Progress in Biomarkers for Huntington's Disease

Multimodal biomarkers Development integration and clinical utility barriers and implications lessons learned

NATIONAL ACADEMIES Sciences Engineering Medicine

National Academies Workshop on Multimodal Biomarkers in CNS Disorders

March 13, 2023

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WISCONSIN UNIVERSITY OF WISCONSIN-MADISON

Outline for Talk

- Review of diagnostic criteria for Huntington's disease (HD)
- Genetic markers
- Biofluid markers
- Imaging markers
- Applications in clinical trials
- Barriers and opportunities

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HD Diagnosis (1979-1999)
Standardized HD diagnosis using the UHDRS motor exam

I. MOTOR ASSESSMENT

Horizontal Vertical

1. OCULAR PURSUIT 1a. ☐ 1b. ☐
   - 0 = complete (normal)
   - 1 = jerky movement
   - 2 = interrupted pursuits/full range
   - 3 = incomplete range
   - 4 = cannot pursue

TMS

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17. DIAGNOSIS CONFIDENCE LEVEL 17. ☐ DCL

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

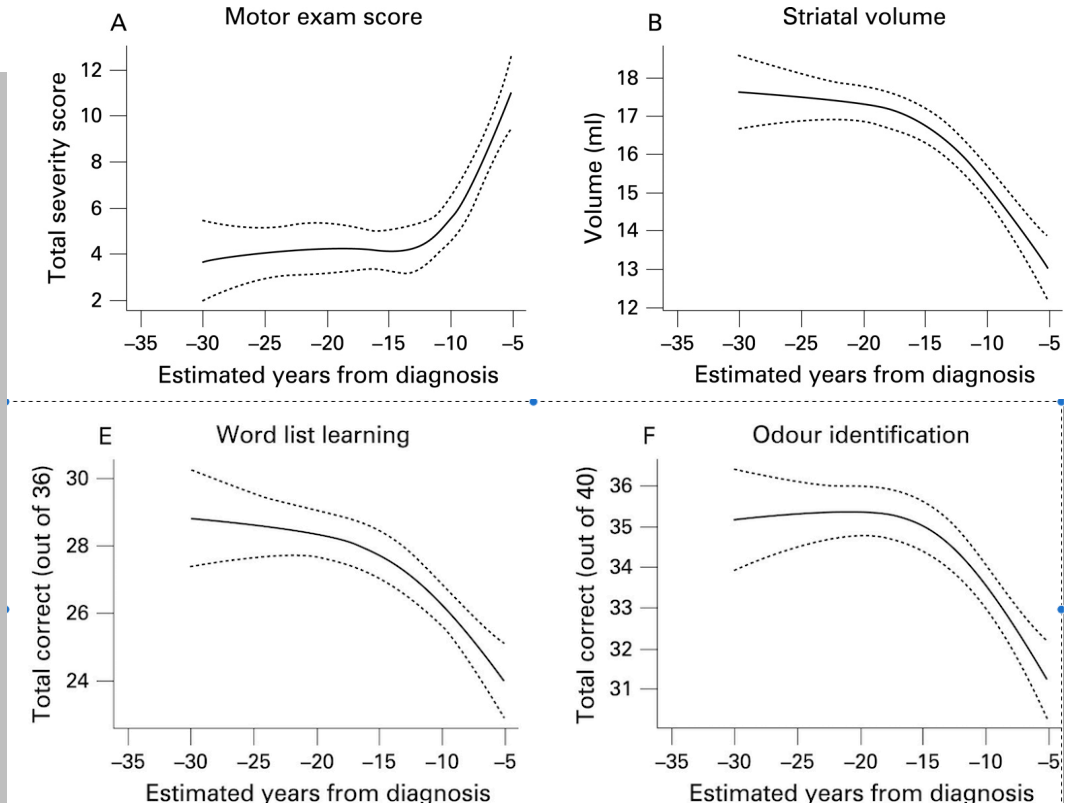
- 0 = normal (no abnormalities)
- 1 = non-specific motor abnormalities (less than 50% confidence)
- 2 = motor abnormalities that may be signs of HD (50%-89% confidence)
- 3 = motor abnormalities that are likely signs of HD (90%-98% confidence)
- 4 = motor abnormalities that are unequivocal signs of HD (≥ 99% confidence)

Marker 1983

Gene 1993

Natural History Studies of HD

COHORT 1995
PREDICT 2000
REGISTRY 2002
TRACK 2008
ENROLL 2012



frontiers in
AGING NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 02 April 2013
doi: 10.3389/fnagi.2013.00012

Refining the diagnosis of Huntington disease: the PREDICT-HD study

Kevin M. Biglan[1], Ying Zhang[2], Jeffrey D. Long[3], Michael Geschwind[4], Gail A. Kang[4], Annie Killoran[1], Wenjing Lu[2], Elizabeth McCusker[5], James A. Mills[3], Lynn A. Raymond[6], Claudia Testa[7], Joanne Wojcieszek[8], Jane S. Paulsen[3], and the PREDICT-HD Investigators of the Huntington Study Group*

VIEWPOINT

Diagnostic Criteria for Huntington's Disease Based on Natural History

Ralf Reilmann, MD,[1,2*] Blair R. Leavitt, MD, CM,[3] and Christopher A. Ross, MD[4*]

[1]George-Huntington-Institute, Technology-Park, Muenster, Germany
[2]Department of Neurodegenerative Diseases and Hertie-Institute for Clinical Brain Research, University of Tuebingen, Tuebingen, Germany
[3]Centre for Molecular Medicine and Therapeutics, and Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada
[4]Division of Neurobiology, Department of Psychiatry, and Departments of Neurology, Neuroscience, and Pharmacology, and Program in Cellular and Molecular Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

TABLE 1 *Criteria for diagnoses in individuals with a CAG-repeat expansion in Huntingtin*

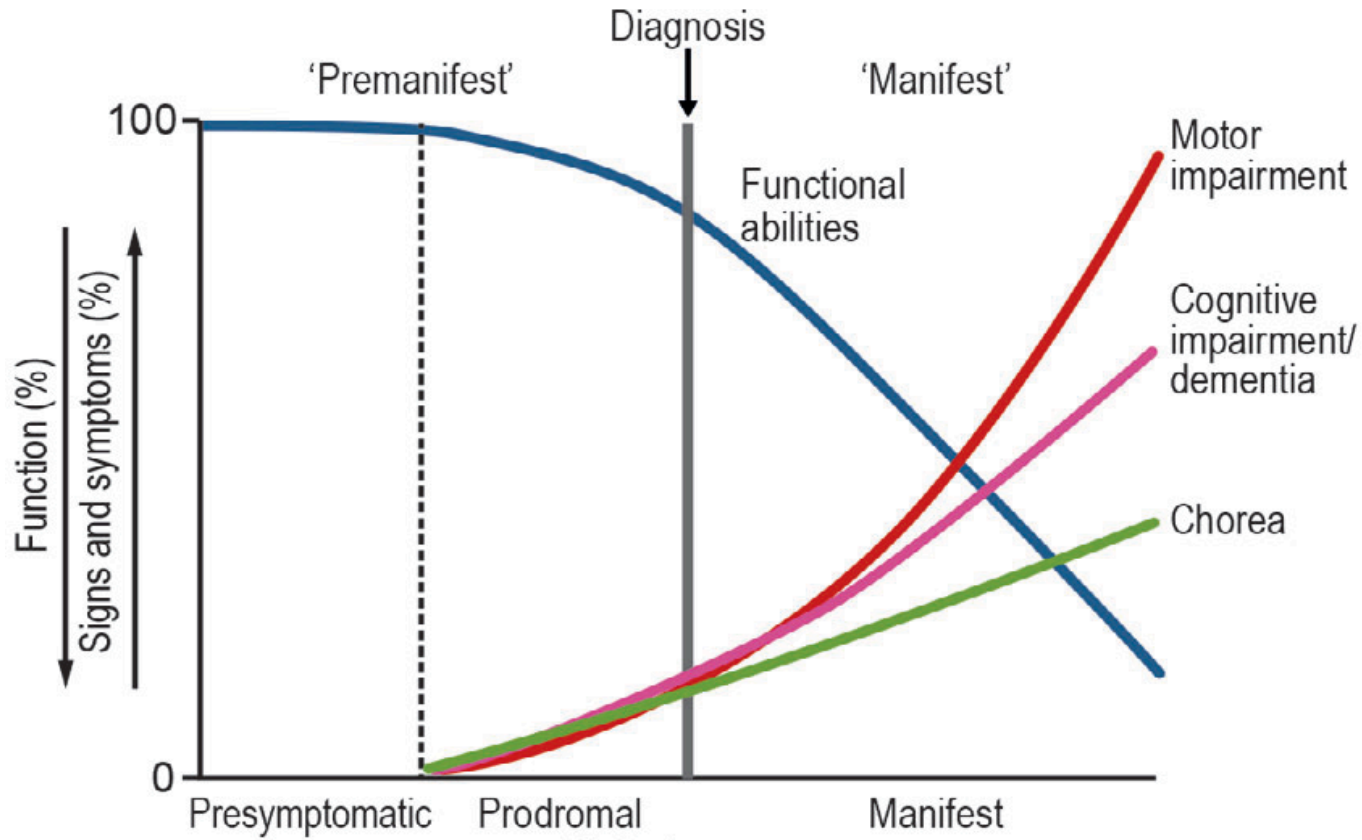
Diagnosis	Motor	Cognitive	Potential Treatment
(1) Presymptomatic HD	Dx conf 0–2	Normal	(1) Disease modifying
(2) Prodromal HD	A) Dx conf 2	(A) + Minor or major neurocognitive changes	(2A or B) Symptomatic or disease modifying
(either A or B)	B) Dx conf 3	(B) With normal (unchanged) cognition	
(3) Manifest HD	A) Dx conf 3	(A) + Minor or major neurocognitive changes	(3A or B) Symptomatic or disease modifying
(either A or B)	B) Dx conf 4	(B) With normal (unchanged) cognition	

Potential treatments apply to each of the 3 diagnoses regardless of the criteria for meeting the diagnosis. It is expected that the ability to

Movement Disorders
CLINICAL PRACTICE
VIEWPOINT

Movement Disorder Society Task Force Viewpoint: Huntington's Disease Diagnostic Categories

Christopher A. Ross, MD, PhD,[1,*] Ralf Reilmann, MD, PhD,[2] Francisco Cardoso, MD, PhD, FAAN,[3] Elizabeth A. McCusker, MB, BS (Hons), FRACP,[4] Claudia M. Testa, MD, PhD,[5] Julie C. Stout, PhD,[6] Blair R. Leavitt, BSc, MDCM, FRCPC,[7] Zhong Pei, MD, PhD,[8] Bernhard Landwehrmeyer, MD, PhD, FRCP,[9] Asuncion Martinez, BS,[10] Jamie Levey, MBA,[11,12] Teresa Srajer, BS, MBA,[10] Jee Bang, MD, MPH,[13] and Sarah J. Tabrizi, MD, PhD[14,15]



Lancet Neurol 2022; 21: 632–44

A biological classification of Huntington's disease: the Integrated Staging System

Sarah J Tabrizi, Scott Schobel*, Emily C Gantman, Alexandra Mansbach, Beth Borowsky, Pavlina Konstantinova, Tiago A Mestre, Jennifer Panagoulias, Christopher A Ross, Maurice Zauderer, Ariana P Mullin, Klaus Romero, Sudhir Sivakumaran, Emily C Turner, Jeffrey D Long, Cristina Sampaio, on behalf of the Huntington's Disease Regulatory Science Consortium (HD-RSC)†*

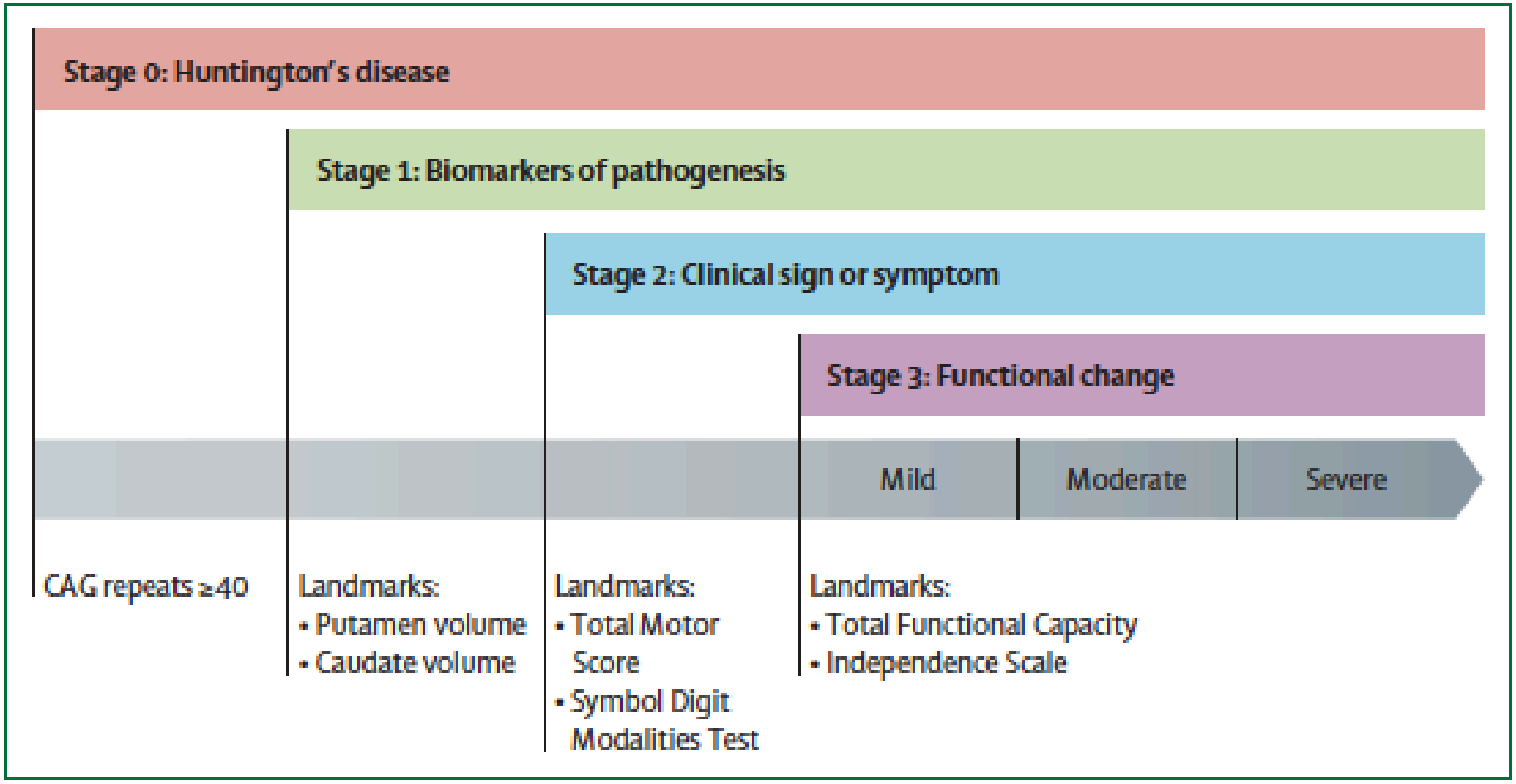


Figure 3: Cumulative staging framework and landmarks of the Huntington's disease Integrated Staging

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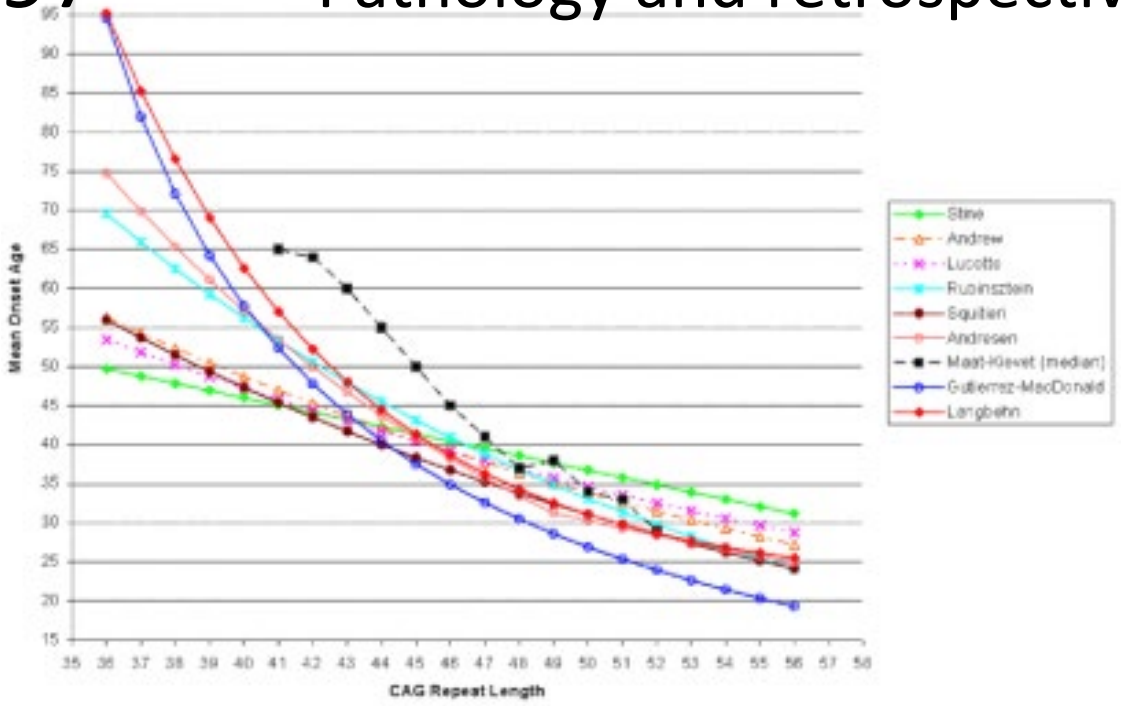
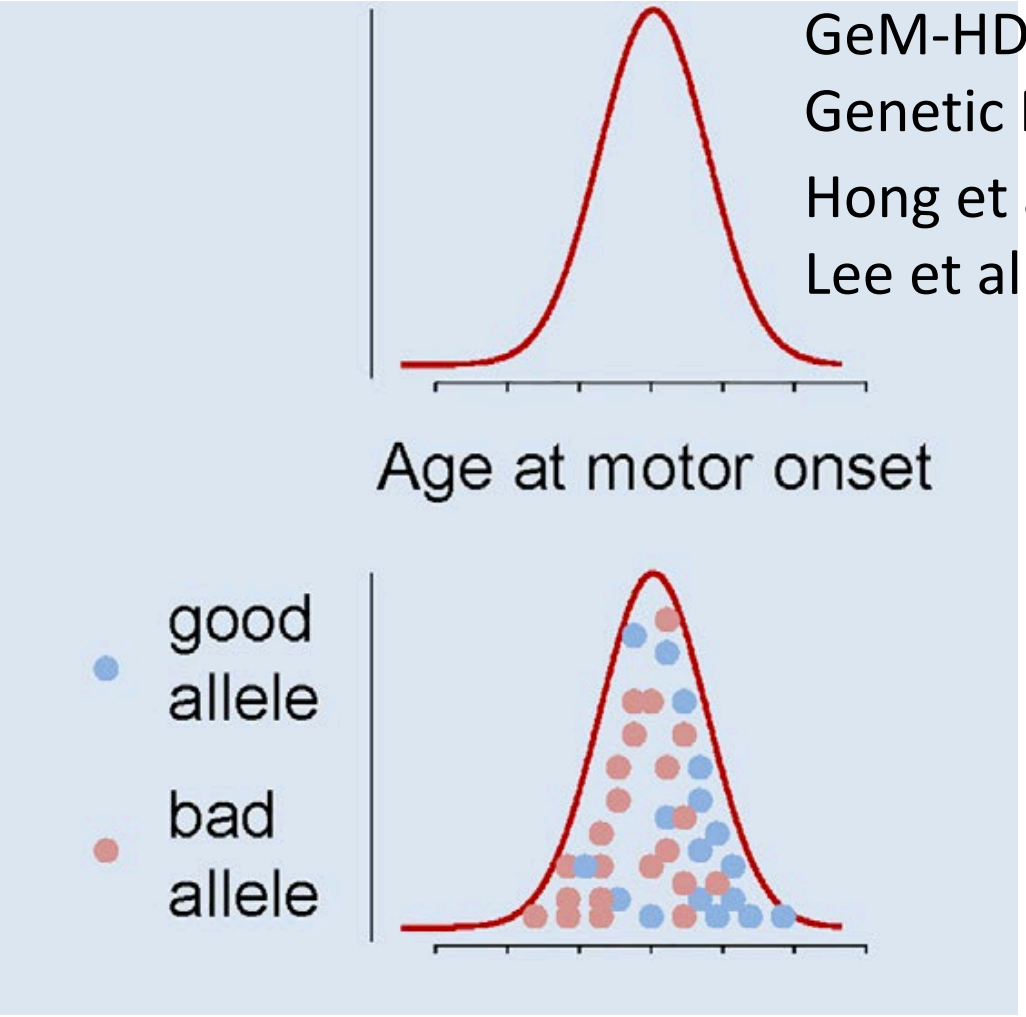
Prognostic and diagnostic genetic biomarkers

Brinkman et al., 1995	Retrospective ww n > 4400
Langbehn et al., 2004	Brinkman data n ~ 2300
Langbehn et al., 2010	Prospectively diagnosed from ww Predict n=81
Zhang et al., 2011	Prospectively diagnosed n=250 of n~ 1500
Penney et al., 1997	Pathology and retrospective AO n=89 brains



HD is the prototypical autosomal dominant genetic disease ----------Timing of disease onset is polygenic



GeM-HD (2015)
Genetic Modifiers of HD Consortium
Hong et al., 2021
Lee et al., 2022

- GWA revealed loci on chromosomes 8, 15 and 3 hastening or delaying onset
- Uninterrupted CAG is better predictor of onset
- Genetic mosaicism
- Somatic expansion throughout life, accelerating pathogenesis

Multimodal biomarkers for HD

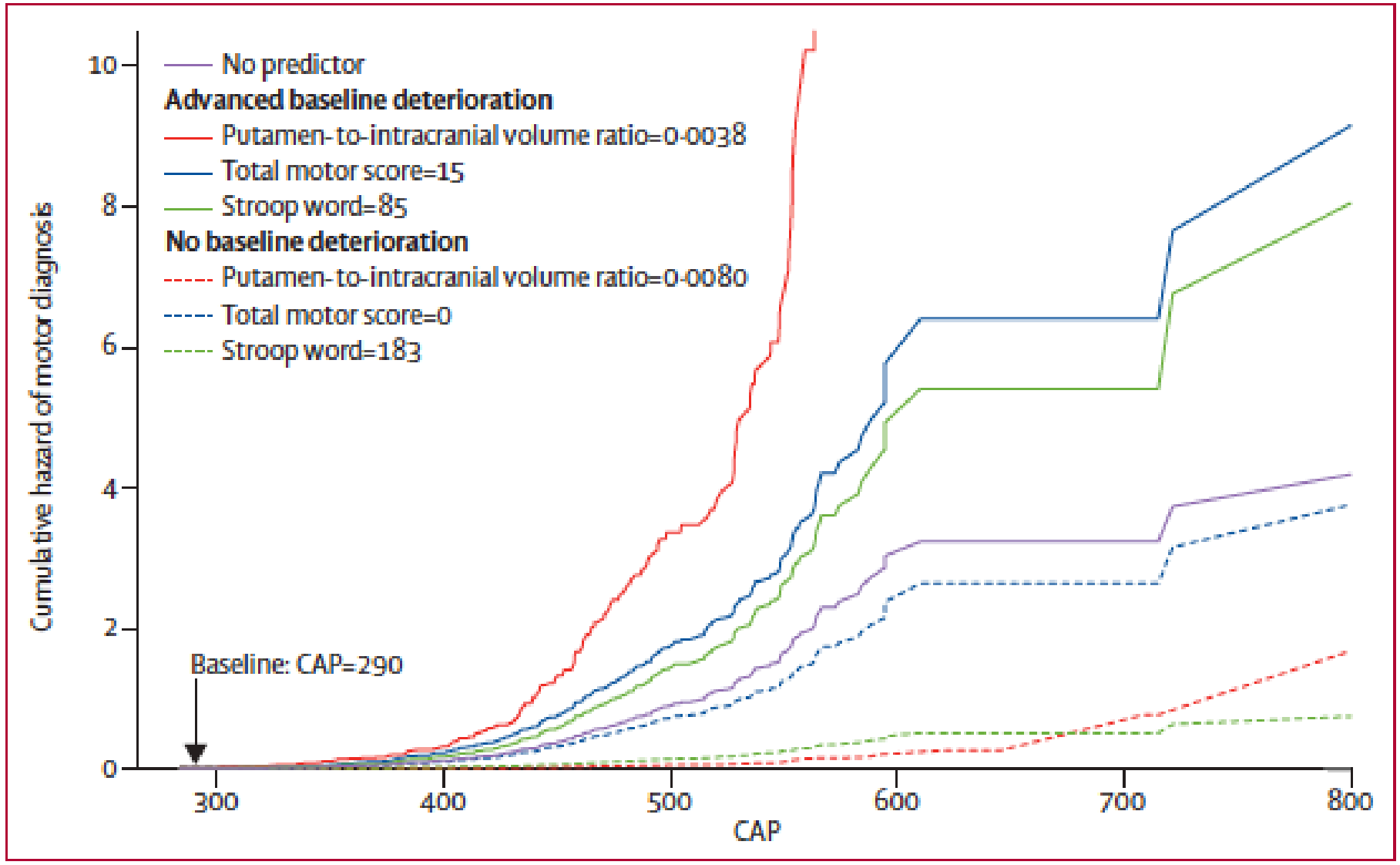
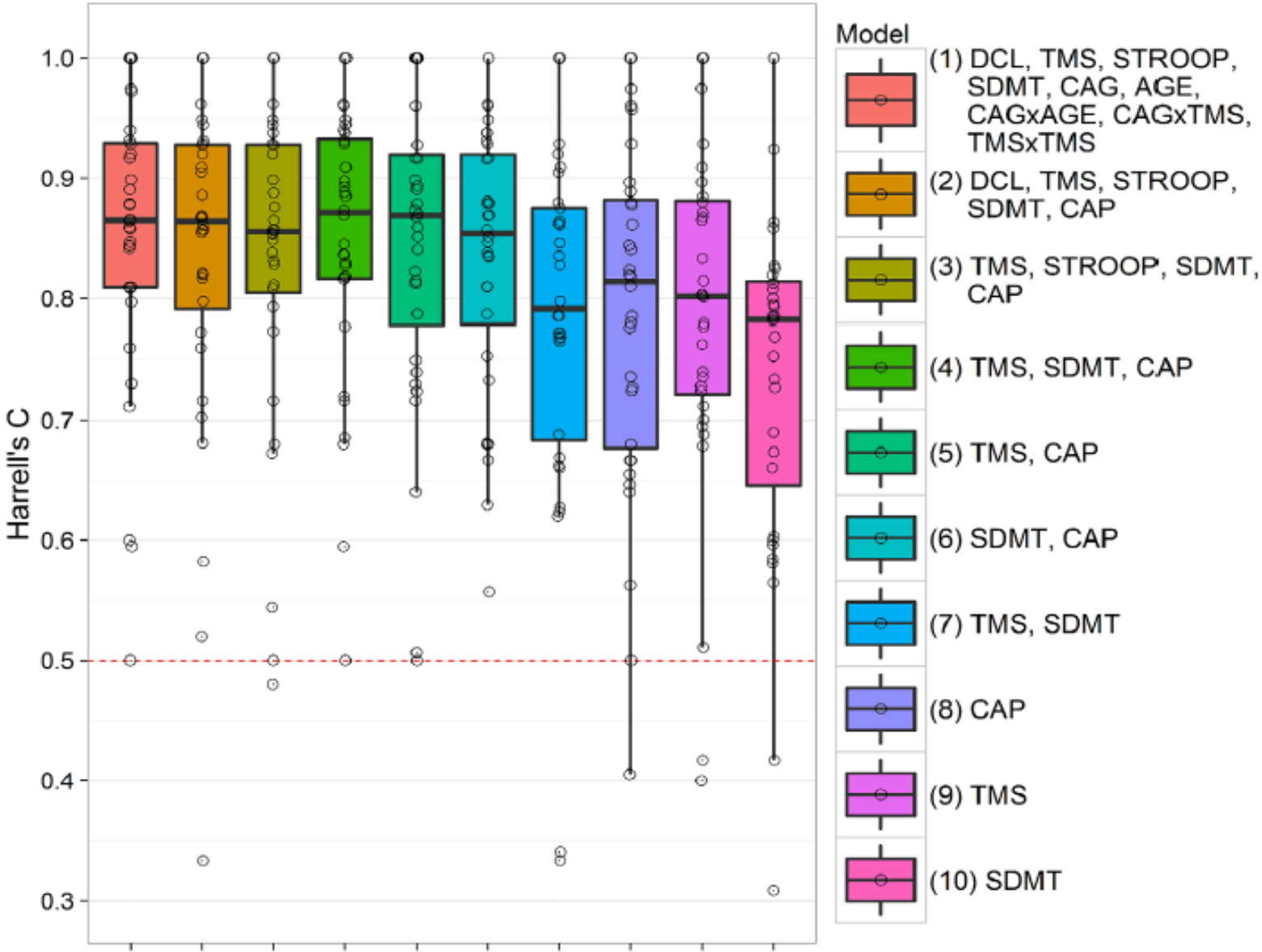


***Figure 2*: Cumulative hazard (accumulated risk rate) of motor diagnosis by CAP for various baseline predictor values**

Prognostic biomarkers to power clinical trials in Huntington disease



Prognostic biomarkers to power clinical trials in Huntington disease

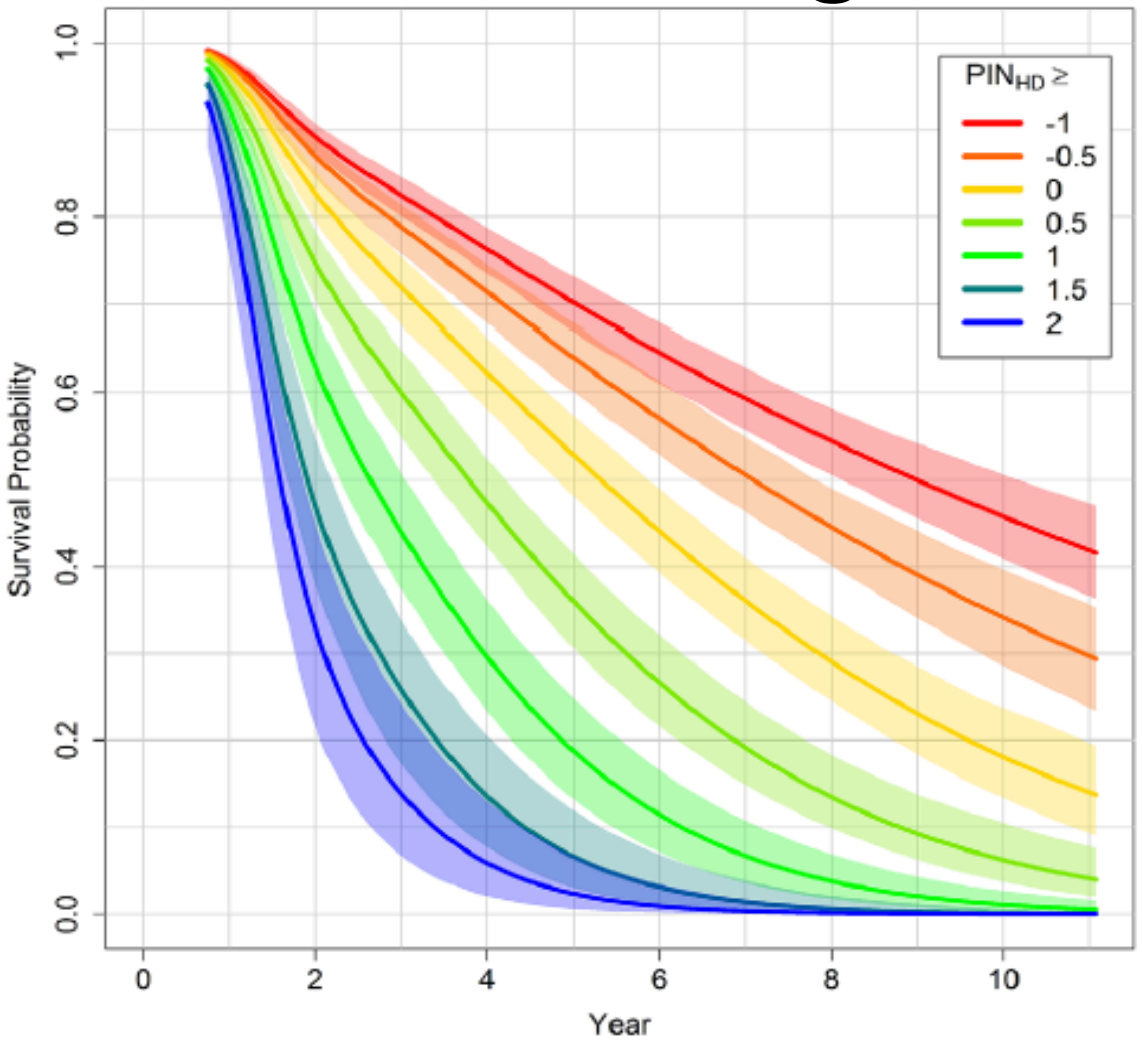


FIG. 3. Cubic spline survival curves (95% CIs) for ranges of the prognositc index normed for Huntington's disease (PIN$_{HD}$). Curves are based on pooling PREDICT-HD, TRACK-HD, and COHORT.

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Biofluid biomarkers for Huntington's disease

- Contributions consistent and frequent; Reviews 2016, 2018, 2021 and 2023
- Evaluations take one of a few approaches:
  - Reflecting/revealing pathogenic process
  - Replications to increase rigor towards validation

Biomarker research summarized by pathogenesis

Neuro degen'n	NFL	GABA	NGF	Tau	NSE	YKL-40	UCHL1	PENK		
immune	IL-6, IL-8	sCD27	IL-18	IL-23	TGF-β1	Chemokines	Clusterin	CRP	Neopterin	GFAP
metabolic	24OHC	5-HT	ApoE	Choles'l	Citrulline	HVA	Isoleucine	Phenylalanine	tryptophan	valine
endocrine	Cortisol	Ghrelin	GH	IGF-1	Leptin	Melatonin	transthyretin	BDNF	angiotensin	
oxidative stress	3HAA	Cu/Zn-SOD	Ferritin	8-OHDG	UA	Kynurenine	Lipid peroxid'n			
miRNA	miR-486-5p	miR-34	miR-10b-5	Has-miR-323b-ep	more…					

Clinically useful Biomarkers

Mutant huntingtin protein (mHTT) and Neurofilament Light Chain (NFL)

I. Value as pharmacodynamic marker is explicit

Requiring novel and ultra-sensitive assays

Associations with disease burden, advancing stage, estimated time (or probability) of onset (stronger in CSF than blood)

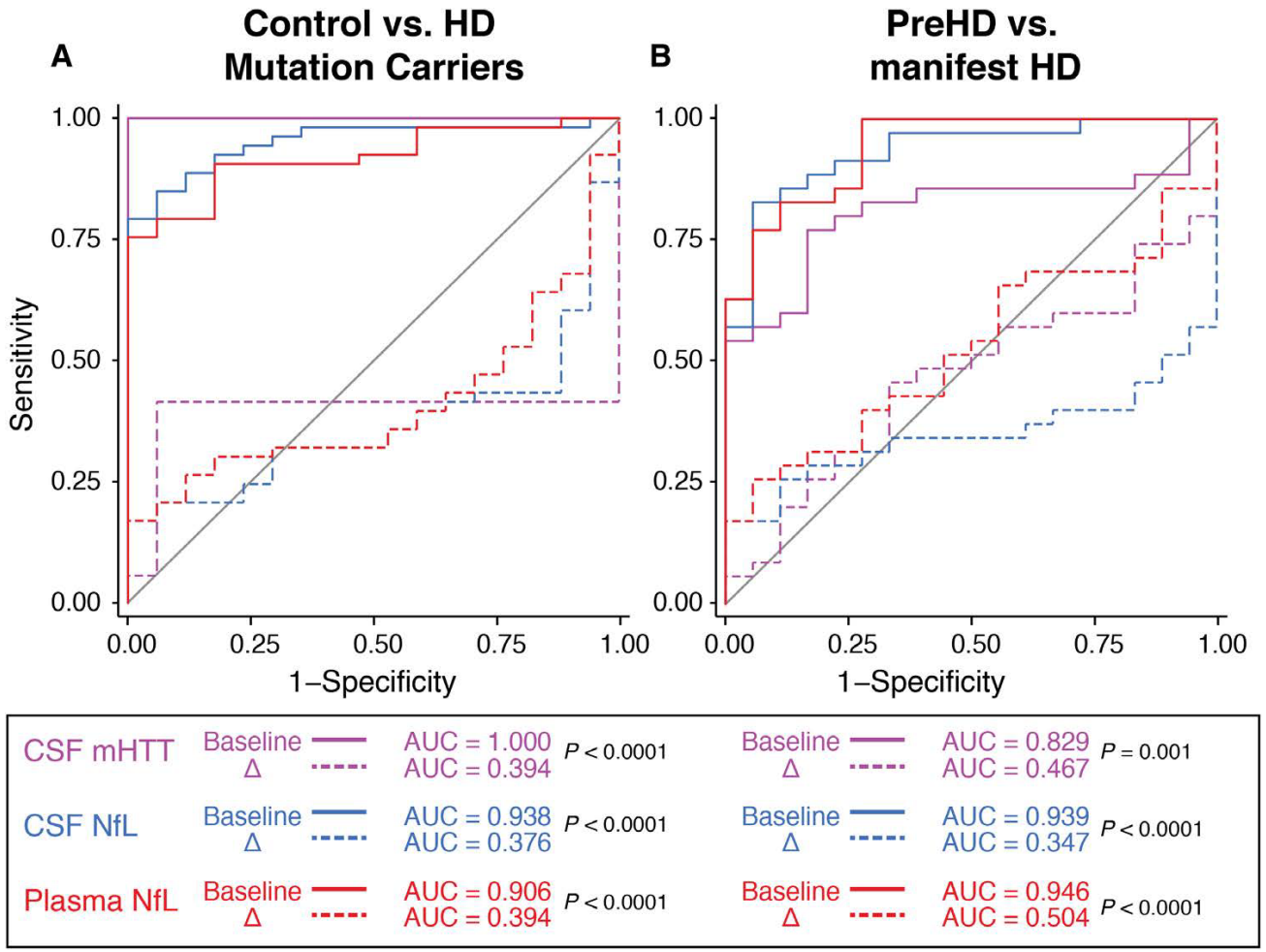
Used in multiple RCTs in HD

II. mHTT and NfL show X-sect'l discrimination

Longitudinal change ineffective for monitoring HD progression. Why?

↓ sample size ↓ follow up time

Or mHTT and NFL are ineffective at detecting change over time



F.B. Rodrigues, L.M. Byrne, R. Tortelli, E.B. Johnson, P.A. Wijeratne, M. Arridge, E. De Vita, N. Ghazaleh, R. Houghton, H.J.S.T.M. Furby, Mutant huntingtin and neurofilament light have distinct longitudinal dynamics in Huntington's disease, Sci. Transl. Med. 12 (574) (2020)

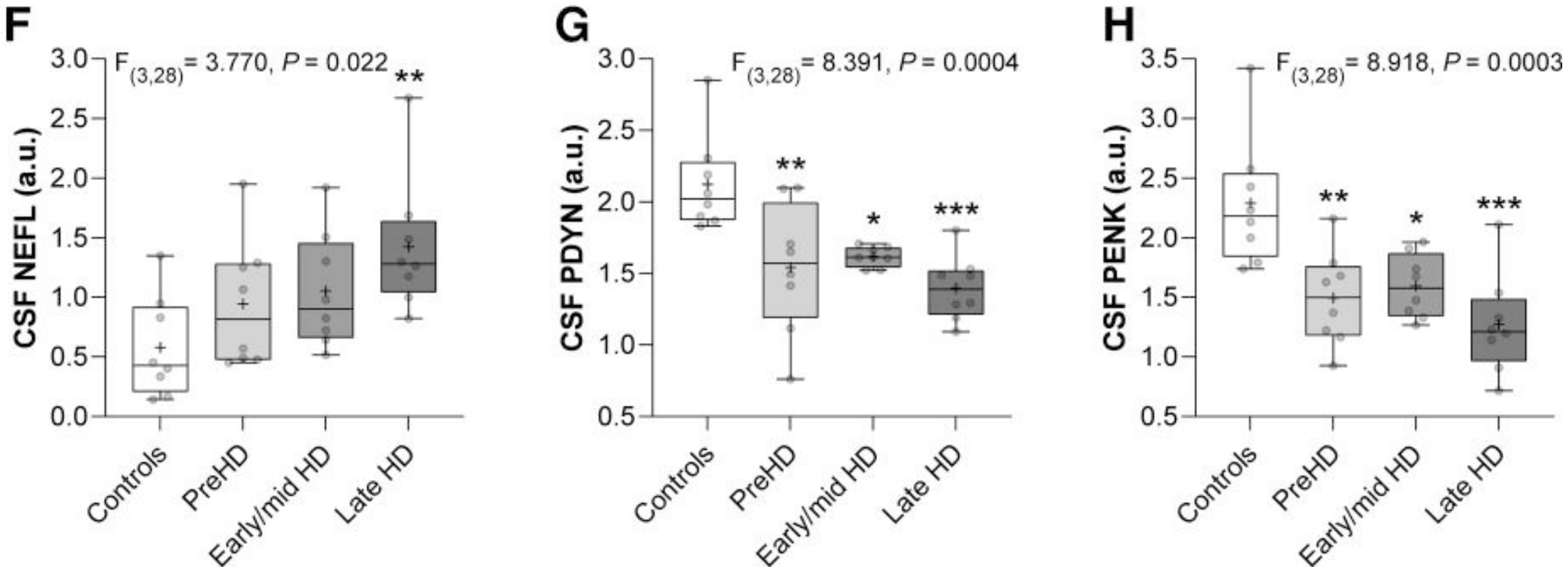
Multimarker comparisons allow interpretation for **Context of Use**

Cerebrospinal fluid biomarkers for assessing Huntington disease onset and severity

Nicholas S. Caron,[1] Arsalan S. Haqqani,[2] Akshdeep Sandhu,[3] Amirah E. Aly,[1] Hailey Findlay Black,[1] Jeffrey N. Bone,[3] Jodi L. McBride,[4,5] Abedelnasser Abulrob,[2] Danica Stanimirovic,[2] Blair R. Leavitt[1] and Michael R. Hayden[1]

Linear progressive changes: progression

NC vs. HD: threshold for treatment



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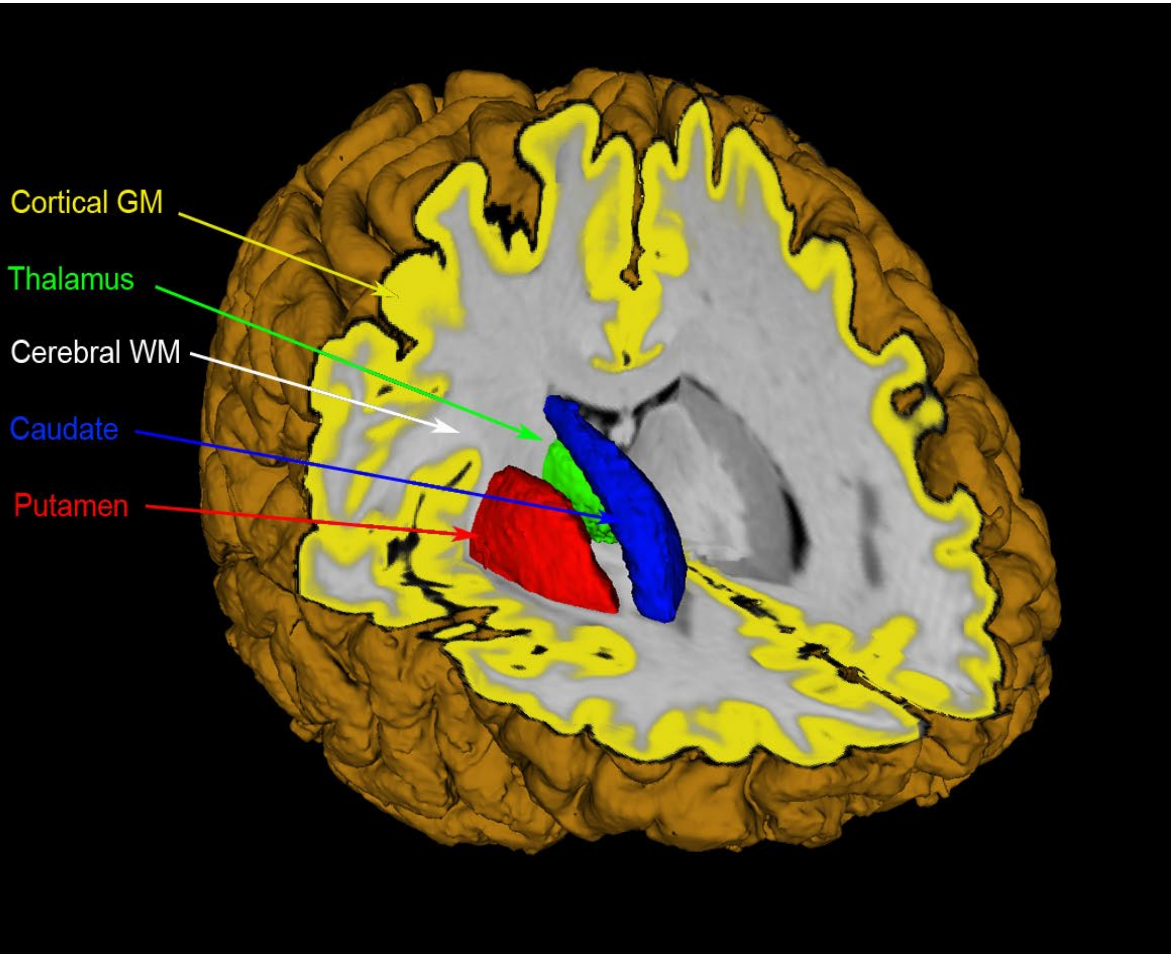
Structural volumetric changes in prodromal HD



CROSS-SECTIONAL – DETECT diffs from NC

LONGITUDINAL – progression

% Volume difference	Cross- sect'l Effect size	Long'l Effect Size	Brain structure
- 2.6	0.669	.18	Cortical GM
-12.7	1.328	.46	Thalamus
-10.3	1.445	1.17	CerebralWM
-31.7	2.290	.81	Caudate
-26.4	2.456	.63	Putamen

Aylward et al (2011); JNNP
Aylward et al (2011); PlosCurrents HD

Structural changes in Huntington's disease

ARTICLE OPEN ACCESS

Revealing the Timeline of Structural MRI Changes in Premanifest to Manifest Huntington Disease

Peter A. Wijeratne, PhD, Sara Garbarino, PhD, Sarah Gregory, PhD, Eileanoir B. Johnson, PhD, Rachael I. Scahill, PhD, Jane S. Paulsen, PhD, Sarah J. Tabrizi, MD, PhD, Marco Lorenzi, PhD,* and Daniel C. Alexander, PhD,* on behalf of the PREDICT-HD investigators and the TRACK-HD investigators.

Neurol Genet 2021;7:e617. doi:10.1212/NXG.0000000000000617

Combined datasets: PREDICT TRACK IMAGE

1. Largest and earliest changes in subcortex (20% change 2 years before impaired based on normals
2. Followed by a cascade of changes over 11 years
3. Imaging measures combined with other formula improve prediction of onset
4. Mean square error=4.5 years; maximum error = 7.9

Received: 27 July 2020 | Accepted: 12 November 2020

DOI: 10.1111/ene.14648

REVIEW

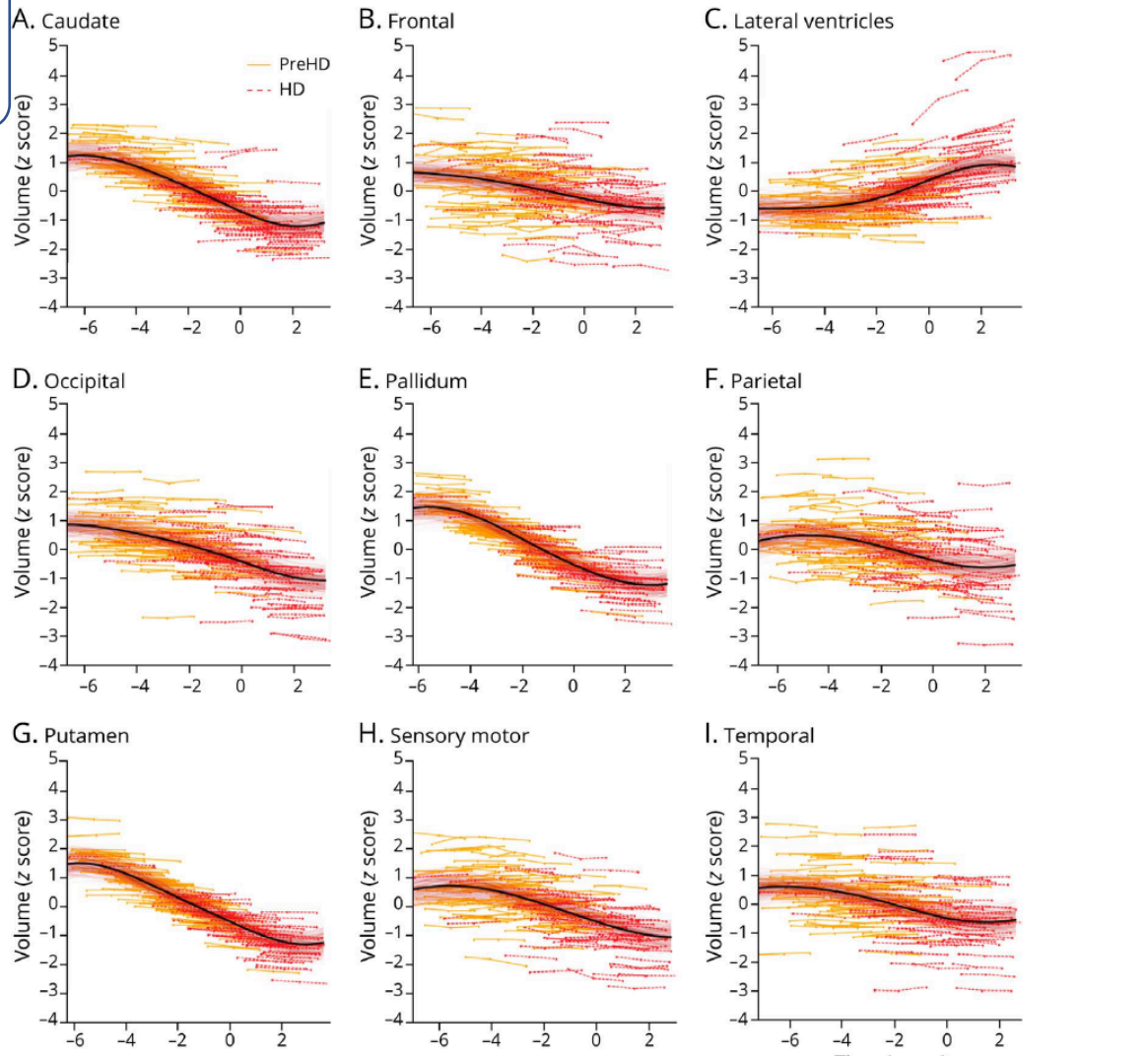
Cortical morphometry and neural dysfunction in Huntington's disease: a review

European Journal of Neurology
November 2020 COI: 10.1111/enc/14648

Brendan Tan[1] | Rosita Shishegar[1,2,3] | Govinda R. Poudel[1,4,5] | Alex Fornito[1,3] | Nellie Georgiou-Karistianis[1]

Systematic reviews

Figure 1 Regional Brain Volume Trajectories in the TRACK-HD Cohort



Diffusion Measures: Structural Connectivity

Diffusion imaging in Huntington's disease: comprehensive review

Carlos Estevez-Fraga ,[1] Rachael Scahill,[1] Geraint Rees,[2,3] Sarah J Tabrizi,[1] Sarah Gregory [1]

Estevez-Fraga C, *et al. J Neurol Neurosurg Psychiatry* 2021;**92**:62–69. doi:10.1136/jnnp-2020-324377

Critical Review of White Matter Changes in Huntington's Disease

Movement Disorders, Vol. 35, No. 8, 2020

Chiara Casella, MSc,[1*] Ilona Lipp,[3] Anne Rosser,[2] Derek K. Jones,[1,4] and Claudia Metzler-Baddeley[1]

Systematic reviews

Reported Change	Proposed Interpretation	Possible Alternative Interpretation
Reduced WM volume	Decreased number of axons attributed to Wallerian degeneration[50-54]	Decrease in axon myelination[6,5]
Reduced axial diffusivity	Axonal degeneration[2]	Inflammation, nonuniform axonal oedema, beads, varicosities parallel to the axon segments, microglia/macrophage activation[100]
Increased radial diffusivity	Demyelination[2,9,18,60,69,70]	Less coherent alignment of fibers, more crossing fibers from other bundles, lower density or less myelination of the fibers, or a combination of any or all these factors[101]
Reductions in the neurite density index	Decrease in axonal density[76]	Reduced MRI signal because of demyelination[102]
Reductions in MPF	Demyelination[59]	Changes in cells and water content attributed to inflammation[79,83]
Shortened T2	Increased ferritin levels[86,89]	Remyelination[103]

MPF, macromolecular proton fraction; MRI, magnetic resonance imaging; WM, white matter.

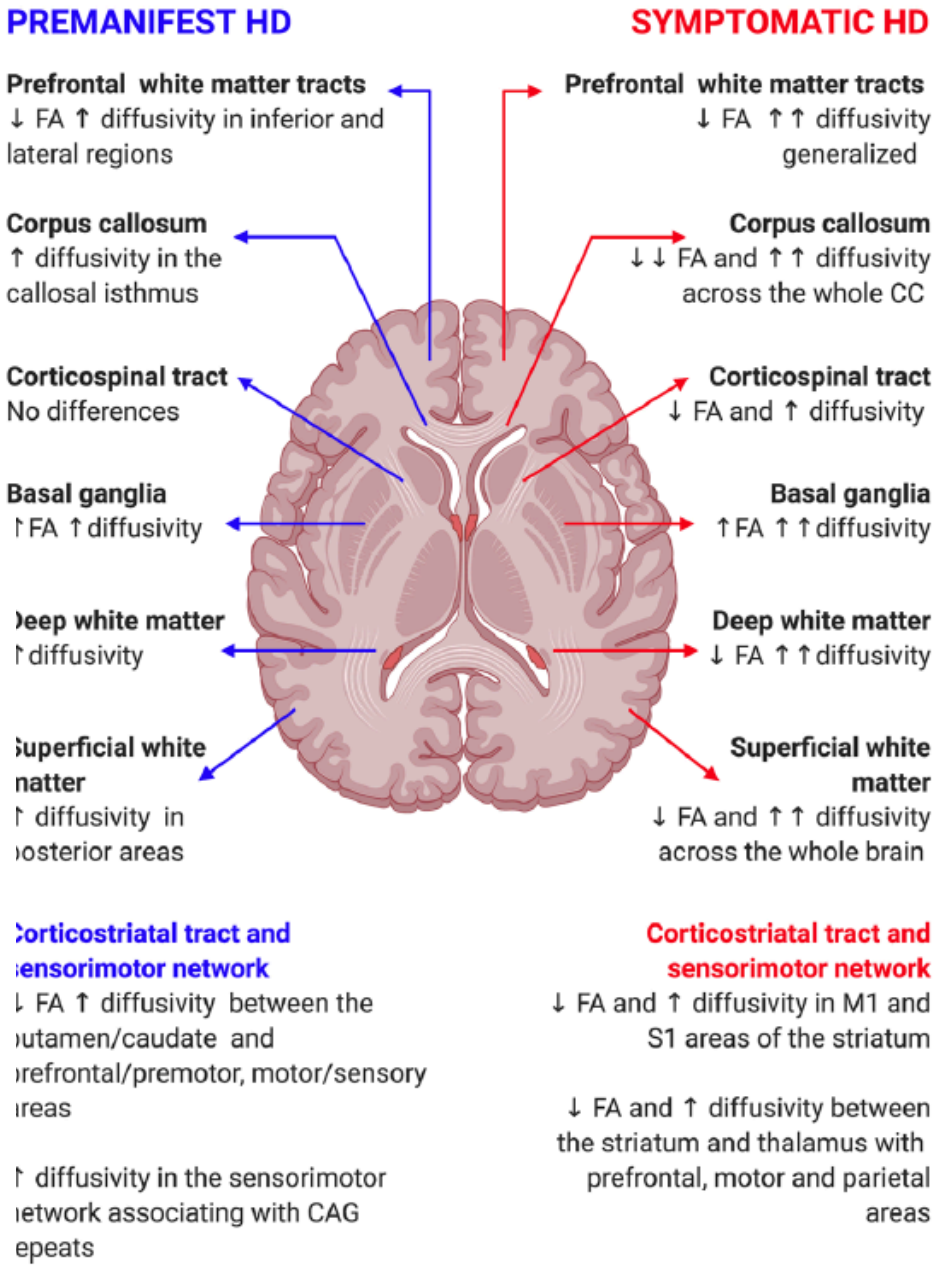
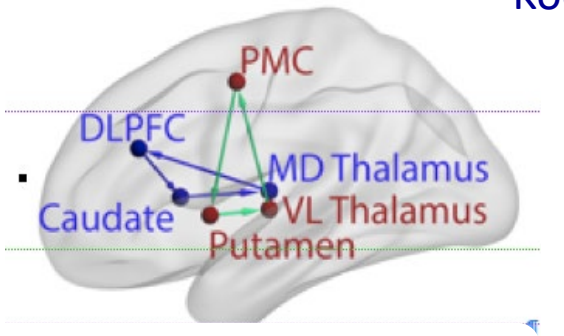


Figure 4 Summary of cross-sectional diffusion studies in HD. ↑, increase;

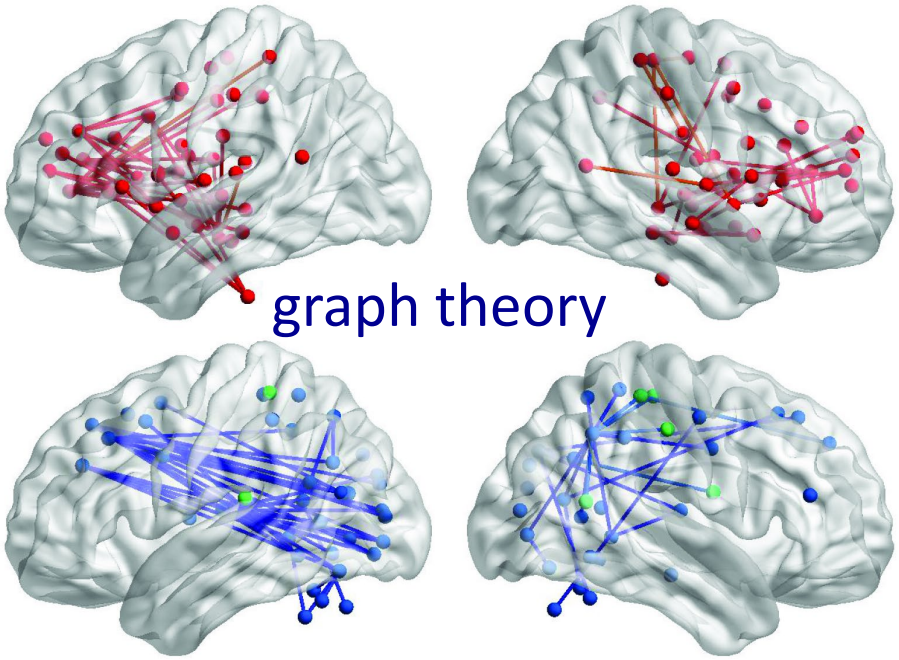
Functional connectivity in Prodromal HD

Harrington et al (2015)
Koenig et al (2014)

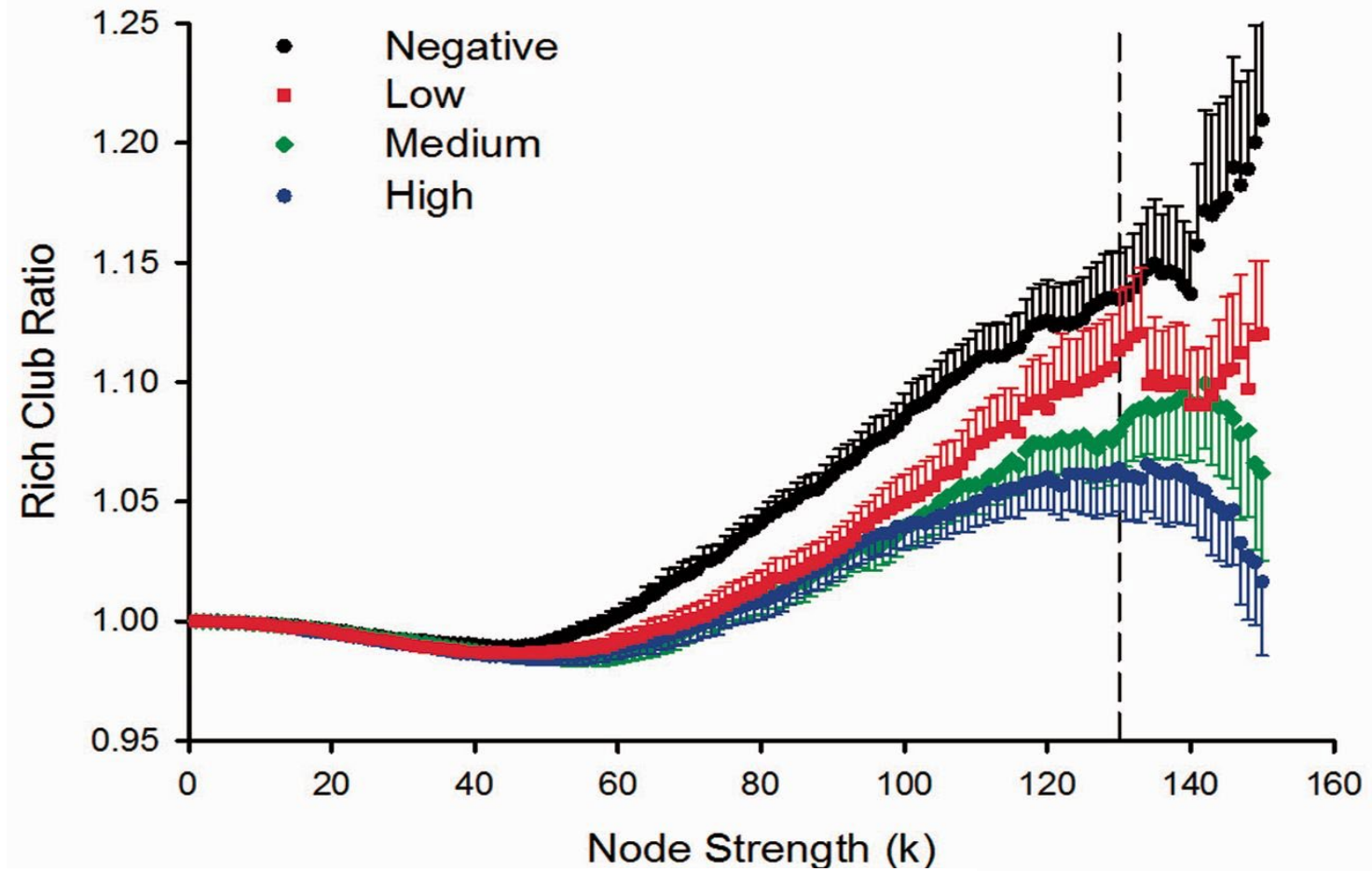


seed-based

rsfMRI whole brain using seed-based networks, graph theory & rich club analyses



graph theory



Topological length of white matter connections predicts their rate of atrophy in premanifest Huntington's disease

Peter McColgan,[1] Kiran K. Seunarine,[2] Sarah Gregory,[1] Adeel Razi,[3,4] Marina Papoutsi,[1] Jeffrey D. Long,[5,6] James A. Mills,[5] Eileanoir Johnson,[1] Alexandra Durr,[7] Raymund A.C. Roos,[8] Blair R. Leavitt,[9] Julie C. Stout,[10] Rachael I. Scahill,[1] Chris A. Clark,[2] Geraint Rees,[3] Sarah J. Tabrizi,[1,11] and the Track-On HD Investigators[12]

Aberrant brain network connectivity in presymptomatic and manifest Huntington's disease: A systematic review

Lorenzo Pini[1] | Charlotte Jacquemot[2,3,4] | Annachiara Cagnin[1] | Francesca Meneghello[5] | Carlo Semenza[1,5] | Dante Mantini[6,7] | Antonino Vallesi[1,7]

Systematic reviews

262 connectivity publications in HD reviewed 5 published pages

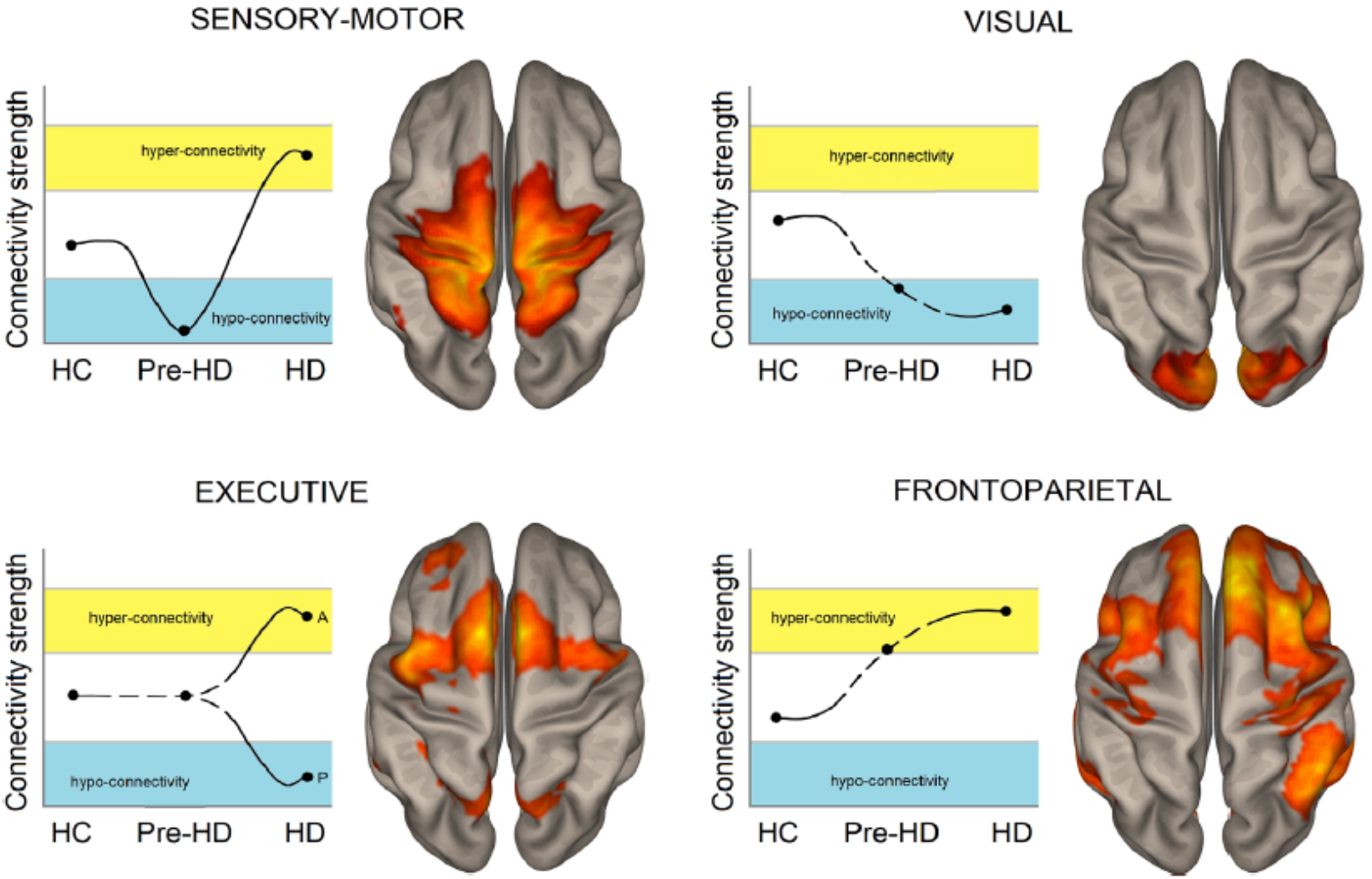


FIGURE 2 Pattern of aberrant connectivity in the sensory-motor and visual networks (top row) and executive and frontoparietal networks (bottom row) in the clinical Huntington disease (HD) spectrum. Dashed lines: unclear pattern of connectivity based on preliminary results from literature for presymptomatic HD. A, anterior/frontal regions; HC, healthy controls; P, posterior/parietal regions; pre-HD, presymptomatic HD

Functional connectome = rsfMRI

frontiers in Neurology

Molecular Imaging Markers to Track Huntington's Disease Pathology

REVIEW
published: 30 January 2017
doi: 10.3389/fneur.2017.00011

*Heather Wilson, Rosa De Micco, Flavia Niccolini and Marios Politis**

Neurodegeneration Imaging Group, Department of Basic and Clinical Neuroscience, King's College London, London, UK

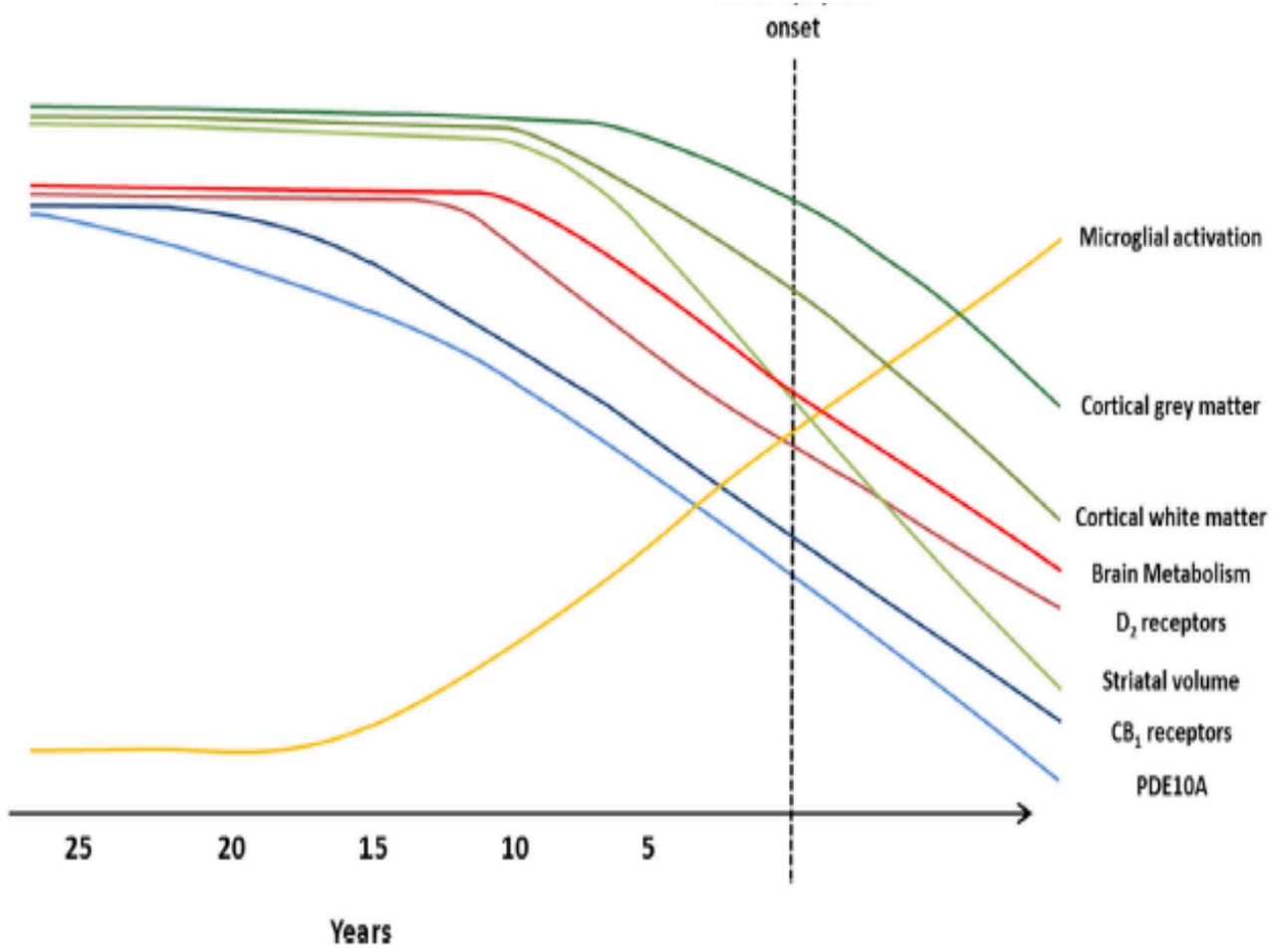


FIGURE 2 | Imaging biomarkers to track Huntington's disease (HD) pathology from premanifest to symptomatic disease stages. Graphical illustration of

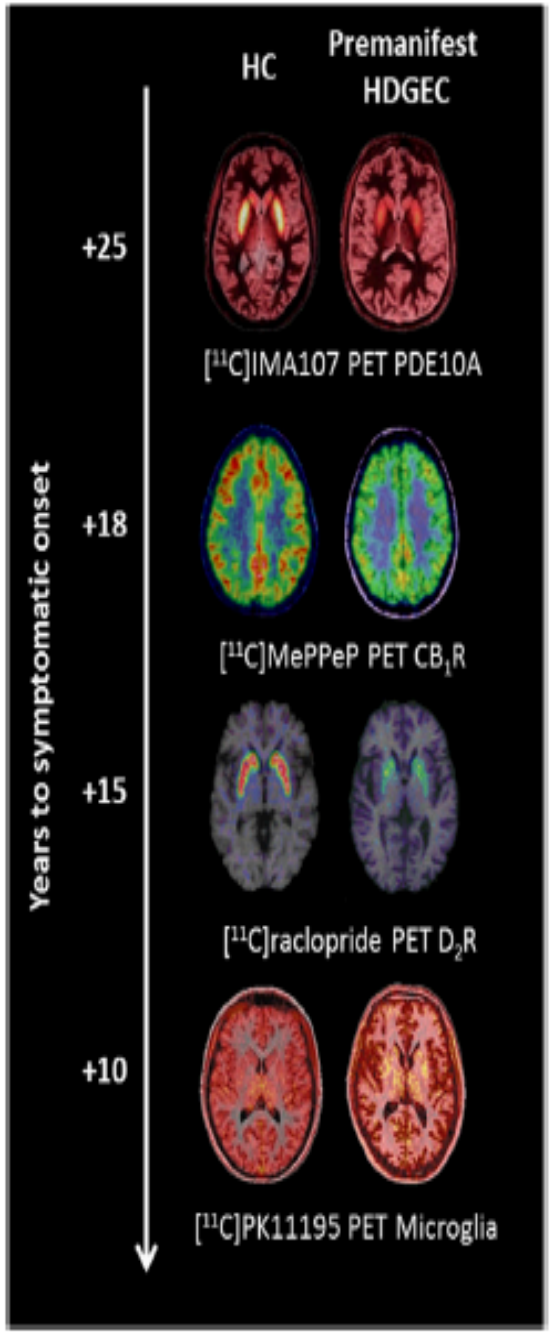


FIGURE 1 | Changes in molecular positron emission tomography

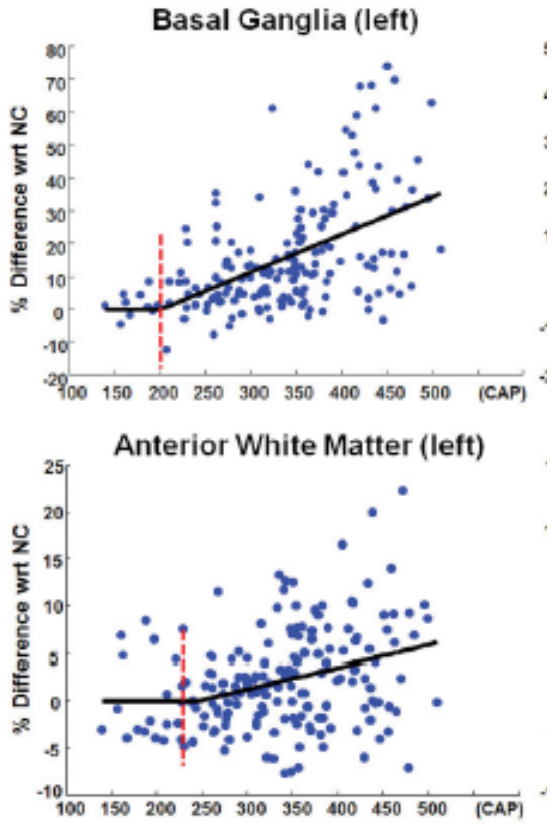
Mapping the order and pattern of structural MRI changes in the brain using change-point analysis in premanifest Huntington's Disease

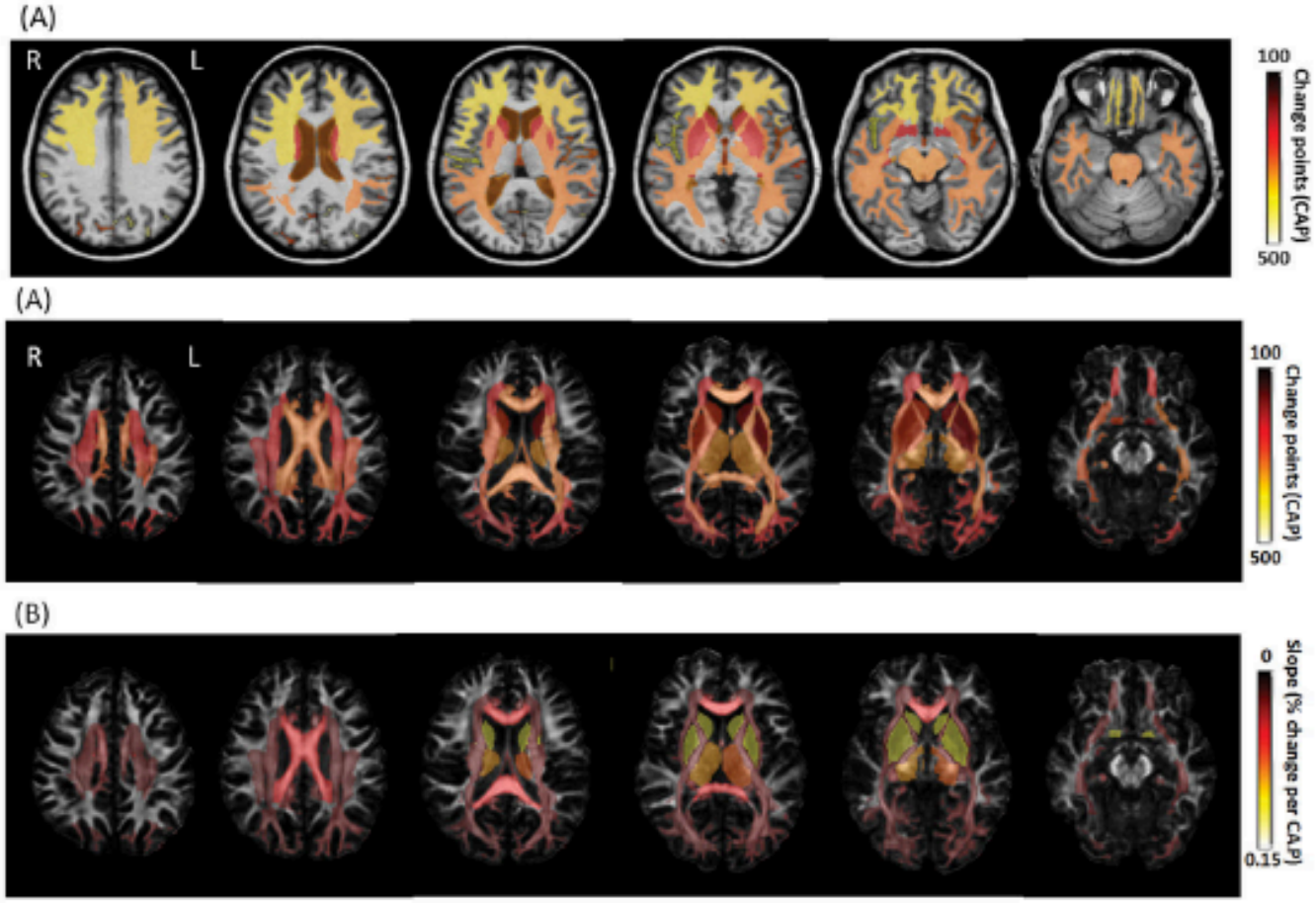
Human Brain Mapping 2017

Dan Wu[1], Andreia V. Faria[1], Laurent Younes[2,3,4], Susumu Mori[1,6], Timothy Brown[2], Hans Johnson[7], Jane S. Paulsen[7], Christopher A. Ross[8], Michael I. Miller[2,3,9], and the PREDICT-HD Investigators and Coordinators of the Huntington Study Group

Disease Course Maps using MRI

- Atrophy deep gray to white matter
- Posterior-to-anterior gradient
- Early MD increases in the basal ganglia & occipital lobe, Late but rapid increases in corpus callosum & thalamus





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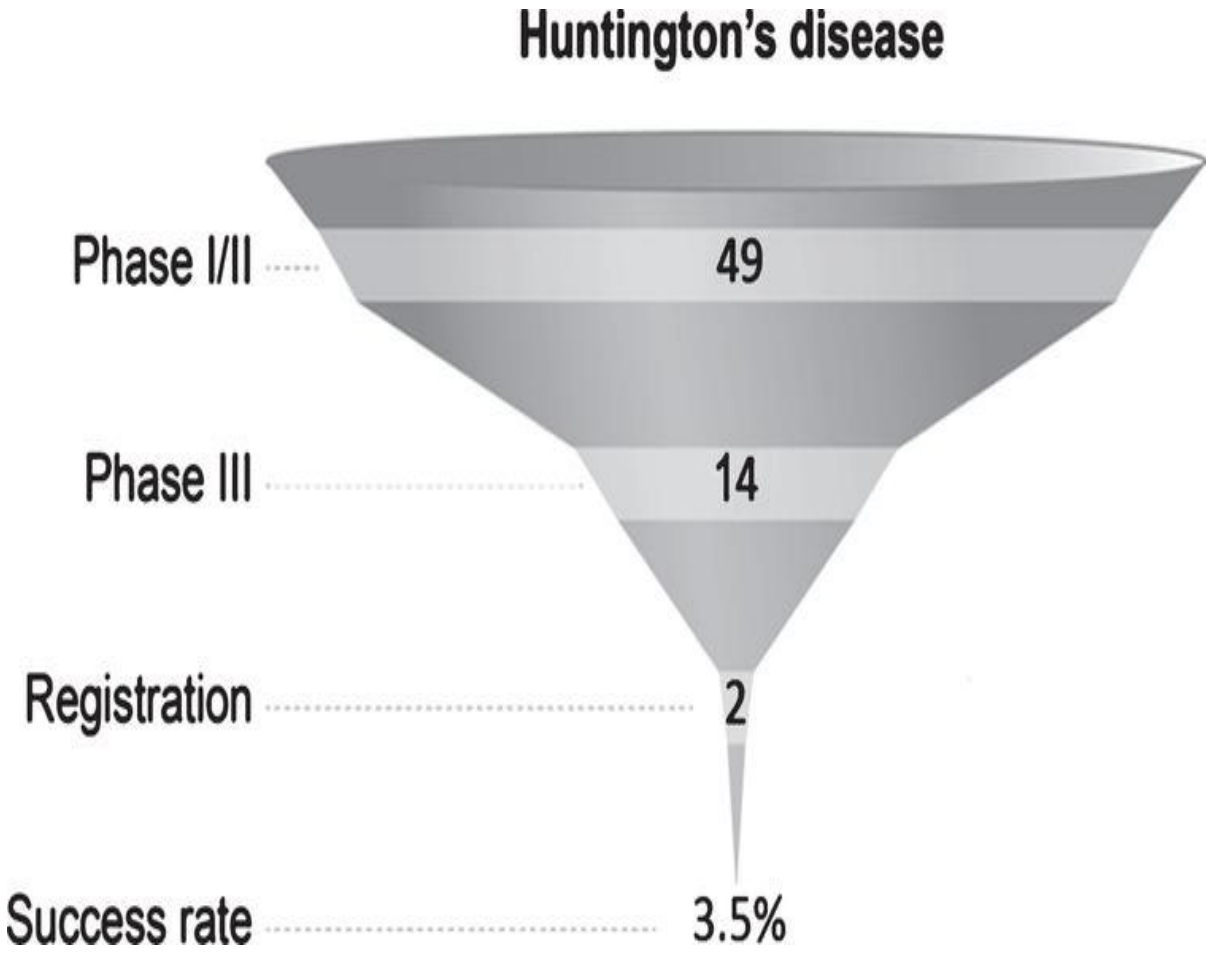
15 years (>60) clinical trials in HD

J Hunt Dis 2017;6:157

Therapeutic Area	Probability of Success
Oncology	3.4
Central Nervous System	15.0
Autoimmune/Inflammation	15.1
Metabolic/Endocrinology	19.6
Genito Urinary	21.6
Infectious Disease	25.2
Cardiovascular	25.5
Opthalmology	32.6
Vaccines	33.4
Overall	13.8

World Health Organization 2022: Global Observatory on Health R&D



41 registered studies today; 9 actively recruiting

RCT Clinical Trials in HD

- ASO lowering HTT protein; n=791; 69 wks; placebo=trts dc'd
  - Follow-on analyses show off-trt>on-trt and low age/low CAP improved
  - New design developing
- ASO selectively lowering mHTT protein;
  - SNP1 and SNP2 dc'd; Now SNP3 ongoing
- AAV-based gene therapy to lower total HTT n=26, n=15, n=18
- VIBRANT-HD; oral HTT lowering - ongoing
  - Branaplam is the small molecule splice modulator; RCT in SMA previously
  - ongoing
- PIVOt-HD Orally taken small molecule splicing modifiers cross BBB and lower HTT ~50-60%; return to baseline in 72 hr - developing
  - Adding wearables
  - TFC and IS at max; age >25; CAG=42-50;
  - Prodromal RCT .18-.493 enriched w/PIN

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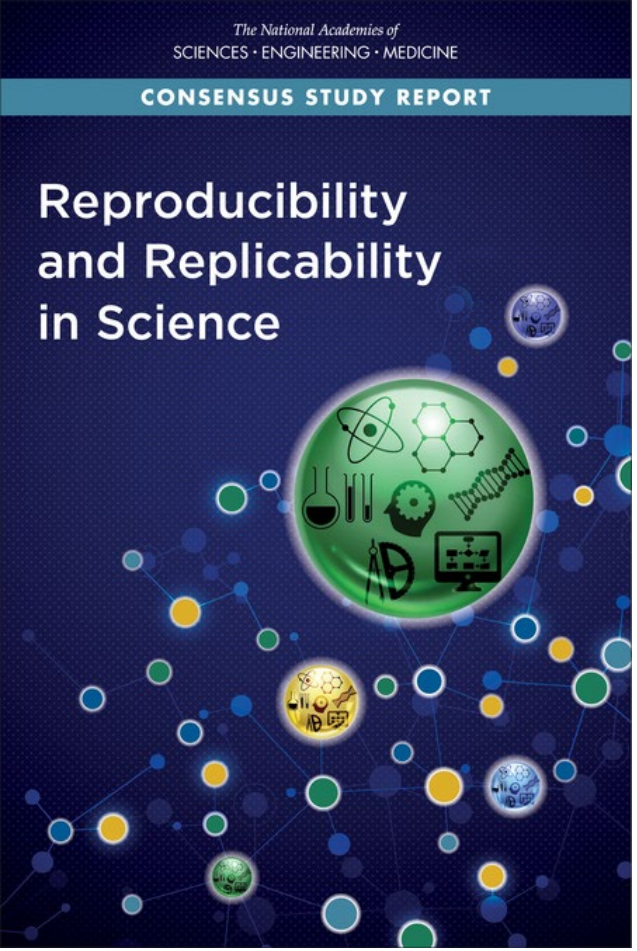
Barriers and Opportunities

Limitations to direct comparisons:

1. Absence of standard disease nomenclature
2. Insufficient descriptions: methods & findings
3. Lack of standard burden scores
4. Variation in modalities and methods
5. Dearth of psychometrics
6. Deficiency of statistical detail
7. Different considerations for confounding/covariance



A = All

… = should

Barriers and Opportunities

1. All researchers …complete description of research.
2. A institutions managing science … train in statistics.
3. A funding agencies … open-source tools and infrastructure
4. A Journals … ensure reproducibility and enforce transparency
5. The National Science Foundation …
   - •criteria for open repositories;
   - •harmonize repository criteria & data management plans
   - •endorse archiving and preservation of digital artifacts
   - •Ww nonpublic data to develop transparency
6. Professional societies … educate public & professionals about the evolving tools & methods of science
7. Researchers … collaborate to meet the multi-disciplinary requirements of research