Parkinson’s Disease

Challenges, Progress, and Promise

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Introduction

In the United States alone, the cost of treating PD is estimated to be $14 billion annually. Indirect costs, such as those associated with the loss of productivity, are conservatively estimated to total $6.3 billion each year. As the U.S. population ages, these figures are expected to rise rapidly. The number of people diagnosed with PD in the United States is expected to double by 2040.

The National Institute of Neurological Disorders and Stroke (NINDS), part of the National Institutes of Health (NIH), has a long history of supporting PD research. For decades, NINDS-funded researchers working nationwide have developed treatment options that have greatly improved motor symptoms for people with PD. For example, dopamine replacement therapy with Sinemet, a mainstay therapy in the treatment of PD, has helped alleviate motor symptoms particularly in the early stages of disease. Deep brain stimulation (DBS) can reduce tremor, rigidity, stiffness, and improve movement. However, much work remains to be done. Despite their many successes, these therapies have limitations. There is no currently available therapy that slows the progression of the underlying disease or adequately relieves the wide range of symptoms in people with more advanced PD.

The NINDS brings scientists, health care providers, individuals with PD, caregivers, advocacy groups, and other stakeholders together to assess the state of PD research, define key challenges, and set priorities for advancing PD research. Most recently, the NINDS held the “Parkinson’s Disease 2014: Advancing Research, Improving Lives” conference, which resulted in a series of prioritized recommendations that will inform ongoing and future efforts in PD research. This booklet highlights the recent progress made in PD research and maps out the challenges and priorities for the road ahead.

Following Alzheimer’s disease, Parkinson’s disease (PD) is the second-most common neurodegenerative disorder in the United States. Most people diagnosed with PD are age 60 years or older, however, an estimated 5 to 10 percent of people with PD are diagnosed before the age of 50. Approximately 500,000 Americans are diagnosed with PD, but given that many individuals go undiagnosed or are misdiagnosed the actual number is likely much higher. Some experts estimate that as many as 1 million Americans have PD. Of course, given the progressive nature of the disabilities associated with PD, the disease affects thousands more wives, husbands, children, and other caregivers.

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1. About Parkinson’s Disease

The effects of PD on the central nervous system are both chronic (meaning they persist) and progressive (meaning the symptoms grow worse over time). By the time a diagnosis is made, PD has typically already progressed to a point where people have difficulty controlling the movement of their bodies due to tremors (involuntary shaking), bradykinesia (slowness of movement and reflexes), stiffness in their limbs or the trunk of their body, and impaired balance. As these symptoms progress, walking, talking, swallowing, and completing other simple tasks can become challenging.

PD disease processes begin well before people start exhibiting motor symptoms. This is the preclinical phase of the disease. During this phase people may experience a range of nonspecific, non-motor symptoms such as hyposmia, depression, anxiety, and sleep disorders. People may also experience disturbances of the autonomic nervous system that manifest as problems with digestion, respiration, salivation as well as excessive sweating, bladder dysfunction, or sexual dysfunction. This phase may last for several years. The onset of motor symptoms marks the clinical phase of PD. People may have a variety of symptoms including resting tremor, bradykinesia, rigidity (resistance to passive movement of the limbs), and balance problems. The progression of these symptoms is typically gradual, often involving only one side of the body at first. This includes things like a reduction of arm swing on one side when walking, soft speech, or intermittent tremor.

More research is needed to better understand, characterize, and identify features of the preclinical phase of PD. A high priority is placed on finding biological identifiers, or biomarkers, of these early phases so that people at high risk for progressing to the clinical phase of PD can be identified. In the future, therapeutics or other interventions may be available to prevent or slow the onset of the clinical phase of the disease among those at high risk for PD.

Currently available PD medications do offer valuable symptomatic relief, but as PD progresses, their use is often associated with significant and sometimes intolerable side effects. For example, levodopa, one of the most effective treatments for PD can normalize motor function for years but later cause involuntary muscle movements known as dyskinesia and dystonia (sustained muscle contractions). In addition, people in the mid to late stages of PD often experience a wearing-off of the beneficial effects of PD drugs and a re-emergence of motor and non-motor symptoms before their next scheduled dose. In more advanced PD, drug-resistant motor symptoms (e.g., postural instability, freezing of gait, loss of balance, frequent falls), behavioral changes (impulse control disorders, hallucinations, and psychosis), and often dementia are leading causes of impairment.

In addition to new therapeutic options, better diagnostic tools are needed to identify PD earlier in the course of the disease. By the time a person exhibits classic motor symptoms and is diagnosed with PD, substantial and widespread loss of brain cells and functions of the brain and autonomic nervous system have already occurred. Earlier diagnosis may provide a therapeutic window to slow or prevent the progression of PD prior to the onset of motor impairments.

Many people with PD eventually develop dementia, but the time from the onset of movement symptoms to the onset of dementia symptoms varies greatly from person to person. Dementia is a leading reason for people with PD to transition from independent living at home to long-term care facilities.

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Parkinson’s Disease: Challenges, Progress, and Promise

The Morris K. Udall Parkinson’s Disease Research Act of 1997 authorized the NIH to greatly accelerate and expand PD research efforts by launching the NINDS Udall Centers of Excellence, a network of research centers that provide a collaborative, interdisciplinary framework for PD research. Udall Center investigators, along with many other researchers funded by the NIH, have made substantial progress in understanding PD, including identifying disease-associated genes; investigating the neurobiological mechanisms that contribute to PD, developing and improving PD research models, and discovering and testing potential therapeutic targets for developing novel treatment strategies.

The Udall Centers continue to conduct critical basic, translational, and clinical research on PD including: 1) identifying and characterizing candidate and disease-associated genes, 2) examining neurobiological mechanisms underlying the disease, and 3) developing and testing potential therapies. As part of the program, Udall Center investigators work with local communities of patients and caregivers to identify the challenges of living with PD and to translate scientific discoveries into patient care. The Centers also train the next generation of physicians and scientists who will advance our knowledge of and treatments for PD. For a full list of Udall Centers, visit http://www.ninds.nih.gov/udall/
The nervous system is made up of individual units called nerve cells or neurons. Neurons serve as a “communication network” within the brain and throughout a person’s body. Parkinson’s disease develops when neurons in the brain and elsewhere in the nervous system fail to function normally or die. The hallmark symptoms of PD — bradykinesia, tremor, postural instability, and rigidity — result primarily from the death of neurons in the substantia nigra, a region in the midbrain critical for motor control.

In order to communicate, neurons use chemical messengers called neurotransmitters. Neurotransmitters send information between neurons by crossing the space between them, called the synapse. Normally, in the substantia nigra produce a neurotransmitter known as dopamine. Dopamine is critical for movement and it helps transmit messages within the brain to make sure muscles produce smooth, purposeful movement. Loss of dopamine results in abnormal nerve firing patterns that impair movement. By the time Parkinson’s is diagnosed, most people have lost an estimated 60 to 80 percent of their dopamine-producing cells in the substantia nigra.

While loss of dopamine accounts for the characteristic features of the disease, recent studies have revealed that a number of other brain systems are also damaged. These include the brain structures that regulate the chemical pathways that depend on norepinephrine, serotonin, and acetylcholine. The changes in these neurotransmitters and circuits may account for many of the non-motor features of PD.

While normal alpha-synuclein functions are related to the storage and release of neurotransmitters, evidence suggests the buildup of excessive and abnormal alpha-synuclein plays a key role in the development of PD. There are rare examples of families in which certain genetic mutations in alpha-synuclein have been shown to cause the alpha-synuclein protein to misfold into an abnormal configuration. Most individuals with PD do not have a mutation in alpha-synuclein, but even when there is no mutation present, nearly every case of PD is associated with a buildup of abnormal and misfolded alpha-synuclein. As the misfolded protein accumulates, it clumps together into aggregates, or collections, that join together to form tiny protein threads called fibrils. Fibrils are the building blocks for Lewy bodies, abnormal structures that form inside nerve cells in the substantia nigra and elsewhere in the brain. Lewy bodies are a pathological hallmark of PD. Research suggests that the harmful buildup of alpha-synuclein may affect normal function and trigger nerve cell death.

Lewy bodies were discovered more than 100 years ago, and there are still unanswered questions about their role in disease. They are found in the brain of almost every patient affected by PD, but whether the Lewy bodies themselves contribute to the death of neurons is still unclear. Alternatively, the accumulation of protein in Lewy bodies may be part of an unsuccessful attempt to protect the cell from the toxicity of aggregates of alpha-synuclein.

A key objective for researchers moving forward is to better understand the normal and abnormal functions of alpha-synuclein and its relationship to genetic mutations that impact PD.
Genetic Studies

In the past decade, NINDS-funded researchers have discovered much about the genetic factors that contribute to PD. In most instances the cause of PD is unknown, however, a small proportion of cases can be attributed to genetic factors. An estimated 15 to 25 percent of people with Parkinson's disease have a family history of the disorder. It is relatively rare for PD to be caused by a single mutation of one of several specific genes. This only accounts for about 3 percent of cases in which there is a family history of PD and only 3 to 5 percent of sporadic cases — instances with no known family history.

Researchers increasingly believe that most, if not all, cases of PD probably involve both a genetic and environmental component. Early-onset Parkinson's disease is relatively rare and is more likely to be influenced by genetic factors than the forms of the disease that develop later in life.

Multiple NIH projects helped build an infrastructure for PD genetics research. The Human Genome Project and the International HapMap Project laid the groundwork for this research, producing tools to help researchers find genetic contributions to common diseases. Using these tools, researchers supported the Parkinson's Disease Genome Wide Association Study (PD-GWAS). Funded by both the NINDS and the National Institute on Aging (NIA), this effort aims to detect genetic risk factors for PD from groups around the world. Included in PD-GWAS are data from nearly 14,000 people with PD and more than 95,000 people without PD. By comparing these two groups, researchers can identify patterns in certain regions, or loci, of the human genome where genes that cause or increase the risk of PD are likely to reside. Much like a zip code, genetic loci describe the general neighborhood of a gene.

Based on an analysis of PD-GWAS data and other sources, NIH-funded scientists have identified 28 loci believed to be independently associated with PD risk and many more loci have been tentatively linked to the disorder.

Next generation genetic technologies have led to a number of new discoveries and allowed scientists learn more about what genetic factors contribute to the risk of developing PD. The first successes were a result of high-content genotyping, a method of identifying common variants in the human genome. Currently, there is a great deal of excitement regarding next generation sequencing — methods of genetic sequencing that allow for rapid sequencing of DNA base pairs in particular loci of the genome. These methods have significantly cut the time and costs required to identify genes involved with PD and will continue to facilitate the identification of PD-related genes in the future.

Another breakthrough in genetic sequencing is NeuroX, the first DNA chip able to identify genetic variants in a person's genome to determine risk for developing a number of late-onset neurodegenerative diseases, including PD. A joint venture between the NINDS and investigators at the NIA, the NeuroX chip was developed as a result of a 2011 NINDS workshop. The workshop led to an analysis of data from worldwide PD-GWAS investigations. Those studies helped correlate genetic variants and common traits among people with PD, which made the NeuroX chip possible.

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Despite these innovations, significantly more research is needed to identify PD-related genes and the cellular processes they support in order to understand how these functions contribute to the onset and progression of PD. Common genetic variations alone cannot fully explain how genetics contributes to the risk of developing PD. Instead, researchers hypothesize there must be additional genetic contributions from variants that are not common enough to be detected by PD-GWAS investigations.

Known Genetic Mutations

Inherited PD has been found to be associated with mutations in a number of genes including SNCAl, LRRK2, PARK2, PARK7, and PINK1. Many more genes may yet be identified. Genome-wide association studies have shown that common variants in these genes also play a role in changing the risk for sporadic cases.

Mutations in other types of genes, including GBA, the gene in which a mutation causes Gaucher’s disease, do not cause PD, but appear to modify the risk of developing the condition in some families. There may also be variations in other genes that have not been identified that contribute to the risk of the disease.

- **Gene for alpha-synuclein (SNCAl)**
  
  In 1997, scientists identified the first genetic mutation (SNCAl) associated with PD among three unrelated families with several members affected with PD. The SNCAl gene provides instructions for making the protein alpha-synuclein, which is normally found in the brain as well as other tissues in the body. Finding this mutation led to the discovery that alpha-synuclein aggregates were the primary component of the Lewy body. This is an example of how a disease-causing rare mutation can shed light on the entire disease process.

  PD related to SNCAl gene mutations is autosomal dominant, meaning that just one mutated copy of the gene in each cell is sufficient for a person to be affected. People with this mutation usually have a parent with the disease.
Though more than a dozen mutations in the SNCA gene have been linked to PD, these mutations are considered a relatively rare cause of the disease. In some cases, SNCA gene mutations are believed to cause the alpha-synuclein protein to misfold. Other SNCA mutations create extra copies of the gene, leading to excessive production of the alpha-synuclein protein. Even when no mutation is present, buildup of abnormal synuclein is a hallmark of PD. The NINDS is funding multiple studies aimed at determining how misfolded and excessive levels of alpha-synuclein might contribute to developing PD.

**Gene for leucine-rich repeat kinase 2 (LRRK2)**

Mutations of the LRRK2 gene are the most common genetic cause of autosomal dominant PD. These mutations play a role in about 10 percent of inherited forms of PD and about 4 percent of people who have no family history of the disease. Studies show that one particular LRRK2 mutation, G2019S, accounts for up to 20 percent of PD in specific groups, such as the Ashkenazi Jewish population.

Researchers are still studying exactly how LRRK2 gene mutations lead to PD, but it appears these mutations influence both the manufacturing and disposal of unwanted proteins in multiple ways. PD associated with LRRK2 mutations involves both early- and late-onset forms of the disease. The LRRK2 gene is a kinase enzyme, a type of protein that tags molecules within cells with chemicals called phosphate groups. This process of tagging, called phosphorylation, regulates protein enzymes by turning them “on” or “off” and it is fundamental to basic nerve cell function and health.

NINDS-supported investigators at the Udall Center at Johns Hopkins University (JHU) have found that LRRK2 mutations increase the rate at which the gene’s protein tags ribosomal proteins, a key component of the protein-making machinery inside cells. This can cause the machinery to manufacture too many proteins, leading to cell death.

LRRK2 gene mutations also are believed to inhibit a waste disposal method called autophagy, the process by which cells breakdown nutrients, recycle cellular components, and get rid of unusable waste. Autophagy is a critical means for quality control by enabling the cell to eliminate damaged organelles and abnormal proteins.

LRRK2 gene mutations inhibit a type of autophagy called chaperone-mediated autophagy. During this type of autophagy a “chaperone” protein escorts a damaged protein to the lysosome, spherical vesicles within cells that contain acid that help breakdown unwanted molecules. As a result, the LRRK2 gene mutations may lead to the buildup of alpha-synuclein into toxic aggregates within the cells. Researchers are exploring whether certain compounds might be capable of overriding LRRK2 gene mutation effects by reboasing the chaperone-mediated disposal system.

**Gene for parkin (PARK2)/ Gene for PTEN induced putative kinase 1, or PINK1 (PARK6)**

PARK2 mutations are the most common genetic mutations associated with early-onset PD, which first appear at age 50 or younger. PARK6 gene mutations also are associated with early-onset PD, but they are far more rare. Both types of mutations are associated with autosomal recessive PD, meaning that two mutated copies of the gene are present in each cell and that anyone affected may have unaffected parents who each carried a single copy of the mutated gene.

Findings from a NINDS-funded study suggest that people with PARK2 mutations tend to have slower disease progression compared with those who do not carry PARK2 mutations.

The genes PARK2, PARK6, PINK1, along with the protein parkin, are all involved at different points along a pathway that controls the integrity of mitochondria, the powerhouses inside cells that produce energy by regulating quality control processes. Brain cells are especially energetic and dependent upon mitochondrial energy supply. Specifically, parkin and PINK1 regulate mitochondrial autophagy — a process known as mitophagy. These processes are critical for maintaining a healthy pool of mitochondria by providing a means to eliminate those that no longer function properly.

Much work remains to be done to understand the association of PARK2 and PARK6 mutations and mitochondrial dysfunction, as well as to investigate if and how mitochondrial dysfunction leads to PD. Evidence suggests that parkin and PINK1 function together. When PINK1 (which is located on mitochondria) senses mitochondrial damage, it recruits parkin to get the process of mitophagy underway.

NINDS researchers are exploring ways to stimulate the PINK1/parkin pathway to encourage mitophagy. Scientists hope this will help them develop treatments for people with mitochondrial diseases, including certain forms of PD. Additionally, NINDS researchers are screening chemicals to identify agents that may be able to stimulate the expression of PINK1, and looking for other genes that may affect the functions of PINK1 and parkin.

Evidence suggests that parkin is a factor in several additional pathways leading to PD, including sporadic forms of the disease associated with alpha-synuclein toxicity.
• Gene for DJ-1 (PARK7)
The PARK7 gene encodes for the protein DJ-1. Several mutations in the gene for DJ-1 are associated with some rare, early-onset forms of PD. The function of the DJ-1 gene remains a mystery. However, one theory is it can help protect cells from oxidative stress. Oxidative stress occurs when unstable molecules called free radicals accumulate to levels that can damage or kill cells. Some studies suggest that the DJ-1 gene strengthens the cells’ ability to protect against metal toxicity and that this protective function is lost in some DJ-1 mutations. Animal studies suggest DJ-1 plays a role in motor function and helps protect cells against oxidative stress.

• Gene for beta-glucocerebrosidase (GBA)
Mutations in the gene encoding the lysosomal enzyme beta-glucocerebrosidase (GBA) are associated with a lysosomal storage disorder, Gaucher’s disease. People with Gaucher’s disease are also more likely to have parkinsonism, a group of nervous disorders with symptoms similar to Parkinson’s disease. This has spurred investigators to look for a possible link between the two diseases. NIH-funded researchers have conducted studies of individuals with both disorders to assess their brain changes, family histories, and to screen tissues and DNA samples, which have helped confirm this link.

An NIH-led, multicenter study involving more than 10,000 people with and without PD showed that people with PD were more than 5 times more likely to carry a GBA mutation than those without the disease. Mutation carriers also were more likely to be diagnosed with PD earlier in their lives and to have a family history of the disease. Scientists have observed that depletion of beta-glucocerebrosidase results in alpha-synuclein accumulation and neurodegeneration.

Further research is needed to understand the association between GBA gene mutations and PD. The NINDS supports many lines of research investigating the role of GBA gene mutations. Projects are aimed at estimating the risk of PD associated with being a GBA carrier and identifying the phenotypic traits.

Studying the genes responsible for inherited cases of PD can help shed light on both inherited and sporadic cases of PD. The same genes and proteins that are altered in inherited cases of PD may play a role in sporadic cases of the disease. In some cases genetic mutations may not directly cause PD but may increase the susceptibility of developing the disease, especially when environmental toxins or other factors are present.

Cellular and Molecular Pathways to PD

What happens in a person’s brain that causes him or her to develop PD? To answer this question scientists are working to understand the cellular and molecular pathways that lead to PD.

Mitochondrial Dysfunction
Research suggests that damage to mitochondria plays a major role in the development of PD. Mitochondria are unique parts of the cell that have their own DNA entirely separate from the genes found in the nucleus of every cell.

Mitochondrial dysfunction is a leading source of free radicals — molecules that damage membranes, proteins, DNA, and other parts of the cell. Oxidative stress is the main cause of damage by free radicals. Oxidative stress-related changes, including free radical damage to DNA, proteins, mitochondria, and fats has been detected in the brains of individuals with PD. A number of the genes found to cause PD disturb the process by which damaged mitochondria are disposed of in the neuron (mitophagy).

To learn more about how the process of mitophagy relates to PD, scientists have turned to RNA interference (RNAi), a natural process occurring in cells that helps regulate genes. Scientists are able to use RNAi as a tool to turn off genes of interest to investigate their function in cultured cells or animal models of PD. A technique known as high-throughput RNAi technology enabled NIH scientists to turn off nearly 22,000 genes one at a time. This process helped scientists identify dozens of genes that may regulate the clearance of damaged mitochondria. Researchers continue to study how these genes regulate the removal of damaged mitochondria from cells and the genes identified in this study may represent new therapeutic targets for PD.
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The contribution of UPS to the development of PD appears to be multifactorial, meaning UPS influences the interactions of several genes. NINDS-funded researchers have found that UPS is critical for the degradation of misfolded alpha-synuclein in cells. Conversely, evidence suggests that abnormal or misfolded alpha-synuclein may also inhibit the proper functioning of UPS. A feedback loop may exist whereby abnormal alpha-synuclein inhibits the functions of UPS, causing more abnormal alpha-synuclein to accumulate and additional suppression of UPS activity. NINDS-funded researchers have also identified proteins that accumulate in the absence of parkin that contribute to the loss of dopaminergic neurons.

Several NINDS-funded investigators are exploring ways of enhancing UPS function as a potential therapeutic strategy.

Cell-to-cell Transmission of Abnormally-folded Proteins

Researchers have learned more about how PD-related damage spreads to various parts of the brain and nervous system. A characteristic pattern has emerged by which Lewy bodies are distributed in various regions of the brain. The earliest brain changes appear to involve Lewy bodies in the brain stem region (medulla oblongata and pontine tegmentum, as well as the olfactory bulb). Break staging is a six-tier classification method used to identify the degree of postmortem pathology resulting from PD. According to this classification, people in Braak stages 1 and 2 are generally thought to be presymptomatic. As the disease advances to Braak stages 3 and 4, Lewy bodies spread to the substantia nigra, areas of the midbrain, the basal forebrain, and the neocortex.

More recent evidence suggests that even before such brain changes have occurred, alpha-synuclein aggregates and Lewy bodies can be found in the nervous system of the gastrointestinal tract and in the salivary glands, a finding that supports the theory that PD may originate not in the brain but in the autonomic nervous system. Non-motor symptoms such as constipation may in fact be a sign of the disease affecting nerves outside the brain before the disease moves into the brain where it later affects regions that control movement.

Researchers at the Udall Center at the Perelman School of Medicine of the University of Pennsylvania injected mice with a synthetic form of abnormal alpha-synuclein and found that misfolded alpha-synuclein appeared to spread throughout the brain. The researchers hypothesize that the injected abnormal alpha-synuclein may act like a seed that triggers the mouse’s own alpha-synuclein to misfold, leading to a cell-to-cell transmission of PD-like brain changes, especially in regions of the brain important for motor function. The mice also exhibited PD-like motor symptoms.

Understanding more about how abnormal proteins spread through the nervous system may provide a potential window for a therapeutic strategy that interrupts the process of protein transmission and slows or halts disease progression. For example, NINDS-funded investigators are looking at immune therapy and antibodies or immunization against alpha-synuclein, to block PD transmission in the brains of mice.

The development of PD is a complex interplay between environmental, genetic, and lifestyle factors. Scientists are increasingly aware that in any given individual, there may be multiple factors that cause the disease.

Environmental Influences

Environmental circumstances are thought to impact the development of PD. Exposure to certain toxins may have a direct link to the development of PD. This was the case among people exposed to MPTP, a by-product accidentally produced in the manufacture of a synthetic opioid with effects similar to morphine. During the 1980s, street drugs contaminated with this substance caused a syndrome similar to PD. MPTP is also structurally similar to some pesticides. The brain converts MPTP into MPP+, which is toxic to substantia nigra neurons. MPP+ exposure produces severe, permanent parkinsonism and has been used to create animal models of PD.

In other cases, exposure to the metal manganese among those working in the mining, welding, and steel industries has been associated with an increased risk of developing parkinsonism. Some evidence suggests that exposure to certain herbicides such as paraquat and maneb increase the risk of PD. Scientists believe that these are other yet-to-be identified environmental factors that play a role in PD among people who are already genetically susceptible to developing the disease.

The National Institute of Environmental Health Sciences (NIEHS) is the lead institute at the NIH investigating the association between PD and environmental influences such as pesticides and solvents as well as other factors like traumatic brain injury. For example, NIEHS is funding a project at the University of Washington aimed at developing and validating biomarkers to identify early-stage neurological disease processes associated with toxic agents such as chemicals, metals, and pesticides. Animal models are being developed to study the impact of pesticides on farmworkers and metals on professional welders.

The NIEHS also funds the Parkinson’s, Genes & Environment study. The study is designed to determine the role genes as well dietary, lifestyle, and environmental factors play on the risk for developing PD and their potential to cause the illness. The more than 500,000 study participants were originally recruited in 1995 as part of the National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study. Researchers will continue to follow participants over time to address some of the most interesting theories about the causes of PD. Already they have found, for example, that people who consume low levels of healthy dietary fats, such as those from fish, or high levels of saturated fats are more vulnerable to developing PD after being exposed to neurotoxins such as pesticides. The findings need to be confirmed, however, they suggest the possibility that diets rich in healthy fats and low in saturated fats may reduce the risk of PD.
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In some cases, environmental factors may also have a protective effect. Population-based studies have suggested, for example, that people with high levels of vitamin D in their blood have a much lower risk of developing PD compared with people with very low concentrations of vitamin D. Further research is needed to determine if vitamin D deficiency puts people at higher risk for PD, but such findings suggest the possibility that vitamin D supplements may have a beneficial effect. However, there may be genetic factors that cause people with low vitamin D levels to have higher rates of PD in which case vitamin D supplements would not be helpful.

To answer this question, researchers at the Udall Center at the University of Miami are examining the pharmacogenetics of vitamin D. The investigators are studying a large dataset to confirm the finding that low levels of vitamin D is a risk factor for PD. At the same time, they are trying to identify any potential genetic modifiers of vitamin D’s effect on PD risk.

Certain drugs and chemicals available as a supplement or in a person’s diet also have been shown to have a neuroprotective effect for PD and other disorders. For example, regular use of caffeine (coffee, tea) was found to reduce the loss of dopamine-producing neurons. Studies hope to define the optimal caffeine dose in treating movement disorders like PD while gaining a better understanding of the mechanisms involving caffeine’s benefit. Uric acid, because of its antioxidative effect, may lower the risk for multiple neurodegenerative disorders, in particular, PD. A preliminary clinical trial funded by the Michael J. Fox Foundation examined the effectiveness of the drug inosine to safely raise uric acid levels and possibly slow the progression of Parkinson’s disease.

Neuroinflammation

Neuroinflammation is a protective biological response designed to eliminate damaged cells and other harmful agents in nervous system tissue. Mounting evidence suggests that neuroinflammation plays a role in PD. Several lines of research funded by the NINDS are investigating this connection.

Compared to people without PD, those with PD tend to have higher levels of pro-inflammatory substances known as cytokines in their cerebrospinal fluid. Immune cells in the brain called microglia also are more likely to be activated in the brains of individuals with PD. Epidemiological studies suggest that rates of PD among people who frequently use non-steroidal anti-inflammatory drugs (NSAIDS) are lower than in those who do not use NSAIDS.

Evidence from animal studies also suggests that elevated levels of the protein alpha-synuclein may trigger microglia to become activated in the brains of people with PD.

Currently, scientists are investigating whether inflammation itself is a cause of brain cell death or if it is a response to an already occurring process that contributes to the development of a disease. If researchers can interrupt the neuroinflammatory processes, they may be able to develop neuroprotective treatments for people with PD that prevent or slow the progression of the disease by halting, or at least reducing, the loss of neurons.

Models for Studying PD

Much of the research advancing our understanding and treatment of PD would not be possible without research models — yeast, fruit flies, worms, fish, rodents, and non-human primates — that have specific characteristics that mimic PD biology in humans. Scientists depend on these models to investigate questions about what goes wrong in PD, how cellular processes fit into the context of neuronal circuits, and how potential new treatments affect these disease processes.

The NINDS supports ongoing studies at the Udall Centers and elsewhere to refine existing research models and develop new ones. Better models are needed to more accurately mimic human disease in animals and to study PD’s mechanisms and potential treatments. Currently, none of the models express all the key pathologic features of PD or reflect the complement of clinical motor and non-motor features of the disease in humans.

In addition to creating new animal models, NINDS-funded researchers also look for ways of combining different types of models (i.e., genetic and toxin-induced) to better understand the interplay between genetic and environmental factors that contribute to the development of PD.

Genetic Models

The identification of genetic mutations among some families with hereditary forms of PD led to the development of animal models (rodent, non-human primate, worm, and fly) engineered to have mutations or deletions of PD genes. Each model has its strengths and shortcomings in helping researchers study the disease.

For example, mice with SNCA mutations develop an adult-onset degenerative disease characterized by movement dysfunction and aggregation of alpha-synuclein, but these mice have no loss of dopaminergic neurons. Other mice have been engineered to express LEKK2 mutations, but show little evidence of PD symptoms. Fruit flies and worms...
Toxin-induced Models

For decades, the most widely used models for studying PD involved those in which toxins were used to induce PD-like motor symptoms. Such models were used to evaluate potential therapies. The first toxin-induced models relied on MPTP or the neurotoxin 6-hydroxydopamine to kill dopamine-producing neurons in the substantia nigra, causing PD-like motor symptoms. Later, researchers developed another type of model that examined how toxins interfered with the activities of mitochondria. Toxins for this purpose included the pesticide rotenone and the herbicides paraquat and maneb. Rats exposed to such toxins develop large inclusions in substantia nigra neurons that resemble Lewy bodies and contain alpha-synuclein and ubiquitin. The animals also developed bradykinesia, rigidity, and gait problems. Such toxin models are helpful for studying the consequences of dopamine depletion. However, they are limited in their ability to model all the factors that cause PD in humans.

Induced Pluripotent Stem Cells

Genetic engineering is another mechanism for modeling some of the processes that go wrong in PD. Recently scientists developed a breakthrough modeling mechanism using induced pluripotent stem cells (iPSCs), which are cells that can become any type of cell in the body. Researchers take samples of skin, blood, hair follicles, or other types of tissue from a person with PD and then manipulate those cells to become iPSCs. These cells are then programmed to become dopaminergic neurons, making it possible for scientists to study the molecular and cellular mechanisms that lead to PD as well as potential treatments. NIH-funded researchers have also coaxed iPSCs to become tissue from other parts of the body such as the gastrointestinal tract and the heart, allowing them to study the mechanisms of PD in other regions of the body.

Biomarkers

There is no single definitive test for diagnosing PD in a living person and there is no way to track disease progression on a biological level. Aside from finding a cure, the holy grail of PD research is the discovery of biomarkers—detectable and measurable changes in the body that can be used to predict, diagnose, and monitor disease activity and progression. Biomarkers can be identified through a number of different methods, including imaging scans (e.g., MRI, CT), biological samples (e.g., cerebrospinal fluid, plasma), and genetic studies. The risk for heart disease, for example, can be detected by measuring cholesterol or blood pressure. People at risk for PD currently lack a similar means for risk detection.

The ideal PD biomarker would be one that can be easily tested, varies with disease severity, and is abnormal during the preclinical phase of the illness before a person has any symptoms. Reliable biomarkers would allow physicians to screen and identify people at increased risk of developing PD and more accurately monitor disease progression among people who have been diagnosed with the disease.

Biomarkers would also greatly accelerate clinical research efforts by shortening the timeframe needed to show that a drug has successfully engaged a disease-specific target in the brain or nervous system. Such measures may be available long before meaningful clinical changes are evident after a person has tried a particular therapy or intervention. Biomarkers may also be useful for determining optimal drug dosage.

Progress toward the development of biomarkers is occurring on several fronts. The U.S. Food and Drug Administration (FDA) has approved the use of brain imaging technology to detect dopamine transporters (DaT), an indicator of dopamine neurons, to help evaluate adults with suspected parkinsonism. The DaTscan uses an iodine-based radioactive chemical along with single-
In 2012, the NINDS dramatically accelerated efforts to identify biomarkers by establishing the Parkinson's Disease Biomarkers Program (PDBP). This unprecedented program unites a range of stakeholders from basic and clinical researchers to healthcare professionals, the NINDS staff, information technology experts, and people living with PD and their families. PDBP supports research and builds resources aimed at accelerating the discovery of biomarkers to ultimately slow the progression of PD. For example, the program has established a repository of biological specimens and a Data Management Resource (DMR) system maintained by the NIH Center for Information Technology. The DMR allows researchers to access clinical, imaging, genetic, and biologic data, while a complementary PDBP-supported project develops statistical tools to analyze vast quantities of data so that patterns can be identified across these diverse sources of information.

PDBP supports several new and existing clinical studies that collect and analyze biospecimens such as blood, urine, and cerebrospinal fluid from people with all stages of PD as well as those without the disease. Several lines of research are looking at various proteins in these biospecimens to explore their value as markers of PD and its progression. Biospecimens are analyzed along with detailed clinical information on signs and symptoms such as gait, balance, sleep problems, memory deficits, and hyposmia. Imaging techniques are used at different stages of disease to analyze brain function in areas associated with movement and cognition.

Given the critical contribution that alpha-synuclein is believed to play in the development of PD, a high-priority goal is to develop a positron emission tomography (PET) imaging agent that can show alpha-synuclein accumulation in the brain. Currently, alpha-synuclein levels and localization in the brain can only be confirmed by an autopsy. The ability to detect the protein with an imaging technology in a living person would enable physicians to track the severity of alpha-synuclein accumulation over time, as well as to provide a means to gauge the success or failure of therapies aimed at reducing alpha-synuclein levels. Such a tool would be a game changer for accelerating drug development.

PET imaging produces a three-dimensional image of functional processes in the body. The technique requires the injection of a radiotracer agent to target the alpha-synuclein protein so that it can be visualized. Several NINDS-funded researchers and a consortium of researchers assembled by the Michael J. Fox Foundation are working to develop such an alpha-synuclein radiotracer.

NINDS researchers are conducting a longitudinal study of a large population of people — half of whom have multiple risk factors for PD while the other half have no obvious risk factors — as a way of identifying and validating biomarkers for predicting the development of PD. Many of the biomarkers being tested measure functioning of the autonomic nervous system because, as research suggests, non-motor symptoms associated with the autonomic nervous system often precede motor symptoms.

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Once a potential biomarker is identified, the next step is to validate it to make sure that it consistently and reliably provides meaningful information about PD. The PDBP studies complement work being done through the Michael J. Fox Foundation's biomarker project and the Parkinson's Progression Markers Initiative (PPMI), which seeks to validate biomarkers. The NINDS also works with the Michael J. Fox Foundation on BioFIND, a two-year observational clinical study in which investigators collect blood and cerebrospinal fluid from people with and without PD. The samples can be used in multiple research projects designed to discover and verify biomarkers of PD.

**Parkinson's Disease Biomarkers Program (PDBP)** supports research and builds resources aimed at accelerating the discovery of biomarkers to ultimately slow the progression of PD.
4. Advancing Treatments

A personalized medicine approach that treats an individual with PD in a timely manner with the optimal treatment requires understanding the enormously complex and diverse set of factors that contribute to PD. The disease processes that lead to PD involve numerous potential variables and pathways operating at cellular and molecular levels. Most of these processes unfold over the course of many years and begin well before individuals start having symptoms. People with PD may also differ significantly in terms of the symptoms they experience, the severity of those symptoms, disease progression, and their response to treatment and risk of complications.

Improving our understanding of what causes the complexity and diversity of PD is a major challenge for researchers. Tools are needed to group people with similar types of PD so that individuals who are most likely to benefit from clinical trials can be studied and their responses to treatment can be compared in a meaningful way.

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Neuroprotection and Disease Modification

A current NINDS study is focused on a potentially neuroprotective treatment that modulates calcium levels for newly-diagnosed individuals with PD. Cells in the body, including dopamine neurons in the brain, maintain optimal levels of calcium by pumping it in and out of their membranes through pore-like openings called channels. When calcium levels are too low, cells do not function properly. If they are too high, cells die. Scientists have long observed that imbalances in calcium may play a role in the development of PD.

Recent research also suggests that modifying the effects of calcium with calcium channel blockers — some of which are already on the market for treating high blood pressure — may potentially slow the progression of PD. Some population studies report that people who take calcium channel-blocking medications have decreased risk of PD. Using a mouse model of PD, researchers at the Northwestern Udall Center have shown that the calcium channel blocker isradipine can protect dopamine neurons from a variety of toxins. A preliminary study of isradipine in people with PD demonstrated relative safety. Researchers hope to confirm results in a larger, ongoing multicenter trial that is currently recruiting early-stage PD patients. Other NINDS-funded researchers continue to screen additional calcium channel blocking agents in order to develop potential neuroprotective treatments for people with PD.

In people with sporadic forms of PD, evidence suggests that parkin, normally neuroprotective, becomes inactive, pointing to a possible link between parkin and sporadic PD. NINDS-funded researchers have discovered ways of modifying the parkin protein to boost its neuroprotective activity.

The brain contains numerous connections among neurons known as neural circuits. Research on such connections and networks within the brain have advanced rapidly in the past few years. A wide spectrum of tools and techniques can now map connections between neural circuits. Using animal models, scientists have shown how circuits in the brain can be turned on and off. For example, researchers can see correlations between the firing patterns of neurons in a zebrafish’s brain and precise behavioral responses such as seeking and capturing food.

Potential opportunities to influence the brain’s circuitry are starting to emerge. Optogenetics is an experimental technique that involves the delivery of light-sensitive proteins to specific populations of brain cells. Once in place, these light-sensitive proteins can be inhibited or stimulated by exposure to light delivered via fiber optics. Optogenetics has never been used in people, however the success of the approach in animal models demonstrates a proof of principle: A neural network can be precisely targeted.

Thanks in part to the BRAIN Initiative, research on neural circuitry is gaining momentum. The “Brain Research through Advancing Innovative Neurotechnologies” Initiative is accelerating the development and application of new technologies that enable researchers to produce dynamic pictures of the brain that show how individual brain cells and complex neural circuits interact at the speed of thought.

BRAIN is expected to yield tools and technologies that will deepen our understanding of how the nervous system functions in health and disease. These advances are likely to shed light on many neurological diseases, including PD.
Parkinson’s Disease: Challenges, Progress, and Promise

Since PD is caused by the death of dopamine-producing neurons, a trial of embryonic cell replacement was attempted but did not demonstrate benefit. As researchers learn more about induced pluripotent stem cells they may be able to create healthy dopamine cells that can be transplanted into the brain as a form of therapy.

Animal models and clinical studies suggest that the body’s immune system may contribute to the pathology of Parkinson’s disease. NINDS-supported researchers are looking at whether a drug called sargramostim, which is a synthetic version of a substance that helps bone marrow manufacture new white blood cells to fight infection, can be used to restore immune system functions.

Deep Brain Stimulation

The U.S. Food and Drug Administration first approved deep brain stimulation (DBS) for the treatment of PD-related tremor in 1997. The NINDS supported pioneering research contributing to the development of DBS, which has become widely used and is one of the most effective options for treating PD once levodopa treatment becomes problematic. Much of the research that led to the development of DBS was performed by NINDS-funded scientist Dr. Mahlon DeLong and his colleagues, who have been instrumental in defining the complex circuits in the brain that malfunction in PD. Ongoing NINDS-funded research is currently building upon this scientific foundation to understand the therapeutic mechanisms and long-term effects of circuit-based treatment of PD by DBS.

DBS involves the implantation of electrodes into deep parts of the brain, typically the subthalamic nucleus or the globus pallidus. A pulse generator is also implanted under the individual’s collarbone to send finely controlled electrical signals to the DBS electrodes through wires placed under the skin. When turned on externally, the pulse generator and electrodes stimulate the brain to block signals that cause many of the motor symptoms of PD. How DBS helps control the symptoms of PD is not well understood.

In a study conducted by the NINDS and the Department of Veterans Affairs, bilateral DBS was found to more successfully control PD motor function symptoms and improve quality of life than even the most effective medications. DBS provides symptom relief for many people with PD, but it does not work for everyone. PD symptoms persist in some people despite DBS treatment. Researchers continue to look for ways of improving DBS so that it benefits a greater number of people.

For example, NINDS-supported researchers are attempting to deliver a more highly targeted stimulation of specific regions of the brain—the globus pallidus interna (GPI) and the subthalamic nucleus (STN) — to see if it makes a difference in terms of the duration of motor improvements. Other researchers are studying the effects of combining STN DBS with stimulation of the pedunculopontine nucleus (PPN, located in the brain stem) to improve gait control in people who continue to have difficulty walking and talking following STN DBS alone.

NINDS-funded researchers are also investigating different forms of brain stimulation that may be less invasive than DBS. Transcranial direct current stimulation (tDCS) involves attaching electrodes to the skin, or just beneath it, to deliver low doses of electrical current to the brain. Researchers, with support and funding from the NINDS, have also developed ParkinStim, a device that people with PD wear while sleeping. People with PD often feel worst in the morning because the medication they took the night before has worn off. Stimulation during the night may help these individuals wake up feeling better. While tDCS may not replace DBS, it may allow people to delay starting DBS therapy. It may also help individuals with PD decrease the amount or frequency of their medication.

Other NINDS-funded investigators aim to improve DBS success by understanding how DBS works. For example, NINDS-funded researchers developed a device known as WINCS (wireless instantaneous neurotransmitter concentration sensor system) that measures the release of chemicals or neurotransmitters in the brain. The WINCS device is being used in conjunction with functional MRI (fMRI) to look at brain activity and neurotransmitter release during DBS. Such information may be used to design closed-loop controllers capable of monitoring neurochemical activity so that DBS stimulation can be adjusted accordingly.

Taken together, these advances in understanding, tools, and techniques may begin to point to entirely new ways of modulating the brain’s circuits that will benefit people with treatment-resistant PD. For example, researchers at the Udall Center at Emory University are using animal model systems to understand the effects of DBS and other neurosurgical interventions on brain network elements downstream from the basal ganglia, the part of the brain responsible for voluntary motor function. These studies will not only allow researchers to better understand how DBS works but also to improve treatment and care for people with PD.

Gene Therapy

Glial cell-derived neurotrophic factor (GDNF) is a protein that may help protect and strengthen brain cells that produce dopamine. Researchers are testing the ability of these cells to deliver GDNF to key areas of the brain with the help of a viral vector known as adeno-associated virus (AAV). Using a brain infusion technique, researchers deliver AAVs that have been developed to stimulate the brain to block signals that cause many of the motor symptoms of PD. How DBS helps control the symptoms of PD is not well understood.

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Drug-Induced, Treatment-resistant, Non-motor symptoms

A major objective of PD research is to develop treatments for symptoms that do not respond to currently available medications or DBS. Therapies are still lacking for motor symptoms such as freezing of gait and non-motor symptoms such as cognitive impairment, dementia, sleep disorders, and symptoms involving the autonomic nervous system. The NINDS supports many studies that address these features.

- **Levodopa-induced dyskinesias.** Early on, Parkinson’s disease can generally be effectively managed for many years with dopaminergic treatments using a drug known as levodopa. However, the majority of people using this drug eventually develop levodopa-induced dyskinesias (e.g., tics, tremors). Based on the results from animal studies, one hypothesis is that levodopa may be associated with neurovascular changes that alter the ability of the drug to pass through the blood-brain barrier.

  The Udall Center at the Feinstein Institute for Medical Research is leading investigations into strategies for preventing drug-induced symptoms, which are such an important quality of life issue for many people with PD. Using advanced PET imaging, Feinstein researchers are examining blood flow dynamics among people with and without levodopa-induced dyskinesias. Using an animal model, the researchers hope to determine whether changes in blood flow are associated with structural changes in the tiny blood vessels surrounding the brain or with the permeability of the blood-brain barrier.

- **Dementia.** NINDS-supported researchers are conducting several clinical trials aimed at gaining a better understanding PD-related dementia, which affects a substantial portion of people with PD and for which there are virtually no treatments. Among the many lines of research addressing PD-related dementia, one longitudinal study is following people with PD and healthy volunteers over time. Participants take thinking and memory tests as researchers measure their brain activity using imaging studies, among other tests. Researchers also analyze participant’s brain tissue after they die. Investigators hope that these studies will provide information on the pathology occurring in regions of the brain that are affected in people who have PD-related dementia.

  Several Udall Centers, including the Pacific Northwest Udall Center (PANUC) and the Penn Udall Center also have projects devoted to PD-related dementia and cognitive impairment. In a study of more than 600 people with PD, PANUC researchers found that at baseline nearly 60 percent had mild cognitive impairment and 22 percent had dementia. Men were more likely to have cognitive impairment than women.

- **Disruption of sleep.** Excessive daytime sleepiness and an inability to sleep throughout the night are some of the most common and most disabling non-motor symptoms of PD. Mechanisms leading to impaired sleep are not well understood and treatment options are limited. NINDS-supported researchers are examining markers of the circadian system — which controls the body’s “biological clock” — sleepiness, and sleep quality in people with PD and healthy controls. They are also looking at the effects of bright light exposure to see if it has an effect on circadian rhythms and sleepiness.

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- **Freezing of gait.** This condition is a common and disabling symptom of PD, often leading to significant declines in quality of life. Walking requires shifting from one leg to the other. A person suffering from freezing of gait experiences a sense of falling every time he or she lifts a foot up off the floor. Every step forward resembles a controlled fall. Research has shown that auditory stimuli (sounds of a metronome) or visual cues (a flash of light or lines on the floor indicating stride length) can reduce episodes of freezing, but how these cues work is a mystery. NINDS-supported researchers are trying to determine the best way to treat freezing of gait. For example, researchers at the Udall Center for Excellence at the University of Michigan are using innovative Positron emission tomography (PET) imaging techniques to examine the mechanisms involved with gait, postural control, and attentional function.

- **Neurogenic orthostatic hypotension.** The autonomic nervous system controls blood pressure. People with diseases that disrupt the autonomic nervous system, such as PD, are therefore at risk of sudden drops in blood pressure that can lead to fainting. Research funded by the NINDS led the FDA to approve the use of Northera capsules (droxidopa) for the treatment of neurogenic orthostatic hypotension in 2014.
5. Living Well with Parkinson’s

While medication and DBS surgery are the most effective treatments for PD, individuals often choose to delay these treatments because of their adverse side effects. Until a therapy is developed that can halt the progression of PD, there is a significant need for strategies that provide symptom relief without causing negative side effects.

Diet, Exercise, and Stress Reduction

Findings from several studies suggest that exercise has the potential to provide relief from certain PD symptoms. Anecdotally, people with Parkinson’s disease who exercise typically do better. However, many questions remain. Among them is whether exercise provides a conditioning effect by strengthening muscles and improving flexibility or whether it has a direct effect on the brain.

In an NINDS-funded trial comparing the benefits of tai chi, resistance training, and stretching, tai chi was found to reduce balance impairments in people with mild-to-moderate PD. People in the tai chi group also experienced significantly fewer falls and greater improvements in their functional capacity.

The NINDS funds many studies aimed at determining how exercise benefits PD and identifying exercise regimens that improve PD symptoms. An important question is whether exercise provides people with newly-diagnosed PD a means for delaying treatment with drug therapy or DBS. NINDS-supported researchers are comparing the effects of moderate and vigorous exercise regimens with no exercise (control group) in a clinical trial to see if it can help slow the progression of symptoms.

Another study is using neuroimaging techniques to compare the neurophysiologic effects of tango dancing, treadmill training, and stretching (control group) on brain function and connectivity. The results may help explain how exercise influences function in PD and help identify which brain regions are involved. The hope is that these findings will lead to better treatments for gait difficulties by identifying specific exercise interventions and targets for DBS.

Technologies that Improve Quality of Life

New technologies may provide measurable quality of life improvements among people with PD. For example, wearable “smart home” devices may present a far more accurate and nuanced picture of an individual’s symptoms status compared to a typical physical exam performed in a physician’s office. NINDS has funded a technology laboratory at the University of Rochester to develop and test technologies for PD research and the care of patients. Scientists there have worked with Apple to develop smartphone apps to assess PD symptoms. NINDS researchers are testing the feasibility of using a portable computer module, called a quantitative motor assessment tool (QMAT), to collect information about a person’s disease impairment — all without requiring a trip to a medical center.

The NINDS also supports the development of adaptive technologies that enable people with neurological disorders to independently perform daily activities. The NINDS funding led to the development of the Liftware spoon, a chargeable electronic spoon that uses a microchip and sensors to detect the direction and force of a tremor before motorizing the spoon in the opposite direction to cancel out the movement and make it easier to eat. Studies show that the spoon reduces the disruption of tremor by 70 percent.
Research using brain tissue, donated after death, is critical to advancing the understanding of Parkinson’s disease and other neurodegenerative diseases. However, this precious resource is in short supply. New approaches to brain banking are necessary and better communication is needed with all stakeholders, including people with neurodegenerative diseases and their families. The NINDS supports several projects aimed at securing resources for research.

- The NIH NeuroBioBank (https://neurobiobank.nih.gov) is a network of brain and tissue repositories throughout the United States that coordinates the collection, evaluation, processing, storage, and distribution of nervous system tissue and associated clinical data. The project, funded by the NINDS, the National Institute of Mental Health, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, brings together researchers, NIH program staff, information technology experts, disease advocacy groups, and individuals seeking information about opportunities to donate. Repositories in the network are dedicated to collecting specimens in a standardized and transparent way so they can be made available for use by the broader research community. The repositories are linked through a common informatics platform, providing researchers with easy access to a centralized resource housing thousands of biospecimens from donors with a variety of diseases of the nervous system.

- The National Brain and Tissue Resource for Parkinson’s Disease and Related Disorders (http://www.ninds.nih.gov/research/parkinsonsweb/brain_banks/U24_BSHRL.htm) at the Banner Sun Health Research Institute in Sun City, Arizona, conducts ongoing clinical assessments of healthy elderly individuals and people with PD and related disorders who are willing to donate their brain and other biospecimens for research purposes. Participants are autopsied when they die and biospecimens are stored and available to the broader research community.

- The NINDS Human Genetics DNA and Cell Line Repository at the Coriell Institute (https://catalog.coriell.org/1/NINDS) provides researchers with resources for studying genetic causes of nervous system disorders. The bank includes a variety of samples including iPSCs from participants with Parkinson’s disease as well as other forms of parkinsonism. Also included in the collection are samples from participants’ family members and normal healthy controls.

PD research has progressed enormously in recent years. Scientists are rapidly working to unlock the mysteries of Parkinson’s, and treatments that restore lost function, halt disease progression, and prevent the condition are now realistic goals. Many of these advances are the result of discoveries from NINDS-funded basic, translational, and clinical investigators across the United States as well as NINDS-supported research at the Udall Parkinson’s Disease Research Centers of Excellence. Studies funded by the NIH have identified several genetic mutations that make individuals susceptible to Parkinson’s disease and breakthroughs in genetic research make finding new genetic factors easier and more efficient. A number of promising new therapies have been developed and are currently being tested in animals as well as people. As scientists work to learn more about the underlying biology of the disease and the complex interplay between genetic and environmental influences, new biomarkers will be discovered, therapies for relieving PD symptoms will continue to improve, and ultimately the disease may be halted, reversed, or even prevented from occurring at all.