QUESTIONS AND ANSWERS ON BIOMARKERS:

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

THE MICHAEL J. FOX FOUNDATION

QUESTIONS AND ANSWERS ON BIOMARKERS:

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

The search for biomarkers of Parkinson's disease (PD) may seem far-removed from patients' everyday lives. But the absence of these important tools not only affects Parkinson's care options today — it is also a major impediment to the development of better treatments for the future.

What is a biomarker?

A **progression biomarker** (or progression marker) is an 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 clinical trials, particularly trials of potential disease-modifying treatments.

A **diagnostic biomarker** (or diagnostic or risk marker) is an objectively measurable physical characteristic associated with the presence of disease.

Examples from other health conditions are:

» White blood cell count is a progression marker of leukemia. A count that rises to abnormal levels indicates that the condition is getting worse, while a count that returns toward normal indicates improvement.

» Cholesterol level, 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 could run a straightforward, standardized laboratory test to understand how or if a new treatment were successfully slowing the disease process. A progression marker could be that yardstick to measure, helping to speed effective therapies toward pharmacy shelves.

Diagnostic markers could help transform diagnosis and treatment for people living with PD today. With such a tool your doctor could draw some blood or order a brain scan and confirm a PD diagnosis.

Diagnostic and progression markers may also tell how far the disease had already progressed and help make an informed prediction about the rate and nature of progression.

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 (e.g., DaTscan) that can help researchers 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 often stated 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 have degenerated. A diagnostic marker would allow us to identify people at risk for PD — and ultimately intervene — earlier.

» Diagnosis is subjective, based on observing symptoms and rating them on a clinical scale. This translates to a high rate of misdiagnosis and thereby non-optimized care.

PD clinical trials are frequently and frustratingly inconclusive.

» With no diagnostic marker, some PD trial enrollees may not have Parkinson's disease pathology, 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 drug makers 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 — a biomarker is not the same thing as a gene or genetic mutation. It's possible to have one or more genetic irregularities linked to PD but never get the disease. We do not have a firm grasp of the penetrance or risk associated with these mutations.

Genetic research leads scientists to biomarker candidates. Other physical and cellular characteristics could be biomarkers if we validate that they are measurable and provide an accurate window into disease presence or progression. Here are the major avenues of pursuit today:

» Imaging markers 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 are under development.

» Biological markers in blood, urine, cerebral spinal fluid or tissue biopsies may serve as 'signatures' of the disease. These can antioxidants such as urate or measures of proteins produced by PD-implicated genes such as alpha-synuclein and DJ-1.

» Clinical measures — tests of motor ability or the presence of symptoms including loss of sense of smell, sleep disorders, constipation or early speech problems — though not Parkinson's specific, may 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.

It is likely that we need to measure a combination of markers (imaging, biologics and clinical) 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?

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 to measure disease-modifying effects in this way. This may have contributed to a history of inconclusive results from trials of disease-modifying treatments.

Do other diseases have biomarkers?

Some do, but 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 and has reinvigorated research focused on disease-modifying treatments for the disease.

What can I do to help identify a Parkinson's biomarker?

In 2010, The Michael J. Fox Foundation launched a biomarkers study modeled after ADNI. The Parkinson's Progression Markers Initiative (PPMI) is an observational clinical study to validate biomarkers and identify risk factors for PD. PPMI is following volunteers with and without PD for at least five years at 33 clinical sites around the world to better understand biologic changes over time.

The study has enrolled people with recently diagnosed Parkinson's, without Parkinson's but with smell loss or REM sleep behavior disorder, and control volunteers. PPMI is currently recruiting people with genetic mutations associated with PD. Certain mutations are more prevalent in certain populations.

If you are of Ashkenazi Jewish, North African Berber or Basque descent and either have Parkinson's or have a relative with PD, you may be eligible for the study. PPMI provides free genetic counseling and screening to all potential participants.

Visit **www.michaeljfox.org/ppmi/genetics** to learn more.

Research volunteers are needed in studies beyond PPMI. Fox Trial Finder is a clinical study matching tool that helps patients and their loved ones get involved in speeding a cure for Parkinson's disease. Volunteers who sign up for Fox Trial Finder receive a list of trials in their area and email updates about new studies that start recruiting. By matching volunteers to the clinical trials that need them, Fox Trial Finder speeds progress toward therapeutic breakthroughs, bringing better treatments to patients faster.

Visit **www.foxtrialfinder.org** to register today.