Questions and Answers on Biomarkers:

A Crucial Missing Link in the Development of Next-generation Parkinson's Treatments

The search for biomarkers of PD may seem far-removed from patients' everyday lives. But in fact the lack of biomarkers not only directly affects Parkinson's patients' treatment options today — it is also a major impediment to the development of better treatment options for the future.

What is a biomarker?

A *progression biomarker (*or *progression marker)* can be any objectively measurable characteristic that changes over time in a way that can be correlated to the progression of disease. This type of marker is a critically needed tool for successful clinical trials, particularly trials of potential disease-modifying treatments. A *diagnostic biomarker (*or *diagnostic* or *risk marker)* can be any objectively measurable physical characteristic associated with the presence of disease. Here are two examples from other health conditions:

- White blood cell count is objectively measurable and a progression marker of leukemia. A count that rises to abnormal levels indicates that the condition is getting worse, while a count that returns to normal indicates improvement.
- Cholesterol is objectively measurable and, when high, acts as a risk marker of potential heart disease.

Progression markers could help transform the development of next-generation PD treatments. Imagine that researchers conducting Parkinson's clinical trials could run a straightforward, standardized laboratory test to understand how or if a possible new treatment were successfully slowing the disease process, helping to speed effective therapies toward pharmacy shelves. This is the kind of acceleration that a progression marker could make possible.

Diagnostic markers could help transform diagnosis and treatment for people living with PD today. Imagine that your doctor could simply draw some blood and instantly confirm a PD diagnosis, know how far the disease had already progressed, and make an informed prediction about the rate and nature of your disease progression going forward. While it may not ultimately come in the form of a blood test, this is the kind of simplicity and objectivity that a diagnostic marker for PD could make possible.

What are the biomarkers of Parkinson's disease?

Unfortunately, no practical, definitive biomarkers of Parkinson's have yet been identified. There are a few markers used in advanced neuroimaging techniques (approved for clinical use in Europe but not yet in the United States) that can help clinicians diagnose PD in its earliest stages. But no widely and easily applicable, affordable diagnostic markers, and no progression markers whatsoever, have been conclusively validated.

What are some specific ways that Parkinson's patients are affected by the lack of biomarkers?

- There is no way to identify people at risk for PD or to establish strategies for PD prevention. It is an often-stated reality that, by the time the first symptoms of Parkinson's become evident, as many as 60-70 percent of an individual's dopamine neurons may already have died. A diagnostic marker would allow us to identify people at risk for PD earlier.

- Diagnosis is subjective, based on observing symptoms and rating them on a clinical scale. This translates to a high rate of misdiagnosis, especially among general practice physicians and neurologists who do not specialize in movement disorders.

- PD clinical trials are frequently and frustratingly inconclusive. Why?
  - With no diagnostic marker, an estimated 10 percent of PD trial enrollees unwittingly do not have Parkinson's disease, confounding results.
  - With no progression marker to track the disease, there is no way to objectively measure treatment effects.
  These factors make PD trials highly risky for drugmakers and prolong the wait for next-generation PD therapies.

I thought a biomarker was basically a gene — and don't we know the genes that play a role in PD?

No — in fact, a biomarker is not the same thing as a gene or genetic mutation. Remember, it's possible to have one or more genetic irregularities linked to PD but never get the disease. Genetic research leads scientists to certain biomarker candidates, but many other physical and cellular characteristics are valid as possible biomarkers if they are measurable and provide an accurate window into disease presence or progression. Here are the major avenues of pursuit today:

- Imaging-based markers (such as PET/SPECT) can provide indirect measures of dopamine neuron function, but do not have sufficient resolution to measure actual cell numbers. More sensitive neuroimaging markers for PD, capable of measuring dopamine function in the brain, are also under development. These include DATscan (already approved for clinical use in Europe) and other ways to measure dopamine activity. These dopamine-based markers may provide a way to monitor disease in its earliest stages. MRI and ultrasound markers are also in development.

- Biological markers in blood, urine, cerebral spinal fluid or tissue biopsies can serve as 'signatures' of the disease. These can include genetic, protein or other chemical and molecular signposts. Leading biological marker candidates include measures of antioxidants such as urate, or measures of proteins produced by PD-implicated genes such as alpha-synuclein and DJ-1.

- Clinical measures – such as tests of motor ability, or the presence of disease-associated symptoms such as loss of sense of smell, sleep disorders, constipation, or early speech problems – can be good markers, though not necessarily Parkinson's specific, may still provide a means for detecting early stages of PD or tracking disease progression. The downside is that clinical measures are subjective,

variable over time, and very sensitive to symptom-masking effects of drugs, limiting their utility to measure disease-modifying effects sought in neuroprotective trials.

Overall, it is likely that we need to develop a combination of markers (imaging, biologics and clinical) and measure them in the same individuals over time to identify useful biomarkers for PD.

In the absence of a PD biomarker, how have there been clinical trials of disease-modifying treatments at all?

Most trials use some form of clinical measure, such as the Unified Parkinson's Disease Rating Scale (UPDRS), to determine whether a treatment is working. However, given the subjectivity and variance in clinical measures, and because symptoms of PD are affected by the medications and therapies patients have already used, it is difficult or impossible to measure disease-modifying effects in this way. This may have contributed to a history of inconclusive results from trials of disease-modifying treatments in particular.

Do other diseases have biomarkers?

Some do, but most don't, and the lack of biomarkers is a particular problem for neurodegenerative diseases (such as Alzheimer's and ALS in addition to PD). You may have heard of a study called the Alzheimer's Disease Neuroimaging Initiative (ADNI). Launched in 2004, ADNI has made important strides toward discovering biomarkers of Alzheimer's disease and has reinvigorated research focused on disease-modifying treatments for AD. We anticipate similar outcomes for Parkinson's from PPMI and related biomarkers studies.

To learn more about biomarkers clinical trials in Parkinson's disease visit www.foxtrialfinder.org