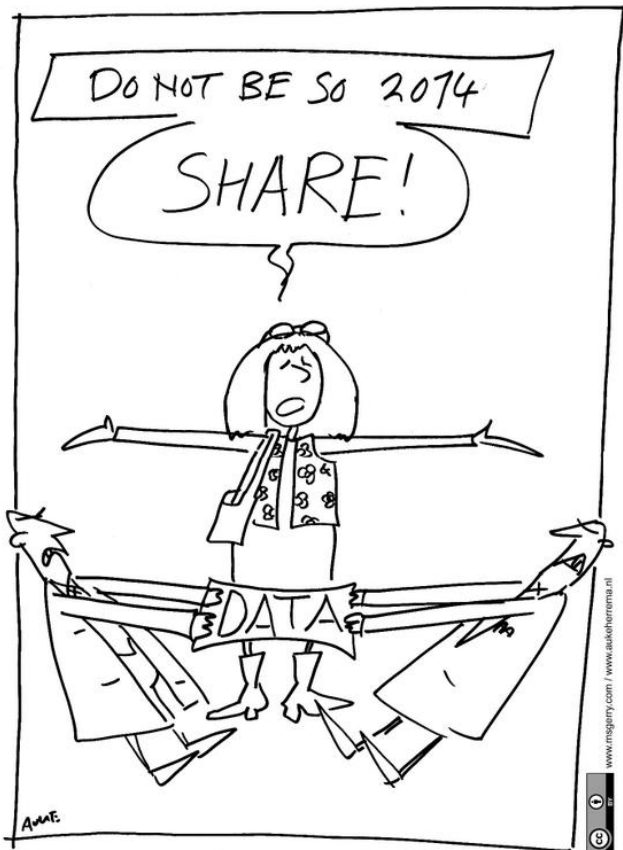


HD-RSC

HUNTINGTON'S
CONSORTIUM

CRITICAL PATH INSTITUTE



Rationale and Impact of Building a Comprehensive HD Clinical Database (HD-CCD)

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CHIEF MEDICAL OFFICER,

CHDI FOUNDATION

NOVEMBER 6TH, 2017

HD-RSC – “It takes a Village!”

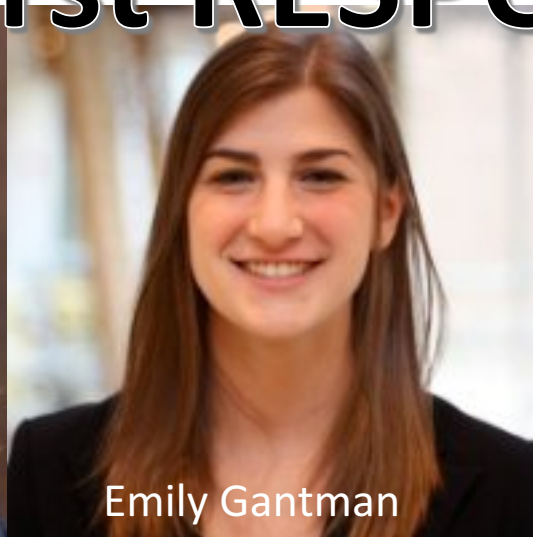


HD-RSC – “It takes a Village!”

CHDI- First RESPONDERS!



Cheryl Fitzer-Attas



Emily Gantman



Sandra Gonzalez

What is a Comprehensive
HD Clinical Database?

Why do we want one?

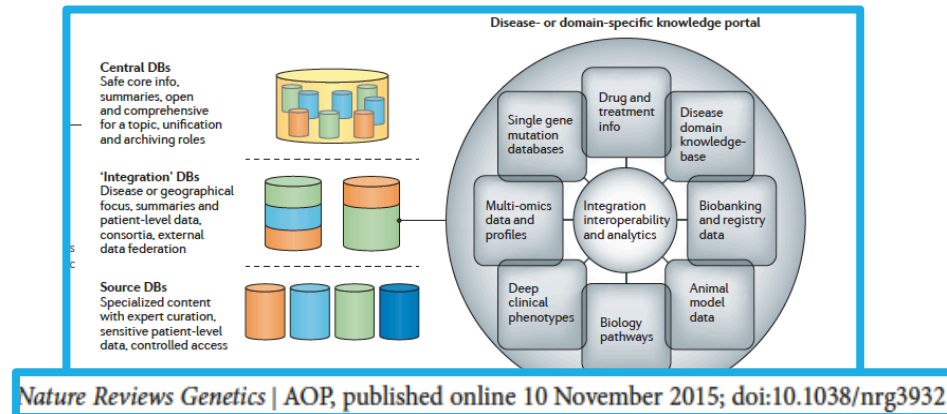
How far are we to get
one?

Summary

What is a Comprehensive HD Clinical Database (HD-CCD)?

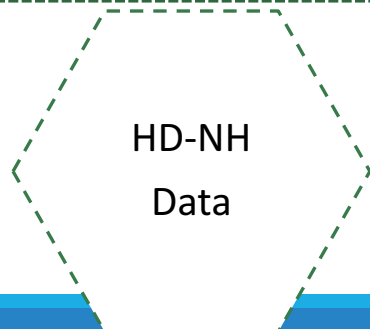
- Fully Federated Database that combines all individual datasets in larger single unit. Overlaps are identified and clear-out!

(It is what FDA, in the context of dossier submissions that is not the this context, calls Pooling not Integration, which is a different concept).



IBM-CHDI collaboration resulted in the largest HD natural history Dataset, yet HD-RSC can go further!

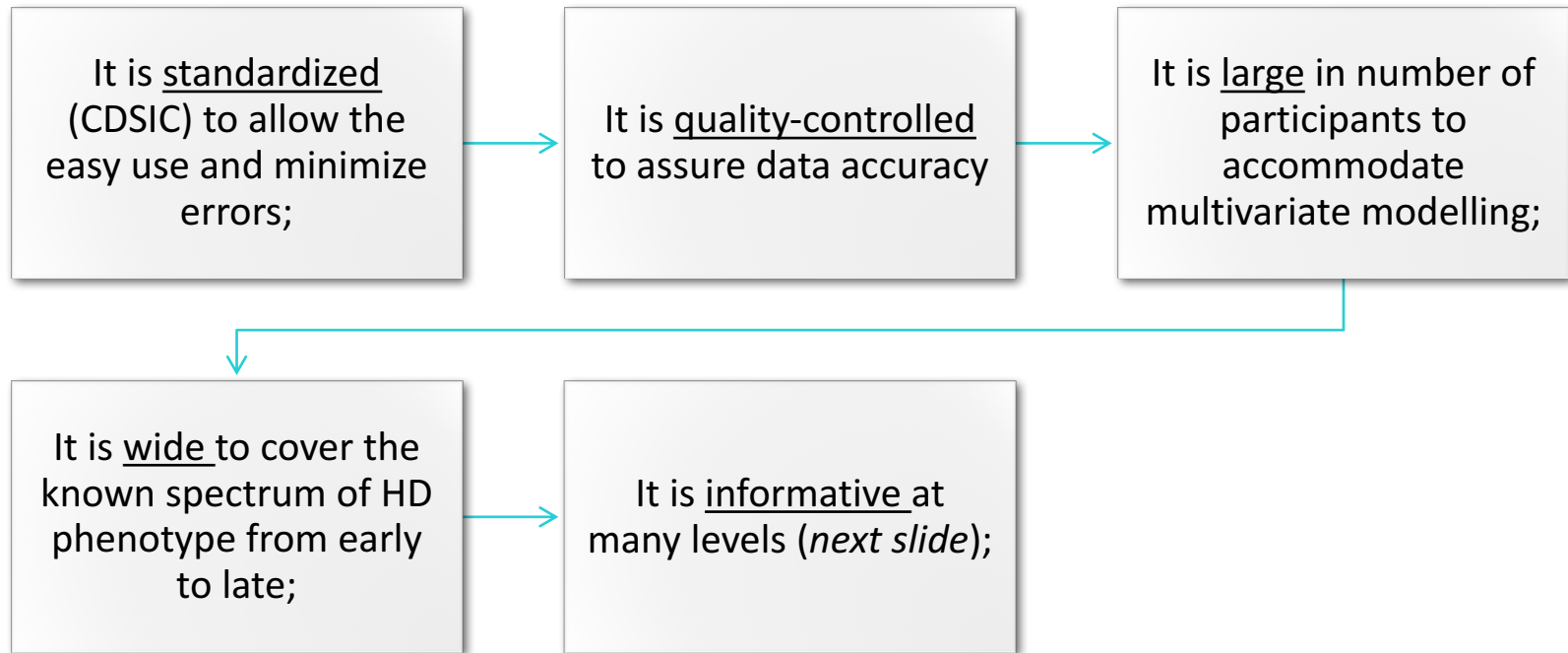
Cohort study	# Approx. Participants	CAG	Max visits	Mean visits	Motor	Functional	Psychiatric	Cognitive
Enroll-HD	7,500	✓	4	1	✓	✓	✓	✓
Registry-HD	12,000	✓	15	3	✓	✓	✓	✓
Track-HD/ON	450	✓	7	4	✓	✓	✓	✓
PREDICT-HD	1,500	✓	14	5	✓	✓	✓	✓



- Criteria

- Large participant base
- Longitudinal visit data
- Clinical assessment data

What is a Comprehensive HD Clinical Database?



Comprehensive HD Clinical Database – Information Levels – Participant Characteristics

01

Demographics;

02

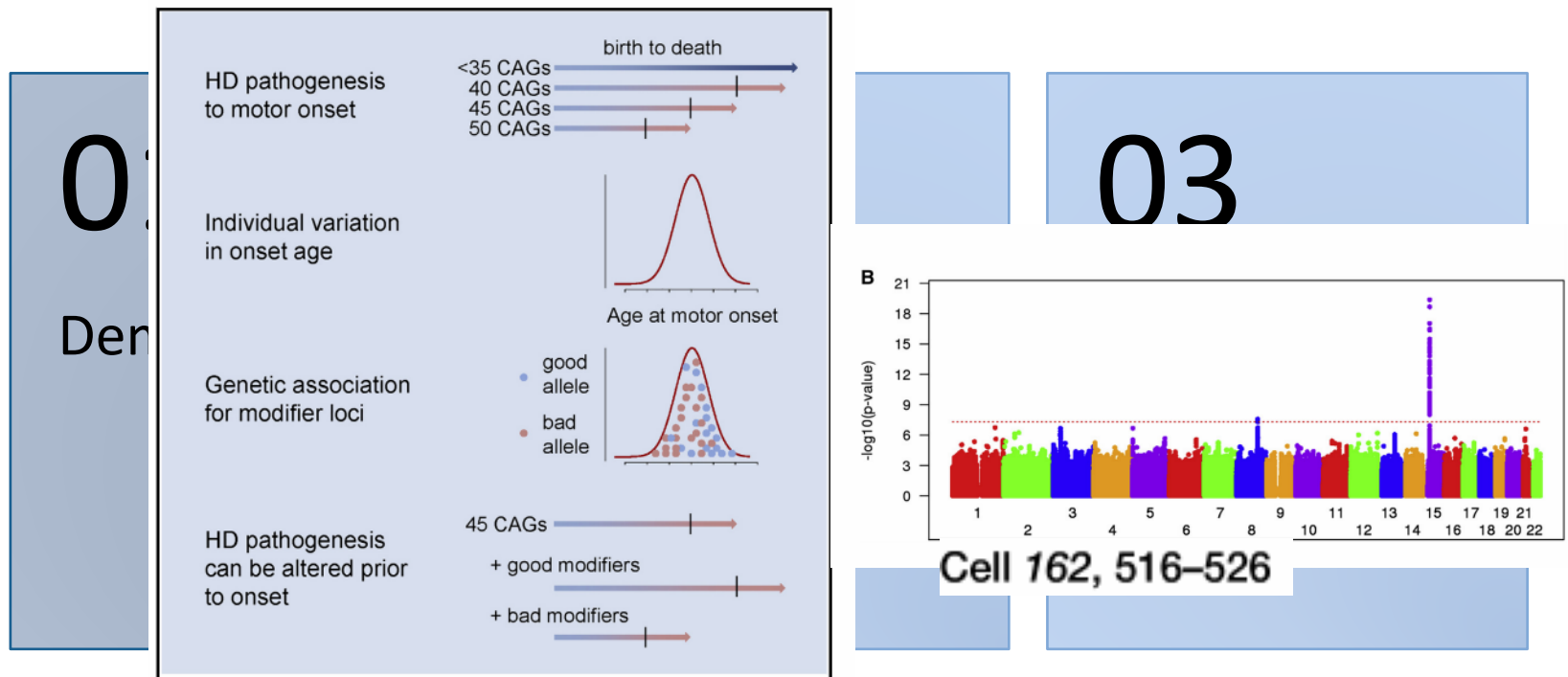
Genetics – (Far
beyond CAG
sizing)

03

Environmental

Comprehensive HD Clinical Database – Information Levels – Participant Characteristics

Graphical Abstract



Comprehensive HD Clinical Database – Information Levels

01

Natural History –
described by clinical
outcomes and
biomarker data;

02

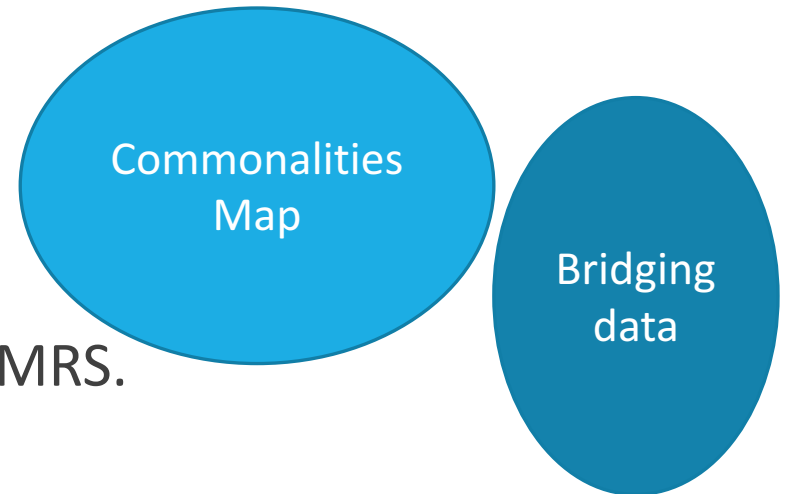
Placebo
effect/response –
described by clinical
outcomes and
biomarker data.

03

Specific interventions
response data –
described by clinical
outcomes and
biomarker data

Comprehensive HD Clinical Database – Information Levels – Clinical outcomes and Biomarker data

- Clinical outcomes that cover all relevant domains in HD:
 - Motor
 - Cognitive
 - Behavior
- Multimodal Biomarker Data
 - Imaging –MRIs, fMRI, DTI, PET, MRS.
 - BioFluids – CSF, Plasma, Cells
 - Performance
 - Digital



why?

why?

why?

why?

why?

Novel more powerful analytical strategies



Multimodality Integration



Predictive Models at Individual level

Illness biomarkers

Treatment response prediction

Individual-level assessment

The successful development of therapeutic interventions calls for efficient clinical trials!

Efficient Clinical Trials are predicated in the ability of correctly choose *apriori* the following:

- **P**articipants
- **I**ntervention
- **C**omparator
- **O**utcomes

The HD-CCD is the tool to achieve this!

HOW →

Participants

- Discovery and Validation of Prognostic Biomarkers that allow precise prediction at individual level

Intervention

- *Secondarily interventions will out select in accordance to the knowledge generated but it is not the immediate output of HD-CCD*



Comparator

- The placebo behavior in short and long-term; its variability and determinants is of critical importance of trial design and can be learned by modeling data in HD-CCD.

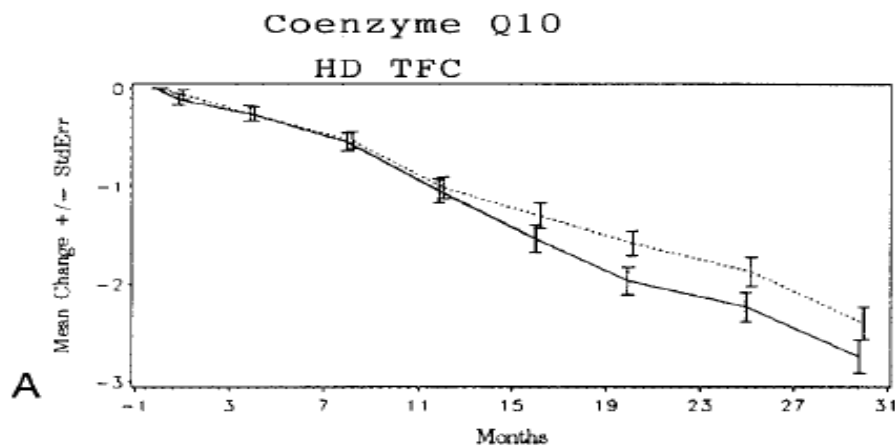
Outcomes

- Understanding the clinimetrics characteristics of the assessments in the different stages and settings allows the identification and development of the best adapted suit of tests.

You may say...we have done all that in the individual datasets, why bother?

- The answer is NO... you haven't done THAT!
- There is great research published in the individual datasets but:
 - Size has been a limitation; AND more importantly
 - External validation another;
- There are **many** publications supporting different measurements as disease progression biomarkers **very few** supporting prognostic biomarkers and almost **none** supporting predictive biomarkers. 
- Placebo data and Placebo studies are very scarce in HD. Importantly there are no comparative studies of Placebo response across studies, neither meta-analytic studies no even in aggregate, let alone with IPD. **!!**
 - Placebo data is important to establish the rates of decline, not just improvement under placebo. 

PLACEBO TEASER



TFC decline in CARE-HD TRIAL

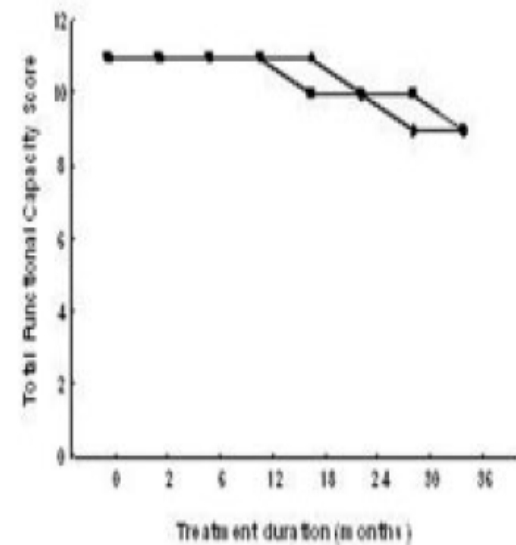
NEUROLOGY 2001;57:397-404

1.25/p per year*

* Rough estimates extrapolated from the figures

Riluzole
HD TFC

C.



TFC decline in RILUZOLE TRIAL

Ann Neurol 2007;62:262-272

0.8/p per year*

PLACEBO TEASER

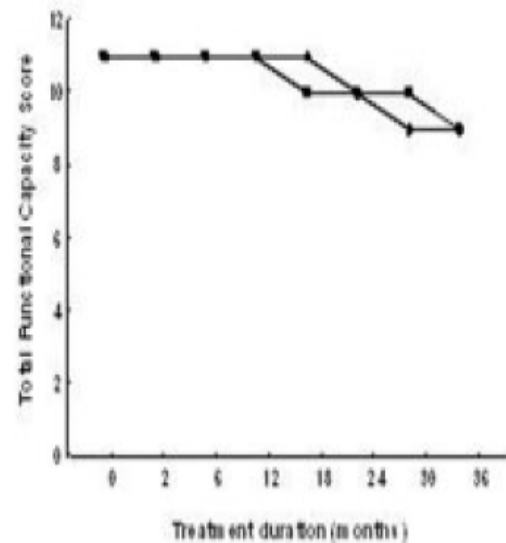
PARAMETER	CARE-HD 2001	EHDN-Ri 2007
SEX, female	55.2%	49.4%
AGE, years	46.6 ± 10.4	46.6 ± 9.5
DDURATION	4.7 ± 3.7	5.8 ± 5.1
CAG	44.6 ± 4.8	44.7 ± 3.7
Motor Score	31.1 ± 14.0	28.8 ± 16.0
TFC	10.2 ± 1.8	10.8 ± 1.8



figures

Riluzole
HD TFC

C.



TFC decline in RILUZOLE TRIAL

Ann Neurol 2007;62:262-272

0.8/p per year*



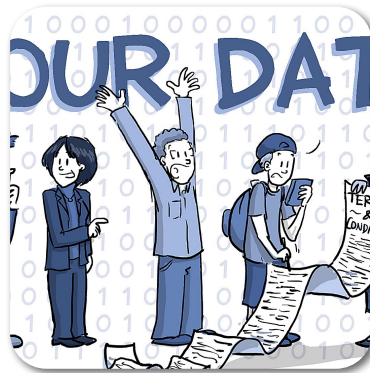
HOW
FAR

The logo consists of the word "HOW" in a white, sans-serif font, enclosed within a white speech bubble shape. Below the speech bubble, the word "FAR" is written in a larger, white, sans-serif font. A white arrow points from the bottom of the speech bubble towards the letter "A" in "FAR".



The Technical infrastructure of the Database

- C-Path has the means.
- It has been done before.
- The Consortium is fully financed
- CDSIC Standards are under way.



The Data

- Natural history data has been federate in IBM-CHDI collaboration. It is a success story.
 - It likely can be repeated in the realms of the consortium.
- Of the Outmost importance is to move on step further and collect Clinical trial –Placebo ARM data.



The Analysis

- C-Path will create the mechanisms that will allow wide access per DUA for multiple users analysis.
- There will be the Analysis conducted at C-Path per agreement at the Consortium Level.

Success is dependent on:

1. HD-RSC ability to leverage new datasets;
2. Data and Analytical Science to deliver useful results.

Number 2 is not completely in HD-RSC members hands but Number 1 is.

LETS MAKE **HD-CCD** HAPPEN!

together

HD-CCD

