Biomarkers in Parkinson's Disease

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PD Biomarkers

- **Key definitions**
- **What is a biomarker?**
- **Why are PD biomarkers important?**
- **How are PD biomarkers identified?**
  - What are some challenges in PD biomarker development?
  - What are some exciting developments in the arena of PD biomarkers?

Key Definitions

- **Parkinsonism: presence of characteristic pattern of stiffness, slowness of movement, and tremor**
- **A neurodegenerative disorder: one in which there is degeneration (loss) of neurons (brain cells)**
- **In Parkinson's disease, there is degeneration of neurons that make the chemical dopamine, among other groups of neurons**

What is a biomarker?

- **Biomarker = biological marker**
  - A measure of a biologic state
  - "A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention"

Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 2001;69:89-95.

Why are PD biomarkers important?

- **Diagnosis**
- **Prognostication**
- **Prediction**

Why are PD biomarkers important?

- **Accurate diagnosis**
  - Overall, diagnosis is very accurate when made by a Movement Disorders specialist
  - Improving over time
  - Diagnostic accuracy still low among some groups of patients
  - Time helps improve diagnostic certainty
    - time=anxiety, frustration, uncertainty
  - Diagnostic certainty of 100% currently only possible post-mortem

Why are PD biomarkers important?

- **Accurate diagnosis**
  - Diagnosing a degenerative parkinsonian syndrome is relatively straightforward
  - Determining which degenerative parkinsonian syndrome is more difficulty
  - Parkinson's disease=most common degenerative parkinsonian syndrome
  - Others: Multiple System Atrophy, Progressive Supranuclear palsy
  - Diagnostic accuracy improves with time and medication trials
  - Early on difficult to distinguish between
  - Big challenge for both patients and in research studies

Why are PD biomarkers important?

- **"Prognostication":**
  - "what is going to happen?"
  - "what will my disease be like in 10 years?"
  - "how long can I keep working?"

- **Current tools available are limited**

- **Some clinical features predict certain outcomes in research studies but may not translate to the individual patient**

- **Clinical trials: if we have a measure that predicts outcomes at 5 years (a "surrogate"), clinical trials can be much shorter**

Why are PD biomarkers important?

- **Markers of PD progression**
  - Parkinson's Disease was described in 1817
  - Significant advances in its treatment have occurred
  - Interventions to slow the disease down, stop it from progressing, and reversing neuronal injury are lacking
  - Are we measuring the disease right?

Why are PD biomarkers important?

- **Markers of PD progression**
  - Is a medication slowing/stopping the disease from progressing?
  - Which patients will respond to which therapies?
  - Which patients are most susceptible to side effects?
  - Which patients will develop specific motor outcomes (falling) or cognitive or psychiatric outcomes?

Why are PD biomarkers important?

- **What is an example of a commonly used surrogate measure?**
  - Blood pressure as surrogate of cardiovascular risk
  - LDL as a surrogate of cardiovascular risk

Why are PD biomarkers important?

- **Prediction**
  - Can we identify individuals at risk for PD and stop it manifesting?
  - “Prodromal” PD (preclinical, premanifest)
  - Can we prevent neurodegeneration?

How are biomarkers identified?

- **Ideal biomarker, logistically:**
  - Safe to obtain
  - Easy to measure
  - Cost efficient

- **Ideal biomarker scientifically:**
  - Reliable and valid
  - Consistent across different groups
  - When used for diagnosis: sensitive and specific
  - When used for prediction
    - Measure of clinically meaningful outcome
    - Changes predictably with intervention

How are biomarkers identified?

- **What are the sources of PD biomarkers?**
  - Biofluids:
    - Blood
    - Cerebrospinal fluid
    - Urine
    - Saliva
  - Body tissues
    - Skin
    - Submandibular Gland
    - Intestines

How are biomarkers identified?

- **What are the sources of PD biomarkers?**
  - Imaging
  - Genetics
  - Objective motor measurements

How are biomarkers identified?

- **Clinical features: Certain signs and symptoms are highly suggestive of PD**
  - Loss of sense of smell
    - May be helpful as a diagnostic marker, in combination with other more specific measures
    - May be helpful as a marker predictive of future PD risk, in combination with other more specific measures
  - REM sleep behavior disorder
    - Predictive of future PD risk
    - Combination with other markers needed

How are biomarkers identified?

- **What are the sources of PD biomarkers?**
  - Most PD centers collecting different sources of PD biomarkers
  - "Biobanks" of specimens are being established
    - Parkinsons Disease Biomarker Program at NIH
    - Large cooperative studies:
      - Parkinson Progression Marker Initiative (PPMI, sponsored by Michael J Fox Foundation)
      - Biofind (sponsored by Michael J Fox Foundation)

Parkinson's Progression Markers Initiative (PPMI)

- **PPMI is a landmark clinical study to better understand the progression of Parkinson's disease.**

- **The goal of PPMI is to identify indicators of PD progression to ultimately:**
  - Earlier diagnosis to one day treat motor symptoms sooner or even prevent their onset
  - Better disease tracking to help patients and clinicians better manage a treatment regimen
  - More efficient testing of new therapies to improve the odds of success and reduce costs and timelines to get more treatments to market

Parkinson's Progression Markers Initiative (PPMI)

- **30 sites worldwide**
- **Launched in 2010**
  - 423 newly diagnosed PD patients
  - 196 control volunteers
  - 500 prodromal (“at risk)
- **Robust infrastructure**
- **Biobank**
- **Flow of information**
- **Industry partners**

www.ppmi-info.org

How are biomarkers identified?

- **How do researchers know where to look and what to look for?**
  - "Candidate" biomarkers: measure proteins or other substances known to be affected in PD
  - "Unbiased" approach: "fishing" but then interpreting and following up on results systematically

Candidate Biomarker Example: α-Synuclein

("alpha-sinooclein")

α-Synuclein: a candidate PD biomarker

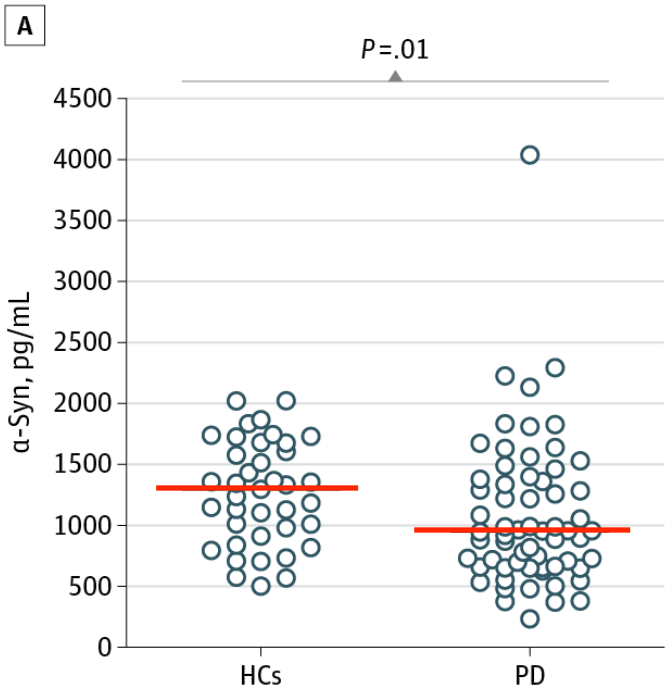
- **What is α-Synuclein?**
  - A protein found in the brain and throughout the body
  - Precise function unknown. Involved in vesicle trafficking (movement of substances)
  - Aggregates and accumulates in PD ("clumps up")
  - Component of "Lewy bodies", the structure found in neurons of individuals with PD
  - Thought to be not only a pathologic marker of the disease but also a contributor to its cause
  - Intensive research on α-Synuclein:
    - What is it? what does it do?
    - How can we stop clumping, without affecting normal function?
    - How can we measure it?

α-Synuclein: a candidate PD biomarker

- **α-Synuclein as a PD biomarker**
  - α-Synuclein found throughout the body
  - Very high levels in red blood cells
  - “normal” vs. “abnormal”: abnormal α-Synuclein has additional molecules added to it
  - Intensive efforts to measure “abnormal” α-Synuclein are underway

α-Synuclein: a candidate PD biomarker

- **α-Synuclein as a PD biomarker**
  - In the cerebrospinal fluid, levels found to be lower in PD compared to comparator group without PD (lower=worse)

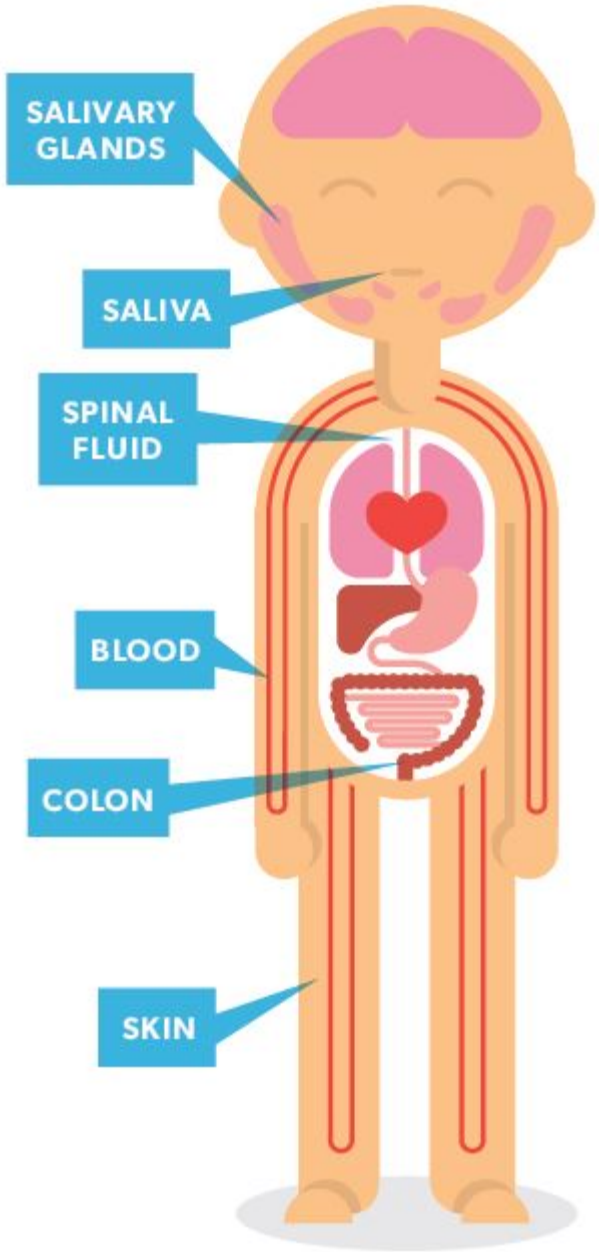


Kang et al. JAMA Neurology 2013.

α-Synuclein: a candidate PD biomarker

- **α-Synuclein as a PD biomarker**
  - Being examined in various body tissues and fluids

  In the Systemic Synuclein Sampling Study (S4), biofluids and tissues are being collected from each participant to compare α-Synuclein within a participant and across participants



α-Synuclein: a candidate PD biomarker

- **α-Synuclein as a PD biomarker**
  - Measuring the abnormal forms
  - Measuring it in individuals at risk for PD
  - Imaging it
  - CSF α-Synuclein already being examined in clinical trials of agents aiming to reduce α-Synuclein

“Unbiased” Approach in Biofluids

Perelman School of Medicine
University of Pennsylvania

How are biomarkers identified?

- **(Figure removed for copyright reasons)**

Chen-Plotkin A. Neuron. 2014

How are biomarkers identified?

- **(Figure removed for copyright reasons)**

Rifai et al. Nature Biotechnology. 2006

How are biomarkers identified?

- **Serum ApoA1**
  - Identified by screening for ~1000 proteins in samples of individuals with PD and a comparison group without PD
  - Replicated (results reproduced) in an independent cohort
  - Found to be associated with age of PD onset
  - Associated with dopamine transporter level on imaging
  - Biologically plausible=“makes sense”
    - Component of HDL (“good cholesterol”)

Genetics

Genotype as a PD biomarker

- **Gene sequence as a PD biomarker**
  - Specific genetic mutations “cause” disease
  - The gene “sequence” (variations of “normal” genetic code) may predispose or protect from a disease
  - “Genetic risk score”: a combination of 30 gene sequences more often present in individuals with PD compared to those without

Nalls A et al. Lancet neurology 2015.

Genotype as a PD biomarker

- **Gene expression as a PD biomarker**
  - Gene expression levels in the blood can be measured (RNA)
  - Gene expression of several genes (gene "panel") found to be different in individuals with PD compared to controls (blood, brain)

Genotype as a PD biomarker

- **Gene mutations to identify "at-risk" group**
  - Most common genetic mutations have a "penetrance" of ~30%
  - Mutation carriers very common among certain geographic and/or ethnic groups
  - Can we use biomarkers to predict who among the mutation carriers are at highest risk of developing PD?

Imaging

Imaging

- PET
- SPECT
- MRI

Metabolism (PET Scan, glucose use)

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Compared to those without PD, participants with PD had higher metabolism in red areas and lower metabolism in blue areas

Peng & Eidelberg 2014. Neurosci Bull

Dopamine Transporter Scan (SPECT)

- **(Figure removed for copyright reasons)**

MRI

- **Routine MRI done in clinic is not helpful**
- **MRI machines and/or sequences used to develop biomarkers are research-based at this time**

MRI

- **(Figure removed for copyright reasons)**

Neuron=brain cell

Midbrain: location of dopamine neurons affected in Parkinson's Disease.

Specific location: substantia nigra

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Person without Parkinson's disease: bright (whitish) area seen at green arrows

Schwartz et al. 2014 Plos One.

- **(Figure removed for copyright reasons)**

Person with Parkinson's disease: bright (whitish) area not seen

Schwartz et al. 2014 Plos One.

Imaging as a PD biomarker

- Lots of potential as diagnostic marker of neurodegenerative parkinsonism
- Limited use distinguishing among degenerative parkinsonism
- Potential to help identify at-risk individuals

Summary and Conclusions

PD Biomarkers

- Great need
- Infrastructure built (biobanks)
- Standards increasingly adopted
- Many many potential sources: great opportunity!
- Much interest from scientific community, industry, research participants

Questions