

Predictors of Onset in
Huntington's Disease:
PREDICT-HD



BIG QUESTION:

What do we need before we can treat HD?

How does PREDICT-HD contribute ?

What have we learned so far from PREDICT?

Why is your continued participation so important?

What do we need before we can treat HD?

- Potential treatment(s)
- Methods for figuring out whether treatment works
- Knowing when treatment is most effective

Development of HD Treatments is Underway

- Many potential treatments being considered
- New methods allow “high throughput” screening—
methods to test potential treatments more quickly
- Testing occurs at cellular level and in animal models
- Bottom Line: Will treatment work in humans???

What do we need before we can treat HD?

- Potential treatment(s): Underway in other studies
- Methods for figuring out whether treatment works
- Knowing when to begin treatment

Effectiveness of Treatment for HD after Diagnosis

- Trials already underway
- Treatment considered effective if it slows progression of symptoms
- Accepted outcome measure: UHDRS
- Limitations:
 - Unlikely that any treatment will reverse symptoms
 - Treatments that work in slowing symptom progression after diagnosis may not be effective in preventing or delaying symptom onset

Need for Presymptomatic Treatment

- By the time of diagnosis:
 - Many patients have experienced psychiatric disturbance and personality change
 - Many patients (or family members) have noticed difficulty in thinking skills and reasoning
 - Shrinkage in brain structures is already visible
- Therefore: to be most effective, treatment probably needs to begin before onset of symptoms

Current Limitations of Trial Design

- **Problem:** How do you know if a treatment works if you can't measure improvement in symptoms?
- There is not a reliable test to measure improvement in people without clinical symptoms.
- **Solution:** Develop a longitudinal study to follow people who have the gene for HD, but are not diagnosed. (*Does this sound familiar?*)

Measuring Treatment Effectiveness

After Diagnosis

Before Diagnosis

Measure: Balance

No obvious symptoms

Potential Treatment



Potential Treatment



Balance: Improved,
Worsened or No Change

How do you know if it worked?

Measuring Prevention

NEED TO IDENTIFY GOOD MEASURES

Potential Treatment


Improved, Worsened, or No Change

Detecting Treatment Effectiveness in Presymptomatic HD: Two Strategies

- Strategy I: Does treatment delay onset of symptom?
- Strategy II: Does treatment slow rate of change in measures that are associated with presymptomatic disease progression?

Strategy I: Does treatment delay onset of symptoms?

- Inefficient because:
 - Will require studies that last many years
 - Will need many subjects
 - Only a few treatments could be tested
- Can be made more efficient if we can include only those subjects who are close to symptom onset at the beginning of the clinical trial
- PREDICT-HD GOAL #1: To learn how to predict when onset of symptoms will occur

Strategy I: Does treatment delay onset of symptoms?

- PREDICT-HD GOAL #1: To learn how to predict when onset of symptoms will occur:
 - Will allow prediction of symptom onset
 - Will allow selection of subjects who are close to onset at beginning of clinical trial
 - Will result in more efficient clinical trials
 - fewer subjects, shorter duration, more compounds can be tested

Strategy II: Does treatment slow rate of change in measures that are associated with presymptomatic disease progression?

Will allow us to determine whether treatment is effective even in the very earliest stages of disease progression, where it will probably be most effective

PREDIC-HD GOAL #2: To find a “biomarker” that can be used to determine if treatment is slowing down disease progression before the onset of diagnosable symptoms

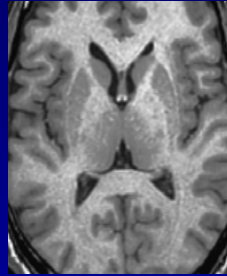
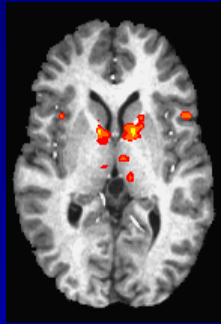
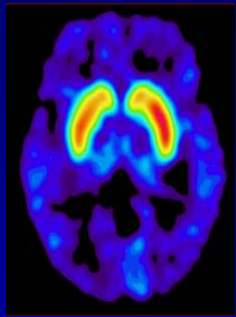
WHAT IS A BIOMARKER?

A CHARACTERISTIC THAT:

- Is objectively and reliably measured +
- Change in a predictable manner over time +
- Predicts known endpoints (e.g., onset of diagnosable symptoms) +
- Is associated with known mechanisms of pathology (or suggest plausible new ones) +

= **Biomarker**

Possible Biomarkers



PET Imaging

fMRI

MRI

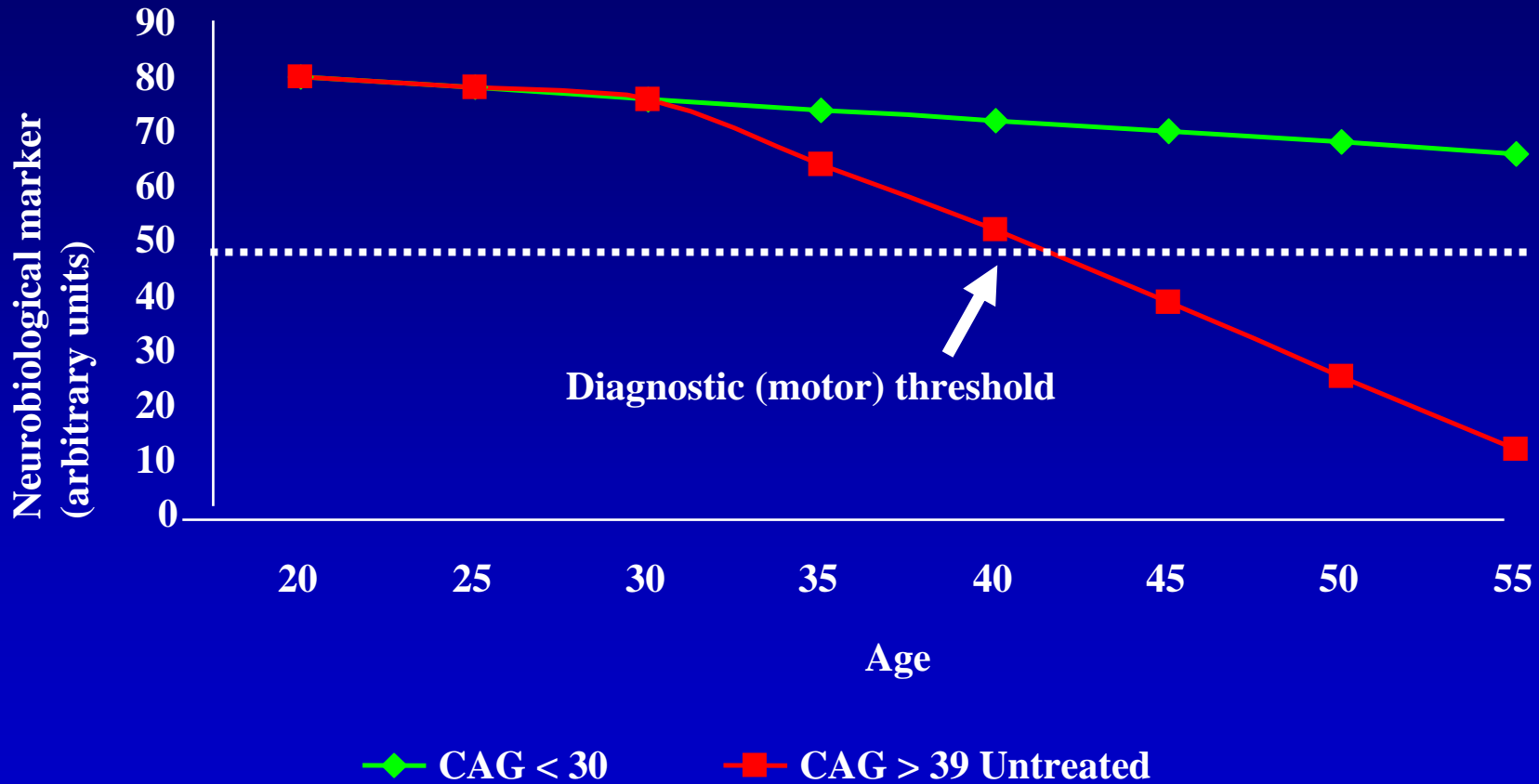
Computerized
Cognitive
Assessment

NP Test

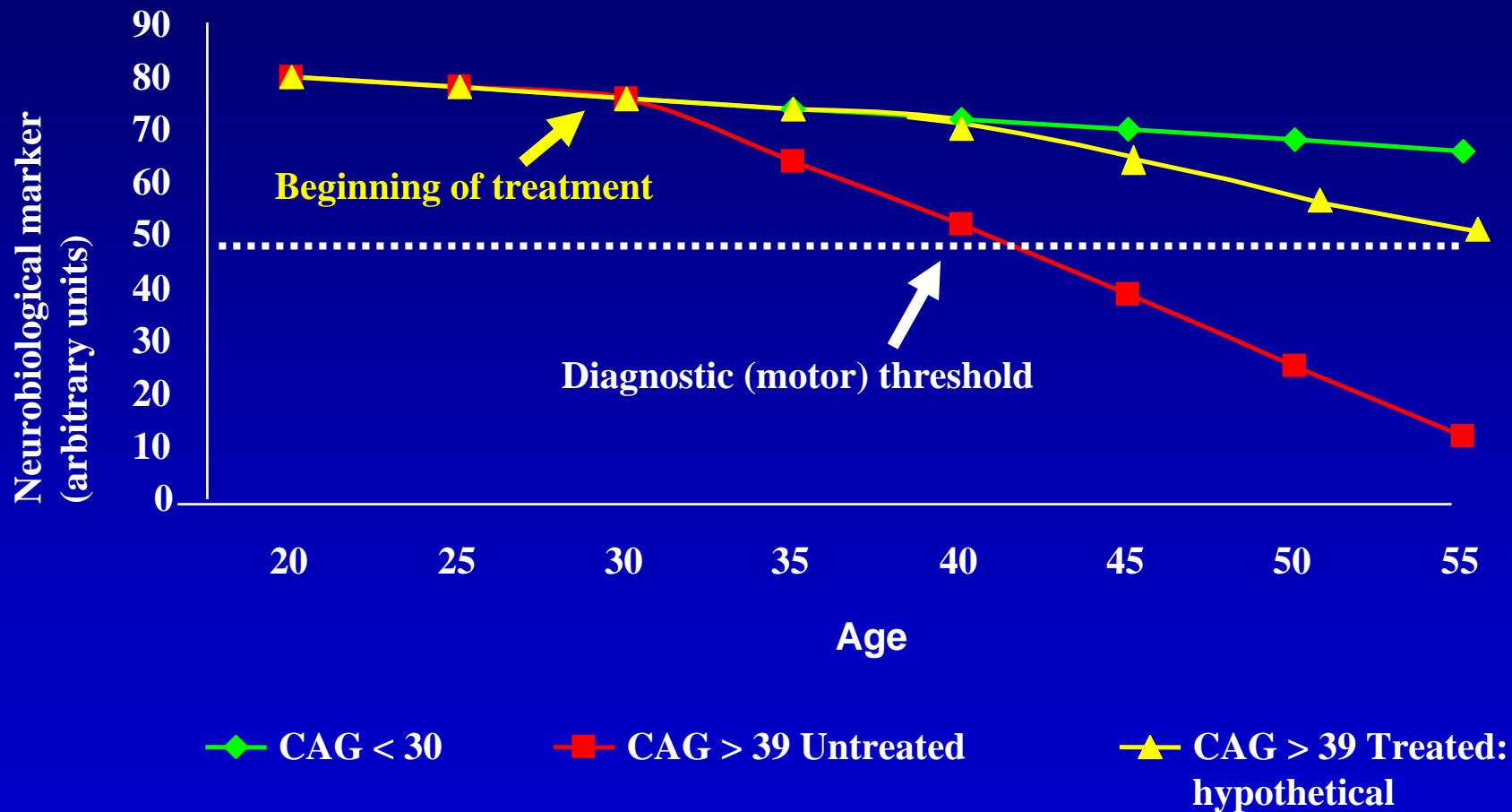
Paper and Pencil
Assessment

Others?
DNA, Blood

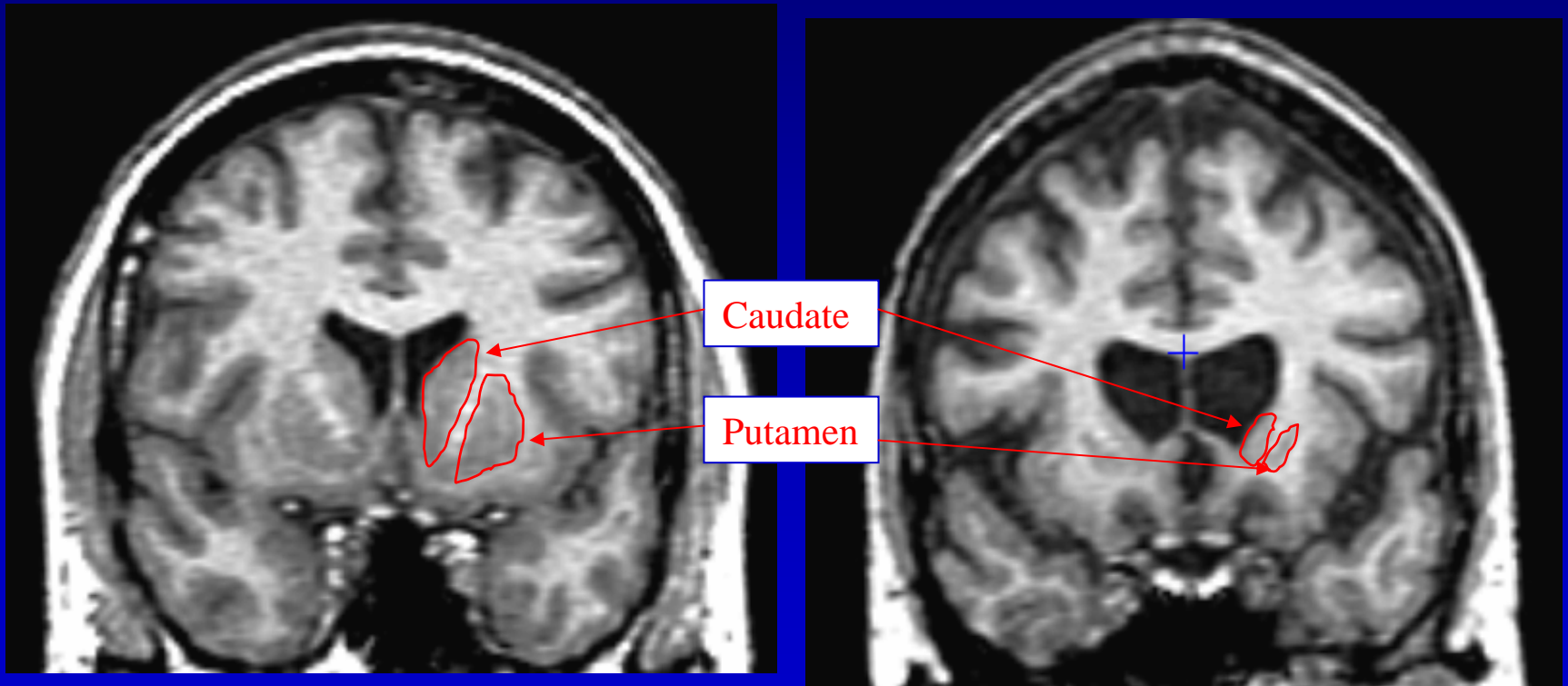
Current Approach: Treatment begins at Diagnosis



Future Approach: Begin Treatment Earlier to Slow Progression



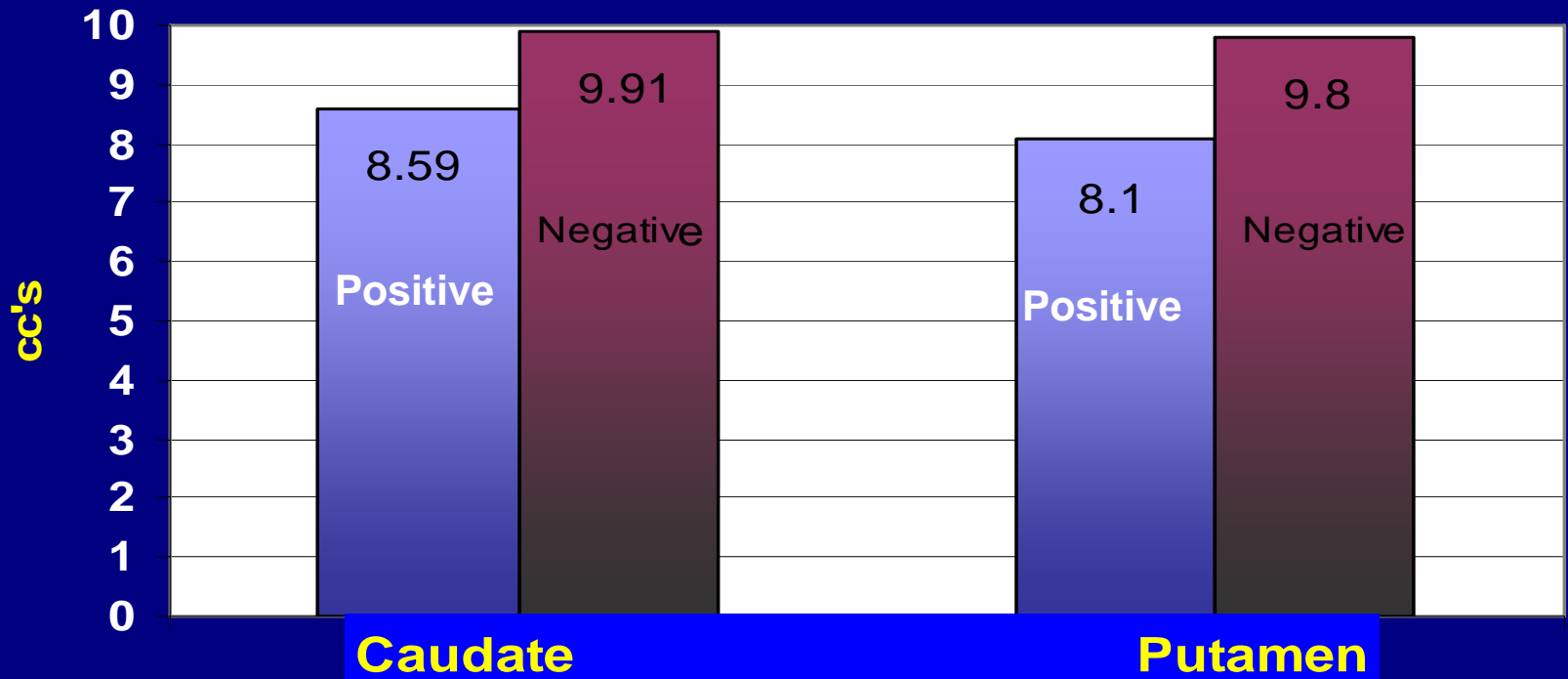
Striatum (caudate & putamen) is the brain region most affected in HD



Unaffected

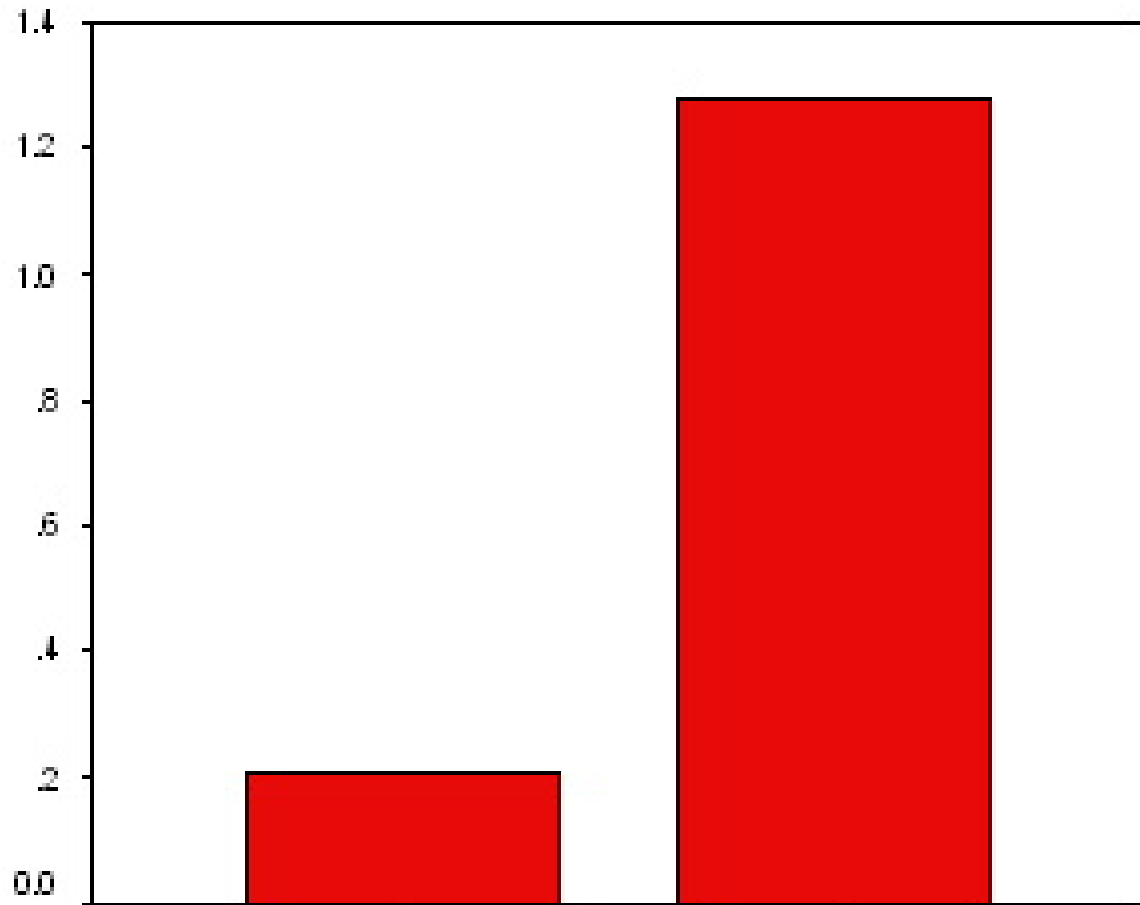
Patient with HD

GeneEXP vs. GeneNOR Volumes



Change in Striatal Volume from First Year to Third Year Visit

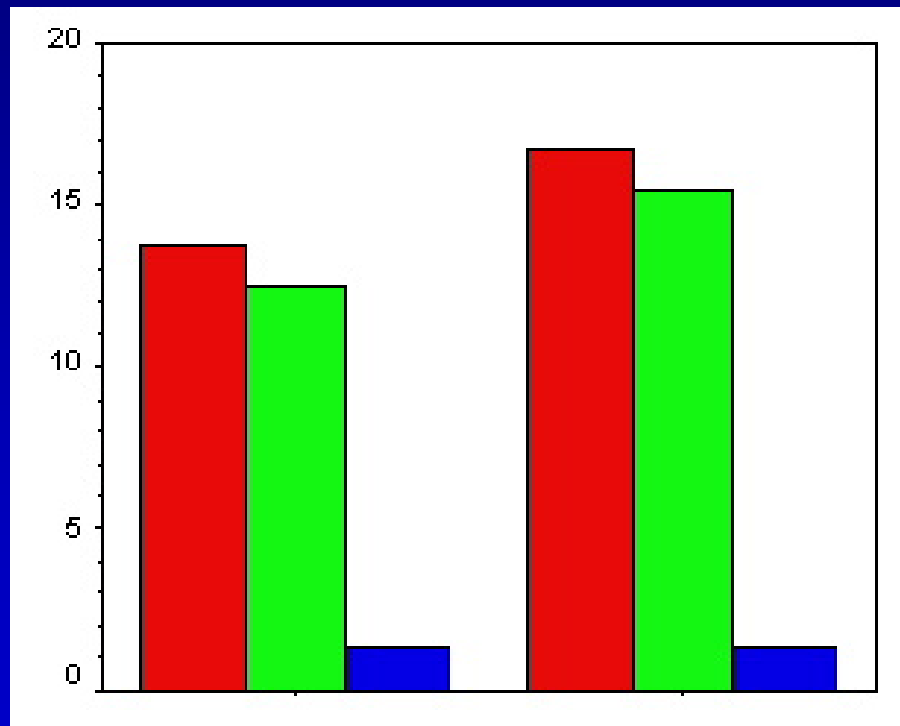
Change in Striatal Volume (cc)



Controls

Presymptomatic HD

Striatal Volumes in Presymptomatic Subjects who are Closer to and Farther from Estimated Onset

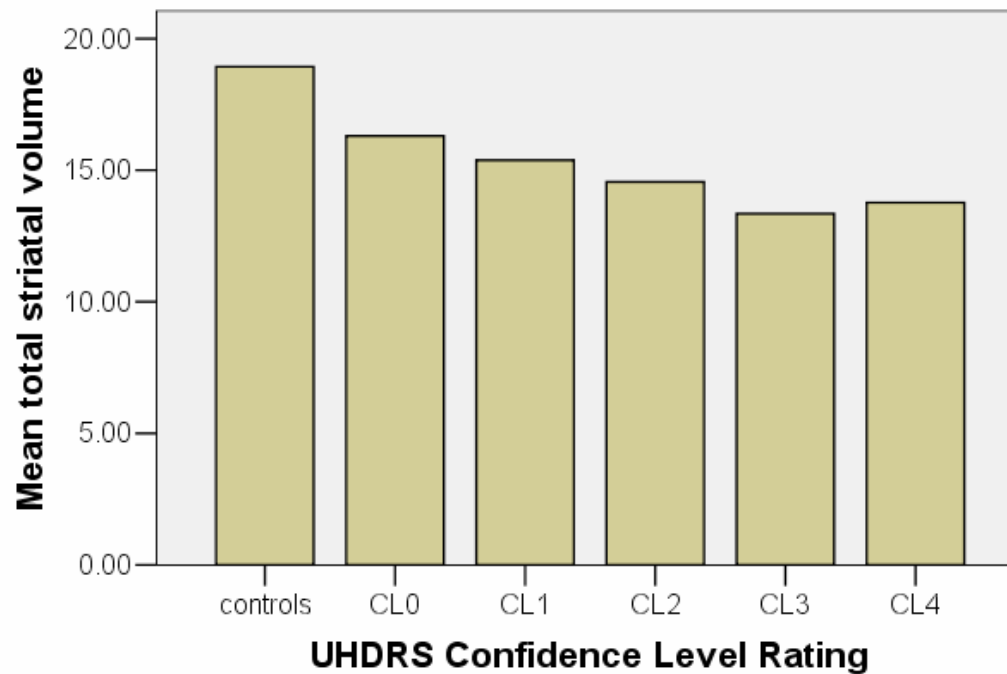


■ = YEAR 1 VOLUME
■ = YEAR 3 VOLUME
□ = VOLUME CHANGE

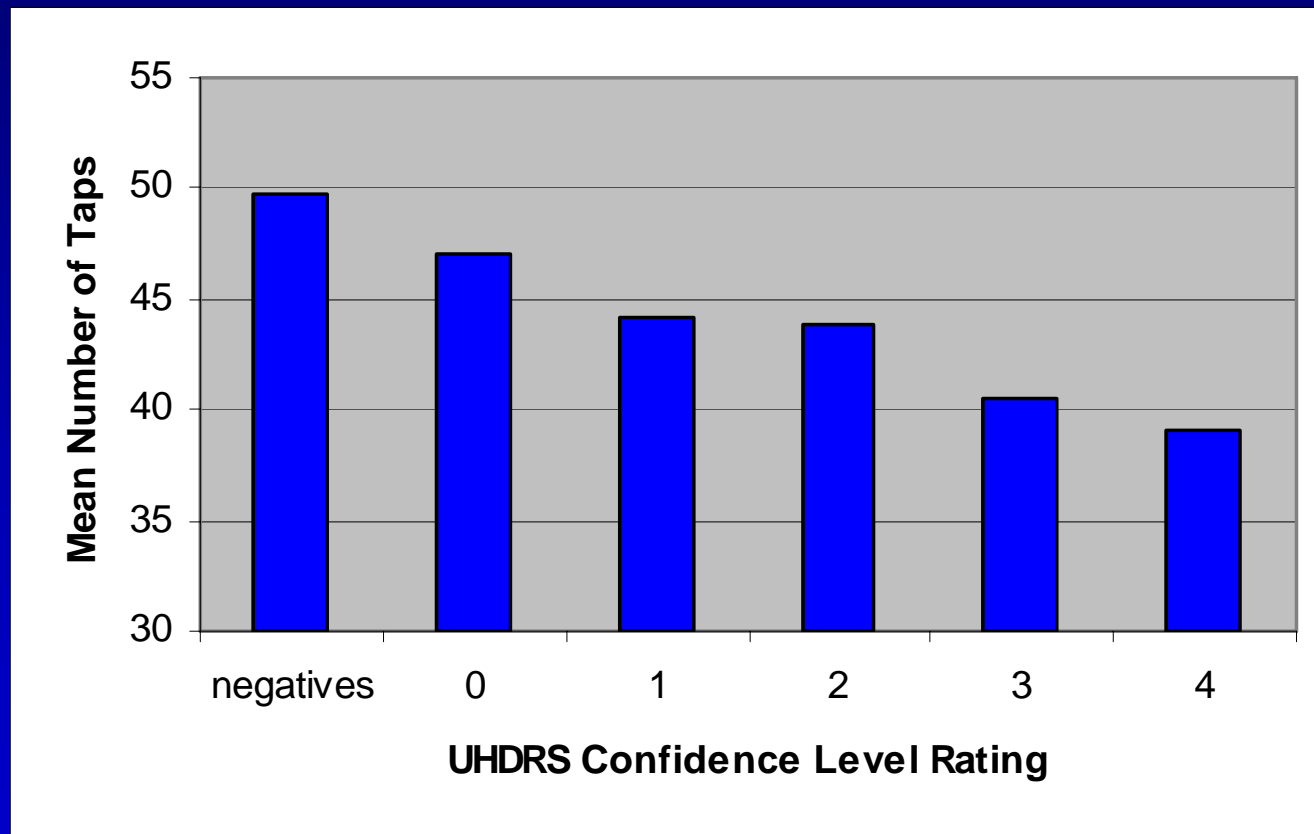
CLOSER TO
ESTIMATED ONSET

FARTHER FROM
ESTIMATED ONSET

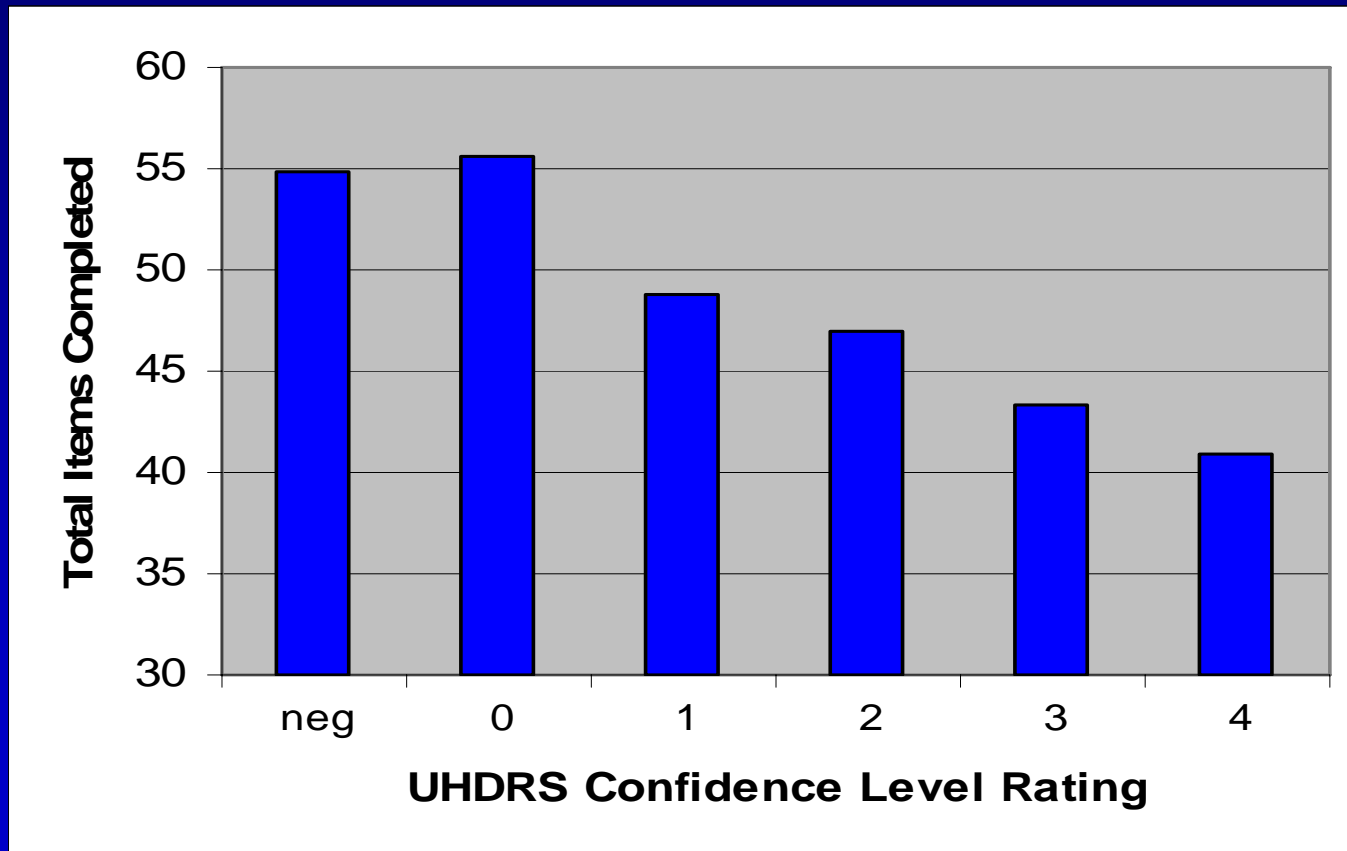
Striatal Volume



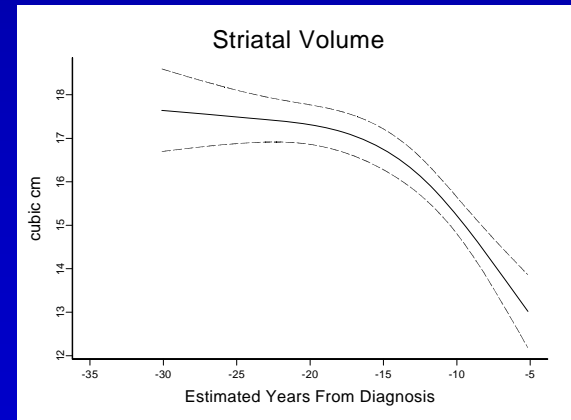
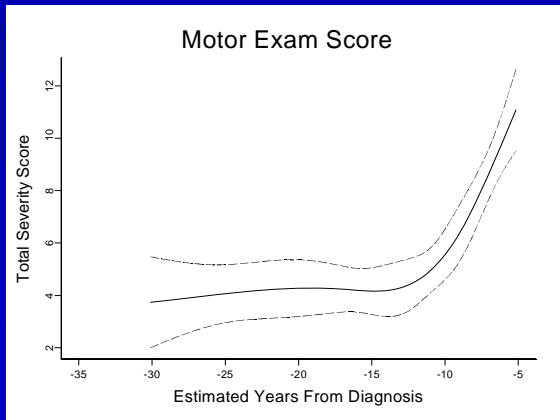
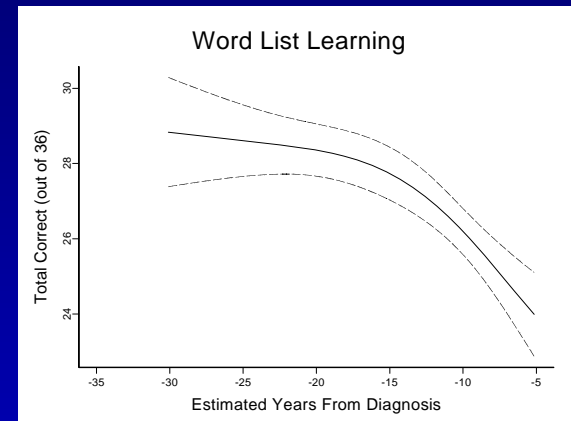
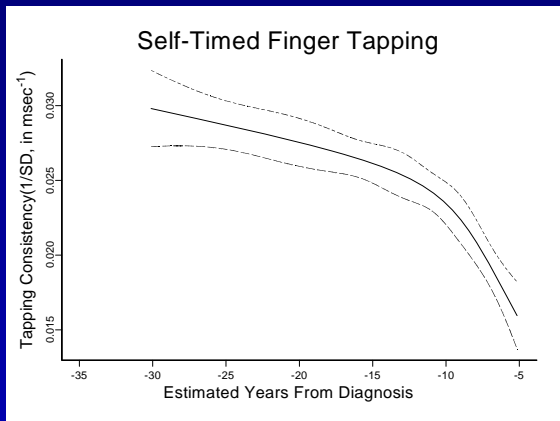
Dominant Hand Finger Tapping



Symbol Digit Modalities Test



Possible Biomarkers: Cross-Sectional Data from Predict



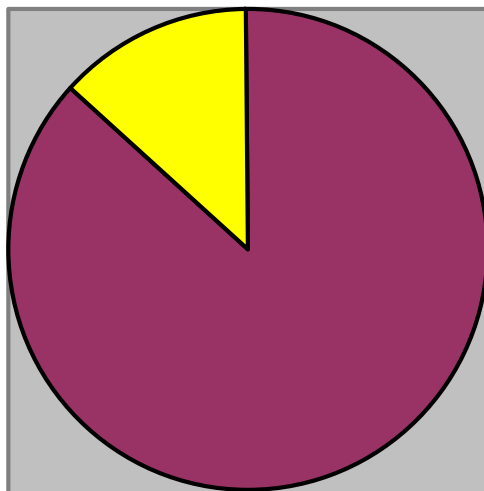
What else have we learned from Predict-HD?

- It is possible to recruit and characterize a very large sample of at-risk, gene-tested individuals
- How to work as an international team to achieve common HD research goals

PREDICT-HD

How are we doing?

703 Participants Enrolled

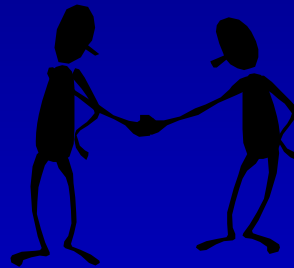


■ **Gene Positive**
N = 609 (87%)

■ **Gene Negative**
N = 94 (23%)

Points to Remember

- PREDICT-HD volunteers are extremely valuable partners in this research endeavor



- This study will provide information that is critical to the design and interpretation of future clinical trials

Studies that provide the critical methodology for clinical trials prior to diagnosis are well underway.

PREDICT-HD is preparing for treatment studies in pre-diagnosed and early-symptomatic persons.

Many thanks to our participants and their families for helping making this research possible.

PREDICT-HD SITES

International Collaboration





PREDICT-HD Investigators



Welcoming our new European Investigators!