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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The word biomarker was first used by Karpetsky, Humphrey and Levy in 1977 (J Natl Cancer Inst. 1977 Apr;58(4):875-80.).


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
The Rapid Growth of Technology is Reshaping Health Care and Research

- Microelectronics
- Optics
- Materials
- Computing
- Miniaturization

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Pfizer
WORLDWIDE RESEARCH & DEVELOPMENT
Pharmacokinetics, Dynamics & Metabolism – NCE
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 \textbf{≥36 CAG repeat} expansion in the huntingtin gene.
- Estimated prevalence in the Western countries is \textbf{7-10/100,000}.
- HD \textbf{usually manifests between age 30 - 44 years}.
- Typical triad of clinical manifestations:
  - Motor
  - Behavior
  - Cognition
- \textbf{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
HD is Characterized by Progressive Corticostriatal Pathology

**Neuropathological hallmarks of HD:**
- accumulation of aggregated mutated huntingtin (mHtt)
- progressive loss of medium spiny neurons (MSNs) in the striatum

**Pathophysiology:**
MSNs dysfunction/loss $\rightarrow$ corticostriatal dysfunction $\rightarrow$ 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

<table>
<thead>
<tr>
<th>Early Stage</th>
<th>Middle Stage</th>
<th>Late Stage</th>
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<tbody>
<tr>
<td>• Clumsiness</td>
<td>• Dystonia</td>
<td>• Rigidity</td>
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<tr>
<td>• Agitation</td>
<td>• Involuntary movements</td>
<td>• Bradykinesia (difficulty initiating and continuing movements)</td>
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<tr>
<td>• Irritability</td>
<td>• Trouble with balance and walking</td>
<td>• Severe chorea (less common)</td>
</tr>
<tr>
<td>• Apathy</td>
<td>• Chorea, twisting and writhing motions, jerks, staggering, swaying, disjointed gait (can seem like intoxication)</td>
<td>• Serious weight loss</td>
</tr>
<tr>
<td>• Anxiety</td>
<td>• Trouble with activities that require manual dexterity</td>
<td>• Inability to walk</td>
</tr>
<tr>
<td>• Disinhibition</td>
<td>• Slow voluntary movements, difficulty initiating movement</td>
<td>• Inability to speak</td>
</tr>
<tr>
<td>• Delusions</td>
<td>• Inability to control speed and force of movement</td>
<td>• Swallowing problems, danger of choking</td>
</tr>
<tr>
<td>• Hallucinations</td>
<td>• Slow reaction time</td>
<td>• Inability to care for oneself</td>
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<tr>
<td>• Abnormal eye movements</td>
<td>• General weakness</td>
<td></td>
</tr>
<tr>
<td>• Depression</td>
<td>• Weight loss</td>
<td></td>
</tr>
<tr>
<td>• Attention and concentration problems</td>
<td>• Speech difficulties</td>
<td></td>
</tr>
<tr>
<td>• Loss of mental flexibility</td>
<td>• Forgetfulness</td>
<td></td>
</tr>
<tr>
<td>• Deficits in mental planning</td>
<td>• Stupor</td>
<td></td>
</tr>
<tr>
<td>• Forgetfulness</td>
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</tbody>
</table>

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)
HD Leads to Progressive Disability and Loss of Independence

- Cognitive symptoms (dementia)
- Motor symptoms: Chorea, Dystonia
- Psychiatric/behavioral symptoms
- Weight loss
- Life milestones
- Disease milestones

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

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

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
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

Modified from Clinical Pharmacology & Therapeutics
Continuous Glucose Monitoring System as a Model for DB

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

<table>
<thead>
<tr>
<th>Promises</th>
<th>Challenges</th>
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<tbody>
<tr>
<td>Continuous real-time data acquisition</td>
<td>Intrusiveness</td>
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<tr>
<td>Higher ecological validity</td>
<td>Compliance</td>
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<tr>
<td>Increased sensitivity</td>
<td>Higher background noise</td>
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<tr>
<td>Increased reliability and objectivity</td>
<td>Need for frequent calibration</td>
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<tr>
<td>Multi-domain measurements</td>
<td>Validation</td>
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<tr>
<td>Complex datasets</td>
<td>Complex analysis</td>
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Validation of DB in Natural History Studies and Clinical Trials – A Shared Effort
Thank you