The #1 Most Important Aspect of HD Research:

YOU

Huntington's Disease Society of America

The information provided by speakers in workshops, forums, sharing/networking sessions and any other educational presentation made as part of the HDSA convention program is for informational use only.

HDSA encourages all attendees to consult with their primary care provider, neurologist or other healthcare provider about any advice, exercise, medication, treatment, nutritional supplement or regimen that may have been mentioned as part of any presentation.

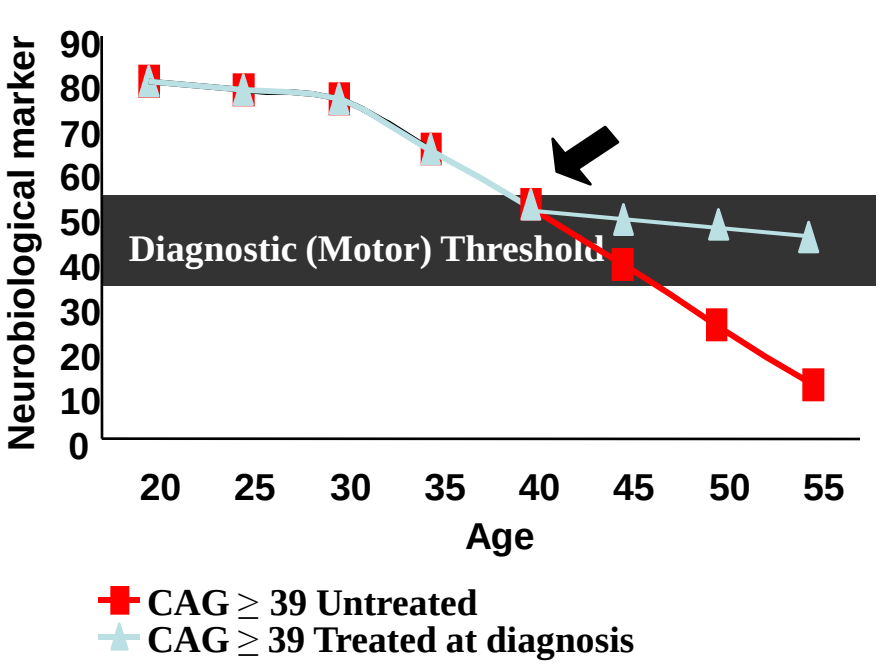
PREDICTing Care: The Value of Pre-Diagnostic Observation

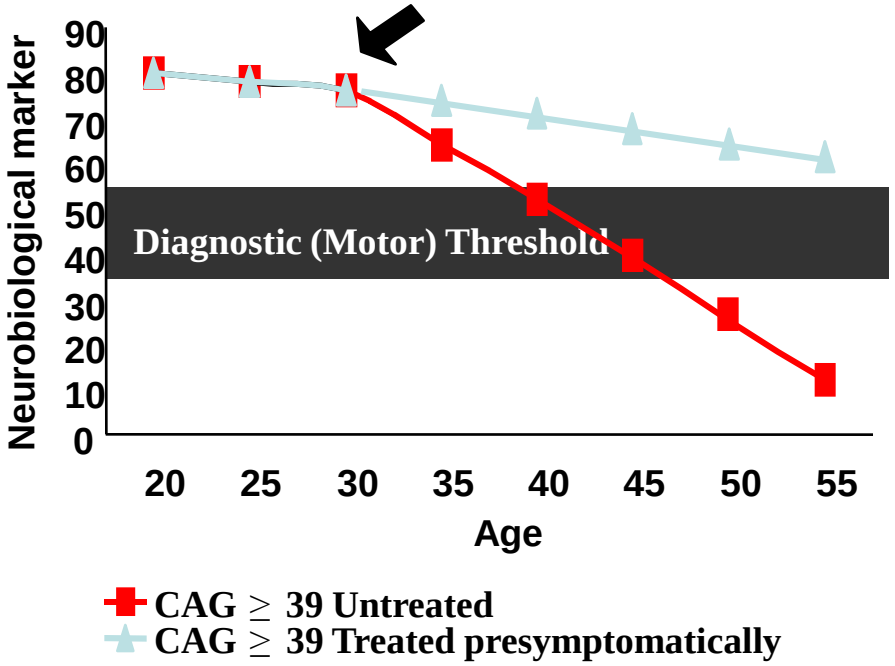
CHDI and NIH grant NS40068 2001- 2013

Jane S. Paulsen
The University of Iowa

University of Iowa Carver College of Medicine
University of Iowa Health Care

Clinical Trials: Model of Intervention in HD





Paulsen JS, Hayden M, et al. Preparing for preventive clinical trials: The Predict-HD study. Arch Neurol 2006;63:890.

PREDICT DEMOGRAPHICS 2009

	NC N=224	PRE FAR N=233	PRE MID N=245	PRE NEAR N=218	DX STAGE I N=66	DX STAGE II N=36	DX STAGE III N=7
Age	45.9 (11.8)	38.3 (8.3)	44.6 (9.7)	45.9 (10.5)	50.0 (10.7)	47.6 (8.8)	60.0 (10.0)
Gender %Fe	65	68	64	59	64	64	57
Disease burden		197.5 (37.9)	279.2 (26.8)	364.2 (46.8)	352.3 (69.8)	396.5 (110.8)	369.9 (88.1)
5-yr Prob of DX		.050 (.033)	.203 (.067)	.447 (.102)	.440 (.167)	.504 (.171)	.466 (.171)
% Motor < 4	72.2	74.1	57.6	36.9	0.0	0.0	0.0
Mean Motor	2.0 (3.2)	3.3 (4.1)	4.8 (4.8)	8.1 (7.2)	23.2 (9.8)	28.2 (10.8)	34.9 (14.8)

N~1099 TOTAL
N~855 CAG exp
N~244 CAG nor

Each Study Site

Cognitive
Brown Univ.
Wash U-St. Louis
UCSD

Genetics
Harvard

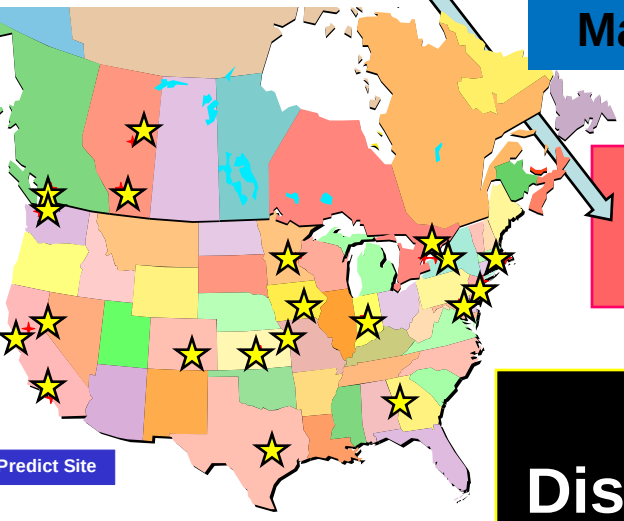
Biomarker Lab
UBC

Psychiatric
Manchester
Columbia
Maryland

Motor
Rochester
Columbia
UCSF
Munster

MRI
U Wash Seattle
U of Iowa
Johns Hopkins

Brain
Columbia



Study Coordination
University of Iowa

Data Sharing and
Dissemination: dbGaP at NIH

5.3 - 8.5%/y

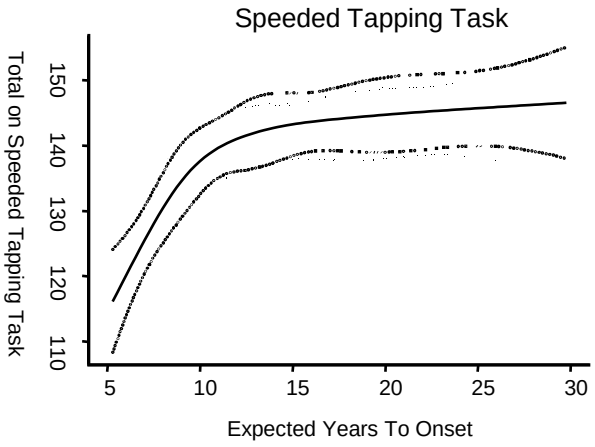
To date Predict has…

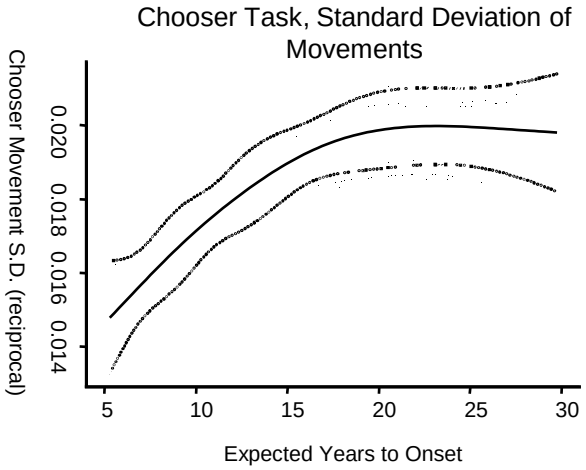
- **Reduced sample size** for pre-HD clinical trials (from 2097 for 5y 2-grp 80% P 20% effect to 880)
- **Identified markers** ~15 y prior to diagnosis
- Developed a database of scans, bloods, dna, phenotypic assessment
- Data being used to develop **models of disease**
- **Facilitated the collaboration** of clinical research teams
- papers, presentations, new investigators, additional grants
- **Policy statement for disability** legislation
- Diagnostic consensus conference planning

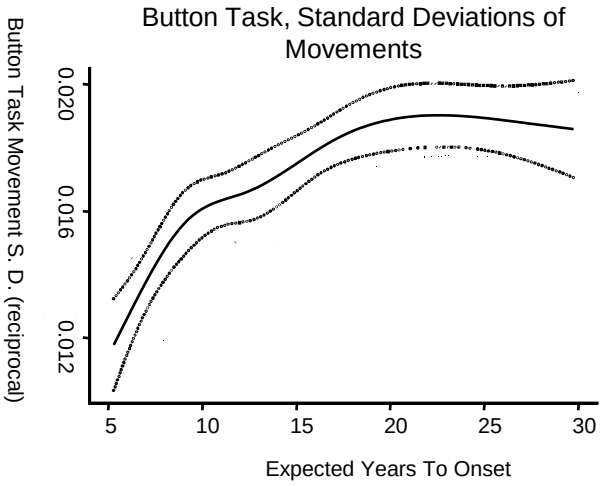
MOTOR, cognitive, psychiatric, IMAGING, BLOODS

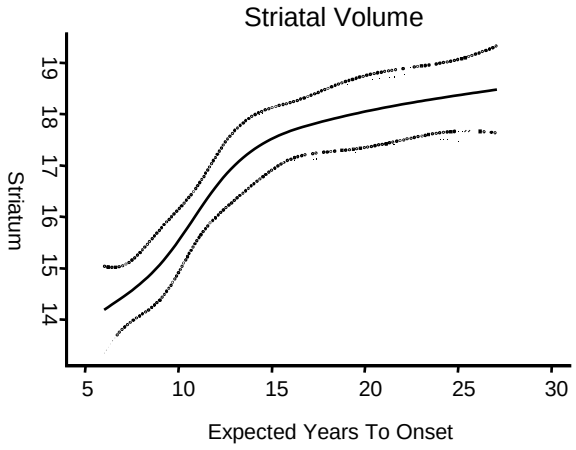
Markers of HD

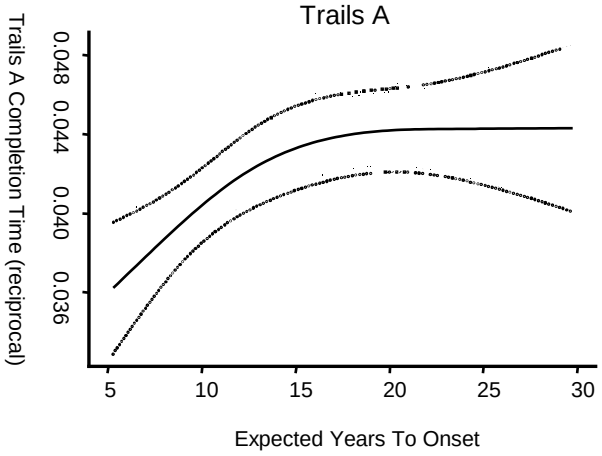
Paulsen JS, et al. Detection of Huntington's disease decades before diagnosis: The Predict HD study. J Neurol Neurosurg and Psychiatry 2007 Dec 20.

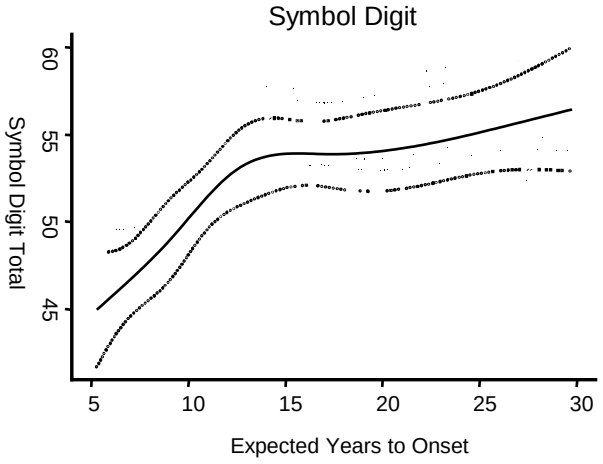




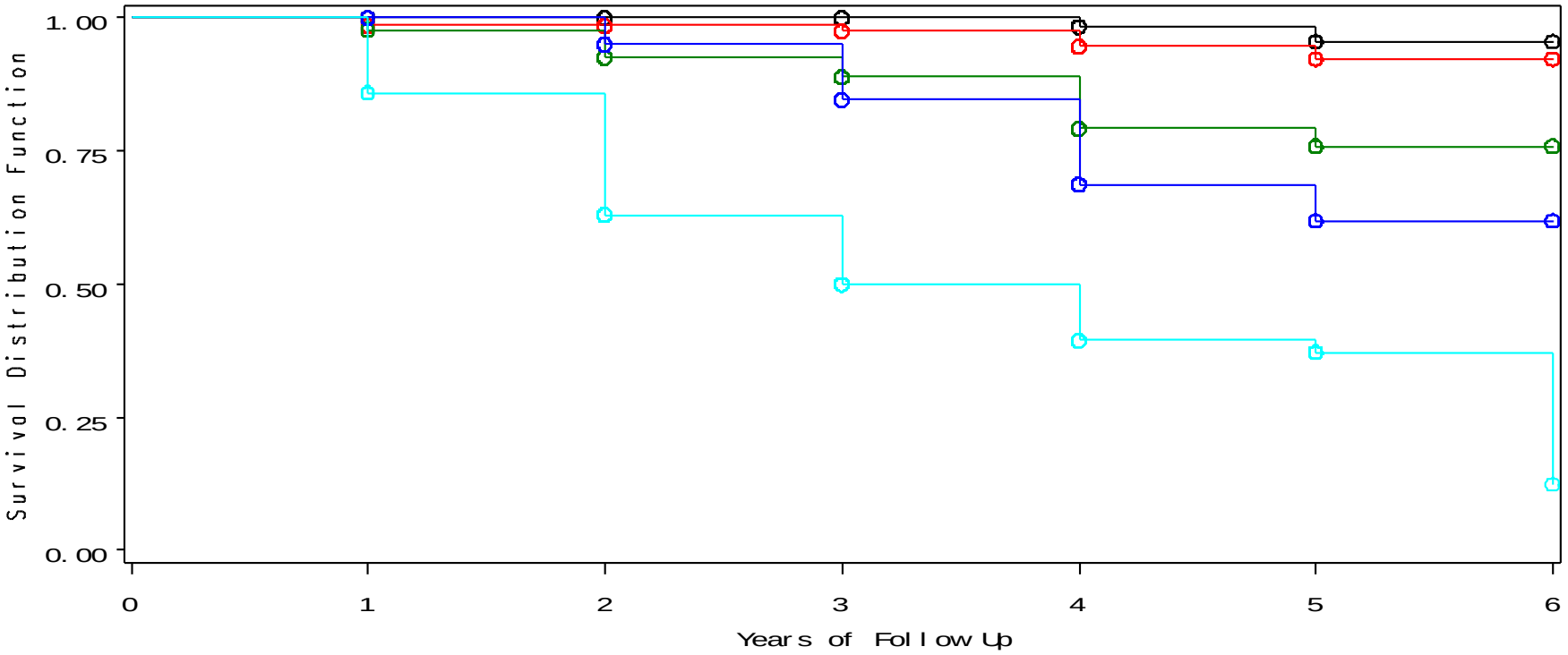








Observed time until diagnosis, by quintile of estimated risk

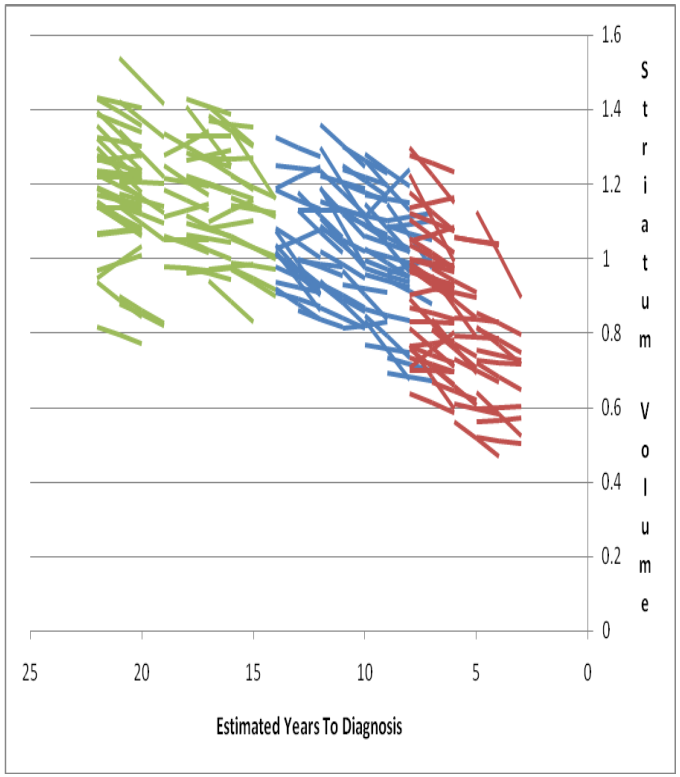


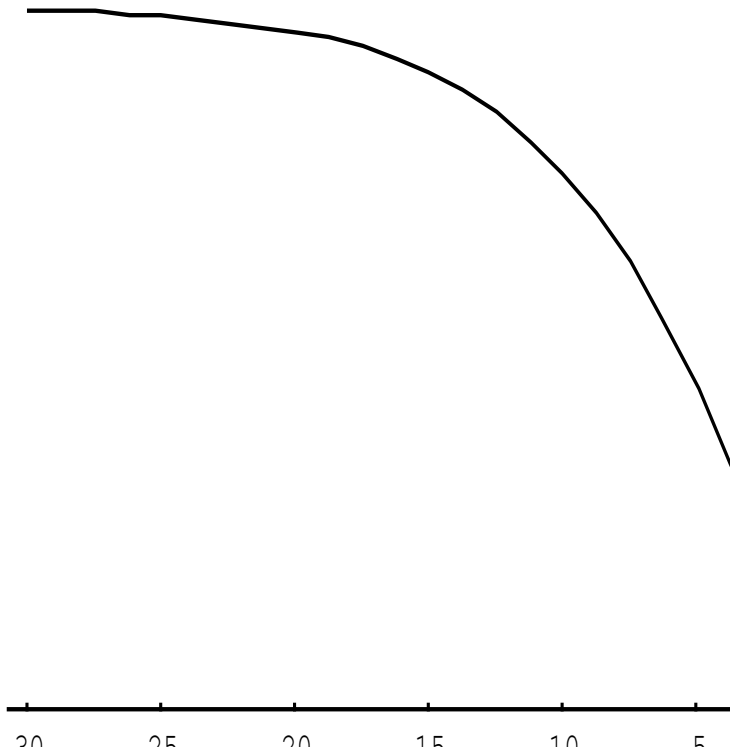
When should treatment begin?

- Birth?
- Age 18?
- When predictive testing shows exp+?
- Motor symptoms?
- Cognitive or behavioral changes?
- Brain tissue loss?
- Brain metabolism changes?
- Marital breakdown?
- Loss of job?

❑ Is the acute change of motor score predictive of the HD-onset?

This question stems from the early observations in cross-sectional study.

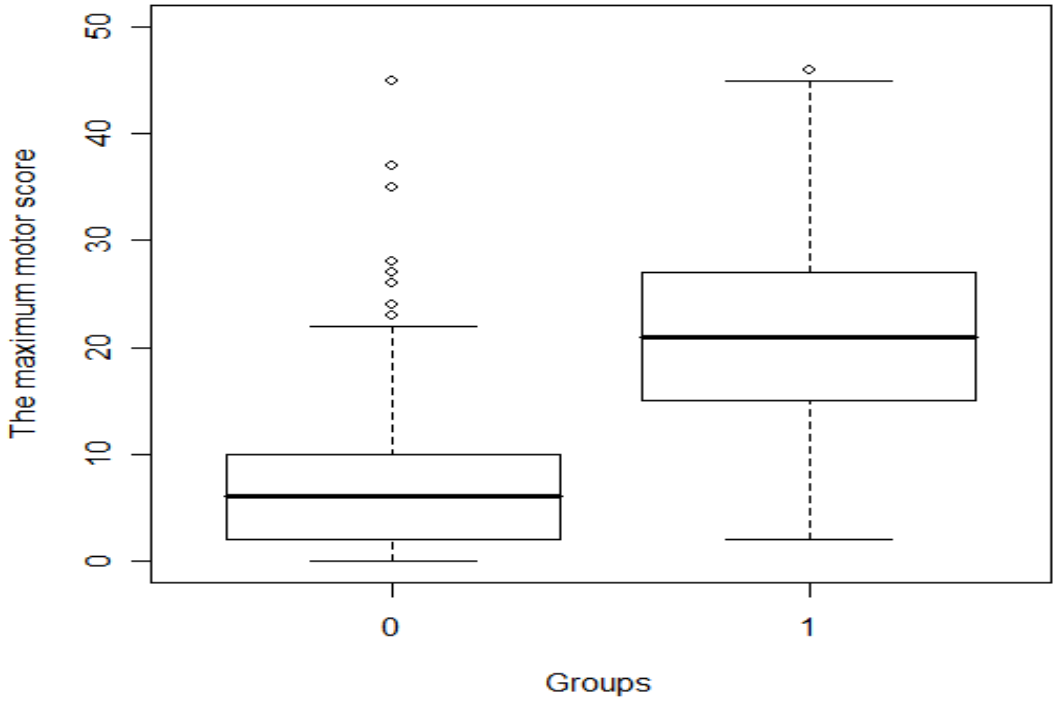




Estimated Years to Diagnosis

PREDICT-HD

Comparison of motor score between converters and non-converters



- It is apparent that the motor score is predictive of HD-onset
- However, there is no clear cut-off for the motor score to determine the onset

Acute change is also predictive of HD diagnosis and adds prediction power--in addition to the original motor score

Positive Prediction Rates

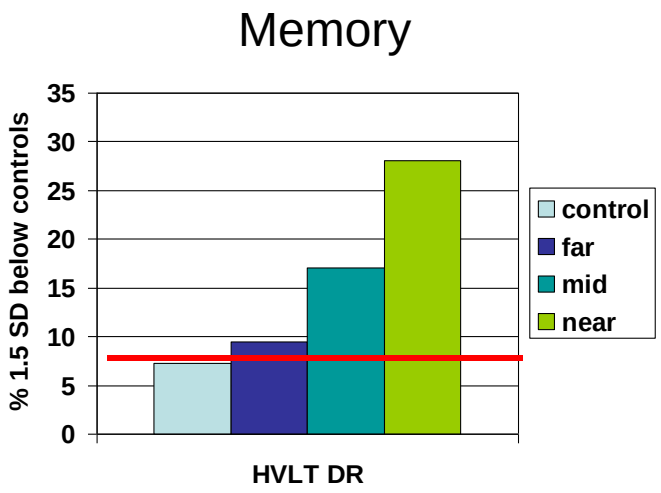
Diagnosis	# of Subjects	% of HD-onset
mvalue ≥ 10	309	39.8
• maxslope ≥ 5	232	49.6
• maxslope ≥ 10	97	66.0
• maxslope ≥ 15	35	**88.6**
mvalue ≥ 15	169	59.2
• maxslope ≥ 5	147	65.3
• maxslope ≥ 10	80	70.0
• maxslope ≥ 15	32	**87.5**
mvalue ≥ 20	91	78.0
• maxslope ≥ 5	85	**81.2**
• maxslope ≥ 10	58	**81.0**
• maxslope ≥ 15	29	**89.7**

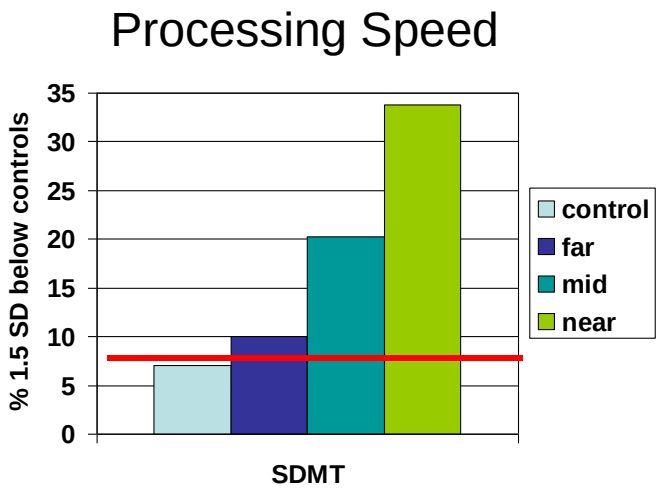
PREDICT-HD

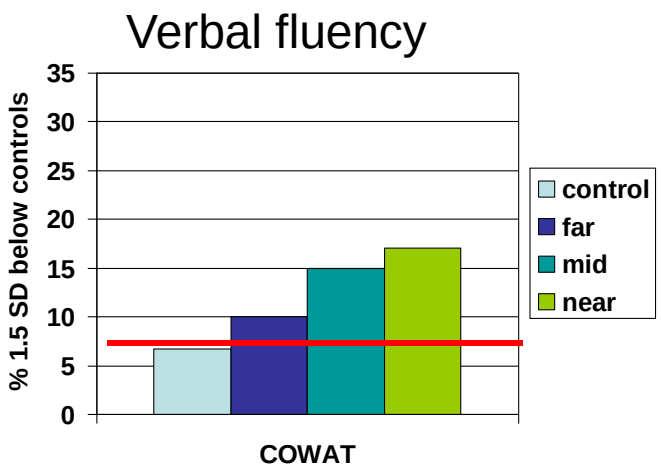
A potentially useful predictive model for diagnosing HD-onset

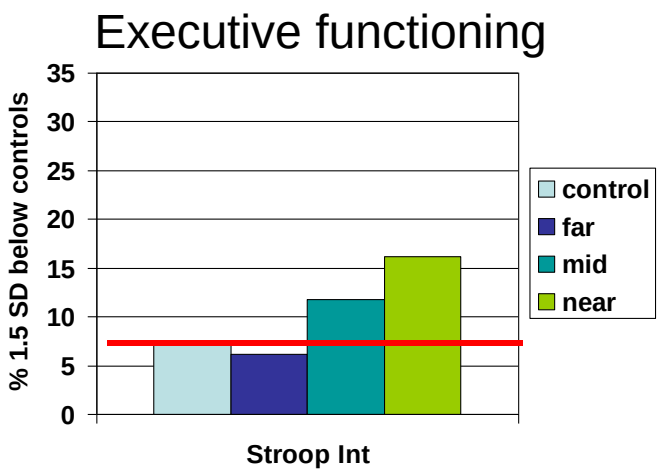
- The same data mining technique can be applied to other markers in the areas of imaging, cognitive, psychiatric.. etc.
- Ultimately, a powerful predictive model for diagnosing HD will be built on those features
- A computer program needs to be developed to provide an objective diagnosis toolkit
- This diagnosis toolkit can be delivered in the form of decision tree as it is an easily interpretable model for clinical practice.

MCI in PREDICT-HD









Duff et al. (2010)

Model 1: DNA and Age

Variables	Estimate	S.E.	p-value
age	-0.0072	0.0128	0.5745
cag	0.0355	0.0722	0.6226
burden	-0.0069	0.0019	**0.0003**

Model 2: DNA, Age and PREDICT markers

Variables	Estimate	S.E.	p-value
age	0.0200	0.0122	0.1022
cag	0.0860	0.0647	0.1836
burden	-0.0038	0.0018	**0.0402**
putamen	0.2549	0.0431	**<0.0001**
stroopin	0.0147	0.0056	**0.0087**
neurotot	-0.0295	0.0087	**0.0007**

Model Comparison

The two newly proposed models are compared to the previous working model (Langbehn model) regarding its prediction accuracy for HD diagnosis using PREDICT converters

Years to Diagnosis

Model	N	Mean	s.d.
Model 0	127	5.62	4.33
Model 1	127	3.34	2.73
Model 2	87	2.14	2.15

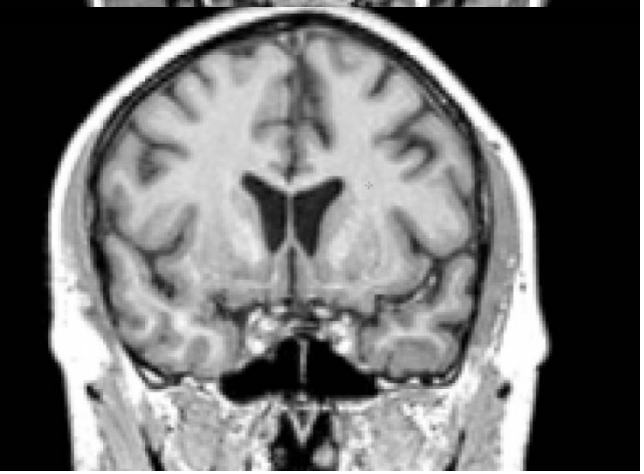
Percent of Diagnosed in each classification group

Models	N	Near (%)	Mid (%)	Far (%)
Model 0	127	**93 (73.2)**	24 (18.9)	10 (7.9)
Model 1	127	**113(89.0)**	12 (9.5)	2 (1.5)
Model 2	87	**82 (94.3)**	4 (4.6)	1 (1.1)

STUDY	PURPOSE	DRUG	SITES	N	CONTACT
2CARE	To assess the safety and tolerability of coenzyme Q10 and its effect on the progression of functional decline in HD	1. 2400mg CoQ10 2. Placebo	42	608	HSG 800-487-7671
CIT-HD	To evaluate the effect of citalopram (Celexa) on attention, thinking ability, movements and daily activities	1. 20mg Celexa 2. Placebo	3	36	Bill Adams 319-353-4411
CREST-E	To assess the safety and tolerability of creatine monohydrate and its effect on the progression of functional decline in HD	1. Creatine 2. Placebo	44	650	HSG 800-487-7671
HART	To assess the safety and tolerability of ACR16 and its effect on the progression of motor and cognitive decline in HD	1. 20mg ACR16 2. 45mg ACR16 3. 90mg ACR16 4. Placebo	35	220	HSG 800-487-7671
HORIZON	To assess the safety of dimebon and its effect on the progression of cognitive and motor decline in HD	1. 60mg Dimebon 2. Placebo	60	350	HSG 800-487-7671
PREQUEL	To determine the safety and tolerability of three doses of coenzyme Q10 in **pre-manifest**	1. 600mg CoQ10 2. 1200mg CoQ10 3. 2400mg CoQ10	10	90	HSG 800-487-7671

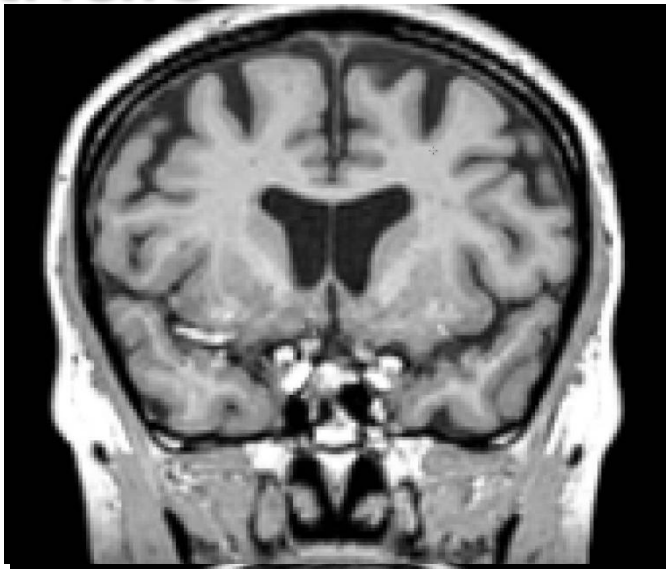
Imaging to reduce sample size in clinical trials

NC



NEAR

FAR



DIAGNOSED

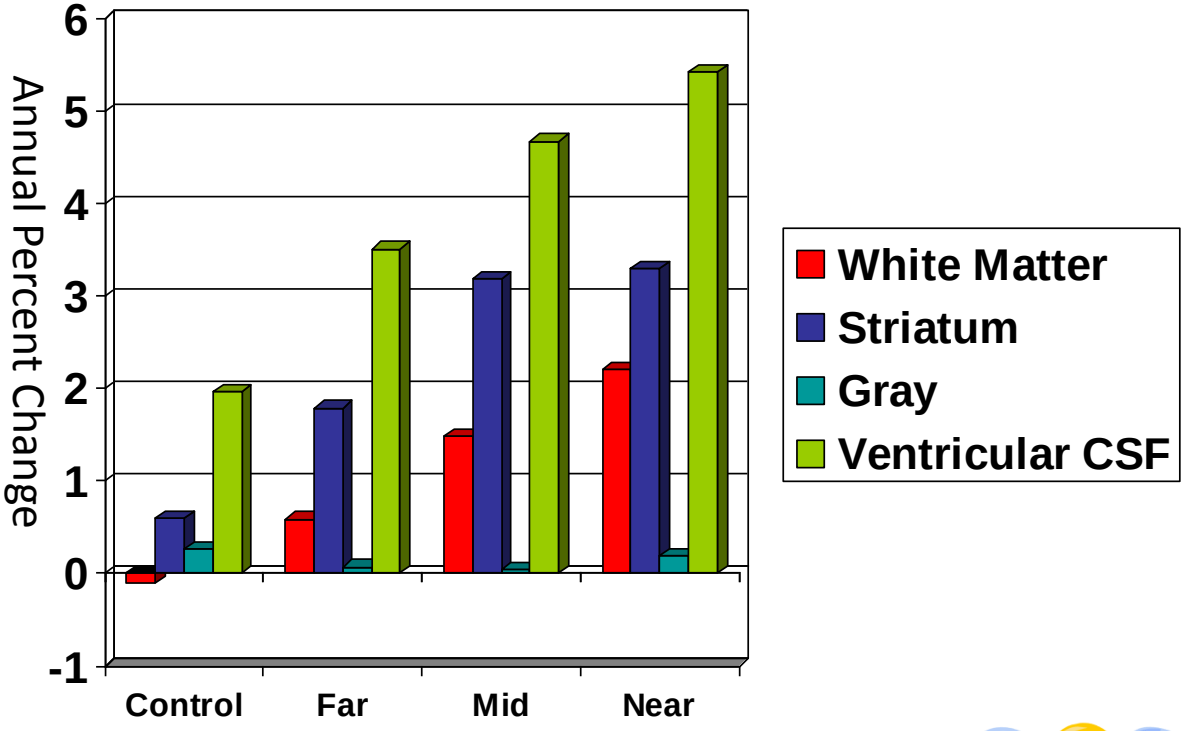
MID

Annual Percent Change (Based on 2-Year Follow-up)

- All prodromal HD groups show greater longitudinal change than controls in white and striatum ($p < .0001$), not in gray

Controls differ significantly on Ventricular CSF change from Mid and Near; trend for Control-Far difference)

Gray-White Segmentation



Estimated Sample Sizes for Trials Using Striatum, Cerebral White, Frontal White, or Ventricular CSF as Outcome (percent reduction in DISEASE-RELATED change*)

	FAR			MID			NEAR		
Expected reduction in atrophy	50%	40%	30%	50%	40%	30%	50%	40%	30%
Total striatum	524	819	1457	108	169	300	140	219	390
Cerebral white	343	535	951	106	166	295	61	96	171
Frontal white	286	447	795	112	175	311	63	98	174
Ventricular CSF	879	1374	2443	188	294	524	59	92	163

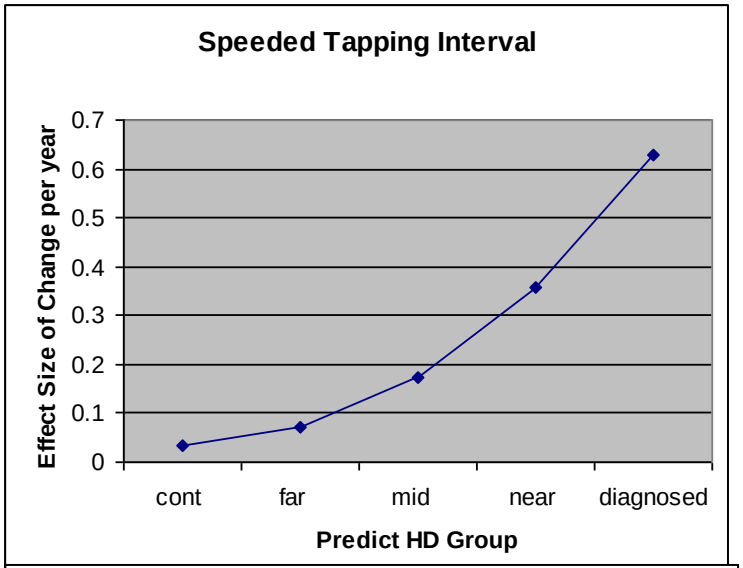
*Based on effect size for pre-HD group minus effect size for normal controls

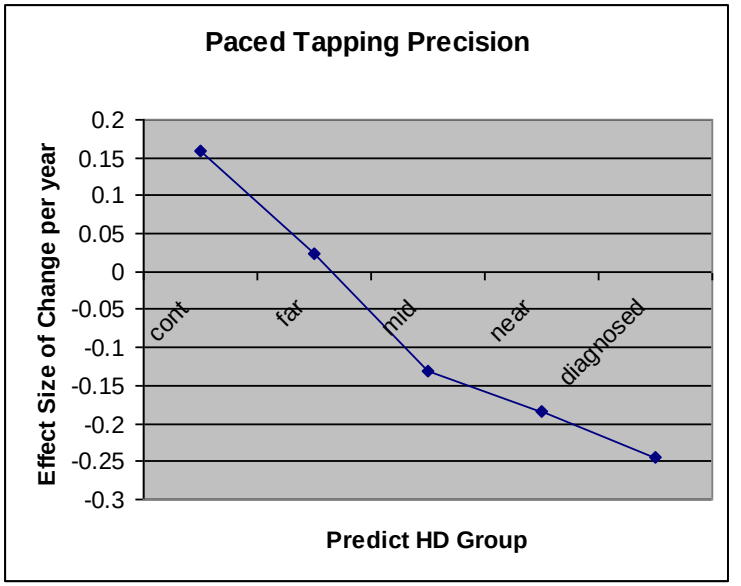
PREDICT-HD

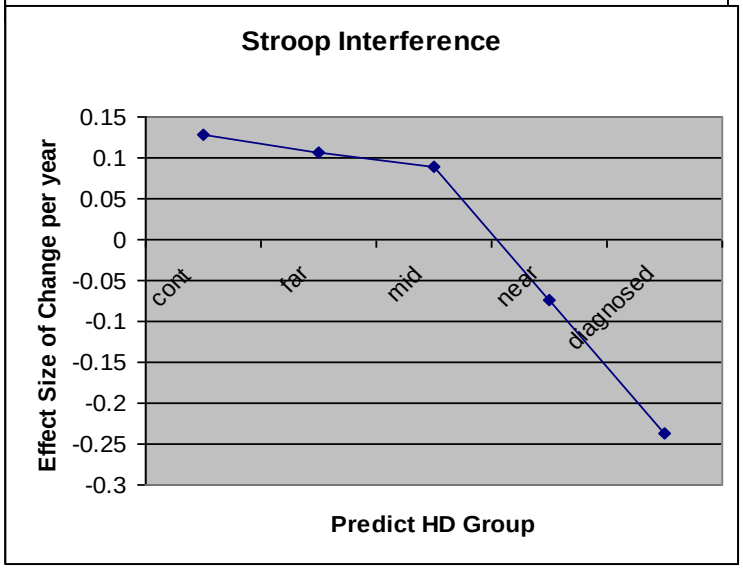
Bottom Line

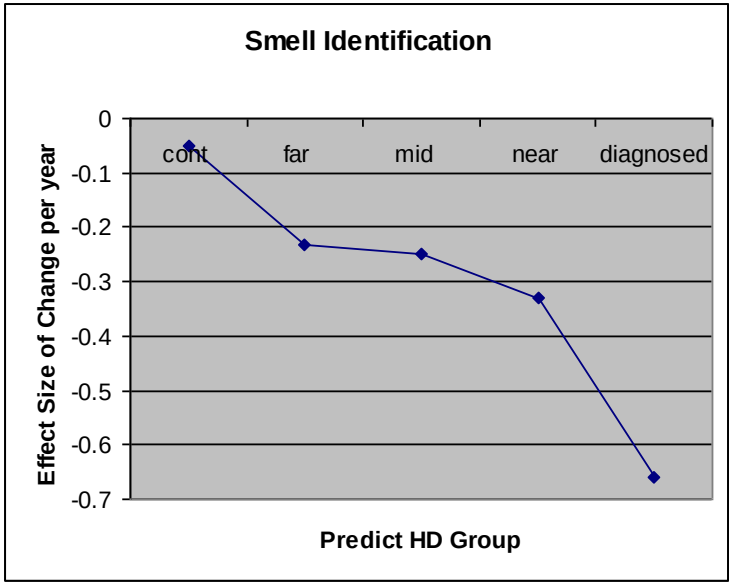
- WM change, especially in frontal lobe, may be an excellent outcome measure in addition to striatum
- Studies restricted to "near" and "mid" subjects can be accomplished with reasonable sample sizes (N=59 to 311)

Longitudinal marker of disease progression









Longitudinal Change Scores* by Prodromal Stage *[-NC]

DX'd	Near	Mid	Far
Mot tot 1.1	WM .58	WM .44	WM .25
Chorea .99	Timing .39	Striat .44	Striat .20
Brady .77	Striat .38	Timing .34	Timing .14
Tap spd.59	Strp-C .29	TrailsA .14	Strp-C .10
SymDig.51	SymDig.27	SymDig.14	
TrailsB .49	Button .25	Strp-C .14	
Oculo .48			
Button .47			
Strp-W .46			

Study in **PRE**-Manifest Huntington's disease of coenzyme **Q**$_{10}$ (**U**biquinon**E**) **L**eading to preventive trials

Primary Study Objectives

To identify the highest dosage of CoQ amongst 600, 1200, or 2400 mg/day that is tolerable in pre-manifest participants with the CAGn expansion for use in future preventive trials.

To determine the effects of CoQ on measures of oxidative injury (8OHdG)

To determine the feasibility of performing therapeutic trials in prodromal (presymptomatic) HD

PREQUEL Protocol Design

- Randomized, double-blind parallel group trial
- Assigned to 600mg, 1200mg or 2400mg per day of CoQ10 and followed for 20 weeks
- Blinded dosage reductions will be allowed for intolerability
- **Primary Outcome:** Ability to complete the study on the *originally assigned dosage of CoQ*

PREQUEL

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Version 2.26.2009

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H·S·G
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For more information
please visit the HSG website at :

www.huntington-study-group.org

A clinical research study of PRE-manifest Huntington's disease of coenzyme Q10 (UbiquionE) Leading to preventive trials

~ PREQUEL ~

A MULTI-CENTER DOUBLE-BLIND RANDOMIZED CLINICAL STUDY

SUPPORTED BY A GRANT FROM THE NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE (NINDS)

Clinical Research Hurdles towards Treatment

- Knowledge of HD mechanisms
  - Biomarkers
  - Genetic modifiers
  - Patterns of progression
- Measures are lacking
  - Functional outcomes
  - Reliable and standard motor ratings
  - Brief and standard cognitive tasks
  - Valid behavioral measures
- **Volunteers**

The #1 Most Important Aspect of HD Research:

YOU

Volunteerism and retention: What motivates participants?

- To connect with services or professionals that they may need
- To contribute to finding a treatment and a cure
- To make a difference in the fight against HD
- To keep more up-to-date on HD research happenings and findings by being in research studies

THANK YOU FOR BEING A TEAM PLAYER IN PREDICT-HD!

PREDICT HD SITE STAFF 2010

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University of California San Francisco, San Francisco, California	M. Geschwind	M. Guzijan M. Wetzel	M. Guzijan
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University of Minnesota; Hennepin County Medical Center, Minneapolis, Minnesota	M. Nance	D. Norberg D. Tupper	D. Radtke
University of Rochester, Rochester, New York	P. Como	P. Como	A. Chesire
University of Toronto/Centre for Addiction & Mental Health, Markham, Ontario, Canada	M. Guttman	M. Guttman C. Giambattista J. Stober	C. Giambattista
University of ULM, Ulm, Germany	B. Landwehrmeyer S. Trautman	K. Barth S. Trautman	K. Barth S. Trautman
University of Washington and VA Puget Sound Health Care System, Seattle, Washington	A. Samii	K. Weaver	H. Lipe
Washington University, St. Louis, Missouri	J. Perlmutter	S. Barton	S. Barton
Westmead Hospital, Westmead, Australia	E. McCusker	B. Bibb K. Richardson	J. Griffith

Iowa Personnel

- William Adams
- Christine Anderson
- Jessica Deaderick
- Nick Doucette
- Ann Dudler
- Kevin Duff
- Mackenzie Elbert
- Jana Hanson
- Andrew Juhl
- Douglas Langbehn
- Anne Leserman
- Brenda McAreavy
- Gerry Murray
- Jane Paulsen
- Stacie Vik
- Chiachi Wang
- Elijah Waterman
- Christine Werling-Witkoske

CTCC Personnel

- Catherine Covert
- Elaine Julian-Baros
- Elise Kayson
- Nichole McMullen
- Kay Meyers
- Donna Moszkowicz
- Nichole Muraco
- Beverly Olsen
- Karen Rothenburgh
- Lisa Rumfola
- Aileen Shinaman
- Mary Slough
- Joe Weber
- Hongwei Zhao

Consultants

- Donald Black
- David Watson
- Andrew Hollingsworth

Imaging Personnel

- Eric Axelson
- Hans Johnson
- Vincent Magnotta
- Peg Nopoulos
- Ron Pierson
- Ben Rogers
- Jim Smith
- Kent Williams
- Shuhua Wu
- Karl Helmer
- Kelvin Lim
- Sasumu Mori
- Steve Potkin
- Arthur Toga

Cognitive Personnel

- David Caughlin
- Terren Green
- Sarah Queller
- Julie Stout
- Shelley Swain
- Greg Ashby

DNA Personnel

- Marcy McDonald
- Jim Gusella
- Elana Aatteneo
- Stefano DiDonato
- Asa Peterson
- Sarah Tabrizi

Plasma Personnel

- Blair Leavitt
- Wayne Matson

Consultants *(continued)*

- Jean Paul Vonsattel
- Robert Pacifici

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- Christopher Ross
- Julie Stout

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- Kevin Biglan
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- Michael Hayden
- Bernhard Landwehrmeyer
- Douglas Langbehn
- Martha Nance
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- Jane Paulsen
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- Ira Shoulson
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- Katrin Barth
- Amy Chesire
- Jane Griffith
- Mira Guzian
- Jenny Naji
- Norm Reynolds
- Stacie Vik