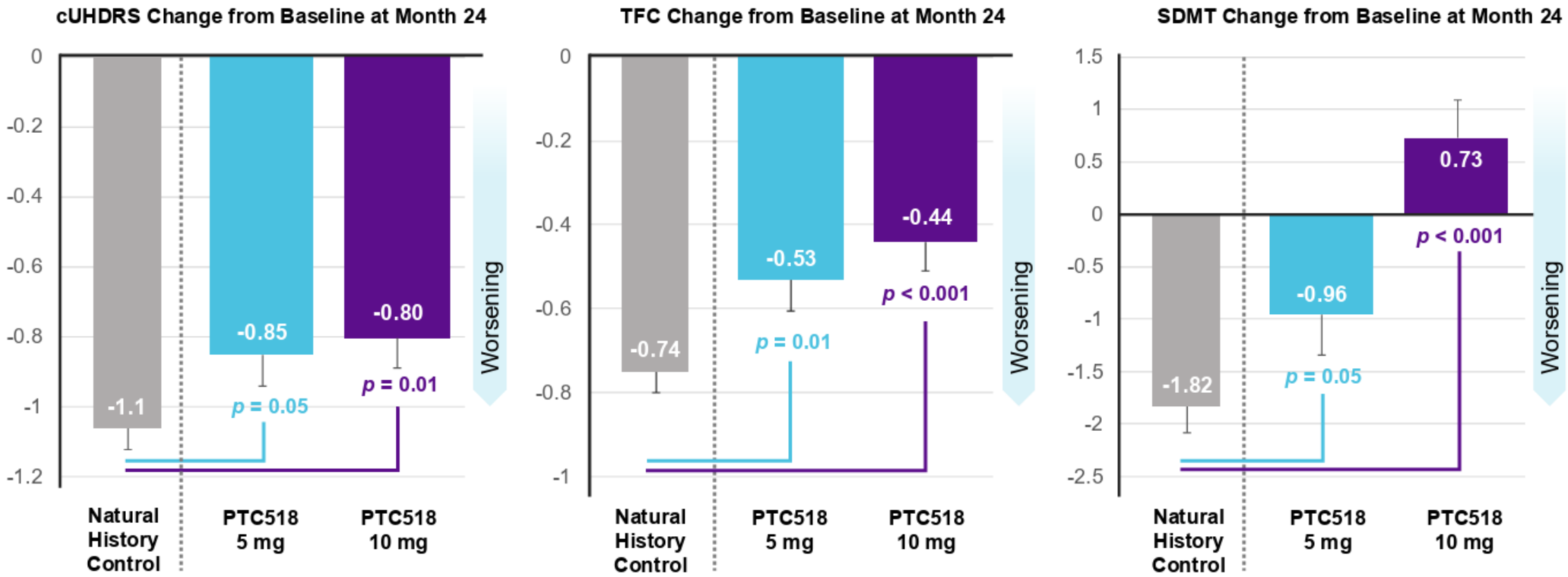
- Minimal overall side effects and no serious side effects

PIVOT-HD Votoplam Phase 2 Study Results

- Trend toward NfL lowering at 24 months?



PIVOT-HD Votoplam Phase 2 Study Results



TMS trend at Month 12 not maintained at Month 24

Votoplam Key Learnings and Next Steps

- First promising oral DMT
- Splice modification can be effective without significant off target effects ie neuropathy
- Can modest Htt-lowering with low AE profile be successful?
- Phase 3 trial underway

PTC Therapeutics Enters into a Global License and Collaboration Agreement with Novartis for PTC518 Huntington's Disease Program

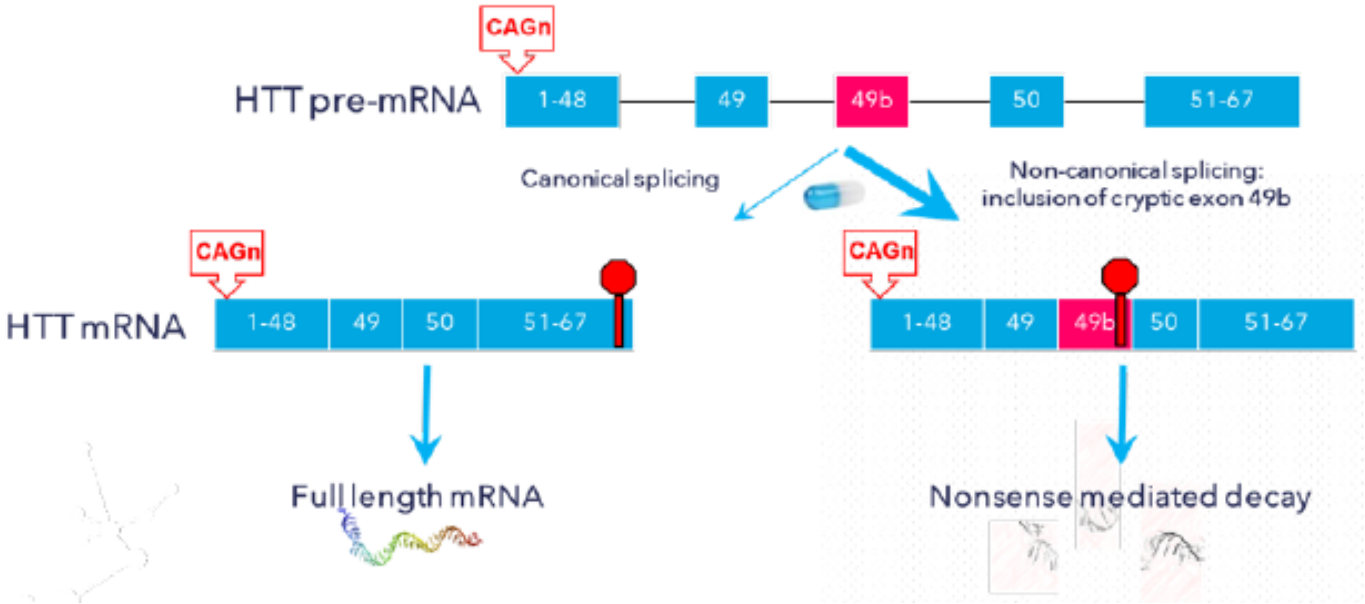
December 2, 2024

PDF Version

- PTC to receive $1.0B in cash at closing -
- PTC is eligible to receive up to $1.9B in development, regulatory and sales milestones -
- PTC to share profits in the U.S. and tiered double-digit royalties on ex-U.S. net sales -
- Novartis will assume global development, manufacturing and commercial responsibilities following completion of placebo-controlled portion of ongoing PIVOT-HD study -
- PTC will host a conference call on Dec. 2, 2024, at 8:30 am EST-

Sky-0515

- Oral splicing modifier inserting stop codon between exon 49 and 50 and secondary mechanism of interfering with PMS1 (somatic instability)
- 10 patients received 9mg dose
  - 62% lowering of Htt at 84 days
- 10 patients received 3mg dose
  - 29% lowering of Htt at 84 days
- Good safety, no spikes in NfL, no signs of neuropathy



- Still very early, stay tuned!

Other Future Exciting DMT Trials

- Wave and Roche both pursuing different allele-specific ASO's
- VICO with ASO targeting CAG sequence itself
  - Planning basket study with both HD and SCA3 patients
- Latus with gene therapy targeting MSH3 to address somatic instability
- Alnylam with intrathecal siRNA approach
- Sarepta with subQ injected gene therapy

Learnings for Other Neurologic Diseases

- Even in a monogenic neurodegenerative disease like HD, a simple toxic gain of function model is likely oversimplistic
- Somatic instability may be a key player for other trinucleotide repeat disorders
- NfL seems to be an important biomarker of both safety and disease progression for a broad group of neurodegenerative disorders
- The simple FDA model of positive biomarkers and mild clinical benefit leading to accelerated approval may prove insufficient for neurologic disease

Summary

- Though HD pathophysiology proving to be more complex than simple toxicity of mHtt protein, multiple potential targets for disease modification
- Multiple therapeutics in late stage human trials means the future is bright in HD!
- Approaches could have broader implications for other neurologic disease

Thanks to my UAB Team!!

Huntington's Disease Society of America
Center of Excellence
University of Alabama Birmingham

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Q&A