Digital Biomarkers for Huntington's Disease: Promises and Challenges

Use of Biosensors in Clinical Trials:

Barriers & Solutions to the Current Landscape

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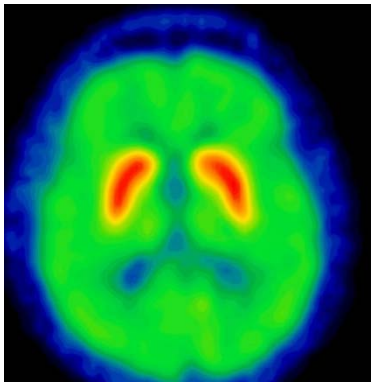
Pfizer WORLDWIDE RESEARCH & DEVELOPMENT

Definitions and Purposes of Biomarkers – Biomarkers Definitions Working Group 2001

- The word biomarker was first used by Karpetsky, Humphrey and Levy in 1977 (J Natl Cancer Inst. 1977 Apr;58(4):875-80.).
- First wearable heart rate monitor for athletes introduced in 1981 (http://www.polar.com/usen/about_polar/news/polar_RS800)
- Biomarkers can be defined as:
  - Diagnostic
  - Prognostic
  - Predictive
  - Pharmacodynamic
- Biomarker characteristic:
  - Can be objectively measured
  - Predicts clinically meaningful endpoints
  - Associated with known disease mechanisms and pathology
  - Predicts response to treatment
  - Associated with biologically relevant response to treatment



Clinical Pharmacology & Therapeutics
Volume 69, Issue 3, pages 89-95, 18 MAR 2001 DOI: 10.1067/mcp.2001.113989

The Rapid Growth of Technology is Reshaping Health Care and Research

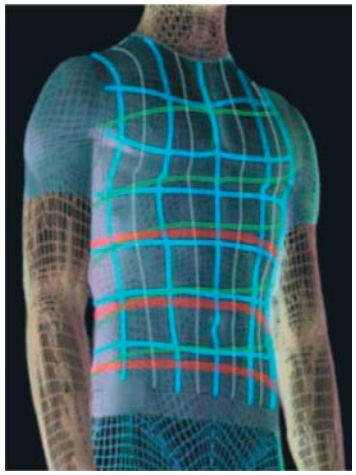
Optics

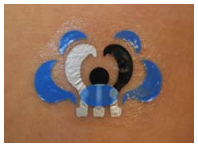
Microelectronics

Materials

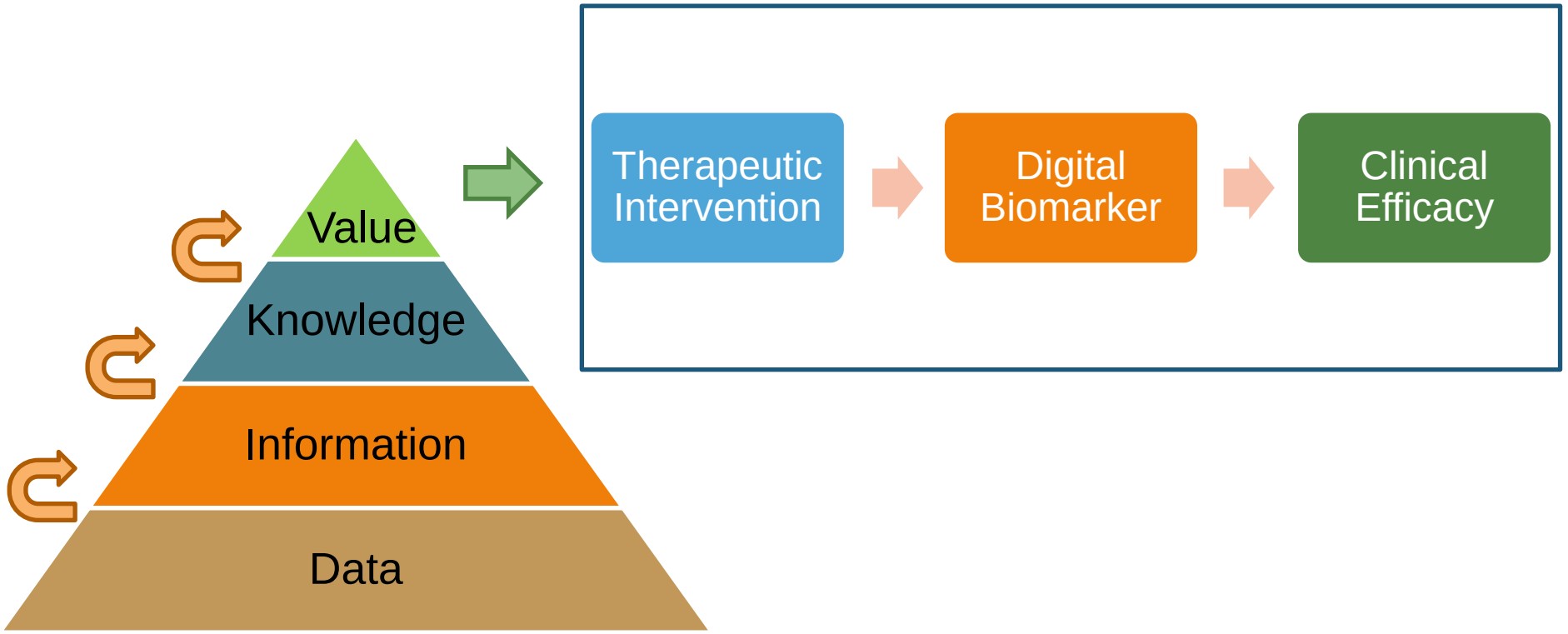
Computing

Miniaturization





The Promises and Challenges of Big Data: Can DB Deliver Value for Clinical Trials?



Adapted from Sungmee Park et al. Chapter 1; Wearable Sensors, 1st Ed. Fundamentals, Implementation and Applications; Editor(s) : Sazonov & Neuman. Release Date: 03 Sep 2014

Huntington's Disease: A Rare, Autosomal Dominant Neurodegenerative Disorder with High Unmet Need

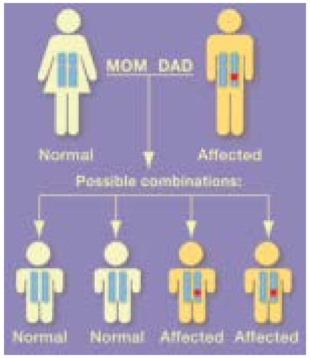
- Caused by a **≥36 CAG repeat** expansion in the huntingtin gene.
- Estimated prevalence in the Western countries is **7-10/100,000**
- HD **usually manifests between age 30 - 44 years**.
- Typical triad of clinical manifestations:
  - **Motor**
  - **Behavior**
  - **Cognition**
- **Diagnosis**: clinical presentation, confirmed by genetic testing (+family history).
- Median survival time: 15-18 years (range: 5 to >25 years).
- **Tetrabenazine is the only approved HD drug:**
  - **Only for chorea**
  - **Black box warning for depression and suicidality**
- **Off-label use of psychotropic medications approved for other conditions**


THE
MEDICAL AND SURGICAL REPORTER.
No. 789.] PHILADELPHIA, APRIL 13, 1872. [Vol. XXVI.—No. 15.
ORIGINAL DEPARTMENT.
Communications.
ON CHOREA.
By George Huntington, M. D.,
Of Pomeroy, Ohio.

Chorea is essentially a disease of the nervous system. The name "chorea" is given to the disease on account of the dancing propensities of those who are affected by it, and it is a very appropriate designation. The disease, as it is commonly seen, is by no means a dangerous or serious affection, however distressing it may be to the one suffering from it, or to his friends. Its most marked and char-

The upper extremities may be the first affected, or both simultaneously. All the voluntary muscles are liable to be affected, those of the face rarely being exempted.

If the patient attempt to protrude the tongue it is accomplished with a great deal of difficulty and uncertainty. The hands are kept rolling—first the palms upward, and then the backs. The shoulders are shrugged, and the feet and legs kept in perpetual motion; the toes are turned in, and then everted; one foot is thrown across the other, and then suddenly withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions gone through with, that a complete description of



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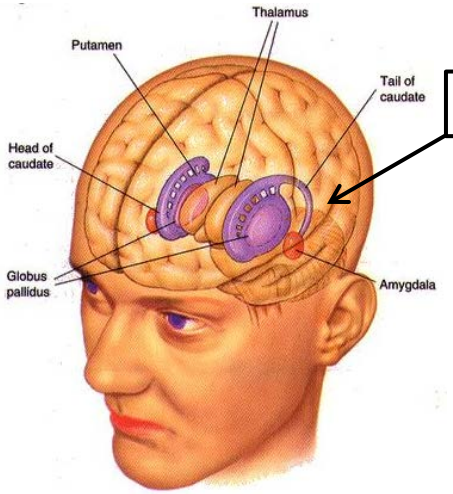
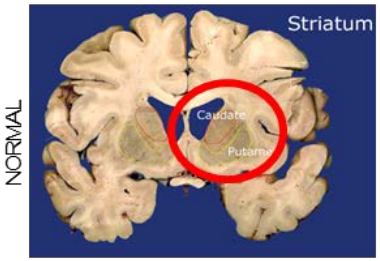
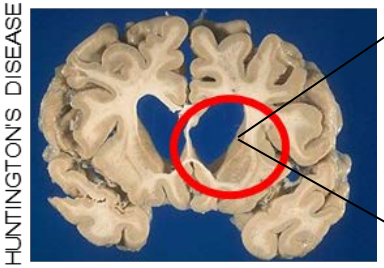
HD is Characterized by Progressive Corticostriatal Pathology

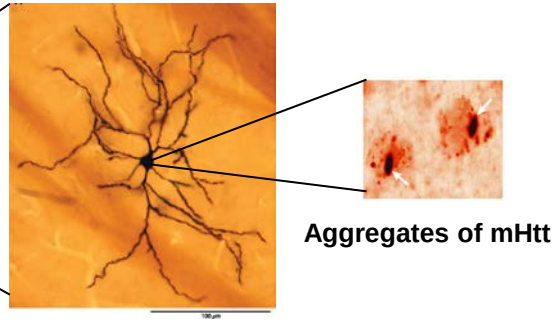


Striatum (purple)





Medium Spiny Neuron



Aggregates of mHtt

Neuropathological hallmarks of HD:

- accumulation of aggregated mutated huntingtin (mHtt)
- progressive loss of medium spiny neurons (MSNs) in the striatum

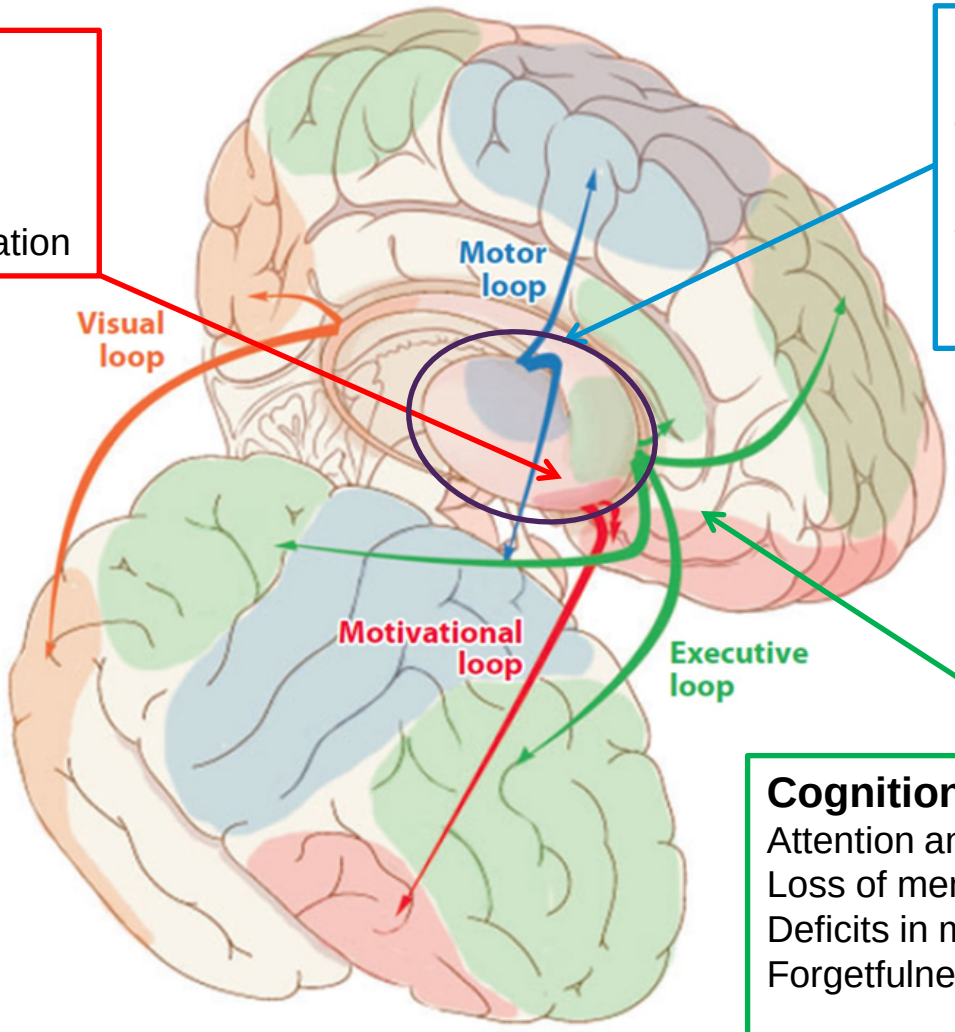
Pathophysiology:

MSNs dysfunction/loss → corticostriatal dysfunction → HD cognitive, behavioral and motor manifestations

Corticostriatal Connectivity Impairment Leads to the Major Clinical Manifestations of HD

Behavioral Control
Lack of motivation
Impulsivity
Inflexibility
Emotional Dysregulation

Motor Control
Chorea
Twisting and writhing motions
Jerks
Staggering, swaying, disjointed gait



Cognition
Attention and concentration problems
Loss of mental flexibility
Deficits in mental planning
Forgetfulness

Seger and Spering, Front. Syst. Neurosci., 30 August 2011

HD is a Neurodegenerative Disorder Characterized by Progressive Deficits in Motor, Behavior and Cognitive Functions

Early Stage

- Clumsiness
- Agitation
- Irritability
- Apathy
- Anxiety
- Disinhibition
- Delusions
- Hallucinations
- Abnormal eye movements
- Depression
- Attention and concentration problems
- Loss of mental flexibility
- Deficits in mental planning
- Forgetfulness

Middle Stage

- Dystonia
- Involuntary movements
- Trouble with balance and walking
- Chorea, twisting and writhing motions, jerks, staggering, swaying, disjointed gait (can seem like intoxication)
- Trouble with activities that require manual dexterity
- Slow voluntary movements, difficulty initiating movement
- Inability to control speed and force of movement
- Slow reaction time
- General weakness
- Weight loss
- Speech difficulties
- Stubbornness

Late Stage

- Rigidity
- Bradykinesia (difficulty initiating and continuing movements)
- Severe chorea (less common)
- Serious weight loss
- Inability to walk
- Inability to speak
- Swallowing problems, danger of choking
- Inability to care for oneself

Some disease manifestations may be due to a combination of deficits (e.g. cognitive and motor) particularly in the late stage (e.g. speech problems)

Motor
Behavior
Cognition

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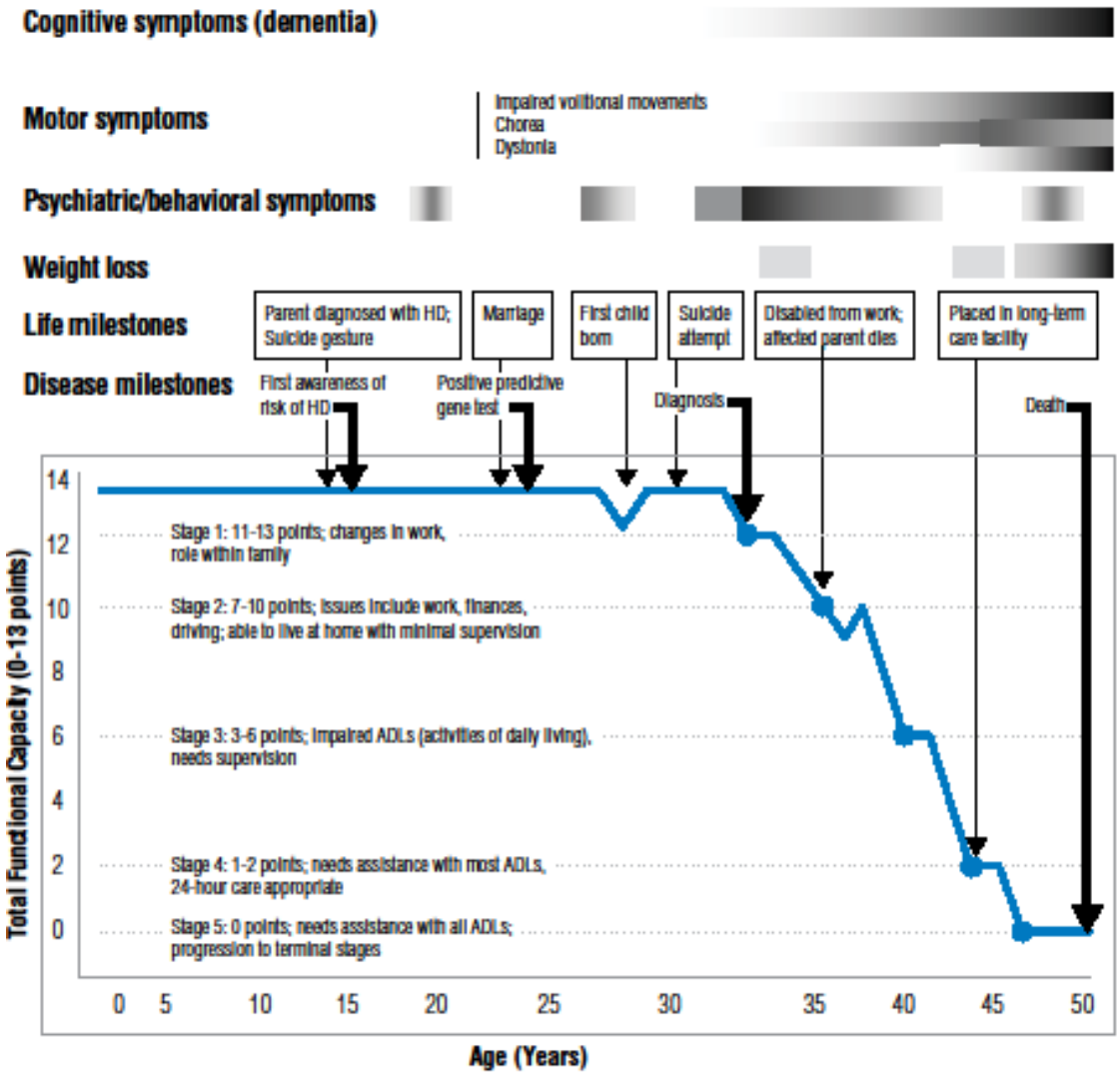
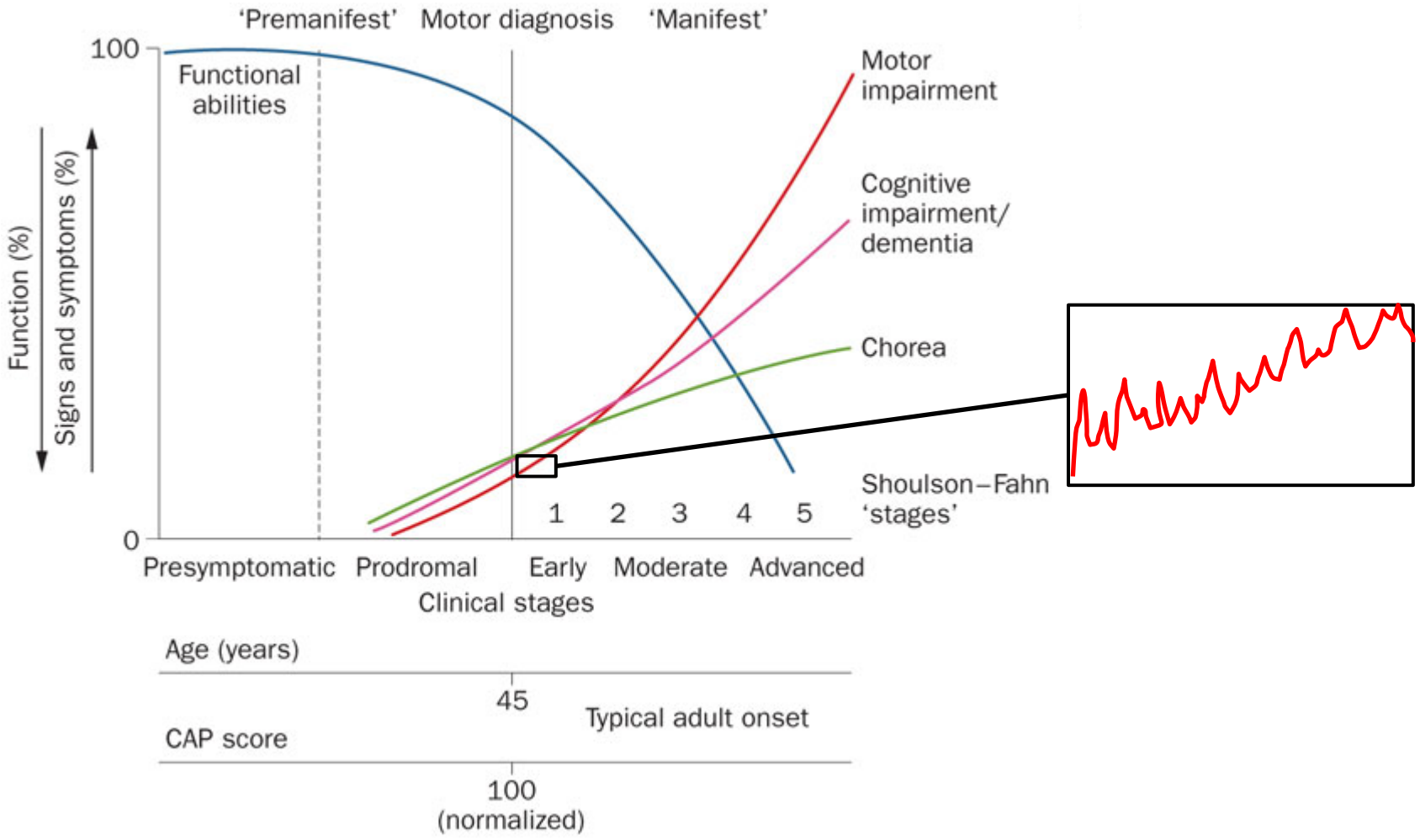
HD Leads to Progressive Disability and Loss of Independence



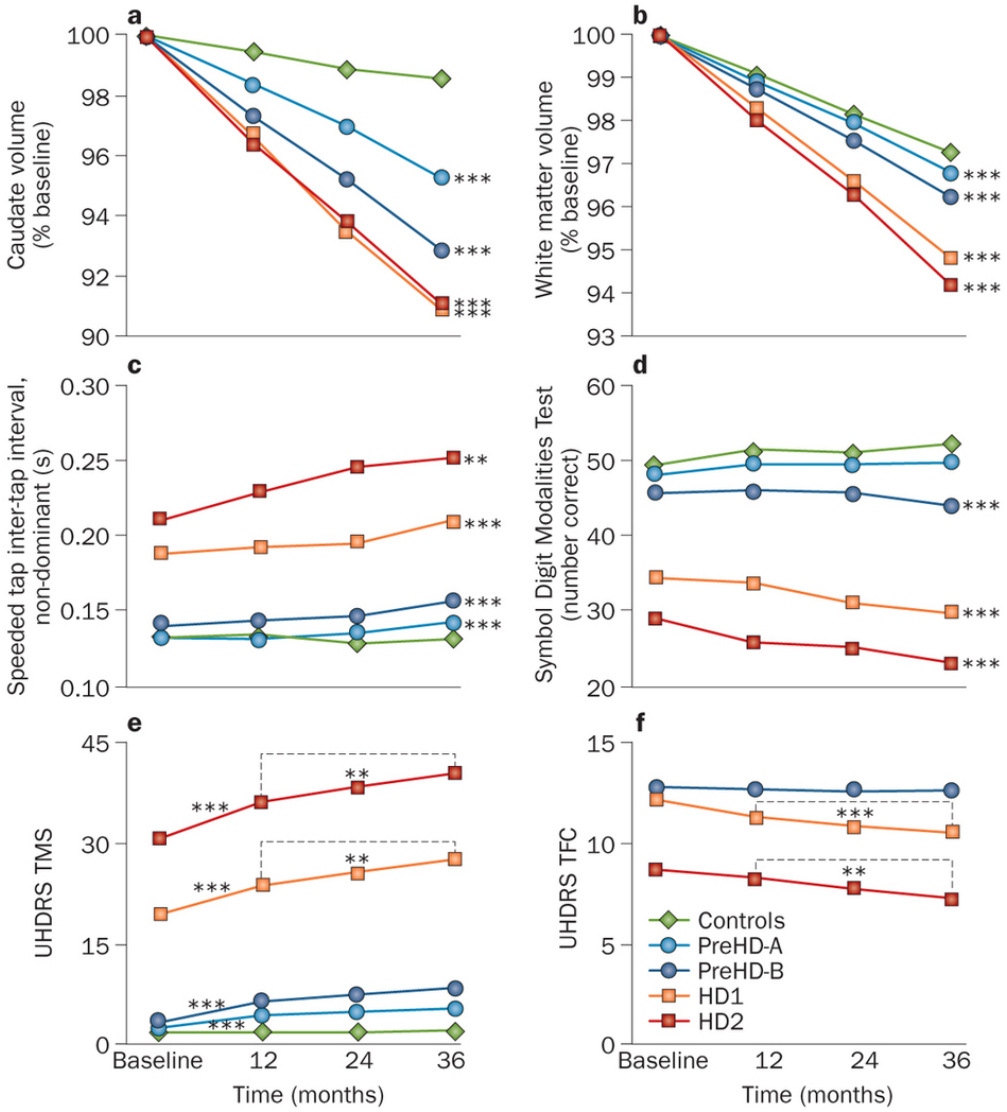
Nance et al., A physician guide to the management of Huntington's disease, 2011

Natural history of Huntington's Disease



Adapted from Ross, C. A. *et al.* (2014) Huntington disease: natural history, biomarkers and prospects for therapeutics
Nat. Rev. Neurol. doi:10.1038/nrneurol.2014.24

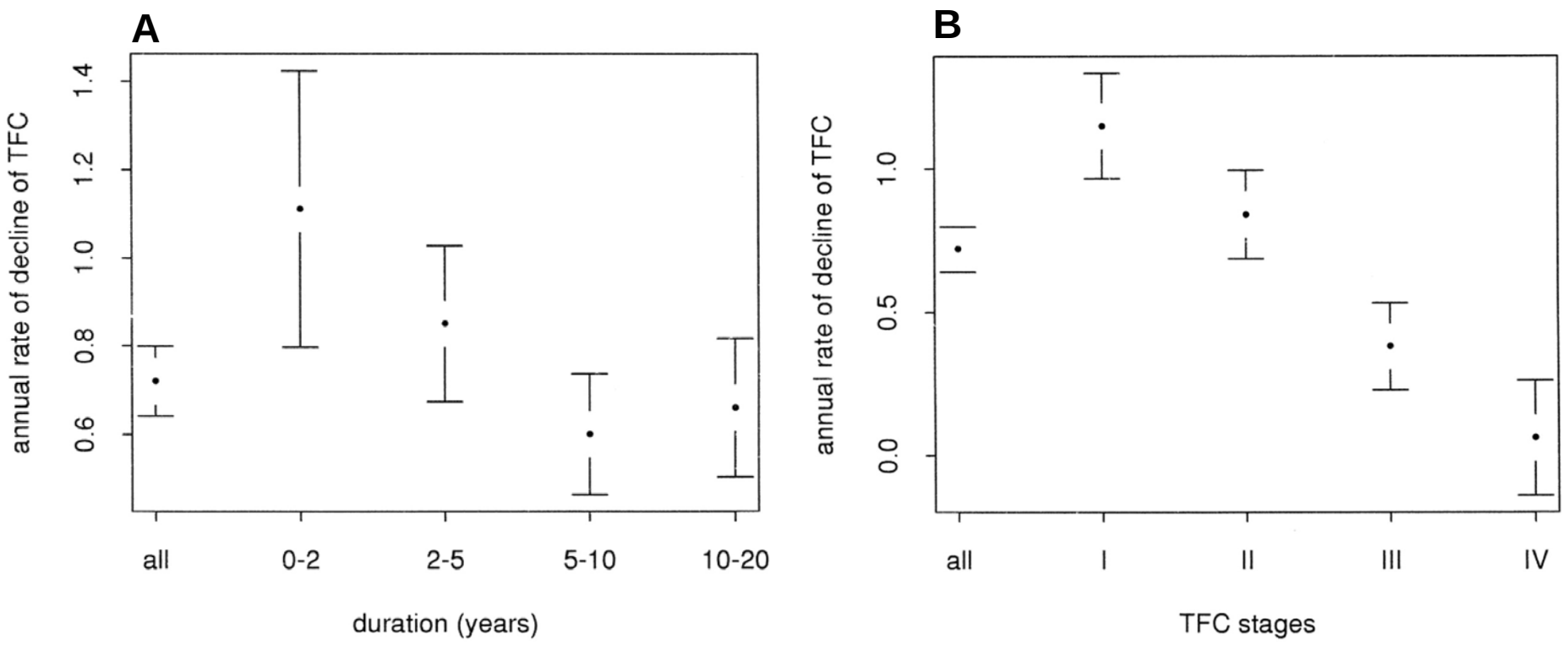
Changes in Selected Biomarkers over 36-months: TRACK-HD data



WORLDWIDE RESEARCH & DEVELOPMENT
Pharmacokinetics, Dynamics & Metabolism – NCE

The Lancet Neurology, **12(7)**, Tabrizi, S. J. *et al.*, Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data, 637–649 © (2013),

Rate of Functional Decline in Huntington's Disease



A. The annual rates of decline of total functional capacity (TFC) and their confidence intervals for disease duration groups.

B. The annual rates of decline of total functional capacity (TFC) and their confidence intervals for different baseline TFC stages.

K. Marder et al. Neurology 2000;54:452

Case Scenario

Ms. A. is a 45 year old working woman, mother of 2 children, diagnosed with HD. She is currently enrolled in a clinical trial to test the efficacy of a novel compound.

She has been tolerating the study treatment well for the previous 6 months and feels better than before the study.

The day before the last visit one of her daughters becomes ill. Ms. A. has to stay home to take care of her and is unable to meet an important work deadline.

As a result, she experiences much worse anxiety and her choreic movements become more frequent and severe.

The following day she goes to the clinic for her last visit. The study outcome measures scores are worse than at baseline.

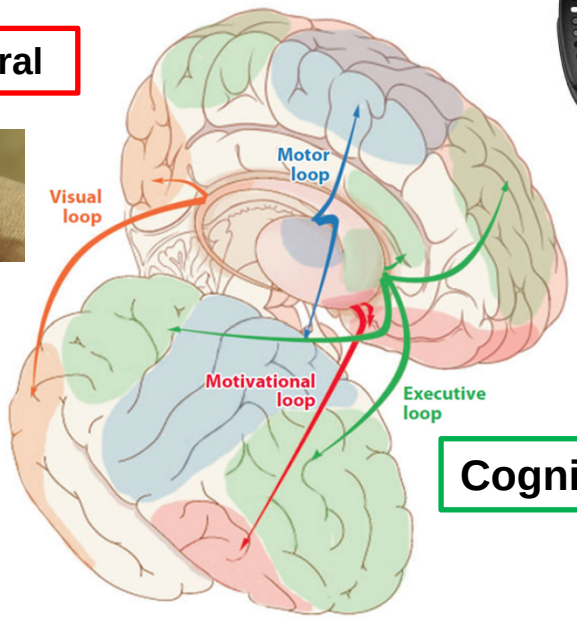
A day later, her daughter feels better and Ms. A. is reassured by her boss who allows her an additional week to get her work done.

Ms. A. feels relieved and her condition improves again.

DB Could Allow "Ecological" Monitoring of All Disease Domains over Time - Importance for Clinical Trials

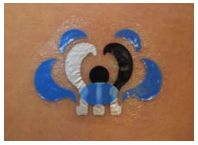
Therapeutic Intervention

Behavioral



Motor

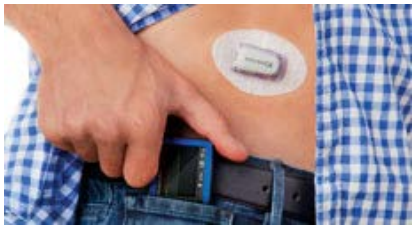
Cognition

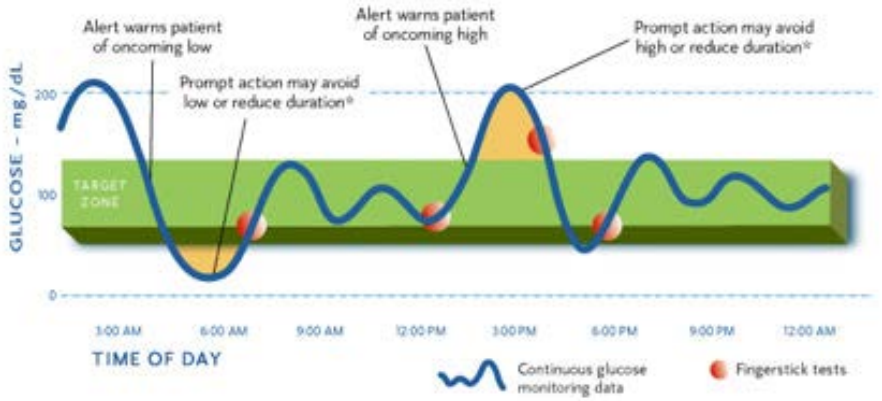


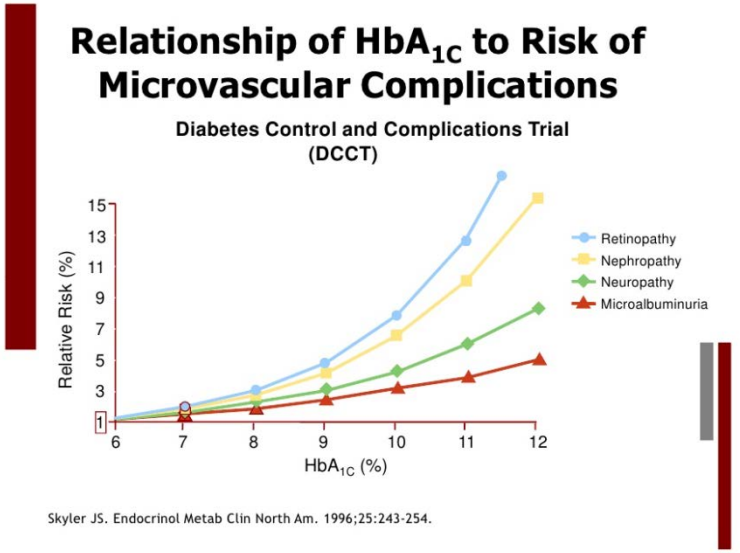
Clinical Endpoint

Modified from Clinical Pharmacology & Therapeutics
Volume 69, Issue 3, pages 89-95, 18 MAR 2001 DOI: 10.1067/mcp.2001.113989

Continuous Glucose Monitoring System as a Model for DB







Langendam M1, Luijf YM, Hooft L, Devries JH, Mudde AH, Scholten RJ. Continuous glucose monitoring systems for type 1 diabetes mellitus. Cochrane Database Syst Rev. 2012 Jan 18;1:

Promises and Challenges for the Use of Digital Biomarkers in HD Clinical Trials

Promises	Challenges
Continuous real-time data acquisition	Intrusiveness
Higher ecological validity	Compliance
Increased sensitivity	Higher background noise
Increased reliability and objectivity	Need for frequent calibration
Multi-domain measurements	Validation
Complex datasets	Complex analysis

Validation of DB in Natural History Studies and Clinical Trials – A Shared Effort

Thank you