Huntington's Disease

An Update on Latest Research

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HD Treatment

- Current treatments are symptomatic.
- Several compounds have delayed onset and slowed progression in mouse models.
- Question remains to translate discoveries for human cures.

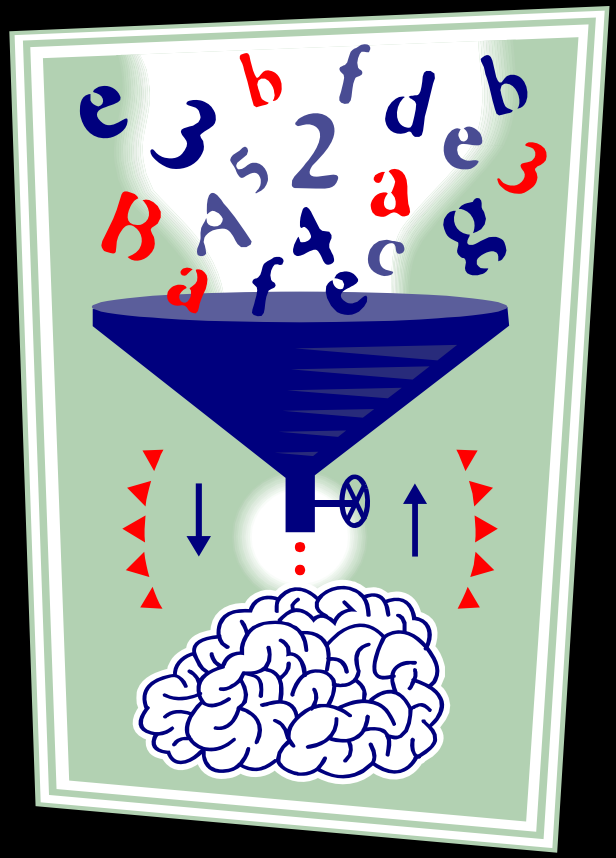
Developing HD Treatments

Cellular level

Animal models

Biomarker studies

Clinical trials



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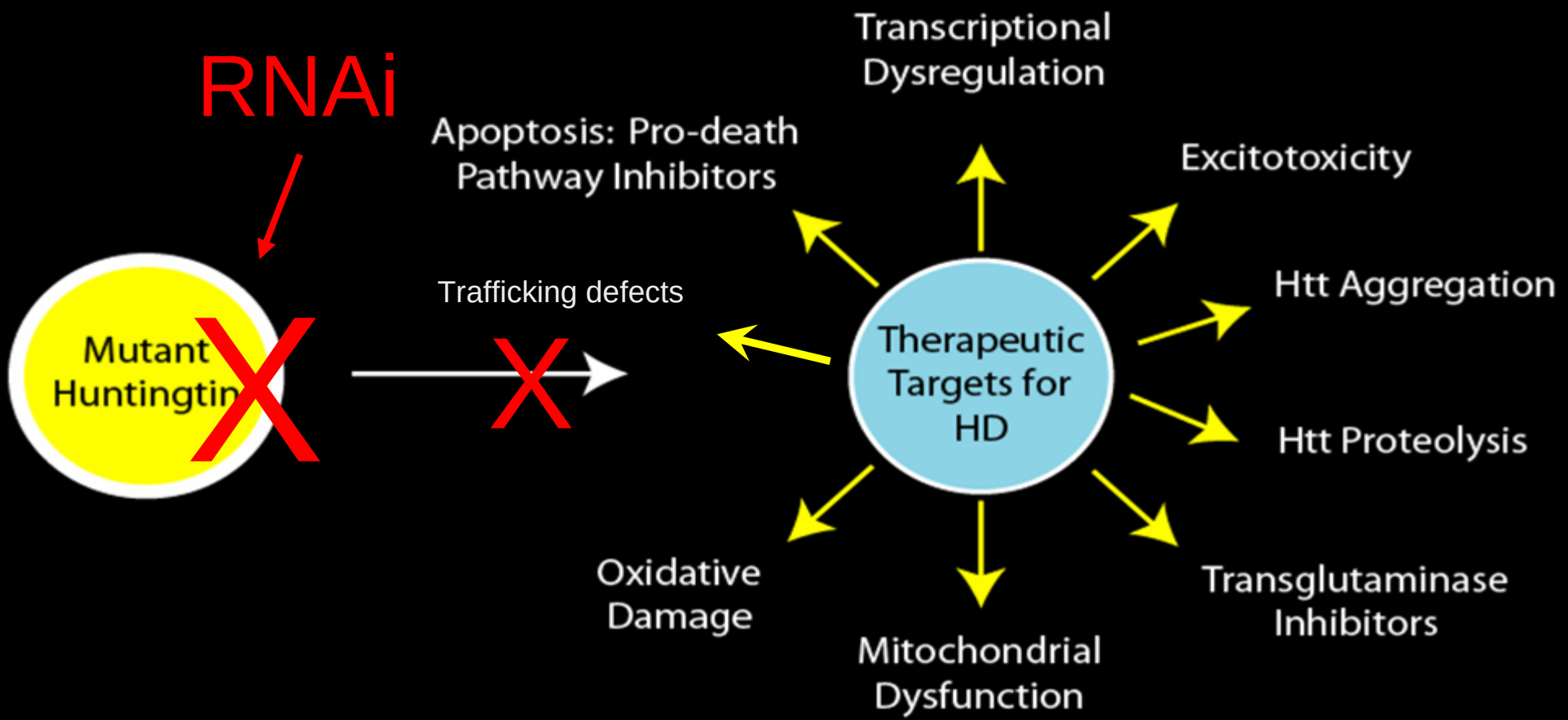

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The Development of RNAi

http://www.macalester.edu/~montgomery/RNAi.html

- When this system is activated, it causes an enzyme to chop up the RNA to find the relevant section of code.
- It then binds that relevant section, containing the gene that we are trying to eliminate, and travels around the cell “looking” for other RNA that matches the code of that section.
- When it finds the same code in other RNA it binds to these “target” RNA’s effectively blocking the production of harmful proteins.

What does this mean?

- It means, at the most simple level, that by “interfering” in the translation of certain genes into protein, RNAi may be able to offer a means to stop the progression of a disease in its tracks.

*Davidson and Henry L Paulsen (2004).*Molecular Medicine for the brain: silencing of disease genes with RNA interference. The Lancet, Neurology Vol 3 pp145-149.

- Targets the defective Huntington's gene, leaving the healthy version of the same gene to carry out its vital duties.
- Mice who were given the RNAi treatment did not develop the symptoms seen in untreated mice. Nor did the treated mice show any signs of suffering from toxic side-effects, indicating that the technique is safe.
- The first clinical trials are likely to begin within the next five years provided there are no signs that the technique is dangerous in humans.

CLINICAL TRIALS

TREND-HD

2CARE

ATOMOXETINE

CITALOPRAM

CREST-E

PREQUEL

TREND-HD

- Participants consume 1g bid ethyl-EPA (i.e., Miraxion) vs. placebo
- Unique protocol design allows all participants exposure to ethyl-EPA (minimizing exposure to placebo)
- Hypothesis: May offer neuronal mitochondria protection. May decrease chorea.

2CARE

- Participants consume 1200mg bid coenzyme Q10 (i.e., CoQ-10)
- 60 month study design. Includes participants aged 16 and 17, as well adults.
- Hypothesis: Participants taking CoQ-10 vs. placebo will prevent (or minimize) functional decline. CoQ-10 may prevent tissue degradation, improving neuronal health

ATOMOXETINE

- Participants consume 40mg bid atomoxetine vs. placebo
- Unique protocol design, allowing all participants exposure to atomoxetine (i.e., crossover design)
- Hypothesis: Participants taking atomoxetine vs. placebo will demonstrate an improvement in executive functions and motor functions. Participants taking atomoxetine vs. placebo will also experience a decrease in psychiatric impairment.

CITALOPRAM

- Participants consume 20mg qd citalopram vs. placebo
- Unique study design: Two week single-blind placebo run-in
- Hypothesis: Participants taking citalopram vs. placebo will experience an increase in their executive function capabilities and a decrease in psychiatric impairment. Interestingly, improvement in motor symptoms is not expected.

CREST-E

- Participants consume 30g qd Creatine vs. placebo for 36 months
- Simple study design. Parallel groups, 1:1 ratio.
- Hypothesis: Participants taking Creatine vs. placebo will maintain (or increase) their total functional capacity from baseline.

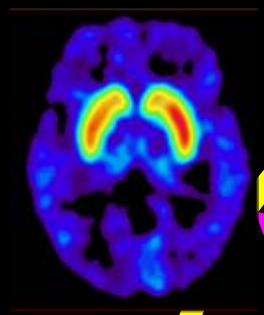
PREQUEL

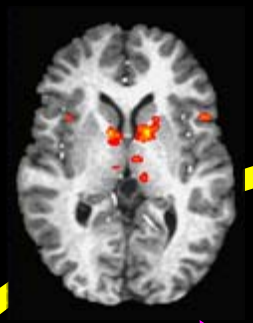
- Presymptomatic participants consume 1200mg qd or 2400mg qd coenzyme Q10 vs. placebo
- Unique protocol design: Participants are presymptomatic. Participants are enrolled for 18 months.
- Objective: To establish treatment tolerability aspects (i.e., 1200mg vs. 2400mg) in presymptomatic participants. To assess the feasibility of implementing a preventative therapeutic trial.

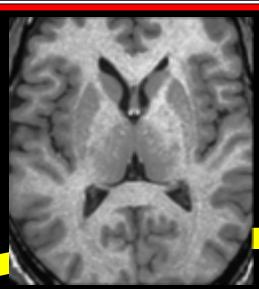
Research to Detect HD As Soon As Possible

- Movement-Motor measures
- Thinking measures
- Mood measures
- Brain measures
- Potential blood measures?
- Potential genetic markers?

Measures for clinical trials in HD







NP Test

Low Cost and Time

MRI

fMRI

Computerized Cognitive Assessment

Paper and Pencil Assessment

High Cost and Time

PET Imaging

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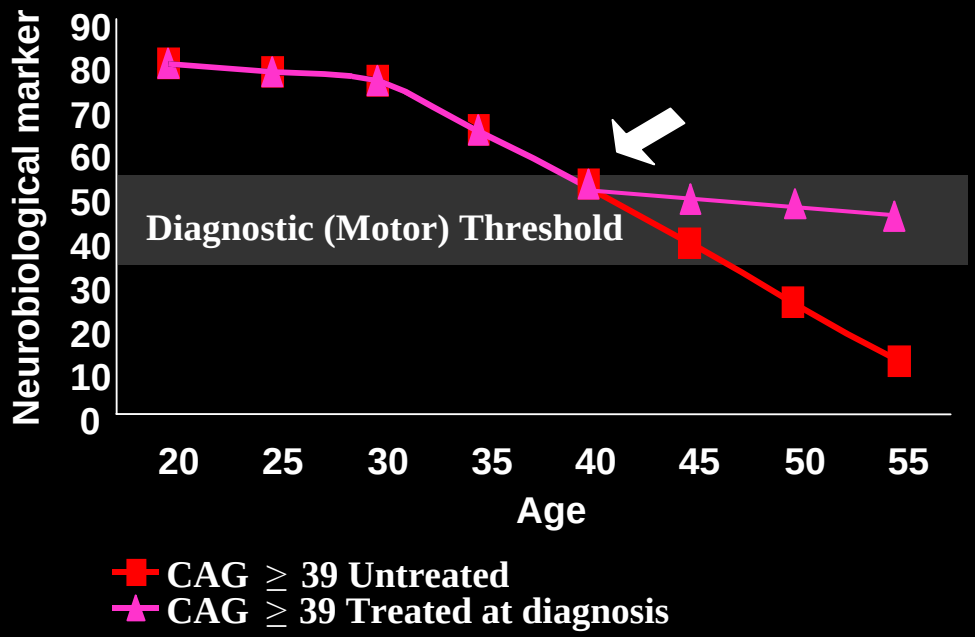
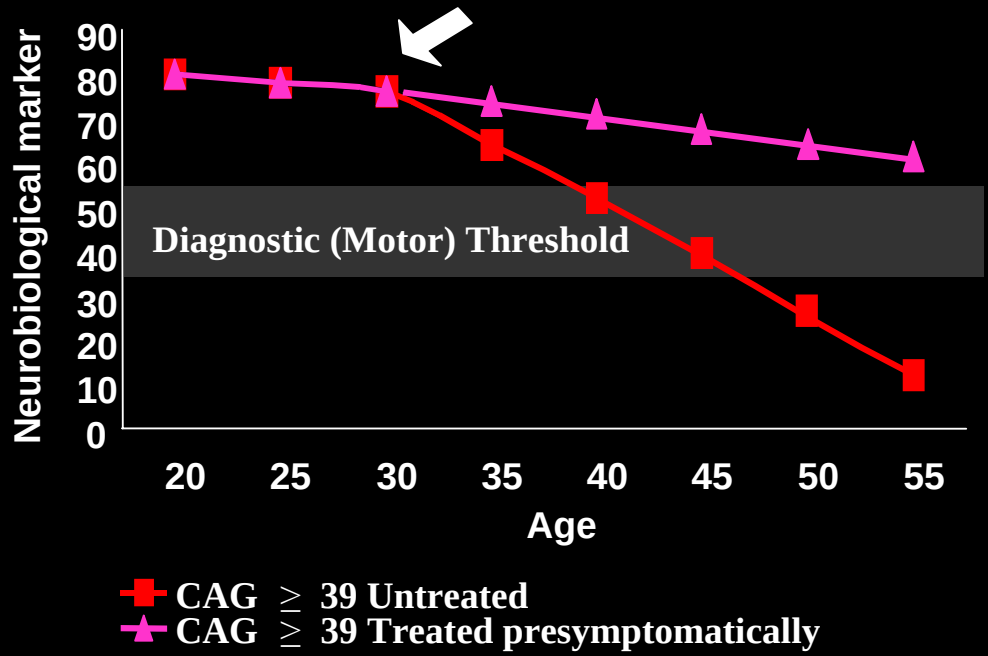
Clinical Trials: Model of Intervention in HD





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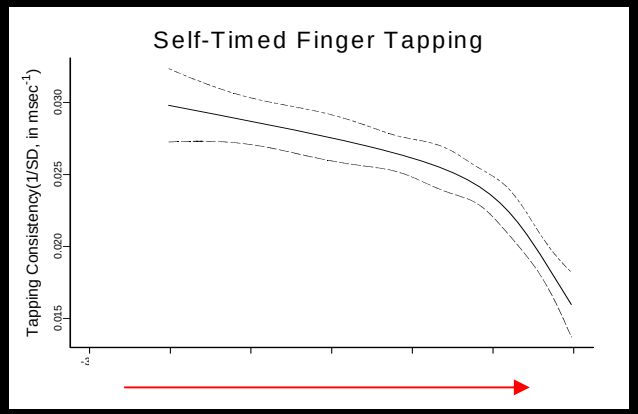
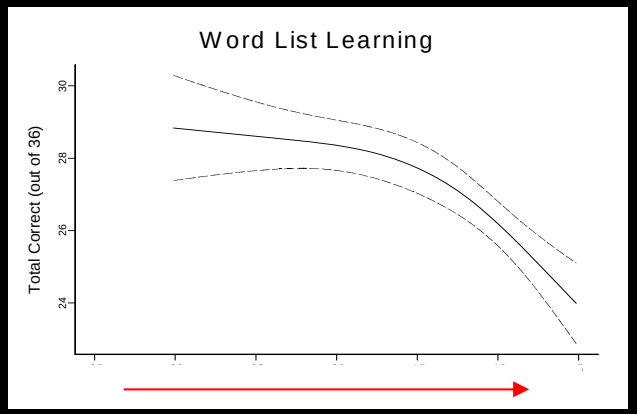
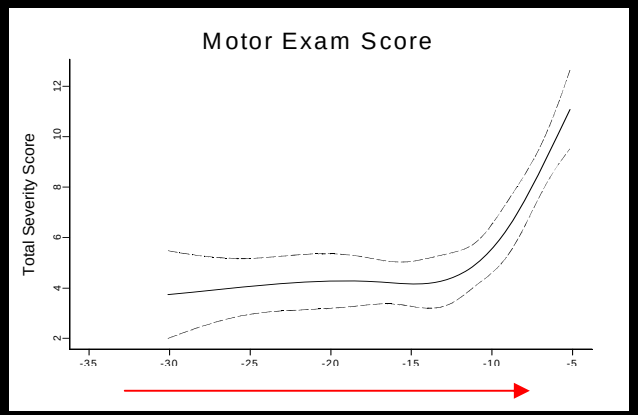
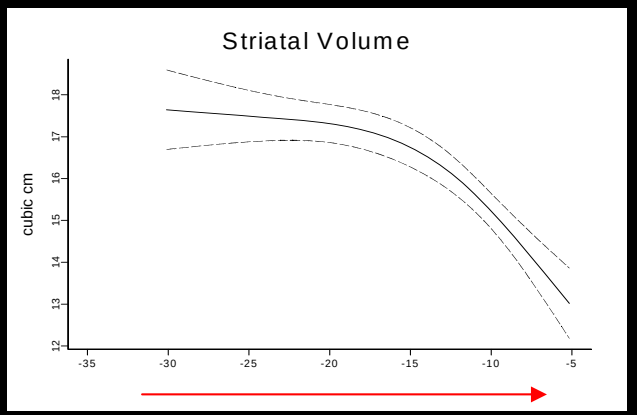
Possible Biomarkers: Cross-Sectional Data from Predict









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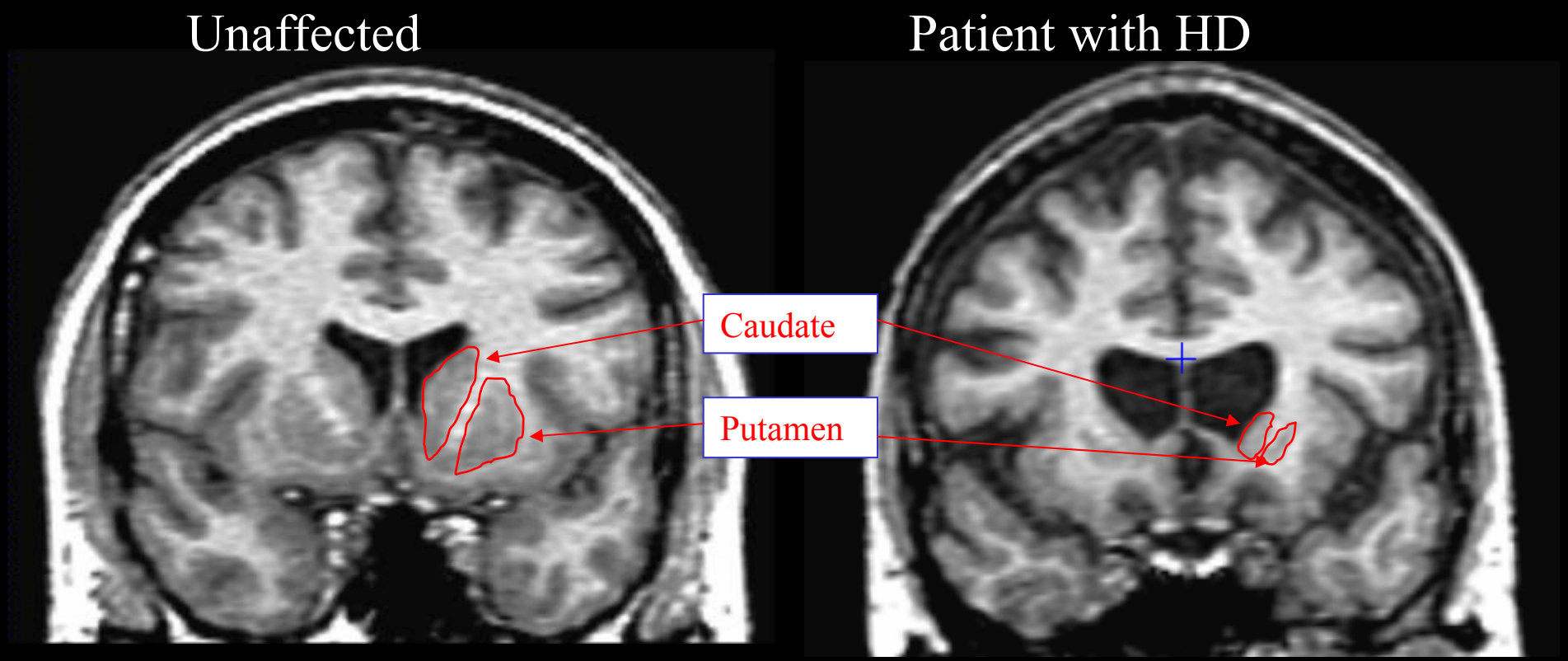
Striatum (caudate & putamen): the brain region most affected in HD



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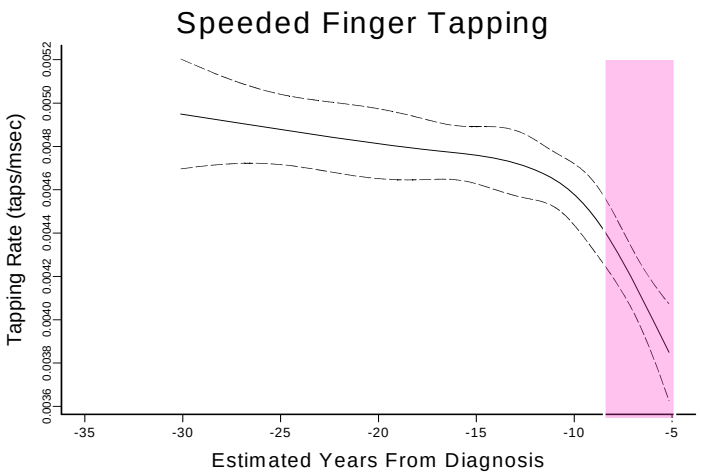
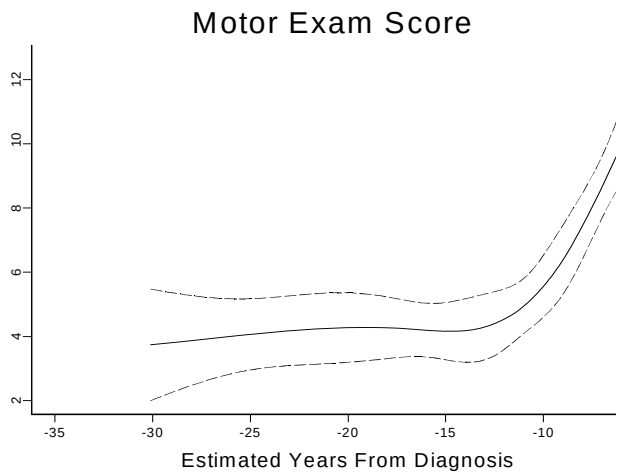
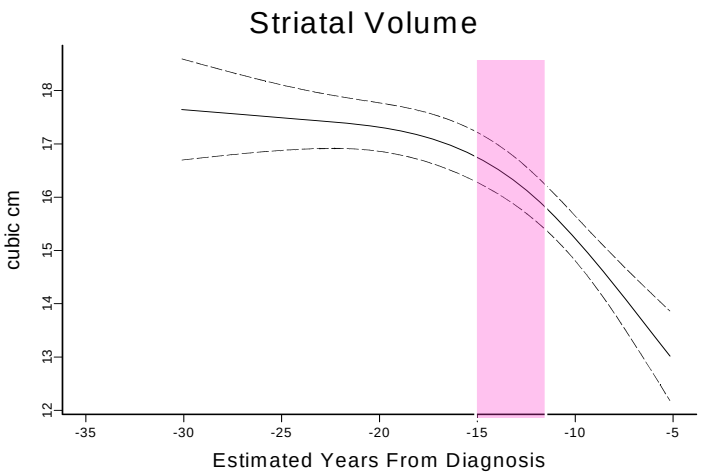
Uses of Markers in Clinical Trials

- Closer to clinical diagnosis?
- Near transition to period of more rapid decline?

Paulsen et al. Predict baseline curves paper, in review (2007)







ORIGINAL CONTRIBUTION

Preparing for Preventive Clinical Trials

The Predict-HD Study

Jane S. Paulsen, PhD; Michael Hayden, MD, PhD; Julie C. Stout, PhD; Douglas R. Langbehn, MD, PhD; Elizabeth Aylward, PhD; Christopher A. Ross, MD, PhD; Mark Guttman, MD; Martha Nance, MD; Karl Kieburtz, MD; David Oakes, PhD; Ira Shoulson, MD; Elise Kayson, MS; Shannon Johnson, PhD; Elizabeth Penziner, MA, MPH; and the Predict-HD Investigators of the Huntington Study Group

Background: The optimal design and outcome measures for preventive clinical trials in neurodegenerative diseases are unknown.

Objective: To examine measures that may be associated with disease in the largest cohort ever recruited of prediagnosed individuals carrying the gene expansion for Huntington disease (HD).

Design: The Predict-HD study is a multicenter observational research study in progress at 17 sites in the United States, 4 in Canada, and 3 in Australia.

Setting: Genetics and HD outpatient clinics.

Participants: Five hundred five at-risk individuals who had previously undergone elective DNA analyses for the CAG expansion in the HD gene (predictive testing) and did not currently have a clinical diagnosis of HD.

Main Outcome Measures: Basal ganglia volumes on magnetic resonance images, estimated probability of diagnosis (based on CAG repeat length), performances on 21 standardized cognitive tasks, total scores on 3 scales of psychiatric distress, and motor diagnosis based on the Unified Huntington's Disease Rating Scale.

Results: Several variables showed progressive decline as the diagnostic ratings advanced toward manifest disease. Estimated probability of diagnosis was associated with Unified Huntington's Disease Rating Scale prediagnostic stages and varied from 15% in persons with no motor abnormalities to nearly 40% in those with abnormalities suggestive of probable disease. Striatal volumes, cognitive performances, and even psychiatric ratings declined significantly with motor manifestations of disease.

Conclusions: The documentation of biological and refined clinical markers suggests several clinical end points for preventive clinical trials. Longitudinal study is critical to further validate possible markers for prediagnosed HD.

Arch Neurol. 2006;63:883-890

Acknowledgments

Study Investigators

Henry Paulson, M.D., PhD

Bev Davidson, M.D., PhD

Leigh Beglinger, PhD

Research Assistants

Elizabeth Penziner, M.A., M.P.H.

William Adams, B.A.

Stacie Vik, B.A.

Special thanks to the faculty and staff of the Paulsen Neuropsychology Lab at The University of Iowa Carver College of Medicine

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