Overview of PREDICT-HD

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December 2011

PREDICT-HD

Huntington's Disease (HD)

- HD is a neurodegenerative disease with a known genetic pathology.
  - Prevalence: approximately 7 per 100,000.
  - Age of Onset: 2-82 years; mean = 40.
  - Death within 15-20 years of onset.
  - No known cure.
- At-risk individuals have expanded cytosine-adenine-guanine (CAG) trinucleotide sequence.
- CAG expansion is thought to have a toxic effect on the huntingtin protein.
  - Deterioration primarily of the striatum (caudate and putamen), but other brain areas are also affected.

Huntington's Disease Continued

- Clinical "triad" of signs (symptoms).
  - Motor, cognitive, psychiatric.
  - E.g., abnormal physical movements, attention and memory problems, irritability and depression.
- HD research diagnosis.
  - Based on unequivocal movement disorder.
  - E.g., chorea (abnormal uncontrollable movements).
- Prodromal-HD: clinically asymptomatic period prior to disease manifestation.
  - "Disease manifestation" is often synonymous with HD diagnosis.

PREDICT-HD

- Neurobiological Predictors of Huntington's Disease.
  - Funding: NIH (NINDS) and the CHDI Foundation, Inc.
- Longitudinal observational study of initially healthy persons without any HD symptoms.
  - *N* > 1200 (63.8% F, 36.2% M)
  - Average Baseline Age=41.1 (Min=18.1, Max=83.7)
  - 10 year period.
  - 32 sites.
  - Cases: expansion-positive people.
  - Controls: expansion-negative people.
  - Lab-verified CAG expansion.
  - To date, 169 participants have received diagnosis.
- Over 80 variables collected.
  - Imaging, cognitive, motor, psychiatric, daily functioning, biosamples.

PREDICT-HD

PREDICT-HD Variables

- Standardized and videotaped clinical ratings of movement disorders, abnormal motor signs, psychiatric symptoms, and daily functioning.
- Objective assessments of motor speed, attention, learning, memory, language, emotional processing, olfaction, visual perception, reasoning, problem-solving, IQ, and cognitive regulation.
- Self-reported and companion-reported stress, coping, and beliefs and attitudes regarding health care, genetic testing, and clinical trials.
- Magnetic Resonance Imaging (MRI) brain scans with associated volumes, surface area, and cortical thickness.
- Urine and plasma samples with associated metabolomic and proteinomic indicators
- A genome-wide association that is currently being completed for each participant.

PREDICT-HD

Multiple Version of PREDICT-HD

- There are different “versions” of PREDICT-HD.
  - The protocol changed.
  - Variables were added and deleted.
  - Procedures may have changed for processing of biosamples (blood and urine), etc.
- Focus is on PREDICT-HD 1.0 and 2.0.
  - Data are cleaned for 1.0.
  - Data for 2.0 are being cleaned and added.
  - Data for 2.1, 2.2 are not currently available.
- Reporting descriptive statistics.
  - Descriptive statistics that follow are based on data that are cleaned and can be analyzed.
  - Sample sizes based on cleaned data are a subset of the total sample sizes.

PREDICT-HD 1.0 & 2.0 Measures

- PREDICT-HD 1.0 had a duration of 7 years.
- PREDICT-HD 2.0 had a duration of 3 years.
  - Not all data for 2.0 is cleaned.
- Data dictionary.
  - Some variables are not consistent across 1.0 and 2.0.
  - The following slides contain a list of variables and pertinent information about the variables.
- Key.
  - **Section**: Refers to the domain of the measure.
  - **Delivery**: Mode of administration, interview or self-report.
  - **Informant**: Report of who responded, participant (P) or companion (C), or both (P,C).
  - **Status**: Gene-positive (+) or gene-negative (-) or both (±).
  - **1.0** and **2.0** versions.
    - ✓ **B** = administered at baseline.
    - ✓ **I** = initial visit for 1.0 participants continuing in 2.0.
    - ✓ **F** = follow-up visits.

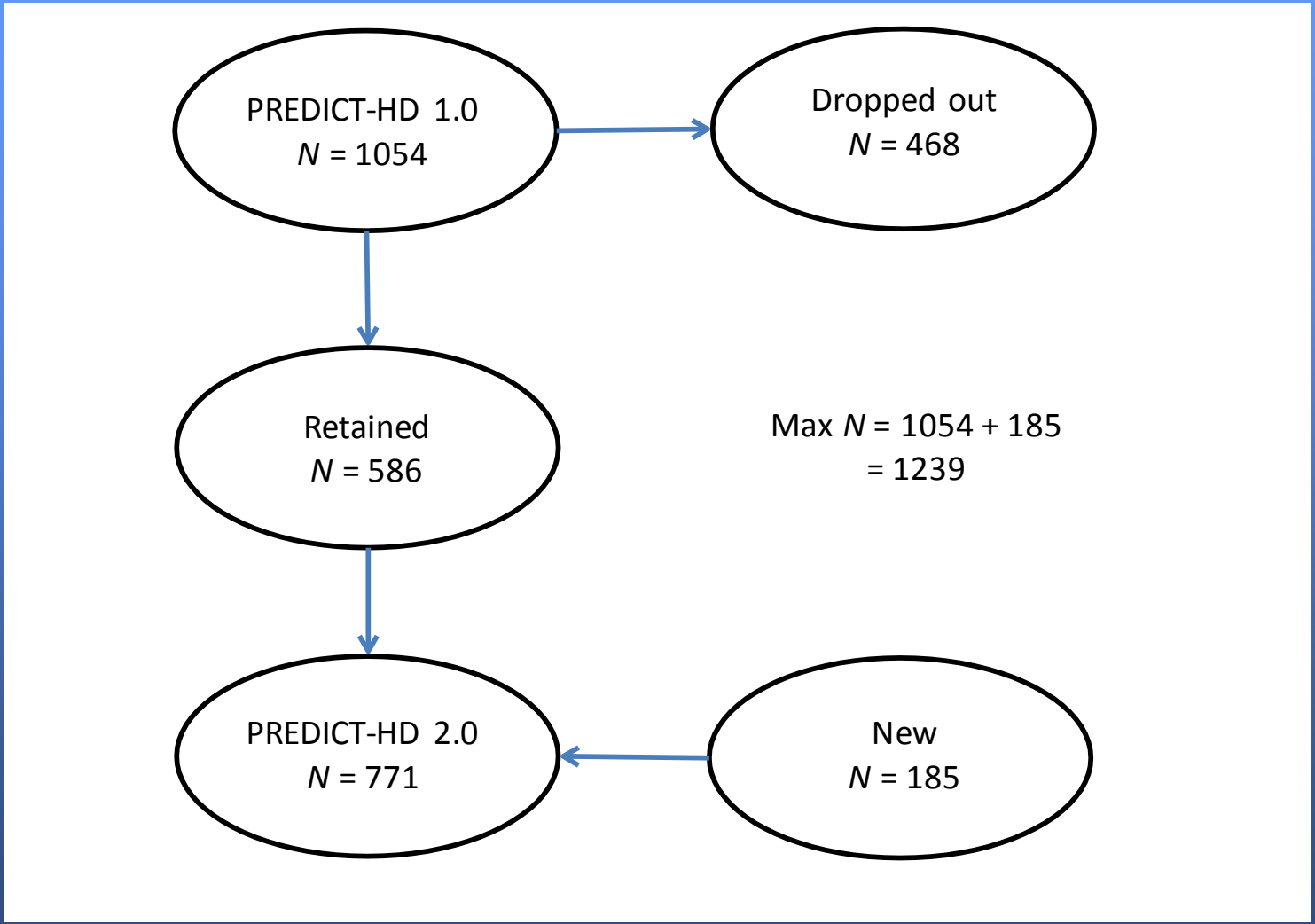
Behavioral and Functional Measures

Section	Delivery	Informant	Status	1.0	2.0	Measure
Behavioral	Interview	P	±	B,F	n/a	Beck's Depression Scale (BDI)
	Interview	P	±	B,F	n/a	Beck's Hopelessness Scale (BHS)
	Interview	P	±	n/a	B,I	Columbia Suicide Severity
	Self-report	P,C	±	B,F	B,I,F	Frontal Systems Behavioral Scale
	Interview	P	±	F	n/a	HAIDT Scale
	Self-report	P,C	±	n/a	B,I,F	HD Behavioral
	Interview	P,C	±	B,F	n/a	Leyton Inventory
	Interview	P	±	B,F	n/a	Life Experiences Scale
	Interview	P	±	B,F	n/a	Perceived Stress Scale
	Interview	P,C	±	B,F	n/a	SCOPI
	Self-report	P,C	±	B,F	B,I,F	Substance Abuse
	Self-report	P,C	±	B,F	B,I,F	Symptom Checklist-90
	Interview	P	+	B,F	B,I,F	UHDRS Behavioral
Function	Self-report	P,C	±	n/a	B,I,F	FAEHD (includes work function survey)
	Interview	P	±	B,F	n/a	Functional Assessment Scale (FAS)
	Interview	P	±	B,F	n/a	Total Functional Capacity (TFC)
	Self-report	P,C	±	n/a	B,I,F	WHODAS II

Cognitive, Demographics, Motor Measures

Section	Delivery	Informant	Status	1.0	2.0	Measure
Cognitive	Interview	P	±	B,F	B,I,F	ANART
	Interview	P	±	B	n/a	Dual Verbal Working Memory
	Interview	P	±	B,F	B,I,F	Emotion Recognition
	Interview	P	±	B,F	n/a	Facial Recognition
	Interview	P	±	B,F	B,I,F	HVLT-R
	Interview	P	±	B,F	n/a	Letter-number Sequencing
	Interview	P	±	B,F	B,I,F	Paced Tapping
	Interview	P	±	B,F	B,I,F	Smell Identification Test (UPSIT)
	Interview	P	±	B,F	B,I,F	Stroop (Color, Word, Interference)
	Interview	P	±	B,F	B,I,F	Symbol Digit Modalities
	Interview	P	±	B,F	n/a	Towers 3 and 4
	Interview	P	±	B,F	B,I,F	Trail Making Test (A & B)
	Interview	P	±	B,F	n/a	Verbal Fluency
	Interview	P	±	B,F	n/a	Letter-number Sequencing
	Interview	P	±	B,F	n/a	Weschler Abbreviate Scale of Intelligence
Demographics	Interview	P	±	B,F	B,I,F	Concomitant Medical Log
	Interview	P	±	B	B,I	Demographics
	Interview	P	±	n/a	B,I,F	Medical Events Log
Motor	Interview	P	±	B,F	B,I,F	Speeded Tapping
	Interview	P	±	B,F	B,I,F	UHDRS Total Motor Score

Sample Sizes for Cleaned Data



Frequencies (%) based on Status

Status		PREDICT 1.0	PREDICT 2.0	Combined
Controls		233 (22.11%)	221 (28.66%)	292 (23.57%)
Cases	Low	215 (20.40%)	160 (20.75%)	255 (20.58%)
	Medium	288 (27.32%)	200 (25.94%)	338 (27.28%)
	High	318 (30.17%)	190 (24.64%)	354 (28.57%)
	Total Cases	821 (77.89%)	550 (71.34%)	947 (76.43%)
	Grand Total	**1054**	**771**	**1239**

- Controls are non-CAG expansive.
- Cases are CAG expansive.
- Low-Med-High are CAP groups (see Zhang et al., 2011).
- Combined refers to non-overlapping 1.0 and 2.0 participants.

Frequencies (%) of Diagnosed for Cases

Diagnosis	PREDICT 1.0	PREDICT 2.0	Combined
No	684 (83.31%)	460 (83.64%)	774 (81.73%)
Yes	137 (16.69%)	86 (15.64%)	169 (17.85%)
Missing	0 (0%)	4 (.72%)	4 (.42%)
Total	**821**	**550**	**947**

- Diagnosis is based on Diagnostic Confidence Level = 4.
- For PREDICT 1.0, diagnosis can occur at any time other than visit 1 (baseline).
- Combined refers to non-overlapping 1.0 and 2.0 participants.

Longitudinal Data: Maximum Visits

PREDICT-HD 1.0			
Max n(V)	*f*	cum *f*	r cum *f*
1	130	130	1054
2	97	227	924
3	148	375	827
4	272	647	679
5	119	766	407
6	211	977	288
7	77	1054	77

PREDICT-HD 2.0			
Max n(V)	*f*	cum *f*	r cum *f*
1	380	380	771
2	348	728	391
3	43	771	43

PREDICT 1.0 & 2.0			
Max n(V)	*f*	cum *f*	r cum *f*
1	200	200	1239
2	137	337	1039
3	99	436	902
4	176	612	803
5	162	774	627
6	179	953	465
7	94	1047	286
8	138	1185	192
9	53	1238	54
10	1	1239	1

Note. Max n(V) = maximum number of visits; *f* = frequency; cum *f* = cumulative frequency: r cum *f* = reverse cum f.

Longitudinal Conversion

PREDICT-HD 1.0		
Visit	*f*	cum *f*
1	0	0
2	26	26
3	43	69
4	30	99
5	27	126
6	9	135
7	2	137

PREDICT-HD 2.0		
Visit	*f*	cum *f*
1	13	13
2	19	32

PREDICT 1.0 & 2.0		
Visit	*f*	cum *f*
1	0	0
2	28	28
3	44	72
4	31	103
5	30	133
6	14	147
7	8	155
8	12	167
9	2	169

Active Participants December 2011

Sites	Cases	Controls	Total	PREDICT 1.0 %	Diagnosed
US	358	148	506	66%	23
CA	59	15	74	65%	5
AU	83	28	111	84%	5
EU	121	17	138	81%	6
Total	621	208	829	71%	39

Note. PREDICT 1.0 % = percentage of active participants who started in original study (PREDICT 1.0).

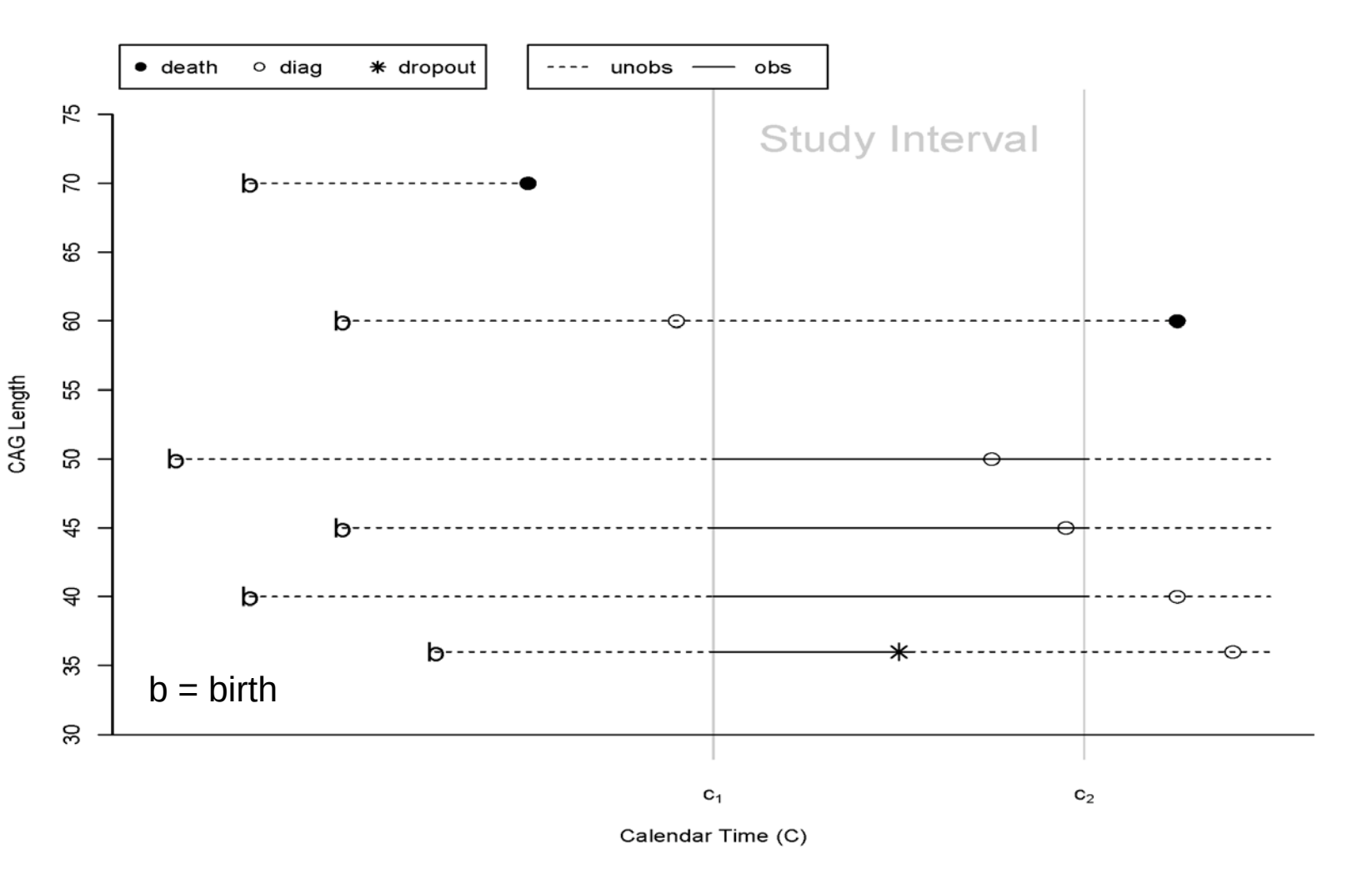
Classifying PREDICT-HD Participants

- Observational cohort studies like PREDICT-HD make it necessary to control for pre-existing differences.
  - Index of disease progression is key.

- A common method is to classify or group people according to baseline (first visit) variables.
  - Diagnosis
  - CAG expansion.
  - Age.
  - Daily functioning.

PREDICT-HD is a Cohort Study

- Problems: sampling bias, length bias, time metric.



Approaches to Classifying Participants

- Over-arching goal.
  - Distinguish pre-manifest (prodromal) and manifest.
  - Finer-grade distinctions.

- Approaches to classifying vary by study/researcher.
  - TRACK (Tabrizi et al., 2011): five groups.
  - PREDICT-HD (Zhang et al., 2011): four groups.
  - Aziz et al. (2010): three groups.

- PREDICT-HD participants can be classified based on a number of criteria.
  - The following slides illustrate.

TRACK's Five Groups (Tabrizi et al.)

- Baseline values: Gene Status (Cases, Controls), Diagnosis (DCL), Total Functional Capacity (TFC), Burden = [age x (CAG - 35.5)], Total Motor Score (TMS), predicted time to Dx (Farther, Nearer).

(1) **Control**

Gene-negative

(2) **preHD-A**

DCL < 4, Burden > 250, TMS $\leq$ 5, Farther from Dx

(3) **predHD-B**

DCL < 4, Burden > 250, TMS $\leq$ 5, Nearer to Dx

(4) **HD1**

DCL = 4, TFC = 11-13

"early HD"

(5) **HD2**

DCL = 4, TFC = 7-10

"early HD"

PREDICT-HD "TRACK-Like" Groups

- PREDICT-HD has no one is diagnosed at baseline. No "early HD".
- Baseline values: Gene Status, Burden, TMS.

(1) **Controls** Gene-Negative	(2) **preHD-A** Burden $\leq$ 250 TMS $\leq$ 5
(3) **preHD-B** Burden > 250 TMS $\leq$ 5	(4) **preHD-C** Burden > 250 TMS > 5

PREDICT-HD

PREDICT-HD CAP Groups

- CAP groups; CAP = [age x (CAG – 33.66)]
- Baseline values: Gene Status (Cases, Controls), CAP.

(1) **Controls** Gene-Negative	(2) **Low** CAP $\leq$ 287.16
(3) **Medium** 287.16 < CAP $\leq$ 367.12	(4) **High** CAP> 367.12

PREDICT-HD