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”

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 difficult
  - 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)
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-synuclein”)
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)

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.

www.michaeljfox.org/
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
How are biomarkers identified?

- (Figure removed for copyright reasons)
How are biomarkers identified?

- (Figure removed for copyright reasons)
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
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

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)

- (Figure removed for copyright reasons)

Compared to those without PD, participants with PD had higher metabolism in red areas and lower metabolism in blue areas.
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
Person without Parkinson’s disease: bright (whitish) area seen at green arrows

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

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