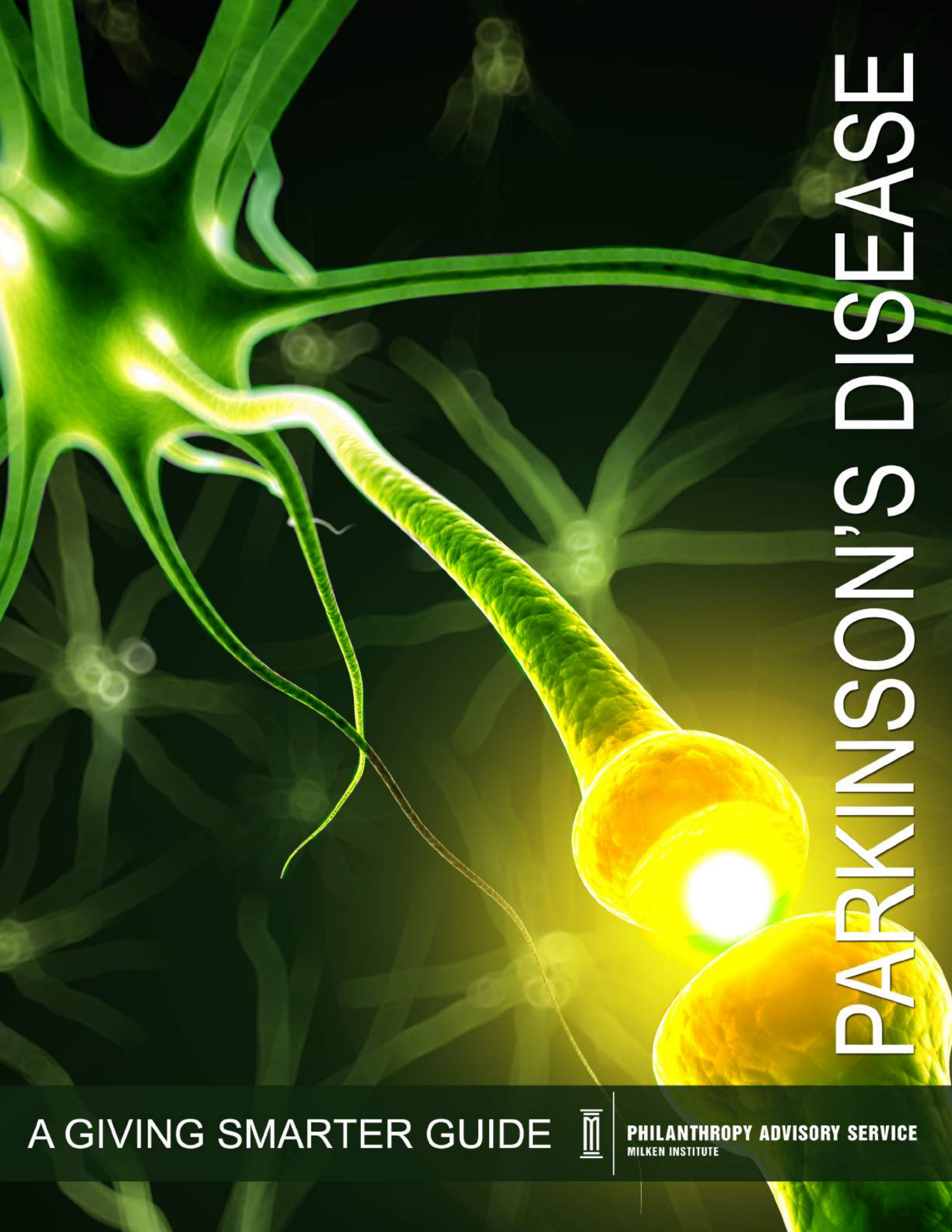

# PARKINSON'S DISEASE

A GIVING SMARTER GUIDE

PHILANTHROPY ADVISORY SERVICE
MILKEN INSTITUTE

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## CONTENTS

## EXECUTIVE SUMMARY

Parkinson's disease (PD) is a chronic, neurodegenerative movement disorder that affects the lives of more than 1 million Americans. PD slowly worsens over time, increasingly robbing patients of coordinated movement and inflicting a number non-motor symptoms ranging from cognitive impairment to gastrointestinal issues. Approximately 90 percent of PD cases occur spontaneously, while 10 percent of cases are familial. PD mainly affects the elderly, however the cause of PD is unknown. There are currently no treatments that can slow or stop the relentless progression of the disease.

As the size and proportion of the elderly population grows, so too will the societal and economic burden. The current estimated annual cost of PD is a staggering $14.4 billion, which is projected to double by 2040. This projection may be even higher if no effective treatments are found. In addition to the lack of disease-modifying therapies, there are no established biomarkers of disease. In other words, there are no objective measures to diagnose patients, track disease progression or response to treatment. Rather, physicians rely on imprecise, qualitative rating scales, ultimately hampering drug development efforts and clinical trial success. Misdiagnosis is also a serious issue due to the difficulty in distinguishing several early symptoms of PD from the natural effects of aging or other neurological disorders. It is overwhelmingly clear that progress is desperately needed to combat this disorder.

The PD field is fraught with a number of other unmet needs that hamper progress, including:

- Poor understanding of underlying PD disease biology and lack of funding to support basic research
- Poor understanding of the underlying biology of non-motor and treatment-induced symptoms
- Slow progress in biomarker discovery and the need for a more predictive translational pipeline

There is renewed interest in PD due to recent breakthroughs in the genetics of the disease and in digital health. Genetic discoveries have expanded our understanding of PD heredity and broadened insights into spontaneous disease. Moreover, key therapeutic targets have been uncovered, which are driving drug development strategy. Digital health advancements in mobile applications and wearable technology are allowing investigators to amass an unprecedented amount of patient data. These new technologies have the potential to broaden clinical trial participation and revolutionize the way PD symptoms are monitored and quantified. Capitalizing on this momentum through strategic investment in discovery science, infrastructure, and research tools are essential for continued progress.

The Milken Institute Philanthropy Advisory Service has developed this Giving Smarter Guide for Parkinson's Disease with the express purpose of empowering patients, supporters, and stakeholders to make strategic and informed decisions when directing their philanthropic investments and energy into research and development efforts. Readers will be able to use this guide to pinpoint research solutions aligned with their interests. This guide will help to answer the following questions:

- *Why should I invest in PD research?*
- *What is the current standard of care?*
- *What are the barriers preventing development of new therapeutics?*
- *What key things should I know about this disease?*
- *What is the current state of PD research efforts?*
- *How can philanthropy leverage existing infrastructure to support PD research and advance new therapies?*

## OVERVIEW

Parkinson's disease (PD) is a debilitating neurodegenerative disorder that severely affects movement and coordination. More than 1 million Americans are currently suffering from PD, and it is estimated that nearly 60,000 new cases will be diagnosed this year alone. This disorder most commonly occurs in people age 60 and older; however, those with specific inherited genetic mutations linked to PD (referred to as familial PD) can experience symptoms in their 40s or even earlier.

PD causes a variety of motor symptoms including tremors, muscle stiffness, postural instability and others. The disease also causes a range of non-motor symptoms that include, but are not limited to, cognitive impairment, mood disorders and gastrointestinal issues. There are a litany of challenges associated with identifying, understanding and treating PD. It is currently unclear what causes PD. In addition, diagnosing the disease is a challenge because definitive diagnosis requires autopsy. Finally, and most importantly, there is no cure.

While current treatments help to manage symptoms, they do not modify the disease to slow or halt its progression. With longer life expectancies and an aging population, the societal burden of PD is enormous and is only expected to increase. Consequently there is an urgent need to accelerate PD research progress to identify novel treatments that can modify the disease rather than just manage symptoms.

## SOCIETAL IMPACT OF PARKINSON'S DISEASE

### POPULATION BURDEN

PD is the second most common neurodegenerative disease, following Alzheimer's disease, and the fourteenth leading cause of death in the United States. According to the American Parkinson Disease Association, an American is diagnosed with PD every nine minutes, culminating in 5,000 new cases per month. The prevalence of PD increases with age, and thus is three to six times higher in people over the age of 65, and thirteen to sixteen times higher in people over the age of 85 compared to the general population (as depicted in Figure 1).

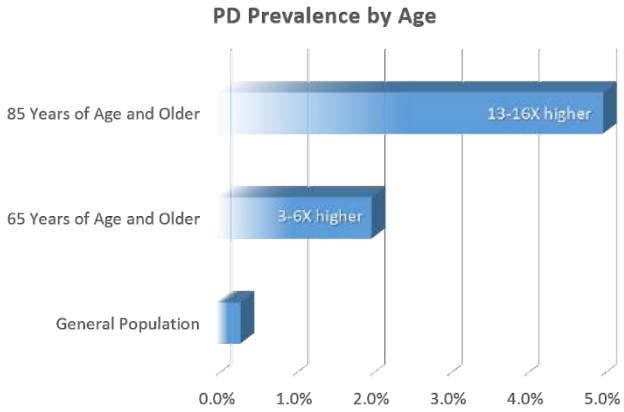



**Figure 1. PD Prevalence by Age.**
About 0.3% of the general population have PD, whereas 1-2% of people age 65 and older and 4-5% of people age 85 and older have PD.

Unfortunately as the global population continues to age into demographics with higher PD prevalence, the supply of neurologists (the medical specialists trained to diagnose and treat nervous system disorders) are projected to fall 20 percent below demand by 2020, according to the American Academy of Neurology. This will result in an overloaded medical system and will likely become a major impediment to improving care and treatment options for Parkinson's patients.

## ECONOMIC BURDEN

The increasingly debilitative course of the disease contributes to high medical and non-medical costs. Annually, the total national economic burden is estimated to be $14.4 billion ($22,800 per patient) according to a 2013 study published in Movement Disorders (see Figure 2). That estimate is comprised of disease-related medical costs of approximately $8.1 billion ($12,800 per patient) and non-medical costs of approximately $6.3 billion ($10,000 per patient). Taxpayers bear the brunt of the medical cost of PD, with an estimated 48 percent ($3.8 billion) paid for by Medicare, Medicaid or other government programs, as illustrated in Figure 3.

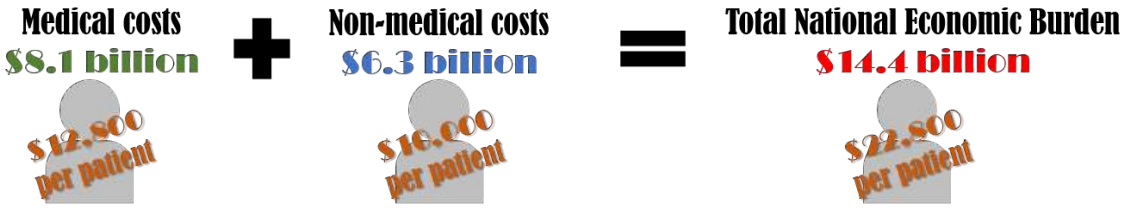
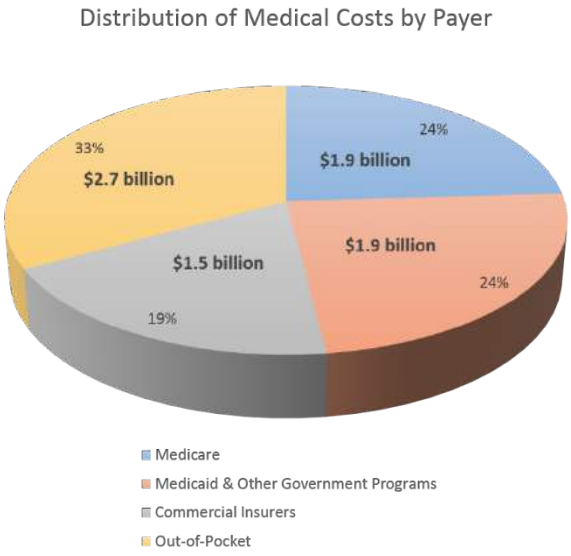



**Figure 2. Economic Burden of PD-related Care.**

As the prevalence of PD increases with age, so too does the cost. PD patients under age 45 incur costs of about $3,500 per year, whereas PD patients age 85 and older can incur costs ranging from $14,000 to $41,500 per year. In total, PD patients pay about $2.7 billion in out-of-pocket expenses annually – an oftentimes huge financial strain on a population that experiences a reduced ability to work as symptoms worsen over time. The annual cost of PD is expected to at least double by 2040 and may increase even more if no progress toward disease-modifying therapies are made.




| Medical Costs | Non-Medical Costs |
|---|---|
| Hospitalization | Patient and/or Caregiver Wage and Productivity Loss |
| Medication | Specialized Transportation |
| Physical Therapy | Home Renovations |
| Nursing Home Care | Personal Aides |

**Figure 3. Distribution of Medical Costs by Payer.**

## PARKINSON'S DISEASE BASICS

Parkinson's disease (PD) belongs to a group of conditions collectively called movement disorders. There are over 20 different types of movement disorders; some examples include Huntington's disease, cerebral palsy, and Tourette's syndrome. Every bodily movement is a careful coordination between the nervous system and muscles. Nerve cells, known as neurons, communicate in order to facilitate movement and virtually all other bodily processes.

Movement execution and coordination is controlled, in part, by a very small structure deep within the midbrain called the substantia nigra (SN) as illustrated in Figure 4. Neurons in the SN produce dopamine, a chemical signal (also known as a neurotransmitter), which is responsible for smooth, coordinated movement. The death of these dopamine-producing neurons leads to the classic motor symptoms seen in PD patients.

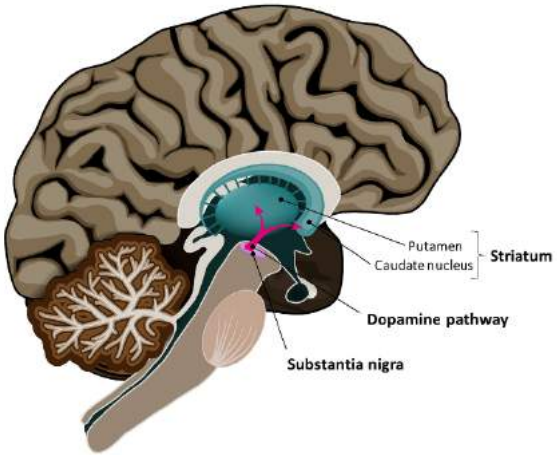



**Figure 4. Brain Anatomy - Parts of the Midbrain.**
Cross section of brain depicting the location of the substantia nigra (SN). SN neurons produce the neurotransmitter dopamine, essential for smooth movement. SN neurons project directly to the striatum (also pictured above). The death of SN neurons alters the dopamine pathway, having direct effects on the striatum and other brain structures.

PD progression results in a continuous chemical imbalance in the brain that affects other regions in addition to the SN. Ultimately this can lead to the development of additional motor and non-motor symptoms, as well as treatment resistance to the standard therapy levodopa.

***Unfortunately, it is not known what triggers these neurons to die. By the time PD is clinically diagnosed, nearly 60-80 percent of the dopamine-producing neurons are already dead, which highlights the critical need for better diagnostic criteria for this disease***.

## CHARACTERISTICS OF PARKINSON'S DISEASE

There are two types of PD, idiopathic (spontaneous) and familial (inherited). The cause of PD is unknown; however, development of familial PD is strongly associated with mutations in certain PD susceptibility genes (discussed later in PD Genetics section on page 22). The majority of patients have idiopathic PD, as only 10 percent of PD causes are familial.

Tremors are perhaps the most well-known symptom associated with PD. There are several other motor, non-motor and treatment-induced symptoms that contribute to the complicated nature of this disease. The severity and number of symptoms experienced can vary wildly from patient to patient. Table 1 highlights several of the most common PD symptoms, although this list is not exhaustive.

**Table 1. Common PD Symptoms.**

| Motor Symptoms | Non-Motor Symptoms | Treatment-Related Symptoms |
|---|---|---|
| Tremor at rest – trembling of the hands, arms, legs, jaw, and face | Cognitive impairment – difficulty recalling learned tasks, mild cognitive impairment, dementia | "Wearing off" effect – treatment dose starts to wear off before next dose can be taken |
| Rigidity – muscle stiffness, often causing pain | Sleep disorders including rapid eye movement sleep behavior disorder (RBD) or insomnia | "On-off" effect – sudden motor fluctuations that develop as a result of chronic medication usage |
| Bradykinesia – slowness of movement execution | Mood disorders such as anxiety and depression | Dyskinesia – sporadic involuntary movements that typically occur after long-term Levodopa therapy |
| Postural instability – stooping, impaired balance | Gastrointestinal problems, difficulty swallowing, loss of sense of smell | Impulse control disorders (ICDs) – gambling, sexual hyperactivity |
| Gait freezing – being stuck in place while walking | Loss of bladder control and sexual dysfunction | Psychiatric issues – psychosis, hallucinations |
| Falling | Small handwriting (micrographia) | Worsening of motor and non-motor symptoms |

Symptoms typically occur at varying times during the disease course, with several non-motor symptoms appearing before motor symptoms become apparent. Treatment-induced symptoms typically occur after four to seven years. Since PD is a chronic, progressive disease, virtually all PD patients will experience these symptoms and more.

The disease course of PD is often described in phases as depicted in Figure 5: prodromal, early, and advanced. PD phases are benchmarked by clinically overt motor symptoms; however, by this point, significant neurodegeneration has already taken place as nearly 60-80 percent of SN neurons have already died.

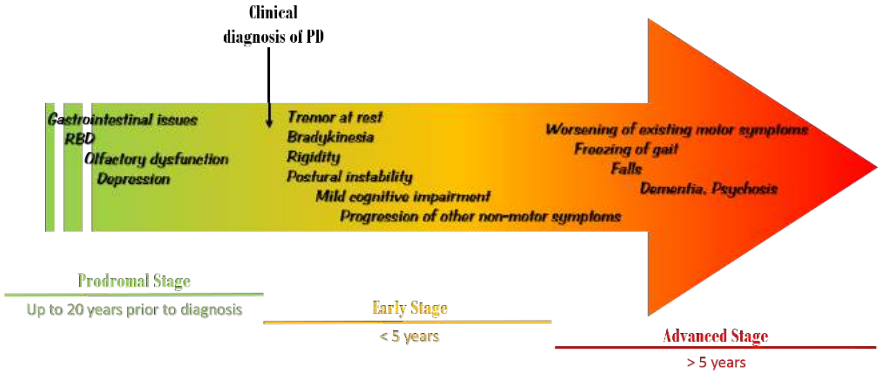



**Figure 5. Progression of PD and Associated Symptoms.**
Symptoms in the prodromal stage are oftentimes indistinguishable from various other diseases. The "classic" PD symptoms are not seen until the transition into the next stage of disease progression ('Early Stage') and this is the stage where the clinical diagnosis is made. Advanced stage symptoms also include severe cognitive impairment along with worsening of existing motor conditions. The image above depicts the myriad of symptoms according to when they generally appear during the natural progression of PD.

## RISK FACTORS AND PREVENTION

While the cause of PD is unknown, investigators have identified general and genetic factors that increase the risk of developing both idiopathic and familial PD.

### GENERAL RISK FACTORS

**General risk factors** include but are not limited to:

- Age – the incidence and prevalence of PD increases substantially with age (see Figure 1).
- Sex – men are 50 percent more likely to develop PD than women.
- Environmental factors – exposure to pesticides and other toxins are suggested to increase the risk of developing PD.
- Medical conditions – prior head injury or depression are suggested to increase the likelihood of developing PD.

**Common Genetic Risk Factors for PD**

*Mutations in the following genes are associated with increased risk for developing PD:*

*GBA* –the greatest genetic risk factor developing PD.

*LRRK2* – most common cause of familial PD but is also found in idiopathic PD cases.

*Parkin* – common in young-onset PD.

*SNCA* – first gene associated with familial PD.

### GENETIC RISK FACTORS

There are a number of genetic mutations that are thought to contribute to the development of PD – known as **genetic risk factors**. These genetic risk factors are discussed further in the PD Genetics section on page 22.

### PREVENTION

While there are no known ways to prevent development of PD, investigators have identified factors that decrease the risk of developing PD:

- Exercise – Research has shown that exercise is vital for both prevention and management of PD. Recent evidence shows that early-stage PD patients who maintained an active lifestyle could delay the start of treatment by as much as two years.
- Nicotine exposure
- Caffeine consumption
- Nonsteroidal anti-inflammatory drug (NSAIDs) or calcium channel blocker use

# DIAGNOSIS

## CLINICAL OBSERVATIONS USED TO DIAGNOSE PD

> ***All cases of PD diagnosis in living patients are considered probable until confirmed by autopsy.*** *A definitive diagnosis requires postmortem analysis of brain tissue to detect protein clumps, or aggregates, containing alpha-synuclein – the culprit protein in PD.*

PD is currently diagnosed based on the clinical presentation of motor symptoms. ***To date, there is no objective diagnostic exam or biomarker for PD.*** A biomarker is a characteristic that is objectively measured and evaluated as an indicator of disease state or treatment efficacy. A biomarker can be detected in biofluids (e.g. blood, urine, cerebrospinal fluid), tissues (e.g. skin, brain) or an imaging scan of the brain. Some examples of widely used biomarkers are blood sugar level for diabetes or cholesterol level for cardiovascular diseases. Without a biomarker, a neurologist has to rely on patient history and motor symptoms present during a neurological exam to give a formal PD diagnosis. A neurologist typically uses a combination of the following clinical observations and tests to diagnose PD:

- **Primary motor symptoms** – Resting tremor, rigidity, slowness of movement (bradykinesia) and impaired balance (postural instability) are the four primary motor symptoms of PD. Physicians will often look for two or more of these hallmark motor symptoms when making a formal diagnosis.
- **Rating scales** – Because PD is a progressive disease that becomes increasingly debilitating over time, physicians will employ rating scales to track disease symptoms. These rating scales are used to aid diagnosis, as physicians often need to track patients over time before rendering a PD diagnosis. Additionally, rating scales are used to track patient response to treatment, and as an evaluation tool in clinical trials. Points are assigned for various symptoms and the composite number is used to compare patient status. The most widely used clinical rating scale for PD is the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS).
- **Neuroimaging techniques** – The presence of dopamine is assessed using brain imaging. Imaging alone is not sufficient to diagnose PD because there are other overlapping parkinsonian syndromes (such as progressive supranuclear palsy [PSP] or multiple system atrophy [MSA]), which produce dopamine loss in the brain as well. While current brain imaging techniques are not diagnostic, physicians can use the images to rule out other parkinsonian syndromes, track dopamine loss over time and to assess patient eligibility for certain clinical trials.

## THE CHALLENGE OF ACCURATELY DIAGNOSING PD

Accurately diagnosing PD is especially challenging for two key reasons:

- *Difficulty identifying patients in the prodromal stage* – many non-motor symptoms, such as constipation or difficulty recalling tasks, often occur several years before motor symptoms are apparent and are often attributed to the natural course of aging; therefore, PD can go undetected for several years. There is great interest in the field to identify prodromal PD patients since, theoretically, therapeutic intervention in the early prodromal phase could be the crucial window to slow disease progression before patients experience significant SN neuronal loss.

- *Overlapping symptoms with other disorders* – the classic PD motor symptoms can be present in other neurodegenerative diseases, often resulting in misdiagnosis.

Being overtly symptomatic is central to PD diagnosis; however, studies demonstrate that by the time symptoms are clinically present, significant degeneration of SN neurons has already occurred, and continuous progression of the disease is eminent. Current therapies are not equipped to slow or halt the relentless progression of PD, and efforts to do so are hampered by the lack of biomarkers available to 1) identify patients in the prodromal phase, 2) objectively diagnose patients and 3) track treatment efficacy. This lack of biomarkers to support clinical research has been a key contributor to failed clinical trials and a lack of overall progression in the space.

## TREATMENT

There is no way to slow or halt the natural progression of PD, and currently available treatments only treat the symptoms of PD rather than modify the relentless progression of PD. Moreover, given the progressive nature of PD, even the most effective symptomatic therapy has limited efficacy over time. Patients report having to take medication up to once every hour simply to alleviate motor symptoms, severely compromising quality of life (QOL). As such, ***the lack of effective disease-modifying therapies is arguably one of the largest unmet needs for the PD community.*** The following medications used to treat PD are discussed below:

- Levodopa/Carbidopa
- Dopamine Agonists
- Monoamine oxidase B (MAO-B) inhibitors
- Catechol-*O*-methlytransferase (COMT) inhibitors
- Anticholinergic agents
- Amantadine

## PHARMACOLOGICAL TREATMENT OPTIONS

### DOPAMINERGIC MOTOR SYMPTOM THERAPY

This treatment strategy aims to increase the dopamine concentration in the brain, which is significantly decreased due to neuronal cell death in the SN. Figure 6 illustrates the following ways that increased dopamine can be achieved:

#### LEVODOPA/CARBIDOPA

Levodopa is a dopamine precursor that is converted to dopamine. Levodopa is administered in combination with carbidopa, a drug that prevents levodopa from being converted to dopamine before it crosses the

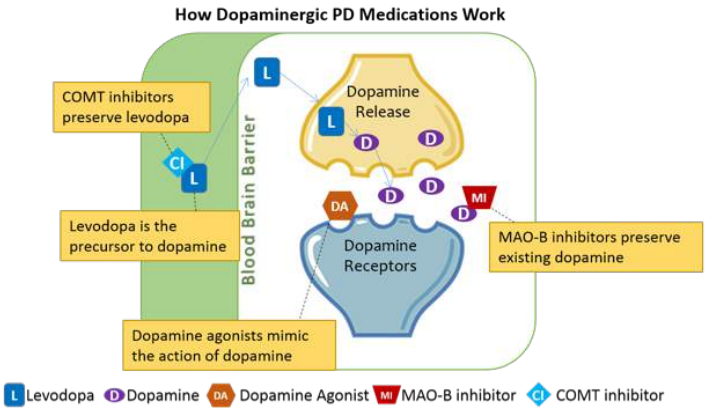



**Figure 6. Dopaminergic Motor Symptom Therapy.**
This figure illustrates the mechanism of action for the following dopamine-based medications: levodopa, dopamine agonists, MAO-B inhibitors and COMT inhibitors.

blood-brain barrier (BBB), a semi-permeable filtering mechanism that only allows certain molecules to pass into the central nervous system (CNS). Levodopa was first introduced into the clinic in 1967, ***yet more than 45 years later levodopa is still the most effective treatment for PD motor symptoms.*** However, its efficacy decreases with disease progression. Levodopa can remain highly effective for about four to seven years, but as symptoms worsen, patients may experience loss of benefit between doses, known as the "wearing off" effect. The emergence of motor fluctuations and levodopa-induced dyskinesias (as indicated in Table 1) severely affects patient QOL. ***The limited duration of levodopa efficacy highlights the need for more effective symptomatic therapies to increase the QOL for PD patients.*** U.S. Food and Drug Administration (FDA)-approved levodopa/carbidopa agents are listed in the Appendix.

### DOPAMINE AGONISTS

These agents mimic the action of dopamine by binding directly to and activating dopamine receptors in the brain. The prolonged use of dopamine agonists is associated with the onset of impulse control disorders (see Table 1). FDA-approved dopamine agonists are listed in the Appendix.

### MONOAMINE OXIDASE B (MAO-B) INHIBITORS

These inhibitors are responsible for preserving existing dopamine in the synapse (the junction between neurons). They selectively block the activity of the enzyme MAO-B, which metabolizes (or breaks down) existing dopamine in the synapse. FDA-approved MAO-B inhibitors are listed in the Appendix.

### CATECHOL-*O*-METHLYTRANSFERASE (COMT) INHIBITORS

These inhibitors are responsible for increasing the bioavailability of levodopa. They block the activity of the enzyme COMT, which metabolizes (or breaks down) levodopa in the periphery before it can be converted to dopamine. FDA-approved COMT inhibitors are listed in the Appendix.

## NON-DOPAMINERGIC MOTOR SYMPTOM THERAPY

These treatment options are designed to target non-dopaminergic signaling pathways in the brain and may have an effect on some, but not all, motor symptoms. FDA-approved non-dopaminergic agents are listed in the Appendix.

### ANTICHOLINERGIC AGENTS

Acetylcholine is a neurotransmitter that works in coordination with dopamine to produce smooth movement. In PD, the acetylcholine-dopamine balance is disturbed. This drug class blocks the action of acetylcholine and is used to treat resting tremor and rigidity. However, they are not effective for bradykinesia or other features of advanced PD.

### AMANTADINE

This drug is an antiviral agent with widespread properties. It functions to increase dopamine release and block dopamine reuptake. Amantadine is used to treat tremor, bradykinesia, rigidity and levodopa-induced dyskinesia.

## NON-MOTOR SYMPTOM THERAPY

Non-motor symptoms are common in PD, with several studies indicating that almost all PD patients will experience at least one non-motor symptom during the course of their disease. There are FDA-approved treatments available for several non-motor symptoms, such as anti-depressants, cognitive enhancers and agents to treat a range of gastrointestinal issues. Depending on the non-motor symptom that presents, the neurologist may collaborate with a physician that specializes in the non-motor symptom area to treat the symptom. In these scenarios it is important to carefully consider how the treatment of one symptom may affect the treatment of another so as to limit adverse effects.

Patients find non-motor symptoms particularly debilitating and a negative influence on QOL. When patient experiences were surveyed at recent meetings, including the FDA Patient-Focused PD Drug Development Public Meeting (September 2015 in White Oak, Md.) and the Grand Challenges in PD conference (October 2015 in Grand Rapids, Mich.), patients reported that oftentimes non-motor symptoms pose even a greater challenge to QOL than the motor symptoms.

## NON-PHARMACOLOGICAL TREATMENT OPTIONS

Exercise has been shown to have an enormous benefit in helping PD patients manage pain and maintain QOL. Data from the National Parkinson Foundation-sponsored *Parkinson's Outcomes Project* demonstrated that exercise can slow the rate of decline in the QOL experience by PD patients when started earlier rather than later in the disease course. Results of the study were presented at the 19th International Congress of Parkinson's Disease and Movement Disorders held in San Diego, Calif., in June 2015.

Complementary practices such as meditation, yoga and tai chi are often recommended for mood and pain management. Depending on pain severity, physical therapy may be recommended. For patients experiencing speech issues, speech therapy may be recommended.

## SURGICAL TREATMENT OPTIONS

Deep brain stimulation (DBS) is a surgical procedure approved for the treatment of advanced PD in patients whose motor symptoms are not adequately controlled with medications. DBS is used to treat tremor, bradykinesia, rigidity and gait issues. Approved in the 1990s, DBS is noted as the most important therapeutic advancement since levodopa, with patients usually reporting motor symptom relief. While effective, DBS is not suitable for all PD patients, and usually benefits patients who have previously responded to pharmacological treatment.

The DBS system uses the following components (see Figure 7):

- Electrodes (also known as leads or probes) – these are thin, insulated wires that are surgically implanted in the

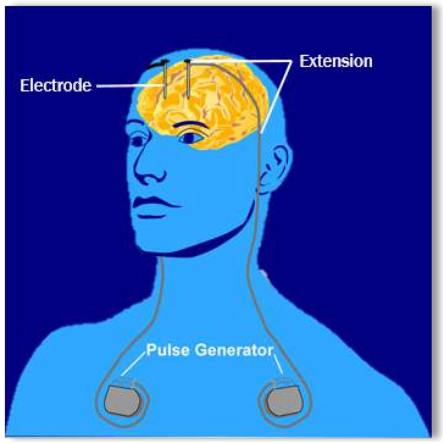



**Figure 7. DBS System Components.**
The three components of the DBS system are illustrated above. Image reused under Creative Commons license (Source).

brain through a small opening in the skull. The electrode tips are inserted into certain areas deep within the brain.

- Extensions – this is an insulated wire that connects the electrode to the implantable pulse generator. The extensions lie under the skin of the head, neck and shoulder.
- Implantable pulse generator (IPG) – this is the "battery pack" that delivers high frequency electrical stimulation to the brain, similar to a heart pacemaker. The IPG is usually implanted under the skin near the collarbone.

### MONITORING TREATMENT EFFICACY

Treatment efficacy is primarily monitored by patient diaries to assess motor symptom severity in the course of daily living and through physician assessment using the MDS-UPDRS rating system. Dependence on PD patient diaries presents challenges as many patients deal with both motor and cognitive impairment; thus they do not always have the capacity to accurately record and convey symptoms to their physicians. Also, given the variability in the patient perception of pain and degree of impairment, it is hard to compare treatment efficacy across patient populations.

Objective measurement of patient response to treatment, at a molecular and whole body movement level, would lessen the reliance on self-reported patient diaries and provide physicians with more accurate information with which to determine treatment decisions, again underscoring the need for biomarkers in the PD space. Currently the use of technology, such as wearable devices and mobile technology, is also being explored as a means to provide objective measurement of motor symptoms.

## THE MECHANICS OF PARKINSON'S DISEASE

### HOW THE NERVOUS SYSTEM WORKS

In order to fully appreciate the disease course of PD, it is helpful to understand the anatomy of the nervous system and how neurons in the nervous system (also known as nerve cells) communicate.

The nervous system is made up of two parts as seen in Figure 8:

- Central nervous system (CNS) – comprised of the brain and spinal cord.
- Peripheral nervous system (PNS) – comprised of all the nerves and nerve bundles (known as ganglia) outside of the CNS.

The PNS connects the CNS to our extremities and organs. Similar to the function performed by electrical wiring in a home – carrying electrical impulses to outlets to power

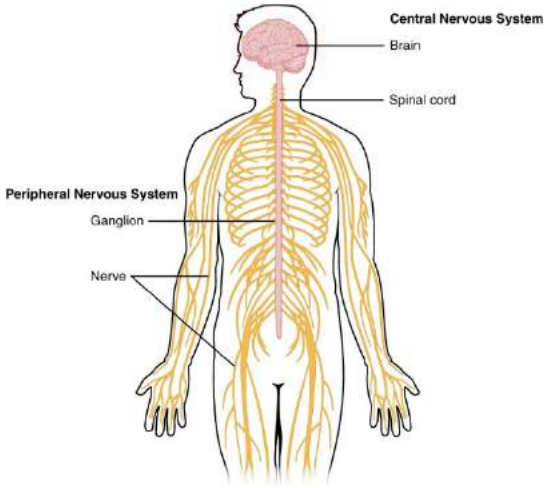



**Figure 8. The Human Nervous System.**
The CNS (pink) contains the brain and spinal cord. The PNS (yellow) contains all the nerves and nerve bundles outside of brain and spinal cord. Image reused under Creative Commons license (Source).

appliances – the nervous system executes a similar function by carrying electrical impulses through nerve cells to power movement and other functions. Nerve cells, known as neurons, are the basic building blocks of the nervous system, and their ability to communicate is absolutely necessary for nervous system function.

## TALKING NEURONS – HOW NERVE CELLS COMMUNICATE

Neurons have a cell body with two types of cellular extensions: dendrites and axons (see Figure 9, left). On one end, dendrites receive information from a neighboring neuron and carry that information to the cell body. The information then travels away from the cell body, in the form of an electrical impulse, through the axon down to the terminal branches of the axon.

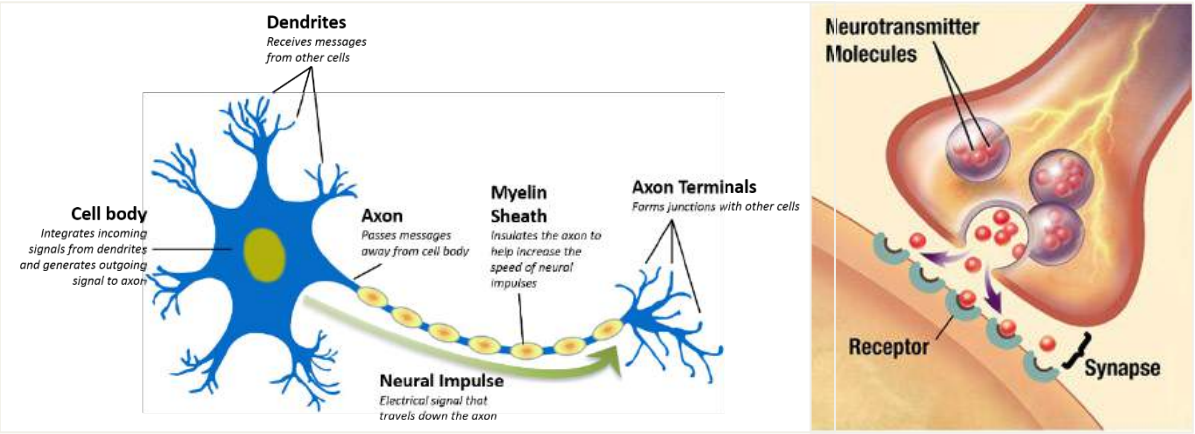



**Figure 9. Neuronal Anatomy and Communication.**
(Left) The parts of a neuron are illustrated above. Image adapted from the National Institute of Health (Source).

(Right) A close-up of the small gap between two neurons, the synapse, is illustrated above. Images adapted from the National Institute on Aging [Public Domain] via Wikipedia Commons (Source).

The electrical impulse triggers the release of chemical signals called neurotransmitters. Neurotransmitters are released across a small gap in between two neurons called the synapse (see Figure 9, right).

The type and amount of neurotransmitter released affects communication between two neurons. Without the right amount of neurotransmitters, communication is lost, and the function that those neurons govern will suffer.

The central neurotransmitter in PD is dopamine. Dopamine signaling between neurons facilitates smooth coordinated movement. As previously mentioned, SN neurons produce, release and are activated by dopamine, therefore they are described as being “dopaminergic.” As PD kills dopaminergic neurons, less dopamine is available for proper communication within the SN and other brain regions, thereby compromising the ability to perform smooth coordinated movements.

## HALLMARKS OF PD PATHOLOGY

The cause of PD is unknown; however, PD is marked by the following critical pathological features:

- Irreversible neuronal cell death in the substantia nigra (SN) region of the brain
- Accumulation and abnormal aggregation of the protein alpha-synuclein

There are several risk factors (detailed in the Risk Factors and Prevention section of page 12), such as genetic abnormalities and exposure to environmental toxins, that are proposed to accelerate the processes that lead to the aforementioned pathological features.

### IRREVERSIBLE SN NEURONAL CELL DEATH

As mentioned previously, the irreversible loss of dopamine-producing neurons in the SN leads to the overt motor symptoms experienced by PD patients. By the time a PD patient presents with the motor symptoms necessary for PD diagnosis, approximately 60-80 percent of the dopamine-producing SN neurons have already been lost.

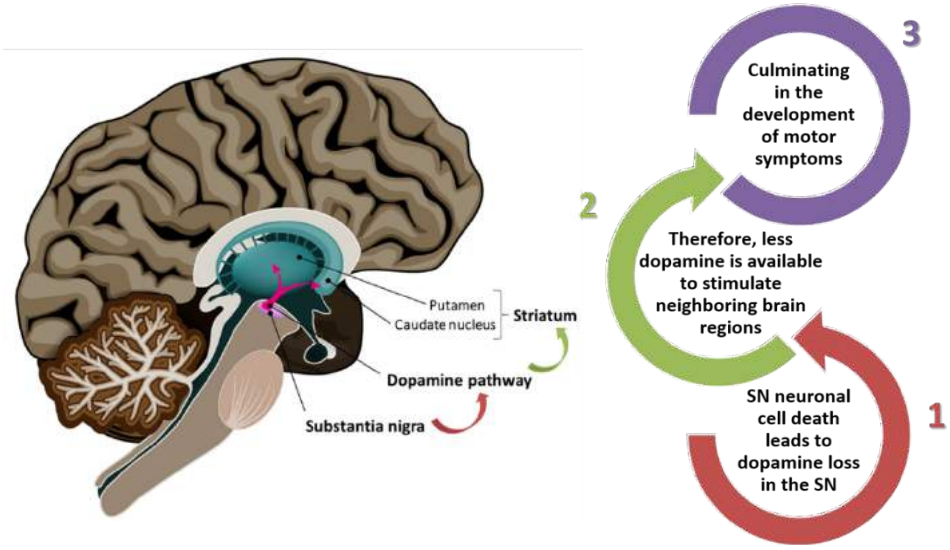



**Figure 10. Sequence of Events Following Dopamine Loss.**
The dopamine imbalance caused by the death of SN neurons causes a chain reaction furthering affecting other brain structures.

The death of these neurons leads to a chain reaction in the brain as depicted in Figure 10. As explained previously, neurons are interconnected and communicate with each other by sending chemical signals in the form of neurotransmitters. The neurotransmitter dopamine stimulates a collection of brain structures called the striatum, thereby facilitating normal movements.

## TOXIC ALPHA-SYNUCLEIN-CONTAINING AGGREGATES

Alpha-synuclein is a protein that is found predominately in the brain, with lesser amounts found throughout the body. Proteins undergo an intricate folding process upon production to ensure appropriate function in the cell; however, some proteins misfold and can become toxic to the cell. In PD patients, alpha-synuclein is commonly found in the misfolded form. This misfolded protein clumps together to form toxic aggregates, including structures called Lewy bodies. A definitive diagnosis of PD is dependent on the presence of these toxic alpha-synuclein aggregates at autopsy (see Figure 11).

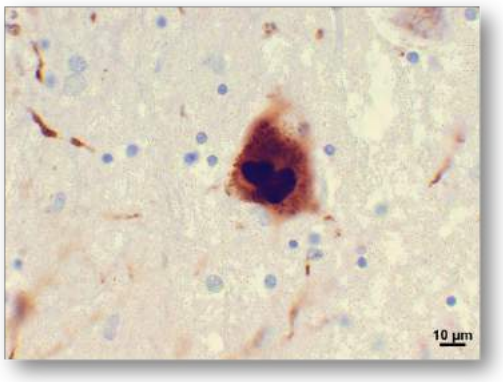



**Figure 11. Alpha-synuclein Lewy Body.** Microscopic image of an alpha-synuclein-containing Lewy body in the SN. Image by Suraj Rajan (own work) via Wikipedia Commons, reused and modified under Creative Common license 3.0 (Source).

It is believed that the abnormal build-up of Lewy bodies leads to a dysfunctional neuronal state that precedes SN neuronal cell death. Recently, scientists have discovered that Lewy bodies are able to spread to other neurons and induce alpha-synuclein misfolding and aggregation, possibly explaining the progressive nature of PD.

Because alpha-synuclein is found consistently in the brain of PD patients, the ability to image alpha-synuclein while patients were still living, rather than at autopsy, could decrease misdiagnosis and facilitate better patient selection for clinical trials. ***The development of an alpha-synuclein imaging biomarker could potentially revolutionize PD diagnostics and drug development.***

Understanding abnormal alpha-synuclein dynamics is an area under intense investigation as they represent "druggable" processes that can be targeted pharmacologically. The hope is that PD disease modification can be achieved if either alpha-synuclein aggregation and/or spread can be prevented or halted.

While alpha-synuclein-containing Lewy bodies are a hallmark of PD pathology, other types of protein aggregates (such as the common protein aggregates found in Alzheimer's disease) are also found in the brains of PD patients. This suggests that the pathology of PD is far more complex than the current model centered primarily on alpha-synuclein.

## OTHER DYSFUNCTIONAL CELLULAR PROCESSES INVOLVED IN PD

Described below are several other dysfunctional cellular processes believed to contribute to PD.

### MITOCHONDRIAL DYSFUNCTION

Mitochondrial dysfunction makes cells susceptible to death, thus promoting neurodegeneration. The mitochondria is the cellular structure responsible for generating energy for all cellular processes and is considered the powerhouse of the cell. It also plays a key role in cellular survival. Mitochondrial dysfunction has been linked consistently to several neurodegenerative diseases, including both sporadic and familial PD, thereby representing an attractive drug target.

### NEUROINFLAMMATION

Chronic inflammation can lead to cell death. Chronic neuroinflammation has long been implicated in PD, although this area of study has been largely neglected. The inflammatory response is driven by the activation of microglial cells (resident immune cells of the CNS) and infiltration of T cells (a type of immune cell) into the SN. The inflammatory response is also activated by the production of pro-inflammatory molecules. Recent research suggests that mutated *LRRK2* (see Table 2) is implicated in neuroinflammation. Research in this area is experiencing a resurgence in the PD field because cellular events that are triggered by neuroinflammation represent possible therapeutic targets. Both LRRK2-targeting and anti-inflammation therapies are being actively explored by the pharmaceutical industry for potential disease-modifying benefit.

### AUTOPHAGY – A CELLULAR CLEANING PROCESS

Autophagy is a fundamental cellular cleaning process that is a quality control mechanism for the cell. The lysosome, oftentimes referred to as the "garbage can of the cell," is responsible for degrading old or defective cellular components, and is key for the autophagic process. Enhancing the autophagic process is currently being explored as a therapeutic strategy to promote the clearance of alpha-synuclein from neurons.

There are also interesting connections between some genetic risk factors and autophagy. For example, the *GBA* gene (see Table 2) encodes for a protein found in the lysosome, which is the key cellular structure for autophagy. Further, LRRK2 mutations are implicated in autophagic dysfunction as well, and recent research suggests that disrupted autophagy contributes to alpha-synuclein build up in neurons – further highlighting the connection between autophagic dysfunction and PD.

**Rare genetic mutations** are strongly associated with the development of familial PD. Genes code for proteins, which in turn carry out cellular functions. Genetic mutations can give rise to a dysfunctional protein(s), thereby contributing to disease.

**Table 2. Genetic Risk Factors Associated with PD.**

| Gene Name | Protein Encoded for by Gene | Role in Parkinson's Disease |
|---|---|---|
| ***SNCA*** | Alpha synuclein | *SNCA* was the first gene to be associated with familial PD. It is believed that alpha synuclein-containing aggregates (Lewy bodies) in SN neurons contribute to neuronal cell death. |
| ***GBA*** | Beta glucocerebrosidase | *GBA* mutations represent the greatest genetic risk factor for developing PD. *GBA* mutations may play a role in autophagic dysfunction. |
| ***DJ-1*** | DJ-1 | *DJ-1* mutations occur in 1-2% of young-onset PD patients. *DJ-1* mutations may play a role in mitochondrial dysfunction. |
| ***LRRK2*** | Leucine-rich repeat kinase 2 | *LRRK2* mutations are the most common cause of genetic PD and also contribute to idiopathic PD. *LRRK2* mutations occur in about 4% of familial PD and 1% of idiopathic PD patients. *LRRK2* mutations may play a role in neuroinflammation and autophagic dysfunction. |
| ***Parkin*** | Parkin | *Parkin* mutations are seen in up to 50% of young-onset familial PD and 15% of young-onset idiopathic PD cases, with patients developing PD before age 45. *Parkin* mutations may play a role in mitochondrial dysfunction. |
| ***PINK1*** | PTEN-induced putative kinase 1 | *PINK1* mutations occur in 1-8% of young-onset PD patients. *PINK1* mutations may play a role in mitochondrial dysfunction. |

While the rare genetic mutations listed in Table 2 greatly increase the risk of developing PD, there are a large number of common genetic changes that are also seen in idiopathic PD cases. Individually these changes alter risk by only a small amount; however, research that investigates the underlying biology affected by a particular genetic mutation will shed light on the biological processes that lead to familial and idiopathic PD. It is important to remember that investigators are constantly discovering new genetic risk factors. Therefore, Table 2 is not an exhaustive list; rather, it captures some of the most researched genes (listed in alphabetical order by protein name).

The science of PD is still unfolding and, despite intense study, many unanswered questions remain. Nevertheless, PD is no longer recognized as a purely dopaminergic neurodegenerative disease. The field is moving towards a multi-system view of this neurodegenerative disease with both CNS and PNS involvement, having effects on both dopaminergic and non-dopaminergic neurons in various brain regions.

## CLINICAL TRIALS AND INVESTIGATIONAL THERAPIES

### CLINICAL TRIALS – OVERVIEW

Clinical research (also referred to as clinical development) is a branch of biomedical research involving human subjects. The goal of clinical research is to evaluate safety and efficacy of drugs, medical devices or diagnostics intended for use in human patients.

Clinical trials are an important component of clinical research since they are used to evaluate the safety and efficacy of an experimental drug or therapy in human subjects. Clinical trials are divided into phases as described in Figure 12. They can also be used to collect specimens from human subjects for further research. Importantly, information on potential side effects are gathered during the clinical trial period and weighed against the potential therapeutic benefit of the treatment under investigation.

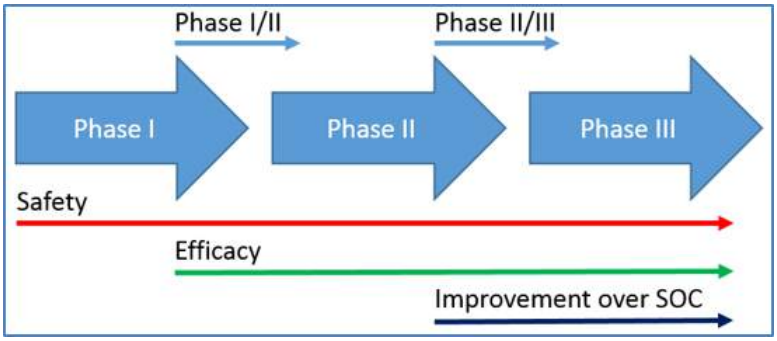



**Figure 12. Phases of Clinical Trials.**
**During Phase I**, researchers test a new drug or treatment for the first time in a small group of people to evaluate its safety, determine a safe dose range and identify potential side effects. **During Phase II**, proof-of-concept studies are performed as the drug or treatment is given to a larger group of people to determine effective and optimal dose. **During Phase III**, the drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects and assess its impact compared to the current standard of care (SOC). Some clinical trials involve multiple phases to facilitate seamless transition from one to another and are written as **Phase I/II** or **Phase II/III**. These designations are also used in adaptive trials, wherein study parameters are modified with respect to ongoing trial results.

The research and development (R&D) process – the process by which a laboratory discovery is developed into a commercial therapeutic, diagnostic or device – is very costly and time-intensive. It is estimated that 95 percent of new drugs fail to make it into the clinic. This is a high failure rate for a process that costs about $1 billion in overall research costs and up to 15 years of time invested.

### PARKINSON'S DISEASE CLINICAL TRIALS

As of January 2016, there are 138 active interventional clinical trials for PD. Figure 13 illustrates the distribution of these trials by phase. PD clinical trials – as with other neurodegenerative diseases – have been fraught with failures in the past, which caused pharmaceutical and biotechnology companies to flee the space. However, this dynamic is rapidly shifting as recent advances have renewed interest and investment in PD.

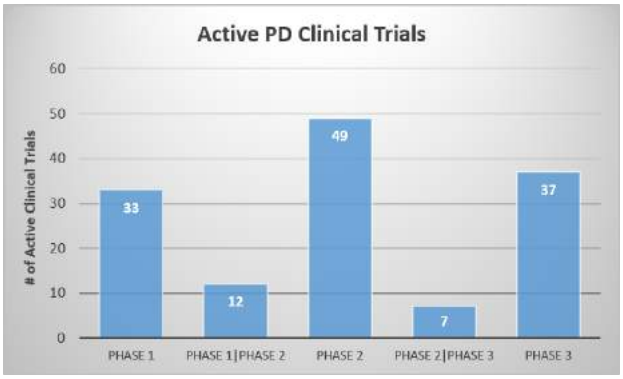



**Figure 13. Current Interventional PD Clinical Trials.**
Of the 138 active, interventional PD clinical trials, 37 (27%) are in Phase 3. Data obtained from www.clinicaltrials.gov.

PD clinical trials are expensive and inherently risky for several reasons:

- **Time needed to complete a study** – Large patient populations need to be followed for long periods of time in order to capture any possible effects on disease progression. In fact, the time to PD clinical trial completion is projected to take nearly 25 percent longer than clinical trials for other therapeutic areas.
- **Lack of reliable biomarkers to monitor treatment response** – The efficacy of an experimental drug or therapy cannot be adequately evaluated without a reliable way to determine if the drug penetrated the target organ and engaged the intended molecular target. ***This is a key challenge in PD, as with most neurological diseases, since the brain is the most difficult organ to penetrate.***
- **Heterogeneous nature of the disease** – Patient heterogeneity can have negative effects on study results. Testing a uniform group of patients would prevent dilution of treatment effect and allow effective treatments to be recognized quicker. This again highlights the need for better patient stratification to ensure that investigational treatments are being applied to the right patients.

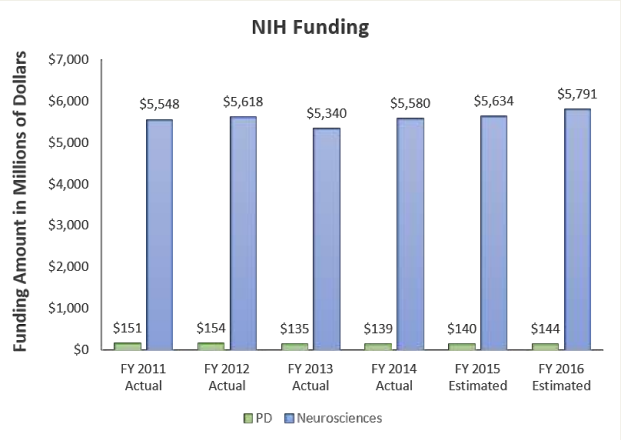



**Figure 14. NIH Funding for PD versus Total Funding for Neurosciences.**
Annual NIH funding for PD-specific research has consistently been less than 3% of the total funding for all neuroscience research since FY 2011. This trend is forecasted to remain unchanged for FY 2015 and 2016. Data obtained from NIH Research Portfolio Online Reporting Tools.

Though the risks are great, ***strategic philanthropic investment is uniquely poised to de-risk PD research by providing scientists with the resources that can accelerate promising science from basic research, through the critical translational research phase, and into clinical development***. Government funding for PD is modest at best, as illustrated in Figure 14, with the majority of funds going towards basic research. PD-specific funding represented 2.5 percent of the total neurosciences funding from the National Institutes of Health (NIH) for FY 2014 – a trend that has been consistent for the past four years – and is estimated to remain unchanged for FY 2015 and 2016. It is evident that funding from other sources is desperately needed, and this is where philanthropy can play a pivotal role.

## INVESTIGATIONAL THERAPIES

As of January 2016, within the 138 total active, interventional clinical trials, there are 64 distinct agents in clinical development for PD. Figure 15 illustrates the distribution of these agents by type and phase of development.

In the sections below, select key therapeutic strategies currently in clinical development for PD as well as promising therapies under investigation are discussed.

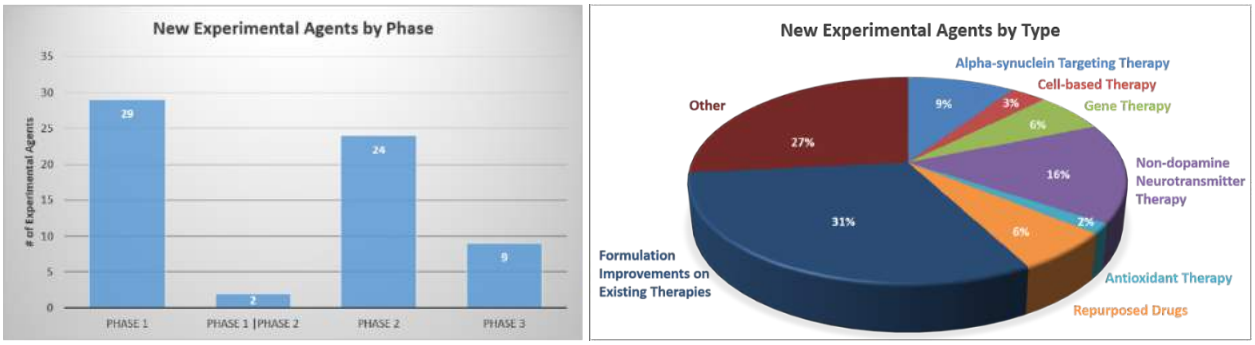



**Figure 15. New Experimental Agents in Clinical Development for PD.**

(Left) New experimental agents are represented by clinical trial phase. Of the 64 new experimental agents in development, 9 (14%) have progressed to Phase 3.

(Right) New experimental agents are represented by therapeutic strategy.

All data obtained from BioCentury Online Intelligence.

### ALPHA-SYNUCLEIN TARGETING THERAPIES

There are six alpha-synuclein targeting agents currently in clinical development. The overall goal of this strategy is to clear alpha-synuclein build-up in the brain in order to prevent Lewy body formation and transmission to other brain regions.

There are two therapeutic approaches being tested to achieve the goals stated above – small molecule inhibitors and immunotherapy.

#### SMALL MOLECULE INHIBITORS (SMI)

SMIs are low molecular weight compounds that are small enough to passively enter a cell, which makes them amenable to oral drug formulations. Of particular importance for neurological drugs is the ability to pass the blood brain barrier (BBB). The brain is the only organ protected by its own selectively permeable defense system, the BBB. The goal is to develop SMIs that can target alpha-synuclein by disrupting the misfolded protein's ability to interact with other misfolded alpha-synuclein proteins to form aggregates. This is a challenge because the protein-protein interfaces typically span large surface areas, thereby making it very difficult to determine which portions of the interface the SMI should target.

#### ALPHA-SYNUCLEIN IMMUNOTHERAPY

In addition to exploring small molecule drugs to target the alpha-synuclein protein, researchers are also testing whether they can activate the immune system to target alpha-synuclein. This strategy, referred to as immunotherapy, works by soliciting either an active or passive immune response. Active immunotherapy involves

administering a substance (e.g., drug, vaccine, etc.) into the body that induces an immune response leading to the natural production of antibodies (proteins used by the immune system to bind and neutralize other molecules in the body) against the intended target (i.e., alpha-synuclein). Passive immunotherapy differs from active immunotherapy in that antibodies against the target are commercially manufactured outside of the body and administered as a drug. Results from early trials using the active immunotherapy approach indicated that the vaccine was well tolerated and there was early evidence of clinical benefit.

One key consideration is the management of the immune response to ensure that the immunotherapeutic approaches do not promote excessive inflammation. The immune system must remain in careful balance as under- or over-stimulation of the immune system can lead to deleterious effects.

## LRRK2 TARGETING THERAPIES

*LRRK2* gene mutations are the most common cause of genetic PD (see Table 2). The *LRRK2* gene encodes for the LRRK2 protein, which is a kinase, a type of protein that catalyzes phosphorylation (the transfer of phosphate groups from one molecule to another).

Several LRRK2 mutations increase its kinase activity, which is toxic to neurons. This is why the overall goal of this therapeutic approach is to inhibit LRRK2 kinase activity. While LRRK2 inhibitors are not yet in clinical trials, they are currently in preclinical development at Pfizer, Merck and Genentech. Recently, toxicity concerns have slowed development. However, The Michael J. Fox Foundation for Parkinson's Research has convened an LRRK2 Industry Advisory Group to promote pre-competitive collaboration across these companies to systematically address concerns and get closer to testing an LRRK2-targeting drug in clinical trials. While this therapy has immediate relevance for PD patients with LRRK2 mutations, there may be potential applications for idiopathic PD patients as well.

## STEM CELL THERAPY

There are currently two stem cell therapies in clinical development. Stem cells have the ability to become (differentiate into) any cell type in the body given the proper biological signals. The hypothetical basis for this therapy is that stem cells could be recruited to or placed in damaged regions and replace SN dopaminergic neurons that were lost as a result of PD and restore proper signaling.

In addition to replacing damaged cells, stem cells are being explored as a disease modeling system to screen new PD therapies.

### USING STEM CELLS TO MODEL PD AND SCREEN NEW THERAPIES

As previously mentioned, PD symptoms can vary significantly among patients, highlighting disease heterogeneity. It is important to be able to model the underlying biological mechanisms driving the heterogeneity of the disease in order to find a cure. Unfortunately, current animal models fail to adequately recapitulate the disease. The tremendous progress in stem cell research has enabled researchers to use this technology to create patient-specific models of PD in a petri dish. This is done by taking skin cells from a PD patient (donor) and reprogramming them to make an induced pluripotent stem cell (iPSC). These iPSCs can be reprogrammed to develop into any cell type, but for the purpose of PD research, they are reprogrammed to become neurons.

Because the cells are derived directly from a patient, despite being grown in petri dishes, they display the same molecular and pathological features identified in the donor patient. The coupling of the patient's clinical symptoms to the biology and behavior of the stem cells could provide new insights into the key mechanisms of PD. These patient-derived iPS cells can also be used to test new drugs. The use of iPS cells to screen drugs that may be effective against PD provides an additional method to validate results observed in animals studies. This is important because animal models are often poor predictors of the clinical success or failure of new drugs, which is a major impediment to clinical trial success in PD.

## GENE THERAPY

There are currently four gene therapies in clinical development. This therapeutic strategy involves delivering a gene as a drug. For PD, this treatment could deliver the enzyme that converts levodopa to dopamine in an effort to increase the amount of dopamine in the brain or to deliver factors that promote neuronal survival. Although the theory is straightforward, in practice it is considerably more complex to achieve this outcome as a result of multiple variables that can be difficult to control. To date, clinical trials testing this strategy in PD as well as other neurodegenerative diseases have failed to show improvement above placebo. Efforts to improve gene therapy are focused on two key areas: vector design and delivery mechanism.

## DRUG REPURPOSING

Drug repurposing investigates whether a drug that is already FDA-approved for another disease may be effective for treating a new disease. The theory is that diseases that have common cellular pathways may benefit from similar drugs. FDA-approved drugs have already been tested for safety, meaning that Phase I requirements have already been met. Therefore testing an FDA-approved drug for potential efficacy in a different disease could go straight to Phase II, thereby reducing time and cost of the clinical trial. This approach has been applied to PD recently with some success:

- *Metabolic agents* – Metabolic agents, such as type II diabetes drugs, have shown efficacy in PD models. Abnormal glucose metabolism (pathological feature of diabetes) and abnormal mitochondrial function (pathological feature of PD) are intricately linked, giving a reasonable basis to explore repurposing metabolic drugs for PD. A recent small pilot study ("proof of concept" clinical trial) using an FDA-approved type II diabetes drug generated excitement in the PD field due to the clinical benefit experienced by patients taking the drug. A Phase II clinical trial has been launched and is currently ongoing.
- *Chemotherapeutic agents* – Recently, PD patients demonstrated evidence of motor and non-motor improvement in a small pilot study using an FDA-approved chemotherapy agent used to treat leukemia. It is believed that the agent works to clear toxic buildup of Lewy bodies. Its effect on PD is currently under investigation.
- *Antioxidant agents* – Elevated levels of the antioxidant urate are associated with a lower risk of developing PD and slower disease progression if diagnosed with PD. Antioxidant agents combat oxidative stress (the imbalance between free radicals and natural antioxidants generated in the cell). Mitochondrial Dysfunction, described above, is a major contributor to oxidative stress. An active Phase III clinical trial is investigating whether the use of the nutritional supplement inosine (which the body naturally converts to the antioxidant urate), can slow disease progression in early-stage PD patients.

- *High blood pressure medication* – Previous studies show that calcium channel blockers, a particular class of high blood pressure medication, may reduce the risk of developing PD and slow disease progression if diagnosed with PD. Mitochondrial Dysfunction occurs if too much calcium enters the cell. Calcium channel blockers are designed to prevent this excessive calcium influx into the cell. An active Phase III clinical trial is investigating whether the repurposed high blood pressure drug, isradipine, can slow the progression of early stage PD.

## BARRIERS TO PD RESEARCH PROGRESS AND KEY PHILANTHROPIC OPPORTUNITIES

PD is a multifactorial disease with a number of challenges and unmet needs that stand in the way of desperately needed progress. In November 2015, the Milken Institute Philanthropy Advisory Service convened world-renowned PD experts to discuss the state of science relevant to PD and the challenges currently impeding research progress. The goal of the retreat was to identify high-impact, actionable solutions where strategic philanthropic investment could accelerate progress in PD. The experts prioritized the following challenges:

- Incomplete understanding of underlying disease biology
- Slow progress in biomarker discovery and drug development
- Inadequate preclinical models
- Lack of disease-modifying therapies (DMTs) and clinical trial failures
- Suboptimal current treatment options to manage symptoms

This section outlines each of the key challenges along with potential solutions and corresponding philanthropic opportunities to address the challenges and accelerate PD research progress. *Please note that the opportunities presented below are high-level representations and should be considered carefully with respect to your philanthropic goals and discussed in detail with a philanthropic advisor.*

### INCOMPLETE UNDERSTANDING OF UNDERLYING DISEASE BIOLOGY

#### THE PROBLEM

***The underlying biology of PD is still poorly understood, especially with respect to key proteins such as alpha-synuclein and LRRK2.*** Evidence overwhelmingly suggests that PD converges on the aberrant processing of alpha-synuclein, yet several questions remain pertaining to how abnormal alpha-synuclein mechanistically contributes to PD. Further, *LRRK2* mutations are the most common cause of hereditary PD and may also play a role in spontaneous PD, yet very little is known about this protein's normal biological function in the cell and its associated signaling pathways. *Strategically addressing high priority basic science questions would enhance our understanding of the underlying PD disease pathology and thus improve chances of identifying new disease-modifying treatments*.

Funding to explore basic biology typically comes from NIH (the largest source of funding for medical research in the world). However, constrained federal spending has crippled the NIH budget in recent years, thereby affecting PD research funding, which is already only a small fraction of NIH spending for all neurosciences (as illustrated in Figure 14). A deeper understanding of PD biology will inform drug development efforts, as alpha-synuclein and LRRK2 represent major drug targets for several industry programs (see Investigational Therapies section on page 25).

#### POTENTIAL SOLUTIONS

- *Basic research investment* – While there has been considerable investment in translational and clinical PD research, basic science has been neglected. Better scientific understanding will inform drug development efforts, selection of patients, biomarkers and endpoints for clinical studies. Experts suggested employing a

model that allows investigators to embark on higher risk projects than have typically been funded by the government. Key priorities areas to consider are:

  - Biological mechanism and impact of alpha-synuclein protein
  - Biological mechanism and impact of LRRK2 protein
  - Biological mechanism and impact of other PD-related genes
  - Selective vulnerability of neuronal death
  - Compensatory neurotransmitter pathways

- *Human capital investment* – There is a need to better support existing investigators and to attract new investigators to the field. Doing so will not only accelerate the pace of research, but also make it sustainable by training the next generation of investigators. There is a dearth of funding for postdoctoral-level and early career investigators, who perform the majority of the early basic science studies. This has the potential to negatively affect both academic and industry-led research efforts, as basic science studies form the basis for future translational and clinical research. Additionally, decreased support for both established and new investigators increases the likelihood that scientists will leave research in pursuit of other career options, thus decreasing the pool of scientists available to attack key scientific problems.

### EXAMPLES OF CORRESPONDING PHILANTHROPIC OPPORTUNITIES

- Fund basic science research initiatives that enable better understanding of disease pathology. There are several models to support this approach, ranging from funding investigator-initiated research to funding a collaborative group of investigators.
- Fund additional training programs that invest in postdoctoral fellows and early-stage investigators, who generally cannot compete for major grant support as they do not have the track of record of established investigators. However, they are important to provide for the future basis of the field.

**Table 3. Summary of Solutions to Catalyze Change in Basic Research.**

| Potential Solutions | Corresponding Philanthropic Opportunities |
|---|---|
| ***Basic research investment*** | • Fund basic science research initiatives that enable better understanding of disease pathology. |
| ***Human capital investment*** | • Fund additional training programs that invest in postdoctoral fellows and early stage investigators. |

## SLOW PROGRESS IN BIOMARKER DISCOVERY AND DRUG DEVELOPMENT

### THE PROBLEM

***At present, there are no biomarkers available to objectively diagnose PD, assess disease progression or to track treatment efficacy in patients.*** The process of biomarker discovery and validation is central to drug development. Efforts to increase efficiency in the process have the potential to reduce the time and cost of clinical trials. In order for a biomarker to be accepted as a true objective measure of disease state or treatment efficacy, it must first be

identified (biomarker discovery), then confirmed through replication (biomarker validation) and finally detected in clinically relevant tests (assay development). A large amount of biological samples is necessary to successfully hone in on the few candidate biomarkers that possess the appropriate sensitivity and selectivity to be adopted as true biomarkers.

Recent large-scale efforts – such as the Parkinson's Disease Biomarkers Program (PDBP), sponsored by the National Institute of Neurological Disorders and Stroke (NINDS), and the Parkinson's Progression Markers Initiative (PPMI), sponsored by the Michael J. Fox Foundation for Parkinson's Research (MJFF) – have established critical infrastructure to support biomarker discovery and/or validation using patient biological samples (e.g., blood, urine, cerebrospinal fluid [CSF], DNA, RNA). However, there is potential to maximize the utility of these data-rich resources to support both biomarker discovery and validation (as opposed to one or the other) within their already established patient cohorts.

As mentioned, biomarker discovery efforts necessitate large amounts of biological samples. Unfortunately, human brain tissue from living patients is not available to study in neurodegenerative diseases, like PD, as the brain is not typically biopsied. While PDBP and PPMI collect a wide variety of biological samples from patients, brain tissue is not collected. Alternatively there are various brain banks across the country that house post-mortem brain donations from both patients with healthy brains and those that suffered from a variety of neurodegenerative diseases. Although brain tissue from these facilities can be requested, obtaining sufficiently large amounts of tissue is cost prohibitive for many research laboratories. Further, these brain banks are severely fragmented, each having their own processes and handling protocols which can create data variability when analyzing samples from various sources. Finally these facilities are often understaffed and underfunded, thereby creating systemic inefficiencies that ultimately make the brain tissue inaccessible. However, *if these challenges could be overcome, elucidating differences in the molecular profile (e.g. genes, proteins, lipids, metabolic state) of PD-diagnosed brains versus healthy brains could augment biomarker discovery efforts and accelerate drug discovery*.

## POTENTIAL SOLUTIONS

- *Leverage existing infrastructures for biomarker discovery* – Existing programs such as PDBP and PPMI have extensive support in place, including standardized collection and storage of biospecimens. However, their original intended use was either to support biomarker discovery (PDBP) or validation (PPMI). Yet, their utility could be more powerful if they were augmented to support both biomarker discovery and validation within their established cohorts. Strategic patient cohort expansion within these programs could support the dual biomarker activities by extending study duration overall, re-opening closed patient cohorts and/or recruiting new patient cohorts. These actions could allow for more in-depth analysis of disease progression and heterogeneity in the search for candidate biomarkers.
- *Leverage existing brain bank infrastructure to catalyze biomarker discovery* – To date there has been no large-scale effort to perform deep molecular characterization of brain tissue across U.S. brain banks. Coordinating existing PD brain banking programs across the country to perform large scale "-omics" studies could increase the utility of the resource and inform biomarker discovery efforts.
- *Create a biomarker validation and assay development team* – Following biomarker discovery within the above mentioned infrastructures, validation teams could be established with the overall goal of gathering sufficient data on a target to make it attractive for industry to pick up. Once a candidate biomarker is validated, a method to detect its presence in the appropriate biofluid and/or imaging scan must be established. As such, this team could also develop standardized, robust assays to be used in clinical

research. Strategic philanthropic investment to support assay development will increase the efficiency of drug discovery efforts

## EXAMPLES OF CORRESPONDING PHILANTHROPIC OPPORTUNITIES

- Fund ongoing longitudinal assessments and/or the expansion of prodromal and genetic cohorts within existing PPMI and PDBP infrastructures. These expanded infrastructures would be able to support biomarker discovery due to the increased amount of samples available. Additionally, funding a large-scale effort to deeply characterize the samples by performing "-omics" studies would expand the utility of this resource. Such an effort would allow each patient's entire genome (genomics), expressed gene profile (transcriptomics), protein profile (proteomics), lipid profile (lipidomics), and metabolic state (metabolomics) to be studied over time. This dataset could then be made open access for the scientific community as a resource to fuel all stages of research.
- Fund the coordination of existing PD brain banks around the country to develop a PD brain bank network. Deep characterization of PD patient brains using large-scale "-omics" studies and big data analytics could lower the barrier of discovery and provide an additional platform for biomarker research. This dataset, as suggested above, could then be made open access for the scientific community as a resource to fuel all stages of research.
- Fund Biomarker Discovery SWAT (**S**pecial **W**eapons **a**nd **T**actics) Teams to utilize PPMI and PDBP infrastructure. Functionally, the teams would propose a biomarker target, peer-reviewed by scientists, and then bring together groups of researchers to validate the target and develop an associated assay. Pharmaceutical and diagnostic kit manufacturing representatives should work with the SWAT Teams to advise on key elements needed to successfully validate a drug target and increase the likelihood of proceeding with development efforts around the proposed target in their respective industries.

**Table 4. Summary of Solutions to Accelerate the Pace of Biomarker Discovery.**

| Potential Solutions | Corresponding Philanthropic Opportunities |
|---|---|
| ***Leverage existing infrastructures for biomarker discovery*** | • Fund on-going longitudinal assessments and/or the expansion of prodromal and genetic cohorts within existing PPMI and/or PDBP infrastructures.<br>• Fund large-scale "-omics" studies on existing patient samples in PPMI and/or PDBP. Make dataset open-access to research community to encourage discovery. |
| ***Leverage existing brain bank infrastructure to catalyze biomarker discovery*** | • Fund the development of a PD brain bank network by coordinating with existing PD brain bank programs across the country.<br>• Fund large-scale "-omics" studies on PD-diagnosed brains. Make dataset open-access to research community to encourage discovery. |
| ***Create biomarker validation and assay development teams*** | • Fund multi-stakeholder Biomarker Discovery SWAT Teams. |

## INADEQUATE PRECLINICAL MODELS

### THE PROBLEM

***No single PD preclinical model fully recapitulates the key features of human disease.*** Animal models are used to study disease biology and test experimental therapeutics in order to demonstrate potential benefit before they are approved for testing on humans in clinical trials (preclinical). Poor reliability and predictive capability of the preclinical translational pipeline negatively affect drug development and contributes to the high cost and failure of clinical trials.

As described previously in the Stem Cell Therapy section on page 26, there is momentum across the neurodegenerative space (e.g., Alzheimer's disease, ALS, PD, etc.) to utilize induced pluripotent stem cells (iPSCs), generated from patient skin biopsies and/or blood samples, as both a biomarker and drug discovery platform. Human iPSCs have the advantage of retaining each patient's molecular disease signatures and can be differentiated into various cell types (e.g., neurons, heart cells, liver cells, etc.) in a dish (*in vitro),* which resemble that functional cell type in a patient's body. As such, this technique lends itself to modeling genetic risk factors of disease particularly well. This ability to generate multiple cell lineages from iPSCs provides investigators with a way to evaluate the effect of an experimental drug on multiple cell types simultaneously. For example, investigators can assay for on target effects on neurons generated from iPSCs or for potential safety signals in heart and liver cells generated from iPSCs earlier in the drug development process.

### POTENTIAL SOLUTIONS

- *Develop a more predictive preclinical pipeline* – There are several preclinical models available through the Parkinson's Disease Research Tools Consortium (PDRTC) sponsored by MJFF and the iPSC Consortium sponsored by NINDS; however, they could be better utilized through rational alignment with research goals. Additionally, deep molecular characterization efforts through large-scale "-omics" studies (as recommended for solutions described in the previous section) could also improve model utility to support more robust translational research efforts.

### EXAMPLES OF CORRESPONDING PHILANTHROPIC OPPORTUNITIES

- Fund a large-scale patient-derived iPSC effort that employs a systems biology approach through comprehensive biological analytics (e.g., proteomics, transcriptomics, epigenomics, whole genome sequencing, metabolomics, etc). This dataset could then be available for the scientific community as a resource to fuel all stages of research. Further, this iPSC platform could also be used for high-throughput drug screening. An iPSC effort could be achieved by:
    - Creating a PD iPSC network with existing iPSC banks across the country, or
    - Spearheading a new effort to create iPSCs from newly recruited patients, or
    - Expanding the PPMI and/or PDBP biospecimen resource by creating patient-derived iPSC lines from enrolled patients.

**Table 5. Summary of Solutions to Improve the Preclinical Pipeline.**

| Potential Solutions | Corresponding Philanthropic Opportunities |
|---|---|
| ***Develop a more predictive preclinical pipeline*** | • Fund a large-scale patient-derived iPSC effort to perform large-scale "-omics" studies. Make dataset open-access to research community to encourage discovery.<br>  • Coordinate with existing iPSC banks which house PD patient-derived iPSCs.<br>  • Create new iPSCs from newly-recruited patients. |

## LACK OF DISEASE-MODIFYING THERAPIES (DMTS) AND CLINICAL TRIAL FAILURES

### THE PROBLEM

***Of all the available treatments for PD, none is proven to slow, halt or reverse the natural progression of the disease. Moreover, all new investigational drugs for PD have failed to show a disease-modifying effect in pivotal clinical trials.*** Clinical trials are costly and risky endeavors, with the most expensive failures occurring in late phase II and III studies. While this issue is largely due to the incomplete understanding of the underlying disease biology that is driving PD, there are other contributing factors, such as:

- *Poor patient selection and stratification* – It is extremely difficult to select patients in the earliest stages of disease as the signs and symptoms are subtle, variable and many are distinct from the motor symptoms that later predominate. This prodromal period is theoretically when patients would benefit most from a DMT. The inability to stratify patients appropriately (i.e., by disease severity and subtype) has serious ramifications for successful clinical trials and ultimately for developing DMTs.
- *Lack of biomarkers* – Again, as mentioned previously, the inability to reliably and objectively diagnose PD, assess disease progression, assess target engagement, or monitor treatment response hampers the evaluation of a potential DMT. Without appropriate measures, it is not possible to know whether a potential therapeutic is actually slowing the progression of PD.

Additionally, investigators need to integrate patient perspective and input into the clinical trial process – an emerging imperative in clinical research. Patients are required for clinical research, and their input in study design, parameters and outcome measures can inform tradeoffs between desired benefits and tolerable risks that are unaccounted for or misjudged by physicians and regulators. Poor patient recruitment into clinical trials is a contributing factor to high costs. In fact, many trials are terminated early if they cannot recruit the appropriate number of patients. Efforts to engage patients in the clinical trial process can increase clinical trial success and will better inform product development. For example, conducting benefit-risk analyses with patients could shed light on what type and level of side effects, study conditions, and burdens that patients themselves may be willing to accept, which physicians may not have expected.

## POTENTIAL SOLUTIONS

- *Validate mobile apps and wearable/sensing technology platforms* – Such objective measures could be beneficial for current clinical treatments (as described in the next section) as well as future clinical trials. For clinical trial purposes, these measures may allow investigators to quantify motor and non-motor symptoms, detect smaller changes in performance and monitor patients remotely. As a result, the data can inform patient stratification and the development of digital biomarkers. However, at present, the field is ill-equipped to handle the enormous amount of data generated by these new technological platforms. Moreover, there is no set of quantitative data standards that can be applied across clinical trials independent of the technology developer and/or trial sponsor. Therefore validation of these digital health platforms is essential to address limitations and facilitate adoption of these platforms by regulatory agencies.
- *Integrate patient perspective* – Accounting for the patient's experience will enrich clinical trial study design, promote study accrual and adherence and identify acceptable risks that were previously not considered. Further, this is an opportunity to take into account what benefits are actually important to patients. For example, patients may find that a treatment which allows them more predictability of "on" time within a 48-hour period more valuable than an extra hour of unpredictable "on" time within a 48-hour period, thus allowing them the control to plan their day. These preferences could affect patient participation in one trial over another. As we are entering an era of patient-centered care, it is important to actively seek and integrate the patient voice into clinical development and planning, as these treatments are ultimately being developed for the benefit of patients.
- *Drug repurposing clinical trials* – These trials, as described previously in the Drug Repurposing section on page 27, offer the benefits of decreased time and cost for clinical trials by using compounds that were developed for other indications that show evidence of possible therapeutic benefit in PD. It is worth noting that there are current clinical trials that are investigating repurposed drugs for the treatment of PD (e.g., exenatide, a type II diabetes drug; isradipine, a high blood pressure drug; nilotinib, a cancer drug).

## EXAMPLES OF CORRESPONDING PHILANTHROPIC OPPORTUNITIES

- Fund a precompetitive, multi-stakeholder mobile technology initiative to design and run validation studies for a pre-determined set of motor, non-motor and treatment-induced symptoms. The goal of this effort is to establish a quantitative global standard for the determined symptoms that can be applied to any digital health platform.
    - This effort will affect all members of the PD research community, including competitors in the pharmaceutical and medical device manufacturing industries, as well as academic and nonprofit partners. Therefore, precompetitive collaboration will allow these competitors to safely share in developing the standards that will benefit the whole ecosystem.
    - Ideally, this initiative will lead to globally accessible quantitation measurement tools, as well as data that are clinically actionable and available to both patients and investigators.
- Fund patient preference studies to gain insight into what outcome measures are meaningful to patients. The results of these studies would then be scaled to inform trial design, eligibility criteria, trial endpoints and secondary measures. Further, patient engagement could be included as a condition of grant funding

for investigators seeking clinical trial funding. This will ensure that the patient perspective is incorporated into trial design prior to Institutional Review Board (IRB) approval.

- Fund novel drug repurposing efforts. Prior to clinical trials, iPSC platforms could be used as a repurposed drug screening platform. Additionally, the use of bioinformatics-guided approaches to drug repurposing could provide a more robust method to explore new therapies.

**Table 6. Summary of Solutions to Support DMT Research and Clinical Trials.**

| Potential Solutions | Corresponding Philanthropic Opportunities |
|---|---|
| ***Validate digital health platforms*** | • Fund a precompetitive, multi-stakeholder mobile technology initiative to design and run validation studies for a pre-determined set of motor, non-motor, and treatment-induced symptoms. |
| ***Integrate patient perspective*** | • Fund patient preference studies to inform trial design, eligibility criteria, trial endpoints and secondary measures. |
| ***Drug repurposing clinical trials*** | • Fund a high-throughput drug screen of repurposed drugs using a patient-derived iPSC platform. |

## SUBOPTIMAL CURRENT TREATMENT OPTIONS TO MANAGE SYMPTOMS

### THE PROBLEM

***While finding a treatment that slows or halts the progression of PD (disease-modifying therapy) is a long-term goal in the PD field, efforts to make patients' lives more manageable in the short term should not be ignored.*** Patients consistently identify the progressive motor and non-motor symptoms as particularly debilitating. There have been recent improvements to levodopa formulations (e.g., extended release tablets, patch and continuous infusion via intestinal pump); however, chronic levodopa therapy leads to motor fluctuations, the mechanism of which is poorly understood. Further, progressive motor symptoms, such as freezing of gait and falls, continue to be huge unmet needs for the field, yet no treatment exists for these symptoms. A deeper understanding of the underlying biology associated with disease progression would support efforts to develop more effective symptomatic therapies.

There is also now a greater appreciation for non-motor symptoms, yet the etiology and underlying biology driving these non-motor symptoms are also poorly understood. Cognitive dysfunction in particular remains a significant unmet need, as the field lacks measures to adequately assess degree of cognitive decline. Near-term efforts to improve therapeutic options for patients would aid in improving the quality of life for patients, and long term efforts to characterize PD features would contribute to DMT development.

### POTENTIAL SOLUTIONS

- *Fund basic research efforts* – An understanding of the non-dopaminergic compensatory pathways in the brain could uncover new "druggable" targets and signaling pathways that could be exploited for therapeutic benefit. DBS is a successful example of a surgical therapy that came from the field's increased understanding of non-dopaminergic pathways. Additionally, the underlying biology associated with non-motor symptoms needs to be explored to support development of rational therapeutics.

- *Harmonize and standardize large clinical trial databases* – Clinical trials are typically performed independent of each other and, as such, inconsistencies in how data were/are captured render the majority of clinical trial databases incompatible. Data aggregation, harmonization and standardization of multiple datasets would allow researchers to seamlessly query across the wealth of information stored in large interventional clinical trial databases. Capitalizing on these existing databases could uncover new insights into PD regarding the natural history of disease, disease subtypes and the basis of treatment-resistant features. This process is time intensive; however, database harmonization technology is being developed to create process efficiency.
- *Data gathering with mobile apps and wearable/sensing technology* – Such objective measures could allow investigators to quantify symptoms, monitor patients remotely and personalize care. PD is a heterogeneous disease; therefore, employing methods to assess the motor and non-motor features of prodromal and treatment-resistant PD would aid DMT development. Additionally, this effort would enable patients to participate in studies remotely, thus allowing for large-scale natural history studies to characterize the natural progression of PD.

## EXAMPLES OF CORRESPONDING PHILANTHROPIC OPPORTUNITIES

- Fund basic science research initiatives that enable better understanding of treatment-induced motor symptoms as well as non-motor symptoms. There are several models to support this approach, ranging from funding investigator-initiated research to funding a collaborative group of investigators.
- Fund an effort to harmonize and standardize large interventional PD clinical trial databases. Ideally, this effort would include access to and harmonization across both public (typically government-funded trials) and private (typically industry-funded trials) databases.
- Fund a technology initiative to encourage supplementary data collection with mobile apps and wearable technology in future large-scale natural history studies. Additionally, fund a data analytics effort to support algorithm development, which would translate the large amounts of data generated from wearable/sensing technology into functional information that can be interpreted by physicians to inform care decisions, such as drug class or dosing changes.

**Table 7. Summary of Solutions to Improve Symptomatic Treatments.**

| Potential Solutions | Corresponding Philanthropic Opportunities |
|---|---|
| ***Basic research investment*** | • Fund basic science research initiatives that enable better understanding of treatment-induced motor symptoms as well as non-motor symptoms. |
| ***Harmonize and standardize large clinical trial databases*** | • Fund an effort to harmonize and standardize large interventional PD clinical trial databases. |
| ***Data gathering with mobile apps and wearable/sensing technology*** | • Fund a technology initiative to encourage supplementary data collection with mobile apps and wearable technology in future large scale natural history studies.<br>• Fund a data analytics effort to support algorithm development. |

# KEY STAKEHOLDERS IN THE PD COMMUNITY

## DOMESTIC RESEARCH GRANT-MAKING ORGANIZATIONS

There are several nonprofit organizations specifically focused on charitable giving to support PD and other neurodegenerative diseases. This section provides a brief overview of the nonprofit organizations involved in PD research. Their involvement can be through directly funding research or supporting research. This section only includes U.S.-based PD organizations with a research focus; organizations that are solely involved in patient support, advocacy, awareness or whose mission is to fund one specific research center are excluded. Table 8 displays the top four nonprofit funders of PD research. Additional information regarding their mission, key research funding mechanisms and clinical trials support activities is also provided below.

**Table 8. Top Nonprofit Organization Funding PD Research in FY 2014.**

| Organization | Year Founded | Revenue | Research Support Provided | Research Grants/ Expense Ratio | Total Amount of Research Support Provided Since Inception |
|---|---|---|---|---|---|
| The Michael J Fox Foundation for Parkinson's Research (MJFF) | 2000 | $83,234,503 | $ 62,595,476 | 75% | > $450M |
| National Parkinson Foundation (NPF) | 1957 | $10,206,111 | $ 3,133,172 | 26% | > $180M |
| American Parkinson Disease Association (APDA) | 1961 | $ 9,359,710 | $ 2,493,165 | 30% | > $42M |
| Parkinson's Disease Foundation (PDF) | 1957 | $ 7,794,472 | $ 5,292,198 | 52% | > $110M |

## THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH (MJFF)

### MISSION

The MJFF mission is to find a cure for Parkinson's disease through an aggressively funded research agenda and to ensure the development of improved therapies for those living with Parkinson's today.

### RESEARCH FUNDING MECHANISMS

MJFF mainly supports translational and early clinical research. MJFF has a large footprint in the global PD community as they have injected over $450M in research funds since their inception. They invested over $60M in FY 2014. MJFF supports research efforts in both academia and industry spanning drug target validation, therapeutic development for both DMT and symptomatic treatments, as well as research tool development and data science. A significant amount of funding also goes to support the Parkinson's Progressive Marker Initiative (see page 43), MJFF's signature program to develop disease progression biomarkers.

For more information about available awards, please visit MJFF's website.

## NATIONAL PARKINSON FOUNDATION (NPF)

### MISSION

NPF's mission is to improve the lives of Parkinson's patients through expert care and research.

### RESEARCH FUNDING MECHANISMS

NPF's research funding has a clear clinical focus. They have infused over $180M in research funds into the PD field since their inception. They awarded over $3M in research support in FY 2014. NPF funds investigator-initiated research that covers a wide range of PD-relevant topic areas. Additionally, NPF supports human capital investment into the field as they provide clinical fellowships to train neurologists in the movement disorder specialty. This is desperately needed as most PD patients do not see a movement disorder specialist. They also provide research grants to support career development of young investigators.

For more information about available awards, please visit NPF's website.

## AMERICAN PARKINSON DISEASE FOUNDATION (APDA)

### MISSION

The APDA mission is to "Ease the Burden – Find the Cure for Parkinson's disease." As the country's largest grassroots organization serving more than 1 million Americans with Parkinson's disease and their families, APDA's energy is focused on research, patient services, education and raising public awareness.

### RESEARCH FUNDING MECHANISMS

APDA has a strong focus on patient support, advocacy and awareness, however they do also fund PD research. They have awarded over $42M in research funds since their inception, including over $2M to support research activities in FY 2014. APDA's research funding is primarily focused on supporting the careers of aspiring and early stage PD scientists as 75 percent of their funding mechanisms are intended for young investigators, postdoctoral fellows or practicing neurologists.

For more information about available awards, please visit APDA's website.

## PARKINSON'S DISEASE FOUNDATION (PDF)

### MISSION

The PDF mission is to improve the lives and futures of people touched by PD by funding promising scientific research while supporting people living with Parkinson's through educational programs and services.

### RESEARCH FUNDING MECHANISMS

PDF's research funding mainly supports basic and translational research. Since their inception, they have awarded over $110M in research funds, including over $5M during FY 2014. PDF supports both investigator-initiated as well

as collaborative, center-wide research. PDF has a global reach as they fund domestically and internationally. Training and career development is also a priority for PDF since they actively fund research and clinical fellowships.

For more information about available awards, please visit PDF's website.

## OTHER KEY GRANT-MAKING ORGANIZATIONS

### PARKINSON STUDY GROUP (PSG)

The PSG is the longest standing, largest, not-for-profit, scientific network of PD Centers in North America consisting of 132 centers. The PSG aims to conduct clinical trials to advance knowledge about the cause(s), disease progression and treatment of PD and related disorders. PSG-sponsored clinical trials have been instrumental in the FDA approval of four PD drugs: Rasagiline, Rotigotine, Entacapone and Pramipexole. PSG provides funding for retrospective data-mining, mentored clinical research, and biomarker discovery and validation.

For more information about available awards, please visit PSG's website.

### PARKINSON'S UK

Parkinson's UK's vision and ultimate ambition are to find a cure and improve life for everyone affected by PD. Parkinson's UK is the largest charity funder of PD research in the UK. Parkinson's UK funds multi-year research grants across all levels of research (basic to clinical) and research experience (pre-doctoral to senior independent investigator). It provides funding for large projects and career development for aspiring PD investigators.

For more information about available awards, please visit Parkinson's UK's website.

### THE CURE PARKINSON'S TRUST (CPT)

CPT is focused on finding a cure for Parkinson's. It funds projects that can demonstrate the potential to slow, stop or reverse the condition. CPT actively encourages collaboration among scientists and fosters these relationships to accelerate progress. CPT funds both preclinical research and clinical trials. Most of the current clinical trials supported are a part of its Linked Clinical Trials Initiative. CPT's recent research portfolio supports regenerative medicine, mitochondrial function studies, alpha-synuclein-targeting and drug delivery mechanisms.

For more information about available awards, please visit CPT's website.

# COLLABORATIVE INITIATIVES

## GOVERNMENT-SPONSORED PROGRAMS

### PARKINSON'S DISEASE BIOMARKERS PROGRAM (PDBP)

PDBP , launched in 2012, is a program of the National Institute of Neurological Disorders and Stroke, whose goal is to support PD biomarker discovery efforts by funding research and resource development using collected patient samples. The PDBP has collected thousands of patient biospecimens (e.g. DNA, RNA, CSF, blood) for 30 months in 6 month intervals, allowing for longitudinal studies. Grants totaling over $5M have been awarded under PDBP to date with active funding announcements out to support future work.

### MORRIS K. UDALL CENTERS FOR EXCELLENCE IN PARKINSON'S DISEASE

This NINDS program was named in honor of Congressman Morris K. Udall of Arizona, who was diagnosed with PD in 1979. Udall remained active in Congress until his retirement in 1991, and passed away in 1998 after a long battle with PD. Udall Centers utilize a multidisciplinary research approach to elucidate the fundamental causes of PD as well as to improve the diagnosis and treatment of patients with PD and related neurodegenerative disorders. Udall Centers are required to share data and engage patients to promote knowledge advancement in both the PD research and patient communities. There are currently nine Udall Centers across the country:

- The Brigham and Women's Hospital (Boston, MA)
- Feinstein Institute for Medical Research (Manhasset, NY)
- Johns Hopkins University School of Medicine (Baltimore, MD)
- Mayo Clinic, Jacksonville
- Northwestern University (Chicago, IL)
- University of Miami
- University of Michigan
- University of Pennsylvania School of Medicine
- University of Washington

## CONSORTIA AND STRATEGIC PARTNERSHIPS

Consortia are temporary associations of stakeholders from various sectors – academia, industry, government, nonprofits, etc. – that share resources in order to achieve a common goal. According to *FasterCures'* Consortia-pedia Catalogue, a database of biomedical research consortia, there are currently nearly 10 consortia for PD. Table 9 lists select consortia that are focused exclusively on PD research, resource building and/or therapeutic development. Patient cohorts are excluded from this analysis. For a full list, please visit www.consortiapedia.fastercures.org.

**Table 9. PD Consortia.**

| Consortium Name | Abbreviation |
|---|---|
| Biomarkers Across Neurodegenerative Diseases | BAND |
| International Parkinson's Disease Genomics Consortium | IPDGC |
| Network for Excellence in Neuroscience Clinical Trials | NeuroNEXT |
| Parkinson's Disease Research Tools Consortium | PDRTC |
| Parkinson's Progressive Marker Initiative | PPMI |

### BIOMARKERS ACROSS NEURODEGENERATIVE DISEASES (BAND)

The BAND consortium consists of the Alzheimer's Association, Alzheimer's Research UK, MJFF and the Weston Brain Institute. The goal of the BAND consortium is to stimulate analyses across the Alzheimer's disease and PD research enterprises to engage in further data analysis of existing cohorts. Data analysis will contribute to biomarker discovery, standardization of assays, genetic profiles and imaging modalities. The goal is to enable preliminary pilot research or proof-of-principle studies utilizing data and/or samples from two large biomarker studies – the Alzheimer's Disease Neuroimaging Initiative and the PPMI – in order to garner further research support from other funding agencies.

### INTERNATIONAL PARKINSON'S DISEASE GENOMICS CONSORTIUM (IPDGC)

The IPDGC is a multinational collaborative group. Members of the IPDGC have led the effort to define and understand the genetic basis of PD, identifying the majority of known genetic risk factors for this disease. To date, the largest genome-wide association analysis for PD was performed by IPDGC members. IPDGC also spearheaded the creation of inexpensive and powerful genotyping tools, such as the NeuroX chip, through an industry collaboration with Illumina. The tools have been widely adopted for the study of multiple neurodegenerative diseases.

Their work is being extended to include biomarker identification, risk prediction, disease subtyping, and the molecular basis of disease. The members of the IPDGC, who are based in the USA, France, England, Wales, Germany, The Netherlands, and Estonia, meet in person biannually.

## NETWORK FOR EXCELLENCE IN NEUROSCIENCE CLINICAL TRIALS (NEURONEXT)

NeuroNEXT was created to conduct studies of treatments for neurological diseases through partnerships with academia, private foundations and industry. The network is designed to expand the NINDS' capability to test promising new therapies, increase the efficiency of clinical trials before embarking on larger studies and respond quickly as new opportunities arise to test promising treatments for people with neurological disorders.

NeuroNEXT provides an established infrastructure, including a data coordinating center (University of Iowa), Clinical Coordinating Center (Massachusetts General Hospital) and approximately 28 study sites. Funded NeuroNEXT studies will use this infrastructure, which includes a central IRB and pre-established contractual agreements with all sites. All but three NeuroNEXT sites are also PSG sites.

## PARKINSON'S DISEASE RESEARCH TOOLS CONSORTIUM (PDRTC)

The PDRTC formalizes previously ad hoc input and feedback to the MJFF from tool developers and end users in pursuit of more robust tools for the PD research community. The current landscape of laboratory tool development is a costly and time-consuming practice where scientists create and validate tools for specific experiments. These self-produced tools create challenges related to lengthy material transfer agreements and intellectual property issues and, unfortunately, in many cases cannot be used reproducibly in other labs. Since 2010, the MJFF Tools Program has strived to liberate researchers from these challenges by creating validated, characterized research tools and distributing them to academic and industry researchers at little to no cost through an expedited process. MJFF currently offers 260 preclinical research tools to scientists and counts 8,500 tools distributed.

## PARKINSON'S PROGRESSIVE MARKER INITIATIVE

PPMI, sponsored and coordinated by MJFF, is an observational clinical study partnership involving researchers, funders and study participants working toward the goal of identifying progression biomarkers to improve PD therapeutics. PPMI was established six years ago as a biomarker validation platform. To that end, PPMI has established a comprehensive, standardized, longitudinal PD database and biological sample (biospecimen) repository that is available to the research community. The PPMI biospecimen repository houses urine, plasma, serum, cerebrospinal fluid, DNA and RNA for every patient participant. The database and biorepository include advanced imaging and biospecimen analysis with clinical and behavioral assessments. Over 700 patients are currently enrolled in PPMI, with a few cohorts still enrolling patients. PPMI is taking place at clinical sites in the United States, Europe, Israel and Australia.

# APPENDIX

## FDA-APPROVED PHARMACOLOGICAL TREATMENTS

### Table 10. FDA-Approved Levodopa/Carbidopa Agents.

| Drug Name (Brand Name in parentheses) | Manufacturer | Delivery Method | Usage Indications |
|---|---|---|---|
| **Levodopa/Carbidopa (Sinemet®; Sinemet-CR®)** | Merck | Immediate release tablet; Extended release tablet | Treatment for tremor, bradykinesia, and rigidity. |
| **Levodopa/Carbidopa (Parcopa®)** | Jazz Pharmaceuticals | Oral disintegrating tablet | Same as above. This formulation is beneficial for swallowing-impaired PD patients. |
| **Levodopa/Carbidopa (Rytary™)** | Impax Pharmaceuticals | Extended-release capsules | Treatment for tremor, bradykinesia, and rigidity. |
| **Levodopa/Carbidopa (Duopa™)** | AbbVie | Small, portable infusion pump that delivers Levodopa/Carbidopa directly into the small intestine for 16 continuous hours. | Treatment of motor fluctuations in advanced PD patients. This formulation bypasses the stomach and as such is beneficial for advanced PD patients since the spontaneous emptying of the stomach becomes delayed and unpredictable as PD progresses. |
| **Levodopa/Carbidopa/*Entacapone – see COMT inhibitors below* (Stalevo®)** | Novartis | Tablet | Treatment of motor fluctuations. Replacement for Levodopa/Carbidopa. |

### Table 11. FDA-Approved Dopamine Agonists.

| Drug Name (Brand Name in parentheses) | Manufacturer | Delivery Method | Usage Indications |
|---|---|---|---|
| **Ropinirole; Ropinirole-XL (Requip®; Requip-XL®)** | GlaxoSmithKline | Tablet | Treatment for tremor, bradykinesia, and rigidity. |
| **Pramipexole; Pramipexole-ER (Mirapex®; Mirapex-ER®)** | Boehringer Ingelheim | Tablet | Same as above. |
| **Rotigotine (Neupro®)** | UCB, Inc. | Patch | Same as above. |
| **Apomorphine (Apokyn®)** | Britannia Pharmaceuticals | Injection | Treatment for sudden "wearing off". |

### Table 12. FDA-Approved MAO-B Inhibitors.

| Drug Name (Brand Name in parentheses) | Manufacturer | Delivery Method | Usage Indications |
|---|---|---|---|
| **Selegline (Eldepryl®)** | Somerset Pharmaceuticals | Tablet | Treatment for tremor, bradykinesia, rigidity, and motor fluctuations. |
| **Zydis Selegiline HCL (Zelapar®)** | Valeant Pharmaceuticals | Oral disintegrating tablet | Same as above. This formulation is beneficial for swallowing-impaired PD patients. |
| **Rasagiline (Azilect®)** | Teva Pharmaceuticals | Tablet | Same as above. |

### Table 13. FDA-Approved COMT Inhibitors.

| Drug Name (Brand Name in parentheses) | Manufacturer | Delivery Method | Usage Indications |
|---|---|---|---|
| **Entacapone (Comtan®)** | Novartis | Tablet | Treatment for motor fluctuations. This agent is used in combination with Levodopa/Carbidopa as it is not pharmalogically active on its own. |
| **Tolcapone (Tasmar®)** | Valeant Pharmaceuticals | Tablet | Same as above. |

### Table 14. FDA-Approved Non-Dopaminergic Agents.

| Drug Name (Brand Name in parentheses) | Manufacturer | Delivery Method | Usage Indications |
|---|---|---|---|
| *ANTICHOLINERGIC AGENTS* | | | |
| **Trihexyphenidyl (formerly Artane®)** | Generic only, previously Lederle Pharmaceuticals | Tablets or liquid | Treatment for tremor, typically in younger patients. |
| **Benztropine (Cogentin®)** | Oak Pharmaceuticals | Tablet | Same as above. |
| *OTHER NON-DOPAMINERGIC AGENTS* | | | |
| **Amantadine (Symmetrel®)** | Alliance Pharmaceuticals; DuPont Pharmaceuticals; Novartis | Capsules or liquid | Treatment for tremor, bradykinesia, and rigidity. Also indicated for levodopa-induced motor fluctuations. |

## GLOSSARY

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| **ACETYLCHOLINE (ACH)** | A neurotransmitter that plays an important role in many neurological functions, including learning and memory. Acetylcholine also works in coordination with dopamine to produce smooth movement. |
| **ACTIVE IMMUNOTHERAPY** | Administration of a drug vaccine into the body to induce an immune response leading to the natural production of antibodies against a target |
| **ADENO-ASSOCIATED VIRUSES (AAVS)** | A common type of viral vector |
| **AKINESIA** | Slowness of movement initiation |
| **ANTIBODIES** | Proteins used by the immune system to bind and neutralize other molecules in the body |
| **ANTICHOLINERGIC AGENTS** | This drug class blocks the action of acetylcholine and is used to treat resting tremor and rigidity |
| **AUTOPHAGY** | A fundamental cellular cleaning process that is a quality control mechanism for the cell |
| **AXON** | The appendage of a neuron that transmits impulses away from the cell body. |
| **BASAL GANGLIA** | One of the major regions of the brain involved in motor control |
| **BILATERAL** | Involving both sides of the body |
| **BIOMARKER** | Measurable substance or molecule whose presence is indicative of disease, infection or environmental exposure |
| **BIOPSY** | Tissue removed from a living body |
| **BLOOD-BRAIN BARRIER** | A layer of cells lining the inner surface of brain capillaries. It protects the brain from infectious agents and toxic compounds by letting nutrients and oxygen in and waste products out. Because the barrier strictly regulates the passage of larger molecules and often prevents drug molecules from entering the brain, it has long posed one of the most difficult challenges in developing treatments for brain disorders. |
| **BRADYKINESIA** | Slowness of movement execution |
| **CATECHOL-*O*-METHLYTRANSFERASE (COMT) INHIBITORS** | Drugs that are responsible for increasing the bioavailability of levodopa. |
| **CENTRAL NERVOUS SYSTEM (CNS)** | Comprised of the brain and spinal cord |
| **CEREBROSPINAL FLUID (CSF)** | Clear, colorless body fluid that bathes the brain and spinal cord. While the primary function of CSF is to cushion the brain within the skull and serve as a shock absorber for the central nervous system, CSF also circulates nutrients and chemicals filtered from the blood and removes waste products from the brain. |
| **CLINICAL RESEARCH** | Branch of biomedical research involving human subjects |
| **CLINICAL TRIALS** | Research studies on human subjects that are designed to evaluate the safety and efficacy of potential interventions, including drugs, vaccines and medical devices |
| **DATA MINING** | Examining large databases in order to generate new information. |
| **DEEP BRAIN STIMULATION (DBS)** | A surgical procedure approved for the treatment of advanced PD in patients whose motor symptoms are not adequately controlled with medications |

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| **DENDRITE** | Neuronal projection that receives chemical messages for neurons |
| **DISEASE-MODIFYING THERAPY** | Drug that can modify or change the course of a disease |
| **DJ-1 GENE** | Encodes for the DJ-1 protein |
| **DOPAMINE** | Primary neurotransmitter involved in Parkinson's disease |
| **DOPAMINE AGONISTS** | These drugs mimic the action of dopamine by binding directly to and activating dopamine receptors in the brain |
| **DYSKINESIA** | Sporadic involuntary movements that typically occur after long-term levodopa therapy |
| **EFFICACY** | Measure of the ability of the drug to treat whatever condition it is indicated for. It is not a statement about the drug's tolerability or ease of use. |
| **ENZYME** | A protein originating from living cells that catalyzes a specific biochemical reaction |
| **FAMILIAL PD** | Inherited PD |
| **FIBRIL** | A molecular complex that consists of a few oligomeric units |
| **GBA GENE** | Encodes for the β-glucocerebrosidase protein |
| **GENETIC MUTATION** | Permanent alteration in the DNA sequence that makes up a gene, such that the sequence differs from what is found in most people |
| **GENOME** | An organism's complete set of DNA |
| **IDIOPATHIC PD** | Spontaneous PD |
| **IMPULSE CONTROL DISORDERS (ICDS)** | A class of psychiatric disorders characterized by failure to resist a temptation, urge or impulse that may harm oneself or others (e.g. gambling, sexual hyperactivity, etc.) |
| **INDUCED PLURIPOTENT STEM CELLS (IPS CELLS)** | Stem cells derived from any cell in the body |
| **INTRAVENOUS (IV)** | Existing or taking place within, or administered into, a vein or veins |
| **KINASE** | An enzyme that catalyzes the addition of phosphorous and oxygen groups to a protein |
| **LENTIVIRUS** | A common type of viral vector |
| **LEVODOPA** | A precursor to dopamine. Primary dopamine replacement therapeutic agent used to treat PD. |
| **LEWY BODIES** | Accumulation of toxic protein clumps (aggregates) |
| **LRRK2 GENE** | Encodes for the leucine-rich repeat kinase 2 protein |
| **LYSOSOME** | A highly acidified cellular structure that is key for autophagy |
| **METABOLIZE** | To break down or convert to another molecule |
| **MICROGLIA** | The resident immune cells of the central nervous system that respond to and remove damaged neurons |
| **MICROTUBULE** | A hollow cylindrical protein structure in neurons that holds the cell in its proper shape and also helps transport nutrients within the cell |
| **MITOCHONDRIA** | The powerhouse of the cell responsible for generating energy for all cellular processes |
| **MONOAMINE OXIDASE B (MAO-B) INHIBITORS** | Drugs that are responsible for preserving existing dopamine in the synapse |

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| **NATIONAL INSTITUTES OF HEALTH (NIH)** | Primary agency of the U.S. government responsible for biomedical and health-related research. The NIH comprises 27 separate institutes and centers that conduct research in different disciplines of biomedical science. |
| **NEUROINFLAMMATION** | An innate immune response in the central nervous system that involves the accumulation of activated immune cells to a site of injury or foreign substances |
| **NEUROLOGISTS** | The medical specialists trained to diagnose and treat nervous system disorders |
| **NEURON** | A type of cell found in the nervous system that processes and transmits information to other cells through electrical and chemical signals. Also called nerve cell. |
| **NEUROTRANSMITTER** | A chemical that transmits signals across a synapse from one neuron to another cell |
| **NON-VIRAL VECTOR** | These vectors retain the circular DNA vector structure but are stripped of the viral replication factors present in viral vectors |
| **OFF-TARGET EFFECT** | Having an effect on something other than the intended target |
| **OLIGOMER** | A molecular complex that consists of a few monomer units |
| **OXIDATIVE STRESS** | The increased generation of reactive oxygen species, (ROS) which makes the cell more susceptible to death |
| **PARKIN GENE** | Encodes for the Parkin protein |
| **PASSIVE IMMUNOTHERAPY** | Administration of antibodies or other immune system components that are made outside of the body |
| **PERIPHERAL NERVOUS SYSTEM (PNS)** | Comprised of all the nerves and nerve bundles outside the CNS |
| **PINK1 GENE** | Encodes for the PTEN-induced putative kinase 1 protein |
| **POSTURAL INSTABILITY** | Impaired balance |
| **PRECLINICAL MODEL** | Stage of research before clinical trials where feasibility and drug safety are collected |
| **REPROGRAMMING** | The process of using molecular factors to create iPS cells |
| **RESEARCH AND DEVELOPMENT (R&D)** | The process by which a laboratory discovery is developed into a commercial therapeutic, diagnostic or device |
| **RIGIDITY** | Stiff muscles |
| **SMALL MOLECULE INHIBITORS (SMIS)** | Low molecular weight compounds that are small enough to passively enter a cell |
| **SNCA GENE** | Encodes for the α-synuclein protein |
| **SUBSTANTIA NIGRA** | Brain region that contains dopamine region |
| **SYMPTOMATIC THERAPY** | Therapies that alleviate symptoms |
| **SYNAPSE** | Specialized connections between neurons where information is transmitted |
| **SYNAPTIC CLEFT** | The space between neurons into which neurotransmitters are released |
| **SYNAPTIC TRANSMISSION** | Process by which signaling molecules (neurotransmitters) are released by a neuron and bind to and activate the neurons of another neuron |
| **TAU PROTEIN** | A protein that binds to and regulates the assembly and stability of neuronal microtubules, found in an abnormal form in Alzheimer's disease |
| **UNILATERAL** | Involving one side of the body |
| **VIRAL VECTOR** | These vectors are modified by removing viral genes and replacing them with the desired therapeutic gene so that they can be used clinically |

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